

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
1 February 2007 (01.02.2007)

PCT

(10) International Publication Number
WO 2007/014254 A2

(51) International Patent Classification:
A61K 31/21 (2006.01)

(21) International Application Number:
PCT/US2006/028997

(22) International Filing Date: 26 July 2006 (26.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/702,277 26 July 2005 (26.07.2005) US

(71) Applicant (for all designated States except US): **REGENERX BIOPHARMACEUTICALS, INC.** [US/US]; 3 Bethesda Metro Center, Suite 630, Bethesda, MD 20814 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SPURNEY, Christopher, F.** [US/US]; Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010 (US). **GOLDSTEIN, Allan, L.** [US/US]; 800 25th Street, NW, Apt. 1005, Washington, DC 20037 (US).

(74) Agents: **REPPER, George, R.** et al.; Rothwell, Figg, Ernst & Manbeck, 1425 K Street, NW, Suite 800, Washington, DC 20005 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF TREATING OR PREVENTING TISSUE DETERIORATION, INJURY OR DAMAGE DUE TO HYPERTROPHIC MUSCLE DISEASE

(57) Abstract: A method of treatment for treating, preventing, inhibiting or reducing tissue deterioration, injury or damage due to a hypertrophic muscle disease, or for restoring tissue adversely affected by said disease, in a subject, includes administering to a subject in need of such treatment an effective amount of a composition including a peptide agent including amino acid sequence LKKTET or LKKTNT, a conservative variant thereof, or a peptide agent that stimulates production of an LKKTET or LKKTNT peptide, or a conservative variant thereof, in the tissue.



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**METHOD OF TREATING OR PREVENTING TISSUE DETERIORATION,
INJURY OR DAMAGE DUE TO HYPERTROPHIC MUSCLE DISEASE****BACKGROUND OF THE INVENTION****CROSS-REFERENCE TO RELATED APPLICATION**

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/702,277, filed 26 July 2005.

Field of the Invention

[0002] The present invention relates to the field of treating or preventing tissue deterioration, injury or damage due to hypertrophic muscle disease.

Description of the Background Art

[0003] Diseases associated with muscle hypertrophy are among the most debilitating maladies among humans, and may affect both heart and skeletal muscle. These include degenerative muscle diseases such as hypertrophic cardiomyopathy, and the like.

[0004] Hypertrophic cardiomyopathy results in the progressive deterioration and weakness of the heart. Hypertrophic cardiomyopathy can lead to arrhythmias, heart failure, and sudden death. For many patients with hypertrophic cardiomyopathy, transplantation of a new heart is the only viable treatment.

[0005] Hypertrophic cardiomyopathy results in the enlargement (thickening) of the muscle mass of the left ventricle in response to increased stress on the heart. It typically is caused by hypertension and stenosis of the aortic valve. The muscle mass is also stiff and has difficulty relaxing, increasing the amount of pressure required to expand when blood flows into the heart. This reduces the capacity of the heart itself. In some cases the disease is hereditary, resulting from a gene abnormality, related to weakness of the individual muscle fibers of the heart. One example of such a genetic abnormality is the x-linked cardiomyopathy that results from the loss of dystrophin, a cytoskeletal protein found at the inner surface of heart muscle fibers. Also, in hypertrophic cardiomyopathy the muscle mass of the left ventricle is larger than it should be, causing among other things, the mitral valve to touch the septum (dividing wall between the two sides of the heart). The effect of the narrowing of the passage is to obstruct blood flow out of the heart.

[0006] In one form of hypertrophic cardiomyopathy, the septum between the two heart

ventricles becomes enlarged and obstructs the blood flow from the left ventricle. The syndrome is known as hypertrophic obstructive cardiomyopathy or asymmetric septal hypertrophy. It is also called idiopathic hypertrophic subaortic stenosis. Besides obstructing blood flow, the thickened wall sometimes distorts one leaflet of the mitral valve, causing it to leak. In over half the cases, the disease is hereditary. Close blood relatives (parents, children or siblings) of such persons often have enlarged septums, although they may have no symptoms. This disease is most common in young adults.

[0007] Symptoms of hypertrophic cardiomyopathy include shortness of breath on exertion, dizziness, fainting and angina pectoris. Some people have cardiac arrhythmias. The obstruction to blood flow from the left ventricle increases the ventricle's work, and a heart murmur may be heard.

[0008] In the U.S., there are about 50,000 patients with cardiomyopathy.

[0009] There remains a need in the art for methods of treatment for treating, preventing, inhibiting or reducing tissue deterioration, injury or damage due to hypertrophic muscle disease.

SUMMARY OF THE INVENTION

[0010] In accordance with one aspect, a method of treatment for treating, preventing, inhibiting or reducing tissue deterioration, injury or damage due to a hypertrophic muscle disease, or for restoring tissue adversely affected by said disease, in a subject, comprises administering to a subject in need of such treatment an effective amount of a composition comprising a peptide agent comprising amino acid sequence LKKTET or LKKTNT, a conservative variant thereof, or a stimulating agent that stimulates production of an LKKTET or LKKTNT peptide, or a conservative variant thereof, in said tissue, so as to inhibit said tissue deterioration, injury or damage due to a hypertrophic muscle disease, or restore tissue adversely affected by said disease.

DETAILED DESCRIPTION OF THE INVENTION

[0011] Without being bound to any specific theory, actin-sequestering peptides such as thymosin beta 4 (T β 4 or TB4) and other agents including actin-sequestering peptides or peptide fragments containing amino acid sequence LKKTET or LKKTNT, or conservative variants thereof, promote reversal or prevention of tissue deterioration, injury or damage due to a hypertrophic muscle disease.

[0012] Thymosin beta 4 was initially identified as a protein that is up-regulated during endothelial cell migration and differentiation *in vitro*. Thymosin beta 4 was originally isolated from the thymus and is a 43 amino acid, 4.9 kDa ubiquitous polypeptide

identified in a variety of tissues. Several roles have been ascribed to this protein including a role in a endothelial cell differentiation and migration, T cell differentiation, actin sequestration, vascularization and wound healing.

[0013] Hypertrophic cardiomyopathy muscle diseases to which the invention is applicable include, but are not limited to, cardiomyopathy including hypertrophic cardiomyopathy, and the like.

[0014] In accordance with one embodiment, the invention is a method of treatment for treating, preventing, inhibiting or reducing tissue deterioration, injury or damage due to a hypertrophic muscle disease, or for restoring tissue adversely affected by said disease, in a subject, comprising administering to a subject in need of such treatment an effective amount of a composition comprising a peptide agent, which may be a polypeptide comprising amino acid sequence LKKTET or LKKTNT, or a conservative variant thereof having hypertrophic muscle disease-inhibiting activity, such as Thymosin β 4, and/or T β 4 isoforms, analogues or derivatives, including KLKKTET, LKKTETQ, oxidized T β 4, N-terminal variants of T β 4, C-terminal variants of T β 4 and antagonists of T β 4. In accordance with one embodiment, the peptide agent is other than T β 4 and/or other than oxidized T β 4.

[0015] Compositions which may be used in accordance with the present invention include peptide agents such as Thymosin β 4 (T β 4), and/or T β 4 isoforms, analogues or derivatives, including oxidized T β 4, N-terminal variants of T β 4, C-terminal variants of T β 4 and antagonists of T β 4, polypeptides or peptide fragments comprising or consisting essentially of the amino acid sequence LKKTET or LKKTNT, or conservative variants thereof, having hypertrophic muscle disease-inhibiting activity. International Application Serial No. PCT/US99/17282, incorporated herein by reference, discloses isoforms of T β 4 which may be useful in accordance with the present invention as well as amino acid sequence LKKTET and conservative variants thereof, which may be utilized with the present invention. International Application Serial No. PCT/GB99/00833 (WO 99/49883), incorporated herein by reference, discloses oxidized Thymosin β 4 which may be utilized in accordance with the present invention. Although the present invention is described primarily hereinafter with respect to T β 4 and T β 4 isoforms, it is to be understood that the following description is intended to be equally applicable to amino acid sequence LKKTET or LKKTNT, peptides and fragments comprising or consisting essentially of LKKTET or LKKTNT, conservative variants thereof having hypertrophic muscle disease-inhibiting activity, and/or T β 4 isoforms, analogues or derivatives, including oxidized T β 4, N-terminal variants of T β 4, C-terminal variants of

T β 4 and the like.

[0016] In one embodiment, the invention provides a method of treatment for treating, preventing, inhibiting or reducing tissue deterioration, injury or damage due to a hypertrophic muscle disease other than muscular dystrophy, or for restoring tissue adversely affected by said disease, in a subject, comprising administering to a subject in need of such treatment an effective amount of a composition comprising a peptide agent comprising amino acid sequence LKKTET or LKKTNT, a conservative variant thereof, or a stimulating agent that stimulates production of an LKKTET or LKKTNT peptide, or a conservative variant thereof, in said tissue, so as to inhibit said tissue deterioration, injury or damage due to a hypertrophic muscle disease, or restore tissue adversely affected by said disease.

[0017] In one embodiment, the invention provides a method of treatment for treating, preventing, inhibiting or reducing tissue deterioration, injury or damage due to a hypertrophic muscle disease, or for restoring tissue adversely affected by said disease, in a subject, by contacting the tissue with an effective amount of a composition which contains a peptide agent as described herein. As a non-limiting example, the tissue may be muscular tissue of said subject. The contacting may be directly or systemically. Examples of direct administration include, for example, contacting the tissue, by direct application or inhalation, with a solution, lotion, salve, gel, cream, paste, spray, suspension, dispersion, hydrogel, ointment, foam or oil comprising a peptide agent as described herein. Systemic administration includes, for example, intravenous, intraperitoneal, intramuscular injections of a composition containing a peptide agent as described herein, in a pharmaceutically acceptable carrier such as water for injection.

[0018] Peptide agents for use in the invention, as described herein, may be administered in any effective amount. For example, a peptide agent as described herein may be administered in dosages within the range of about 0.0001-1,000,000 micrograms, more preferably in amounts within the range of about 0.1-5,000 micrograms, most preferably within the range of about 1-30 micrograms.

[0019] A composition in accordance with the present invention can be administered daily, every other day, every other week, every other month, etc., with a single application or multiple applications per day of administration, such as applications 2, 3, 4 or more times per day of administration.

[0020] Many T β 4 isoforms have been identified and have about 70%, or about 75%, or about 80% or more homology to the known amino acid sequence of T β 4. Such isoforms include, for example, T β 4^{ala}, T β 9, T β 10, T β 11, T β 12, T β 13, T β 14 and T β 15.

Similar to T β 4, the T β 10 and T β 15 isoforms have been shown to sequester actin. T β 4, T β 10 and T β 15, as well as these other isoforms share an amino acid sequence, LKKTET or LKKTNT, that appears to be involved in mediating actin sequestration or binding. Although not wishing to be bound by any particular theory, the activity of peptide agents as described herein may be due, at least in part, to the anti-inflammatory and/or actin modulating activity of such agents. T β 4 modulates actin polymerization (e.g. β -thymosins appear to depolymerize F-actin by sequestering free G-actin). T β 4's ability to modulate actin polymerization may be due to its ability to bind to or sequester actin via the LKKTET or LKKTNT sequence. Thus, as with T β 4, other proteins which are anti-inflammatory and/or bind or sequester actin, or modulate actin polymerization, including T β 4 isoforms having the amino acid sequence LKKTET or LKKTNT, are likely to be effective, alone or in a combination with T β 4, as set forth herein.

[0021] Peptide agents as described herein, such as T β 4 and T β 4 isoforms including oxidized T β 4, decrease inflammatory chemokine, cytokine and capase activity.

[0022] Thus, it is specifically contemplated that known T β 4 isoforms, such as T β 4^{ala}, T β 9, T β 10, T β 11, T β 12, T β 13, T β 14 and T β 15, as well as T β 4 isoforms not yet identified, will be useful in the methods of the invention. As such T β 4 isoforms are useful in the methods of the invention, including the methods practiced in a subject. The invention therefore further provides pharmaceutical compositions comprising T β 4, as well as T β 4 isoforms T β 4^{ala}, T β 9, T β 10, T β 11, T β 12, T β 13, T β 14 and T β 15, and a pharmaceutically acceptable carrier.

[0023] In addition, other agents or proteins having anti inflammatory activity and/or actin sequestering or binding capability, or that can mobilize actin or modulate actin polymerization, as demonstrated in an appropriate sequestering, binding, mobilization or polymerization assay, or identified by the presence of an amino acid sequence that mediates actin binding, such as LKKTET or LKKTNT, for example, can similarly be employed in the methods of the invention. Such proteins may include gelsolin, vitamin D binding protein (DBP), profilin, cofilin, depactin, Dnasel, villin, fragmin, severin, capping protein, β -actinin and acumentin, for example. As such methods include those practiced in a subject, the invention further provides pharmaceutical compositions comprising gelsolin, vitamin D binding protein (DBP), profilin, cofilin, depactin, Dnasel, villin, fragmin, severin, capping protein, β -actinin and acumentin as set forth herein. Thus, the invention includes the use of an polypeptide comprising the amino acid sequence LKKTET or LKKTNT and conservative variants thereof.

[0024] As used herein, the term "conservative variant" or grammatical variations thereof denotes the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the replacement of a hydrophobic residue such as isoleucine, valine, leucine or methionine for another, the replacement of a polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like.

[0025] T β 4 has been localized to a number of tissue and cell types and thus, agents which stimulate the production of an LKKTET or LKKTNT peptide such as T β 4 or another peptide agent as described herein, can be added to or comprise a composition to effect production a peptide agent from a tissue and/or a cell. Such stimulating agents may include members of the family of growth factors, such as insulin-like growth factor (IGF-1), platelet derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor beta (TGF- β), basic fibroblast growth factor (bFGF), thymosin α 1 (T α 1) and vascular endothelial growth factor (VEGF). More preferably, the stimulating agent is transforming growth factor beta (TGF- β) or other members of the TGF- β superfamily.

[0026] In accordance with one embodiment, subjects are treated with a stimulating agent that stimulates production in the subject of a peptide agent as defined herein.

[0027] Additionally, other agents that assist in reduction of tissue deterioration, injury or damage due to hypertrophic muscular disease, or restoring tissue adversely affected by said disease may be added to a composition along with a peptide agent as described herein. For example, and not by way of limitation, a peptide agent as described herein alone or in combination can be added in combination with any one or more of the following agents: antibiotics, VEGF, KGF, FGF, PDGF, TGF β , IGF-1, IGF-2, IL-1, prothymosin α and/or thymosin α 1 in an effective amount.

[0028] The invention also includes a pharmaceutical composition comprising a therapeutically effective amount of a peptide agent as described herein in a pharmaceutically acceptable carrier. Such carriers include those listed herein.

[0029] The actual dosage or reagent, formulation or composition that provides treatment may depend on many factors, including the size and health of a subject. However, persons of ordinary skill in the art can use teachings describing the methods and techniques for determining clinical dosages as disclosed in PCT/US99/17282, *supra*, and the references cited therein, to determine the appropriate dosage to use.

[0030] Suitable formulations may include a peptide agent as described herein at a concentration within the range of about 0.001 - 50% by weight, more preferably within

the range of about 0.01 - 0.1% by weight, most preferably about 0.05% by weight.

[0031] The therapeutic approaches described herein involve various routes of administration or delivery of a peptide agent as described herein, including any conventional administration techniques (for example, but not limited to, direct administration, local injection, inhalation, or systemic administration), to a subject. The methods and compositions using or containing a peptide agent as described herein may be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable non-toxic excipients or carriers.

[0032] The invention includes use of antibodies which interact with, enhance or inhibit a peptide agent as described herein. Antibodies which consist essentially of pooled monoclonal antibodies with different epitopic specificities, as well as distinct monoclonal antibody preparations are provided. Monoclonal antibodies are made from antigen containing fragments of the protein by methods well known to those skilled in the art as disclosed in PCT/US99/17282, *supra*. The term antibody as used in this invention is meant to include monoclonal and polyclonal antibodies.

[0033] In yet another embodiment, the invention provides a method of treating a subject by administering an effective amount of stimulating agent which modulates gene expression. The term "modulate" refers to inhibition or suppression of expression when a peptide agent as described herein is over expressed, and induction of expression when a peptide agent as described herein is underexpressed. The term "effective amount" means that amount of stimulating agent which is effective in modulating gene expression of a peptide agent as described herein, resulting in reducing the symptoms of tissue deterioration, injury or damage due to a hypertrophic muscular disease, or restoring tissue adversely affected by said disease. A stimulating agent which modulates gene expression of a peptide agent as described herein may be a polynucleotide, for example. The polynucleotide may be an antisense, a triplex agent, or a ribozyme. For example, an antisense directed to the structural gene region or to the promoter region of a peptide agent as described herein may be utilized. The stimulating agent which modulates gene expression of a peptide agent as described herein may also be a small interfering RNAs (siRNAs).

[0034] In another embodiment, the invention provides a method for utilizing compounds that modulate activity of a peptide agent as described herein. Compounds that affect activity of a peptide agent as described herein (e.g., antagonists and agonists) include peptides, peptidomimetics, polypeptides, chemical compounds, minerals such as zincs, and biological agents.

[0035] A method for screening for a stimulating agent as defined herein, comprises contacting a tissue exhibiting hypertrophic muscular disease, with a candidate compound; and measuring activity in said tissue of an LKKTET peptide, wherein an increase of activity of said peptide in said tissue, compared to a level of activity of said peptide in a corresponding tissue lacking said candidate compound, indicates that said compound is capable of inducing said stimulating agent.

Example 1

[0036] The use of thymosin beta 4 was studied during the development of dystrophic cardiomyopathy. We used the naturally occurring dystrophin deficient mdx mouse model and followed the cardiac function longitudinally with non-invasive echocardiography. Thymosin beta 4 may have beneficial effects on slowing the progression of the cardiomyopathy through its properties of membrane stabilization and anti-fibrosis. In dystrophic cardiomyopathies, shear forces are poorly tolerated due to the lack of the dystrophin and its connections to the extracellular matrix. These forces lead to tearing of the muscle cell membranes leading to cell death and fibrosis.

Thymosin beta 4 has been shown to have membrane stabilizing properties, likely related to effects on actin polymerization. We also followed functional parameters of skeletal muscle function that may also benefit from administration of thymosin beta 4. Preliminary data is presented in table 1. Thymosin beta 4 also has anti-fibrotic properties. Cardiac muscle injured due to shear forces and calcium influx may benefit from thymosin beta 4's modulation of muscular remodeling. Less fibrosis maintains cardiac function for a longer period of time.

[0037] Test parameters and experimental design:

[0038] Four groups of mice were treated with thymosin beta 4. Group 1 was normal mice (BL10) that were given placebo (untreated). Group 2 was normal mice that were treated with thymosin beta 4. Group 3 was dystrophin deficient (mdx) mice treated with placebo and Group 4 was mdx mice treated with thymosin beta 4. Mice were treated with 150 micrograms of thymosin beta 4 in 300 microliters of buffer given intraperitoneally twice a week and placebo mice were given 300 microliters of buffer only. The mice exercised on a treadmill at a speed of 12 meters/ minute for 30 minutes twice a week. Functional, behavioral and echocardiographic data were obtained at baseline and after 2 months, 4 months and 6 months of treatment.

[0039] Functional data were non-invasive measurements of skeletal muscle function. The muscle strength of the forelimbs and hindlimbs was assessed using a grip strength meter. The animals were allowed to hold onto the meter platform and then were slowly

pulled until they lost their grip. The amount of force needed to free the grip was recorded. Multiple measurements were taken for each mouse at each time point. The same protocol was followed for hindlimb muscle strength. Another functional assessment was the Rotarod test. Here, mice were placed on a rotating bar and kept their balance and position as the bar rotated with increasing speed (10 RPM for 1 minute and then increased 0.2 RPM over the next three minutes). The time until the mouse falls was measured. This test was also repeated multiple times.

[0040] Behavioral data was collected using the VersaMax™ animal activity monitoring system. Mice were placed in a monitored box and activity was quantified by different sensors. Data includes horizontal activity, vertical activity and total distance traveled and many other activity parameters were measured. Multiple measurements were made over a 3 day period.

[0041] Echocardiographic assessment was performed using the VisualSonics Vevo 660™ high frequency system. Evaluation of cardiac chamber size, ventricular function and inflow/outflow Doppler velocities were completed under isoflurane anesthesia. The cardiologist performing and measuring the echocardiograms was blinded to study groups.

[0042] Table 1: Functional parameters measured in normal (BL10) and dystrophin deficient (mdx) mice at baseline and after two months of treatment with thymosin beta 4.

Group	BL10 untreated	BL10 untreated	BL10 treated	BL10 treated	Mdx untreated	Mdx untreated	Mdx treated	Mdx treated
Time	Baseline	2 month	Baseline	2 month	Baseline	2 month	Baseline	2 month
Avg max forelimb strength (KGF/kg)	5.57	6.10	5.57	5.73	4.46	4.07	4.46	3.78
Avg max hindlimb strength (KGF/kg)	7.35	9.01	7.35	9.18	6.29	7.54	6.29	7.29
Avg horizontal activity	1761	1302	1761	1287	1071	875	1071	961
Avg vertical activity	28	15.6	28	13.1	12	9.0	12	8.2
Avg total distance (cm)	375	252	375	239	209	162	209	167
Avg movement time (s)	41	28.4	41	27	25	19.2	25	18.9
Rotorod	214	170	214	191	211	172	211	147

Example 2

[0043] Study of Thymosin β 4 in Mouse Myocardial Infarction (MI) Heart Failure Model

Objective:

[0044] The objective of the present study was to evaluate the effect of thymosin β 4 in mouse MI-induced heart failure model.

Models

[0045] The procedures used in this study are exactly same as that reported in Nature (432:466-472, 2004). Briefly, C57 black mice, 14 weeks old, were used in this study.

Mice were given thymosin β 4 (Bachem, Lot # FTHYB40501B) (150 μ g/mouse) immediately after myocardial infarction and then every three days for 4 weeks by i.p. injection. The parameters of this study included cardiac morphology and function by echocardiography (echo), invasive cardiac function measurement using Millar catheter, survival rate, and histochemical analysis.

[0046] Although treatment with thymosin β 4 did not affect mouse survival following MI, treatment with thymosin β 4 attenuated left ventricular end diastolic volume following MI. Treatment with thymosin β 4 also attenuated left ventricular end systolic volume following MI, and treatment with thymosin β 4 significantly improved ejection fraction following MI. Treatment with thymosin β 4 further showed a trend but was not significant in improvement of left ventricular systolic pressure following MI, and treatment with thymosin β 4 significantly reduced left ventricular end diastolic pressure following MI. Treatment with thymosin β 4 improved left ventricular dP/dt following MI, but treatment with thymosin β 4 did not affect left ventricular $-dP/dt$ following MI.

[0047] Importantly, treatment with thymosin β 4 attenuated cardiac hypertrophy (thickening of the heart muscle due to stress/injury) following MI.

Example 3

[0048] The effects of β 4 are studied on the development of cardiomyopathy and skeletal muscle hypertrophy in the dystrophin deficient (*mdx*) mouse. The *md* mouse is the genetic homologue to human Duchenne muscular dystrophy.

[0049] The *mdx* and control mice are treated for 6 months with β 4. The treatment, 300 micrograms of β 4 given once every three days via intraperitoneal injection at a concentration of 2 μ g/ μ l, will begin at 4 weeks of age and end at approximately 9 months of age. The mice will have an initial echocardiogram to define baseline cardiac

function. The echocardiogram will be repeated at 1 month, 3 months, 6 months, and 9 month time periods. Grip strength of the forelimbs will also be performed at these times for a simple, non-invasive measurement of skeletal muscle strength. Two mice will be sacrificed at each time period to obtain ventricular tissue for histology to follow disease progression. At the end of the treatment period, the mice will undergo a procedure known as synergistic ablation. The mice will be anesthetized and one hindlimb is cleaned and the skin is opened. The gastrocnemius and the soleus muscles are identified and then removed at their origins and insertions. This leaves the plantaris muscle to perform the duties of the three-muscle group. The physiological overload model has been shown to result in hypertrophy of the plantaris muscle in two weeks. The mice will continue to be treated with $T\beta 4$ as before during this two-week period.

[0050] At the end of the two-week treatment, the mice will be sacrificed. The heart will be removed and the left ventricle frozen in isopentane. The left ventricle will be used for histological studies to quantify the amount of fibrosis/collagen deposition in the ventricular wall. The ventricular tissue will also be used for generic profiling to better understand gene expression modification in *mdx* cardiomyopathy and the effects of $T\beta 4$. The plantaris muscle will undergo similar histology and gene profiling to understand the effects of beta-4-thymosin on dystrophic skeletal muscle.

[0051] The experiment will require four groups of 15 mice in each group. Group #1 will include normal C57BL/10ScSnJ mice given PBS injections. C57BL/10ScSnJ is the background strain for the *mdx* mice. Group #2 will include C57BL/10ScSnJ mice treated with beta-4-thymosin. Group #3 will include *mdx* mice treated with PBS and group #4 will include *mdx* mice treated with beta-4-thymosin.

[0052] This study that will incorporate non-invasive functional assessments using state-of-the-art high frequency small animal echocardiography and genetic profiling. The results are applicable to the treatment of cardiomyopathy and the like.

CLAIMS

1. A method of treatment for treating, preventing, inhibiting or reducing tissue deterioration, injury or damage due to a hypertrophic muscle disease, or for restoring tissue adversely affected by said disease, in a subject, comprising administering to a subject an effective amount of a composition comprising a peptide agent comprising amino acid sequence LKKTET or LKKTNT, a conservative variant thereof, or a stimulating agent that stimulates production of an LKKTET or LKKTNT peptide, or a conservative variant thereof, in said tissue, so as to inhibit said tissue deterioration, injury or damage due to a hypertrophic muscle disease, or restore tissue adversely affected by said disease.
2. The method of claim 1 wherein said disease is hypertrophic cardiomyopathy.
3. The method of claim 2 wherein said peptide agent is thymosin beta 4 (T β 4).
4. The method of claim 2 wherein said peptide agent is other than T β 4.
5. The method of claim 2 wherein said peptide agent is other than oxidized T β 4.
6. The method of claim 4 wherein said peptide agent comprises amino acid sequence KLKKTET, amino acid sequence LKKTETQ, and N-terminal variant of T β 4, a C-terminal variant of T β 4, or an isoform of T β 4.
7. The method of claim 2 wherein said peptide agent is administered to said subject at a dosage within a range of about 1-30 micrograms.
8. The method of claim 2 wherein said agent is administered by direct administration to said tissue, or by intravenous, intraperitoneal, intramuscular, subcutaneous, inhalation, transdermal or oral administration, to said subject.
9. The method of claim 2 wherein said composition is administered systemically.
10. The method of claim 2 wherein said composition is administered directly.
11. The method of claim 2 wherein said composition is in the form of a solution, gel, cream, paste, lotion, spray, suspension, dispersion, salve, hydrogel, ointment, foam or oil.

12. The method of claim 2 wherein said peptide agent is a recombinant or synthetic peptide.
13. A method for screening for a stimulating agent as defined in claim 1, comprising contacting a tissue exhibiting hypertrophic muscle disease, with a candidate compound; and measuring activity in said tissue of an LKKTET or LKKTNT peptide, wherein an increase of activity of said peptide in said tissue, compared to a level of activity of said peptide in a corresponding tissue lacking said candidate compound, indicates that said compound is capable of inducing said stimulating agent.
14. The method of claim 13 wherein said peptide is thymosin beta 4.