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(54) Title: METHOD OF TREATMENT OF HIV OR AIDS

(57) Abstract: The invention relates to a method of treating HIV or AIDS comprising administering a composition comprising a polypeptide comprising LKKTETQ (SEQ ID NO: 1) or a variant thereof, or administering a composition comprising a peptidomimetic of a polypeptide comprising amino acid sequence LKKTETQ (SEQ ID NO: 1) or a variant thereof.

METHOD OF TREATMENT OF HIV OR AIDS

The present invention relates to methods of treatment of HIV or AIDS.

Background

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acguired immunodeficiency syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections.

HIV infects primarily vital cells in the human immune system such as $CD4^+$ T cells), macrophages and dendritic cells. HIV infection leads to low levels of $CD4^+$ T cells through three main mechanisms: First, direct viral killing of infected cells; second, increased rates of apoptosis in infected cells; and third, killing of infected $CD4^+$ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When $CD4^+$ T cell numbers decline below a critical level, cell mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections.

Most untreated people infected with HIV-1 eventually develop AIDS. These individuals mostly die from opportunistic infections or malignancies associated with the progressive failure of the immune system. HIV progresses to AIDS at a variable rate affected by viral, host, and environmental factors; most will progress to AIDS within 10 years of HIV infection: some will have progressed much sooner, and some will take much longer. Treatment with anti-retrovirals increases the life expectancy of people infected with HIV. Even after HIV has progressed to diagnosable AIDS, the average survival time with antiretroviral therapy was

estimated to be more than 5 years as of 2005. Without antiretroviral therapy, someone who has AIDS typically dies within a year.

Current treatment for HIV infection consists of highly active antiretroviral therapy, or HAART . This has been highly beneficial to many HIV-infected individuals since its introduction in 1996, when the protease inhibitor-based HAART initially became available. Current HAART options are combinations (or "cocktails") consisting of at least three drugs belonging to at least two types, or "classes, " of antiretroviral agents. Typically, these classes are two nucleoside analogue reverse transcriptase inhibitors (NARTIs or NRTIs) plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI) .

Despite the success of HAART in controlling HIV infection and reducing HIV-associated mortality, current drug regimens are unable to completely eradicate HIV infection. Many people on HAART achieve suppression of HIV to levels below the limit of detection of standard clinical assays for many years. However, upon withdrawal of HAART, HIV viral loads rebound quickly with a concomitant decline in CD4+ T cells, which, in most cases, absent a resumption of treatment, leads to AIDS and death.

It is an aim of an embodiment of the invention to provide a treatment for HIV or AIDs.

Summary

A first aspect of the invention provides a method of treating HIV or AIDS comprising administering a composition comprising a polypeptide comprising LKKTETQ (SEQ ID NO: 1) or a variant thereof.

An alternative first aspect provides a composition comprising a polypeptide comprising LKKTETQ (SEQ ID NO: 1) or a variant thereof for treating HIV or AIDS.

An alternative first aspect provides use of a composition comprising a polypeptide comprising LKKTETQ (SEQ ID NO: 1) or a variant thereof in the manufacture of a medicament for treating HIV or AIDS.

A second aspect of the invention provides a method of treating HIV or AIDS comprising administering a composition comprising a peptidomimetic of a polypeptide comprising amino acid seguence LKKTETQ (SEQ ID NO: 1) or a variant thereof .

An alternative second aspect provides a composition comprising a peptidomimetic of a polypeptide comprising amino acid seguence LKKTETQ (SEQ ID NO: 1) or a variant thereof for treating HIV or AIDs.

An alternative second aspect provides use of a composition comprising a peptidomimetic of a polypeptide comprising amino acid seguence LKKTETQ (SEQ ID NO: 1) or a variant thereof in the manufacture of a medicament for treating HIV or AIDs.

In one embodiment of the first aspect the polypeptide is LKKTETQ (SEQ ID NO:1) or Ac-LKKTETQ-OH or comprises a fragment of thymosin beta 4 comprising LKKTETQ (SEQ ID N0:1) or consists essentially of SEQ ID NO: 3.

In one embodiment of the second aspect the peptidomimetic is based on the polypeptide LKKTETQ (SEQ ID N0:1) . In one embodiment of the second aspect the peptidomimetic is based on a thymosin beta 4 fragment thereof comprising LKKTETQ (SEQ ID N0:l)or a peptide consisting essentially of SEQ ID NO: 3.

Detailed Description

The present invention is based on the discovery that administration of the peptide of SEQ ID NO: 1, a peptide derived from thymosin beta 4 (Tβ4), to HIV positive patients and those that had progressed to showing symptoms of AIDS increased CD4 and CD8 positive white blood cell counts and decreased viral load significantly.

The peptide of SEQ ID NO: 1 has no effect on T-cell tropic or macrophage tropic HIV isolates cultured in primary cells, indicating its anti-HIV activity is caused by an alternative mechanism.

Tβ4 is a small naturally occurring 43 amino acid peptide (SEQ ID NO: 2) first isolated from the thymus in 1981 and now identified in many tissues. Tβ4 has been implicated in many biological activities, including wound healing, angiogenesis, actin binding, cell migration and cell adhesion. It is anti-microbial , anti-apoptotic and has anti-inflammatory activity.

MSDKPDMAEI EKFDKSKLKK TETQEKNPLP SKETIEQEKQ AGES (SEQ ID NO: 2)

Until the present invention, it had not been disclosed or suggested that LKKTETQ (SEQ ID NO: 1) can be used for the treatment of HIV or AIDs.

In one embodiment the polypeptide does not comprise full length human wild type Tβ4 of SEQ ID NO: 2.

The polypeptide for use in the first and second aspects may include Tβ4, and/or Tβ4 isoforms, analogues or derivatives comprising SEQ ID NO: 1 or a variant thereof.

Variants of SEQ ID NO: 1 are polypeptides in which at one or more amino acids positions there is an amino acid

insertion, deletion or substitution, either conservative or non-conservative. There may be a mutation at one, two, three or four of the positions of the polypeptide sequence LKKTETQ (SEQ ID NO: 1).

A conservative substitution is a substitution of a similarly sized or charged residue for another, for example substitution of one residue in the following groups with another in the same group would be considered conservative:

Gly, Ala

Val, lie, Leu

Asp, Glu

Asn, Gin,

Ser, Thr

Lys, Arg

Phe, Tyr

In one embodiment variants are based on the consensus sequence X_1LKX2TX3X_4X_5X6 (SEQ ID NO: 3), wherein X is any amino acid. Preferably X is a conservative substitution of the native amino acid of Tβ4 given in SEQ ID NO: 2,

In one embodiment X_1 is 1, 2, 3, 4, or 5 amino acid residues or is absent, X_2 is K, H or A, X_3 is E or N, X_4 is T or M, X_5 is Q, N, E or A and X_6 is 1, 2, 3, 4 or 5 amino acid residues or is absent.

Preferably X_1 comprises (F/L) (D/N) (S/A/T/K/N) (K/N/G)

Preferably X_6 comprises (E/T) (K/E) (N/E).

The polypeptide may comprise one of amino acid sequences :

FDKSKLKKTETQEKN (SEQ ID NO: 4)

FDKAKLKKTETQEKN (SEQ ID NO: 5)

FDRSKLKKTETNTEE (SEQ ID NO: 6)

FDKTKLKKTE TQEKN (SEQ ID NO: 7)

FDKSKLKKTNTEEKN (SEQ ID NO: 8)

FDRSKLKKTNTEEKN (SEQ ID NO: 9)

FDKTKLKKTE TAEKN (SEQ ID NO: 10)

FNRAKLKKTE TQEKN (SEQ ID NO: 11)

FNKAKLKKTEMQEKN (SEQ ID NO: 12)

FDAKKLKHTETNEKN (SEQ ID NO: 13)

FNQNNLKHTE TNEKN (SEQ ID NO: 14)

LDKAKLKATEMQEKN (SEQ ID NO: 15)

FDKAGLKKTETEEKE (SEQ ID NO: 16) .

In one embodiment the polypeptide consists essentially of the amino acid sequence provided in SEQ ID NO: 1 or in any one of SEQ ID NOs: 3-16.

In one embodiment the polypeptide has an N terminal acetyl group and a C terminal hydroxy! group, for example Ac-LKKTETQ-OH.

In another embodiment the polypeptide comprises or consists essentially of oxidized TB4, N-terminal variants of Tβ4, C-terminal variants of Tβ4, polypeptides or peptide fragments comprising or consisting essentially of the amino acid sequence LKKTETQ, LKKTETQ, LKKTNTQ, KLKKTETQ, LKKTETQQ, conservative variants thereof, or other peptide agents as described herein, having activity as described herein.

International Application Serial No. PCT/US99/17282, incorporated herein by reference, discloses LKKTET (SEQ ID NO: 17) and isoforms of Tβ4 which may be useful in accordance with the present invention as well as amino acid sequence LKKTETQ 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 Tβ4 which may be utilized in accordance with the present invention.

Although the present invention is described primarily hereinafter with respect to SEQ ID NO: 1, it is to be understood that the following description is intended to be equally applicable to amino acid sequences provided as SEQ ID NOs: 3-17 and to Tβ4 and Tβ4 isoforms.

Many Tβ4 isoforms have been identified and have about 70%, or about 75%, or about 80% or more homology to the known amino acid sequence of Tβ4. Such isoforms include, for example, $T\beta4^{ala}$, Tβ9, TβIO, Tβ11, Iβ12, Iβ13, Iβ14 and Tβ15. Thus, it is specifically contemplated that known Tβ4 isoforms, such as $T\beta4^{ala}$, Tβ9, TβIO, Tβ11, Tβ12, Tβ13, Tβ14 and Tβ15, as well as Tβ4 isoforms not yet identified, will be useful in the methods of the invention. The invention therefore further provides a composition comprising Tβ4 or fragments or variants or Tβ4 isoforms $T\beta4^{ala}$, Tβ9, Tβ10, Tβ11, Iβ12, Tβ13, Tβ14 and Tβ15 or fragments or variants for treating HIV or AIDS.

In one embodiment the composition is a pharmaceutical composition and comprises a pharamceutically acceptable carrier.

In another embodiment the composition is a veterinary composition and comprises a carrier suitable for veterinary use.

By the term "derivative thereof", we mean a peptide within which amino acids residues are replaced by residues (whether natural amino acids, non-natural amino acids or amino acid mimics) with similar side chains or peptide backbone properties.

Additionally, either one or both terminals of such peptides may be protected by N and C-terminal protecting groups, for example, groups with similar properties to acetyl or amide groups. It will be appreciated that the

amino acid sequence may be varied, truncated or modified once the final peptide is formed.

Such derivatives may increase or decrease the peptide half-life in vivo. Examples of derivatives capable of increasing the half-life of peptide and polypeptides according to the invention include peptoid derivatives of the polypeptides, D-amino acid derivatives of the polypeptides, and peptide-peptoid hybrids.

The preparation of polypeptides is a routine process. For example, the polypeptide can be synthesised, and many companies offer the commercial synthesis of peptides.

Laboratory techniques are also well known for the preparation of peptides, such methods being readily performed by a skilled person; for example, using recombinant DNA technologies as set out in Sambrook et al (2001) : Molecular cloning, a laboratory manual, 3rd edition, Cold Spring Harbor Press, Cold Spring Harbor, New York. Hence the skilled person can prepare thymosin β 4 polypeptides using the information provided herein and from common general knowledge.

The terms polypeptide and peptide herein are used interchangeably and no size restriction is intended when the term peptide is used instead of polypeptide or vice versa.

Peptides and polypeptides used according to the invention may be subject to degradation by a number of means (such as protease activity in biological systems) . Such degradation may limit the bioavailability of the polypeptides and hence the ability of the polypeptides to achieve their biological function. There are wide ranges of well established techniques by which derivatives that have enhanced stability in biological contexts can be designed and produced. Such polypeptide derivatives may have improved

bioavailability as a result of increased resistance to protease-mediated degradation.

In one embodiment, a derivative or analogue suitable for use according to the invention is more protease-resistant than the peptide from which it is derived.

The polypeptide may be made more protease-resistant by protecting the N and/or C terminal. For example, the N terminal may be protected by an acetyl group, or by an alkyl or aryl group, or an alkyl-CO- or aryl-CO- group, each of which may be optionally substituted. The C terminal may be protected by an amide group or by a substituted amide group.

Protease-resistance of a polypeptide derivative and the polypeptide from which it is derived may be evaluated by means of well-known protein degradation assays. The relative values of protease resistance for the polypeptide derivative and polypeptide may then be compared.

Peptoid derivatives of the polypeptides of the invention may be readily designed from knowledge of the structure of the polypeptide. Commercially available software may be used to develop peptoid derivatives according to well-established protocols.

A further embodiment of a modified form of peptides according to the invention comprises D-amino acid forms of the peptide. The preparation of peptides using D-amino acids rather than L-amino acids greatly decreases any unwanted breakdown of such an agent by normal metabolic processes, decreasing the amounts of agent which need to be administered, along with the frequency of its administration .

Peptides, analogues, or derivatives represent products that may advantageously be expressed by biological cells and

the invention includes use of such agents produced recombinantly.

The term "peptidomimetic" refers to a compound that mimics the conformation and desirable features of a particular peptide as a therapeutic agent, but that avoids the undesirable features. For example, morphine is a compound which can be orally administered, and which is a peptidomimetic of the peptide endorphin. There are a number of different approaches to the design and synthesis of peptidomimetics, as is well known in the art.

The peptides can also contain further amino acid sequences which are not derived from the amino acid sequence of thymosin: for example, other amino acid sequences which provide a separate function of the peptide (such as a tag, or a catalytic domain). Such peptides are also included in the aspects of the invention.

Also, it will be appreciated that the invention may be put into effect using derivatives or analogues of these preferred peptides that still lie within the scope of the claims with regard to SEQ ID NO: 1 and variants thereof.

All peptides, polypeptides, fragments, variants, derivatives or peptidomimetics of Tβ4 comprising or based on SEQ ID NO:1 or a variant thereof are hereinafter referred to as therapeutic agent(s). Such therapeutic agents are all capable of reducing CD4 positive cell levels in subjects infected with HIV or AIDS.

As can be appreciated, the medicament may be administered to a variety of different subjects. By "subject" we include any animal that is susceptible to developing HIV or AIDS or who is infected with the disease, preferably a vertebrate, more preferably a mammal such as a

domesticated or farmyard animal or a human. Most preferably the subject is a human.

The therapeutic agent may be administered orally, topically, or parenterally in medicaments containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles.

The term parenteral as used herein includes intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, subconjunctival, intracavity, transdermal and subcutaneous injection, aerosol for administration to lungs or nasal cavity or administration by infusion by, for example, osmotic pump.

Various means by which a medicament comprising a therapeutic agent can be formulated are provided below.

The therapeutic agent may be formulated into compositions having a number of different forms depending, in particular on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micelle, transdermal patch, liposome or any other suitable form that may be administered to a person or animal. It will be appreciated that the vehicle for the polypeptide should be one which is well tolerated by the subject to whom it is given, and preferably enables delivery of the therapeutic agents to the target cell, tissue, or organ.

Hence, it is preferred that that polypeptide is delivered by means of a suitably protected carrier particle, for example, a micelle.

The therapeutic agents may be used in a number of ways. For instance, systemic administration may be required in which case therapeutic agents may be contained within a

composition which may, for example, be ingested orally in the form of a tablet, capsule or liquid. It is preferred that therapeutic agents are administered by injection into the blood stream. Injections may be intravenous (bolus or infusion) or subcutaneous (bolus or infusion) .

Therapeutic agents may be combined in pharmaceutical compositions having a number of different forms depending, in particular on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micelle, transdermal patch, liposome or any other suitable form that may be administered to a person or animal. It will be appreciated that the vehicle used to provide the treatment should be one which is well tolerated by the subject to whom it is given, and preferably enables delivery of the therapeutic to the target cell, tissue, or organ.

In a preferred embodiment, the pharmaceutical vehicle is a liquid and the pharmaceutical composition is in the form of a solution. In another embodiment, the pharmaceutical vehicle is a gel and the composition is in the form of a cream or the like.

Therapeutic agents may also be incorporated within a slow or delayed release device. Such devices may, for example, be inserted on or under the skin, and the therapeutic agent may be released over weeks or even months. Such devices may be particularly advantageous when long term treatment with the therapeutic agents is required and which would normally require frequent administration (e.g. at least daily injection) .

It will be appreciated that the amount of a therapeutic agent that is required is determined by its biological

activity and bioavailability which in turn depends on the mode of administration, the physicochemical properties of the therapeutic agent employed, and whether the therapeutic agent is being used as a mono-therapy or in a combined therapy. Also, the amount will be determined by the number and state of target cells to be treated. The frequency of administration will also be influenced by the above-mentioned factors and particularly the half-life of the therapeutic agent within the subject being treated.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular therapeutic agent in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. in vivo experimentation, clinical trials, etc.), may be used to establish specific formulations of therapeutic agents and precise therapeutic regimes (such as daily doses of the therapeutic agents and the frequency of administration) .

Daily doses may be given as a single administration (e.g. a single daily injection).

Alternatively, the therapeutic agents used may require administration twice or more times during a day. As an example, an therapeutic agents may be administered as two (or more depending upon the severity of the condition) daily doses of between 1 mg and 1000 mg (i.e. assuming a body weight of 70kg) . A patient receiving treatment may take a first dose upon waking and then a second dose in the evening

(if on a two dose regime) or at 3 or 4 hourly intervals thereafter. Alternatively, a slow release device may be used to provide optimal doses to a patient without the need to administer repeated doses.

In one embodiment the medicament comprising the therapeutic agent is administered subcutaneously or is formulated for subcutaneous administration to a subject. In one embodiment the medicament is an injectable composition.

In one embodiment the medicament is formulated to provide between 1 to 1000 mg of the therapeutic agent per administration .

A fifth aspect of the invention provides a population of stem cells that secrete thymosin β4 for use as a medicament for the prevention or treatment HIV or AIDS. Until the present disclosure, it had not been disclosed or suggested that such stem cells would have this utility.

Stem cells are cells that have the potential to differentiate into a number of cell types in the body. Theoretically, stem cells may divide without limit to replenish other cells for as long as the organism is alive. Upon differentiation, the daughter cell has the potential to remain a stem cell or become another cell type, for example lung cell and display its characteristics, thus holding promise for many 5 diseases by replacing damaged tissues. These phenomena may be induced under specific physiological and experimental conditions.

In general, stem cell therapy represents a therapeutic method by which degenerative and/progressive diseases (such as those caused by premature death or malfunction of cell types that the body is unable to replace) may be treated. It is hoped that addition of stem cells may help nucleate and promote the development of functional cells and/or tissues

to replace those lost, thereby restoring normal healthy activity/ function .

For the purposes of the present invention, "stem cells" are taken to comprise nullipotent, totipotent or pluripotent cells, and progenitor cells (or precursor cells) to comprise multipotent cells. For the avoidance of doubt, the medicament and methods of the invention can comprise a therapeutically effective quantity of either stem or progenitor cells, or both stem and progenitor cells.

A suitable source of stem cells that may be used in accordance with the present invention are cells derived from the inner cell mass/epiblast of pre-implantation embryos. Such embryonic stem (ES) cells are readily obtainable and are capable of giving rise to all possible embryonic and adult cell lineages. In particular, the undifferentiated human ESC (HI line from WiCell Research Institute, Inc, Madison, WI: www.wicell.org) could be used in the invention; this cell line is commercially available.

A further source of stem cells that can be used in the present invention are umbilical cord-derived cells. A still further source of stem cells, are those isolated from adult tissues, including adipose tissues.

Where the medicament of the invention involves the use of biological cells, preferably the formulation for comprises biological cells in a suitable liquid carrier. Such a liquid carrier is preferably non-immunogenic, and may comprise a saline solution, cell culture medium, or distilled water. Formulations for injection may be as described above, or may also be provided in the form of a gel, which may preferably be capable of resolution by the body of the subject treated. Formulations suitable for implantation may take the forms described for injection or

inhalation, and may also comprise biological cells provided in a scaffold or matrix capable of providing a foundation for new tissue development.

The methods of the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's sarcoma, thromobocytopenic purpura, AIDS-related neurological conditions such as AIDS dementia complex, multiple sclerosis or tropical paraperesis, anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients,

As well as treating AIDS or HIV the invention can also be used to treat or prevent the symptoms or effects of a viral infection in an infected patient. In one embodiment the viral infection is a retroviral infection, in particular an HIV infection.

The treatment in accordance with the present invention may be supplemented with treatment with another therapeutic agent. The treatments may be administered simultaneously (i.e., concurrently) in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient (s) and pharmaceutically active agent (s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Examples of other therapeutic agents include nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavidine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, and similar agents; non-nucleotide reverse transcriptase

inhibitors (including an agent having anti- oxidation activity such as iramunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, TMC-278, TMC-125, etravirine, and similar agents; protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, raltegravir, atazanavir, tipranavir, palinavir, lasinavir, and similar agents; entry inhibitors such as enfuvirtide (T-20), T-1249, PRO-542, PRO-140, TNX-355, BMS-806, 5-Helix and similar agents; lntegrase inhibitors such as L-870, 810, raltegravir and similar agents; Budding inhibitors such as PA--344 and PA--457, and similar agents; and CXCR4 and/or CCR5 inhibitors such as vicriviroc (Sch-C), Sch-D, TAK779, maraviroc (UK 427,857), TAK449 and similar agents .

In one embodiment the method comprises administering the therapeutic agent a subject being treated with another therapeutic agent as listed above or otherwise.

In one embodiment the therapeutic agent is for administering to a subject being treated with another therapeutic agent as listed above or otherwise.

In an embodiment the therapeutic agent and other therapeutic agent act synergistically in the treatment of HIV or AIDS.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms (prophylaxis) and/or their underlying cause, and improvement or remediation of damage. Thus, for example, the present method of "treating" a disorder encompasses both prevention of the disorder in a predisposed individual and treatment of the disorder in a

clinically symptomatic individual.

"Treating" as used herein covers any treatment of, or prevention of a condition in a vertebrate, a mammal, particularly a human, and includes: inhibiting the condition, i.e., arresting its development; or relieving or ameliorating the effects of the condition, i.e., cause regression of the effects of the condition.

"Prophylaxis" or "prophylactic" or "preventative" therapy or "prevent" or "prevention" as used herein includes preventing the condition from occurring or ameliorating the subsequent progression of the condition in a subject that may be predisposed to the condition, but has not yet been diagnosed as having it.

In one embodiment the method or composition prevents or slows progression from HIV infection to AIDS. In another embodiment the method or composition lessens the symptoms of AIDS. In another embodiment the method or composition improve immune response in subjects with AIDS. In another embodiment the method or composition improve quality of life for subjects with AIDS. In another embodiment the method or composition prolong life span in subjects with AIDS.

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

It must also be noted that, as used in the subject specification, the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise .

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification .

The invention is now further described in detail by reference to the following example. The example is provided for purposes of illustration only, and is not intended to be limiting unless otherwise specified. Thus, the invention encompasses any and all variations which become evident as a result of the teaching provided herein.

Example 1:

LKKTETQ (SEQ ID NO:1) is a fragment of Thymosin B4 ($T\beta_4$).

The peptide Ac-LKKTETQ-OH was the active therapeutic agent investigated in a pilot trial on twenty similar HIV positive men and women, some who had progressed to severe AIDS .

Each man or women was injected subcutaneously with a composition comprising the peptide Ac-LKKTETQ-OH (lOmg), once a week for 12 weeks. Blood tests for CD4 and CDs-positive cells and HIV viral load (by PCR) and routine pathology were conducted at baseline, 8 weeks and 12 weeks. The results are displayed in the three Tables below. Hemoglobin levels, Creatinine, ALT, AST, Alkaline Phos, Bilirubin, GGT, Albumin, Total Protein and globulin tests did not show anything remarkable. A small drop in blood glucose was seen but this was not determined to be significant. No adverse effect has been reported so far.

Table 1. WEIGHT

Patient	Sex	Weight		
		Initial	8 weeks	12 weeks
A	M	44	55	58
B	F	67	70	70.5
C	M	74	78	78.5
D	F	75	78	78.5
E	F	88	92	92
F	M	47	52	52
G	M	52	59	72
H	M	66	71	72
1	F	78	82	82
J	F	76	79	79
K	F	67	72	71
L	F	60	60.5	71
M	F	48	50.5	51
N	M	48	58	65
0	F	71	72	72
P	F	78	79	80
Q	F	69	71.5	72
R	M	67	68.5	69
S	F	58	61	60
T	F	55	56	55

Table 2: CD4-positive and CD8-positive white blood cell counts

Patient	CD4		
	Initial	8 weeks	12 weeks
A	110	300	430
B	262	316	416
C	496	602	675
D	732	816	879
E	146	415	604
F	96	158	175
G	130	407	425
H	292	456	625
1	383	477	662
J	126	348	404
K	127	381	498
L	169	439	510
M	317	301	424
N	119	335	452
0	595	543	749
P	595	428	616
Q	269	466	602
R	249	259	368
S	200	471	469
T	196	466	571

Patient	CD8		
	Initial	8 weeks	12 weeks
A	101	980	1330
B	318	360	459
C	1059	1310	1718
D	688	1379	1394

E	321	1044	1339
F	1310	1296	1226
G	208	959	1190
H	1031	2120	2647
1	759	866	958
J	652	773	800
K	278	594	712
L	621		893
M	786	606	983
N	245	939	1034
0	613	617	880
P	612	648	890
Q	247	456	521
R	618	1108	1384
S	323	1125	1201
T	407	594	660

Table 3: HIV Viral Load

Patient	HIV Viral Load (copies/ml)		
	Initial	8 weeks	12 weeks
A	214000	200	undetectable
B	50809	98687	5151
C	120	24	undetectable
D	10130	undetectable	undetectable
E	223767	undetectable	undetectable
F	256228	28410	undetectable
G	257000	450	undetectable
H	114594	8214	undetectable
1	59509	17616	undetectable
J	38988	undetectable	undetectable
K	128685	15201	undetectable

L	53814	undetectable	undetectable
M	139786	undetectable	undetectable
N	144000	145	undetectable
0	13803	undetectable	undetectable
P	5060	undetectable	undetectable
Q	3567	undetectable	undetectable
R	52915	undetectable	undetectable
S	14921 2	12004	undetectable
T	115281	8781	undetectable

Example 2:

The peptide Ac-LKKTETQ-OH was evaluated in fresh human peripheral blood mononuclear cells (PBMCs) against CXCR4 coreceptor-trophic HT/92/599 and the CCR5 coreceptor-trophic BaL subtype B strains of HIV-1. The peptide was added to the cells at 8 hours prior to infection and immediately prior to infection. The AZT control compound was evaluated in parallel with the peptide and yielded $EC5_0$ values of 8 and 6 nM against $HIV\text{-}1_{HT/92/599}$ and values of 6 and 10 nM against $HIV\text{-}l_{BAL}$. The peptide of SEQ ID NO:1 did not demonstrate antiviral activity in the PBMC assays when evaluated at concentrations up to a high test concentration of 500 μM.

The results of the pilot trial were very encouraging. The key parameters of HIV viral load, CD4 positive and CD8 positive white cell blood counts, and weight gain have all shown extremely significant improvements from the baseline - perhaps the most significant is the HIV viral load which, in one patient, has gone from levels of 257000 to undetectable over the 12 week period of the pilot trial.

CLAIMS :

1. A method of treating HIV or AIDS comprising administering a composition comprising a polypeptide comprising LKKTETQ (SEQ ID NO: 1) or a variant thereof.

2. A method of treating HIV or AIDS comprising administering a composition comprising a peptidomimetic of a polypeptide comprising amino acid sequence LKKTETQ (SEQ ID NO: 1) or a variant thereof.

3. The method of claim 1 in which the polypeptide is LKKTETQ (SEQ ID NO:1) or Ac-LKKTETQ-OH .

4. The method of claim 1 in which composition comprises thymosin beta 4 or a fragment thereof comprising LKKTETQ (SEQ ID NO:l) or SEQ ID NO: 3.

5. The method of claim 2 in which the peptidomimetic is based on the polypeptide LKKTETQ (SEQ ID NO:l) or SEQ ID NO: 3.

6. The method of claim 2 in which the peptidomimetic is based on thymosin beta 4 or a fragment thereof comprising LKKTETQ (SEQ ID NO:1).

7. The method of claim 1 for treating AIDS, AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's sarcoma, thromobocytopenic purpura, AIDS-related neurological conditions such as AIDS dementia complex, multiple sclerosis or tropical paraperesis, anti-

HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients.

8. The method of claim 1 for treating the symptoms or effects of a viral infection in an infected patient,

9. The method of claim 8 in which the viral infection is a retroviral infection.

10. The method of claim s, in which the retroviral infection is an HIV infection.

11. The method of claim 1 in which the composition is administered to a subject being treated with another therapeutic agent .

12. The method of claim 11 in which the other therapeutic agent is a nucleotide reverse transcriptase inhibitor, a non-nucleotide reverse transcriptase inhibitors, a protease inhibitor, an entry inhibitor, an integrase inhibitor, or a budding inhibitor.

13. The method of claim 1 wherein the subject is being treated with a plurality of other therapeutic agents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU20 11/000878

A. CLASSIFICATION OF SUBJECT MATTER

Int. CI.

A61K 38/08 (2006.01) ***A61P 31/18*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPOQUE:WPI, EPODOC, MEDLINE; GenomeQuest; SEQ ID 1, SEQ ID 3 AIDS, HIV, Thymosin, Beta

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0450240 A l(SOMA,GENICHIRO & MIZUNO.DEN'ICHI) 9 October 1991 Whole document , pages 3-4 and claims	1-13
X	WO2009/033816 A2(MONDOB IOTECH LABORATORIES AG) 19 March 2009 Whole document,	1-13
A	WO2004/09 1550 A2 (REGENEREX PHAMACEUTICALS, INC) 28 October 2004	
A	WO2003/02021 5 A2 (REGENEREX PHAMACEUTICALS, INC) 13 March 2003	

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 201 1	28 July 201 1
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **JONATHAN WILKINSON** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6283 2295

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU20 11/000878

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item l.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. **(means)**

   [X] **on paper**

   [ ] **in electronic form**

   b. (time)

   [X] in the international application as filed

   [ ] together with the international application in electronic form

   [ ] subsequently to this Authority for the purposes of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU201 1/000878

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX