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(54) Title: NOVEL FIBROBLAST GROWTH FACTORS AND METHODS OF USE THEREOF

(57) Abstract: The present invention relates to compositions and methods of treatment of various conditions, including but are not limited to, stroke, wound healing, and joint diseases (e.g., osteoarthritis and rheumatoid arthritis). More particularly, the present invention relates to compositions comprising a member of the fibroblast growth factor family, FGF-CX (also known as CG53135-05 or FGF-20), its related polypeptides, nucleic acids encoding such polypeptides, and their uses for treating a condition, such as but is not limited to, stroke, wound healing, and joint diseases (e.g., osteoarthritis and rheumatoid arthritis).

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NOVEL FIBROBLAST GROWTH FACTORS AND METHODS OF USE THEREOF

[001] This application claims the benefit of U.S. Provisional Application Serial No. 60/469,353, filed May 9, 2003, which is incorporated herein by reference in its entirety.

1. FIELD OF INVENTION

[002] The present invention relates to compositions and methods of treatment of various conditions, including but are not limited to, stroke, wound healing, and joint diseases (*e.g.*, osteoarthritis and rheumatoid arthritis). More particularly, the present invention relates to compositions comprising a member of the fibroblast growth factor family, FGF-CX (also known as CG53135-05 or FGF-20), its related polypeptides, nucleic acids encoding such polypeptides, and their uses for treating a condition, such as but is not limited to, stroke, wound healing, and joint diseases (*e.g.*, osteoarthritis and rheumatoid arthritis).

2. BACKGROUND OF THE INVENTION

[003] The FGF family of proteins, whose prototypic members include acidic FGF (FGF-1) and basic FGF (FGF-2), bind to four related receptor tyrosine kinases. These FGF receptors are expressed on most types of cells in tissue culture. Dimerization of FGF receptor monomers upon ligand binding has been reported to be a requisite for activation of the kinase domains, leading to receptor trans phosphorylation. FGF receptor-1 (FGFR-1), which shows the broadest expression pattern of the four FGF receptors, contains at least seven tyrosine phosphorylation sites. A number of signal transduction molecules are affected by binding with different affinities to these phosphorylation sites.

[004] Expression of FGFs and their receptors in brains of perinatal and adult mice has been examined. Messenger RNA of all FGF genes, with the exception of FGF-4, is detected in these tissues. FGF-3, FGF-6, FGF-7 and FGF-8 genes demonstrate higher expression in the late embryonic stages than in postnatal stages, suggesting that these members are involved in the late stages of brain development. In contrast, expression of FGF-1 and FGF-5 increased after birth. In particular, FGF-6 expression in perinatal mice has been reported to be restricted to the central nervous system and skeletal muscles, with intense signals in the developing cerebrum in embryos but in cerebellum in 5-day-old neonates. FGF-receptor (FGFR)-4, a cognate receptor for FGF-6, demonstrates similar spatiotemporal expression, suggesting that FGF-6 and FGFR-4 play significant roles in the maturation of

nervous system as a ligand-receptor system. According to Ozawa *et al.*, these results strongly suggest that the various FGFs and their receptors are involved in the regulation of a variety of developmental processes of brain, such as proliferation and migration of neuronal progenitor cells, neuronal and glial differentiation, neurite extensions, and synapse formation. See, *e.g.*, Ozawa *et al.*, Brain Res. Mol. Brain Res. 1996 41(1-2):279-88.

[005] Other members of the FGF polypeptide family include the FGF receptor tyrosine kinase (FGFR TK) family and the FGF receptor heparan sulfate proteoglycan (FGFR HS) family. These members interact to regulate active and specific FGFR signal transduction complexes. These regulatory activities are diversified throughout a broad range of organs and tissues, and in both normal and tumor tissues, in mammals. Regulated alternative messenger RNA (mRNA) splicing and combination of variant subdomains give rise to diversity of FGFR TK monomers. Divalent cations cooperate with the FGFR HS to conformationally restrict FGFR TK trans-phosphorylation, which causes depression of kinase activity and facilitates appropriate activation of the FGFR complex by FGF. For example, it is known that different point mutations in the FGFR TK commonly cause craniofacial and skeletal abnormalities of graded severity by graded increases in FGF-independent activity of total FGFR complexes. Other processes in which FGF family exerts important effects are liver growth and function, and prostate tumor progression.

[006] Glia-activating factor (GAF), another FGF family member, is a heparin-binding growth factor that was purified from the culture supernatant of a human glioma cell line. See, Miyamoto *et al.*, 1993, Mol. Cell Biol. 13(7): 4251-4259. GAF shows a spectrum of activity slightly different from those of other known growth factors, and is designated as FGF-9. The human FGF-9 cDNA encodes a polypeptide of 208 amino acids. Sequence similarity to other members of the FGF family was estimated to be around 30%. Two cysteine residues and other consensus sequences found in other family members were also well conserved in the FGF-9 sequence. FGF-9 was found to have no typical signal sequence in its N-terminus like those in acidic FGF and basic FGF. Acidic FGF and basic FGF are known not to be secreted from cells in a conventional manner. However, FGF-9 was found to be secreted efficiently from cDNA-transfected COS cells despite its lack of a typical signal sequence. It could be detected exclusively in the culture medium of cells. The secreted protein lacked no amino acid residues at the N-terminus with respect to those predicted by the cDNA sequence, except the initiation methionine. The rat FGF-9 cDNA was also cloned, and the structural analysis indicated that the FGF-9 gene is highly conserved.

[007] FGFs have been shown to induce neuronal sprouting. See Proc. Natl. Acad. Sci. U.S.A. 1997 94 (15): 8179-84. Kawamata *et al.* (Journal of Cerebral Blood Flow and Metabolism, 16:542-547, 1996) proposed that basic FGF, an 18 kDa and 154 amino acid long polypeptide, supports the survival and outgrowth of a wide variety of brain neurons. US Patent Application US 2002/0151496 A1 suggests that FGF-20 is a neurotrophic factor and stimulate survival of cells of neuronal origin.

2.1. Inflammation: Osteoarthritis and Rheumatoid Arthritis

[008] Osteoarthritis ("OA") is a degenerative joint disease and a frequent cause of joint pain that affects a large and growing population. OA is estimated to be the most common cause of disability in adults. The disease typically manifests itself in the 2nd to 3rd decades, with most people over forty years exhibiting some pathologic change in weight bearing joints, although the change may be asymptomatic. A systematic review of incidence and prevalence of OA of the knee in people older than 55 years in the United Kingdom reported an incidence of 25 percent per year, a prevalence of disability of 10 percent, and severe disability in about two to three percent. The National Health and Nutrition Examination Survey (Center for Health Statistics, Centers for Disease Control and Prevention) found the prevalence of this disease to be over 80 percent in people over age 55, compared to less than 0.1 percent in those aged 25 to 34 years old. OA results from a complex interplay of multiple factors, including joint integrity, genetics, local inflammation, mechanical forces, and cellular and biochemical processes. Characteristic features of the disease are degradation of articular cartilage, hypertrophy of bone at the margins, and changes in the synovial membrane, typically accompanied by pain and stiffness of the joint. For the majority of patients, OA is linked to one or more factors, such as aging, occupation, trauma, and repetitive and small insults over time. The pathophysiologic process of OA is almost always progressive.

[009] CG53135-05 and their variants belong to the FGF family that regulates proliferation (see U.S. Application Serial No. 10/174,394, which is incorporated herein by its entirety). The identification of a polymorphism (CG53135-12) in the gene encoding an FGF20-like protein, CG53135-01, in humans, and a method for identifying individuals who are carriers of the genetic risk-altering factor for OA have been described in U.S. Application Serial No. 10/702,126 ("the '126 application"), which is incorporated herein by its entirety. The '126 application describes a DNA-based diagnostic test for identifying individuals with increased risk for OA and resultant musculoskeletal complications.

[0010] There are several well-established treatment modes for OA, ranging from non-pharmaceutical to pharmaceutical intervention. Non-pharmaceutical interventions include behaviour modification, weight loss, exercise, walking aids, avoidance of aggravating activities, as well as joint irrigation, and arthroscopic and surgical interventions. Current pharmaceutical interventions include nonsteroidal antiinflammatory drugs, intraarticular corticosteroids, and colchicine. In addition, FGF-18 has been shown to repair damaged cartilage in a rat meniscal tear model for OA (See Paper #0199, 50th Annual Meeting of the Orthopaedic Research Society, San Francisco CA, 2004).

[0011] However, satisfactory treatment of OA is an unmet medical need, as existing therapeutics have not been successful in curtailing the incidence or the severity of the disease. Consequently, a therapeutic that can successfully treat osteoarthritis has the beneficial effects of decreasing morbidity, while potentially saving the healthcare system millions of dollars in costs associated with invasive surgical procedures, disability and ancillary support services.

[0012] Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

3. SUMMARY OF THE INVENTION

[0013] The present invention provides methods of preventing or treating a disease (e.g., stroke, joint diseases, and trauma) comprising administering to a subject in need thereof a FGF-CX polypeptide, which has homology to Fibroblast Growth Factor (FGF) protein. The present invention also encompasses FGF-CX polynucleotide sequences and the FGF-CX polypeptides encoded by these nucleic acid sequences, and fragments, homologs, analogs, and derivatives thereof.

[0014] In accordance with the present invention, the diseases to be prevented or treated include, but are not limited to, joint diseases (non-limiting examples being arthritis, osteoarthritis, joint pathology, ligament and tendon injuries, and meniscal injuries), ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning, and neurodegenerative diseases (non-limiting examples being Alzheimer's, Parkinson's Disease, Amyotrophic Lateral Sclerosis, Huntington's Disease).

[0015] In one aspect, the invention encompasses an isolated FGF-CX nucleic acid (SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, as shown in Table A), that encodes a FGF-CX polypeptide, or a fragment, homolog, analog or derivative thereof. The nucleic acid can include, but not limited to, nucleic acid sequence encoding a polypeptide at least 85% identical to a polypeptide comprising the amino acid sequence of

Table A (SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36). The invention also encompasses the polypeptides resulting from the proteolytic cleavage of CG53135-05 (SEQ ID NO: 2) that includes SEQ ID Nos: 37, 38, 39, 40. The nucleic acid can be, but is not limited to, a genomic DNA fragment, and a cDNA molecule.

[0016] The present invention also encompasses a vector containing one or more of the nucleic acids described herein, and a cell containing the vectors or nucleic acids described herein.

[0017] The present invention further encompasses host cells transformed with a recombinant expression vector comprising any of the nucleic acid molecules described above.

[0018] In one embodiment, the invention provides a pharmaceutical composition that comprises a FGF-CX nucleic acid and a pharmaceutically acceptable carrier. In another embodiment, the invention provides a substantially purified FGF-CX polypeptide, *e.g.*, any of the FGF-CX polypeptides encoded by a FGF-CX nucleic acid, and fragments, homologs, analogs, and derivatives thereof. The invention also provides a pharmaceutical composition that comprises a FGF-CX polypeptide and a pharmaceutically acceptable carrier.

[0019] In another embodiment, the invention provides an antibody that binds specifically to a FGF-CX polypeptide. The antibody can be, but is not limited to, a monoclonal or polyclonal antibody, and fragments, homologs, analogs, and derivatives thereof. The invention also provides a pharmaceutical composition including FGF-CX antibody and a pharmaceutically acceptable carrier. The present invention also encompasses isolated antibodies that bind to an epitope on a polypeptide encoded by any of the nucleic acid molecules described above.

[0020] The present invention further provides kits comprising antibodies that bind to a polypeptide encoded by any of the nucleic acid molecules described above and a negative control antibody.

[0021] The invention encompasses a method for producing a FGF-CX polypeptide. The method includes providing a cell containing a FGF-CX nucleic acid, *e.g.*, a vector that includes a FGF-CX nucleic acid, and culturing the cell under conditions sufficient to express the FGF-CX polypeptide encoded by the nucleic acid. The expressed FGF-CX polypeptide is then recovered from the cell. Preferably, the cell produces little or no endogenous FGF-CX polypeptide. The cell can be, *e.g.*, a prokaryotic cell or eukaryotic cell.

[0022] The present invention provides a method of inducing an immune response in a subject against a polypeptide encoded by any of the nucleic acid molecules disclosed above

by administering to the mammal an amount of the polypeptide sufficient to induce the immune response.

[0023] The present invention also provides methods of identifying a compound that binds to FGF-CX polypeptide by contacting the FGF-CX polypeptide with a compound and determining whether the compound binds to the FGF-CX polypeptide.

[0024] The invention provides a prophylactic treatment with FGF-CX polypeptide wherein an injury that predisposes the subject to osteoarthritis has occurred but the cartilage is intact.

[0025] The invention also provides a therapeutic treatment with FGF-CX polypeptide wherein intrinsic or extrinsic factors (*e.g.* genetic predisposition or meniscal injury, respectively) has led to osteoarthritic changes and cartilage damage.

4. BRIEF DESCRIPTION OF THE FIGURES

[0026] **Figure 1** shows Liquid Chromatography and Mass Spectrometry analysis of CG53135-05. CG53135-05 was injected onto the phenyl-hexyl column in an aqueous mobile phase containing 95% water, 5% acetonitrile, and 0.1% trifluoroacetic acid. The protein was then eluted by using a non-linear gradient with an organic mobile phase containing 95% acetonitrile, 5% water, and 0.085% trifluoroacetic acid. Each of the 4 peaks was characterized using LC/ESI/MS, MALDI-TOF MS, and N-terminal amino acid sequencing.

[0027] **Figure 2A and 2B** depict Peptide Map of CG53135-05. The upper tracing in each panel represents that of CG53135-05 and the lower tracing in each panel represents an identical sample treated similarly but without CG53135-05. Figure 2A: Detection at 214 nm to monitor CG53135 peptides. Figure 2B: Detection at 295 nm to monitor tryptophan-containing peptides.

[0028] **Figure 3** shows Receptor Binding Specificity of CG53135. NIH 3T3 cells were serum-starved, incubated with the indicated factor (green squares=platelet derived growth factor; blue triangle=FGF-1; red circle=CG53135) either alone or together with the indicated soluble FGFR, and DNA synthesis in response to CG53135 was measured in a BrdU incorporation assay. Data points represent the average obtained from triplicate wells, and are represented as the percent BrdU incorporation relative to cells receiving factor alone.

[0029] **Figure 4** shows the results of Forelimb Placing Test. The mean and standard error of the score for groups receiving vehicle (diamonds), 1.0 µg/injection CG53135-05

(square), and 2.5 µg/injection CG53135-05 (triangles) are represented over time. Asterisks indicate significant difference from vehicle control as assessed by one-way ANOVA.

[0030] **Figure 5** shows the results of Hindlimb Placing Test. The mean and standard error of the score for groups receiving vehicle (diamonds), 1.0 µg/injection CG53135-05 (square), and 2.5 µg/injection CG53135-05 (triangles) are represented over time. Asterisks indicate significant difference from vehicle control as assessed by one-way ANOVA.

[0031] **Figure 6** shows the results of Body Swing Test. The mean and standard error of the score for groups receiving vehicle (diamonds), 1.0 µg/injection CG53135-05 (square), and 2.5 µg/injection CG53135-05 (triangles) are represented over time. A score range of ~50% swings to the right indicates no impairment, whereas 0% swings to the right swing indicates maximal impairment. Asterisks indicate significant difference from vehicle control as assessed by one-way ANOVA.

[0032] **Figure 7** shows the results of Cylinder Test. The mean and standard error of the score for groups receiving vehicle (diamonds), 1.0 µg/injection CG53135-05 (square), and 2.5 µg/injection CG53135-05 (triangles) are represented over time.

[0033] **Figure 8** shows the results of Body Weight. The mean and standard errors of the weights for groups receiving vehicle (diamonds), 1.0 µg/injection CG53135-05 (square), and 2.5 µg/injection CG53135-05 (triangles) is represented over time.

[0034] **Figure 9** shows the effect of CG53135-05 on Pro-MMP production in SW1353 cells in the presence of IL-1 beta.

[0035] **Figure 10** shows the effect of CG53135-05 on Pro-MMP production in SW1353 cells in the presence of TNF-alpha.

[0036] **Figure 11** shows the effect of CG53135-05 on TIMP production in SW1353 cells.

[0037] **Figure 12** shows the effect of intra-articular injection of CG53135-05 in the Meniscal Tear Model of Rat Osteoarthritis (Prophylactic Dosing): Mean Tibial Cartilage Degeneration.

[0038] **Figure 13** shows results of intra-articular injection of CG53135-05 in the Meniscal Tear Model of Rat Osteoarthritis: (Prophylactic Dosing): Total Cartilage Degeneration Width.

[0039] **Figure 14** shows results of intra-articular injection of CG53135-05 in the Meniscal Tear Model of Rat Osteoarthritis: (Prophylactic Dosing): Significant Tibial Cartilage Degeneration Width.

[0040] **Figure 15** shows results of intra-articular injection CG53135-05 in the Meniscal Tear Model of Rat Osteoarthritis (Therapeutic Dosing): Mean Tibial Degeneration.

[0041] **Figure 16** shows results of intra-articular injection of CG53135-05 in the Meniscal Tear Model of Rat Osteoarthritis (Therapeutic Dosing): Total Cartilage Degeneration Width.

[0042] **Figure 17** shows results of intra-articular injection of CG53135-05 in Meniscal Tear Model of Rat Osteoarthritis (Therapeutic Dosing): Significant Tibial Cartilage Degeneration Width.

5. DETAILED DESCRIPTION OF THE INVENTION

[0043] The present invention provides methods of preventing or treating a joint disease (*e.g.*, osteoarthritis, other related joint pathologies, such as but are not limited to, ligament and tendon injuries within the ligament and tendon itself, or within their respective insertion sites, meniscal tears, other joint disorders where matrix deposition occurs, joint disorders where remodeling and repair are required, and cartilage and joint pathology occurred as a result of an inflammatory disease (*e.g.*, rheumatoid arthritis)) in a subject comprising administering to the subject a composition comprising an FGF-CX polypeptide.

[0044] The present invention also encompasses methods of using FGF-CX to improve functional recovery following middle cerebral artery (MCA) occlusion in rats. As stroke may result in disturbances of motor strength and coordination, sensory discrimination, visual function, speech, memory or other intellectual abilities, the present invention evaluates the efficacy and safety of FGF-CX in a model that assesses these parameters. In accordance with the present invention, administering FGF-CX will be beneficial in the treatment of pathological conditions including, but are not limited to, ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning, and neurodegenerative diseases (such as Alzheimer's, Parkinson's Disease, Amyotrophic Lateral Sclerosis, Huntington's Disease).

[0045] FGF-CX polypeptides, nucleic acids encoding the polypeptides, and methods of making such polypeptides are described in U.S. Application Serial Nos. 09/494,585 and 10/174,394, both of which are incorporated herein by reference in their entireties. FGF-CX is used interchangeably with the term "CG53135," "CG53135-05," and "FGF-20."

[0046] Included within the invention are FGF-CX nucleic acids, isolated nucleic acids that encode FGF-CX polypeptide or a portion thereof, FGF-CX polypeptides, vectors containing these nucleic acids, host cells transformed with the FGF-CX nucleic acids, anti-FGF-CX antibodies, and pharmaceutical compositions. Also disclosed are methods of making FGF-CX polypeptides, as well as methods of screening, diagnosing, treating conditions using these compounds, and methods of screening compounds that modulate FGF-CX polypeptide activity. Table A provides a summary of the FGF-CX nucleic acids and their encoded polypeptides.

Table A

FGF-CXX Assignment	Internal Identification	SEQ ID NO (nucleic acid)	SEQ ID NO (amino acid)	Homology
FGF-CX1a	CG53135-05	1	2	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1b	CG53135-01	3	4	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1c	CG53135-04	5	6	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1d	250059596	7	8	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1e	250059629	9	10	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1f	250059669	11	12	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1g	316351224	13	14	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1h	317459553	15	16	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1i	317459571	17	18	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1j	CG53135-02	19	20	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1k	CG53135-03	21	22	Fibroblast growth factor-20 (FGF-20) - Homo sapiens

FGF-CX1l	CG53135-06	23	24	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1m	CG53135-07	25	26	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1n	CG53135-08	27	28	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1o	CG53135-09	29	30	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1p	CG53135-10	31	32	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1q	CG53135-11	33	34	Fibroblast growth factor-20 (FGF-20) - Homo sapiens
FGF-CX1r	CG53135-12	35	36	Fibroblast growth factor-20 (FGF-20) - Homo sapiens

[0047] As used herein, the terms “subject” and “subjects” refer to an animal, preferably a mammal, including a non-primate (*e.g.*, a cow, pig, horse, cat, dog, rat, and mouse) and a primate (*e.g.*, a monkey, such as a cynomolgous monkey, chimpanzee, and a human), and more preferably a human. In a certain embodiment, the subject is a mammal, preferably a human, who is suffering from a joint disease (*e.g.*, osteoarthritis, other osteoarthritis-related disorders), ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning, or neurodegenerative diseases (non-limiting examples being Alzheimer's, Parkinson's Disease, Amyotrophic Lateral Sclerosis, Huntington's Disease). In another embodiment, the subject is a mammal, preferably a human, who are at risk for a joint disease, ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning, or neurodegenerative diseases. In one embodiment, the subject is a mammal, preferably a human, who is suffering from a joint disease, but who is not suffering from stroke or a neurodegenerative disease. The term “subject” is used interchangeably with “patient” in the present invention.

[0048] As used herein, the term “therapeutically effective amount” refers to the amount of a therapy (*e.g.*, FGF-CX polypeptide), which is sufficient to reduce the severity of a disease (*e.g.*, a joint disease, ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning, or neurodegenerative diseases), reduce the duration of a disease, prevent the advancement of a disease, cause regression of a disease, ameliorate

one or more symptoms associated with a disease, or enhance or improve the therapeutic effect(s) of another therapy.

[0049] Compositions comprising FGF-CX can also be administered in combination with one or more other therapies to prevent, treat, or ameliorate a disease (*e.g.*, a joint disease, ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning, or neurodegenerative diseases) or one or more symptoms thereof. In a preferred embodiment, compositions comprising FGF-CX is administered in combination with one or more other therapies known to be used in preventing, treating, or ameliorating a disease such as a joint disease, ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning, or neurodegenerative diseases, or one or more symptoms thereof.

[0050] In one embodiment, during a combination therapy, FGF-CX polypeptide and/or another therapy are administered in a sub-optimal amount, *e.g.*, an amount that does not manifest detectable therapeutic benefits when administered alone, as determined by methods known in the art. In such methods, co-administration of FGF-CX polypeptide and another therapy results in an overall improvement in effectiveness of treatment.

[0051] In one embodiment, FGF-CX polypeptide and one or more other therapies are administered within the same patient visit. In another embodiment, FGF-CX polypeptide is administered prior to the administration of one or more other therapies. In yet another embodiment, the FGF-CX polypeptide is administered subsequent to the administration of one or more other therapies. In a specific embodiment, FGF-CX polypeptide and one or more other therapies are cyclically administered to a subject. Cycling therapy involves the administration of FGF-CX polypeptide for a period of time, followed by the administration of one or more other therapies for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[0052] Toxicity and therapeutic efficacy of a composition of the invention (*e.g.*, FGF-CX polypeptide) can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio of LD₅₀/ED₅₀. Compositions that exhibit large therapeutic indices are

preferred. While compositions that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such composition to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0053] In one embodiment, the data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of complexes lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed, the route of administration utilized, the severity of the disease, age and weight of the subject, and other factors normally considered by a medical professional (*e.g.*, a physician). For any composition used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (*i.e.*, the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell cultures. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography. **[INSERT PREFERRED DOSAGE RANGES HERE]**

[0054] The appropriate and recommended dosages, formulation and routes of administration for treatment modalities such as chemotherapeutic agents, radiation therapy and biological/immunotherapeutic agents such as cytokines are known in the art and described in such literature as the Physician's Desk Reference (58th ed., 2004).

[0055] Various delivery systems are known and can be used to administer a composition of the invention. Such delivery systems include, but are not limited to, encapsulation in liposomes, microparticles, microcapsules, expression by recombinant cells, receptor-mediated endocytosis, construction of the nucleic acids of the invention as part of a retroviral or other vectors, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intrathecal, intracerebroventricular, epidural, intravenous, subcutaneous, intranasal, intratumoral, transdermal, rectal, and oral routes. The compositions of the invention may be administered by any convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, vaginal mucosa, rectal and intestinal mucosa, etc.), and may be administered together with other biologically active agents. Administration can be systemic or local.

[0056] In some embodiments, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment. This may be achieved

by, for example, local infusion during surgery, or topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant (said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers). In one embodiment, administration can be by direct injection at the site (or former site) of rapidly proliferating tissues which are most sensitive to an insult such radiation, chemotherapy, or chemical warfare agent.

[0057] In some embodiments, where the composition of the invention is a nucleic acid encoding a prophylactic or therapeutic agent, the nucleic acid can be administered *in vivo* to promote expression of their encoded proteins (*e.g.*, FGF-CX polypeptide), by constructing the nucleic acid as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector, or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus, etc. Alternatively, a nucleic acid of the invention can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0058] The compositions of the invention include bulk drug compositions useful in the manufacture of pharmaceutical compositions that can be used in the preparation of unit dosage forms. In a preferred embodiment, a composition of the invention is a pharmaceutical composition. Such compositions comprise a prophylactically or therapeutically effective amount of one or more compositions (*e.g.*, FGF-CX polypeptide) of the invention, and a pharmaceutically acceptable carrier. Preferably, the pharmaceutical compositions are formulated to be suitable for the route of administration to a subject.

[0059] In one embodiment, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term “carrier” refers to a diluent, adjuvant (*e.g.*, Freund’s adjuvant (complete and incomplete)), excipient, or vehicle with which the prophylactic or therapeutic agent is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils (*e.g.*, oils of petroleum, animal, vegetable or synthetic origins, such as peanut oil, soybean oil, mineral oil, sesame oil and the like), or solid carriers, such as one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet disintegrating agents, or encapsulating material. Water is a

preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include, but are not limited to, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, or a combination thereof. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0060] The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, liquid syrups, tablets, capsules, gel capsules, soft gels, pills, powders, enemas, sustained-release formulations and the like. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers. The composition can also be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc.

[0061] In some embodiments, the compositions of the present invention may be formulated and used as foams. Pharmaceutical foams include formulations such as, but not limited to, emulsions, microemulsions, creams, jellies and liposomes. While basically similar in nature, these formulations vary in the components and the consistency of the final product. The preparation of such compositions and formulations is generally known to those skilled in the pharmaceutical and formulation arts and may be applied to the formulation of the compositions of the present invention.

[0062] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, intratumoral or topical administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection.

[0063] If the compositions of the invention are to be administered topically, the compositions can be formulated in the form of transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful. Preferred topical formulations include those in which the polypeptides of the invention are in admixture with a topical delivery agent, such as but not limited to, lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Preferred lipids and liposomes include, but are not limited to, neutral (*e.g.* dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearoylphosphatidyl choline), negative (*e.g.* dimyristoylphosphatidyl glycerol DMPG), and cationic (*e.g.* dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). The polypeptides of the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, the polypeptides may be complexed to lipids, in particular to cationic lipids. Preferred fatty acids and esters include, but are not limited to, arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprinate, tricaprinate, monoolein, dilaurin, glyceryl 1-monocaprinate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C1-10 alkyl ester (*e.g.* isopropylmyristate IPM), monoglyceride, diglyceride, or pharmaceutically acceptable salt thereof. For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity preferably greater than water are typically employed. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (*e.g.*, a gaseous propellant, such as freon) or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well-known in the art.

[0064] If the method of the invention comprises intranasal administration of a composition, the composition can be formulated in an aerosol form, spray, mist or in the form of drops. In particular, prophylactic or therapeutic agents for use according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide

or other suitable gas). In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges (composed of, *e.g.*, gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0065] If the method of the invention comprises oral administration, compositions can be formulated in the form of powders, granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitables. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. Tablets or capsules can be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone, or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose, or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets may be coated by methods well-known in the art. Liquid preparations for oral administration may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives, or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol, or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring, and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated for slow release, controlled release, or sustained release of a prophylactic or therapeutic agent(s).

[0066] In one embodiment, the compositions of the invention are orally administered in conjunction with one or more penetration enhancers, *e.g.*, surfactants and chelators. Preferred surfactants include, but are not limited to, fatty acids and esters or salts thereof, bile acids and salts thereof. In some embodiments, combinations of penetration enhancers are used, *e.g.*, fatty acids/salts in combination with bile acids/salts. In a specific embodiment, sodium salt of lauric acid, capric acid is used in combination with UDCA. Further penetration enhancers include, but are not limited to, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. Compositions of the invention may be delivered orally in granular form including, but is not limited to, sprayed dried particles, or complexed to form micro or nanoparticles. Complexing agents that can be used for complexing with the peptide of the invention (*e.g.*, FGF-CX polypeptide) include, but are not limited to, poly-amino acids,

polyimines, polyacrylates, polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates, cationized gelatins, albumins, acrylates, polyethyleneglycols (PEG), polyalkylcyanoacrylates, DEAE-derivatized polyimines, pollulans, celluloses, and starches. Particularly preferred complexing agents include, but are not limited to, chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylamino-methylethylene P(TDAE), polyaminostyrene (*e.g.* p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcyanoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG).

[0067] The method of the invention may comprise pulmonary administration, *e.g.*, by use of an inhaler or nebulizer, of a composition formulated with an aerosolizing agent.

[0068] The method of the invention may comprise administration of a composition formulated for parenteral administration by injection (*e.g.*, by bolus injection or continuous infusion). Formulations for injection may be presented in unit dosage form (*e.g.*, in ampoules or in multi-dose containers) with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle (*e.g.*, sterile pyrogen-free water) before use.

[0069] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container, such as an ampoule or sachette, indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0070] The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include, but are not limited to, those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc. Non-limiting examples of pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphatidiphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc.

[0071] In addition to the formulations described previously, the compositions may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophilic drugs.

[0072] In one embodiment, the ingredients of the compositions of the invention (*e.g.*, FGF-CX) are derived from a subject that is the same species origin or species reactivity as recipient of such compositions.

[0073] The invention also provides kits for carrying out the therapeutic regimens of the invention. Such kits comprise in one or more containers prophylactically or therapeutically effective amounts of the composition of the invention (*e.g.*, FGF-CX polypeptide) in pharmaceutically acceptable form. The composition in a vial of a kit of the invention may be in the form of a pharmaceutically acceptable solution, *e.g.*, in combination with sterile saline, dextrose solution, or buffered solution, or other pharmaceutically acceptable sterile fluid. Alternatively, the composition may be lyophilized or desiccated; in

this instance, the kit optionally further comprises in a container a pharmaceutically acceptable solution (*e.g.*, saline, dextrose solution, etc.), preferably sterile, to reconstitute the composition to form a solution for injection purposes.

[0074] In another embodiment, a kit of the invention further comprises a needle or syringe, preferably packaged in sterile form, for injecting the formulation, and/or a packaged alcohol pad. Instructions are optionally included for administration of the formulations of the invention by a clinician or by the patient.

[0075] In some embodiments, the present invention provides kits comprising a plurality of containers each comprising a pharmaceutical formulation or composition comprising a dose of the composition of the invention (*e.g.*, FGF-CX polypeptide) sufficient for a single administration.

[0076] As with any pharmaceutical product, the packaging material and container are designed to protect the stability of the product during storage and shipment. In one embodiment, compositions of the invention are stored in containers with biocompatible detergents, including but not limited to, lecithin, taurocholic acid, and cholesterol; or with other proteins, including but not limited to, gamma globulins and serum albumins. Further, the products of the invention include instructions for use or other informational material that advise the physician, technician, or patient on how to appropriately prevent or treat the disease or disorder in question.

[0077] The present invention is further illustrated by the following Examples.

5.1. Example 1: Sequence Analysis

[0078] Details of the sequence relatedness and domain analysis for each FGF-CX are presented in Table 1A. The FGF-CX1 clone was analyzed, and the nucleotide and encoded polypeptide sequences are shown in Table 1A.

Table 1A. FGF-CX1 Sequence Analysis			
FGF-CX1a, CG53135-05 DNA Sequence	SEQ ID NO: 1	636 bp	
	ORF Start: ATG at 1	ORF Stop: end of sequence	
ATGGCTCCGCTGGCTGAAGTTGGTGGTTTCCTGGGCGGTCTGGAGGGTCTGGGTCAGCAGGTTGGTTCTCACTTCCTGCTGCCGCCGGCTGGTGAACGTCCGCCACTGCTGGGTGAACGTCGCTCCGCAGCTGAACGCTCCGCTCGTGGTGGCCCCGGGTGCTGCTCAGCTGGCTCACCTGCATGGTATCCTGCGTCGCCGTCAGCTGTACTGCCGTACTGGTTTCACCTGCAGATCCTGCCGGATGGTTCTGTTTACAGGGTACCCGTCAGGACCACTCTCTGTTTCGGTATCCTGGAATTCATCTCTGTTGCTGTTGGTCTGGTTTCTATCCGTGGTGTGACTCTGGCCTGTACCTGGGTATGAACGACAAAGGCGAACTGTACGGTTCTGAAAACTGACCTCTGAATGCATCTTCCGTGAACAGTTTGAAGAGAACTGGTACAACACCTACTCTTCCAACATCTACAAACATGGTGACACCGGCCGTCGCTACTTTCGTTGCTCTGAACAAAGACGGTACCCCGCGTGATGGTGCTCGTTCTAACGTCACCAGAAATTCACCCACTTCCTGCCGCGCCAGTTGACCCGGAGCGTGTTCCAGAACTGTATAAAGACCTGCTGATGTACACCTAA			
FGF-CX1a, CG53135-05	SEQ ID NO: 2	211 aa	MW at 23498.4kD

Protein Sequence			
MAPLAEVGGFLLGGLEGLGQQVGSFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHLHGILRRRQLYCRITGFHLQILPDGSLVQGTQRQDHSFLFGILEFISVAVGLVSIIRGVDSGLYLGMDKGEELYGSEKLTSECFIREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLLMYT			
FGF-CX1b, CG53135-01	SEQ ID NO: 3		633 bp
DNA Sequence	ORF Start: ATG at 1		ORF Stop:
ATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGCCAGCAGGTGGGTTCGCATTTCTCTGTTGCCCTCCTGCCGGGAGCGGCCCGCGCTGCTGGGCGAGCGCAGGAGCGCGCGGAGCGGAGCGCGCGCGGGCGGGGGCTGCGCAGCTGGCGCACCTGCACGGCATCCTGCGCCCGCGGAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACACAGCCTCTTCGGTATCTTGAATTCATCAGTGTGGCAGTGGGACTGGTTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAAATGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTCATCTAACATATATAAACATGGAGACACTGGCCCGCAGGTATTTTGTGGCACTTAACAAAGACGGAACCTCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAAATTTACACATTTCTTACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAATTGTACAAGGACCTACTGATGTACACT			
FGF-CX1b, CG53135-01	SEQ ID NO: 4	211 aa	MW at 23498.4kD
Protein Sequence			
MAPLAEVGGFLLGGLEGLGQQVGSFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHLHGILRRRQLYCRITGFHLQILPDGSLVQGTQRQDHSFLFGILEFISVAVGLVSIIRGVDSGLYLGMDKGEELYGSEKLTSECFIREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLLMYT			
FGF-CX1c, CG53135-04	SEQ ID NO: 5		540 bp
DNA Sequence	ORF Start: ATG at 1		ORF Stop: end of sequence
ATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGCCAGCCGGGGGCGAGCGAGCTGGCGCACCTGCACGGCATCCTGCGCCCGCGGAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCGACGGCAGCGCGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGAATTCATCAGTGTGGCAGTGGGACTGGTTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTCATCTAACATATATAAACATGGAGACACTGGCCCGCAGGTATTTTGTGGCACTTAACAAAGACGGAACCTCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAAATTTACACATTTCTTACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAATTGTACAAGGACCTACTGATGTACACTTAG			
FGF-CX1c, CG53135-04	SEQ ID NO: 6	179 aa	MW at 20118.6kD
Protein Sequence			
MAPLAEVGGFLLGGLEGLGQPGAAQLAHLHGILRRRQLYCRITGFHLQILPDGSAQGTQRQDHSFLFGILEFISVAVGLVSIIRGVDSGLYLGMDKGEELYGSEKLTSECFIREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLLMYT			
FGF-CX1d, 250059596	SEQ ID NO: 7		556 bp
DNA Sequence	ORF Start:		ORF Stop:
CACCAGATCTATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGCCAGCCGGGGGCGAGCGCAGCTGGCGCACCTGCACGGCATCCTGCGCCCGCGGAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGAATTCATCAGTGTGGCAGTGGGACTGGTTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTCATCTAACATATATAAACATGGAGACACTGGCCCGCAGGTATTTTGTGGCACTTAACAAAGACGGAACCTCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAAATTTACACATTTCTTACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAATTGTACAAGGACCTACTGATGTACACTGTGTCGACGGC			
FGF-CX1d, 250059596	SEQ ID NO: 8	185 aa	MW at 20762.3kD
Protein Sequence			
TRSMAPLAEVGGFLLGGLEGLGQPGAAQLAHLHGILRRRQLYCRITGFHLQILPDGSLVQGTQRQDHSFLFGILEFISVAVGLVSIIRGVDSGLYLGMDKGEELYGSEKLTSECFIREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLLMYTVDG			
FGF-CX1e, 250059629	SEQ ID NO: 9		415 bp
DNA Sequence	ORF Start:		ORF Stop:
CACCAGATCTATCCTGCGCCGCGGCGAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGAATTCATCAGTGTGGCA			

GTGGGACTGGTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGGGAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTTCATCTAACATATATAAACATGGAGACACTGGCCGCAGGTATTTTGTGGCACTTAACAAAGACGGAATCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAATTTACACATTTCTTACCTAGACCAGTGCACGGC			
FGF-CX1e, 250059629 Protein Sequence	SEQ ID NO: 10	138 aa	MW at 15847.7kD
TRASILRRRLYCRITGFHLQILPDGSVQGTQDHSIFGILEFISVAVGLVSIIRGVDSGLYLGMNDKGELYGSEKLTSECFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDG			
FGF-CX1f, 250059669 DNA Sequence	SEQ ID NO: 11	466 bp	
	ORF Start:	ORF Stop:	
CACCAGATCTATCCTGCGCCGCGGCAGCTCTATTGCGCACCGGCTTCCACCTGCAGATCCTGCCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGGAAATTCATCAGTGTGGCAGTGGGACTGGTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGGAAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTTCATCTAACATATATAAACATGGAGACACTGGCCGCAGGTATTTTGTGGCACTTAACAAAGACGGAATCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAATTTACACATTTCTTACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAAATGTACAAGGACCTACTGATGTACACTGTGCGACGGC			
FGF-CX1f, 250059669 Protein Sequence	SEQ ID NO: 12	155 aa	MW at 17911.1kD
TRASILRRRLYCRITGFHLQILPDGSVQGTQDHSIFGILEFISVAVGLVSIIRGVDSGLYLGMNDKGELYGSEKLTSECFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLLMYTVDG			
FGF-CX1g, 316351224 DNA Sequence	SEQ ID NO: 13	549 bp	
	ORF Start:	ORF Stop:	
AGATCTATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCTGGAGGGCTTGGGCCAGCCGGGGCAGCGCAGCTGGCGCACCTGCACGGCATCTTGCAGCGCCGGCAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGGAAATTCATCAGTGTGGCAGTGGGACTGGTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGGAAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAAGAGAACTGGTATAACACCTATTTCATCTAACATATATAAACATGGAGACACTGGCCGCAGGTATTTTGTGGCACTTAACAAAGACGGAATCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAATTTACACATTTCTTACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAAATGTACAAGGACCTACTGATGTACACTCTCGAG			
FGF-CX1g, 316351224 Protein Sequence	SEQ ID NO: 14	183 aa	MW at 20632.2kD
RSMAPLAEVGGFLGGLEGLQPGAAQLAHLHGILRRRLYCRITGFHLQILPDGSVQGTQDHSIFGILEFISVAVGLVSIIRGVDSGLYLGMNDKGELYGSEKLTSECFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLLMYTLE			
FGF-CX1h, 317459553 DNA Sequence	SEQ ID NO: 15	408 bp	
	ORF Start:	ORF Stop:	
AGATCTATCCTGCGCCGCGGCAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGGAAATTCATCAGTGTGGCAGTGGGACTGGTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGGAAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTTCATCTAACATATATAAACATGAAGACACTGGCCGCAGGTATTTTGTGGCACTTAACAAAGACGGAACTCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAATTTACACATTTCTTACCTAGACCACTCGAG			
FGF-CX1h, 317459553 Protein Sequence	SEQ ID NO: 16	136 aa	MW at 15789.6kD
RSILRRRLYCRITGFHLQILPDGSVQGTQDHSIFGILEFISVAVGLVSIIRGVDSGLYLGMNDKGELYGSEKLTSECFREQFEENWYNTYSSNIYKHEDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPLE			
FGF-CX1i, 317459571 DNA Sequence	SEQ ID NO: 17	408 bp	
	ORF Start: 1	ORF Stop:	
AGATCTATCCTGCGCCGCGGCAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGGAAATTCATCAGTGTGGCAGTGGGACTGGTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGGAAATGAATGACAAAGGAGAACTCTAT			

GGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTA TTCATCTAACATATATAAACATGGAGACACTGGCCGACAGGTATTTTGTGGCACTTAACAAAGACGGAA CTCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAATTTACACATTTCTTACCTAGACCACTCGAG			
FGF-CX1i, 317459571	SEQ ID NO: 18	136 aa	MW at 15717.6kD
Protein Sequence			
RSILRRRQLYCRITGFHLQILPDGSVQGTQRQDHSFLGILEFISVAVGLVSIIRGVDSGLYLGMNDKGELY GSEKLTSECFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPLE			
FGF-CX1j, CG53135-02	SEQ ID NO: 19	477 bp	
DNA Sequence	ORF Start: ATG at 1	ORF Stop: end of sequence	
	ATGGCTCAGCTGGCTCACCTGCATGGTATCCTGCGTCGCCGTCAGCTGTACTGCCGTACTGGTTTCCA CCTGCAGATCCTGCCGATGGTCTGTTCAGGGTACCCGTCAGGACCACTCTCTGTTCCGTATCCTGG AATTCATCTCTGTTGCTGTTGCTTTCATCCGTGGTGTGACTCTGGCCTGTACCTGGGTATG AACGACAAAGGCGAACTGTACGGTTCTGAAAACTGACCTCTGAATGCATCTTCCGTGAACAGTTTGA AGAGAACTGGTACAACACCTACTCTTCCAACATCTACAAACATGGTGACACCGGCCGTCGCTACTTCG TTGCTCTGAACAAAGACGGTACCCCGCGTGATGGTGCTCGTTCTAAACGTCACCAGAAATTCACCCAC TTCTTGCCGCGCCAGTTGACCCGGAGCGTGTTCAGAACTGTATAAAGACCTGCTGATGTACACCTA A		
FGF-CX1j, CG53135-02	SEQ ID NO: 20	158 aa	MW at 18254.6kD
Protein Sequence			
MAQLAHLHGILRRRQLYCRITGFHLQILPDGSVQGTQRQDHSFLGILEFISVAVGLVSIIRGVDSGLYLGM NDKGELYGSEKLTSECFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTH FLPRPVDPERVPELYKDLLMYT			
FGF-CX1k, CG53135-03	SEQ ID NO: 21	636 bp	
DNA Sequence	ORF Start: ATG at 1	ORF Stop: end of sequence	
	ATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGCCAGCAGGTGGGTTC GCATTTCTGTGTTCCCTCCTGCCGGGAGCGGCCCGCGCTGCTGGGCGAGCGCAGGAGCGCGCGGAGC GGAGCGCGCGCGCGCGGGCGGGGCTGCGCAGCTGGCGCACCTGCACGGCATCCTGCGCCGCGGCAG CTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCGACGGCAGCGTGCAGGGCACCCGGCAGGA CCACAGCCTCTTCGGTATCTTGAATTCATCAGTGTGGCAGTGGGACTGGTCAGTATTAGAGGTGTGG ACAGTGGTCTCTATCTTGAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAA TGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTCATCTAACATATATAAACATGG AGACACTGGCCGACAGTATTTTGTGGCACTTAACAAAGACGGAACCTCCAAGAGATGGCGCCAGGTCCA AGAGGCATCAGAAATTTACACATTTCTTACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAAATTTGAC AAGGACCTACTGATGTACACTTGA		
FGF-CX1k, CG53135-03	SEQ ID NO: 22	211 aa	MW at 23498.4kD
Protein Sequence			
MAPLAEVGGFLGGLEGLGQQVGSFLLPPAGERPPLLGERSSAAERSARGGPAAQLAHLHGILRRRQ LYCRTGFHLQILPDGSVQGTQRQDHSFLGILEFISVAVGLVSIIRGVDSGLYLGMNDKGELYGSEKLTSE CIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELY KDLLMYT			
FGF-CX1l, CG53135-06	SEQ ID NO: 23	540 bp	
DNA Sequence	ORF Start: ATG at 1	ORF Stop: end of sequence	
	ATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGCCAGCCGGGGGCGAGC GCAGCTGGCGCACCTGCACGGCATCCTGCGCGCCCGGCAGCTCTATTGCCGCACCGGCTTCCACCTGC AGATCCTGCCCGACGGCAGCGTGCAGGGCACCCGGCAGGACCACAGCCTCTTCGGTATCTTGAATTC ATCAGTGTGGCAGTGGGACTGGTCAGTATTAGAGGTGTGGACAGTGGTCTCTATCTTGAATGAATGA CAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAATGCATCTTTAGGGAGCAGTTTGAAGAGA ACTGGTATAACACCTATTTCATCTAACATATATAAACATGGAGACACTGGCCGACAGGTATTTTGTGGCA CTTAACAAAGACGGAACCTCCAAGAGATGGCGCCAGGTCCAAGAGGCATCAGAAATTTACACATTTCTT ACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAATTGTACAAGGACCTACTGATGTACACTTAG		
FGF-CX1l, CG53135-06	SEQ ID NO: 24	179 aa	MW at 20146.7kD
Protein Sequence			
MAPLAEVGGFLGGLEGLGQPGAAQLAHLHGILRRRQLYCRITGFHLQILPDGSVQGTQRQDHSFLGILEF ISVAVGLVSIIRGVDSGLYLGMNDKGELYGSEKLTSECFREQFEENWYNTYSSNIYKHGDTGRRYFVA LNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLLMYT			
FGF-CX1m, CG53135-07	SEQ ID NO: 25	54 bp	
DNA Sequence	ORF Start: ATG at 1	ORF Stop:	

ATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGC			
FGF-CX1m, CG53135-07	SEQ ID NO: 26	18 aa	MW at 1688.0kD
Protein Sequence			
MAPLAEVGGFLGGLEGLG			
FGF-CX1n, CG53135-08	SEQ ID NO: 27	63 bp	
DNA Sequence		ORF Start:	ORF Stop:
GAGCGGCCCGCTGCTGGGCGAGCGCAGGAGCGCGGCGGAGCGCGCGCGCGGGCCG			
FGF-CX1n, CG53135-08	SEQ ID NO: 28	21 aa	MW at 2262.5kD
Protein Sequence			
ERPPLLGERRSAAERSARGGP			
FGF-CX1o, CG53135-09	SEQ ID NO: 29	63 bp	
DNA Sequence		ORF Start:	ORF Stop:
CGCAGGTATTTGTGGCACTTAACAAAGACGGAACCTCAAGAGATGGCGCCAGGTCCAAGAGG			
FGF-CX1o, CG53135-09	SEQ ID NO: 30	21 aa	MW at 2463.8kD
Protein Sequence			
RRYFVALNKDGTPRDGARSKR			
FGF-CX1p, CG53135-10	SEQ ID NO: 31	60 bp	
DNA Sequence		ORF Start:	ORF Stop:
CCTAGACCAGTGGATCCAGAAAGAGTTCCAGAATTGTACAAGGACCTACTGATGTACACT			
FGF-CX1p, CG53135-10	SEQ ID NO: 32	20 aa	MW at 2431.8kD
Protein Sequence			
PRPVDPERVPELYKDLLMYT			
FGF-CX1q, CG53135-11	SEQ ID NO: 33	51 bp	
DNA Sequence		ORF Start: ATG at 1	ORF Stop:
ATGAACGACAAGGGCGAGCTGTACGGCAGCGAGAAGCTGACCAGCGAGTGC			
FGF-CX1q, CG53135-11	SEQ ID NO: 34	17 aa	MW at 1904.1kD
Protein Sequence			
MNDKGELYGSEKLTSEC			
FGF-CX1r, CG53135-12	SEQ ID NO: 35	633 bp	
DNA Sequence		ORF Start: ATG at 1	ORF Stop:
ATGGCTCCCTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGCCAGCAGGTGGGTTTC GCATTTTCCTGTTGCCTCCTGCCGGGAGCGGCCGCCGCTGCTGGGCGAGCGCAGGAGCGCGGCGGAGC GGAGCGCGCGCGGCGGGCCGGGGGCTGCGCAGCTGGCGCACCTGCACGGCATCCTGCGCCGCCGGCAG CTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCGACGGCAGCGTGCAGGGCACCCGGCAGGA CCACAGCCTCTTCGGTATCTTGAATTCATCAGTGTGGCAGTGGGACTGGTCAGTATTAGAGGTGTGG ACAGTGGTCTCTATCTTGAATGAATGACAAAGGAGAACTCTATGGATCAGAGAACTTACTTCCGAA TGCATCTTTAGGGAGCAGTTTGAAGAGAACTGGTATAACACCTATTCATCTAACATATATAAACATGG AGACACTGGCCGCGAGGTATTTTGTGGCACTTAACAAAGACGGAACCTCAAGAGATGGCGCCAGGTCCA AGAGGCATCAGAAATTTACACATTTCTTACCTAGACCAGTGGATCCAGAAAGAGTTCCAGAATTGTAC AAGAACCCTACTGATGTACACT			
FGF-CX1r, CG53135-12	SEQ ID NO: 36	211 aa	MW at 23497.4kD
Protein Sequence			
MAPLAEVGGFLGGLEGLGQQVGSFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHLHGILRRRQ LYCRTGFHLQILPDGSVQGTQRDHSFLGILEFISVAVGLVSIRGVDGLYLGMNDKGELYGSEKLTSE CIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELY KNLLMYT			

[0079] A ClustalW comparison of the above protein sequences yields the following sequence alignment shown in Table 1B.

Table 1B. Comparison of the FGF-CX1 protein sequences.

FGF-CX1a	MAPLAEVGGFLGGLEGLGQQVGSHFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHL
FGF-CX1b	MAPLAEVGGFLGGLEGLGQQVGSHFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHL
FGF-CX1c	-----
FGF-CX1d	-----
FGF-CX1e	-----T
FGF-CX1f	-----TRSilRRRQLYCRtGFHLQILPDGSVQGT
FGF-CX1g	-----
FGF-CX1h	-----
FGF-CX1i	-----
FGF-CX1j	-----MAQLAHLHGILRRRQLYCRtGFHLQILPDGSVQGT
FGF-CX1k	MAPLAEVGGFLGGLEGLGQQVGSHFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHL
FGF-CX1l	----MAPLAEVGGFLGGLEGLGQPGAAQLAHLHGILRRRQLYCRtGFHLQILPDGSVQGT
FGF-CX1m	-----
FGF-CX1n	-----
FGF-CX1o	-----
FGF-CX1p	-----
FGF-CX1q	-----
FGF-CX1r	MAPLAEVGGFLGGLEGLGQQVGSHFLLPPAGERPPLLGERRSAAERSARGGPGAAQLAHL
FGF-CX1a	HGILRRRQLYCRtGFHLQILPDGSVQGTQDHSLSFGILEFISVAVGLVSIRGVDSGLYLg
FGF-CX1b	HGILRRRQLYCRtGFHLQILPDGSVQGTQDHSLSFGILEFISVAVGLVSIRGVDSGLYLg
FGF-CX1c	-----
FGF-CX1d	-----
FGF-CX1e	RSILRRRQLYCRtGFHLQILPDGSVQGTQDHSLSFGILEFISVAVGLVSIRGVDSGLYLg
FGF-CX1f	RQDHSLSFGILEFISVAVGLVSIRGVDSGLYLGMNDKGELYGSEKLTSECIFREQFEENWY
FGF-CX1g	-----
FGF-CX1h	RSILRRRQLYCRtGFHLQILPDGSVQGTQDHSLSFGILEFISVAVGLVSIRGVDSGLYLg
FGF-CX1i	RSILRRRQLYCRtGFHLQILPDGSVQGTQDHSLSFGILEFISVAVGLVSIRGVDSGLYLg
FGF-CX1j	RQDHSLSFGILEFISVAVGLVSIRGVDSGLYLGMNDKGELYGSEKLTSECIFREQFEENWY
FGF-CX1k	HGILRRRQLYCRtGFHLQILPDGSVQGTQDHSLSFGILEFISVAVGLVSIRGVDSGLYLg
FGF-CX1l	RQDHSLSFGILEFISVAVGLVSIRGVDSGLYLGMNDKGELYGSEKLTSECIFREQFEENWY
FGF-CX1m	-----
FGF-CX1n	-----
FGF-CX1o	-----
FGF-CX1p	-----
FGF-CX1q	-----
FGF-CX1r	HGILRRRQLYCRtGFHLQILPDGSVQGTQDHSLSFGILEFISVAVGLVSIRGVDSGLYLg
FGF-CX1a	MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
FGF-CX1b	MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
FGF-CX1c	-----MAPLAEVGGFLGGLE
FGF-CX1d	-----TRSMAPLAEVGGFLGGLE
FGF-CX1e	MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
FGF-CX1f	NTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLL
FGF-CX1g	-----RSMAPLAEVGGFLGGLE
FGF-CX1h	MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHEDTGRRYFVALNKDGTPRDGAR
FGF-CX1i	MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
FGF-CX1j	NTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLL
FGF-CX1k	MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
FGF-CX1l	NTYSSNIYKHGDTGRRYFVALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPELYKDLL
FGF-CX1m	-----MAPLAEVGGFLGGLE
FGF-CX1n	-----ERPPLLGERRSAAERSAR
FGF-CX1o	-----RRYFVALNKDGTPRDGAR
FGF-CX1p	-----PRPVDPERVPELYKDLL
FGF-CX1q	-----MNDKGELYGSEK
FGF-CX1r	MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
FGF-CX1a	SKRHQKFTHFLPRPVDPERVPELYKDLLMYT-----
FGF-CX1b	SKRHQKFTHFLPRPVDPERVPELYKDLLMYT-----
FGF-CX1c	GLGQPGAAQLAHLHGILRRRQLYCRtGFHLQILPDGSAQGTQDHSLSFGILEFISVAVGL

FGF-CX1d	GLGQPGAAQLAHLHGILRRRQLYCRTGFHLQILPDGSVQGTQDHSLEFGILEFISVAVGL
FGF-CX1e	SKRHQKFTHFLPRPVDG-----
FGF-CX1f	MYTVDG-----
FGF-CX1g	GLGQPGAAQLAHLHGILRRRQLYCRTGFHLQILPDGSVQGTQDHSLEFGILEFISVAVGL
FGF-CX1h	SKRHQKFTHFLPRPLE-----
FGF-CX1i	SKRHQKFTHFLPRPLE-----
FGF-CX1j	MYT-----
FGF-CX1k	SKRHQKFTHFLPRPVDPERVPPELYKDILMYT-----
FGF-CX1l	MYT-----
FGF-CX1m	GLG-----
FGF-CX1n	GGP-----
FGF-CX1o	SKR-----
FGF-CX1p	MYT-----
FGF-CX1q	LTSEC-----
FGF-CX1r	SKRHQKFTHFLPRPVDPERVPPELYKNLLMYT-----
FGF-CX1a	-----
FGF-CX1b	-----
FGF-CX1c	VSIRGVDSGLYLGMNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFV
FGF-CX1d	VSIRGVDSGLYLGMNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFV
FGF-CX1e	-----
FGF-CX1f	-----
FGF-CX1g	VSIRGVDSGLYLGMNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFV
FGF-CX1h	-----
FGF-CX1i	-----
FGF-CX1j	-----
FGF-CX1k	-----
FGF-CX1l	-----
FGF-CX1m	-----
FGF-CX1n	-----
FGF-CX1o	-----
FGF-CX1p	-----
FGF-CX1q	-----
FGF-CX1r	-----
FGF-CX1a	-----
FGF-CX1b	-----
FGF-CX1c	ALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPPELYKDILMYT---
FGF-CX1d	ALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPPELYKDILMYTVDG
FGF-CX1e	-----
FGF-CX1f	-----
FGF-CX1g	ALNKDGTPRDGARSKRHQKFTHFLPRPVDPERVPPELYKDILMYTLE-
FGF-CX1h	-----
FGF-CX1i	-----
FGF-CX1j	-----
FGF-CX1k	-----
FGF-CX1l	-----
FGF-CX1m	-----
FGF-CX1n	-----
FGF-CX1o	-----
FGF-CX1p	-----
FGF-CX1q	-----
FGF-CX1r	-----
FGF-CX1a	(SEQ ID NO: 2)
FGF-CX1b	(SEQ ID NO: 4)
FGF-CX1c	(SEQ ID NO: 6)
FGF-CX1d	(SEQ ID NO: 8)
FGF-CX1e	(SEQ ID NO: 10)
FGF-CX1f	(SEQ ID NO: 12)
FGF-CX1g	(SEQ ID NO: 14)
FGF-CX1h	(SEQ ID NO: 16)

FGF-CX1i	(SEQ ID NO: 18)
FGF-CX1j	(SEQ ID NO: 20)
FGF-CX1k	(SEQ ID NO: 22)
FGF-CX1l	(SEQ ID NO: 24)
FGF-CX1m	(SEQ ID NO: 26)
FGF-CX1n	(SEQ ID NO: 28)
FGF-CX1o	(SEQ ID NO: 30)
FGF-CX1p	(SEQ ID NO: 32)
FGF-CX1q	(SEQ ID NO: 34)
FGF-CX1r	(SEQ ID NO: 36)

[0080] Further analysis of the FGF-CX1a protein yielded the following properties shown in Table 1C.

Table 1C. Protein Sequence Properties FGF-CX1a	
SignalP analysis:	No Known Signal Sequence Predicted
PSORT II analysis:	
PSG: a new signal peptide prediction method N-region: length 6; pos.chg 0; neg.chg 1 H-region: length 8; peak value 0.00 PSG score: -4.40 GvH: von Heijne's method for signal seq. recognition GvH score (threshold: -2.1): -5.49 possible cleavage site: between 16 and 17 >>> Seems to have no N-terminal signal peptide ALOM: Klein et al's method for TM region allocation Init position for calculation: 1 Tentative number of TMS(s) for the threshold 0.5: 1 Number of TMS(s) for threshold 0.5: 1 INTEGRAL Likelihood = -6.42 Transmembrane 94 - 110 PERIPHERAL Likelihood = 5.20 (at 1) ALOM score: -6.42 (number of TMSs: 1) MTOP: Prediction of membrane topology (Hartmann et al.) Center position for calculation: 101 Charge difference: 0.5 C(0.0) - N(-0.5) C > N: C-terminal side will be inside >>> membrane topology: type 1b (cytoplasmic tail 94 to 211) MITDISC: discrimination of mitochondrial targeting seq R content: 0 Hyd Moment(75): 3.24 Hyd Moment(95): 6.56 G content: 4 D/E content: 2 S/T content: 0 Score: -9.30 Gavel: prediction of cleavage sites for mitochondrial preseq cleavage site motif not found NUCDISC: discrimination of nuclear localization signals pat4: none pat7: none bipartite: none content of basic residues: 12.3% NLS Score: -0.47	

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KDEL: ER retention motif in the C-terminus: none
ER Membrane Retention Signals: none
SKL: peroxisomal targeting signal in the C-terminus: none
PTS2: 2nd peroxisomal targeting signal: none
VAC: possible vacuolar targeting motif: none
RNA-binding motif: none
Actinin-type actin-binding motif:
    type 1: none
    type 2: none
NMYR: N-myristoylation pattern : none
Prenylation motif: none
memYQRL: transport motif from cell surface to Golgi: none
Tyrosines in the tail: too long tail
Dileucine motif in the tail: found
    LL at 207
checking 63 PROSITE DNA binding motifs: none
checking 71 PROSITE ribosomal protein motifs: none
checking 33 PROSITE prokaryotic DNA binding motifs: none
NNCN: Reinhardt's method for Cytoplasmic/Nuclear discrimination
    Prediction: cytoplasmic
    Reliability: 89
COIL: Lupas's algorithm to detect coiled-coil regions
    total: 0 residues
-----
Final Results (k = 9/23):
    34.8 %: nuclear
    21.7 %: mitochondrial
    21.7 %: cytoplasmic
    8.7 %: vesicles of secretory system
    4.3 %: vacuolar
    4.3 %: peroxisomal
    4.3 %: endoplasmic reticulum
>> prediction for CG53135-05 is nuc (k=23)

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[0081] A search of the FGF-CX1a protein against the Geneseq database, a proprietary database that contains sequences published in patents and patent publication, yielded several homologous proteins shown in Table 1D.

Table 1D. Geneseq Results for FGF-CX1a

Geneseq Identifier	Protein/Organism/Length [Patent #, Date]	FGF-CX1a Residues/ Match Residues	Identities/ Similarities for the Matched Region	Expect Value
ABP54435	Human fibroblast growth factor (FGF) CX protein - Homo sapiens, 211 aa. [WO200277266-A2, 03-OCT-2002]	1..211 1..211	211/211 (100%) 211/211 (100%)	e-123
ABP54434	Xenopus XFGF-CX amino acid sequence SEQ ID NO:24 - Xenopus laevis, 211 aa. [WO200277266-A2, 03-OCT-2002]	1..211 1..211	211/211 (100%) 211/211 (100%)	e-123
ABP54429	Human fibroblast growth factor (FGF) CX protein SEQ ID NO:2 - Homo sapiens, 211 aa. [WO200277266-A2, 03-OCT-2002]	1..211 1..211	211/211 (100%) 211/211 (100%)	e-123
AAU75323	Human fibroblast growth factor, FGF-CX - Homo sapiens, 211 aa. [WO200202625-A2, 10-JAN-2002]	1..211 1..211	211/211 (100%) 211/211 (100%)	e-123
ABB07261	Human FGF-20 polypeptide - Homo sapiens, 211 aa. [WO200192522-A2, 06-DEC-2001]	1..211 1..211	211/211 (100%) 211/211 (100%)	e-123

[0082] In a BLAST search of public sequence databases, the FGF-CX1a protein was found to have homology to the proteins shown in the BLASTP data in Table 1E.

Table 1E. Public BLASTP Results for FGF-CX1a

Protein Accession Number	Protein/Organism/Length	FGF-CX1a Residues/ Match Residues	Identities/ Similarities for the Matched Portion	Expect Value
Q9NP95	Fibroblast growth factor-20 (FGF-20) - Homo sapiens (Human), 211 aa.	1..211 1..211	211/211 (100%) 211/211 (100%)	e-122
Q8C7A8	Fibroblast growth factor 20 - Mus musculus (Mouse), 211 aa.	1..211 1..211	201/211 (95%) 204/211 (96%)	e-117
Q9EST9	FGF-20 - Rattus norvegicus (Rat), 212 aa.	1..211 1..211	201/211 (95%) 204/211 (96%)	e-117
Q9ESL9	Fibroblast growth factor 20 - Mus musculus (Mouse), 212 aa.	1..211 1..211	200/211 (94%) 204/211 (95%)	e-116
Q9PVY1	XFGF-20 - Xenopus laevis (African clawed frog), 208 aa.	1..211 1..208	170/211 (80%) 189/211 (89%)	5e-97

[0083] PFam analysis predicts that the FGF-CX1a protein contains the domains shown in the Table 1F.

Table 1F. Domain Analysis of FGF-CX1a			
Pfam Domain	FGF-CX1a Match Region	Identities/ Similarities for the Matched Region	Expect Value
FGF	63..194	83/147 (56%) 122/147 (83%)	7.4e-83

5.2. Example 2: Proteolytic Cleavage Products of CG53135-05 (FGF-20)

[0084] Liquid Chromatography, Mass spectrometry and N-terminal sequencing of CG53135-05 resulted in variants that have high activity in the proliferation assays. Thus these variants detailed in this section are expected to have same utility as that of CG53135-05.

Liquid Chromatography (LC) and Mass Spectrometry (MS) analysis of CG53135-05

[0085] Purified CG53135-05 was injected onto a phenyl-hexyl column (Luna 5 mm, 250 mm X 3 mm, Phenomenex) using a standard HPLC system (Agilent 1100, Agilent) in a mobile phase containing acetonitrile, water and trifluoroacetic acid. The resulting analysis revealed detectable levels of micro-heterogeneity, showing 1 major peak (#3) and 3 minor peaks (#1, 2, 4, and 5) related to CG53135-05 (Figure 1). In order to characterize these species, fractions were collected using an automated fraction-collector (Agilent 1100) and the fractions characterized by liquid chromatography electrospray ionization ion trap mass spectrometry (LC/ESI/MS), matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF-MS), and N-terminal amino acid sequencing.

[0086] Peak 0 is not a protein, is not product-related, and is not a residual process impurity (*i.e.*, it is not DNA, endotoxin, kanamycin, or IPTG). The CG53135-05-related species (Peaks 1, 2, 3, and 4) eluted in mobile phase of 36% acetonitrile, 63% water, and 0.1% trifluoroacetic acid. Similar fractions were then pooled and the samples concentrated using an Amicon 10,000 dalton cut-off filter (Millipore, Bedford, MA) in a 4°C centrifuge. The samples were diluted 16-fold in 200 mM arginine, 40 mM sodium acetate, and 3% glycerol and then concentrated to a volume of approximately 500 µl. The concentration of the pooled fractions was determined using amino acid analysis.

[0087] All four CG53135-05-related species (Peaks 1, 2, 3, and 4) were proteolytically digested using trypsin and the peptides analyzed using liquid chromatography

with mass spectrometry detection. Mass Spectrometry was performed using a XP DECA nanospray/ion trap instrument (ThermoFinnigan, San Jose, CA) interfaced with an Ultimate Nanoflow Chromatography System (LC Packings, Amsterdam, Netherlands). Data were collected via Xcalibur Software (ThermoFinnigan) using automated MS to MS/MS switching. In the Instrument Method files, the XP DECA was set to acquire a full MS scan between 400 and 1400 m/z followed by full MS/MS scans between 400 and 2000 m/z of the top 3 ions from the preceding MS scan. Data were processed using TurboSequest (ThermoFinnigan). Database searching and protein identification was performed using MASCOT (Matrix Sciences, Manchester, UK). MASCOT reports a probability-based MOWSE score and percent coverage for the identified protein based on molecular mass of the peptides, MS/MS sequence information, mass accuracy, and number of peptides detected. Table 2 contains the peak number for the CG53135-05-related species, confidence score provide by MASCOT, and percent coverage obtained from MS/MS spectra.

Table 2: Characterization of CG53135-05 (DEV10) by MASCOT

Peak #	Retention Time	% of Total Peak Area	Probability-based MOWSE score	% Coverage by MS/MS
0	10.13	1.12	NA	NA
1	16.29	2.84	434	46%
2	18.03	79.94	562	59%
3	20.17	13.59	708	80%
4	22.25	2.50	428	54%

NA = data not available

[0088] The fractions collected were analyzed by MALDI-TOF and N-terminal sequencing to determine the identity of CG53135-05-related species. N-terminal amino acid sequence of purified CG53135-05 was determined qualitatively. CG53135-05 protein was resolved by SDS-PAGE and electrophoretically transferred to a polyvinylidene fluoride membrane; the Coomassie-stained ~23 kDa major band was excised from the membrane and analyzed by an automated Edman sequencer (Procise, Applied Biosystems, Foster City, CA). Table 3 presents the molecular weight obtained for each species and variant determined by N-terminus sequencing (where N = full-length CG53135):

Table 3: Characterization of CG53135-05 (DEV10) by MALDI-TOF and Sequence Analysis

Peak #	Molecular Weight (by MALDI-TOF)	Variant (determined by N-terminal sequence)
0	NA	NA
1	21343	N-23 N-14
	22380	N-11 N-8
2	23247	N-2
3	23473	N
4	23300	N-1

NA = data not available, not a protein, not product-related

[0089] The molecular weight determined by MALDI-TOF and N-terminus sequencing can identify the 4 species. For peak 1, 4 different species were detected via N-terminal sequencing, 2 of which were also detected by MALDI-TOF. These results are also in agreement with the coverage obtained using LC/MS. The polypeptide sequences of each species derived by N-terminal sequencing are given in Table 4.

Table 4: Polypeptide Sequences of the proteolytic cleavage products

N-8:
GFLGLEGLGQQVGSHFLLPAGERPPLLGERRSAAERSARGGPGAAQLAHL
HGILRRRQLYCRTGFHLQILPDGSVQGTRQDHSFLGILEFISVAVGLVSIRGVDSGLYLG
MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
SKRHQKFTHFLRPVDPERVPELYKDLLMYT (SEQ ID NO: 37)

N-11:
GGLGLEGLGQQVGSHFLLPAGERPPLLGERRSAAERSARGGPGAAQLAHL
HGILRRRQLYCRTGFHLQILPDGSVQGTRQDHSFLGILEFISVAVGLVSIRGVDSGLYLG
MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
SKRHQKFTHFLRPVDPERVPELYKDLLMYT (SEQ ID NO: 38)

N-14:
EGLGQQVGSHFLLPAGERPPLLGERRSAAERSARGGPGAAQLAHL
HGILRRRQLYCRTGFHLQILPDGSVQGTRQDHSFLGILEFISVAVGLVSIRGVDSGLYLG
MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
SKRHQKFTHFLRPVDPERVPELYKDLLMYT (SEQ ID NO: 39)

N-23:
HFLPAGERPPLLGERRSAAERSARGGPGAAQLAHL
HGILRRRQLYCRTGFHLQILPDGSVQGTRQDHSFLGILEFISVAVGLVSIRGVDSGLYLG
MNDKGELYGSEKLTSECIFREQFEENWYNTYSSNIYKHGDTGRRYFVALNKDGTPRDGAR
SKRHQKFTHFLRPVDPERVPELYKDLLMYT (SEQ ID NO: 40)

Table 5: Clustal analysis of CG53135-05 (SEQ ID NO: 2) versus the novel proteolytic cleavage products

Multiple Alignment:						
CG53135-05	1	MAPLAEVGGFLGGLEGLGQQVGS	HFL L P P AGERPPLLGERRSAAERSARGGPGAAQLAHL	60		
N-11	1	-----GGLEGLGQQVGS	HFL L P P AGERPPLLGERRSAAERSARGGPGAAQLAHL	49		
N-14	1	-----EGLGQQVGS	HFL L P P AGERPPLLGERRSAAERSARGGPGAAQLAHL	46		
N-8	1	-----GFLGGLEGLGQQVGS	HFL L P P AGERPPLLGERRSAAERSARGGPGAAQLAHL	52		
N-23	1	-----HFL L P P AGERPPLL	GERRSAAERSARGGPGAAQLAHL	37		
CG53135-05	61	HGILRRRQLYCRTGFHLQILPDGSVQGT	RQDHSLFGILEFISVAVGLVSI	RGVDSGLYLG	120	
N-11	50	HGILRRRQLYCRTGFHLQILPDGSVQGT	RQDHSLFGILEFISVAVGLVSI	RGVDSGLYLG	109	
N-14	47	HGILRRRQLYCRTGFHLQILPDGSVQGT	RQDHSLFGILEFISVAVGLVSI	RGVDSGLYLG	106	
N-8	53	HGILRRRQLYCRTGFHLQILPDGSVQGT	RQDHSLFGILEFISVAVGLVSI	RGVDSGLYLG	112	
N-23	38	HGILRRRQLYCRTGFHLQILPDGSVQGT	RQDHSLFGILEFISVAVGLVSI	RGVDSGLYLG	97	
CG53135-05	121	MNDKGELYGSEKLTSECI	FRQF EENWYNTYSSNIYKHGDT	GRRYFVALNKDGT	PRDGAR	180
N-11	110	MNDKGELYGSEKLTSECI	FRQF EENWYNTYSSNIYKHGDT	GRRYFVALNKDGT	PRDGAR	169
N-14	107	MNDKGELYGSEKLTSECI	FRQF EENWYNTYSSNIYKHGDT	GRRYFVALNKDGT	PRDGAR	166
N-8	113	MNDKGELYGSEKLTSECI	FRQF EENWYNTYSSNIYKHGDT	GRRYFVALNKDGT	PRDGAR	172
N-23	98	MNDKGELYGSEKLTSECI	FRQF EENWYNTYSSNIYKHGDT	GRRYFVALNKDGT	PRDGAR	157
CG53135-05	181	SKRHQKFTHFLPRPVDPERVPELYKD	LLMYT			211
N-11	170	SKRHQKFTHFLPRPVDPERVPELYKD	LLMYT			200
N-14	167	SKRHQKFTHFLPRPVDPERVPELYKD	LLMYT			197
N-8	173	SKRHQKFTHFLPRPVDPERVPELYKD	LLMYT			203
N-23	158	SKRHQKFTHFLPRPVDPERVPELYKD	LLMYT			188

Total Amino Acid Analysis

[0090] The amino acid composition of CG53135-05 was determined. Samples of CG53135-05 were hydrolyzed for 16 h at 115°C in 100 mL of 6 N HCl, 0.2% phenol containing 2 nmol norleucine as an internal standard. Samples were dried in a Speed Vac Concentrator and dissolved in 100 mL sample buffer containing 2 nmol homoserine as an internal standard. The amino acids in each sample were separated on a Beckman Model 7300 ion-exchange instrument. The amino acid composition of CG53135-05 was consistent with the theoretical amino acid composition.

[0091] The experimental amino acid composition was used to derive the extinction coefficient used in estimation of concentration via UV absorbance (protein estimation using the Bradford method). The extinction coefficient at λ_{max} is 0.97 mL/mg-cm.

Table 6: Amino Acid Analysis of CG53135-05 (DEV10)

Amino Acid	Theoretical Mole Percent	Experimental Mole Percent
ala	5.69	5.69
arg	9.00	ND ^A
asx	6.63	6.68 ^D
cys	0.95	ND ^B
gly	12.80	13.46
glx	10.90	8.67 ^D
his	3.79	4.69
ile	3.32	3.46
leu	12.32	13.18
lys	3.32	3.55
met	1.42	0.80
phe	4.74	4.93
pro	5.69	5.69
ser	6.16	4.98
thr	3.79	5.97
trp	0.47	ND ^C
tyr	4.26	4.55
val	4.74	5.26

^A Not determined because of excess arg in the formulation;

^B Not determined because cys is destroyed in the acid hydrolysis during analysis;

^C Not determined because trp is destroyed in the acid hydrolysis during analysis;

^D During acid hydrolysis asn will be converted to asp and gln to glu acid. Therefore, asx represents the sum of asn and asp while glx represents the sum of gln and glu.

Peptide Mapping

[0092] Purified CG53135-05 (25 mg) was denatured and reduced in urea and dithiothreitol at 50°C and then alkylated with iodoacetate. After lowering the concentration of urea, the samples were treated with trypsin for 40 h at 20°C. The resulting peptide fragments were separated by RP-HPLC (using a C-18 column with an acetonitrile gradient in trifluoroacetate) to obtain a peptide map (Figure 2A and 2B). The chromatogram in Figure 2A is consistent with the 20 peptides expected from the digestion of CG53135-05 with trypsin, and the chromatogram in Figure 2B reveals a single peak as expected for the single tryptophan residue in CG53135-05.

Bioassay

[0093] The biological activity of CG53135-05 related species collected from the 4 peaks identified by LC and MS was measured by treatment of serum-starved cultured NIH 3T3 murine embryonic fibroblast cells with various doses of the isolated CG53135-05 related

species and measurement of incorporation of bromodeoxyuridine (BrdU) during DNA synthesis. For this assay, cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. Cells were grown in 96-well plates to confluence at 37°C in 10% CO₂/air and then starved in Dulbecco's modified Eagle's medium for 24 - 72 h. CG53135-05-related species were added and incubated for 18 h at 37°C in 10% CO₂/air. BrdU (10 mM final concentration) was added and incubated with the cells for 2 h 37°C in 10% CO₂/air. Incorporation of BrdU was measured by enzyme-linked immunosorbent assay according to the manufacturer's specifications (Roche Molecular Biochemicals, Indianapolis, IN).

[0094] Peak 4 was not included in this assay since insufficient material was collected (Peak 4 is less than 3% of the total peak area for CG53135-05). CG53135-05 and material collected from all 3 remaining fractions (*i.e.*, Peak 1, 2, and 3) induced DNA synthesis in NIH 3T3 mouse fibroblasts in a dose-dependent manner (Table 7). The PI₂₀₀ was defined as the concentration of protein that resulted in incorporation of BrdU at 2 times the background. CG53135-05 and CG53135-05 related species recovered from all 3 measurable peaks demonstrated similar biological activity with a PI₂₀₀ of 0.7 - 11 ng/mL (Table 9).

Table 7: Biological Activity of CG53135-05 (DEV10): Induction of DNA Synthesis

PI ₂₀₀ (ng/mL)	CG53135-05 (DEV 10)	Peak 1	Peak 2	Peak 3
	1.0	0.7	11	8.6

5.3. Example 3: Receptor Binding Specificity of CG53135 (Study L-116.01)

[0095] FGF family members transduce signals intracellularly via high affinity interactions with cell surface immunoglobulin (Ig) domain-containing tyrosine kinase FGF receptors (FGFRs). Four distinct human genes encode FGFRs (Powers *et al.*, Endocr Relat Cancer 2000, 7:165-97; Klint and Claesson-Welsh, Front Biosci 1999, 4:D165-77; Xu *et al.*, Cell Tissue Res 1999, 296:33-43). A related fifth human sequence lacking a kinase domain has recently been identified and named FGFR-5 (Kim *et al.*, Biochim Biophys Acta 2001, 1518:152-6). These receptors can each bind several different members of this family (Kim *et al.*, Biochim Biophys Acta 2001, 1518:152-6; Ornitz *et al.*, J Biol Chem 1996, 271:15292-7). FGFs also bind, albeit with low affinity, to heparin sulfate proteoglycans (HSPGs) present on most cell surfaces and extracellular matrices (ECM). Interactions between FGFs and HSPGs serve to stabilize FGF/FGFR interactions and to sequester FGF and protect it from degradation (Powers *et al.*, Endocr Relat Cancer 2000, 7:165-97; Szebenyi and Fallon, Int

Rev Cytol 1999,185:45-106). Dimerization of FGF receptor monomers upon ligand binding is reported to be a requisite for activation of the kinase domains, leading to receptor trans-phosphorylation. FGF receptor-1 (FGFR-1), which shows the broadest expression pattern of the four FGF receptors, contains at least seven tyrosine phosphorylation sites. A number of signal transduction molecules are affected by binding with different affinities to these phosphorylation sites.

[0096] FGFR-1, FGFR-2 and FGFR-3 each recognize FGF-1, FGF-2, FGF-4 and FGF-8. In addition, FGFR-1 & FGFR-2 bind FGF-3, FGF-5, FGF-6, FGF-10 and FGF-17 (Powers *et al.*, Endocr Relat Cancer 2000, 7:165-97). Binding of various FGF ligands varies with each receptor splice form, thus allowing a wide repertoire of FGF-mediated signaling events through a limited number of receptor coding genes. Tissue-specific alternate splicing permits cells expressing a single FGFR gene to significantly diversify their biological response by generating distinct receptor isoforms that may exhibit different ligand specificity and function. FGFR-4, binds FGF-1, FGF-2, FGF-4, FGF-6, FGF-8 and FGF-9 but not FGF-3, FGF-5 or FGF-7. FGF-7, or keratinocyte growth factor-1 (KGF-1) is only recognized by FGFR-2, whereas FGF-9 binds to FGFR-2, FGFR-3 and FGFR-4. Receptor specificity of FGFs-11 to -19 is not well understood (Powers *et al.*, Endocr Relat Cancer 2000, 7:165-97; Ornitz *et al.*, J Biol Chem 1996, 271:15292-7).

[0097] Immunohistochemistry studies (Hughes, J Histochem Cytochem 1997, 45:1005-19) in normal human adult tissues from the major organ systems indicated that FGFR-1, FGFR-2 and FGFR-3 are widely expressed, suggesting an important functional role in tissue homeostasis. Protein expression patterns for tissue-specific isoforms have not yet been determined. FGFR-4 has a more limited expression pattern being notably absent from lung, oviduct, placenta, testis, prostate, thyroid, parathyroid, and sympathetic ganglia, tissues where all three other receptors are predominantly expressed (Hughes, J Histochem Cytochem 1997, 45:1005-19).

[0098] To determine the receptor binding specificity of CG53135, we examined the effect of soluble FGFRs on the induction of DNA synthesis in NIH 3T3 cells by recombinant CG53135-01 produced in *E. coli*.

Materials and Methods

[0099] **Protein Purification from *Escherichia coli*:** For production in *E. coli*, plasmid pETMY-hFGF20X was transformed into the *E. coli* expression host BL21 (Novagen, Madison, WI) and the induction of protein CG53135 expression was carried out according to

the manufacturer's instructions. pETMYhFGF20X/BL21 E. coli bacteria were grown in LB medium at 37°C. At an OD of 0.6, bacteriophage lambda (CE6) was added to a final multiplicity of infection of 5. The infected culture was further incubated at 27°C for 3 hours. After induction, total cells were harvested, and proteins were analyzed by Western blotting using anti-HisGly antibody (Invitrogen). Cells were harvested by low-speed centrifugation (5000 rpm in a GS-3 rotor for 15 minutes at 4°C), suspended in phosphate-buffered saline (PBS) containing 0.5M NaCl and 1M arginine, and disrupted with two passes through a microfluidizer. Cell debris was removed by low-speed centrifugation and the soluble protein fraction (supernatant) was clarified by filtration through a 0.2 micron low-protein binding membrane. The protein sample was then loaded onto a metal chelation column (pre-charged with nickel sulfate). The nickel column was washed with PBS/0.5M NaCl + 1M L-arginine and bound proteins were eluted with a linear gradient of imidazole (0-0.5 M). Fractions containing CG53135 (100-150 mM imidazole) were pooled and dialyzed against 1 X 10⁶ volumes of PBS pH 8.0 containing 1M L-arginine. The protein sample was stored at -80°C.

[00100] **Receptor Specificity:** NIH 3T3 cells were cultured in 96-well plates to approximately 100% confluence, washed and fed with DMEM without supplements (Life Technologies), and incubated for 24 h. Recombinant CG53135-01 or control protein was then added to the cells for 18 h. Control proteins used were aFGF (positive control) and platelet derived growth factor-BB (PDGFBB) (negative control). To analyze the effect of soluble FGFRs on CG53135 activity, recombinant CG53135-01, aFGF, or PDGF-BB (final concentrations of 10, 5 and 3 ng/mL, respectively), were mixed with soluble receptors (final concentrations of 0.2, 1 and 5 ug/mL), and incubated for 30 min at 37°C prior to addition to serum-starved NIH 3T3 cells. Factor concentrations represent the amount of ligand needed to generate a half maximal BrdU response in NIH 3T3 cells. Soluble FGFRs were Fc chimeras of the following receptor forms (FGFR1β(IIIc); FGFR2β(IIIb); FGFR2α(IIIb); FGFR2α(IIIc); FGFR3α(IIIc); FGFR4) and were obtained from R&D Systems (Minneapolis, MN). The BrdU assay was performed according to the manufacturer's specifications (Roche Molecular Biochemicals, Indianapolis, IN) using a 4 h BrdU incorporation time.

Results and Conclusions

[00101] To determine the receptor binding specificity of CG53135, we examined the effect of soluble FGFRs on the induction of DNA synthesis in NIH 3T3 cells by recombinant CG53135-01 produced in E. coli. Soluble receptors for FGFR1β(IIIc), FGFR2β(IIIb), FGFR2α(IIIb), FGFR2α(IIIc), FGFR3α(IIIc), and FGFR4 were utilized. We found that

soluble forms of each of these FGFRs were able to specifically inhibit the biological activity of CG53135 (Figure 3).

[00102] Complete or nearly complete inhibition was obtained with soluble FGFR2 α (IIIb), FGFR2 β (IIIb), FGFR2 α (IIIc), and FGFR3 α (IIIc), whereas partial inhibition was achieved with soluble FGFR1 β (IIIc) and FGFR4. None of the soluble receptor reagents interfered with the induction of DNA synthesis by PDGF-BB (Figure 2), thereby demonstrating their specificity. The integrity of each soluble receptor reagent was demonstrated by showing their ability to inhibit the induction of DNA synthesis by aFGF, a factor known to interact with all of the FGFR's under analysis (Figure 3).

5.4. Example 4: Treatment of Stroke

[00103] Thirty male Sprague Dawley rats were allocated to treatment groups as indicated in the study design Table 8 below.

Table 8: Experimental Design

	Number of Animals	Dose *	Volume *
Treatment	Males	(μg)	(μL)
Vehicle 1	10	0	50
CG53135-05	10	1	50
CG53135-05	10	2.5	50

*Administered dose and volume is based on an average bodyweight of 330 g.

Experimental Procedures

[00104] **Middle cerebral artery (MCA) Surgery and Intracisternal Injections:**

Animals were handled for 7 days prior to surgery. Cefazolin sodium (40 mg/kg, i.p) was administered on the day before surgery and just after surgery. At the time of surgery, the rats were anesthetized with 2% halothane in a 2:1 N₂O :O₂ mixture. Body temperature was maintained at 37 $\pm$ 0.50°C. The proximal right MCA was electrocoagulated from just proximal to the olfactory tract to the inferior cerebral vein and was then transected. For intracisternal injections, animals were re-anesthetized as above and placed in a stereotaxic frame. Rats were given CG53135-05 or vehicle [40mM acetate, 200 mM mannitol (pH 5.3)] by percutaneous injection into the cisterna magna, once at 1 day, (approximately 24 hours) and once at 3 days, (approximately 72 hours) after MCA. Animals were given test article (2 dose groups) or vehicle treatment according to the study design.

Clinical Observations/Signs

[00105] Animals were observed immediately over a 1 hour period following injections for signs of seizure (indicated by tremor and violent motion about the cage), pain (indicated by loud vocalization), and lethargy. Animals were also observed daily for mortality and moribundity.

[00106] **Body Weight:** Animals were weighed on Days 1, 3, 7, 14 and 21.

[00107] **Limb Placing Test:** limb placing tests were carried out on all animals on Day -1 (pre-operation), Day 1 (just prior to injection), Day 3 and then every 7 days thereafter (Days 7, 14, 21).

[00108] **Forelimb Placing Test Assessment Score:** The forelimb placing test measures sensorimotor function in each forelimb as the animal places the limb on a table top in response to visual, tactile, and proprioceptive stimuli. The forelimb placing test consists of the following evaluations and scoring, where the combined total score for the forelimb placing test reflects a range from 0 (no impairment) to 10 (maximal impairment):

visual placing (forward, sideways): 0 - 4

tactile placing (dorsal,lateral): 0 - 4

proprioceptive placing: 0 - 2

Total score for all forelimb tests: 0 - 10

[00109] **Hindlimb Placing Test Assessment Score:** Similarly, the hindlimb placing test measures sensorimotor function of the hindlimb as the animal places it on a tabletop in response to tactile and proprioceptive stimuli. The hindlimb placing test consists of the following evaluations and scoring, where the combined total score for the hindlimb placing test reflects a range from 0 (no impairment) to 6 (maximal impairment):

tactile placing (dorsal,lateral): 0 - 4

proprioceptive placing: 0 - 2

Total score for all hindlimb tests: 0 - 6

[00110] **Body Swing Test:** the body swing test was carried out on all animals on Day -1 (pre-operation), Day 1 (just prior to injection), Day 3 and then every 7 days thereafter (Days 7, 14, 21).

[00111] The body swing test examines side preference as the animal is held approximately one inch above the surface of the table, and swings to the right or the left side. Thirty swings are counted, and the score is then calculated based on the percentage of swings

to the right. (score range = ~50% right swing (no impairment) - 0% right swing (maximal impairment))

[00112] **Cylinder Test:** the cylinder test was carried out on all animals on Day -1 (pre-operation) and 7 days thereafter (Days 7, 14, 21). The cylinder test measures spontaneous motor activity of the forelimbs. Animals are placed in a narrow glass cylinder (16.5 x 25 cm) and videotaped for 5 min on the day before stroke surgery and at weekly intervals thereafter. Videotapes are then scored independently by one experienced observer and up to 50 spontaneous movements will be counted (~ 5 min per rat per day). Spontaneous movements include those made by each forelimb to initiate rearing, to land on or to move laterally along the wall of the cylinder, or to land on the floor after rearing.

[00113] **Macroscopic and Histomorphology:** on the day of scheduled termination (Day 3), animals were euthanized by an intraperitoneal injection of Chloral hydrate (500mg/Kg). Brains were examined grossly and removed, postfixed in formalin, dehydrated and embedded in paraffin. Coronal sections (5 mm) will be cut on a microtome mounted on to glass slides, and stained with hematoxylin/eosin (H&E). The area of cerebral infarcts on each of seven slices (+4.7, +2.7, +0.7, -1.3, -3.3, -5.3, and -7.3 mm compared with Bregma) was determined using a computer interface imaging system using the indirect method (area of the intact contralateral hemisphere – area of the intact ipsilateral hemisphere) to correct for brain shrinkage during processing. Infarct volume was then expressed as a percentage of the intact contralateral hemispheric volume. Volumes of the infarction in the cortex and striatum were also determined separately using these same methods. H&E stained section was examined for histological changes such as hemorrhage, abscess or tumor formation.

[00114] **Statistical Analysis:** all intracisternal injections, behavioral testing, and subsequent histological analyses were done by investigators blinded to the treatment assignment of each animal. Data are then expressed as means +/- SEM, and will be analyzed by one or two way (ANOVA) followed by appropriate pairwise post hoc tests with correction for multiple comparisons.

Results

[00115] **Forelimb Placing Test:** on days -1, 1, 3, 7, 14, and 21 relative to MCA occlusion, animals were examined by using a limb placing test to assess sensorimotor function in the forelimb in response to visual, tactile and proprioceptive stimuli (Kawamata, T., Dietrich, W. D., Schallert, T., Gotts, E., Cocke, R. R., Benowitz, L. I. & Finklestein, S. P. (1997) Proc. Natl. Acad. Sci. USA 94, 8179–8184; De Ryck, M., Van Reempts, J.,

Duytschaever, H., Van Deuren, B. & Clincke, G. (1992) *Brain Res.* 573, 44–60.) Visual placing (scored 0–4), tactile placing (scored 0–4), and proprioceptive placing (scored 0–2) were summed to generate a range of potential total scores from 0 to 12, with 12 representing maximal impairment (Figure 4).

[00116] Hindlimb Placing: on days –1, 1, 3, 7, 14, and 21 relative to MCA occlusion, animals were examined by using a limb placing test to assess sensorimotor function in the hindlimb in response to tactile and proprioceptive stimuli [Kawamata, T., Dietrich, W. D., Schallert, T., Gotts, E., Cocke, R. R., Benowitz, L. I. & Finklestein, S. P. (1997) *Proc. Natl. Acad. Sci. USA* 94, 8179–8184; De Ryck, M., Van Reempts, J., Duytschaever, H., Van Deuren, B. & Clincke, G. (1992) *Brain Res.* 573, 44–60]. Tactile placing (scored 0–4), and proprioceptive placing (scored 0–2) were summed to generate a range of potential total scores from 0 to 6, with 6 representing maximal impairment (Figure 5).

[00117] Body Swing Test: On days –1, 1, 3, 7, 14, and 21 relative to MCA occlusion, animals were examined by using a body swing test to assess side preference as the animal is held approximately one inch above the surface of the table, and swings to the right or the left side. (Kawamata, T., Dietrich, W. D., Schallert, T., Gotts, E., Cocke, R. R., Benowitz, L. I. & Finklestein, S. P. (1997) *Proc. Natl. Acad. Sci. USA* 94, 8179–8184; De Ryck, M., Van Reempts, J., Duytschaever, H., Van Deuren, B. & Clincke, G. (1992) *Brain Res.* 573, 44–60.) Thirty swings were counted, and the score calculated based on the percentage of swings to the right (Figure 6).

[00118] Cylinder Test: On days –1, 1, 3, 7, 14, and 21 relative to MCA occlusion, animals were examined by cylinder test to assess spontaneous motor activity of the forelimbs (Kawamata, T., Dietrich, W. D., Schallert, T., Gotts, E., Cocke, R. R., Benowitz, L. I. & Finklestein, S. P. (1997) *Proc. Natl. Acad. Sci. USA* 94, 8179–8184; De Ryck, M., Van Reempts, J., Duytschaever, H., Van Deuren, B. & Clincke, G. (1992) *Brain Res.* 573, 44–60.) Briefly, animals are placed in a narrow glass cylinder (16.5 x 25 cm) and videotaped for 5 min on the day before stroke surgery and at weekly intervals thereafter. Videotapes are then scored independently by one experienced observer and up to 50 spontaneous movements will be counted (~ 5 min per rat per day). Spontaneous movements include those made by each forelimb to initiate rearing, to land on or to move laterally along the wall of the cylinder, or to land on the floor after rearing (Figure 7).

[00119] Body Weight: animals were weighed on days -1, 1, 3, 7, 14, and 21 relative to MCA occlusion and the results indicate no significant difference between the vehicle and CG53135-05 treatment (Figure 8).

Conclusion

[00120] Administering CG53135-05 following MCA occlusion suggested that both the low and high doses produced a significant enhancement of recovery on forelimb (Figure 4) and hindlimb placing tests (Figure 5) for the contralateral (affected) limbs, and improvement on the body swing test (Figure 6). This pattern of activity with other therapeutics in this model has generally been shown to reflect improvement in cerebrocortical and subcortical (striatal) function, respectively (Dijkhuizen RM, Ren J, Mandeville JB, Wu O, Ozdag FM, Moskowitz MA, Rosen BR, Finklestein SP. 2001, Proc Natl Acad Sci U S A 98(22):12766-71). No apparent differences were seen on the cylinder test (Figure 7) of spontaneous limb use or on animal body weight (Figure 8).

[00121] Therefore, CG53135-05 administration will be useful in the treatment of pathological conditions including ischemic stroke, hemorrhagic stroke, trauma, spinal cord damage, heavy metal or toxin poisoning and neurodegenerative diseases (such as Alzheimer's, Parkinson's Disease, Amyotrophic Lateral Sclerosis, Huntington's Disease).

5.5. Example 5: Matrix Metalloproteinase Production Assay

[00122] The matrix metalloproteinases (MMPs) are a family of related enzymes that degrade the extracellular matrix in bone and cartilage. These enzymes operate during normal development in tissues differentiation and remodeling. In arthritic diseases, such as Osteoarthritis (OA) and Rheumatoid Arthritis (RA), elevated expression of these enzymes contribute to irreversible matrix degradation. Thus, effect of CG53135-05 on MMP production was assayed.

[00123] The activity of CG53135 on matrix metalloproteinase (MMP) production was assessed using the SW1353 chondrosarcoma cell line (ATCC HTB-94). This cell line is a well-established chondrocytic cellular model for matrix metalloproteinases (MMP) production. SW1353 cells were plated in a 24-well plate at 1×10^5 cells/ml (1 ml) in DMEM medium-10 % FBS. Following overnight incubation, the medium was replaced with DMEM + 0.2 % Lactalbumin serum. CG53135-05 was added to the wells at doses ranging from 10 to 5000 ng/ml, in the absence or presence of IL-1 beta (0.1 to 1 ng/ml, R&D systems Minneapolis, MN), TNF-alpha (10 ng/ml, R&D systems) or vehicle control to a final volume of 0.5 ml. IL-1 beta and TNF-alpha are both potent stimulators of MMP activity. All

treatments were done in triplicate wells. After 24 h, the supernatants were collected and Pro-MMP-1, and -13, as well as TIMP-1 (tissue inhibitor of matrix metalloproteinase), a natural inhibitor of MMP activity, was measured by ELISA (R&D systems). The measurements were normalized to the number of cells by an MTS assay.

Results

[00124] CG53135-05 significantly decreased MMP-13 production in the presence of either IL-1 beta or TNF-alpha as demonstrated in Figure 14 and Figure 15 respectively. IL-1 beta and TNF-alpha are both potent stimulators of MMP activity. MMP-13 affinity for type II collagen, the main collagen that is degraded in OA, is ten times higher than that of MMP-1. Since MMP-13 expression increases in OA and RA, the decrease of MMP-13 observed with addition of CG53135-05 indicates that the protein can be used as an OA and RA therapeutic (Figure 10). Furthermore, CG53135-05 up-regulated the production of TIMP-1, a natural inhibitor of MMP activity (Figure 11). This enhancement of TIMP-1 production by CG53135-05 is beneficial in reducing the matrix breakdown by MMP-1 and -13 observed in OA and RA. In addition, CG53135-05 had no effect on MMP-3 production constitutively or after IL-1 induction (data not shown.). Similarly, CG53135-05 (FGF-20) showed increase in basal expression of MMP-1 in SW1353 cells (data not shown).

5.6. Example 6: Effect of CG53135-05 on Normal Rats: Proof of Principle to the Meniscal Tear Model

[00125] The effect of CG53135-05 on the normal rats was studied as a proof of principle to drive further studies in disease model (ex: meniscal tear model of osteoarthritis in rats). The effect of CG53135-05 on synovium and cartilage was assessed by injecting the protein into normal male Lewis rats.

Effects of Intra-articular injection of CG53135-05 in Normal Rats

[00126] The rats were injected intra-articularly three times per week for 2 weeks with vehicle solution (8mM acetate, 40 mM arginine, and 0.6% glycerol (pH 5.3) in approximately 1% hyaluronic acid), 10 µg CG 53135-05 or 100 µg CG 53135-05.

[00127] Study Design: Male Lewis rats weighing 293-325 grams on day 0 were obtained from Harlan Sprague Dawley (Indianapolis, Indiana) and acclimated for 8 days. The rats were divided into three treatment groups with three animals in each group: two groups received CG53135 and one received only the vehicle control. The rats were anesthetized with Isoflurane and injected through the patellar tendon into the area of the cruciate attachments of both knees. CG53135 was injected at doses of 0.1 mg/ml (0.01

mg/joint) or 1.0 mg/ml (0.1 mg/joint). Controls were injected with the vehicle solution as described above. Injections were done Monday, Wednesday and Friday for 2 weeks. The animals were terminated on day 15 at which time they were injected ip with BRDU (100 mg/kg) in order to pulse label proliferating cells.

Observations and Analysis of Markers of Pathology

[00128] Gross observations Rats were observed daily for abnormal swelling or gait alterations and were weighed weekly.

[00129] Histopathology Preserved and decalcified (5% formic acid) knees were trimmed into 2 approximately equal longitudinal (ankles) or frontal (knees) halves, processed through graded alcohols and a clearing agent, infiltrated and embedded in paraffin, sectioned, and stained with toluidine blue (knees). Multiple sections (3 levels) of right knee were analyzed microscopically with attention to the parameters of interest listed below. Each parameter was graded as normal, minimal, mild, moderate, marked or severe. Evaluation of the cartilage was done using descriptive parameters rather than the scoring criteria generally used in the osteoarthritis model because of the type of alterations generated by the repetitive injection of the protein. Although animals were injected with BRDU prior to termination, the proliferative changes were readily observed in toluidine blue stained sections.

RESULTS

Table 9: Microscopically Monitored Parameters

Synovial Alterations	Cartilage Alterations	Central Cruciate Attachment Area Alterations	Chondrogenesis
-hyperplasia -infiltration of synovium with macrophages -fibroplasia -matrix (proteoglycan deposition in fibrotic synovium)	-cartilage proteoglycan loss -cartilage fibrillation	-inflammation and fibroplasia -bone or cartilage damage	-marginal zone or periosteal chondrogenesis

[00130] Live Phase Parameters Body weights were similar in vehicle and protein injected animals throughout the study (Table 12). Knees injected with 100 µg of protein had some evidence of fibrosis clinically during the injection process beginning with the 3rd injection.

[00131] Morphologic Pathology Vehicle injected rats had minimal to mild synovial hyperplasia, inflammation and fibroplasia with none to minimal matrix deposition in fibrotic

synovium. Articular cartilage had no proteoglycan loss or fibrillation. The central area of the joint where the cruciates attach and in which the intra-articular injections are made had none to minimal fibroplasia and cartilage/bone damage. No marginal zone chondrogenesis was present.

[00132] Knees injected with 10 µg CG 53135-05 had mild to moderate synovial hyperplasia, inflammation and fibroplasia with minimal to moderate matrix deposition in fibrotic synovium. Articular cartilage had no proteoglycan loss or fibrillation. The central area of the joint where the cruciates attach and in which the intra-articular injections are made had none to minimal fibroplasia and cartilage/bone damage. One knee had minimal marginal zone chondrogenesis.

[00133] Knees injected with 100 µg CG 53135-05 had moderate to marked synovial hyperplasia, inflammation and fibroplasia with moderate matrix deposition in fibrotic synovium. Articular cartilage had none to minimal proteoglycan loss or fibrillation. The central area of the joint where the cruciates attach and in which the intra-articular injections are made had minimal to marked fibroplasia and cartilage/bone damage. All knees had mild to moderate marginal zone chondrogenesis. One animal had chondrogenesis in areas associated with articular cartilage.

Conclusion

[00134] These results demonstrate that repetitive intra-articular injection of CG53135-05 induces synovial fibroplasia and chondrogenesis. Vehicle injections resulted in mild inflammation and fibroplasia thus suggesting that this vehicle has some irritant potential. Concentration responsive increases in synovial proliferative response as well as marginal zone chondrogenesis occurred in animals injected with protein. The area of the cruciate attachment where injections occurred had areas of bone resorption and fibroplasia which also increased in severity with increasing concentrations of the protein as did the synovial inflammation. The potentially adverse effects of observed synovial fibroplasia and bone resorption could have been due to either FGF-20 activity or endotoxin levels within the non-clinical grade hyaluronic acid used to formulate the protein. In addition, inflammation in the joint can induce bone resorption and marginal zone chondrogenesis so these results need to be interpreted in light of the possibility that the inflammatory response to the protein injection contributed to the proliferative response. The morphologic appearance of the proliferative changes and chondrogenesis clearly indicates that the biological activity of this protein (CG53135-05) is important in generating the response.

[00135] The results of the experiments reported herein indicate repetitive intra-articular injection of CG53135-05 induces synovial fibroplasia and chondrogenesis.

5.7. Example 7: Intra-articular injection of CG53135-05 in Meniscal Tear model of Rat Osteoarthritis: Prophylactic and Therapeutic Dosing

[00136] Example 6 utilized CG53135-05 administration into the joints of normal rats to identify effects on relevant cell populations by histomorphometric analysis. At the dose of 100 ug/joint, CG53135-05 induced significant marginal zone chondrogenesis similar to that seen with other growth factors such as TGF-beta, suggesting an effect on pluripotent stem cells within the marginal zone. There was no apparent effect on mature chondrocytes as evidenced by the lack of a response in the mature cartilage areas of the joints. The potentially adverse effects of observed synovial fibroplasia and bone resorption could have been due to either FGF-20 activity or endotoxin levels within the non-clinical grade hyaluronic acid used to formulate the protein.

[00137] Further studies in osteoarthritic animals performed addressed the following: 1) synergy with an anti-inflammatory drug (standard approach for osteoarthritis patients), 2) whether CG53135-05 (FGF-20) can induce functional repair or protection of joint cartilage layers, and 3) whether synovial fibroplasia and bone resorption were FGF-20-induced or due to contaminating endotoxin within the formulation.

[00138] Thus one aspect of this study was to evaluate the protective and therapeutic effects of intra-articular injection of CG53135-05 on joint damage in osteoarthritis in the meniscal tear model of rat osteoarthritis. This relatively new model of OA has been shown to have morphologic alterations of cartilage degeneration and osteophyte formation that resemble changes occurring in spontaneous disease and surgically induced disease in other species (Bendele, A.M., Animal Models of Osteoarthritis. J. Musculoskel. Neuron Interact. 2001; 1:363-376, Bendele, A. M. and Hulman, J. F. Spontaneous cartilage degeneration in guinea pigs. Arthritis Rheum. 1988; 31:561-565). The model can be used to evaluate potential beneficial effects of anti-degenerative as well as regenerative therapies.

Experimental Design

[00139] Animals (10/group), housed 2/cage, were anesthetized with Isoflurane and the right knee area is prepared for surgery. A skin incision was made over the medial aspect of the knee and the medial collateral ligament was exposed by blunt dissection, and then transected. The medial meniscus was then reflected medially with a fine scissor and a cut was made through the full thickness to simulate a complete tear. The skin was closed with suture.

[00140] **Prophylactic Dosing:** intra-articular dosing (CG53135-05) of the right knee joint was initiated on the day of surgery and is continued for 2 weeks post-surgery with intra-articular injections given Thursday, Saturday, and Monday (day 0, 2, 4, 7, 9, and 11) with rats under Isoflurane anesthesia. Indomethacin, a nonsteroidal anti-inflammatory drug, was dosed (1mg/kg/day) daily by the oral route starting on the day of surgery to reduce any potential inflammation due to the injection. Body weights were recorded on days 0, 7 and 14. After animal termination on day 14 post-surgery, both knees were collected for histopathologic evaluation. The study design is shown in Table 10.

Table 10. Prophylactic Dosing Study Design

Group	CG53135-05 Treatment ^a	Co-therapy Treatment ^b	Number of Animals Males
1	Vehicle (intra-articular)	Vehicle	10
2	Vehicle (intra-articular)	Indomethacin	10
3	CG53135-05 (intra-articular)	Vehicle	10
4	CG53135-05 (intra-articular)	Indomethacin	10
5	None	None	10

^aAdministration 3 times per week for 2 weeks (100 µg/joint, intra-articular)

^bAdministration daily for 2 weeks (0.5 mg/kg, PO)

[00141] **Therapeutic Dosing:** intra-articular dosing (CG53135-05) of the right knee joint is initiated on day 21 of post-surgery and is continued for 2 weeks with intra-articular injections given Friday, Sunday, and Tuesday (day 22, 25, 27, 29, 32, and 34) with rats under Isoflurane anesthesia. Indomethacin is dosed daily by the oral route starting on the day of surgery. Body weights are recorded on days 0, 7, 14, 21, 28, and 35. On day 35, both knees are collected for histopathologic evaluation. The study design is shown in Table 11.

Table 11. Therapeutic Dosing Study Design

Group	CG53135-05 Treatment ^a	Co-therapy Treatment ^b	Number of Animals Males
1	Vehicle (intra-articular)	Vehicle	10
2	Vehicle (intra-articular)	Indomethacin	10

3	CG53135-05 (intra-articular)	Vehicle	10
4	CG53135-05 (intra-articular)	Indomethacin	10
5	None	None	10

^aAdministration 3 times per week for 2 weeks (100 µg/joint, intra-articular)

^bAdministration daily for 2 weeks (0.5 mg/kg, PO)

[00142] **Results of prophylactic dosing study:** Observations made include the standards followed for this model. Multiple sections (3 levels) of right knee were analyzed microscopically and scored according to the following methods. In scoring the 3 sections, the worst case scenario for the 2 halves on each of the 3 slides representing 3 levels was determined for cartilage degeneration and osteophyte formation. This value for each parameter for each slide was then averaged to determine overall subjective cartilage degeneration scores for tibia and femur and osteophyte scores for tibia.

[00143] Cartilage degeneration was scored none to severe (numerical values 0-5) for depth and area (surface divided into thirds) using the following criteria:

0=no degeneration

1=minimal degeneration, chondrocyte and proteoglycan loss with or without fibrillation involving the superficial zone

2= mild degeneration, chondrocyte and proteoglycan loss with or without fibrillation involving the upper 1/3

3=moderate degeneration, chondrocyte and proteoglycan loss with fibrillation extending well into the midzone and generally affecting 1/2 of the total cartilage thickness

4=marked degeneration, chondrocyte and proteoglycan loss with fibrillation extending well into the deep zone but without complete (to the tidemark) loss of matrix

5=severe degeneration, matrix loss to tidemark

[00144] Strict attention to zones (outside, middle, inside thirds) was adhered to in this scoring method and the summed scores reflect a global summation of severity of tibial degeneration.

[00145] In addition to this overall subjective analysis of cartilage degeneration, an additional subjective assessment was done using similar criteria to evaluate severity of degeneration but with attention to specific regional differences across the tibial plateau. In this OA model, generally the outside 1/3 of the tibia is most severely affected by the meniscal

tear injury with lesions often extending to the tidemark by 3 weeks post-surgery. The middle 1/3 is usually a transition zone where severe or marked change becomes moderate or mild and the inner 1/3 seldom has changes greater than mild or minimal. In an attempt to determine potential differences of treatment on the severe lesion of the outside 1/3 vs. the milder lesions of the middle 1/3 and inside 1/3, these regions were each scored separately. The sum of the regional values was calculated and expressed as sum of 3 zones.

[00146] In addition to the above subjective scoring, a micrometer measurement of total extent of tibial plateau affected by any severity of degeneration (Total Tibial Cartilage Degeneration Width μm) extended from the origination of the osteophyte or marginal zone if no osteophyte was present with adjacent cartilage degeneration (outside 1/3) across the surface to the point where tangential layer and underlying cartilage appeared histologically normal.

[00147] An additional measurement (Significant Cartilage Degeneration Width μm) reflected areas of tibial cartilage degeneration in which chondrocyte and matrix loss extended through greater than 50% of the cartilage thickness.

[00148] Finally, a micrometer depth of any type of lesion (cell/proteoglycan loss, change in metachromasia, but may have good retention of collagenous matrix and no fibrillation) expressed as a ratio of depth of changed area vs. depth to tidemark was included and taken over 4 equally spaced points on the tibial surface. These measurements were taken (1st) matrix adjacent to osteophyte (2nd) 1/4 of the distance across the tibial plateau (3rd) 1/2 of the distance across the tibial plateau (4th) 3/4 of the distance across the tibial plateau. This measurement was the most critical analysis of any type of microscopic change present. The depth to tidemark measurement (denominator) also gives an indication of cartilage thickness across the tibial plateau and therefore allows comparisons across groups when trying to determine if hypertrophy or hyperplasia has occurred.

[00149] A single tibial growth plate measurement was taken for each section in an area thought to best represent the overall width in the non tangential plane of the section.

[00150] Scoring of the osteophytes and categorization into small, medium and large was done with an ocular micrometer.

None = 0 no measurable proliferative response at marginal zone

Small osteophytes = 1 (up to 299 μm)

Medium osteophytes = 2 (300-399 μm)

Large osteophytes = 3 (>400 μm)

[00151] The score (0-3) was included in the overall joint score. In addition, the mean $\pm$ SE for the actual osteophyte measurement (average for 3 sections) was also determined.

[00152] Generally, in doing the surgery, attempts were made to transect the collateral ligament at a location that results in the meniscus being reflected proximally toward the femur. The cut was then made by inserting the scissors tip toward the femur rather than the tibia. Some mechanical damage may then be detected in the femoral condylar cartilage but is rarely encountered on the tibia, thus making the tibia the most appropriate site for assessment of chondroprotection.

[00153] Focal small areas of proteoglycan and cell loss that were likely a result of physical trauma to the femoral cartilage were described but not included in the score with larger more diffuse areas receiving subjective scores according to methods described for the tibia. These larger areas were more consistent with non traumatic degeneration. Because of the possibility of iatrogenic lesions on the femur, overall joint scores were expressed both with and without femoral cartilage degeneration scores.

[00154] Damage to the calcified cartilage layer and subchondral bone was scored using the following criteria:

0=No changes

1=Increased basophilia at tidemark: no fragmentation of tidemark or marrow changes

2=Increased basophilia at tidemark: minimal to mild fragmentation of calcified cartilage of tidemark, mesenchymal change in marrow involves 1/4 of total area but generally is restricted to subchondral region under lesion

3=Increased basophilia at tidemark: Mild to marked fragmentation of calcified cartilage, Mesenchymal change in marrow is up to 3/4 of total area, Areas of marrow chondrogenesis may be evident but no collapse of articular cartilage into epiphyseal bone

4=Increased basophilia at tidemark: Marked to severe fragmentation of calcified cartilage, Marrow mesenchymal change involves up to 3/4 of area and articular cartilage has collapsed into the epiphysis to a depth of 250 μ m or less from tidemark

5=Increased basophilia at tidemark: Marked to severe fragmentation of calcified cartilage, Marrow mesenchymal change involves up to 3/4 of area and Articular cartilage has collapsed into the epiphysis to a depth of greater than 250 μ m from tidemark

[00155] Descriptive comments were made on degree of synovial inflammation, synovial fibrosis, marginal zone chondrogenesis, bone resorption, fibrous overgrowth with or without chondrogenesis/incorporation into existing cartilage

[00156] **Statistical Analysis:** statistical analysis of histopathologic parameters was done by comparing group means using the Student's two-tailed t-test with significance set at $p \leq 0.05$. Because of the nature of the data, a non Parametric ANOVA (Kruskal-Wallis test) was used to analyze the scored parameters and a parametric ANOVA was used to analyze the measurements. The appropriate post test used was Dunnett's multiple comparisons test on the parametric data and a Dunn's test was used on the non parametric data. Significance was set at $p \leq 0.05$ for all parameters.

[00157] **Results:** intra-articular injection of 100 μ g CG53135-05 with or without concurrent indomethacin administration resulted in significant inhibition (39%) of tibial cartilage degeneration on the middle 1/3 (40-43% for zone 1) and an overall insignificant inhibition of the summed 3 zones of 41% (Figure 12). Total cartilage degeneration width was significantly decreased 35-37% (Figure 13) and significant degeneration was reduced 70-89% with this inhibition being significant only in the group treated with protein and indomethacin (Figure 14).

[00158] **Results of the prophylactic dosing study:** the data described indicate that intra-articular injection of 100 μ g of CG53135-05 in knee joints of rats with medial meniscal tear results in chondroprotective effects as a result of both inhibition of cartilage degeneration and stimulation of cartilage repair. Some joints had layering of proliferated new cartilage over existing normal appearing or damaged cartilage. This observation is particularly exciting as it demonstrates the potential for resurfacing to occur.

[00159] These beneficial effects were always associated with diffuse synovial fibroplasia, bone resorption and increased synovial inflammation. Concurrent indomethacin treatment (1 mg/kg/day) had minimal if any effect on the disease process in knees injected with Synvisc alone or the disease process and reaction to the protein in knees injected with Synvisc containing protein. The single exception to this statement is reflected in the data for osteophyte measurements where all groups had similar measurements except the group treated with protein and **vehicle po**. This group had greater measurements thus suggesting greater marginal zone stimulation, not an uncommon occurrence in inflamed joints.

[00160] The morphologic changes induced by injection of 100 μ g of this protein demonstrate the potential for CG53135-05 to be effective in cartilage repair processes. It has

the capacity to induce fibrous tissue proliferation with differentiation to cartilage and importantly, integration of that newly proliferated tissue. The proliferative processes are somewhat disorganized and counter productive in areas such as the marginal zone and subchondral bone. However, rodents definitely have much greater propensity to exhibit marginal zone, periosteal and marrow proliferation from a variety of stimuli including inflammatory mediators so some of the excessive and counter productive responses seen in rats might not occur in dogs or primates. Also, there may have been some induction of an antibody response thus leading to enhanced knee inflammation that would not occur in humans or other animals that did not have an antibody response.

[00161] Additional studies that are useful in delineating the potential efficacy of CG53135-05 in osteoarthritis include:

[00162] 1. Evaluation in a dog model of OA-this would allow evaluation in a larger joint with cartilage and bone structure that is more similar to humans and this is a species that has less tendency to exhibit hyperproliferative responses such as those that occur in rodents.

[00163] 2. Evaluation of ia injections for 3-4 weeks, possibly with more aggressive anti-inflammatory systemic therapy followed by a recovery period to see how the new tissue remodels would be interesting. It may be that allowing the joint to remodel with no further proliferative stimulus would result in a more pleasing morphologic endpoint. Cycles of treatment with periods of remodeling might be the way to achieve the most satisfactory repair. Studies such as these would also answer the question of whether the repair tissue will hold up long term. Generally fibrocartilage has less of a tendency to do this.

[00164] **Results:** Intra-articular injection of 100 µg CG53135-05 with or without concurrent oral indomethacin administration did not result in significant inhibition of tibial cartilage degeneration scores (Figure 15). Total or significant cartilage degeneration width was not decreased (Figures 16, 17).

[00165] **Results of the therapeutic dosing study:** The data described demonstrated the potential chondroproliferative activities of CG53135-05 administered intra-articularly. However, protein injected joints had markedly increased inflammation, fibroplasia and connective tissue resorptive process.

[00166] The most important difference between the prophylactic and therapeutic dosing studies was the nature of the OA lesion at the time of initiation of dosing. Rats in the therapeutic dosing study had an area of severe matrix loss in the outer to middle 1/3 of the

cartilage thus exposing the calcified cartilage/subchondral bone to the protein. Effective repair thus required filling of this defect with newly proliferated tissue coming from the marginal zone or exposed marrow pleuripotential cells. In the prophylactic dosing study, beneficial effects required inhibition of matrix degradation and stimulation of repair on a degenerating scaffold with repair tissue originating from the marginal zone only. Since the filling of a defect would be much more difficult than repairing a damaged scaffold, it may be that a longer duration of treatment would be required in a therapeutic model in order to see beneficial effects.

[00167] Indomethacin treatment was not effective in reducing the inflammatory changes and it had no beneficial effects on inhibiting the resorptive processes occurring in bone. In order to achieve effective proliferation and differentiation to cartilage in the absence of inflammation and tissue destruction, following modification to the therapeutic dosing study can be attempted: Increasing the dosing interval to once or twice weekly and/or increasing the study duration to allow time for the proliferative tissue to fill the large cartilage defects induced by this disease process. Another possibility is to investigate the effects of CG53135-05 in a larger species such as the dog as dogs have less of a tendency to proliferate connective tissue and resorb bone in response to various stimuli than rodents.

[00168] The results detailed herein (both prophylactic and therapeutic dosing studies) indicate that CG53135-05 has specific utility in severely osteoarthritic joints that are destined for joint replacement. These types of agents would be injected into joints that have little or no normal cartilage remaining and are in need of resurfacing. In this situation, repair could originate from pleuripotential cells in the marginal zones or bone marrow. Repair originating from these locations will likely result in production of fibrocartilage rather than hyaline cartilage. However, some cartilage would be preferable to no cartilage and it may be that an injectable method of sustaining a cartilage surface would be acceptable even though treatments would likely have to be repeated over time to sustain the repair. Treatments with injectable anabolic agents will likely require some kind of cyclical process in conjunction with continuous passive motion rather than sustained active load bearing motion.

6. EQUIVALENCE AND REFERENCE CITED

[00169] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00170] Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only. We therefore do not wish to be limited to the *précis* terms set forth, but desire to avail ourselves of such changes and alterations that may be made for adapting the invention to various usages and conditions. Such alterations and changes may include, but not limited to, different compositions for the administration of the polypeptides according to the present invention to a subject; different amounts of the polypeptide; different times and means of administration; different materials contained in the administration dose including, for example, combinations of different peptides, or combinations of peptides with different biologically active compounds. Such changes and alterations also are intended to include modifications in the amino acid sequence of the specific polypeptides described herein in which such changes alter the sequence in a manner as not to change the functionality of the polypeptide, but as to change solubility of the peptide in the composition to be administered to a subject, absorption of the peptide by the body, protection of the polypeptide for either shelf life or within the body until such time as the biological action of the peptide is able to bring about the desired effect, and such similar modifications. Accordingly, such changes and alterations are properly intended to be within the full range of equivalents of the present invention.

WHAT IS CLAIMED IS:

1. A method of treating osteoarthritis-related disorders in a subject comprising administering to the subject a composition comprising CG53135-05 polypeptide.
2. The method of claim 1, wherein the subject is a human.
3. The method of claim 1, wherein a prophylactic effective dose of the said polypeptide is administered to the subject.
4. The method of claim 1, wherein a therapeutically effective dose of the said polypeptide is administered to the subject.
5. The method of claim 1, wherein the said polypeptide is administered by parenteral route.
6. The method of claim 5, wherein the said route of administration consists of intra-articular, intravenous, intramuscular, subcutaneous or intradermal administration.
7. The method of claim 1, wherein a therapeutically effective amount of the said polypeptide is formulated in a pharmaceutical composition.
8. A method of reducing cartilage degeneration in a subject comprising administering to the subject a composition comprising CG53135-05 polypeptide.
9. A method of stimulating cartilage repair in a subject comprising administering to the subject a composition comprising CG53135-05 polypeptide.

Figure 1

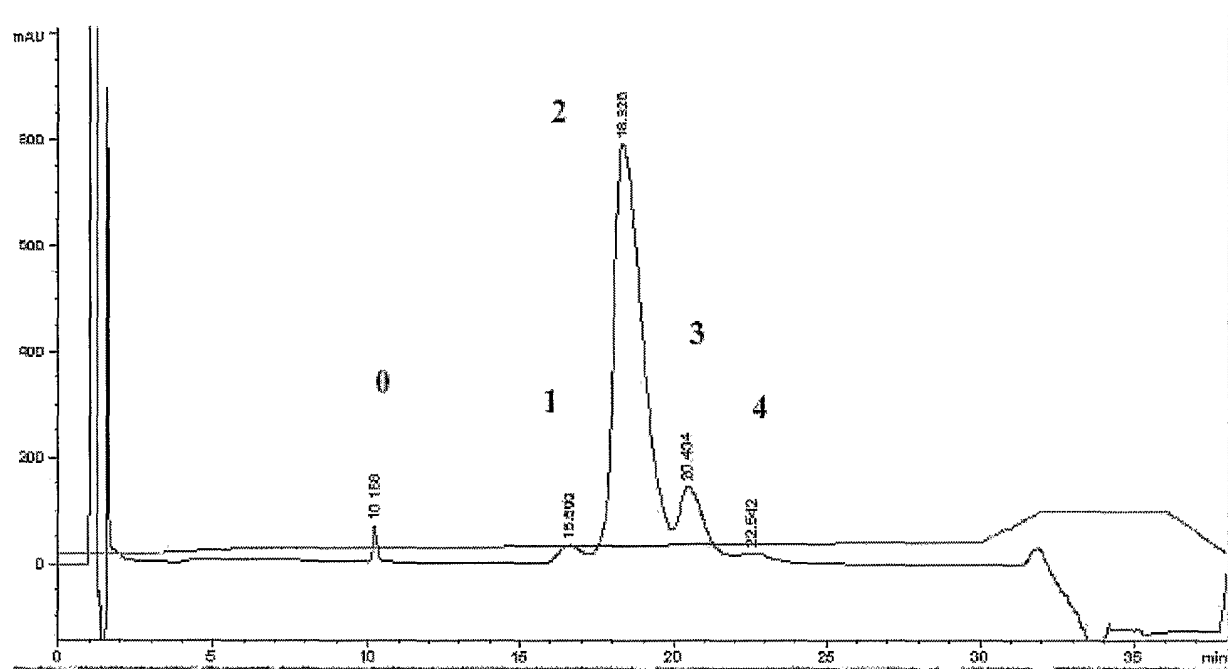


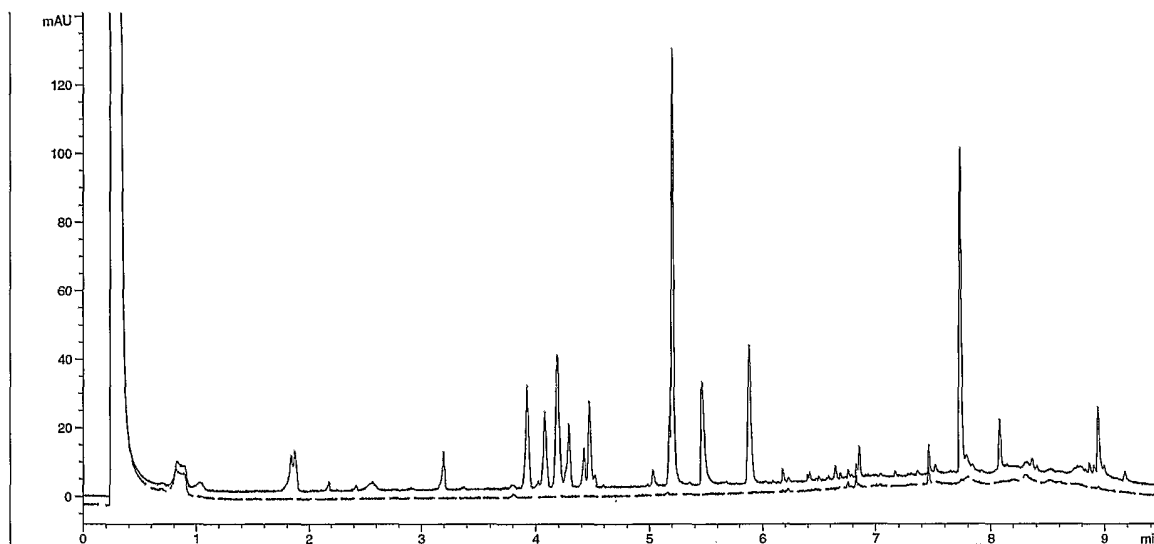
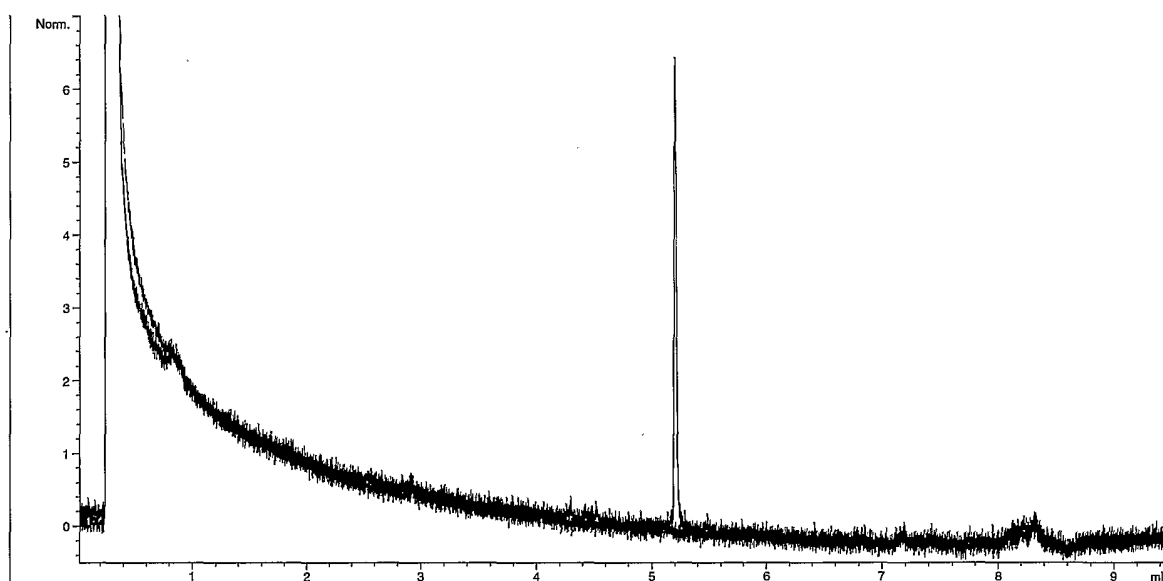
Figure 2A**Figure 2B**

Figure 3

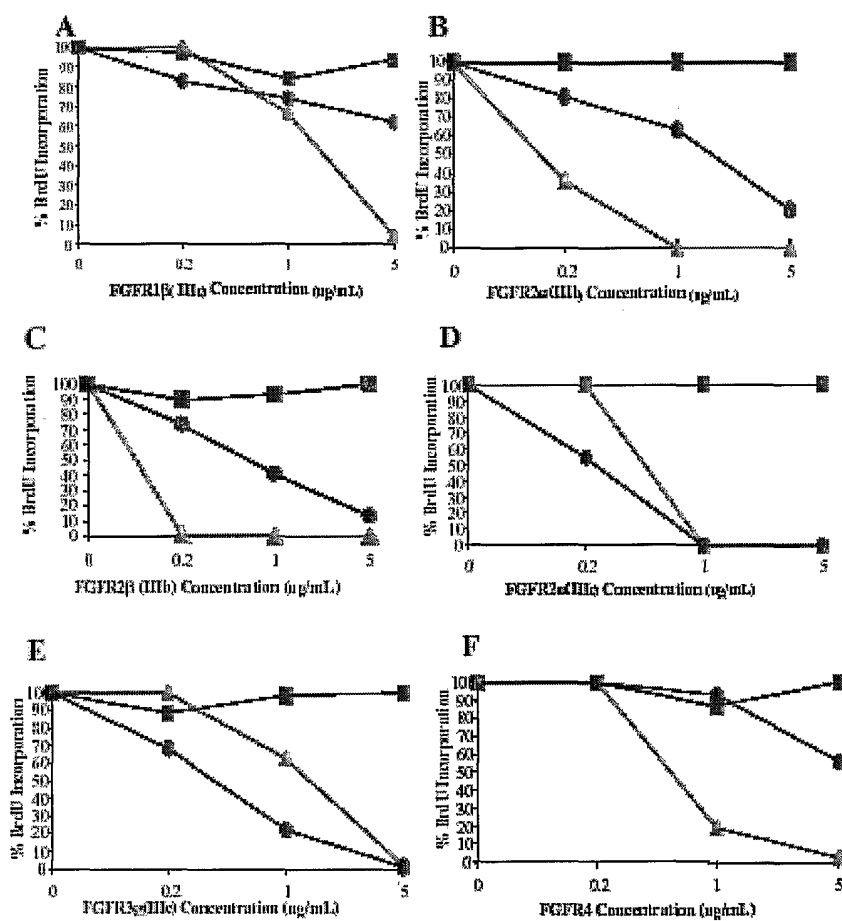


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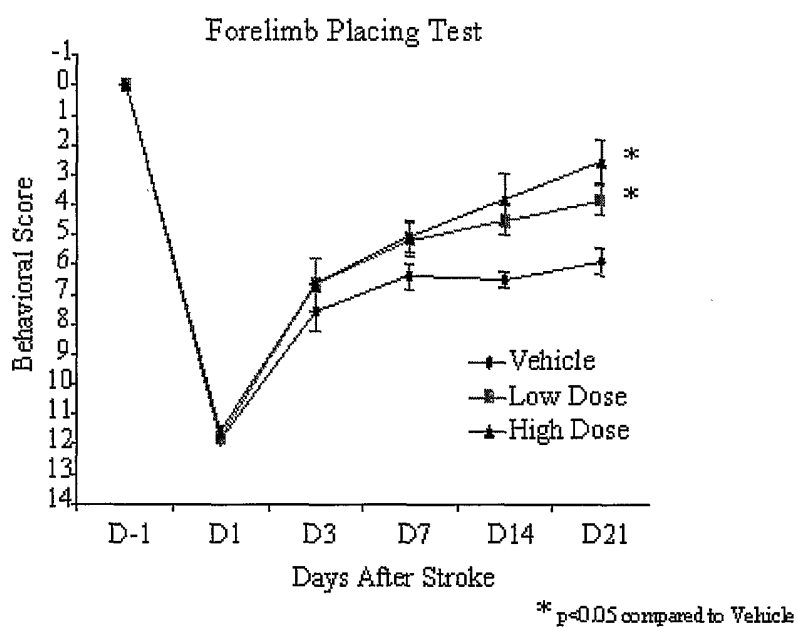


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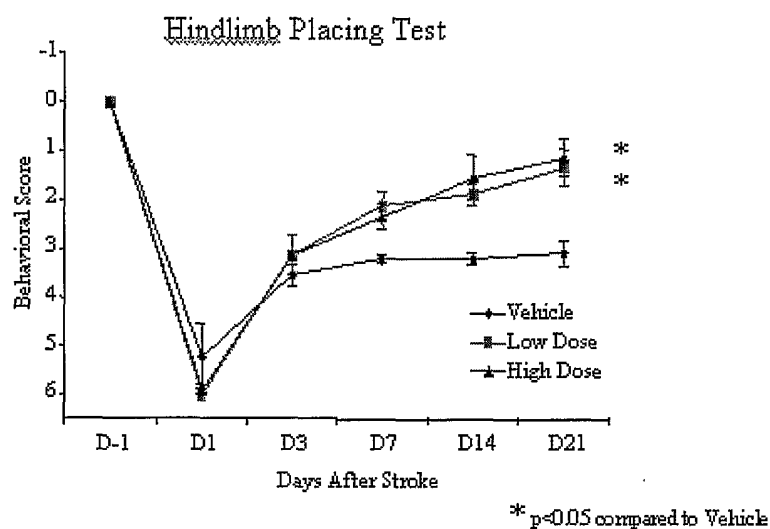


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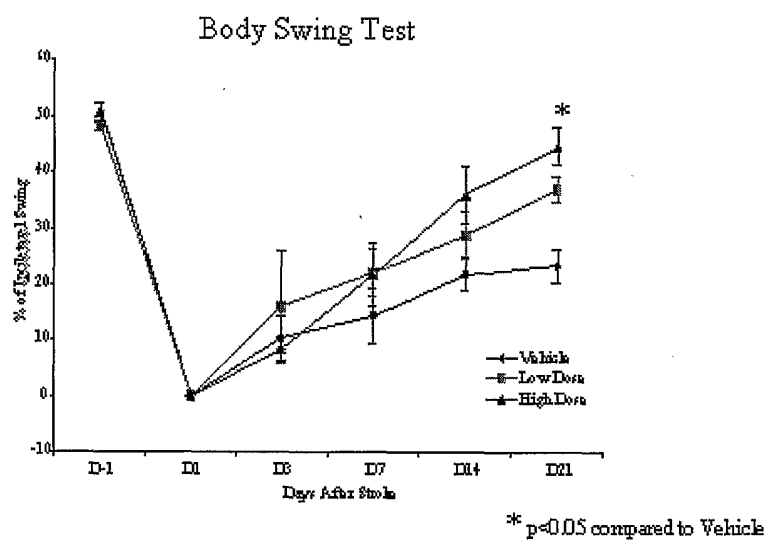


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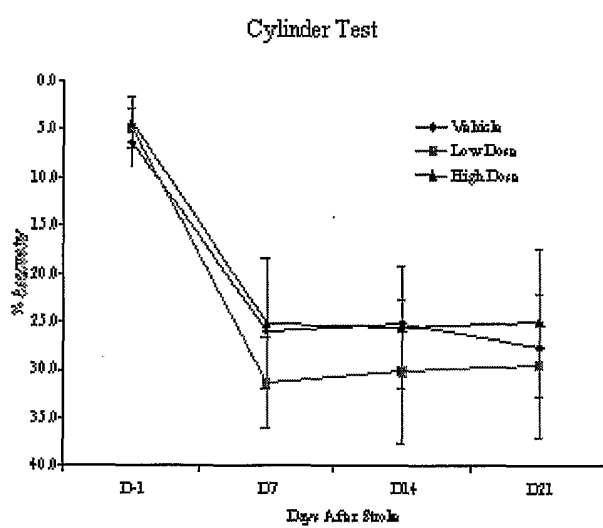


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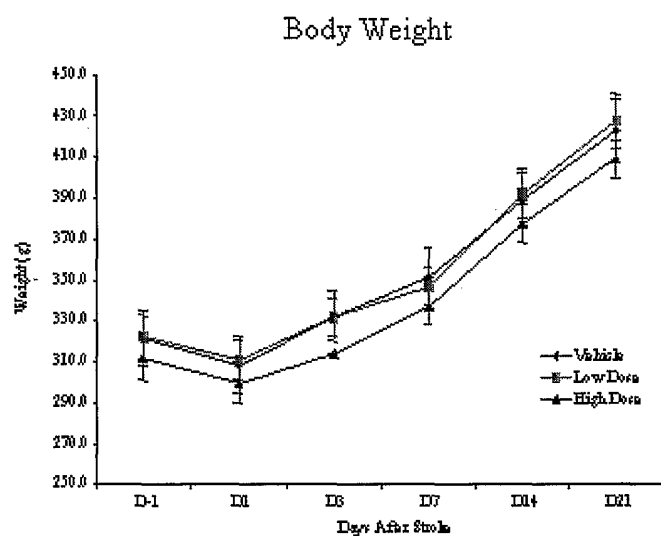


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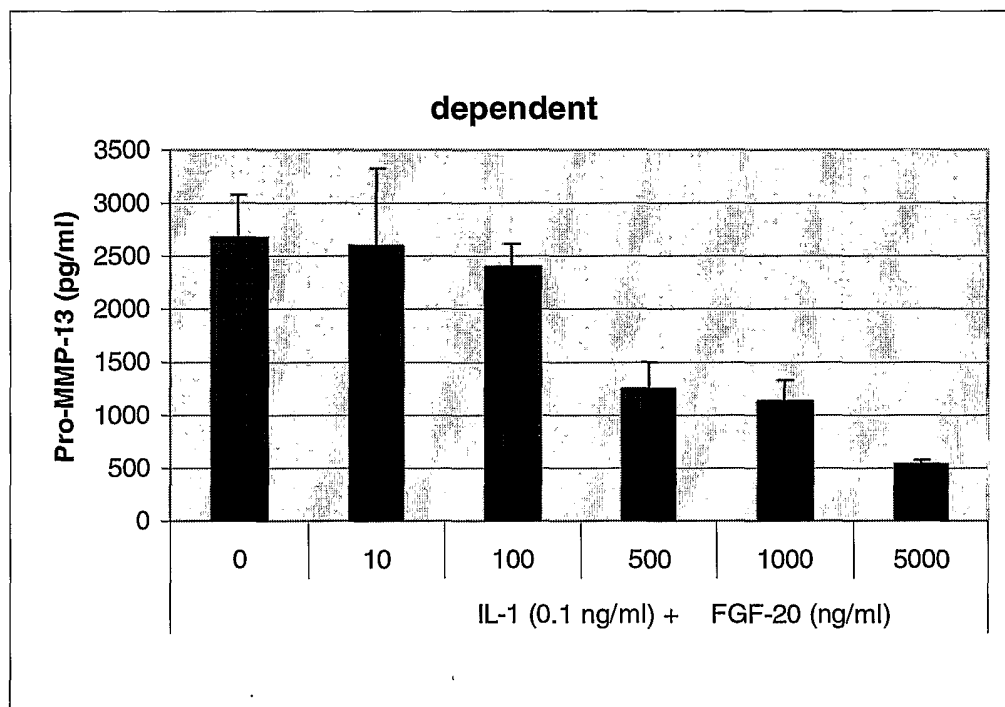


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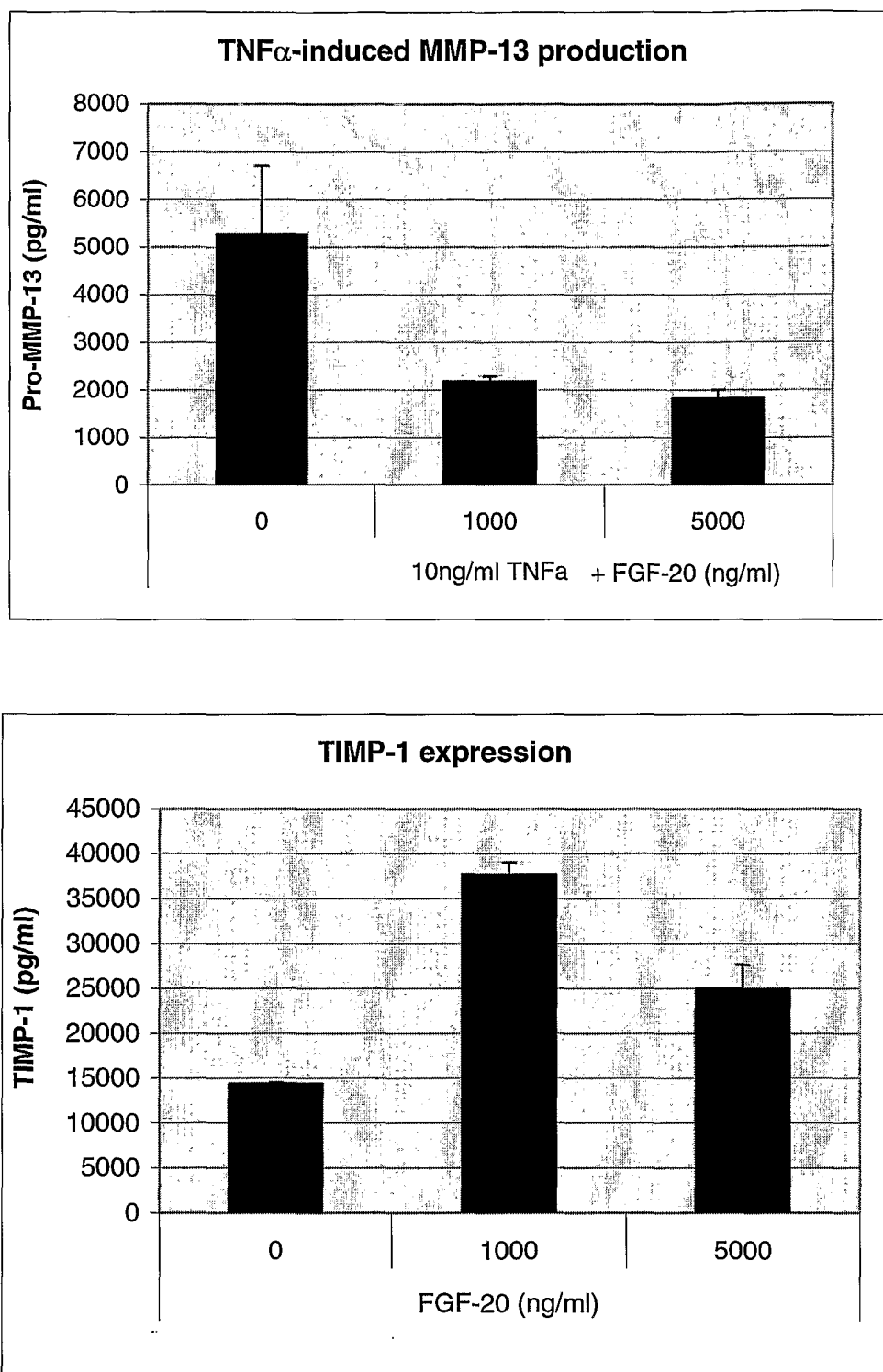
**Figure 11**

FIGURE 12

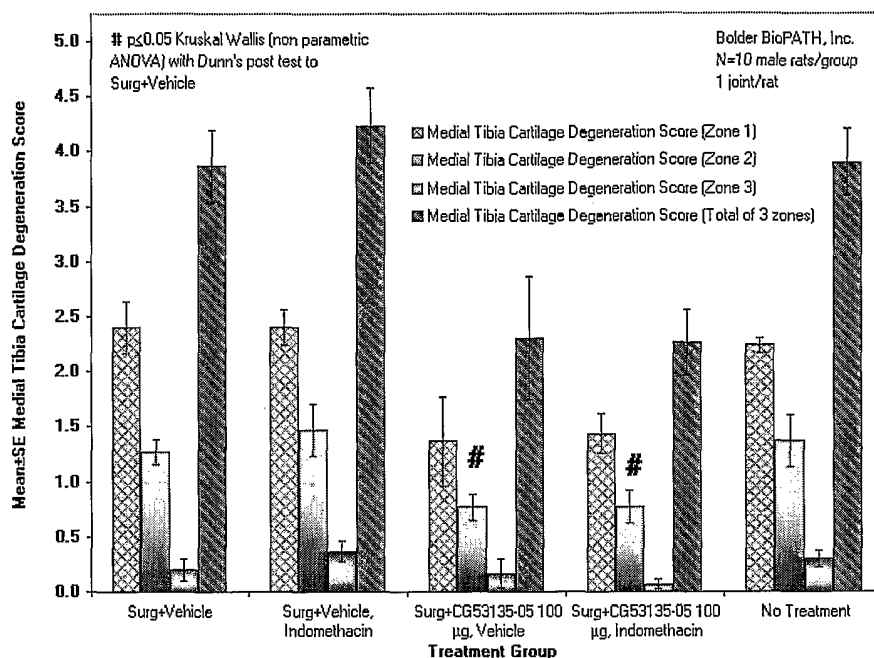


FIGURE 13

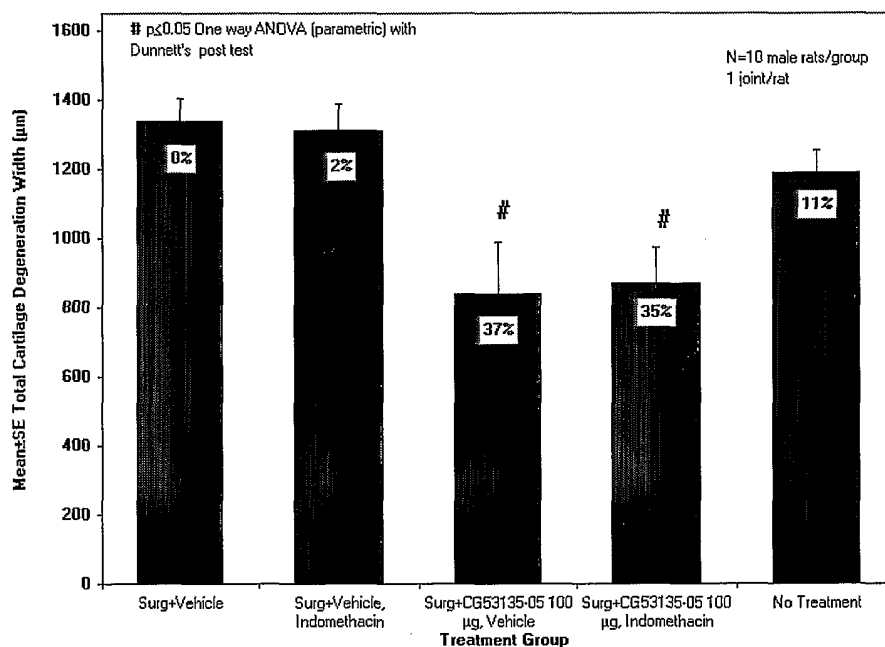


FIGURE 14

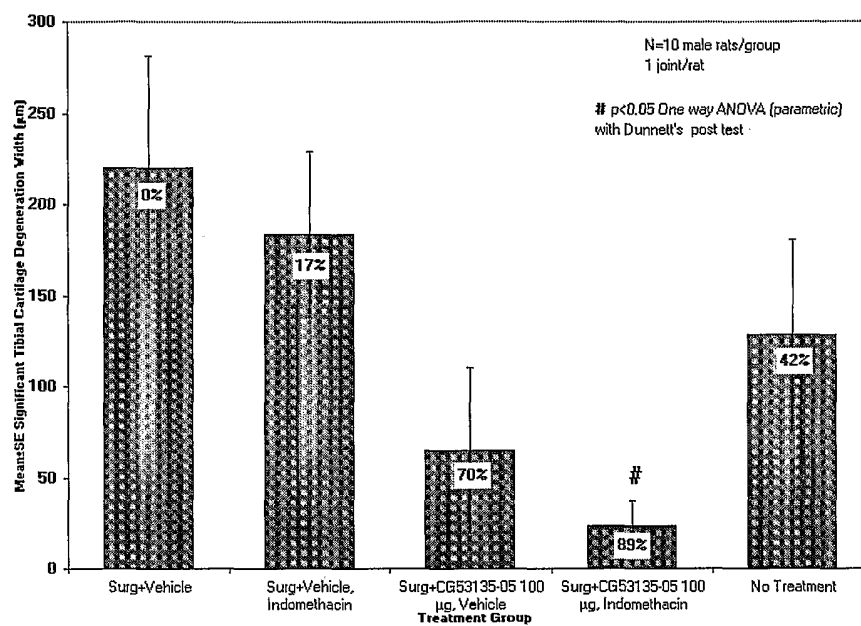


Figure 15

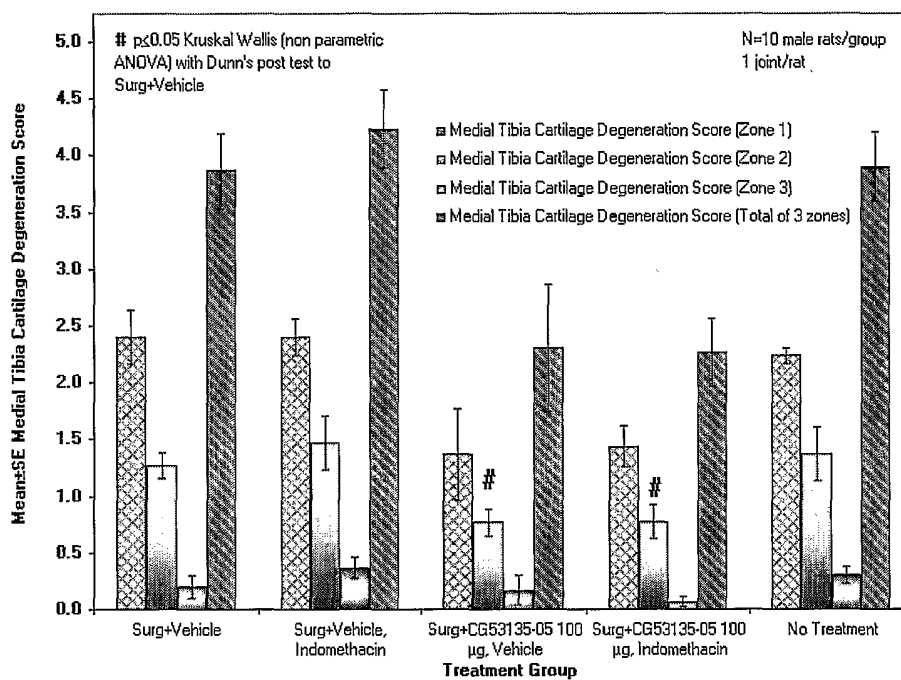


Figure 16

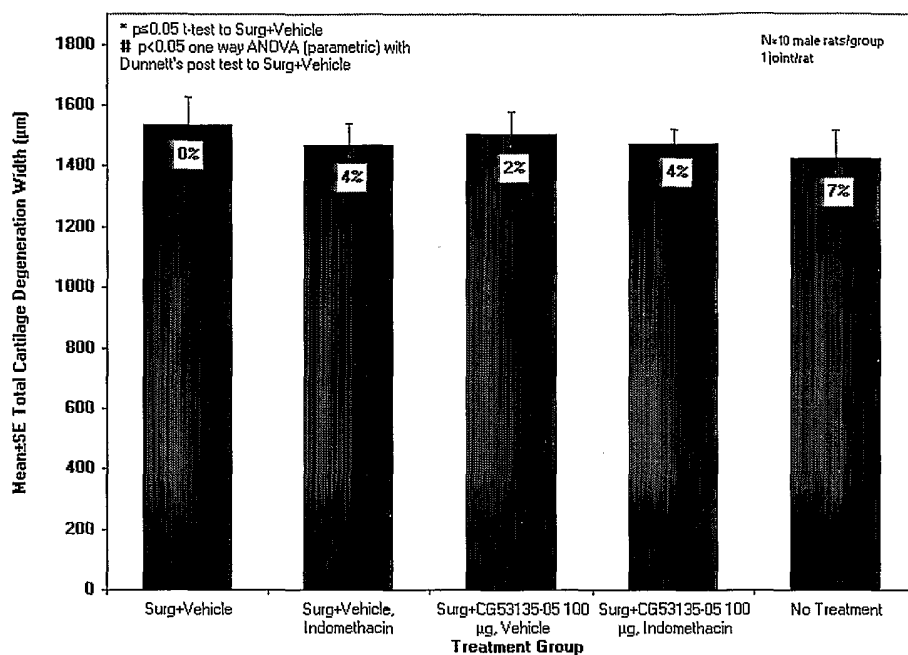
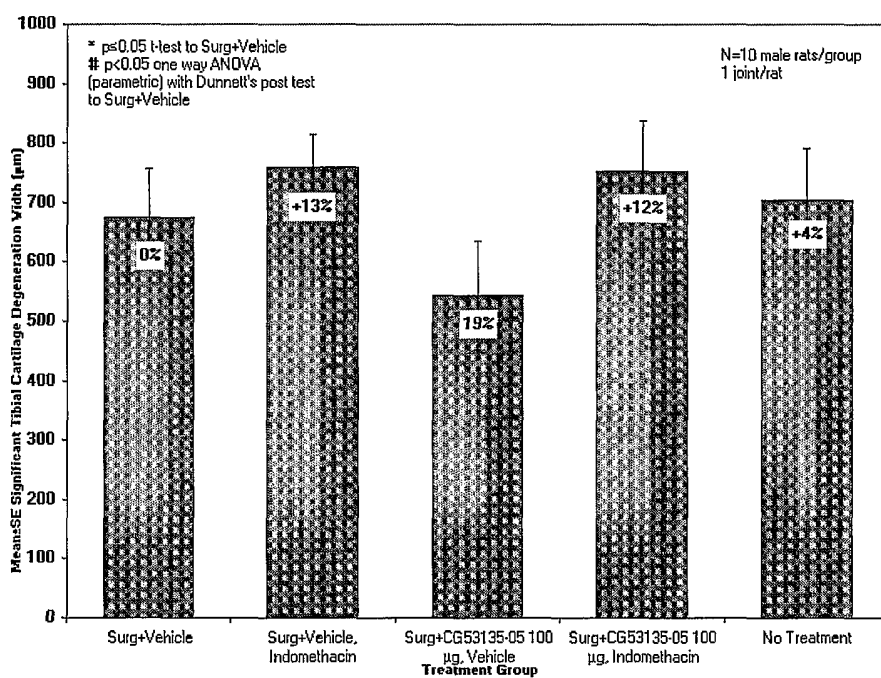


Figure 17



Cura 570A Sequence Listing PCT

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Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg	
165 170 175	

Cura 570A Sequence Listing PCT

gat ggt gct cgt tct aaa cgt cac cag aaa ttc acc cac ttc ctg ccg 576
 Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro
 180 185 190

cgc cca gtt gac ccg gag cgt gtt cca gaa ctg tat aaa gac ctg ctg 624
 Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu
 195 200 205

atg tac acc taa 636
 Met Tyr Thr
 210

<210> 2

<211> 211

<212> PRT

<213> Homo sapiens

<400> 2

Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15

Leu Gly Gln Gln Val Gly Ser His Phe Leu Leu Pro Pro Ala Gly Glu
 20 25 30

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

Arg Gly Gly Pro Gly Ala Ala Gln Leu Ala His Leu His Gly Ile Leu
 50 55 60

Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu
 65 70 75 80

Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His Ser Leu Phe Gly
 85 90 95

Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser Ile Arg Gly
 100 105 110

Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr
 115 120 125

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

Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp
 145 150 155 160

Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg
 165 170 175

Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro
 180 185 190

Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu
 195 200 205

Met Tyr Thr
 210

<210> 3

<211> 633

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(633)

Cura 570A Sequence Listing PCT

<400> 3
 atg gct ccc tta gcc gaa gtc ggg ggc ttt ctg ggc ggc ctg gag ggc 48
 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15

 ttg ggc cag cag gtg ggt tcg cat ttc ctg ttg cct cct gcc ggg gag 96
 Leu Gly Gln Gln Val Gly Ser His Phe Leu Leu Pro Pro Ala Gly Glu
 20 25 30

 cgg ccg ccg ctg ctg ggc gag cgc agg agc gcg gcg gag ccg agc gcg 144
 Arg Pro Pro Leu Leu Gly Glu Arg Arg Ser Ala Ala Glu Arg Ser Ala
 35 40 45

 cgc ggc ggg ccg ggg gct gcg cag ctg gcg cac ctg cac ggc atc ctg 192
 Arg Gly Gly Pro Gly Ala Ala Gln Leu Ala His Leu His Gly Ile Leu
 50 55 60

 cgc cgc ccg cag ctc tat tgc cgc acc ggc ttc cac ctg cag atc ctg 240
 Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu
 65 70 75 80

 ccc gac ggc agc gtg cag ggc acc cgg cag gac cac agc ctc ttc ggt 288
 Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His Ser Leu Phe Gly
 85 90 95

 atc ttg gaa ttc atc agt gtg gca gtg gga ctg gtc agt att aga ggt 336
 Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser Ile Arg Gly
 100 105 110

 gtg gac agt ggt ctc tat ctt gga atg aat gac aaa gga gaa ctc tat 384
 Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr
 115 120 125

 gga tca gag aaa ctt act tcc gaa tgc atc ttt agg gag cag ttt gaa 432
 Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg Glu Gln Phe Glu
 130 135 140

 gag aac tgg tat aac acc tat tca tct aac ata tat aaa cat gga gac 480
 Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp
 145 150 155 160

 act ggc cgc agg tat ttt gtg gca ctt aac aaa gac gga act cca aga 528
 Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg
 165 170 175

 gat ggc gcc agg tcc aag agg cat cag aaa ttt aca cat ttc tta cct 576
 Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro
 180 185 190

 aga cca gtg gat cca gaa aga gtt cca gaa ttg tac aag gac cta ctg 624
 Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu
 195 200 205

 atg tac act 633
 Met Tyr Thr
 210

 <210> 4
 <211> 211
 <212> PRT
 <213> Homo sapiens

 <400> 4
 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15

 Leu Gly Gln Gln Val Gly Ser His Phe Leu Leu Pro Pro Ala Gly Glu

Cura 570A Sequence Listing PCT

20

25

30

Arg Pro Pro₃₅ Leu Leu Gly Glu Arg₄₀ Arg Ser Ala Ala Glu₄₅ Arg Ser Ala
 Arg Gly₅₀ Gly Pro Gly Ala Ala₅₅ Gln Leu Ala His Leu₆₀ His Gly Ile Leu
 Arg₆₅ Arg Arg Gln Leu Tyr₇₀ Cys Arg Thr Gly Phe₇₅ His Leu Gln Ile Leu₈₀
 Pro Asp Gly Ser Val₈₅ Gln Gly Thr Arg Gln₉₀ Asp His Ser Leu Phe₉₅ Gly
 Ile Leu Glu Phe₁₀₀ Ile Ser Val Ala Val₁₀₅ Gly Leu Val Ser Ile₁₁₀ Arg Gly
 Val Asp Ser₁₁₅ Gly Leu Tyr Leu Gly₁₂₀ Met Asn Asp Lys Gly₁₂₅ Glu Leu Tyr
 Gly Ser₁₃₀ Glu Lys Leu Thr Ser₁₃₅ Glu Cys Ile Phe Arg₁₄₀ Glu Gln Phe Glu
 Glu Asn Trp Tyr Asn Thr₁₅₀ Tyr Ser Ser Asn Ile₁₅₅ Tyr Lys His Gly Asp₁₆₀
 Thr Gly Arg Arg Tyr₁₆₅ Phe Val Ala Leu Asn₁₇₀ Lys Asp Gly Thr Pro Arg₁₇₅
 Asp Gly Ala Arg₁₈₀ Ser Lys Arg His Gln₁₈₅ Lys Phe Thr His Phe₁₉₀ Leu Pro
 Arg Pro Val₁₉₅ Asp Pro Glu Arg Val₂₀₀ Pro Glu Leu Tyr Lys₂₀₅ Asp Leu Leu
 Met Tyr Thr
 210

<210> 5
 <211> 540
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(537)

<400> 5
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 1
 ttg ggc cag ccg ggg gca gcg cag ctg gcg cac ctg cac ggc atc ctg 96
 Leu Gly Gln Pro₂₀ Gly Ala Ala Gln Leu₂₅ Ala His Leu His Gly Ile Leu
 20
 cgc cgc cgg cag ctc tat tgc cgc acc ggc ttc cac ctg cag atc ctg 144
 Arg Arg Arg₃₅ Gln Leu Tyr Cys Arg₄₀ Thr Gly Phe His Leu₄₅ Gln Ile Leu
 35
 ccc gac ggc agc gcg cag ggc acc cgg cag gac cac agc ctc ttc ggt 192
 Pro Asp Gly Ser Ala Gln Gly₅₅ Thr Arg Gln Asp His₆₀ Ser Leu Phe Gly
 50
 atc ttg gaa ttc atc agt gtg gca gtg gga ctg gtc agt att aga ggt 240
 Ile Leu Glu Phe Ile Ser₇₀ Val Ala Val Gly₇₅ Leu Val Ser Ile Arg Gly₈₀
 65

Cura 570A Sequence Listing PCT

gtg gac agt ggt ctc tat ctt gga atg aat gac aaa gga gaa ctc tat	288
Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr	
	85 90 95
gga tca gag aaa ctt act tcc gaa tgc atc ttt agg gag cag ttt gaa	336
Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg Glu Gln Phe Glu	
	100 105 110
gag aac tgg tat aac acc tat tca tct aac ata tat aaa cat gga gac	384
Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp	
	115 120 125
act ggc cgc agg tat ttt gtg gca ctt aac aaa gac gga act cca aga	432
Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg	
	130 135 140
gat ggc gcc agg tcc aag agg cat cag aaa ttt aca cat ttc tta cct	480
Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro	
	145 150 155 160
aga cca gtg gat cca gaa aga gtt cca gaa ttg tac aag gac cta ctg	528
Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu	
	165 170 175
atg tac act tag	540
Met Tyr Thr	

<210> 6
 <211> 179
 <212> PRT
 <213> Homo sapiens

<400> 6
 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15
 Leu Gly Gln Pro Gly Ala Ala Gln Leu Ala His Leu His Gly Ile Leu
 20 25 30
 Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu
 35 40 45
 Pro Asp Gly Ser Ala Gln Gly Thr Arg Gln Asp His Ser Leu Phe Gly
 50 55 60
 Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser Ile Arg Gly
 65 70 75 80
 Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr
 85 90 95
 Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg Glu Gln Phe Glu
 100 105 110
 Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp
 115 120 125
 Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg
 130 135 140
 Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro
 145 150 155 160
 Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu
 165 170 175
 Met Tyr Thr

Cura 570A Sequence Listing PCT

<210> 7
 <211> 556
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (2)..(556)

<400> 7
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 Thr Arg Ser Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly
 1 5 10 15
 ctg gag ggc ttg ggc cag ccg ggg gca gcg cag ctg gcg cac ctg cac 97
 Leu Glu Gly Leu Gly Gln Pro Gly Ala Ala Gln Leu Ala His Leu His
 20 25 30
 ggc atc ctg cgc cgc cgg cag ctc tat tgc cgc acc ggc ttc cac ctg 145
 Gly Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu
 35 40 45
 cag atc ctg ccc gac ggc agc gtg cag ggc acc cgg cag gac cac agc 193
 Gln Ile Leu Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His Ser
 50 55 60
 ctc ttc ggt atc ttg gaa ttc atc agt gtg gca gtg gga ctg gtc agt 241
 Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser
 65 70 75 80
 att aga ggt gtg gac agt ggt ctc tat ctt gga atg aat gac aaa gga 289
 Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly
 85 90 95
 gaa ctc tat gga tca gag aaa ctt act tcc gaa tgc atc ttt agg gag 337
 Glu Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg Glu
 100 105 110
 cag ttt gaa gag aac tgg tat aac acc tat tca tct aac ata tat aaa 385
 Gln Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys
 115 120 125
 cat gga gac act ggc cgc agg tat ttt gtg gca ctt aac aaa gac gga 433
 His Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly
 130 135 140
 act cca aga gat ggc gcc agg tcc aag agg cat cag aaa ttt aca cat 481
 Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His
 145 150 155 160
 ttc tta cct aga cca gtg gat cca gaa aga gtt cca gaa ttg tac aag 529
 Phe Leu Pro Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys
 165 170 175
 gac cta ctg atg tac act gtc gac ggc 556
 Asp Leu Leu Met Tyr Thr Val Asp Gly
 180 185

<210> 8
 <211> 185
 <212> PRT
 <213> Homo sapiens

<400> 8
 Thr Arg Ser Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly
 1 5 10 15

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

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<210> 9
<211> 415
<212> DNA
<213> Homo sapiens
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$\langle 220 \rangle$
 $\langle 221 \rangle$ CDS
 $\langle 222 \rangle$ (2) .. (415)

[illegible]

Cura 570A Sequence Listing PCT

tat aaa cat gga gac act ggc cgc agg tat ttt gtg gca ctt aac aaa 337
 Tyr Lys His Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys
 100 105 110

gac gga act cca aga gat ggc gcc agg tcc aag agg cat cag aaa ttt 385
 Asp Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe
 115 120 125

aca cat ttc tta cct aga cca gtc gac ggc 415
 Thr His Phe Leu Pro Arg Pro Val Asp Gly
 130 135

<210> 10
 <211> 138
 <212> PRT
 <213> Homo sapiens

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

<210> 11
 <211> 466
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (2)..(466)

<400> 11
 c acc aga tct atc ctg cgc cgc cgg cag ctc tat tgc cgc acc ggc ttc 49
 Thr Arg Ser Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe
 1 5 10 15
 cac ctg cag atc ctg ccc gac ggc agc gtg cag ggc acc cgg cag gac 97
 His Leu Gln Ile Leu Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp
 20 25 30
 cac agc ctc ttc ggt atc ttg gaa ttc atc agt gtg gca gtg gga ctg 145
 His Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu
 35 40 45
 gtc agt att aga ggt gtg gac agt ggt ctc tat ctt gga atg aat gac 193

Cura 570A Sequence Listing PCT

Val Ser Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp
 50 55 60

aaa gga gaa ctc tat gga tca gag aaa ctt act tcc gaa tgc atc ttt 241
 Lys Gly Glu Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe 80
 65 70 75

agg gag cag ttt gaa gag aac tgg tat aac acc tat tca tct aac ata 289
 Arg Glu Gln Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile 95
 85 90 95

tat aaa cat gga gac act ggc cgc agg tat ttt gtg gca ctt aac aaa 337
 Tyr Lys His Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys 110
 100 105 110

gac gga act cca aga gat ggc gcc agg tcc aag agg cat cag aaa ttt 385
 Asp Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe 125
 115 120 125

aca cat ttc tta cct aga cca gtg gat cca gaa aga gtt cca gaa ttg 433
 Thr His Phe Leu Pro Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu 140
 130 135 140

tac aag gac cta ctg atg tac act gtc gac ggc 466
 Tyr Lys Asp Leu Leu Met Tyr Thr Val Asp Gly 155
 145 150 155

<210> 12
 <211> 155
 <212> PRT
 <213> Homo sapiens

<400> 12
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 1 5 10 15

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

His Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu
 35 40 45

Val Ser Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp
 50 55 60

Lys Gly Glu Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe
 65 70 75 80

Arg Glu Gln Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile
 85 90 95

Tyr Lys His Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys
 100 105 110

Asp Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe
 115 120 125

Thr His Phe Leu Pro Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu
 130 135 140

Tyr Lys Asp Leu Leu Met Tyr Thr Val Asp Gly
 145 150 155

<210> 13
 <211> 549
 <212> DNA
 <213> Homo sapiens

Cura 570A Sequence Listing PCT

<220>

<221> CDS

<222> (1)..(549)

<400> 13

aga tct atg gct ccc tta gcc gaa gtc ggg ggc ttt ctg ggc ggc ctg 48
 Arg Ser Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu
 1 5 10 15

gag ggc ttg ggc cag ccg ggg gca gcg cag ctg gcg cac ctg cac ggc 96
 Glu Gly Leu Gly Gln Pro Gly Ala Ala Gln Leu Ala His Leu His Gly
 20 25 30

atc ctg cgc cgc cgg cag ctc tat tgc cgc acc ggc ttc cac ctg cag 144
 Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln
 35 40 45

atc ctg ccc gac ggc agc gtg cag ggc acc cgg cag gac cac agc ctc 192
 Ile Leu Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His Ser Leu
 50 55 60

ttc ggt atc ttg gaa ttc atc agt gtg gca gtg gga ctg gtc agt att 240
 Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser Ile
 65 70 75 80

aga ggt gtg gac agt ggt ctc tat ctt gga atg aat gac aaa gga gaa 288
 Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu
 85 90 95

ctc tat gga tca gag aaa ctt act tcc gaa tgc atc ttt agg gag cag 336
 Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg Glu Gln
 100 105 110

ttt gaa gag aac tgg tat aac acc tat tca tct aac ata tat aaa cat 384
 Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His
 115 120 125

gga gac act ggc cgc agg tat ttt gtg gca ctt aac aaa gac gga act 432
 Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr
 130 135 140

cca aga gat ggc gcc agg tcc aag agg cat cag aaa ttt aca cat ttc 480
 Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe
 145 150 155 160

tta cct aga cca gtg gat cca gaa aga gtt cca gaa ttg tac aag gac 528
 Leu Pro Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp
 165 170 175

cta ctg atg tac act ctc gag 549
 Leu Leu Met Tyr Thr Leu Glu
 180

<210> 14

<211> 183

<212> PRT

<213> Homo sapiens

<400> 14

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

Glu Gly Leu Gly Gln Pro Gly Ala Ala Gln Leu Ala His Leu His Gly
 20 25 30

Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln
 35 40 45

Cura 570A Sequence Listing PCT

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

Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser Ile
 65 70 75 80

Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu
 85 90 95

Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg Glu Gln
 100 105 110

Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His
 115 120 125

Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr
 130 135 140

Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe
 145 150 155 160

Leu Pro Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp
 165 170 175

Leu Leu Met Tyr Thr Leu Glu
 180

<210> 15
 <211> 408
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(408)

<400> 15
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 Arg Ser Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His
 1 5 10 15

ctg cag atc ctg ccc gac ggc agc gtg cag ggc acc cgg cag gac cac 96
 Leu Gln Ile Leu Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His
 20 25 30

agc ctc ttc ggt atc ttg gaa ttc atc agt gtg gca gtg gga ctg gtc 144
 Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val
 35 40 45

agt att aga ggt gtg gac agt ggt ctc tat ctt gga atg aat gac aaa 192
 Ser Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys
 50 55 60

gga gaa ctc tat gga tca gag aaa ctt act tcc gaa tgc atc ttt agg 240
 Gly Glu Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg
 65 70 75 80

gag cag ttt gaa gag aac tgg tat aac acc tat tca tct aac ata tat 288
 Glu Gln Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr
 85 90 95

aaa cat gaa gac act ggc cgc agg tat ttt gtg gca ctt aac aaa gac 336
 Lys His Glu Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp
 100 105 110

gga act cca aga gat ggc gcc agg tcc aag agg cat cag aaa ttt aca 384
 Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr
 115 120 125

Cura 570A Sequence Listing PCT

cat ttc tta cct aga cca ctc gag 408
His Phe Leu Pro Arg Pro Leu Glu
130 135

<210> 16
<211> 136
<212> PRT
<213> Homo sapiens

<400> 16
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1 5 10 15
Leu Gln Ile Leu Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His
20 25 30
Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val
35 40 45
Ser Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys
50 55 60
Gly Glu Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg
65 70 75 80
Glu Gln Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr
85 90 95
Lys His Glu Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp
100 105 110
Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr
115 120 125
His Phe Leu Pro Arg Pro Leu Glu
130 135

<210> 17
<211> 408
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(408)

<400> 17
aga tct atc ctg cgc cgc cgg cag ctc tat tgc cgc acc ggc ttc cac 48
Arg Ser Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His
1 5 10 15
ctg cag atc ctg ccc gac ggc agc gtg cag ggc acc cgg cag gac cac 96
Leu Gln Ile Leu Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His
20 25 30
agc ctc ttc ggt atc ttg gaa ttc atc agt gtg gca gtg gga ctg gtc 144
Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val
35 40 45
agt att aga ggt gtg gac agt ggt ctc tat ctt gga atg aat gac aaa 192
Ser Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys
50 55 60
gga gaa ctc tat gga tca gag aaa ctt act tcc gaa tgc atc ttt agg 240
Gly Glu Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg
65 70 75 80

Cura 570A Sequence Listing PCT

gag cag ttt gaa gag aac tgg tat aac acc tat tca tct aac ata tat 288
Glu Gln Phe Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr

aaa cat gga gac act ggc cgc agg tat ttt gtg gca ctt aac aaa gac 336
Lys His Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp
100 105 110

gga act cca aga gat ggc gcc agg tcc aag agg cat cag aaa ttt aca 384
Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr

cat ttc tta cct aga cca ctc gag 408
His Phe Leu Pro Arg Pro Leu Glu
130 135

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<210> 18
<211> 136
<212> PRT
<213> Homo sapiens
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<400> 18
Arg Ser Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His
1 5 10 15

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

Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val
35 40 45

Ser Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys
50 55 60

Gly₆₅ Glu Leu Tyr Gly₇₀ Ser₇₅ Glu Lys Leu Thr Ser₈₀ Glu Cys Ile Phe Arg₈₅

Glu Gln Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr
85 90 95

Lys His Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp
100 105 110

Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr
115 120 125

His Phe Leu Pro Arg Pro Leu Glu
130 135

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<210> 19
<211> 477
<212> DNA
<213> Homo sapiens
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<220>
<221> CDS
<222> (1)..(474)

<400> 19
atg gct cag ctg gct cac ctg cat ggt atc ctg cgt cgc cgt cag ctg 48
Met Ala Gln Leu Ala His Leu His Gly Ile Leu Arg Arg Arg Gln Leu
1 5 10 15

tac tgc cgt act ggt ttc cac ctg cag atc ctg ccg gat ggt tct gtt 96
Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu Pro Asp Gly Ser Val
20 25 30

caq ggt acc cgt caq gac cac tct ctg ttc ggt atc ctg gaa ttc atc 144

Cura 570A Sequence Listing PCT

Gln Gly Thr Arg Gln Asp His Ser Leu Phe Gly Ile Leu Glu Phe Ile
 35 40 45

tct gtt gct gtt ggt ctg gtt tct atc cgt ggt gtt gac tct ggc ctg 192
 Ser Val Ala Val Gly Leu Val Ser Ile Arg Gly Val Asp Ser Gly Leu
 50 55 60

tac ctg ggt atg aac gac aaa ggc gaa ctg tac ggt tct gaa aaa ctg 240
 Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr Gly Ser Glu Lys Leu
 65 70 75 80

acc tct gaa tgc atc ttc cgt gaa cag ttt gaa gag aac tgg tac aac 288
 Thr Ser Glu Cys Ile Phe Arg Glu Gln Phe Glu Glu Asn Trp Tyr Asn
 85 90 95

acc tac tct tcc aac atc tac aaa cat ggt gac acc ggc cgt cgc tac 336
 Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp Thr Gly Arg Arg Tyr
 100 105 110

ttc gtt gct ctg aac aaa gac ggt acc ccg cgt gat ggt gct cgt tct 384
 Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg Asp Gly Ala Arg Ser
 115 120 125

aaa cgt cac cag aaa ttc acc cac ttc ctg ccg cgc cca gtt gac ccg 432
 Lys Arg His Gln Lys Phe Thr His Phe Leu Pro Arg Pro Val Asp Pro
 130 135 140

gag cgt gtt cca gaa ctg tat aaa gac ctg ctg atg tac acc taa 477
 Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu Met Tyr Thr
 145 150 155

<210> 20

<211> 158

<212> PRT

<213> Homo sapiens

<400> 20

Met Ala Gln Leu Ala His Leu His Gly Ile Leu Arg Arg Arg Gln Leu
 1 5 10 15

Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu Pro Asp Gly Ser Val
 20 25 30

Gln Gly Thr Arg Gln Asp His Ser Leu Phe Gly Ile Leu Glu Phe Ile
 35 40 45

Ser Val Ala Val Gly Leu Val Ser Ile Arg Gly Val Asp Ser Gly Leu
 50 55 60

Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr Gly Ser Glu Lys Leu
 65 70 75 80

Thr Ser Glu Cys Ile Phe Arg Glu Gln Phe Glu Glu Asn Trp Tyr Asn
 85 90 95

Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp Thr Gly Arg Arg Tyr
 100 105 110

Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg Asp Gly Ala Arg Ser
 115 120 125

Lys Arg His Gln Lys Phe Thr His Phe Leu Pro Arg Pro Val Asp Pro
 130 135 140

Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu Met Tyr Thr
 145 150 155

<210> 21

Cura 570A Sequence Listing PCT

<211> 636

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(633)

<400> 21

atg	gct	ccc	tta	gcc	gaa	gtc	ggg	ggc	ttt	ctg	ggc	ggc	ctg	gag	ggc	48
Met	Ala	Pro	Leu	Ala	Glu	Val	Gly	Gly	Phe	Leu	Gly	Gly	Leu	Glu	Gly	
1				5					10					15		

ttg	ggc	cag	cag	gtg	ggt	tcg	cat	ttc	ctg	ttg	cct	cct	gcc	ggg	gag	96
Leu	Gly	Gln	Gln	Val	Gly	Ser	His	Phe	Leu	Leu	Pro	Pro	Ala	Gly	Glu	
				20				25					30			

cgg	ccg	ccg	ctg	ctg	ggc	gag	cgc	agg	agc	gcg	gcg	gag	cgg	agc	gcg	144
Arg	Pro	Pro	Leu	Leu	Gly	Glu	Arg	Arg	Ser	Ala	Ala	Glu	Arg	Ser	Ala	
		35					40					45				

cgc	ggc	ggg	ccg	ggg	gct	gcg	cag	ctg	gcg	cac	ctg	cac	ggc	atc	ctg	192
Arg	Gly	Gly	Pro	Gly	Ala	Ala	Gln	Leu	Ala	His	Leu	His	Gly	Ile	Leu	
	50					55					60					

cgc	cgc	cgg	cag	ctc	tat	tgc	cgc	acc	ggc	ttc	cac	ctg	cag	atc	ctg	240
Arg	Arg	Arg	Gln	Leu	Tyr	Cys	Arg	Thr	Gly	Phe	His	Leu	Gln	Ile	Leu	
65					70					75					80	

ccc	gac	ggc	agc	gtg	cag	ggc	acc	cgg	cag	gac	cac	agc	ctc	ttc	ggt	288
Pro	Asp	Gly	Ser	Val	Gln	Gly	Thr	Arg	Gln	Asp	His	Ser	Leu	Phe	Gly	
				85					90					95		

atc	ttg	gaa	ttc	atc	agt	gtg	gca	gtg	gga	ctg	gtc	agt	att	aga	ggt	336
Ile	Leu	Glu	Phe	Ile	Ser	Val	Ala	Val	Gly	Leu	Val	Ser	Ile	Arg	Gly	
			100					105					110			

gtg	gac	agt	ggt	ctc	tat	ctt	gga	atg	aat	gac	aaa	gga	gaa	ctc	tat	384
Val	Asp	Ser	Gly	Leu	Tyr	Leu	Gly	Met	Asn	Asp	Lys	Gly	Glu	Leu	Tyr	
		115					120					125				

gga	tca	gag	aaa	ctt	act	tcc	gaa	tgc	atc	ttt	agg	gag	cag	ttt	gaa	432
Gly	Ser	Glu	Lys	Leu	Thr	Ser	Glu	Cys	Ile	Phe	Arg	Glu	Gln	Phe	Glu	
	130					135					140					

gag	aac	tgg	tat	aac	acc	tat	tca	tct	aac	ata	tat	aaa	cat	gga	gac	480
Glu	Asn	Trp	Tyr	Asn	Thr	Tyr	Ser	Ser	Asn	Ile	Tyr	Lys	His	Gly	Asp	
145					150					155					160	

act	ggc	cgc	agg	tat	ttt	gtg	gca	ctt	aac	aaa	gac	gga	act	cca	aga	528
Thr	Gly	Arg	Arg	Tyr	Phe	Val	Ala	Leu	Asn	Lys	Asp	Gly	Thr	Pro	Arg	
				165					170					175		

gat	ggc	gcc	agg	tcc	aag	agg	cat	cag	aaa	ttt	aca	cat	ttc	tta	cct	576
Asp	Gly	Ala	Arg	Ser	Lys	Arg	His	Gln	Lys	Phe	Thr	His	Phe	Leu	Pro	
			180					185					190			

aga	cca	gtg	gat	cca	gaa	aga	gtt	cca	gaa	ttg	tac	aag	gac	cta	ctg	624
Arg	Pro	Val	Asp	Pro	Glu	Arg	Val	Pro	Glu	Leu	Tyr	Lys	Asp	Leu	Leu	
		195					200					205				

atg	tac	act	tga													636
Met	Tyr	Thr														
		210														

<210> 22

<211> 211

<212> PRT

Cura 570A Sequence Listing PCT

<213> Homo sapiens

<400> 22

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

<210> 23

<211> 540

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(537)

<400> 23

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 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15
 ttg ggc cag ccg ggg gca gcg cag ctg gcg cac ctg cac ggc atc ctg 96
 Leu Gly Gln Pro Gly Ala Ala Gln Leu Ala His Leu His Gly Ile Leu
 20 25 30
 cgc cgc cgg cag ctc tat tgc cgc acc ggc ttc cac ctg cag atc ctg 144
 Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu
 35 40 45
 ccc gac ggc agc gtg cag ggc acc cgg cag gac cac agc ctc ttc ggt 192

Cura 570A Sequence Listing PCT

Pro	Asp	Gly	Ser	Val	Gln	Gly	Thr	Arg	Gln	Asp	His	Ser	Leu	Phe	Gly		
	50					55					60						
atc	ttg	gaa	ttc	atc	agt	gtg	gca	gtg	gga	ctg	gtc	agt	att	aga	ggc	240	
Ile	Leu	Glu	Phe	Ile	Ser	Val	Ala	Val	Gly	Leu	Val	Ser	Ile	Arg	Gly	80	
	65				70				75								
gtg	gac	agt	ggc	ctc	tat	ctt	gga	atg	aat	gac	aaa	gga	gaa	ctc	tat	288	
Val	Asp	Ser	Gly	Leu	Tyr	Leu	Gly	Met	Asn	Asp	Lys	Gly	Glu	Leu	Tyr	95	
				85					90								
gga	tca	gag	aaa	ctt	act	tcc	gaa	tgc	atc	ttt	agg	gag	cag	ttt	gaa	336	
Gly	Ser	Glu	Lys	Leu	Thr	Ser	Glu	Cys	Ile	Phe	Arg	Glu	Gln	Phe	Glu	110	
			100					105									
gag	aac	tgg	tat	aac	acc	tat	tca	tct	aac	ata	tat	aaa	cat	gga	gac	384	
Glu	Asn	Trp	Tyr	Asn	Thr	Tyr	Ser	Ser	Asn	Ile	Tyr	Lys	His	Gly	Asp	125	
		115					120										
act	ggc	cgc	agg	tat	ttt	gtg	gca	ctt	aac	aaa	gac	gga	act	cca	aga	432	
Thr	Gly	Arg	Arg	Tyr	Phe	Val	Ala	Leu	Asn	Lys	Asp	Gly	Thr	Pro	Arg	140	
	130					135											
gat	ggc	gcc	agg	tcc	aag	agg	cat	cag	aaa	ttt	aca	cat	ttc	tta	cct	480	
Asp	Gly	Ala	Arg	Ser	Lys	Arg	His	Gln	Lys	Phe	Thr	His	Phe	Leu	Pro	160	
	145				150					155							
aga	cca	gtg	gat	cca	gaa	aga	gtt	cca	gaa	ttg	tac	aag	gac	cta	ctg	528	
Arg	Pro	Val	Asp	Pro	Glu	Arg	Val	Pro	Glu	Leu	Tyr	Lys	Asp	Leu	Leu	175	
				165					170								
atg	tac	act	tag													540	
Met	Tyr	Thr															

<210> 24
 <211> 179
 <212> PRT
 <213> Homo sapiens

<400> 24
 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15
 Leu Gly Gln Pro Gly Ala Ala Gln Leu Ala His Leu His Gly Ile Leu
 20 25 30
 Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu
 35 40 45
 Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His Ser Leu Phe Gly
 50 55 60
 Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser Ile Arg Gly
 65 70 75 80
 Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr
 85 90 95
 Gly Ser Glu Lys Leu Thr Ser Glu Cys Ile Phe Arg Glu Gln Phe Glu
 100 105 110
 Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp
 115 120 125
 Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg
 130 135 140

Cura 570A Sequence Listing PCT

Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro
 145 150 155 160

Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu Leu
 165 170 175

Met Tyr Thr

<210> 25
 <211> 54
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(54)

<400> 25
 atg gct ccc tta gcc gaa gtc ggg ggc ttt ctg ggc ggc ctg gag ggc 48
 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15

ttg ggc 54
 Leu Gly

<210> 26
 <211> 18
 <212> PRT
 <213> Homo sapiens

<400> 26
 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15

Leu Gly

<210> 27
 <211> 63
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(63)

<400> 27
 gag cgg ccg ccg ctg ctg ggc gag cgc agg agc gcg gcg gag cgg agc 48
 Glu Arg Pro Pro Leu Leu Gly Glu Arg Arg Ser Ala Ala Glu Arg Ser
 1 5 10 15

gcg cgc ggc ggc ccg 63
 Ala Arg Gly Gly Pro
 20

<210> 28
 <211> 21
 <212> PRT
 <213> Homo sapiens

<400> 28
 Glu Arg Pro Pro Leu Leu Gly Glu Arg Arg Ser Ala Ala Glu Arg Ser
 1 5 10 15

Ala Arg Gly Gly Pro
 20

Cura 570A Sequence Listing PCT

<210> 29
 <211> 63
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(63)

<400> 29
 cgc agg tat ttt gtg gca ctt aac aaa gac gga act cca aga gat ggc 48
 Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg Asp Gly
 1 5 10 15

gcc agg tcc aag agg 63
 Ala Arg Ser Lys Arg
 20

<210> 30
 <211> 21
 <212> PRT
 <213> Homo sapiens

<400> 30
 Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg Asp Gly
 1 5 10 15

Ala Arg Ser Lys Arg
 20

<210> 31
 <211> 60
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(60)

<400> 31
 cct aga cca gtg gat cca gaa aga gtt cca gaa ttg tac aag gac cta 48
 Pro Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu
 1 5 10 15

ctg atg tac act 60
 Leu Met Tyr Thr
 20

<210> 32
 <211> 20
 <212> PRT
 <213> Homo sapiens

<400> 32
 Pro Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asp Leu
 1 5 10 15

Leu Met Tyr Thr
 20

<210> 33
 <211> 51
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS

Cura 570A Sequence Listing PCT

<222> (1)..(51)

<400> 33

atg	aac	gac	aag	ggc	gag	ctg	tac	ggc	agc	gag	aag	ctg	acc	agc	gag	48
Met	Asn	Asp	Lys	Gly	Glu	Leu	Tyr	Gly	Ser	Glu	Lys	Leu	Thr	Ser	Glu	
1				5					10					15		

tgc																51
Cys																

<210> 34

<211> 17

<212> PRT

<213> Homo sapiens

<400> 34

Met	Asn	Asp	Lys	Gly	Glu	Leu	Tyr	Gly	Ser	Glu	Lys	Leu	Thr	Ser	Glu
1				5					10					15	

Cys

<210> 35

<211> 633

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(633)

<400> 35

atg	gct	ccc	tta	gcc	gaa	gtc	ggg	ggc	ttt	ctg	ggc	ggc	ctg	gag	ggc	48
Met	Ala	Pro	Leu	Ala	Glu	Val	Gly	Gly	Phe	Leu	Gly	Gly	Leu	Glu	Gly	
1				5					10					15		

ttg	ggc	cag	cag	gtg	ggt	tcg	cat	ttc	ctg	ttg	cct	cct	gcc	ggg	gag	96
Leu	Gly	Gln	Gln	Val	Gly	Ser	His	Phe	Leu	Leu	Pro	Pro	Ala	Gly	Glu	
			20					25					30			

cgg	ccg	ccg	ctg	ctg	ggc	gag	cgc	agg	agc	gcg	gcg	gag	cgg	agc	gcg	144
Arg	Pro	Pro	Leu	Leu	Gly	Glu	Arg	Arg	Ser	Ala	Ala	Glu	Arg	Ser	Ala	
		35					40					45				

cgc	ggc	ggg	ccg	ggg	gct	gcg	cag	ctg	gcg	cac	ctg	cac	ggc	atc	ctg	192
Arg	Gly	Gly	Pro	Gly	Ala	Ala	Gln	Leu	Ala	His	Leu	His	Gly	Ile	Leu	
	50				55					60						

cgc	cgc	cgg	cag	ctc	tat	tgc	cgc	acc	ggc	ttc	cac	ctg	cag	atc	ctg	240
Arg	Arg	Arg	Gln	Leu	Tyr	Cys	Arg	Thr	Gly	Phe	His	Leu	Gln	Ile	Leu	
65				70					75					80		

ccc	gac	ggc	agc	gtg	cag	ggc	acc	cgg	cag	gac	cac	agc	ctc	ttc	ggc	288
Pro	Asp	Gly	Ser	Val	Gln	Gly	Thr	Arg	Gln	Asp	His	Ser	Leu	Phe	Gly	
				85				90						95		

atc	ttg	gaa	ttc	atc	agt	gtg	gca	gtg	gga	ctg	gtc	agt	att	aga	ggc	336
Ile	Leu	Glu	Phe	Ile	Ser	Val	Ala	Val	Gly	Leu	Val	Ser	Ile	Arg	Gly	
			100					105					110			

gtg	gac	agt	ggc	ctc	tat	ctt	gga	atg	aat	gac	aaa	gga	gaa	ctc	tat	384
Val	Asp	Ser	Gly	Leu	Tyr	Leu	Gly	Met	Asn	Asp	Lys	Gly	Glu	Leu	Tyr	
		115					120					125				

gga	tca	gag	aaa	ctt	act	tcc	gaa	tgc	atc	ttt	agg	gag	cag	ttt	gaa	432
Gly	Ser	Glu	Lys	Leu	Thr	Ser	Glu	Cys	Ile	Phe	Arg	Glu	Gln	Phe	Glu	
	130					135					140					

Cura 570A Sequence Listing PCT

gag aac tgg tat aac acc tat tca tct aac ata tat aaa cat gga gac 480
 Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp
 145 150 155 160

act ggc cgc agg tat ttt gtg gca ctt aac aaa gac gga act cca aga 528
 Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg
 165 170 175

gat ggc gcc agg tcc aag agg cat cag aaa ttt aca cat ttc tta cct 576
 Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro
 180 185 190

aga cca gtg gat cca gaa aga gtt cca gaa ttg tac aag aac cta ctg 624
 Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asn Leu Leu
 195 200 205

atg tac act 633
 Met Tyr Thr
 210

<210> 36
 <211> 211
 <212> PRT
 <213> Homo sapiens

<400> 36
 Met Ala Pro Leu Ala Glu Val Gly Gly Phe Leu Gly Gly Leu Glu Gly
 1 5 10 15

Leu Gly Gln Gln Val Gly Ser His Phe Leu Leu Pro Pro Ala Gly Glu
 20 25 30

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

Arg Gly Gly Pro Gly Ala Ala Gln Leu Ala His Leu His Gly Ile Leu
 50 55 60

Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe His Leu Gln Ile Leu
 65 70 75 80

Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp His Ser Leu Phe Gly
 85 90 95

Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu Val Ser Ile Arg Gly
 100 105 110

Val Asp Ser Gly Leu Tyr Leu Gly Met Asn Asp Lys Gly Glu Leu Tyr
 115 120 125

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

Glu Asn Trp Tyr Asn Thr Tyr Ser Ser Asn Ile Tyr Lys His Gly Asp
 145 150 155 160

Thr Gly Arg Arg Tyr Phe Val Ala Leu Asn Lys Asp Gly Thr Pro Arg
 165 170 175

Asp Gly Ala Arg Ser Lys Arg His Gln Lys Phe Thr His Phe Leu Pro
 180 185 190

Arg Pro Val Asp Pro Glu Arg Val Pro Glu Leu Tyr Lys Asn Leu Leu
 195 200 205

Met Tyr Thr
 210

Cura 570A Sequence Listing PCT

<210> 37
 <211> 203
 <212> PRT
 <213> Homo sapiens

<400> 37
 Gly Phe Leu Gly Gly Leu Glu Gly Leu Gly Gln Gln Val Gly Ser His
 1 5 10 15
 Phe Leu Leu Pro Pro Ala Gly Glu Arg Pro Pro Leu Leu Gly Glu Arg
 20 25 30
 Arg Ser Ala Ala Glu Arg Ser Ala Arg Gly Gly Pro Gly Ala Ala Gln
 35 40 45
 Leu Ala His Leu His Gly Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg
 50 55 60
 Thr Gly Phe His Leu Gln Ile Leu Pro Asp Gly Ser Val Gln Gly Thr
 65 70 75 80
 Arg Gln Asp His Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala
 85 90 95
 Val Gly Leu Val Ser Ile Arg Gly Val Asp Ser Gly Leu Tyr Leu Gly
 100 105 110
 Met Asn Asp Lys Gly Glu Leu Tyr Gly Ser Glu Lys Leu Thr Ser Glu
 115 120 125
 Cys Ile Phe Arg Glu Gln Phe Glu Glu Asn Trp Tyr Asn Thr Tyr Ser
 130 135 140
 Ser Asn Ile Tyr Lys His Gly Asp Thr Gly Arg Arg Tyr Phe Val Ala
 145 150 155 160
 Leu Asn Lys Asp Gly Thr Pro Arg Asp Gly Ala Arg Ser Lys Arg His
 165 170 175
 Gln Lys Phe Thr His Phe Leu Pro Arg Pro Val Asp Pro Glu Arg Val
 180 185 190
 Pro Glu Leu Tyr Lys Asp Leu Leu Met Tyr Thr
 195 200

<210> 38
 <211> 200
 <212> PRT
 <213> Homo sapiens

<400> 38
 Gly Gly Leu Glu Gly Leu Gly Gln Gln Val Gly Ser His Phe Leu Leu
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 Pro Pro Ala Gly Glu Arg Pro Pro Leu Leu Gly Glu Arg Arg Ser Ala
 20 25 30
 Ala Glu Arg Ser Ala Arg Gly Gly Pro Gly Ala Ala Gln Leu Ala His
 35 40 45
 Leu His Gly Ile Leu Arg Arg Arg Gln Leu Tyr Cys Arg Thr Gly Phe
 50 55 60
 His Leu Gln Ile Leu Pro Asp Gly Ser Val Gln Gly Thr Arg Gln Asp
 65 70 75 80
 His Ser Leu Phe Gly Ile Leu Glu Phe Ile Ser Val Ala Val Gly Leu

Cura 570A Sequence Listing PCT

	85		90		95										
Val	Ser	Ile	Arg	Gly	Val	Asp	Ser	Gly	Leu	Tyr	Leu	Gly	Met	Asn	Asp
			100					105					110		
Lys	Gly	Glu	Leu	Tyr	Gly	Ser	Glu	Lys	Leu	Thr	Ser	Glu	Cys	Ile	Phe
		115					120					125			
Arg	Glu	Gln	Phe	Glu	Glu	Asn	Trp	Tyr	Asn	Thr	Tyr	Ser	Ser	Asn	Ile
		130				135					140				
Tyr	Lys	His	Gly	Asp	Thr	Gly	Arg	Arg	Tyr	Phe	Val	Ala	Leu	Asn	Lys
		145			150					155					160
Asp	Gly	Thr	Pro	Arg	Asp	Gly	Ala	Arg	Ser	Lys	Arg	His	Gln	Lys	Phe
				165					170					175	
Thr	His	Phe	Leu	Pro	Arg	Pro	Val	Asp	Pro	Glu	Arg	Val	Pro	Glu	Leu
			180					185					190		
Tyr	Lys	Asp	Leu	Leu	Met	Tyr	Thr								
		195					200								
<210> 39															
<211> 197															
<212> PRT															
<213> Homo sapiens															
<400> 39															
Glu	Gly	Leu	Gly	Gln	Gln	Val	Gly	Ser	His	Phe	Leu	Leu	Pro	Pro	Ala
1				5					10					15	
Gly	Glu	Arg	Pro	Pro	Leu	Leu	Gly	Glu	Arg	Arg	Ser	Ala	Ala	Glu	Arg
			20					25					30		
Ser	Ala	Arg	Gly	Gly	Pro	Gly	Ala	Ala	Gln	Leu	Ala	His	Leu	His	Gly
		35					40					45			
Ile	Leu	Arg	Arg	Arg	Gln	Leu	Tyr	Cys	Arg	Thr	Gly	Phe	His	Leu	Gln
	50					55					60				
Ile	Leu	Pro	Asp	Gly	Ser	Val	Gln	Gly	Thr	Arg	Gln	Asp	His	Ser	Leu
	65				70				75						80
Phe	Gly	Ile	Leu	Glu	Phe	Ile	Ser	Val	Ala	Val	Gly	Leu	Val	Ser	Ile
			85					90					95		
Arg	Gly	Val	Asp	Ser	Gly	Leu	Tyr	Leu	Gly	Met	Asn	Asp	Lys	Gly	Glu
			100					105					110		
Leu	Tyr	Gly	Ser	Glu	Lys	Leu	Thr	Ser	Glu	Cys	Ile	Phe	Arg	Glu	Gln
		115					120					125			
Phe	Glu	Glu	Asn	Trp	Tyr	Asn	Thr	Tyr	Ser	Ser	Asn	Ile	Tyr	Lys	His
	130					135					140				
Gly	Asp	Thr	Gly	Arg	Arg	Tyr	Phe	Val	Ala	Leu	Asn	Lys	Asp	Gly	Thr
	145				150				155						160
Pro	Arg	Asp	Gly	Ala	Arg	Ser	Lys	Arg	His	Gln	Lys	Phe	Thr	His	Phe
			165					170					175		
Leu	Pro	Arg	Pro	Val	Asp	Pro	Glu	Arg	Val	Pro	Glu	Leu	Tyr	Lys	Asp
			180					185					190		
Leu	Leu	Met	Tyr	Thr											
		195													

Cura .570A Sequence Listing PCT

<210> 40

<211> 188

<212> PRT

<213> Homo sapiens

<400> 40

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