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- (73) Patenthaver: **Yissum Research and Development Company of the Hebrew University of Jerusalem Ltd., Hi-Tech Park, The Edmond J. Safra Campus , The Hebrew University of Jerusalem , Givat Ram , P.O. Box 39135, 9139002 Jerusalem, Israel**
- (72) Opfinder: **NAOR, David, 30 Rotschild Boulevard, 6688209 Tel-Aviv, Israel**
ESHKAR-SEBBAN, Lora, 23A Einav Street, Beit Hasmonai, 9978900 Doar-Na Shimshon, Israel
AMAR, Keren-Or, 13b HaRakafot Street, 2707050 Kiryat-Bialik, Israel
COHEN, Shmuel, 284 Teana Street, P.O. Box 131, 9983300 Nehusha, Israel
- (74) Fuldmægtig i Danmark: **Dennemeyer & Associates S.A, P.O. Box 700425, DE-81304 Munich, Tyskland**
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DESCRIPTION

FIELD AND BACKGROUND OF THE INVENTION

[0001] The present invention, in some embodiments thereof, relates to an isolated polypeptide of CD44 and, more particularly, but not exclusively, to an isolated polypeptide of CD44vRA and its use in the treatment of inflammatory disease.

[0002] CD44 is a cell surface adhesion molecule involved in multiple cellular functions, including cell-cell and cell-matrix interactions, cell migration, programmed cell death (apoptosis), or, conversely, cell survival and proliferation.

[0003] CD44 is the major cell surface receptor for hyaluronic acid (HA) but it has also been shown to bind proteins such as collagens, fibronectin, fibrinogen, laminin, mucosal vascular addressin and osteopontin. CD44 is essential for recruitment of circulating lymphocytes to the site of inflammation and marked accumulation of CD44, and sometimes hyaluronic acid, is detected in areas of intensive cell migration and cell proliferation, as in wound healing, tissue remodeling, inflammation, morphogenesis and carcinogenesis.

[0004] The genomic sequence of mouse and human CD44 includes 5 constant exons at the 5' terminus, and 5 constant exons at the 3' end. The mouse CD44 gene includes 10 variant exons in the middle of the molecule, designated V₁-V₁₀, resulting in a total of 20 exons. The human CD44 gene comprises only 9 of these 10 variant exons (V₂-V₁₀) thus comprising a total of 19 exons. Differential V₂-V₁₀ alternative splicing generates many isoforms of CD44 that express various combinations of variant exons (designated exon V_x, x = 1-10), which are inserted in the membrane proximal domain and constitute the variable region of the molecule. These molecules are designated CD44 variants (CD44v). A few dozens isoforms of CD44 are known to date.

[0005] CD44s, which does not contain any variant exon, is the most ubiquitous form and is expressed by most cell types [Ponta, H., et al. Nat Rev Mol Cell Biol. 2003 Jan;4(1):33-45]. CD44 variant proteins, in which one or more of the 10 variant exons are included, are mostly reported in association with cancer, and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [see e.g. Naor et al. Adv. Cancer Res., 71, 241-319, 1997; and Naor et al. Critical Reviews in Clinical Laboratory Sciences. 39, 527-579, 2002].

[0006] Joint inflammatory cells of patients with rheumatoid arthritis (RA) display a sequence of alternatively spliced CD44 variant designated CD44vRA. Human CD44vRA contains the same sequence as that of keratinocytes CD44v3-v10 isoform with an addition of extra alanine in the splicing junction between variant exon 4 and variant exon 5, which does not interfere with the reading frame. Mice with collagen-induced arthritis (CIA) contain at the same site a similar sequence that also includes the alanine. The CD44vRA sequence is expressed on joint

inflammatory synovial cells of RA patients and Psoriatic Arthritis (PA) patients, but neither on keratinocytes nor peripheral blood leukocytes (PBLs) of healthy donors. Furthermore, while joint inflammatory cells of RA patients express CD44vRA, PBLs from the same patients and synovial fluid cells from osteoarthritis patients hardly express this variant, demonstrating the exclusivity of this isoform. (Nedvetzki et al., J Clin Invest 111:1211-1220, 2003; Golan et al., J Autoimm 28:99-113, 2007).

[0007] It has been reported that administration of anti-CD44 antibodies, CD44 proteins, peptides or derivatives can be used for treating various autoimmune diseases (e.g. Naor et al., Adv. Cancer Res., 71, 241-319, 1997; Naor et al., Critical Reviews in Clinical Laboratory Sciences. 39, 527-579, 2002; Turley EA, and Naor D. Front Biosci. 17:1775-1794, 2012). In addition, anti-CD44vRA monoclonal antibodies and CD44vRA-derived peptides were previously suggested (Golan et al., J Autoimm 28:99-113, 2007, International Application Publication Nos: WO2010/058396, WO 2005/007700; WO 2003/014160, WO 2000/075312; US Patent Nos: US 7,534,605 and US 8,193,311; and US Patent Application Publication No: US 20060019340).

SUMMARY OF THE INVENTION

[0008] According to an aspect of some embodiments of the present invention there is provided an isolated polypeptide consisting of an amino acid of SEQ ID No. 1. Further disclosed are peptides according to SEQ ID Nos. 2 and 3.

[0009] According to an aspect of some embodiments of the present invention there is provided an isolated end-capping modified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1-3, wherein the modified polypeptide comprises an anti-inflammatory activity.

[0010] According to some embodiments of the invention, the end-capping comprises an N terminus end-capping.

[0011] According to some embodiments of the invention, the N terminus end-capping comprises an Acetyl.

[0012] According to some embodiments of the invention, the end-capping comprises a C terminus end-capping.

[0013] According to some embodiments of the invention, the C terminus end-capping comprises an Amide.

[0014] According to some embodiments of the invention, the polypeptide consists of an amino acid sequence of SEQ ID NOs: 1.

[0015] According to some embodiments of the invention, the polypeptide is as set forth in SEQ

ID NO: 1.

[0016] According to some embodiments of the invention, the end-capping modified polypeptide consisting to SEQ ID No. 4.

[0017] According to some embodiments of the invention there is provided a composition of matter comprising the isolated polypeptide and a non-proteinaceous moiety attached to the isolated polypeptide, wherein the isolated fusion polypeptide comprises an anti-inflammatory activity.

[0018] According to some embodiments of the invention there is provided an isolated fusion polypeptide comprising the isolate polypeptide having a C and/or N terminally attached amino acid sequence, wherein the C terminally amino acid sequence is a non-contiguous CD44vRA amino acid sequence with the isolated fusion polypeptide; and wherein the fusion polypeptide comprises an anti-inflammatory activity.

[0019] According to some embodiments of the invention, the attached is covalent attachment.

[0020] According to some embodiments of the invention, the anti-inflammatory activity is not dependent on vaccination or mucosal tolerance.

[0021] According to some embodiments of the invention, the isolated polypeptide or the composition of matter being capable of binding a protein selected from the group consisting of serum amyloid A, Transthyretin and apolipoprotein B.

[0022] According to some embodiments of the invention there is provided a pharmaceutical composition comprising as an active agent the isolated polypeptide or the composition of matter; and a pharmaceutically acceptable carrier or diluent.

[0023] According to some embodiments of the invention there is provided a method of treating an inflammatory disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the isolated polypeptide, the composition of matter or the pharmaceutical composition, thereby treating the inflammatory disease in the subject.

[0024] According to some embodiments of the invention there is provided a use of the isolated polypeptide, the composition of matter or the pharmaceutical composition, for the manufacture of a medicament for the treatment of an inflammatory disease.

[0025] According to some embodiments of the invention, the administering comprises oral administering.

[0026] According to some embodiments of the invention, the composition is formulated for oral administration.

[0027] According to some embodiments of the invention, the inflammatory disease involves cells expressing CD44vRA.

[0028] According to some embodiments of the invention, the inflammatory disease is selected from the group consisting of Rheumatoid arthritis, psoriatic arthritis, Alzheimer's disease, cancer and cardiovascular disease.

[0029] According to some embodiments of the invention, the inflammatory disease is Rheumatoid arthritis.

[0030] According to some embodiments of the invention, there is provided an isolated polynucleotide comprising a nucleic acid sequence encoding the isolated polypeptide.

[0031] According to some embodiments of the invention there is provided a nucleic acid construct comprising the isolated polynucleotide.

[0032] According to some embodiments of the invention there is provided a method of determining potency of a batch of the isolated polypeptide, the composition of matter or the pharmaceutical composition, the method comprising:

1. (a) contacting a batch of the isolated polypeptide, the composition of matter or the pharmaceutical composition with fibroblasts obtained from an inflammatory joint of a Rheumatoid arthritis patient; and
2. (b) determining survival of the fibroblasts following a predetermined incubation time, so as to determine the potency of the batch.

[0033] According to some embodiments of the invention, the method comprising synthesizing the isolated polypeptide, the composition of matter or the pharmaceutical composition with a modification prior to the contacting.

[0034] According to some embodiments of the invention, reduced survival of the fibroblasts following the contacting is indicative that the batch is potent.

[0035] According to some embodiments of the invention, the method comprising comparing the survival of the cells with survival of the cells following contacting with a reference standard batch of the isolated polypeptide, the composition of matter or the pharmaceutical composition, so as to determine the relative potency of the batch.

[0036] According to some embodiments of the invention, the method is effected *in-vitro* or *ex-vivo*.

[0037] Unless otherwise defined, all technical and/or scientific terms used herein have the

same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0038] Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

[0039] In the drawings:

FIG. 1 shows Liquid chromatography-mass spectrometry (LCMS) analysis demonstrating the % stability of the 5-mer RA peptide (SEQ ID NO: 1) following storage at the indicated temperatures; assuming that storage at -20 °C represents 100 % stability.

FIGs. 2A-C are graphs demonstrating that the 9-mer RA peptide (SEQ ID NO: 3) reduces joint inflammation in collagen-induced arthritis (CIA) mice on DBA/1 background. The Figures show paw swelling following injection of the 9-mer peptide at a dose of 25 µg (Figure 2A), 100 µg (Figure 2B) or 150 µg (Figure 2C) at the indicated time points (marked by arrow heads). PBS was injected as control. The y-axis represents Δ paw swelling indicating the difference (by mm) between the width of the paw at each of the measurement time points and the width of the paw at the onset of disease (time 0). The results are expressed as mean $\pm$ SE; the number of mice in each group (n) is indicated in insets of each Figure; * P < 0.05.

FIGs. 3A-C demonstrate that treatment with the 5-mer RA peptide (SEQ ID NO: 1) can restore normal histology of the inflamed joint in CIA mice on C57BL/6 background. Figures 3A and 3B are representative photomicrographs of H&E stained hind limb joint sections from mice treated with PBS control (Figure 3A) or 5-mer RA peptide (Figure 3B). Figure 3C is a graph summarizing the average inflammatory score as evaluated by histological examination of H&E stained hind limb joint sections from mice treated with PBS control (n = 7) or 5-mer RA peptide (n = 7), wherein 0 indicates no infiltration and 4 indicates massive infiltration. p < 0.0001.

FIG. 4 is a graph demonstrating that the 7- and 9-mer protected RA peptides (SEQ ID NOs: 5-6) reduce joint inflammation in CIA mice on DBA/1 background. The Figure shows paw swelling following injection of the peptides at a dose of 200 µg at the indicated time points (marked by arrows). PBS was injected as control. The y-axis represents Δ paw swelling indicating the difference (by mm) between the width of the paw at each of the measurement time points and

the width of the paw at the onset of disease (time 0). The results are expressed as mean $\pm$ SE; the number of mice in each group (n) is indicated in insets of each Figure; * $P < 0.05$, ** $p < 0.01$.

FIGs. 5A-B are graphs demonstrating that the 5-mer protected RA peptide (SEQ ID NO: 4) reduces joint inflammation in CIA mice on DBA/1 background. The Figures show paw swelling following injection of the peptide at a dose of 200 μ g at the indicated time points (marked by arrows). PBS (Figures 5A and 5B) or Dexamethasone (Dex) (Figure 5A) were injected as control. The y-axis represents Δ paw swelling indicating the difference (by mm) between the width of the paw at each of the measurement time points and the width of the paw at the onset of disease (time 0). The results are expressed as mean $\pm$ SE; the number of mice in each group (n) is indicated in insets of each Figure; * $P < 0.05$, ** $p < 0.01$.

FIG. 6 is a graph demonstrating that the 5-mer protected RA peptide (SEQ ID NO: 4) reduces joint inflammation in CIA mice on C57BL background. The Figures show paw swelling following injection of the peptide at a dose of 70 μ g for 10 consecutive days following onset of disease. PBS was injected as control. The y-axis represents Δ paw swelling indicating the difference (by mm) between the width of the paw at each of the measurement time points and the width of the paw at the onset of disease (time 0). The results are expressed as mean $\pm$ SE; * $P < 0.006$.

FIGs. 7A-C are graphs demonstrating that the 7-mer protected RA peptide, which includes the core MTADV sequence (SEQ ID NO: 5), reduces joint inflammation in CIA mice on DBA/1 background, while the non-specific core scrambled 7-mer peptide (SEQ ID NO: 7) has no effect on joint inflammation in this model. The Figures show paw swelling following injection of the peptides at a dose of 200 μ g at the indicated time points (marked by arrows). PBS was injected as control. The y-axis represents paw swelling in mm (Figures 7A and 7C) or Δ paw swelling (Figure 7B) indicating the difference between the width of the paw at each of the measurement time points and the width of the paw at the onset of disease (time 0, Figure 7B). The results are expressed as mean $\pm$ SE; the number of mice in each group (n) is indicated in insets of each Figure; * $P < 0.05$, ** $p < 0.005$.

FIG. 8 is a bar graph showing the percentages of healthy hind paws in CIA mice following injection of 7-mer protected RA peptide (SEQ ID NO: 5) or non-specific scrambled 7-mer peptide (SEQ ID NO: 7) according to the experimental method described in Table 6. PBS was injected as control.

FIGs. 9A-B are graphs demonstrating that a dose of 70 μ g per injection is the optimal dose for inhibiting joint inflammation in CIA mice on C57BL/6 background by the 5-mer protected RA peptide (SEQ ID NO: 4). The Figures show paw swelling following injection of the peptide at a dose of 70, 200 and 600 μ g (Figure 9A) or 10, 25 and 70 μ g (Figure 9B) for 10 consecutive days following onset of disease. PBS was injected as control. The y-axis represents Δ paw swelling indicating the difference between the width of the paw at each of the measurement time points and the width of the paw at the onset of disease (time 0). The results are expressed as mean $\pm$ SE; the number of mice in each group (n) is indicated in insets of each graph; * P is indicated on each graph.

FIG. 10 shows graphs demonstrating the effect of the 5-mer RA peptide (SEQ ID NO: 1) on delayed type hypersensitivity (DTH) response in C57BL/6 mice. The y-axis represents the difference in thickness between the right and the left ears on day 7. Treatment with PBS and anti-TNF α served as positive and negative control, respectively. The results are expressed as mean $\pm$ SE. The DTH protocol comprised sensitization with Oxazolone on day 0; elicitation (challenge) in the ear with Oxazolone on day 6; and measurement of ear thickness day 7. PBS or peptide were injected from day -1 to day 7.

FIG. 11 is a graph showing absence of neutralizing anti-peptide specific antibodies in the serum of mice treated with the 5-mer peptide (SEQ ID NO: 1), as determined by ELISA. ELISA plates coated with the 5-mer peptide or with collagen and mouse IgG, which served as positive controls. Sera from mice treated with the 5-mer peptide or with PBS were added to plate wells. Serum from naive mice and mice treated with PBS served as negative controls.

FIG. 12 is a schematic representation of the procedure used for identification of the 5-mer peptide target proteins.

FIG. 13 is a graph showing the pharmacokinetic elimination of the 5-mer RA peptide (SEQ ID NO: 1) in the serum of mice following a single injection of the peptide.

FIG. 14 is a graph demonstrating the *in vitro* effect of the 5-mer RA peptide (SEQ ID NO: 1) on survival of fibroblasts isolated from the inflammatory joint of an RA patient, as determined by a MTT assay.

FIG. 15 is a graph demonstrating that Serum Amyloid A (SAA) prevents the *in vitro* effect of the 5-mer RA peptide (SEQ ID NO: 1) on survival of fibroblasts isolated from the inflammatory joint of an RA patient, as determined by a MTT assay. Lactalbumin (LA) was used as a non-specific control. The 5-mer peptide was added in a constant concentration (25 μ g/ml); the x-axis indicates SAA and LA concentration.

FIG. 16 is a graph demonstrating the *in vitro* effect of the 5-mer RA peptide (SEQ ID NO: 1) on survival of fibroblasts isolated from the inflammatory joint of an RA patient in comparison to the 5-mer protected RA peptide (SEQ ID NO: 4), as determined by a MTT assay.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

[0040] The present invention, in some embodiments thereof, relates to an isolated polypeptide of CD44 and, more particularly, but not exclusively, to an isolated polypeptide of CD44vRA and its use in the treatment of inflammatory disease.

[0041] Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other

embodiments or of being practiced or carried out in various ways.

[0042] CD44 is a cell surface adhesion molecule involved in multiple cellular functions, including cell-cell and cell-matrix interactions, cell migration, programmed cell death or, conversely, cell survival and proliferation. The genomic sequence of human CD44 includes 5 constant exons at the 5' terminus and 5 constant exons at the 3' terminus, as well as 9 variant exons encompassed therebetween. Several dozens of splice variants of CD44 are known to date. CD44s (SEQ ID NO: 9), which does not contain any variant exon, is the most ubiquitous form and is expressed by most cell types. Joint inflammatory cells of patients with psoriatic arthritis (PA), rheumatoid arthritis (RA) present a sequence of alternatively spliced CD44 variant designated CD44vRA (SEQ ID NO: 11), not expressed on keratinocytes nor peripheral blood leukocytes (PBLs) of healthy donors.

[0043] Whilst reducing the present invention to practice, the present inventors have now uncovered that peptides as short as 5 mers comprising a MTADV sequence resulting from inclusion of alanine in the splicing junction between variant exon 4 and variant exon 5 of CD44vRA are capable of inhibiting joint inflammation in a CIA mouse model (the mouse analogue of human RA). Without wishing to be bound by theory it is believed that the polypeptides of some embodiments of the invention elicit their activity by competing with the natural ligand of CD44vRA.

[0044] As is illustrated hereinunder and in the examples section, which follows, the present inventors have synthesized 5-, 7- and 9- mer peptides (SEQ ID NOs: 1-3, also denoted herein as "RA peptides") and respective peptides with Acetyl and Amide protecting residues, at the amino and carboxyl terminal ends of the peptides respectively (SEQ ID NOs: 4-6, also denoted herein as "RA protected peptides"). The peptides comprise hydrophobic amino acids, no proteolytic sites and are stable at room temperature and 4 °C for at least 22 weeks (Example 1, Figure 1). The synthesized RA peptides and RA protected peptides were able to reduce joint inflammation *in-vivo* in a CIA mouse model (Examples 2-4, Figures 2A-B, 3A-C; 4, 5-A-B, 6, 8 and 9A-B). Moreover, the peptides did not elicit generation of neutralizing anti-peptide specific antibodies nor affected general immune response as evaluated by delayed hypersensitivity (DTH) response (Example 5-6, Figures 10-11). Importantly, a scrambled non-specific 7-mer protected peptide (SEQ ID NO: 7) had no effect on joint inflammation in the CIA mouse model (Example 3 Figures 7A-B and 8). Mass spectrometry analysis further revealed few potential target proteins of the RA peptides, namely Serum amyloid A, Transthyretin and Apolipoprotein B (Example 7, Figure 12). In addition the inventors have developed a novel *in-vitro* assay to test the activity of the RA peptides and RA protected peptides (Example 9, Figures 14-16).

[0045] Consequently, the present teachings suggest the use of compositions comprising the RA- and RA-protected peptides in the treatment of inflammatory diseases.

[0046] Thus, according to a first aspect of the present invention, there is provided an isolated polypeptide consisting of an amino acid sequence of SEQ ID No. 1.

[0047] According to specific embodiments the polypeptide is as set forth in SEQ ID NO: 1.

[0048] According to specific disclosure the polypeptide is as set forth in SEQ ID NO: 2.

[0049] According to specific disclosure the polypeptide is as set forth in SEQ ID NO: 3.

[0050] According to an aspect of the present invention, there is provided an isolated end-capping modified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1, wherein said modified polypeptide comprises an anti-inflammatory activity.

[0051] According to specific embodiments, the polypeptide amino acid sequence of the end-capping modified polypeptide consists of an amino acid sequence of SEQ ID No. 1.

[0052] According to another aspect of the present invention there is provided a composition of matter comprising the isolated polypeptide and a non-proteinaceous moiety attached to the isolated polypeptide, wherein the isolated fusion polypeptide comprises an anti-inflammatory activity.

[0053] According to another aspect of the present invention there is provided an isolated fusion polypeptide comprising the isolated polypeptide having a C and/or N terminally attached amino acid sequence, wherein said C terminally amino acid sequence is a non-contiguous CD44vRA amino acid sequence with said isolated fusion polypeptide; and wherein said fusion polypeptide comprises an anti-inflammatory activity.

[0054] The terms "peptide" and "polypeptide" which are interchangeably used herein encompass native peptides (either degradation products, synthetically synthesized peptides or recombinant peptides) and peptidomimetics (typically, synthetically synthesized peptides), as well as peptoids and semipeptoids which are peptide analogs, which may have, for example, modifications rendering the peptides more stable while in a body, more capable of penetrating into cells improving clearance, biodistribution and/or pharmacokinetics. Such modifications include, but are not limited to N terminus modification, C terminus modification, peptide bond modification, backbone modifications, and residue modification. Methods for preparing peptidomimetic compounds are well known in the art and are specified, for example, in Quantitative Drug Design, C.A. Ramsden Gd., Chapter 17.2, F. Choplin Pergamon Press (1992), which is incorporated by reference as if fully set forth herein. Further details in this respect are provided hereinunder.

[0055] Peptide bonds (-CO-NH-) within the peptide may be substituted, for example, by N-methylated amide bonds (-N(CH₃)-CO-), ester bonds (-C(=O)-O-), ketomethylene bonds (-CO-CH₂-), sulfinylmethylene bonds (-S(=O)-CH₂-), α-aza bonds (-NH-N(R)-CO-), wherein R is any alkyl (e.g., methyl), amine bonds (-CH₂-NH-), sulfide bonds (-CH₂-S-), ethylene bonds (-CH₂-CH₂-), hydroxyethylene bonds (-CH(OH)-CH₂-), thioamide bonds (-CS-NH-), olefinic double bonds (-CH=CH-), fluorinated olefinic double bonds (-CF=CH-), retro amide bonds (-NH-CO-),

peptide derivatives (-N(R)-CH₂-CO-), wherein R is the "normal" side chain, naturally present on the carbon atom.

[0056] These modifications can occur at any of the bonds along the peptide chain and even at several (e.g. 2-3) bonds at the same time.

[0057] Natural aromatic amino acids, Trp, Tyr and Phe, may be substituted by non-natural aromatic amino acids such as 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic), naphthylalanine, ring-methylated derivatives of Phe, halogenated derivatives of Phe or O-methyl-Tyr.

[0058] The peptides of some embodiments of the invention may also include one or more modified amino acids or one or more non-amino acid monomers (e.g. fatty acids, complex carbohydrates etc).

[0059] The term "amino acid" or "amino acids" is understood to include the 20 naturally occurring amino acids; those amino acids often modified post-translationally in vivo, including, for example, hydroxyproline, phosphoserine and phosphothreonine; and other unusual amino acids including, but not limited to, 2-aminoadipic acid, hydroxylysine, isodesmosine, nor-valine, nor-leucine and ornithine. Furthermore, the term "amino acid" includes both D- and L-amino acids (stereoisomers).

[0060] Tables 1 and 2 below list naturally occurring amino acids (Table 1), and non-conventional or modified amino acids (e.g., synthetic, Table 2) which can be used with some embodiments of the invention.

Table 1

<i>Amino Acid</i>	<i>Three-Letter Abbreviation</i>	<i>One-letter Symbol</i>
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic Acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F

Amino Acid	Three-Letter Abbreviation	One-letter Symbol
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	w
Tyrosine	Tyr	Y
Valine	Val	V
Any amino acid as above	Xaa	X

Table 2

Non-conventional amino acid	Code	Non-conventional amino acid	Code
ornithine	Orn	hydroxyproline	Hyp
α -aminobutyric acid	Abu	aminonorbonyl-carboxylate	Norb
D-alanine	Dala	aminocyclopropane-carboxylate	Cpro
D-arginine	Darg	N-(3-guanidinopropyl)glycine	Narg
D-asparagine	Dasn	N-(carbamylmethyl)glycine	Nasn
D-aspartic acid	Dasp	N-(carboxymethyl)glycine	Nasp
D-cysteine	Dcys	N-(thiomethyl)glycine	Ncys
D-glutamine	Dgln	N-(2-carbamylethyl)glycine	Ngln
D-glutamic acid	Dglu	N-(2-carboxyethyl)glycine	Nglu
D-histidine	Dhis	N-(imidazolylethyl)glycine	Nhis
D-isoleucine	Dile	N-(1-methylpropyl)glycine	Nile
D-leucine	Dleu	N-(2-methylpropyl)glycine	Nleu
D-lysine	Dlys	N-(4-aminobutyl)glycine	Nlys
D-methionine	Dmet	N-(2-methylthioethyl)glycine	Nmet
D-ornithine	Dorn	N-(3-aminopropyl)glycine	Norn
D-phenylalanine	Dphe	N-benzylglycine	Nphe
D-proline	Dpro	N-(hydroxymethyl)glycine	Nser
D-serine	Dser	N-(1-hydroxyethyl)glycine	Nthr
D-threonine	Dthr	N-(3-indolylethyl) glycine	Nhtrp
D-tryptophan	Dtrp	N-(p-hydroxyphenyl)glycine	Ntyr
D-tyrosine	Dtyr	N-(1-methylethyl)glycine	Nval
D-valine	Dval	N-methylglycine	Nmgly
D-N-methylalanine	Dnmala	L-N-methylalanine	Nmala
D-N-methylarginine	Dnmarg	L-N-methylarginine	Nmarg

<i>Non-conventional amino acid</i>	<i>Code</i>	<i>Non-conventional amino acid</i>	<i>Code</i>
D-N-methylasparagine	Dnmasn	L-N-methylasparagine	Nmasn
D-N-methylaspartate	Dnmasp	L-N-methylaspartic acid	Nmasp
D-N-methylcysteine	Dnmcys	L-N-methylcysteine	Nmcys
D-N-methylglutamine	Dnmglu	L-N-methylglutamine	Nmglu
D-N-methylglutamate	Dnmglu	L-N-methylglutamic acid	Nmglu
D-N-methylhistidine	Dnmhis	L-N-methylhistidine	Nmhis
D-N-methylisoleucine	Dnmile	L-N-methylisoleucine	Nmile
D-N-methylleucine	Dnmleu	L-N-methylleucine	Nmleu
D-N-methyllysine	Dnmlys	L-N-methyllysine	Nmlys
D-N-methylmethionine	Dnmmet	L-N-methylmethionine	Nmmet
D-N-methylornithine	Dnmorn	L-N-methylornithine	Nmorn
D-N-methylphenylalanine	Dnmphe	L-N-methylphenylalanine	Nmphe
D-N-methylproline	Dnmpro	L-N-methylproline	Nmpro
D-N-methylserine	Dnmser	L-N-methylserine	Nmser
D-N-methylthreonine	Dnmthr	L-N-methylthreonine	Nmthr
D-N-methyltryptophan	Dnmtrp	L-N-methyltryptophan	Nmtrp
D-N-methyltyrosine	Dnmtyr	L-N-methyltyrosine	Nmtyr
D-N-methylvaline	Dnmval	L-N-methylvaline	Nmval
L-norleucine	Nle	L-N-methylnorleucine	Nmnle
L-norvaline	Nva	L-N-methylnorvaline	Nmnva
L-ethylglycine	Etg	L-N-methyl-ethylglycine	Nmetg
L-t-butylglycine	Tbug	L-N-methyl-t-butylglycine	Nmtbug
L-homophenylalanine	Hphe	L-N-methyl-homophenylalanine	Nmhphe
α -naphthylalanine	Anap	N-methyl- α -naphthylalanine	Nmanap
penicillamine	Pen	N-methylpenicillamine	Nmpen
γ -aminobutyric acid	Gabu	N-methyl- γ -aminobutyrate	Nmgabu
cyclohexylalanine	Chexa	N-methyl-cyclohexylalanine	Nmchexa
cyclopentylalanine	Cpen	N-methyl-cyclopentylalanine	Nmcpen
α -amino- α -methylbutyrate	Aabu	N-methyl- α -amino- α -methylbutyrate	Nmaabu
α -aminoisobutyric acid	Aib	N-methyl- α -aminoisobutyrate	Nmaib
D- α -methylarginine	Dmarg	L- α -methylarginine	Marg
D- α -methylasparagine	Dmasn	L- α -methylasparagine	Masn
D- α -methylaspartate	Dmasp	L- α -methylaspartate	Masp

<i>Non-conventional amino acid</i>	<i>Code</i>	<i>Non-conventional amino acid</i>	<i>Code</i>
D- α -methylcysteine	Dmcys	L- α -methylcysteine	Mcys
D- α -methylglutamine	Dmgln	L- α -methylglutamine	Mgln
D- α -methyl glutamic acid	Dmglu	L- α -methylglutamate	Mglu
D- α -methylhistidine	Dmhis	L- α -methylhistidine	Mhis
D- α -methylisoleucine	Dmile	L- α -methylisoleucine	Mile
D- α -methyllleucine	Dmleu	L- α -methyllleucine	Mleu
D- α -methyllysine	Dmlys	L- α -methyllysine	Mlys
D- α -methylmethionine	Dmmet	L- α -methylmethionine	Mmet
D- α -methylornithine	Dmorn	L- α -methylornithine	Morn
D- α -methylphenylalanine	Dmphe	L- α -methylphenylalanine	Mphe
D- α -methylproline	Dmpro	L- α -methylproline	Mpro
D- α -methylserine	Dmser	L- α -methylserine	Mser
D- α -methylthreonine	Dmthr	L- α -methylthreonine	Mthr
D- α -methyltryptophan	Dmtrp	L- α -methyltryptophan	Mtrp
D- α -methyltyrosine	Dmtyr	L- α -methyltyro sine	Mtyr
D- α -methylvaline	Dmval	L- α -methylvaline	Mval
N-cyclobutylglycine	Ncbut	L- α -methylnorvaline	Mnva
N-cycloheptylglycine	Nchep	L- α -methylethylglycine	Metg
N-cyclohexylglycine	Nchex	L- α -methyl- <i>t</i> -butylglycine	Mtbug
N-cyclodecylglycine	Ncdec	L- α -methyl- homophenylalanine	Mhphe
N-cyclododecylglycine	Ncdod	α -methyl- α -naphthylalanine	Manap
N-cyclooctylglycine	Ncoct	α -methylpenicillamine	Mpen
N-cyclopropylglycine	Ncpro	α -methyl- γ -aminobutyrate	Mgab
N-cycloundecylglycine	Ncund	α -methyl-cyclohexylalanine	Mchexa
N-(2-aminoethyl)glycine	Naeg	α -methyl-cyclopentylalanine	Mcpen
N-(2,2-diphenylethyl)glycine	Nbhm	N-(N-(2,2-diphenylethyl) carbanylmethyl- glycine	Nnbhm
N-(3,3-diphenylpropyl)glycine	Nbhe	N-(N-(3,3-diphenylpropyl) carbanylmethyl- glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl ethylamino)cyclopropane	Nmbc	1,2,3,4- tetrahydroisoquinoline-3- carboxylic acid	Tic
phosphoserine	pSer	phospho threonine	pThr
phospho tyrosine	pTyr	O-methyl-tyrosine	

<i>Non-conventional amino acid</i>	<i>Code</i>	<i>Non-conventional amino acid</i>	<i>Code</i>
2-aminoadipic acid		hydroxylysine	

[0061] The amino acids of the polypeptides of the present invention may be substituted either conservatively or non-conservatively.

[0062] The term "conservative substitution" as used herein, refers to the replacement of an amino acid present in the native sequence in the peptide with a naturally or non-naturally occurring amino or a peptidomimetics having similar steric properties. Where the side-chain of the native amino acid to be replaced is either polar or hydrophobic, the conservative substitution should be with a naturally occurring amino acid, a non-naturally occurring amino acid or with a peptidomimetic moiety which is also polar or hydrophobic (in addition to having the same steric properties as the side-chain of the replaced amino acid).

[0063] As naturally occurring amino acids are typically grouped according to their properties, conservative substitutions by naturally occurring amino acids can be easily determined bearing in mind the fact that in accordance with the invention replacement of charged amino acids by sterically similar non-charged amino acids are considered as conservative substitutions.

[0064] For producing conservative substitutions by non-naturally occurring amino acids it is also possible to use amino acid analogs (synthetic amino acids) well known in the art. A peptidomimetic of the naturally occurring amino acid is well documented in the literature known to the skilled practitioner.

[0065] When affecting conservative substitutions the substituting amino acid should have the same or a similar functional group in the side chain as the original amino acid.

[0066] The phrase "non-conservative substitutions" as used herein refers to replacement of the amino acid as present in the parent sequence by another naturally or non-naturally occurring amino acid, having different electrochemical and/or steric properties. Thus, the side chain of the substituting amino acid can be significantly larger (or smaller) than the side chain of the native amino acid being substituted and/or can have functional groups with significantly different electronic properties than the amino acid being substituted. Examples of non-conservative substitutions of this type include the substitution of phenylalanine or cyclohexylmethyl glycine for alanine, isoleucine for glycine, or $\text{-NH-CH[(-CH}_2\text{)}_5\text{-COOH]-CO-}$ for aspartic acid. Those non-conservative substitutions which fall under the scope of the present invention are those which still constitute a peptide having neuroprotective properties.

[0067] The peptides of some embodiments of the invention are preferably utilized in a linear form, although it will be appreciated that in cases where cyclicization does not severely interfere with peptide characteristics, cyclic forms of the peptide can also be utilized.

[0068] Since the present peptides are preferably utilized in therapeutics which requires the peptides to be in soluble form, the peptides of some embodiments of the invention preferably include one or more non-natural or natural polar amino acids, including but not limited to serine and threonine which are capable of increasing peptide solubility due to their hydroxyl-containing side chain.

[0069] As mentioned, the N and C termini of the peptides of the present invention may be protected by functional groups. Suitable functional groups are described in Green and Wuts, "Protecting Groups in Organic Synthesis", John Wiley and Sons, Chapters 5 and 7, 1991, the teachings of which are incorporated herein by reference. Thus, the polypeptide may be modified at the N- (amine) terminus and/or the C- (carboxyl) terminus thereof so as to produce an end capping modified peptide.

[0070] As used herein, the phrases "end-capping modified polypeptide" and "protected polypeptide", which are interchangeably used herein, refer to a polypeptide which has been modified at the N- (amine) terminus and/or the C- (carboxyl) terminus thereof. The end-capping modification refers to the attachment of a chemical moiety to the terminus of the polypeptide, so as to form a cap. Such a chemical moiety is referred to herein as an end capping moiety and is typically also referred to herein and in the art, interchangeably, as a peptide protecting moiety or group. Hydroxyl protecting groups include but are not limited to esters, carbonates and carbamate protecting groups. Amine protecting groups include but are not limited to alkoxy and aryloxy carbonyl groups. Carboxylic acid protecting groups include but are not limited to aliphatic, benzylic and aryl esters.

[0071] The phrase "end-capping moiety", as used herein, refers to a moiety that when attached to the terminus of the peptide, modifies the N and/or C terminal ends(s) of the peptide. The end-capping modification typically results in masking the charge of the peptide terminus, and/or altering chemical features thereof, such as, hydrophobicity, hydrophilicity, reactivity, solubility and the like. By selecting the nature of the end capping modification, the hydrophobicity/hydrophilicity, as well as the solubility of the peptide can be finely controlled. According to specific embodiments, the protecting groups facilitate transport of the peptide attached thereto into a cell. These moieties can be cleaved *in vivo*, either by hydrolysis or enzymatically, inside the cell.

[0072] According to specific embodiments, the end-capping modification does not compromise the biological activity (i.e. anti-inflammatory activity) of the polypeptide. Examples of moieties suitable for peptide end-capping modification can be found, for example, in Green et al., "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991) and Harrison et al., "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996).

[0073] According to specific embodiments, the end-capping comprises an N terminus end-capping.

[0074] Representative examples of N-terminus end-capping moieties include, but are not

limited to, formyl, acetyl (also denoted herein as "Ac"), trifluoroacetyl, benzyl, benzyloxycarbonyl (also denoted herein as "Cbz"), tert-butoxycarbonyl (also denoted herein as "Boc"), trimethylsilyl (also denoted "TMS"), 2-trimethylsilyl-ethanesulfonyl (also denoted "SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (also denoted herein as "Fmoc"), and nitro-veratryloxycarbonyl ("NVOC").

[0075] According to specific embodiments, the N terminus end-capping comprises an Acetyl.

[0076] According to specific embodiments, the end-capping comprises a C terminus end-capping.

[0077] Representative examples of C-terminus end-capping moieties are typically moieties that lead to acylation of the carboxy group at the C-terminus and include, but are not limited to, benzyl and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers, allyl ethers, monomethoxytrityl and dimethoxytrityl. Alternatively the -COOH group of the C-terminus end-capping may be modified to an amide group.

[0078] According to specific embodiments, the C terminus end-capping comprises an Amide.

[0079] Other end-capping modifications of peptides include replacement of the amine and/or carboxyl with a different moiety, such as hydroxyl, thiol, halide, alkyl, aryl, alkoxy, aryloxy and the like.

[0080] According to specific embodiments, the peptide is modified only at the N-terminus or the C-terminus thereof.

[0081] According to other specific embodiments, the peptide is modified at both the N-terminus and the C-terminus.

[0082] According to specific embodiments, the peptide is modified at the N-terminus with an Acetyl and at the C terminus with an Amide.

[0083] According to specific embodiments the end-capping modified polypeptide is selected from the group consisting to SEQ ID NOs: 4-6.

[0084] The present invention further provides polypeptide conjugates and fusion polypeptides comprising peptides, analogs and derivatives according to the invention.

[0085] Thus, as mentioned, according to an aspect of the present invention there is provided an isolated fusion polypeptide comprising the isolated polypeptide having a C and/or N terminally attached amino acid sequence, wherein said C terminally amino acid sequence is a non-contiguous CD44vRA amino acid sequence with said isolated fusion polypeptide; and wherein said fusion polypeptide comprises an anti-inflammatory activity.

[0086] As used herein, the phrase "non-contiguous CD44vRA amino acid sequence" refers to a fusion polypeptide that does not comprise an amino acid sequence of SEQ ID No. 1 directly attached in its C terminus to an amino acid sequence of CD44vRA starting at coordinates 306, 308 or 308, respectively, of SEQ ID NO: 11.

[0087] According to specific embodiments, the isolated polypeptide and the attached amino acid sequence are covalently attached, directly or through a spacer or a linker which can be a synthetic or an amino acid linker.

[0088] As used herein the term "CD44" refers to the cell surface protein that is expressed in a large number of mammalian cell types and is encoded by the CD44 gene. According to a specific embodiment the CD44 is the human CD44 gene. The standard isoform, designated CD44, comprising exons 1-5 and 16-20 is expressed in most cell types and is set forth in GeneBank Accession Numbers NM_000610 and NP_000601 (SEQ ID NOs: 8 and 9).

[0089] As used herein the term "CD44vRA" (SEQ ID NO: 10 and 11) refers to a CD44 variant which is expressed in inflammation sites, e.g. on synovial fluid cells of RA patients but not on PBLs of healthy individuals. CD44vRA variant is a naturally occurring sequence which is presumably produced by alternative splicing of the primary transcript of the known CD44 gene which occurs in cells in inflammatory sites (e.g. in joints of RA patients) and does not arise from truncation or mutation of the known CD44 gene. This CD44vRA variant sequence comprises Exons 1-5, 15-17 and 19 of the constant part of the CD44 gene as well as Exons 7-14 (v3-v10) of the variable region of the gene. The variant coding sequence comprises three additional bases (CAG) that are transcribed from the end of the intron bridging Exon v4 to Exon v5 and are inserted at the 5' end of Exon v5. This extra CAG sequence results in the insertion of a new codon for the amino acid alanine in position 303 of SEQ ID NO: 11 while leaving the reading frame intact.

[0090] The terms "CD44" and "CD44vRA", also refer to CD44 and CD44vRA homologues which exhibit the desired activity (e.g. cell migration and/or cell-cell and cell-matrix interactions). Such homologues can be, for example, at least 80 %, at least 81 %, at least 82 %, at least 83 %, at least 84 %, at least 85 %, at least 86 %, at least 87 %, at least 88 %, at least 89 %, at least 90 %, at least 91 %, at least 92 %, at least 93 %, at least 94 %, at least 95 %, at least 96 %, at least 97 %, at least 98 %, at least 99 % or 100 % identical or homologous to the polypeptide of SEQ ID NOs: 9 and 11, or 80 %, at least 81 %, at least 82 %, at least 83 %, at least 84 %, at least 85 %, at least 86 %, at least 87 %, at least 88 %, at least 89 %, at least 90 %, at least 91 %, at least 92 %, at least 93 %, at least 94 %, at least 95 %, at least 96 %, at least 97 %, at least 98 %, at least 99 % or 100 % identical to the polynucleotide sequence encoding same.

[0091] The homolog may also refer to an ortholog, a deletion, insertion, or substitution variant, including an amino acid substitution, as long as it retains the activity.

[0092] Sequence identity or homology can be determined using any protein or nucleic acid

sequence alignment algorithm such as Blast, ClustalW, and MUSCLE.

[0093] According to other specific embodiments of the invention, the peptide is attached to a non-proteinaceous moiety.

[0094] According to specific embodiments, the isolated polypeptide and the attached non-proteinaceous moiety are covalently attached, directly or through a spacer or a linker.

[0095] The phrase "non-proteinaceous moiety" as used herein refers to a molecule not including peptide bonded amino acids that is attached to the above-described peptide. According to a specific embodiment the non-proteinaceous is a non-toxic moiety. Exemplary non-proteinaceous moieties which may be used according to the present teachings include, but are not limited to a drug, a chemical, a small molecule, a polynucleotide, a detectable moiety, polyethylene glycol (PEG), Polyvinyl pyrrolidone (PVP), poly(styrene comaleic anhydride) (SMA), and divinyl ether and maleic anhydride copolymer (DIVEMA). According to specific embodiments of the invention, the non-proteinaceous moiety comprises polyethylene glycol (PEG).

[0096] Such a molecule is highly stable (resistant to in-vivo proteolytic activity probably due to steric hindrance conferred by the non-proteinaceous moiety) and may be produced using common solid phase synthesis methods which are inexpensive and highly efficient, as further described hereinbelow. However, it will be appreciated that recombinant techniques may still be used, whereby the recombinant peptide product is subjected to in-vitro modification (e.g., PEGylation as further described hereinbelow).

[0097] Bioconjugation of the polypeptide amino acid sequence with PEG (*i.e.*, PEGylation) can be effected using PEG derivatives such as N-hydroxysuccinimide (NHS) esters of PEG carboxylic acids, monomethoxyPEG₂-NHS, succinimidyl ester of carboxymethylated PEG (SCM-PEG), benzotriazole carbonate derivatives of PEG, glycidyl ethers of PEG, PEG p-nitrophenyl carbonates (PEG-NPC, such as methoxy PEG-NPC), PEG aldehydes, PEG-orthopyridyl-disulfide, carbonyldimidazol-activated PEGs, PEG-thiol, PEG-maleimide. Such PEG derivatives are commercially available at various molecular weights [See, e.g., Catalog, Polyethylene Glycol and Derivatives, 2000 (Shearwater Polymers, Inc., Huntsville, Ala.)]. If desired, many of the above derivatives are available in a monofunctional monomethoxyPEG (mPEG) form. In general, the PEG added to the polypeptide of the present invention should range from a molecular weight (MW) of several hundred Daltons to about 100 kDa (e.g., between 3-30 kDa). Larger MW PEG may be used, but may result in some loss of yield of PEGylated polypeptides. The purity of larger PEG molecules should be also watched, as it may be difficult to obtain larger MW PEG of purity as high as that obtainable for lower MW PEG. It is preferable to use PEG of at least 85 % purity, and more preferably of at least 90 % purity, 95 % purity, or higher. PEGylation of molecules is further discussed in, e.g., Hermanson, Bioconjugate Techniques, Academic Press San Diego, Calif. (1996), at Chapter 15 and in Zalipsky et al., "Succinimidyl Carbonates of Polyethylene Glycol," in Dunn and Ottenbrite, eds., Polymeric Drugs and Drug Delivery Systems, American Chemical Society, Washington, D.C.

(1991).

[0098] Conveniently, PEG can be attached to a chosen position in the polypeptide by site-specific mutagenesis as long as the activity of the conjugate is retained. A target for PEGylation could be any Cysteine residue at the N-terminus or the C-terminus of the peptide sequence. Additionally or alternatively, other Cysteine residues can be added to the polypeptide amino acid sequence (e.g., at the N-terminus or the C-terminus) to thereby serve as a target for PEGylation. Computational analysis may be effected to select a preferred position for mutagenesis without compromising the activity.

[0099] Various conjugation chemistries of activated PEG such as PEG-maleimide, PEG-vinylsulfone (VS), PEG-acrylate (AC), PEG-orthopyridyl disulfide can be employed. Methods of preparing activated PEG molecules are known in the arts. For example, PEG-VS can be prepared under argon by reacting a dichloromethane (DCM) solution of the PEG-OH with NaH and then with di-vinylsulfone (molar ratios: OH 1: NaH 5: divinyl sulfone 50, at 0.2 gram PEG/mL DCM). PEG-AC is made under argon by reacting a DCM solution of the PEG-OH with acryloyl chloride and triethylamine (molar ratios: OH 1: acryloyl chloride 1.5: triethylamine 2, at 0.2 gram PEG/mL DCM). Such chemical groups can be attached to linearized, 2-arm, 4-arm, or 8-arm PEG molecules.

[0100] Resultant conjugated molecules (e.g., PEGylated or PVP-conjugated polypeptide) are separated, purified and qualified using e.g., high-performance liquid chromatography (HPLC) as well as biological assays.

[0101] According to specific disclosure the CD44vRA peptide portion of the polypeptides of the invention other than those listed as consisting of SEQ ID No. 1 are 5-100, 5-50, or 5-40, or 5-20, 5-15, 5-10, 5-9, 5-7 amino acids in length.

[0102] According to specific embodiments, the peptide portion of the polypeptides of the invention does not comprise a CD44vRA amino acid sequence other than those listed as consisting of SEQ ID No. 1.

[0103] The peptides and compositions of matter of the present invention may be attached (either covalently or non-covalently) to a penetrating agent.

[0104] As used herein the phrase "penetrating agent" refers to an agent which enhances translocation of any of the attached peptide or composition of matter across a cell membrane.

[0105] According to one embodiment, the penetrating agent is a peptide and is attached to the polypeptide (either directly or non-directly) via a peptide bond.

[0106] Typically, peptide penetrating agents have an amino acid composition containing either a high relative abundance of positively charged amino acids such as lysine or arginine, or have sequences that contain an alternating pattern of polar/charged amino acids and non-polar,

hydrophobic amino acids.

[0107] According to specific embodiments, the polypeptide is provided in a formulation suitable for cell penetration that enhances intracellular delivery of the polypeptide as further described hereinbelow.

[0108] By way of non-limiting example, cell penetrating peptide (CPP) sequences may be used in order to enhance intracellular penetration; however, the disclosure is not so limited, and any suitable penetrating agent may be used, as known by those of skill in the art.

[0109] Cell-Penetrating Peptides (CPPs) are short peptides (≤ 40 amino acids), with the ability to gain access to the interior of almost any cell. They are highly cationic and usually rich in arginine and lysine amino acids. They have the exceptional property of carrying into the cells a wide variety of covalently and noncovalently conjugated cargoes such as proteins, oligonucleotides, and even 200 nm liposomes. Therefore, according to additional exemplary embodiment CPPs can be used to transport the polypeptide or the composition of matter to the interior of cells.

[0110] TAT (transcription activator from HIV-1), pAntp (also named penetratin, *Drosophila antennapedia* homeodomain transcription factor) and VP22 (from Herpes Simplex virus) are examples of CPPs that can enter cells in a non-toxic and efficient manner and may be suitable for use with some embodiments of the invention. Protocols for producing CPPs-cargos conjugates and for infecting cells with such conjugates can be found, for example L Theodore et al. [The Journal of Neuroscience, (1995) 15(11): 7158-7167], Fawell S, et al. [Proc Natl Acad Sci USA, (1994) 91:664-668], and Jing Bian et al. [Circulation Research (2007) 100: 1626-1633].

[0111] The polypeptides of some embodiments of the invention may be synthesized by any techniques that are known to those skilled in the art of peptide synthesis, including solid phase and recombinant techniques.

[0112] Any of the proteinaceous polypeptides described herein can be encoded from a polynucleotide. These polynucleotides can be used as therapeutics *per se* or in the recombinant production of the agent.

[0113] Thus, according to an aspect of the present invention there is provided an isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of the present invention.

[0114] Thus, according to an aspect of the present invention there is provided a nucleic acid construct comprising the isolated polynucleotide.

[0115] Such a nucleic acid construct or system includes at least one cis-acting regulatory element for directing expression of the nucleic acid sequence. Cis-acting regulatory sequences

include those that direct constitutive expression of a nucleotide sequence as well as those that direct inducible expression of the nucleotide sequence only under certain conditions. Thus, for example, a promoter sequence for directing transcription of the polynucleotide sequence in the cell in a constitutive or inducible manner is included in the nucleic acid construct.

[0116] The isolated polypeptides and the compositions of matter of the present invention are endowed with anti-inflammatory activity.

[0117] As used herein, the phrase "anti-inflammatory activity" refers to prevention and/or reduction of acute and/or chronic inflammatory responses and/or in preventing and/or treating an inflammatory-related disease. Assays for qualifying an anti-inflammatory activity include but are not limited to those described in the Examples section which follows using both *in-vitro* and *in-vivo* models for inflammatory conditions (e.g. RA). Non-limiting examples include paw swelling *in vivo* in a CIA mouse model (see e.g. Nedvetzki, et al., (2004) PNAS 101, 18081-18086), histological examination of joint sections obtained from CIA mice and *in-vitro* cell viability of fibroblasts obtained from synovial fluid of an RA patient as further described hereinbelow.

[0118] According to specific embodiments, the anti-inflammatory activity is not dependent on vaccination or mucosal tolerance.

[0119] According to specific embodiments, the isolated polypeptide of the composition of matter does not effect immune response in general, as may be evaluated by a delayed type hypersensitivity assay (DTH) such as disclosed in Weiss et al., (2000) Proc. Natl. Acad. Sci. USA. 97, 285-290; and in Example 5 in the Examples section which follows.

[0120] According to specific embodiments, the isolated polypeptide or the composition of matter is capable of binding a protein selected from the group consisting of serum amyloid A, Transthyretin and apolipoprotein B.

[0121] As used herein, the term "serum amyloid A" or "SAA" refer to the polynucleotide and expression product e.g., polypeptide of the SAA1, SAA2 and SAA4 genes. SAA1 is also known as serum amyloid A1, MGCI 11216, PIG4, SAA, and tumor protein p53 inducible protein 4 (TP53I4). According to specific embodiments the SAA1 refers to the human SAA1, such as provided in the following GeneBank Numbers NM_199161 and NM_000331 and Uniprot Number: P0DJ18 (SEQ ID NOs: 12-14). According to specific embodiments the SAA1 refers to the mouse SAA1, such as provided in the following GeneBank Number NM 009117 (SEQ ID NO: 15). SAA2 is also known as serum amyloid A2 and SAA. According to specific embodiments the SAA2 refers to the human SAA2, such as provided in the following GeneBank Numbers NM_001127380 and NM_030754 and Uniprot number P0DJ18 (SEQ ID NOs: 16-18). According to specific embodiments the SAA2 refers to the mouse SAA2, such as provided in the following GeneBank Numbers NM_011314 (SEQ ID NO: 19). According to specific embodiments the SAA4 refers to the human SAA4, such as provided in the following GeneBank Number NM_006512 and Uniprot Number P35542 (SEQ ID NOs: 20-21).

[0122] According to specific embodiments, the term "SAA" refers to SAA1 and SAA2 genes which belong to the serum amyloid A acute phase family of proteins.

[0123] As used herein, the term "Transthyretin", refers to the polynucleotide and expression product e.g., polypeptide of the TTR gene, which is a protein carrier of the thyroid hormone thyroxine and retinol. According to specific embodiments the transthyretin refers to the human transthyretin, such as provided in the following GeneBank Numbers NP_000362 and NM_000371 (SEQ ID NOs: 22-23). According to other specific embodiments, the transthyretin refers to the mouse transthyretin, such as provided in the following GeneBank Numbers NP_038725 and NM_013697 (SEQ ID NOs: 24-25).

[0124] As used herein, the term "apolipoprotein B ", refers to the polynucleotide and expression product e.g., polypeptide of the APOB gene. According to specific embodiments the apolipoprotein B refers to the human apolipoprotein B, such as provided in the following GeneBank Numbers NP_000375 and NM_000384 (SEQ ID NOs: 26-27). According to other specific embodiments, the apolipoprotein B refers to the mouse apolipoprotein B, such as provided in the following GeneBank Numbers NP_033823 and NM_009693 (SEQ ID NOs: 28-29).

[0125] By virtue of their anti-inflammatory activity, the polypeptides and compositions of matter of the present invention may be used to treat diseases which are dependent on CD44vRA (activity or expression) for their onset or progression, such as for the treatment of inflammatory diseases, such as Rheumatoid Arthritis (RA).

[0126] Thus, according to an aspect of the present invention there is provided a method of treating an inflammatory disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the isolated polypeptide, the composition of matter or the pharmaceutical composition, thereby treating the inflammatory disease in the subject.

[0127] According to another aspect of the present invention there is provided a use of the isolated polypeptide, the composition of matter or the pharmaceutical composition for the manufacture of a medicament for the treatment of an inflammatory disease.

[0128] As used herein the term "treating" refers to inhibiting, preventing or arresting the development of a pathology (disease, disorder, or condition e.g., inflammation e.g., RA) and/or causing the reduction, remission, or regression of a pathology. Those of skill in the art will understand that various methodologies and assays can be used to assess the development of a pathology, and similarly, various methodologies and assays may be used to assess the reduction, remission or regression of a pathology.

[0129] According to specific embodiments, the term "treating" refers to ameliorating symptoms associated with a RA and related diseases, lessening the severity or curing the diseases, or

preventing the disease from occurring, preventing the manifestation of symptoms associated with the disease before they occur, slowing down the progression of the disease or deteriorating of the symptoms associated therewith, enhancing the onset of the remission period, slowing down the irreversible damage caused in the progressive chronic stage of the disease, delaying the onset of said progressive stage, improving survival rate or more rapid recovery, or a combination of two or more of the above.

[0130] As used herein the phrase "subject in need thereof" refers to a mammalian male or female subject (e.g., human being) who is diagnosed with an inflammatory disease or is at risk of to develop an inflammatory disease. Veterinary uses are also contemplated. The subject may be of any age including neonatal, infant, juvenile, adolescent, adult and elderly adult.

[0131] Methods of determining inflammation in a subject are well known in the art and include, but are not limited to, determining in a blood sample from the subject the erythrocyte sedimentation rate (ESR); plasma viscosity; levels of C-reactive protein (CRP); levels of certain inflammatory cytokines such as IL6 and TNF α ; and determination of an inflammation index such as using fibrinogen measurements and hematocrit or hemoglobin.

[0132] According to specific embodiments, the inflammatory disease involves cells expressing CD44vRA. Non-limiting examples of assays that can evaluate the expression of CD44vRA on cells include flow cytometry and immunocytochemistry.

[0133] Examples of inflammatory diseases (also referred to herein as inflammation or inflammatory condition) include, but not limited to, chronic inflammatory disease and acute inflammatory disease.

[0134] Examples for Inflammatory disease include, but not limited to inflammatory diseases associated with hypersensitivity, autoimmune diseases, infectious diseases, graft rejection diseases, allergic diseases and cancerous diseases.

Inflammatory diseases associated with hypersensitivity

[0135] Examples of hypersensitivity include, but are not limited to, Type I hypersensitivity, Type II hypersensitivity, Type III hypersensitivity, Type IV hypersensitivity, immediate hypersensitivity, antibody mediated hypersensitivity, immune complex mediated hypersensitivity, T lymphocyte mediated hypersensitivity and DTH.

[0136] Type I or immediate hypersensitivity, such as asthma.

[0137] Type II hypersensitivity include, but are not limited to, rheumatoid diseases, rheumatoid autoimmune diseases, rheumatoid arthritis (Krenn V. et al., *Histol Histopathol* 2000 Jul;15 (3):791), Psoriatic Arthritis (PA), spondylitis, ankylosing spondylitis (Jan Voswinkel et al., *Arthritis Res* 2001; 3 (3): 189), systemic diseases, systemic autoimmune diseases, systemic

lupus erythematosus (Erikson J. et al., *Immunol Res* 1998;17 (1-2):49), sclerosis, systemic sclerosis (Renaudineau Y. et al., *Clin Diagn Lab Immunol.* 1999 Mar;6 (2):156); Chan OT. et al., *Immunol Rev* 1999 Jun;169:107), glandular diseases, glandular autoimmune diseases, pancreatic autoimmune diseases, diabetes, Type I diabetes (Zimmet P. *Diabetes Res Clin Pract* 1996 Oct;34 Suppl:S125), thyroid diseases, autoimmune thyroid diseases, Graves' disease (Orgiazzi J. *Endocrinol Metab Clin North Am* 2000 Jun;29 (2):339), thyroiditis, spontaneous autoimmune thyroiditis (Braley-Mullen H. and Yu S, *J Immunol* 2000 Dec 15;165 (12):7262), Hashimoto's thyroiditis (Toyoda N. et al., *Nippon Rinsho* 1999 Aug;57 (8):1810), myxedema, idiopathic myxedema (Mitsuma T. *Nippon Rinsho.* 1999 Aug;57 (8):1759); autoimmune reproductive diseases, ovarian diseases, ovarian autoimmunity (Garza KM. et al., *J Reprod Immunol* 1998 Feb;37 (2):87), autoimmune anti-sperm infertility (Diekman AB. et al., *Am J Reprod Immunol.* 2000 Mar;43 (3):134), repeated fetal loss (Tincani A. et al., *Lupus* 1998;7 Suppl 2:S107-9), neurodegenerative diseases, neurological diseases, neurological autoimmune diseases, multiple sclerosis (Cross AH. et al., *J Neuroimmunol* 2001 Jan 1;112 (1-2):1), Alzheimer's disease (Oron L. et al., *J Neural Transm Suppl.* 1997;49:77), myasthenia gravis (Infante AJ. And Kraig E, *Int Rev Immunol* 1999; 18 (1-2):83), motor neuropathies (Kornberg AJ. *J Clin Neurosci.* 2000 May;7 (3):191), Guillain-Barre syndrome, neuropathies and autoimmune neuropathies (Kusunoki S. *Am J Med Sci.* 2000 Apr;319 (4):234), myasthenic diseases, Lambert-Eaton myasthenic syndrome (Takamori M. *Am J Med Sci.* 2000 Apr;319 (4):204), paraneoplastic neurological diseases, cerebellar atrophy, paraneoplastic cerebellar atrophy, non-paraneoplastic stiff man syndrome, cerebellar atrophies, progressive cerebellar atrophies, encephalitis, Rasmussen's encephalitis, amyotrophic lateral sclerosis, Sydeham chorea, Gilles de la Tourette syndrome, polyendocrinopathies, autoimmune polyendocrinopathies (Antoine JC. and Honnorat J. *Rev Neurol (Paris)* 2000 Jan;156 (1):23); neuropathies, dysimmune neuropathies (Nobile-Orazio E. et al., *Electroencephalogr Clin Neurophysiol Suppl* 1999;50:419); neuromyotonia, acquired neuromyotonia, arthrogryposis multiplex congenita (Vincent A. et al., *Ann N Y Acad Sci.* 1998 May 13;841:482), cardiovascular diseases, cardiovascular autoimmune diseases, atherosclerosis (Matsuura E. et al., *Lupus.* 1998;7 Suppl 2:S135), myocardial infarction (Vaarala O. *Lupus.* 1998;7 Suppl 2:S132), thrombosis (Tincani A. et al., *Lupus* 1998;7 Suppl 2:S107-9), granulomatosis, Wegener's granulomatosis, arteritis, Takayasu's arteritis and Kawasaki syndrome (Praprotnik S. et al., *Wien Klin Wochenschr* 2000 Aug 25;112 (15-16):660); anti-factor VIII autoimmune disease (Lacroix-Desmazes S. et al., *Semin Thromb Hemost.* 2000;26 (2):157); vasculitises, necrotizing small vessel vasculitises, microscopic polyangiitis, Churg and Strauss syndrome, glomerulonephritis, pauci-immune focal necrotizing glomerulonephritis, crescentic glomerulonephritis (Noel LH. *Ann Med Interne (Paris)* 2000 May;151 (3):178); antiphospholipid syndrome (Flamholz R. et al., *J Clin Apheresis* 1999;14 (4):171); heart failure, agonist-like beta-adrenoceptor antibodies in heart failure (Wallukat G. et al., *Am J Cardiol.* 1999 Jun 17;83 (12A):75H), thrombocytopenic purpura (Moccia F. *Ann Ital Med Int.* 1999 Apr-Jun;14 (2):114); hemolytic anemia, autoimmune hemolytic anemia (Efremov DG. et al., *Leuk Lymphoma* 1998 Jan;28 (3-4):285), gastrointestinal diseases, autoimmune diseases of the gastrointestinal tract, intestinal diseases, chronic inflammatory intestinal disease (Garcia Herola A. et al., *Gastroenterol Hepatol.* 2000 Jan;23 (1):16), celiac disease (Landau YE. and Shoenfeld Y. *Harefuah* 2000 Jan 16;138 (2):122), autoimmune diseases of the musculature, myositis,

autoimmune myositis, Sjogren's syndrome (Feist E. et al., *Int Arch Allergy Immunol* 2000 Sep;123 (1):92); smooth muscle autoimmune disease (Zauli D. et al., *Biomed Pharmacother* 1999 Jun;53 (5-6):234), hepatic diseases, hepatic autoimmune diseases, autoimmune hepatitis (Manns MP. *J Hepatol* 2000 Aug; 33 (2):326) and primary biliary cirrhosis (Strassburg CP. et al., *Eur J Gastroenterol Hepatol*. 1999 Jun; 11 (6):595).

[0138] Type IV or T cell mediated hypersensitivity, include, but are not limited to, rheumatoid diseases, rheumatoid arthritis (Tisch R, McDevitt HO. *Proc Natl Acad Sci U S A* 1994 Jan 18; 91 (2):437), systemic diseases, systemic autoimmune diseases, systemic lupus erythematosus (Datta SK., *Lupus* 1998; 7 (9):591), glandular diseases, glandular autoimmune diseases, pancreatic diseases, pancreatic autoimmune diseases, Type 1 diabetes (Castano L. and Eisenbarth GS. *Ann. Rev. Immunol.* 8:647); thyroid diseases, autoimmune thyroid diseases, Graves' disease (Sakata S. et al., *Mol Cell Endocrinol* 1993 Mar;92 (1):77); ovarian diseases (Garza KM. et al., *J Reprod Immunol* 1998 Feb;37 (2):87), prostatitis, autoimmune prostatitis (Alexander RB. et al., *Urology* 1997 Dec;50 (6):893), polyglandular syndrome, autoimmune polyglandular syndrome, Type I autoimmune polyglandular syndrome (Hara T. et al., *Blood*. 1991 Mar 1;77 (5):1127), neurological diseases, autoimmune neurological diseases, multiple sclerosis, neuritis, optic neuritis (Soderstrom M. et al., *J Neurol Neurosurg Psychiatry* 1994 May;57 (5):544), myasthenia gravis (Oshima M. et al., *Eur J Immunol* 1990 Dec;20 (12):2563), stiff-man syndrome (Hiemstra HS. et al., *Proc Natl Acad Sci U S A* 2001 Mar 27;98 (7):3988), cardiovascular diseases, cardiac autoimmunity in Chagas' disease (Cunha-Neto E. et al., *J Clin Invest* 1996 Oct 15;98 (8):1709), autoimmune thrombocytopenic purpura (Semple JW. et al., *Blood* 1996 May 15;87 (10):4245), anti-helper T lymphocyte autoimmunity (Caporossi AP. et al., *Viral Immunol* 1998;11 (1):9), hemolytic anemia (Sallah S. et al., *Ann Hematol* 1997 Mar;74 (3):139), hepatic diseases, hepatic autoimmune diseases, hepatitis, chronic active hepatitis (Franco A. et al., *Clin Immunol Immunopathol* 1990 Mar;54 (3):382), biliary cirrhosis, primary biliary cirrhosis (Jones DE. *Clin Sci (Colch)* 1996 Nov; 91 (5):551), nephric diseases, nephric autoimmune diseases, nephritis, interstitial nephritis (Kelly CJ. *J Am Soc Nephrol* 1990 Aug; 1 (2):140), connective tissue diseases, ear diseases, autoimmune connective tissue diseases, autoimmune ear disease (Yoo TJ. et al., *Cell Immunol* 1994 Aug; 157 (1):249), disease of the inner ear (Gloddek B. et al., *Ann N Y Acad Sci* 1997 Dec 29; 830:266), skin diseases, cutaneous diseases, dermal diseases, bullous skin diseases, pemphigus vulgaris, bullous pemphigoid and pemphigus foliaceus. Note that several same diseases are can be classified to different classes of hypersensitivity, because the heterogeneity of these diseases.

[0139] Examples of delayed type hypersensitivity include, but are not limited to, contact dermatitis and drug eruption.

[0140] Examples of types of T lymphocyte mediating hypersensitivity include, but are not limited to, helper T lymphocytes and cytotoxic T lymphocytes.

[0141] Examples of helper T lymphocyte-mediated hypersensitivity include, but are not limited to, T_H1 lymphocyte mediated hypersensitivity and T_H2 lymphocyte mediated hypersensitivity.

Autoimmune diseases

[0142] Include, but are not limited to, cardiovascular diseases, rheumatoid diseases, glandular diseases, gastrointestinal diseases, cutaneous diseases, hepatic diseases, neurological diseases, muscular diseases, nephric diseases, diseases related to reproduction, connective tissue diseases and systemic diseases.

[0143] Examples of autoimmune cardiovascular diseases include, but are not limited to atherosclerosis (Matsuura E. et al., *Lupus*. 1998;7 Suppl 2:S135), myocardial infarction (Vaarala O. *Lupus*. 1998;7 Suppl 2:S132), thrombosis (Tincani A. et al., *Lupus* 1998;7 Suppl 2:S 107-9), Wegener's granulomatosis, Takayasu's arteritis, Kawasaki syndrome (Praprotnik S. et al., *Wien Klin Wochenschr* 2000 Aug 25;112 (15-16):660), anti-factor VIII autoimmune disease (Lacroix-Desmazes S. et al., *Semin Thromb Hemost*.2000;26 (2):157), necrotizing small vessel vasculitis, microscopic polyangiitis, Churg and Strauss syndrome, pauci-immune focal necrotizing and crescentic glomerulonephritis (Noel LH. *Ann Med Interne (Paris)* 2000 May;151 (3):178), antiphospholipid syndrome (Flamholz R. et al., *J Clin Apheresis* 1999;14 (4):171), antibody-induced heart failure (Wallukat G. et al., *Am J Cardiol*. 1999 Jun 17;83 (12A):75H), thrombocytopenic purpura (Moccia F. *Ann Ital Med Int*. 1999 Apr-Jun;14 (2):114; Semple JW. et al., *Blood* 1996 May 15;87 (10):4245), autoimmune hemolytic anemia (Efremov DG. et al., *Leuk Lymphoma* 1998 Jan;28 (3-4):285; Sallah S. et al., *Ann Hematol* 1997 Mar;74 (3):139), cardiac autoimmunity in Chagas' disease (Cunha-Neto E. et al., *J Clin Invest* 1996 Oct 15;98 (8):1709) and anti-helper T lymphocyte autoimmunity (Caporossi AP. et al., *Viral Immunol* 1998;11 (1):9).

[0144] Examples of autoimmune rheumatoid diseases include, but are not limited to rheumatoid arthritis (Krenn V. et al., *Histol Histopathol* 2000 Jul;15 (3):791; Tisch R, McDevitt HO. *Proc Natl Acad Sci units S A* 1994 Jan 18;91 (2):437) and ankylosing spondylitis (Jan Voswinkel et al., *Arthritis Res* 2001; 3 (3): 189).

[0145] Examples of autoimmune glandular diseases include, but are not limited to, pancreatic disease, Type I diabetes, thyroid disease, Graves' disease, thyroiditis, spontaneous autoimmune thyroiditis, Hashimoto's thyroiditis, idiopathic myxedema, ovarian autoimmunity, autoimmune anti-sperm infertility, autoimmune prostatitis and Type I autoimmune polyglandular syndrome. Diseases include, but are not limited to autoimmune diseases of the pancreas, Type 1 diabetes (Castano L. and Eisenbarth GS. *Ann. Rev. Immunol*. 8:647; Zimmet P. *Diabetes Res Clin Pract* 1996 Oct;34 Suppl:S125), autoimmune thyroid diseases, Graves' disease (Orgiazzi J. *Endocrinol Metab Clin North Am* 2000 Jun;29 (2):339; Sakata S. et al., *Mol Cell Endocrinol* 1993 Mar;92 (1):77), spontaneous autoimmune thyroiditis (Braley-Mullen H. and Yu S, *J Immunol* 2000 Dec 15;165 (12):7262), Hashimoto's thyroiditis (Toyoda N. et al., *Nippon Rinsho* 1999 Aug;57 (8):1810), idiopathic myxedema (Mitsuma T. *Nippon Rinsho*. 1999 Aug;57 (8):1759), ovarian autoimmunity (Garza KM. et al., *J Reprod Immunol* 1998 Feb;37 (2):87), autoimmune anti-sperm infertility (Diekman AB. et al., *Am J Reprod Immunol*. 2000

Mar;43 (3):134), autoimmune prostatitis (Alexander RB. et al., Urology 1997 Dec;50 (6):893) and Type I autoimmune polyglandular syndrome (Hara T. et al., Blood. 1991 Mar 1;77 (5):1127).

[0146] Examples of autoimmune gastrointestinal diseases include, but are not limited to, chronic inflammatory intestinal diseases (Garcia Herola A. et al., Gastroenterol Hepatol. 2000 Jan; 23 (1):16), celiac disease (Landau YE. and Shoenfeld Y. Harefuah 2000 Jan 16; 138 (2):122), colitis, ileitis and Crohn's disease.

[0147] Examples of autoimmune cutaneous diseases include, but are not limited to, autoimmune bullous skin diseases, such as, but are not limited to, pemphigus vulgaris, bullous pemphigoid and pemphigus foliaceus.

[0148] Examples of autoimmune hepatic diseases include, but are not limited to, hepatitis, autoimmune chronic active hepatitis (Franco A. et al., Clin Immunol Immunopathol 1990 Mar; 54 (3):382), primary biliary cirrhosis (Jones DE. Clin Sci (Colch) 1996 Nov; 91 (5):551; Strassburg CP. et al., Eur J Gastroenterol Hepatol. 1999 Jun; 11 (6):595) and autoimmune hepatitis (Manns MP. J Hepatol 2000 Aug; 33 (2):326).

[0149] Examples of autoimmune neurological diseases include, but are not limited to, multiple sclerosis (Cross AH. et al., J Neuroimmunol 2001 Jan 1;112 (1-2):1), Alzheimer's disease (Oron L. et al., J Neural Transm Suppl. 1997;49:77), myasthenia gravis (Infante AJ. And Kraig E, Int Rev Immunol (1999) 18(1-2):83; Oshima M. et al., Eur J Immunol (1990) 20(12):2563), neuropathies, motor neuropathies (Kornberg AJ. J Clin Neurosci. (2000) 7(3):191); Guillain-Barre syndrome and autoimmune neuropathies (Kusunoki S. Am J Med Sci. (2000) 319(4):234), myasthenia, Lambert-Eaton myasthenic syndrome (Takamori M. Am J Med Sci. (2000) 319(4):204); paraneoplastic neurological diseases, cerebellar atrophy, paraneoplastic cerebellar atrophy and stiff-man syndrome (Hiemstra HS. et al., Proc Natl Acad Sci units S A (2001) 98(7):3988); non-paraneoplastic stiff man syndrome, progressive cerebellar atrophies, encephalitis, Rasmussen's encephalitis, amyotrophic lateral sclerosis, Sydeham chorea, Gilles de la Tourette syndrome and autoimmune polyendocrinopathies (Antoine JC. and Honnorat J. Rev Neurol (Paris) 2000 Jan;156 (1):23); dysimmune neuropathies (Nobile-Orazio E. et al., Electroencephalogr Clin Neurophysiol Suppl 1999;50:419); acquired neuromyotonia, arthrogryposis multiplex congenita (Vincent A. et al., Ann N Y Acad Sci. 1998 May 13;841:482), neuritis, optic neuritis (Soderstrom M. et al., J Neurol Neurosurg Psychiatry 1994 May;57 (5):544) and neurodegenerative diseases.

[0150] Examples of autoimmune muscular diseases include, but are not limited to, myositis, autoimmune myositis and primary Sjogren's syndrome (Feist E. et al., Int Arch Allergy Immunol 2000 Sep;123 (1):92) and smooth muscle autoimmune disease (Zauli D. et al., Biomed Pharmacother 1999 Jun;53 (5-6):234).

[0151] Examples of autoimmune nephric diseases include, but are not limited to, nephritis and autoimmune interstitial nephritis (Kelly CJ. J Am Soc Nephrol 1990 Aug; 1 (2):140).

[0152] Examples of autoimmune diseases related to reproduction include, but are not limited to, repeated fetal loss (Tincani A. et al., Lupus 1998; 7 Suppl 2:S107-9).

[0153] Examples of autoimmune connective tissue diseases include, but are not limited to, ear diseases, autoimmune ear diseases (Yoo T.J. et al., Cell Immunol 1994 Aug; 157 (1):249) and autoimmune diseases of the inner ear (Gloddek B. et al., Ann N Y Acad Sci 1997 Dec 29; 830:266).

[0154] Examples of autoimmune systemic diseases include, but are not limited to, systemic lupus erythematosus (Erikson J. et al., Immunol Res 1998;17 (1-2):49) and systemic sclerosis (Renaudineau Y. et al., Clin Diagn Lab Immunol. 1999 Mar;6 (2):156); Chan OT. et al., Immunol Rev 1999 Jun; 169:107).

Infectious diseases

[0155] Examples of infectious diseases include, but are not limited to, chronic infectious diseases, subacute infectious diseases, acute infectious diseases, viral diseases, bacterial diseases, protozoan diseases, parasitic diseases, fungal diseases, mycoplasma diseases and prion diseases.

Graft rejection diseases

[0156] Examples of diseases associated with transplantation of a graft include, but are not limited to, graft rejection, chronic graft rejection, subacute graft rejection, hyper-acute graft rejection, acute graft rejection and graft versus host disease.

Allergic diseases

[0157] Examples of allergic diseases include, but are not limited to, asthma, hives, urticaria, pollen allergy, dust mite allergy, venom allergy, cosmetics allergy, latex allergy, chemical allergy, drug allergy, insect bite allergy, animal dander allergy, stinging plant allergy, poison ivy allergy and food allergy.

Cancerous diseases

[0158] Examples of cancer include but are not limited to carcinoma, lymphoma, blastoma, sarcoma, and leukemia. Particular examples of cancerous diseases but are not limited to: Myeloid leukemia such as Chronic myelogenous leukemia. Acute myelogenous leukemia with

maturation, Acute promyelocytic leukemia, Acute nonlymphocytic leukemia with increased basophils, Acute monocytic leukemia. Acute myelomonocytic leukemia with eosinophilia; Malignant lymphoma, such as Burkitt's Non-Hodgkin's; Lymphocytic leukemia, such as Acute lymphoblastic leukemia. Chronic lymphocytic leukemia; Myeloproliferative diseases, such as Solid tumors Benign Meningioma, Mixed tumors of salivary gland, Colonic adenomas; Adenocarcinomas, such as Small cell lung cancer, Kidney, Uterus, Prostate, Bladder, Ovary, Colon, Sarcomas, Liposarcoma, myxoid, Synovial sarcoma, Rhabdomyosarcoma (alveolar), Extraskelatal myxoid chondrosarcoma, Ewing's tumor; other include Testicular and ovarian dysgerminoma, Retinoblastoma, Wilms' tumor, Neuroblastoma, Malignant melanoma, Mesothelioma, breast, skin, prostate, and ovarian.

[0159] According to specific embodiments the inflammatory disease is selected from the group consisting of Rheumatoid arthritis (RA), psoriatic arthritis, Alzheimer's disease, cancer and cardiovascular disease.

[0160] According to other specific embodiments the inflammatory disease comprises RA.

[0161] As used herein, the phrase "rheumatoid arthritis (RA)" refers to an autoimmune disease which primarily affects the joints. RA includes, but is limited to, adult RA, juvenile idiopathic arthritis, juvenile RA and juvenile chronic arthritis. RA can be diagnosed according to the American Rheumatoid Association criteria for the classification of rheumatoid arthritis, or any similar criteria and includes active, early (active RA diagnosed for at least 8 weeks but no longer than four years) and incipient (polyarthritis that does not fully meet the criteria for a diagnosis of RA, in association with the presence of RA-specific prognostic biomarkers such as anti-CCP and shared epitope) RA.

[0162] Example of RA clinical parameters symptoms that can be monitored to indicate improvement during treatment with the isolated polypeptides and composition of matter of the invention are:

- Morning stiffness for at least one hour and present for at least six weeks;
- Swelling of three or more joints for at least six weeks;
- Swelling of wrist, metacarpophalangeal, or proximal interphalangeal joints for at least six weeks
- Symmetric joint swelling;
- Hand x-ray changes that include erosions or unequivocal bony decalcification;
- Rheumatoid subcutaneous nodules; and
- Rheumatoid factors

[0163] Additional parameters that can be used in human for assessing RA improvement can be according to the American College of Rheumatology (ACR) and include e.g. ACR improvement criteria -ACR20, ACR50 and ACR70 representing the percentage of disease activity improvement (20, 50 or 70 %) by the reduction in certain RA symptoms. Thus, for

example, ACR20 refers to patients which achieve a 20 % improvement in tender and swollen joint counts and 20 % improvement in three of the five remaining ACR core set measures.

[0164] As the present inventors discovered 3 potential target proteins of the isolated polypeptides and have also shown that addition of one of these proteins (i.e. SAA) can prevent the *in-vitro* activity of the polypeptide (see Examples 7 and 9 and Figure 15 in the Examples section which follows) the present invention contemplates the use of a combined treatment comprising the isolated polypeptides or the compositions of matter of the present invention and serum amyloid A (SAA), thranthyretin and/or apolipoproteins B inhibitors.

[0165] Thus, according to another aspect of the present invention there is provided a method of treating an inflammatory disease in a subject in need thereof, the method comprising:

1. (a) administering to the subject a therapeutically effective amount of the isolated polypeptide or the composition of matter of some embodiments of the present invention; and
2. (b) administering to said subject a therapeutically effective amount of an inhibitor of a protein selected from the group consisting of serum amyloid A (SAA), thranthyretin and apolipoproteins B,

thereby treating the inflammatory disease in the subject.

[0166] According to another aspect there is provided a use of the isolated polypeptide or the composition of matter of some embodiments of the present invention and an inhibitor of a protein selected from the group consisting of serum amyloid A (SAA), thranthyretin and apolipoprotein B for the manufacture of a medicament for the treatment of an inflammatory disease.

[0167] According to another aspect of the present invention there is provided an article of manufacture or a kit identified for use in treating inflammatory disease, comprising a packaging material packaging the isolated polypeptides or the composition of matter of some embodiments of the present invention and an inhibitor for a protein selected from the group consisting of SAA, thranthyretin and apolipoproteins B.

[0168] According to another aspect of the present invention there is provided a method of treating an inflammatory disease in a subject in need thereof, the method comprising:

1. (a) administering to the subject a therapeutically effective amount of an isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID No. 1, wherein said polypeptide comprises an anti-inflammatory activity; and
2. (b) administering to said subject a therapeutically effective amount of an inhibitor of a protein selected from the group consisting of serum amyloid A (SAA), thranthyretin and apolipoproteins B,
thereby treating the inflammatory disease in the subject.

[0169] According to another aspect there is provided a use of as isolated polypeptide comprising an amino acid sequence consisting of SEQ ID No. 1, wherein said polypeptide comprises an anti-inflammatory activity; and an inhibitor of a protein selected from the group consisting of serum amyloid A (SAA), thranthyretin and apolipoprotein B for the manufacture of a medicament for the treatment of an inflammatory disease.

[0170] According another aspect of the present invention there is provided an article of manufacture or a kit identified for use in treating inflammatory disease, comprising a packaging material packaging the isolated polypeptide comprising an amino acid sequence consisting of SEQ ID No.1, wherein said polypeptide comprises an anti-inflammatory activity; and an inhibitor for a protein selected from the group consisting of SAA, thranthyretin and apolipoproteins B.

[0171] As used herein the term "inhibitor" refers to an agent which downregulates expression and/or activity of a protein (e.g. SAA, thranthyretin and apolipoprotein B) at the genomic (e.g. homologous recombination and site specific endonucleases) and/or the transcript level using a variety of molecules which interfere with transcription and/or translation (e.g., RNA silencing agents e.g. siRNA, shRNA, micro-RNA) or on the protein level (e.g., aptamers, small molecules and inhibitory peptides, antagonists, enzymes that cleave the polypeptide, antibodies and the like).

[0172] Non-limiting example include an antibody which inhibits SAA such as Antiserum albumin A, an RNA interference targeted to SAA mRNA (see e.g. International Publication Application No: WO 2006071691), an antisense oligonucleotides targeted to apolipoprotein B, such as but not limited to Mipomersen (ISIS-301012, KYNAMRO™), Triazolones as apolipoprotein B synthesis inhibitors (see e.g. US Patent No. US 6197972) and an apolipoprotein B secretion inhibitor (see e.g. EP Application Publication No. EP 1099438).

[0173] According to a specific embodiment, step (a) is effected prior to step (b).

[0174] According to another specific embodiment, step (a) is effected following step (b).

[0175] According to yet another specific embodiment, step (a) is effected concomitantly with step (b).

[0176] Multiple rounds of administration according to the methods of the present invention and multiple doses of the isolated polypeptide or the composition of matter and the inhibitor can be administered. According to specific embodiments step (a) is effected multiple times. Thus, according to specific embodiments, administration of inhibitor is effected following at least one administration of the isolated polypeptide or the composition of matter. According to specific embodiments step (B) is effected multiple times. Thus, according to specific embodiments, administering the isolated polypeptide or the composition of matter of the present invention is effected following at least one administration of the inhibitor. According to specific

embodiments, administering the isolated polypeptide or the composition of matter of the present invention is effected in a sequential order with administration of the inhibitor.

[0177] The isolated polypeptide or the composition of matter and the inhibitor may be packaged in the same container or in separate containers; each possibility represents a separate embodiment of the present invention.

[0178] According to specific embodiments, the isolated polypeptide or the composition of matter and the inhibitor are in separate formulations.

[0179] According to other specific embodiments, the isolated polypeptide or the composition of matter and the inhibitor are in a co-formulation.

[0180] The isolated polypeptides, the compositions of matter and the inhibitors of the present invention can be provided to the subject *per se*, or as part of a pharmaceutical composition where it is mixed with a pharmaceutically acceptable carrier.

[0181] Thus, according to an aspect of the present invention there is provided a pharmaceutical composition comprising as an active agent the isolated polypeptide or the composition of matter; and a pharmaceutically acceptable carrier or diluent.

[0182] As used herein a "pharmaceutical composition" refers to a preparation of one or more of the active ingredients described herein with other chemical components such as physiologically suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0183] Herein the term "active ingredient" refers to the polypeptide or composition of matter comprising the polypeptide accountable for the biological effect.

[0184] Hereinafter, the phrases "physiologically acceptable carrier" and "pharmaceutically acceptable carrier" which may be interchangeably used refer to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound. An adjuvant is included under these phrases.

[0185] Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[0186] Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference.

[0187] Suitable routes of administration may, for example, include oral, topical, intradermal,

rectal, transmucosal, especially transnasal, intestinal or parenteral delivery, including intramuscular, subcutaneous and intramedullary injections as well as intrathecal, direct intraventricular, intracardiac, e.g., into the right or left ventricular cavity, into the common coronary artery, intravenous, intraperitoneal, intranasal, or intraocular injections.

[0188] According to specific embodiments the route of administration is oral administration.

[0189] According to other specific embodiments, the route of administration is into the skin. Methods of administering an active agent into a skin are known in the art and include, for example, intradermal injections, gels, liquid sprays and patches which comprise the active agent and which are applied on the outer surface of the skin.

[0190] According to some embodiments of the invention, administration of the active agent into the skin of the subject is performed topically (on the skin).

[0191] According to some embodiments of the invention, administration of the active agent into the skin of the subject is performed non-invasively, e.g., using a gel, a liquid spray or a patch (e.g. reservoir type patch and matrix type patch) comprising the active ingredient, which are applied onto the skin of the subject.

[0192] It should be noted that in order to increase delivery of the active agent into the skin, the active agent can be formulated with various vehicles designed to increase delivery to the epidermis or the dermis layers. Such vehicles include, but are not limited to liposomes, dendrimers, noisome, transfersome, microemulsion and solid lipid nanoparticles.

[0193] According to some embodiments of the invention, administering the is performed by an intradermal injection.

[0194] Conventional approaches for drug delivery to the central nervous system (CNS) include: neurosurgical strategies (e.g., intracerebral injection or intracerebroventricular infusion); molecular manipulation of the agent (e.g., production of a chimeric fusion protein that comprises a transport peptide that has an affinity for an endothelial cell surface molecule in combination with an agent that is itself incapable of crossing the BBB) in an attempt to exploit one of the endogenous transport pathways of the BBB; pharmacological strategies designed to increase the lipid solubility of an agent (e.g., conjugation of water-soluble agents to lipid or cholesterol carriers); and the transitory disruption of the integrity of the BBB by hyperosmotic disruption (resulting from the infusion of a mannitol solution into the carotid artery or the use of a biologically active agent such as an angiotensin peptide). However, each of these strategies has limitations, such as the inherent risks associated with an invasive surgical procedure, a size limitation imposed by a limitation inherent in the endogenous transport systems, potentially undesirable biological side effects associated with the systemic administration of a chimeric molecule comprised of a carrier motif that could be active outside of the CNS, and the possible risk of brain damage within regions of the brain where the BBB is disrupted, which renders it a suboptimal delivery method.

[0195] Alternately, one may administer the pharmaceutical composition in a local rather than systemic manner, for example, via injection of the pharmaceutical composition directly into a tissue region of a patient such as a local injection into the joint. Methods of administering an active agent into the joint are known in the art and include intra-articular injection wherein a hypodermic needle is inserted into the joint to thereby deliver the active agent to the intra-articular space of the intra-articular joint.

[0196] As described the polypeptides and compositions of matter of the invention may be used to treat e.g. Alzheimer's disease. Conventional approaches for drug delivery to the central nervous system (CNS) include: neurosurgical strategies (e.g., intrahippocampal (IH), intracranial (IC), intracerebral injection, intracerebroventricular injection (ICV) or infusion or intrathecal administration); molecular manipulation of the agent (e.g., production of a chimeric fusion protein that comprises a transport peptide that has an affinity for an endothelial cell surface molecule in combination with an agent that is itself incapable of crossing the BBB) in an attempt to exploit one of the endogenous transport pathways of the BBB; pharmacological strategies designed to increase the lipid solubility of an agent (e.g., conjugation of water-soluble agents to lipid or cholesterol carriers); and the transitory disruption of the integrity of the BBB by hyperosmotic disruption (resulting from the infusion of a mannitol solution into the carotid artery or the use of a biologically active agent such as an angiotensin peptide). However, each of these strategies has limitations, such as the inherent risks associated with an invasive surgical procedure, a size limitation imposed by a limitation inherent in the endogenous transport systems, potentially undesirable biological side effects associated with the systemic administration of a chimeric molecule comprised of a carrier motif that could be active outside of the CNS, and the possible risk of brain damage within regions of the brain where the BBB is disrupted, which renders it a suboptimal delivery method.

[0197] Pharmaceutical compositions of some embodiments of the invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

[0198] Pharmaceutical compositions for use in accordance with some embodiments of the invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active ingredients into preparations which, can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0199] For injection, the active ingredients of the pharmaceutical composition may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological salt buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0200] For oral administration, the pharmaceutical composition can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the pharmaceutical composition to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carbomethylcellulose; and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0201] According to specific embodiments, the pharmaceutical composition is formulated for oral administration.

[0202] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0203] Pharmaceutical compositions which can be used orally, include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active ingredients may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

[0204] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0205] For administration by nasal inhalation, the active ingredients for use according to some embodiments of the invention are conveniently delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane or carbon dioxide. 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 of, e.g., gelatin for use in a dispenser may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0206] The pharmaceutical composition described herein may be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers with optionally, an added preservative. The compositions may be suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0207] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active preparation in water-soluble form. Additionally, suspensions of the active ingredients may be prepared as appropriate oily or water based injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acids esters such as ethyl oleate, triglycerides or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the active ingredients to allow for the preparation of highly concentrated solutions.

[0208] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water based solution, before use.

[0209] The pharmaceutical composition of some embodiments of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

[0210] The pharmaceutical composition of some embodiments of the invention may also be formulated for sustained-release to provide elevated serum half-life. Such sustained release systems are well known to those of skill in the art and include e.g. microcapsules and nanoparticles. According to specific embodiments, the ProLease biodegradable microsphere delivery system for proteins and peptides (Tracy, 1998, Biotechnol. Prog. 14, 108; Johnson et al., 1996, Nature Med. 2, 795; Herbert et al., 1998, Pharmaceut. Res. 15, 357) a dry powder composed of biodegradable polymeric microspheres containing the protein in a polymer matrix that can be compounded as a dry formulation with or without other agents.

[0211] Pharmaceutical compositions suitable for use in context of some embodiments of the invention include compositions wherein the active ingredients are contained in an amount effective to achieve the intended purpose. More specifically, a therapeutically effective amount means an amount of active ingredients effective to prevent, alleviate or ameliorate symptoms of a disorder (e.g., RA) or prolong the survival of the subject being treated.

[0212] Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0213] For any preparation used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from in vitro and cell culture assays. For example, a

dose can be formulated in animal models to achieve a desired concentration or titer. Such information can be used to more accurately determine useful doses in humans.

[0214] Toxicity and therapeutic efficacy of the active ingredients described herein can be determined by standard pharmaceutical procedures in vitro, in cell cultures or experimental animals. The data obtained from these in vitro and cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

[0215] Dosage amount and interval may be adjusted individually to provide that the levels of the active ingredient are sufficient to induce or suppress the biological effect (minimal effective concentration, MEC). The MEC will vary for each preparation, but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. Detection assays can be used to determine plasma concentrations.

[0216] The doses shown herein with respect to the mouse animal model can be converted for the treatment other species such as human and other animals diagnosed with the inflammatory disease. Conversion Table approved by the FDA is shown in Reagan-Shaw S., et al., FASEB J. 22:659-661 (2007).

[0217] The human equivalent dose is calculated as follows: $HED\ (mg/kg) = \text{Animal dose}\ (mg/kg) \times (\text{Animal } K_m / \text{human } K_m)$.

[0218] According to some embodiments of the invention, the isolated polypeptide or the composition of matter is provided at an amount equivalent to a range of from about 2.5 - 40 mg/kg/day in mice, including any intermediate subranges and values therebetween.

[0219] According to specific embodiments the isolated polypeptide or the composition of matter is provided at an amount equivalent to about 3.5 mg/kg/day in mice.

[0220] Depending on the severity and responsiveness of the condition to be treated, dosing can be of a single or a plurality of administrations, with course of treatment lasting from several days to several weeks or until cure is effected or diminution of the disease state is achieved.

[0221] The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

[0222] Compositions of some embodiments of the invention may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or

plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accommodated by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a preparation of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition, as is further detailed above.

[0223] It will be appreciated that the therapeutic agents of the present invention can be provided to the individual with additional active agents to achieve an improved therapeutic effect as compared to treatment with each agent by itself. In such therapy, measures (e.g., dosing and selection of the complementary agent) are taken to adverse side effects which may be associated with combination therapies.

[0224] Administration of such combination therapy can be simultaneous, such as in a single capsule having a fixed ratio of these active agents, or in multiple capsules for each agent.

[0225] Thus, the agents of the present invention can be administered alone with other established or experimental therapeutic regimen to treat inflammatory disease such as nonsteroidal anti-inflammatory drugs (NSAID), disease-modifying antirheumatic drugs (DMARDS), corticosteroids, analgesics, Fibromyalgia medications, chemotherapeutic agents and other treatment regimens which are well known in the art.

[0226] As mentioned, the present inventors have developed a novel in-vitro assay to test the activity of the peptides and compositions of matter of the present invention. The assay is based on the realization that the RA peptides can reduce survival of fibroblasts isolated from the synovial fluid of an RA patient. Thus, this assay can be used to compare batch to batch variation of manufactured peptides and compositions of matter peptides of the present invention for qualifying the anti-inflammatory activity as well as for testing e.g. stability of the peptides and compositions of matter of the present invention following exposure to environmental conditions such as storage temperature, modifications to the peptides and the formulations.

[0227] Thus, according to an aspect of the present invention there is provided a method of determining potency of a batch of the isolated polypeptide, the composition of matter or the pharmaceutical composition of some embodiments of the present invention, the method comprising:

1. (a) contacting a batch of the isolated polypeptide, the composition of matter or the pharmaceutical composition with fibroblasts obtained from an inflammatory joint of a Rheumatoid arthritis patient; and

2. (b) determining survival of said fibroblasts following a predetermined incubation time, so as to determine the potency of the batch.

[0228] According to specific embodiments, the method comprising synthesizing the isolated polypeptide, the composition of matter or the pharmaceutical composition with a modification. Such a modification can be any of the modifications presented hereinabove.

[0229] According to specific embodiments, the method is effected *in-vitro* or *ex-vivo*.

[0230] As used herein, the term "potency" refers to the measure of the biological activity of the product (i.e.; the isolated polypeptide or the composition of matter), based on the attribute of the product which is linked to the relevant biological properties (i.e.; reduced survival of fibroblasts obtained from an RA patient).

[0231] As used herein, the term "batch" refers to a specific quantity of a drug that is intended to have uniform character and quality, within specified limits, and is typically produced according to a single manufacturing order during the same cycle of manufacture. Thus, the present teachings can be used in the QA of the manufacturing procedures for assessing the biological activity of the isolated polypeptides, the composition of matter or the pharmaceutical compositions as part of batch qualification.

[0232] According to specific embodiments, the term "batch" also refers to a quantity of the drug exposed to stability characterization and/or peptide and formulation modifications.

[0233] As used herein, the term "fibroblast" refers to a connective tissue cell that synthesizes the extracellular matrix and collagen and is obtained from a synovial fluid of an RA patient. The fibroblasts used according to the method can be a primary culture directly isolated from an RA patient or cell lines obtained from the fibroblasts such as the commercially available cell lines SW 982, PCS-201-010 and ACS-1023 that can be obtained from the ATCC.

[0234] Methods for obtaining a synovial fluid from a subject are well known in the art and include, but are not limited to biopsy such as joint biopsy and joint aspiration. Typically, procedures for obtaining tissue or fluid biopsies are described in details in Hypertext Transfer Protocol://World Wide Web (dot) healthatoz (dot)com/healthatoz/Atoz/search.asp.

[0235] Specifically, a joint aspiration, also known as Arthrocentesis refers to the removal of fluid from the space around a joint using a needle and syringe. This is usually performed under a local anesthetic to either relieve swelling or to obtain fluid for analysis to diagnose a joint disorder and/or problem. Joint aspiration is usually performed on the knee; however, fluid can also be removed from other joints, such as the hip, ankle, shoulder, elbow, or wrist.

[0236] A joint biopsy refers to joint or synovial biopsy. In the procedure a sample of the joint

lining or synovial membrane or fluid is taken. Briefly, the procedure is effected in a clinical facility by a surgeon. A number of approaches are available to perform this biopsy: such as through an incision in the joint; with a scope inserted in the joint; or, more typically, by the insertion of a sharp instrument through the skin. The sample can be taken from any joint, typically the examined joint is the knee. A sharp instrument (trocar) is pushed into the joint space. A needle with an attached syringe is inserted into the joint to withdraw fluid for laboratory analysis. The surgeon may instill analgesic compounds into the joint and along the needle track before the needle is withdrawn. The trocar and then the biopsy needle is inserted and specimens taken. After the specimen is taken, both the trocar and the biopsy needle are removed.

[0237] Regardless of the procedure employed, once the biological sample is obtained, the fibroblast may be further isolated. Enrichment of fibroblasts populations can be obtained by methods well known in the art, and included those disclosed in e.g. Bendersky et al, J Immunol.;188:4349-59, 2012, magnetic cell separation and flow cytometry cell sorting.

[0238] Thus, for example the fibroblasts can be isolated by culturing adherent synovial fluid cells in plastic wells in DMEM-supplemented medium for about 48 hours followed by removal of all of the nonadherent cells. The adherent cells which comprise fibroblasts typically display a fibroblastic morphology and express CD90, low levels of the CD49a integrin, negative for macrophage (CD14), T cell (CD3), and B cell (CD20) surface markers (as determined by e.g. flow cytometry) and stain positively for collagen type I determined by Sirius red staining.

[0239] The primary culture of fibroblasts comprises according to specific embodiments at least 10 %, at least 20 %, at least 30%, at least 40 %, at least 50 %, at least 60 %, at least 70 %, at least 80 %, at least 90 % or more fibroblasts.

[0240] Following preparation of the fibroblasts, predetermined amount of cells are incubated in tissue culture plates (e.g.; 12, 24, 96, 384 wells plates) with the appropriate Growth medium and stimulated with a predetermined amount of the tested isolated polypeptide, the composition of matter or the pharmaceutical composition. Selection of the medium is well within the capabilities of skilled in the art. Thus, for example, RPMI or DMEM (can be obtained for example from Sigma-Aldrich or Biological Industries, Beit Haemek, Israel) can be used as a growth medium. The medium may be supplemented with L-glutamine, non-essential amino acids, sodium pyruvate, antibiotic/ antimycotic solution, 2-mercaptoethanol and serum.

[0241] Selection of the predetermined amount of cells incubated for *in-vitro* testing that will result in detectable effect on cell survival is well within the capabilities of the skilled in the art. Thus, for example cell concentration can be 1×10^4 / ml to 5×10^6 / ml; 1×10^4 / ml to 1×10^6 / ml; 5×10^4 / ml to 5×10^6 / ml; 1×10^5 / ml to 5×10^6 / ml; or 1×10^5 / ml to 1×10^6 / ml.

[0242] According to specific embodiments the cell concentration is 2×10^5 / ml.

[0243] Selection of the peptide or composition of matter concentration used for the *in-vitro* testing that will result in detectable effect on cell survival is well within the capabilities of skilled in the art. Preferably, the concentration used should be within the linear range of the selected stimulation parameter. Thus, for example, the concentration can be 1 µg / ml to 30 µg / ml; 1 µg / ml to 20 µg / ml; 5 µg / ml to 30 µg / ml; or 5 µg / ml to 20 µg / ml.

[0244] The number of tested concentration can be at least 1, at least 2, at least 3, at least 5, at least 6, 1-10, 2-10, 3-10, 5-10, 1-5, 2-5 and 3-5 different concentrations.

[0245] The number of samples repeats for each of the tested concentration can be 2, 3, 4, 5 or 6 repeats.

[0246] Following a pre-determined incubation time the survival of the fibroblasts is determined. Specific methods of monitoring cell survival are known in the art and include for example, the MTT test which is based on the selective ability of living cells to reduce the yellow salt MTT (3-(4, 5- dimethylthiazolyl)-2, 5-diphenyltetrazolium bromide) (can be obtained for example from Sigma, Aldrich) to a purple-blue insoluble formazan precipitate; Apoptosis assays such as the TUNEL assay (can be obtained for example from Roche); and the Annexin V assay [for example ApoAlert® Annexin V Apoptosis Kit (Clontech Laboratories, Inc., CA, USA)].

[0247] The incubation time may vary and determination of the incubation time that will result in detectable effect on cell survival is well within the capabilities of skilled in the art. According to a specific embodiment, the incubation time is between 12 hours to 96 hours. According to some embodiments of the invention, the incubation time is between 12 to 72 hours; 12 to 48 hours; 12 to 24 hours; 24 to 96 hours, 24 to 72 hours or 24 to 48 hours. According to specific embodiments of the invention, the incubation time is between 24-48 hours.

[0248] According to specific embodiments, reduced survival of the fibroblasts following said contacting is indicative that the batch is potent.

[0249] According to specific embodiments the assay may further include positive and negative control samples. The positive control for the assay may include agents inducing non-specific fibroblasts cell death, for example ascorbate (see e.g. Schmidt et al., J Biomed Mater Res. 1993 Apr; 27(4):521-30).

[0250] Negative control for the assay may include agents which prevent the biological activity of the tested polypeptide or composition of matter such as SAA (can be obtained for example from PeproTech).

[0251] According to specific embodiments, the method comprising comparing the survival of the cells with survival of the cells following contacting with a reference standard batch of the isolated polypeptide, composition of matter or the pharmaceutical composition, so as to determine the relative potency of the batch.

[0252] As used herein, the term "relative potency" refers to a qualitative measure of potency of a batch of the isolated polypeptide, composition of matter or the pharmaceutical composition, relatively to a standard reference (RS) of the isolated polypeptide, composition of matter or the pharmaceutical composition, having a known potency.

[0253] According to specific embodiments the potency of a batch of the isolated polypeptide, composition of matter or the pharmaceutical composition, is determined relatively to the known potency of a reference standard (RS).

[0254] As used herein, the phrase "reference standard" or "RS" refers to a standardized isolated polypeptide, composition of matter or pharmaceutical composition, which is used as a measurement base for the isolated polypeptide, composition of matter or the pharmaceutical composition. RS provides a calibrated level of biological effect against which new preparations of the isolated polypeptide, composition of matter or the pharmaceutical composition can be compared to.

[0255] According to a specific embodiment, the RS is characterized by optimum potency and quality of an active component that is effective in treating the disease (e.g., RA).

[0256] Calculating potency and relative potency are known in the art. According to specific embodiments the relative potency is calculated using a software suitable for biological assays, such as parallel line analysis software e.g., PLA (Stegmann Systems GmbH) and Gen5 data analysis software (BioTek).

[0257] Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of embodiments of the method and/or system of the invention, several selected tasks could be implemented by hardware, by software or by firmware or by a combination thereof using an operating system.

[0258] As used herein the term "about" refers to $\pm 10\%$.

[0259] The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

[0260] The term "consisting of" means "including and limited to".

[0261] The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

[0262] As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one

compound" may include a plurality of compounds, including mixtures thereof.

[0263] Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[0264] Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

[0265] As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

[0266] When reference is made to particular sequence listings, such reference is to be understood to also encompass sequences that substantially correspond to its complementary sequence as including minor sequence variations, resulting from, e.g., sequencing errors, cloning errors, or other alterations resulting in base substitution, base deletion or base addition, provided that the frequency of such variations is less than 1 in 50 nucleotides, alternatively, less than 1 in 100 nucleotides, alternatively, less than 1 in 200 nucleotides, alternatively, less than 1 in 500 nucleotides, alternatively, less than 1 in 1000 nucleotides, alternatively, less than 1 in 5,000 nucleotides, alternatively, less than 1 in 10,000 nucleotides.

[0267] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

[0268] Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

[0269] Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non limiting fashion.

[0270] Generally, the nomenclature used herein and the laboratory procedures utilized in the present invention include molecular, biochemical, microbiological and recombinant DNA techniques. Such techniques are thoroughly explained in the literature. See, for example, "Molecular Cloning: A laboratory Manual" Sambrook et al., (1989); "Current Protocols in Molecular Biology" Volumes I-III Ausubel, R. M., ed. (1994); Ausubel et al., "Current Protocols in Molecular Biology", John Wiley and Sons, Baltimore, Maryland (1989); Perbal, "A Practical Guide to Molecular Cloning", John Wiley & Sons, New York (1988); Watson et al., "Recombinant DNA", Scientific American Books, New York; Birren et al. (eds) "Genome Analysis: A Laboratory Manual Series", Vols. 1-4, Cold Spring Harbor Laboratory Press, New York (1998); methodologies as set forth in U.S. Pat. Nos. 4,666,828; 4,683,202; 4,801,531; 5,192,659 and 5,272,057; "Cell Biology: A Laboratory Handbook", Volumes I-III Cellis, J. E., ed. (1994); "Culture of Animal Cells - A Manual of Basic Technique" by Freshney, Wiley-Liss, N. Y. (1994), Third Edition; "Current Protocols in Immunology" Volumes I-III Coligan J. E., ed. (1994); Stites et al. (eds), "Basic and Clinical Immunology" (8th Edition), Appleton & Lange, Norwalk, CT (1994); Mishell and Shiigi (eds), "Selected Methods in Cellular Immunology", W. H. Freeman and Co., New York (1980); available immunoassays are extensively described in the patent and scientific literature, see, for example, U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; 4,098,876; 4,879,219; 5,011,771 and 5,281,521; "Oligonucleotide Synthesis" Gait, M. J., ed. (1984); "Nucleic Acid Hybridization" Hames, B. D., and Higgins S. J., eds. (1985); "Transcription and Translation" Hames, B. D., and Higgins S. J., eds. (1984); "Animal Cell Culture" Freshney, R. I., ed. (1986); "Immobilized Cells and Enzymes" IRL Press, (1986); "A Practical Guide to Molecular Cloning" Perbal, B., (1984) and "Methods in Enzymology" Vol. 1-317, Academic Press; "PCR Protocols: A Guide To Methods And Applications", Academic Press, San Diego, CA (1990); Marshak et al., "Strategies for Protein Purification and Characterization - A Laboratory Course Manual" CSHL Press (1996); all of which are incorporated by reference as if fully set forth herein. Other general references are provided throughout this document. The procedures therein are believed to be well known in the art and are provided for the convenience of the reader. All the information contained therein is incorporated herein by reference.

EXAMPLE 1**PEPTIDE SYNTHESIS AND CHARACTERIZATION**

Materials and Methods

[0271] *Synthesis of 5, 7 and 9 mer peptides* - The 5-, 7- and 9-mer peptides [MTADV (SEQ ID NO: 1), MTADVDR (SEQ ID NO: 2) and TRMTADVDR (SEQ ID NO: 3)], - 3, the Acylated-N and Amidated-C termini 5-, 7- and 9-mer peptides [Ac-MTADV-NH₂ (SEQ ID NO: 4), Ac-MTADVDR-NH₂ (SEQ ID NO: 5) and Ac-TRMTADVDR-NH₂ (SEQ ID NO: 6)] and the scrambled 7-mer peptide [Ac-TMDVADR-NH₂ (SEQ ID NO: 7)], were synthesized by Sigma Israel using solid phase synthesis fmoc chemistry. A purity of 95- to 97 % was reached.

[0272] *Liquid chromatography-mass spectrometry (LCMS)* - Stability, Pharmacokinetic (PK) and target proteins of the peptide were evaluated by LCMS.

[0273] Sample preparation for mass spectrometry: The protein-bound beads were reduced with 2.8mM DTT (60 °C for 30 min) and modified with 8.8 mM iodoacetamide (at room temperature for 30 min under dark conditions) in 8M Urea and 400 mM Ammonium bicarbonate. The proteins were digested in 2M Urea, 25 mM ammonium bicarbonate with modified trypsin (Promega) at a 1:50 enzyme-to-substrate ratio, overnight at 37 °C. The tryptic peptides were desalted using C18 tips (Harvard) dried and re-suspended in 0.1 % Formic acid. Mass Spectrometry measurements. The resulting tryptic peptides were analyzed by LC-MS/MS using an OrbitrapXL mass spectrometer (Thermo-Fisher) fitted with a capillary HPLC (Eksigent). Specifically, the peptides were loaded onto a C18 trap column (0.3 5mm, LC-Packings) connected on-line to a homemade capillary column (75 micron ID) packed with Reprosil C18-Aqua (Dr Maisch GmbH, Germany) and resolved using linear 94 minutes 5 to 40% acetonitrile gradients followed by 12 minutes at 95 % acetonitrile in the presence of 0.1 % formic acid in water at flow rates of 0.25 µl/min. Mass spectrometry was performed in a positive mode using repetitively full MS scan (resolution 60000) followed by collision induces dissociation (CID). Top seven, (>1 charged peptides, 350-2000 M/Z) were selected for fragmentation from each full mass spectrum.

[0274] Data analysis: The mass spectrometry was analyzed using the Discoverer software version 1.4 against the human uniprot database and against decoy databases (in order to determine the false discovery rate (FDR), using the Sequest and Mascot search engines. High confidence refers to 0.01 FDR .

[0275] Semi quantitation was performed by calculating the peak area of each peptide. The area of the protein is the average of the three most intense peptides from each protein.

Results

[0276] Inclusion of alanine in the splicing junction between variant exon 4 and variant exon 5 of CD44vRA variant leading to the presence of the MTADV sequence instead of the original

MTDV sequence was shown to confer the pathological activity of CD44vRA (Nedvetzki et al., J Clin Invest 111:1211-1220,2003).

[0277] The present inventors have synthesized 5-, 7-, and 9-mer peptides (denoted herein as RA peptides) including the MTADV sequence. The 5-mer RA peptide comprises a relative hydrophobic amino acid sequence as well as a low molecular weight (less than 700 Dalton). Therefore, it may easily penetrate into tissues and consequently may be used in topical applications and oral delivery.

[0278] The proteolytic analysis of the RA peptides demonstrated no proteolytic sites (data not shown), indicating that the peptides are at least relatively stable. Quantification analysis by Mass Spectrometry indicated almost identical stability of the 5-mer peptide (SEQ ID NO: 1) upon storage in saline at 4 °C, at room temperature or at -20 °C for 22 weeks (Figure 1). Assuming that storage at -20 °C displays 100 % stability, these results demonstrate that the 5-mer peptide is stable for at least 22 weeks at room temperature and 4 °C.

EXAMPLE 2

THE 5- and 9-MER RA PEPTIDES CAN REDUCE JOINT INFLAMMATION IN THE COLLAGEN-INDUCED ARTHRITIS (CIA) MOUSE MODEL

Materials and Methods

[0279] Mice - Collagen-induced arthritis (CIA) was generated in DBA/1 or C57BL mice by injection of type II collagen as described in Nedvetzki et al., PNAS 101, 18081-18086, 2004.

[0280] Treatment protocol - PBS, or the 9-mer RA peptide (SEQ ID NO: 3) at a dose of 25 µg, 100 µg or 150 µg per injection was administered i.p to CIA mice for 4 times within 6 days (see Table 3 below). PBS (n = 7), or 5-mer RA peptide (SEQ ID NO: 1, n = 7) at a dose of 70 µg per injection were administered i.p to CIA mice on C57BL/6 background for 10 consecutive days. In all groups first injection was given at the onset of disease as determined by paw swelling.

[0281] Evaluation of joint inflammation- Inflammation was evaluated by the paw swelling response. Paw swelling was measured by micro caliber. Paw swelling at range of 2.1-2.3 mm was considered "onset of disease" and the starting point for injection of the peptides. Mice that showed above 2.3 mm paw swelling were excluded from the experiment. All measurements were performed under blind manner (For additional details see Nedvetzki, et al., (2004) PNAS 101, 18081-18086).

[0282] Histology - Mice were sacrificed on day 11 (one day following cessation of treatment) and hind limbs were isolated and fixed overnight with 4 % paraformaldehyde at room temperature (for additional details see Nedvetzki et al. (2004) PNAS 101,18081-18086). Following fixation, diarthrodial Joint sections were prepared, stained with Hematoxylin and Eosin (H&E) and evaluated by a pathologist under blind manner. Joint infiltration score: 0 = no infiltration; 4 = massive infiltration.

[0283] Statistical analysis - Statistical analysis for each measurement point was performed by the Student's t-test for unpaired values.

Table 3: Experimental design- dose response (Figures 2A-C)

Group #	Treatment	#Mice	Injection protocol
1	1XPBS 100µl /injection	8	Injection every other day for 6 constitutive days
2	Peptide 9 mer TRMTADVDR (SEQ ID NO: 3) 25µg/100µl/injection	8	Injection every other day for 6 constitutive days
3	Peptide 9 mer TRMTADVDR (SEQ ID NO: 3) 100µg/100 µl/injection	6	Injection every other day for 6 constitutive days
3	Peptide 9 mer TRMTADVDR (SEQ ID NO: 3) 150µg/100 µl/injection	4	Injection every other day for 6 constitutive days

Results

[0284] The collagen-induced arthritis (CIA) mouse model is the mouse analogue of human Rheumatoid Arthritis (RA). To evaluate the effect of the generated RA peptides on joint inflammation in the CIA mouse model different dosages of the 9-mer RA peptide (SEQ ID NO: 3) were administered to CIA mice on DBA/1 background starting from the onset of disease; and joint inflammation was evaluated by determining paw swelling. As shown in Figures 2A-B, mice that received 25 and 100 µg of the 9-mer RA peptide (SEQ ID NO: 3) did not show significant difference in paw swelling response as compared to mice administered with PBS, implying lack of a significant therapeutic effect. In contrast, mice that received 150 µg of the 9-mer RA peptide (SEQ ID NO: 3) had demonstrated significant reduction in paw swelling (Figure 2C).

[0285] Histological evaluation of hind limbs sections taken from CIA mice on C57BL/6 background following treatment with the PBS control revealed massive infiltration of mononuclear inflammatory cells into the joint capsule, extensive synovial hypertrophy and severe narrowing of the joint space which was filled with reactive cells. In addition, severe erosion of the articular cartilage and the subchondral bone, with destruction of cartilage matrix, was noted. The remaining cartilage matrix was heavily infiltrated as well. Taken together, the average joint Infiltration score in the PBS treated mice = about 4 (Figures 3A and 3C).

[0286] On the contrary, histological evaluation of hind limbs sections taken from CIA mice following treatment with the 5-mer RA peptide (SEQ ID NO: 1) revealed none-to-mild infiltration of mononuclear inflammatory cells into the joint capsule with either no or mild synovial hypertrophy. Inflammatory infiltrate was noted in minority of the samples. The joint space was preserved, with few reactive cells if any. In addition, no erosion of the articular cartilage and the subchondral bone was noted and the cartilage matrix was generally preserved. Furthermore, few of the samples were indistinguishable from unaffected mice (data not shown). Taken together, average joint infiltration score in the 5-mer RA peptide treated mice = about 1 (Figures 3B and 3C).

[0287] Overall, the joint inflammation score of the control PBS treated group was significantly higher ($P < 0.0001$) than that of the 5-mer RA peptide (SEQ ID NO: 1) treated group, indicating that treatment with the peptide can highly restore normal histology of the inflamed joint.

[0288] Taken together, treatment with the 5- and 9-mer RA peptides (SEQ ID NOs: 1 and 3) inhibit joint inflammation in the CIA mouse model.

[0289] Without being bound by theory it is suggested that an interaction between unknown CD44vRA ligand and CD44vRA create a conformational change of CD44vRA glycoprotein. This new epitope allows binding of FGF-2 to the heparin sulfate of v3 exon product resides in the same molecule. The bound FGF-2 is oriented to interact with endothelial cells or fibroblasts expressing FGF receptor 1, resulting in their proliferation and exaggeration of the inflammatory activity (Nedvetzki et al., J Clin Invest 111:1211-1220, 2003). The RA peptide may compete with the cell surface CD44 on the interaction with the unknown ligand resulting in blockade of the FGF-2-induced inflammatory cascade described by Nedvetzki et al. (J Clin Invest 111:1211-1220, 2003).

EXAMPLE 3

THE 5- 7- AND 9-MER PROTECTED RA PEPTIDES CAN REDUCE JOINT INFLAMMATION IN THE CIA MOUSE MODEL

Materials and Methods

[0290] Mice - As described in Example 2 above.

[0291] Treatment protocol - PBS, or the tested peptides [Ac-TRMTADVDR-NH₂ (SEQ ID NO: 6), Ac-MTADVDR-NH₂ (SEQ ID NO: 5), Ac-MTADV-NH₂ (SEQ ID NO: 4) and scrambled Ac-TMDVADR-NH₂ (SEQ ID NO: 7)] at doses of 70 or 200 µg per injection were administered i.p to CIA /1 mice on DBA background for 9-10 consecutive days (see Tables 4-7 below). As a non-

specific control, several mice were administered I.P. with Dexamethsone (Dex) at a dose of 50 µg, following the same protocol. In all groups first injection was given at the onset of disease as determined by paw swelling.

[0292] Evaluation of joint inflammation- As described in Example 2 above. Paw swelling of less than 2mm was considered healthy.

[0293] Statistical analysis - As described in Example 2 above.

Table 4: Experimental design (Figure 4)

Group #	Treatment	#Mice/paws*	Injection protocol
1	PBSx1 100ul/injection	4/5*	One injection per day for 9 constitutive days
2	Peptide 9 mer Ac-TRMTADVDR-NH2 (SEQ ID NO: 6) 200µg/100µl/injection	5/7*	One injection per day for 9 constitutive days
3	Peptide 7 mer Ac-MTADVDR-NH2 (SEQ ID NO: 5) 200µg/100µl/injection	2/3*	One injection per day for 9 constitutive days
*When the two hind paws of a mouse were inflamed, both paws were analyzed for swelling			

Table 5A: Experimental design (Figure 5A)

Group #	Treatment	#Mice	Injection protocol
1	1XPBS 100ul/injection	3	One injection per day for 9 constitutive days
2	Peptide 5 mer Ac-MTADV-NH2 (SEQ ID NO: 4) 200µg/100µl/injection	5	One injection per day for 9 constitutive days
3	Dexamethasone (Dex)	4	One injection per day for 9 constitutive days

Table 5B: Experimental design (Figure 5B)

Group #	Treatment	#Mice/Paws*	Injection protocol
1	1XPBS 100µ/injection 1	10/11*	One injection per day for 10 constitutive days
2	Peptide 5 mer Ac-MTADV-NH2 (SEQ ID NO: 4) 200µg/100µl/injection	11/16*	One injection per day for 10 constitutive days
*When the two hind paws of a mouse were inflamed, both paws were analyzed for swelling			

Table 6: Experimental design (Figure 6)

Group #	Treatment	#Mice	Injection protocol
1	1XPBS 100p/injection 1	13	One injection per day for 10 constitutive days
2	Peptide 5 mer Ac-MTADV-NH ₂ (SEQ ID NO: 4) 70µg/100µl/injection	11	One injection per day for 10 constitutive days

Table 7: Experimental design (Figures 7A-C)

Group #	Treatment	#Mice/Paws*	Injection protocol
1	1XPBS 100µl/injection	8/9*	One injection per day for 9 constitutive days
2	Control: 7- mer scrambled Peptide Ac-TMDVADR-NH ₂ (SEQ ID NO: 7) 200µg/100µl /injection	7/10*	One injection per day for 9 constitutive days
3	Peptide 7- mer Ac-MTADVDR-NH ₂ (SEQ ID NO: 5) 200µg/100µl/injection 1	9/11*	One injection per day for 9 constitutive days

*When the two hind paws of a mouse were inflamed, both paws were analyzed for swelling

Results

[0294] In the next step 9- 7- and 5-mer RA peptides were synthesized with protection residues, namely Acetyl and Amide residues at the amino and carboxyl terminal ends of the peptides [Ac-TRMTADVDR-NH₂ (SEQ ID NO: 6), Ac-MTADVDR-NH₂ (SEQ ID NO: 5) and Ac-MTADV-NH₂ (SEQ ID NO: 4), denoted herein as 9- 7- and 5- mer RA protected peptide, respectively]. These protection residues preserve the natural stage of the peptide in the experimental mouse and stabilize the peptide. The ability of the protected peptides to reduce joint inflammation in DBA/1 mice following their injection at the onset of CIA was evaluated. All measurements were performed under blind manner.

[0295] As can be seen in Figures 4 and 5A-B injection of all protected RA peptides at a dose of 200 µg per injection significantly inhibited joint inflammation in the CIA mice on DBA background, as compared to mice treated with PBS. As also evident in Figure 5A, administration of Dexamethasone decreased footpad swelling as well, possibly by generating a non-specific anti-inflammatory effect of this steroid. The 5-mer protected peptide (SEQ ID NO: 4) was also able to significantly inhibit joint inflammation in the CIA mice on C57BL/6 background when administered at a dose of 70 µg per injection (Figure 6). All measurements were performed under blind manner.

[0296] In the next step, the effect of a scrambled RA peptide on joint inflammation was evaluated. To this end the effect of the 7-mer protected RA peptide (Ac-MTADVDR-NH₂, SEQ ID NO: 5) was compared to the effect of a 7-mer scrambled protected peptide (Ac-TMDVADR-NH₂, SEQ ID NO: 7). As shown in Figures 7A-C, the scrambled non-specific 7-mer protected peptide had no effect on footpad swelling. All measurements were performed under blind manner.

[0297] The results shown in Figures 7A-C were also evaluated by determining the percent of healthy paws in each group. Hence, evaluation of the hind paws of the CIA DBA/1 mice (Figure 8), reflecting the severity of the disease, showed that more than 60 % of the hind paws in CIA mice treated with the 7-mer protected RA peptide remained healthy. In comparison, the percentages of the hind paws that remained healthy in the other groups tested were 15 % in the PBS treated group and 33 % in the 7-mer peptide scrambled group.

[0298] Taken together, 5-, 7- and 9- mer RA protected peptides (SEQ ID NOs: 4-6) inhibit joint inflammation upon injection to CIA mice on both DBA and C57BL/6 background, while non-specific scrambled 7-mer protected peptide (SEQ ID NO: 7) has no effect on joint inflammation. Acetylation and Amidation did not affect the activity of the RA peptides (data not shown); however, they are expected to improve stability and pharmacokinetics of the RA peptide.

EXAMPLE 4

70 µg PER INJECTION IS THE OPTIMAL DOSE FOR THE 5-MER PROTECTED RA PEPTIDE FOR REDUCING JOINT INFLAMMATION IN THE CIA MOUSE MODEL

Materials and Methods

[0299] *Mice* - As described in Example 2 above.

[0300] *Treatment protocol* - PBS, or the tested peptide [Ac-MTADV-NH₂ (SEQ ID NO: 4)] at doses of 10, 25, 70, 200 or 600 µg per injection were administered i.p to CIA mice for 10 consecutive days (see Tables 8-9 below). In all groups first injection was given at the onset of disease as determined by paw swelling.

[0301] *Evaluation of joint inflammation*- As described in Example 2 above. The measurements were effected under blind manner.

[0302] *Statistical analysis* - As described in Example 2 above.

Table 8: Experimental design (Figure 9A)

Group #	Treatment	#Paws	Injection protocol
1	1XPBS 100µl/injection	13	One injection per day for 10 constitutive days
2	5 mer Peptide Ac-MTADV-NH ₂ (SEQ ID NO: 4) 70µg/100µl / injection	11	One injection per day for 10 constitutive days
3	5 mer Peptide Ac-MTADV-NH ₂ (SEQ ID NO: 4) 200µg/100µl / injection	11	One injection per day for 10 constitutive days
4	5 mer Peptide Ac-MTADV-NH ₂ (SEQ ID NO: 4) 600µg/100µl / injection	9	One injection per day for 10 constitutive days

Table 9: Experimental design (Figure 9B)

Group #	Treatment	# Paws	Injection protocol
1	1XPBS 100 µl/injection	13	One injection per day for 10 constitutive days
2	5 mer Peptide Ac-MTADV-NH ₂ (SEQ ID NO: 4) 10µg/100µl / injection	11	One injection per day for 10 constitutive days
3	5 mer Peptide Ac-MTADV -NH ₂ (SEQ ID NO: 4) 25µg/100µl / injection	11	One injection per day for 10 constitutive days
4	5 mer Peptide Ac-MTADV-NH ₂ (SEQ ID NO: 4) 70µg/100µl / injection	9	One injection per day for 10 constitutive days

Results

[0303] To evaluate the optimal anti-inflammatory therapeutic dose of the 5-mer RA peptide, several different doses of the protected peptide (SEQ ID NO: 4) were administered to CIA mice on C57BL/6 background and joint inflammation was determined by footpad swelling measurements (electronic automatic measurements of the volume of the footpad, based on Archimedes observation). As can be seen in Figure 9A, injection of 70, 200 or 600 µg per injection of the 5-mer protected RA peptide (SEQ ID NO: 4) reduced the joint inflammation when compared to PBS control; however, a dose of 70 µg of the peptide generated the most statistically significant anti-inflammatory effect. In addition, as shown in Figure 9B, injection of 10 and 25 µg per injection of the 5-mer protected RA peptide (SEQ ID NO: 4) did not induce a significant anti-inflammatory effect.

[0304] Taken together, the data indicates that a dose of 70 µg per injection is the optimal and the lowest dose for CIA inhibition by the 5-mer protected RA peptide (SEQ ID NO: 4).

EXAMPLE 5

THE 5-MER RA PEPTIDE DOES NOT INHIBIT DTH IN THE CIA MOUSE MODEL**Materials and Methods**

[0305] *DTH model* - C57BL/6 mice were painted at their abdomen with oxazolone solution (sensitization). On day 6, the right ear of each mouse was painted with the same hapten, oxazolone (elicitation), to generate delayed type hypersensitivity (DTH) response. The differences in thickness between the right and the left ears, indicating DTH development, were determined by microcaliper 24 hours later. DTH induction indicates a normal immune response. For additional details see Weiss et al., (2000) Proc. Natl. Acad. Sci. USA. 97, 285-290.

[0306] *Treatment protocol* - PBS and 5-mer peptide (SEQ ID NO: 1) at a dose of 200 µg was administered one day before the sensitization and then every day during the sensitization period (7 days). An anti-TNF antibody (Herrring et al., (2002) Infect Immun 70, 2959-64) was used for comparison, to demonstrate non-specific effect.

[0307] *Statistical analysis* - As described in Example 2 above.

Results

[0308] To evaluate the influence the RA peptides on the immune response in general the effect of the 5-mer RA peptide (SEQ ID NO: 1) on delayed type hypersensitivity (DTH) response was evaluated in a DTH model generated in C57BL/6 mice. DTH reflects acute inflammation, characterizing immune response against microorganism. The results indicate that injection of the 5-mer RA peptide did not affect the DTH response and mice treated with the peptide displayed the same DTH response as the control mice treated with PBS, throughout the 7 days assay period (Figure 10). In comparison mice treated with anti-TNF α antibody displayed inhibited DTH response, which was significant compared to the control mice.

EXAMPLE 6**THE 5-MER PEPTIDE DOES NOT GENERATE NEUTRALIZING ANTIBODIES IN THE CIA MOUSE MODEL****Materials and Methods**

[0309] Mice - As described in Example 2 above.

[0310] Treatment protocol - PBS, or 5-mer RA peptide (SEQ ID NO: 1) at a dose of 70 µg per injection were administered i.p to CIA mice on C57BL/6 background for 10 consecutive days. In all groups first injection was given at the onset of disease as determined by paw swelling.

[0311] ELISA - 96 wells ELISA plates were coated with 5-mer RA peptide (SEQ ID NO: 1), collagen or immunoglobulin (positive control). Serum from CIA mice treated with PBS or the 5-mer RA peptide was added to the coated plates and the presence of neutralizing antibodies against collagen or the RA peptide was detected with anti-immunoglobulin + detection system. The plate wells were coated with 1 mg/ml peptide or protein. Mouse serum was added to the plate wells for 15 hours in cold temperature. The detection system included HRP-anti-mouse IgG and TMB (Bako) substrate. Plates were analysed using an ELISA reader at a wave length of 450 nm.

[0312] Statistical analysis - As described in Example 2 above.

Results

[0313] To determine whether treatment with the RA peptides induces production of specific neutralizing antibodies that may reduce or even block the peptide anti-inflammatory effect the abundance of anti-5-mer peptide antibodies in the serum was determined using an ELISA assay. As shown in Figure 11, no neutralizing antibodies to the 5-mer RA peptide (SEQ ID NO: 1) were detected in the serum of CIA mice following treatment with the peptide. Contrary, as the CIA mouse model is generated by collagen injection, anti-collagen specific antibodies were clearly evident in the serum of the CIA mice.

EXAMPLE 7

SERUM AMYLOID A, TRANSTHYRETIN AND APOLIPOPROTEIN B ARE POTENTIAL TARGET PROTEINS OF THE 5-MER PEPTIDE

Materials and Methods

[0314] Separation of peptide target protein(s) - Synovial fluid was removed from the joint of a Rheumatoid Arthritis (RA) patient. The synovial fluid was diluted 1:1 with PBS and centrifuged at 1,200 rpm. The cell pellet was subjected to lysis buffer containing protease inhibitors. The

cell lysate was incubated with a biotinylated 5-mer peptide (Sigma) or with PBS for 12 hour at 4 °C, with shaking. Streptavidin Sepharose beads (Sephadex) were added to the biotinylated 5-mer peptide-treated cell extract or PBS-treated cell extract for additional one hour at 4 °C, with shaking. The peptide-bound beads and the control beads were separated by centrifugation, extensively washed and sent for mass spectrometry analysis, see Figure 12. The mass spectrometry (MS) measurements and analysis were performed in the Smoler Proteomic Research Center at the Technion in Haifa.

Results

[0315] Mass spectrometry analysis of proteins from cell lysates extracted from synovial fluid cells of an RA patient that bound the 5-mer peptide (SEQ ID NO: 1) identified Serum Amyloid A (SAA), Transthyretin and Apolipoprotein B as potential target proteins of the 5-mer RA peptide (SEQ ID NO: 1). The indicated proteins are known to be involved in the pathology of RA but also in the pathologies of Alzheimer's disease, cancer diseases and cardiovascular disease.

EXAMPLE 8

PHARMACOKINETICS OF THE 5-MER RA PEPTIDE

Materials and Methods

[0316] *Treatment protocol* - C57BL/6 mice were subjected to a single i.p. injection of 200 µg 5-mer peptide (SEQ ID NO: 1). Blood samples were taken by terminal bleeding (500-1000 µl) 15, 35, and 60 minutes following injection and the serum was sent for mass spectrometry evaluation.

[0317] *Mass Spectrometry analysis* - The concentration of the 5-mer RA peptide in the blood was determined by mass spectrum analysis as described above.

Results

[0318] The pharmacokinetic (PK) of the 5-mer RA peptide elimination in the blood of mice following a single i.p. injection is shown in Figure 13.

EXAMPLE 9

AN *IN VITRO* MODEL FOR EVALUATING THE EFFECT OF THE RA PEPTIDES

Materials and Methods

[0319] **Cells** - Fibroblasts from the inflammatory joint of an RA patient were cultured and maintained as shown in Bendersky et al, J Immunol.;188:4349-59, 2012. A quantity of 20,000 cells was added to each one of the 96 well plates with the indicated concentrations of peptide, serum amyloid A or α -lactalbumin.

[0320] **MTT assay** -MTT assay was effected as shown in Madhyastha et al. (2015) J Clin Diagn Res.;9 :ZC05-8.

[0321] **Statistical analysis** - As described in Example 2 above.

Results

[0322] An in-vitro model was developed as a tool to evaluate the biological activity of the generated RA peptides. To this end, fibroblasts from the inflammatory joint of an RA patient were incubated in-vitro and the effect of the peptides on cell survival was evaluated by a MTT assay.

[0323] As shown in Figure 14, increasing the dose of the 5-mer RA peptide (SEQ ID NO: 1) gradually inhibits cell survival. Addition 50 μ g/ml Serum Amyloid A (SAA) into the fibroblast culture in combination with the 5-mer peptide prevents this inhibition. The results also indicate that a low dose of 2.5 μ g/ml ($\sim$ 5 nM) of the peptide is able to significantly inhibit cell survival in this *in-vitro* model, and that the *in-vitro* maximal suppressive effect is 60 %.

[0324] In order to demonstrate the specificity of the effect of the peptide on cell survival, the peptide was added to the cell culture at a constant concentration (25 μ g/ml) and SAA or lactalbumin (LA, a control protein with similar molecular weight) was added at escalating concentrations. As shown in Figure 15, the 5-mer peptide reduced survival of the fibroblast and addition of SAA gradually prevented this reduction in a dose response manner. In contrast, the addition of LA had no effect on the suppressive activity the peptide; indicating the SAA prevents the inhibitory effect of the 5-mer peptide in a specific manner.

[0325] In the next step, the suppressive effect of the 5-mer protected RA peptide (SEQ ID NO: 4) was compared to the 5-mer RA peptide (SEQ ID NO: 1). As shown in Figure 16, peptide modification improved the suppressive effect of the peptide.

SEQUENCE LISTING

[0326]

<110> Yisum Research Development Company of the Hebrew
University of Jerusalem Ltd.

NAOR, David

ESHKAR-SEBBAN, Lora

AMAR, Keren-Or

COHEN, Shmuel

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<211> 742

<212> PRT

<213> Homo sapiens

<400> 9

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Val Phe His Val Glu Lys Asn Gly Arg Tyr Ser Ile Ser Arg Thr Glu
 35 40 45

Ala Ala Asp Leu Cys Lys Ala Phe Asn Ser Thr Leu Pro Thr Met Ala
 50 55 60

Gln Met Glu Lys Ala Leu Ser Ile Gly Phe Glu Thr Cys Arg Tyr Gly
 65 70 75 80
 Phe Ile Glu Gly His Val Val Ile Pro Arg Ile His Pro Asn Ser Ile
 85 90 95
 Cys Ala Ala Asn Asn Thr Gly Val Tyr Ile Leu Thr Ser Asn Thr Ser
 100 105 110
 Gln Tyr Asp Thr Tyr Cys Phe Asn Ala Ser Ala Pro Pro Glu Glu Asp
 115 120 125
 Cys Thr Ser Val Thr Asp Leu Pro Asn Ala Phe Asp Gly Pro Ile Thr
 130 135 140
 Ile Thr Ile Val Asn Arg Asp Gly Thr Arg Tyr Val Gln Lys Gly Glu
 145 150 155 160
 Tyr Arg Thr Asn Pro Glu Asp Ile Tyr Pro Ser Asn Pro Thr Asp Asp
 165 170 175
 Asp Val Ser Ser Gly Ser Ser Ser Glu Arg Ser Ser Thr Ser Gly Gly
 180 185 190
 Tyr Ile Phe Tyr Thr Phe Ser Thr Val His Pro Ile Pro Asp Glu Asp
 195 200 205
 Ser Pro Trp Ile Thr Asp Ser Thr Asp Arg Ile Pro Ala Thr Thr Leu
 210 215 220
 Met Ser Thr Ser Ala Thr Ala Thr Glu Thr Ala Thr Lys Arg Gln Glu
 225 230 235 240
 Thr Trp Asp Trp Phe Ser Trp Leu Phe Leu Pro Ser Glu Ser Lys Asn
 245 250 255
 His Leu His Thr Thr Thr Gln Met Ala Gly Thr Ser Ser Asn Thr Ile
 260 265 270
 Ser Ala Gly Trp Glu Pro Asn Glu Glu Asn Glu Asp Glu Arg Asp Arg
 275 280 285
 His Leu Ser Phe Ser Gly Ser Gly Ile Asp Asp Asp Glu Asp Phe Ile
 290 295 300
 Ser Ser Thr Ile Ser Thr Thr Pro Arg Ala Phe Asp His Thr Lys Gln
 305 310 315 320
 Asn Gln Asp Trp Thr Gln Trp Asn Pro Ser His Ser Asn Pro Glu Val
 325 330 335
 Leu Leu Gln Thr Thr Thr Arg Met Thr Asp Val Asp Arg Asn Gly Thr
 340 345 350
 Thr Ala Tyr Glu Gly Asn Trp Asn Pro Glu Ala His Pro Pro Leu Ile

355	360	365
His His Glu His His Glu Glu Glu Glu Thr Pro His Ser Thr Ser Thr 370 375 380		
Ile Gln Ala Thr Pro Ser Ser Thr Thr Glu Glu Thr Ala Thr Gln Lys 385 390 395 400		
Glu Gln Trp Phe Gly Asn Arg Trp His Glu Gly Tyr Arg Gln Thr Pro 405 410 415		
Lys Glu Asp Ser His Ser Thr Thr Gly Thr Ala Ala Ala Ser Ala His 420 425 430		
Thr Ser His Pro Met Gln Gly Arg Thr Thr Pro Ser Pro Glu Asp Ser 435 440 445		
Ser Trp Thr Asp Phe Phe Asn Pro Ile Ser His Pro Met Gly Arg Gly 450 455 460		
His Gln Ala Gly Arg Arg Met Asp Met Asp Ser Ser His Ser Ile Thr 465 470 475 480		
Leu Gln Pro Thr Ala Asn Pro Asn Thr Gly Leu Val Glu Asp Leu Asp 485 490 495		
Arg Thr Gly Pro Leu Ser Met Thr Thr Gln Gln Ser Asn Ser Gln Ser 500 505 510		
Phe Ser Thr Ser His Glu Gly Leu Glu Glu Asp Lys Asp His Pro Thr 515 520 525		
Thr Ser Thr Leu Thr Ser Ser Asn Arg Asn Asp Val Thr Gly Gly Arg 530 535 540		
Arg Asp Pro Asn His Ser Glu Gly Ser Thr Thr Leu Leu Glu Gly Tyr 545 550 555 560		
Thr Ser His Tyr Pro His Thr Lys Glu Ser Arg Thr Phe Ile Pro Val 565 570 575		
Thr Ser Ala Lys Thr Gly Ser Phe Gly Val Thr Ala Val Thr Val Gly 580 585 590		
Asp Ser Asn Ser Asn Val Asn Arg Ser Leu Ser Gly Asp Gln Asp Thr 595 600 605		
Phe His Pro Ser Gly Gly Ser His Thr Thr His Gly Ser Glu Ser Asp 610 615 620		
Gly His Ser His Gly Ser Gln Glu Gly Gly Ala Asn Thr Thr Ser Gly 625 630 635 640		
Pro Ile Arg Thr Pro Gln Ile Pro Glu Trp Leu Ile Ile Leu Ala Ser 645 650 655		

Leu Leu Ala Leu Ala Leu Ile Leu Ala Val Cys Ile Ala Val Asn Ser
660 665 670

Arg Arg Arg Cys Gly Gln Lys Lys Lys Leu Val Ile Asn Ser Gly Asn
675 680 685

Gly Ala Val Glu Asp Arg Lys Pro Ser Gly Leu Asn Gly Glu Ala Ser
690 695 700

Lys Ser Gln Glu Met Val His Leu Val Asn Lys Glu Ser Ser Glu Thr
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Pro Asp Gln Phe Met Thr Ala Asp Glu Thr Arg Asn Leu Gln Asn Val
725 730 735

Asp Met Lys Ile Gly Val
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<210> 10

<211> 2100

<212> DNA

<213> Homo sapiens

<400> 10

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<210> 11

<211> 700

<212> PRT

<213> Homo sapiens

<400> 11

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Met Asp Lys Phe Trp Trp His Ala Ala Trp Gly Leu Cys Leu Val Pro
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Leu Ser Leu Ala Gln Ile Asp Leu Asn Ile Thr Cys Arg Phe Ala Gly
20          25          30

Val Phe His Val Glu Lys Asn Gly Arg Tyr Ser Ile Ser Arg Thr Glu
35          40          45

Ala Ala Asp Leu Cys Lys Ala Phe Asn Ser Thr Leu Pro Thr Met Ala
50          55          60

Gln Met Glu Lys Ala Leu Ser Ile Gly Phe Glu Thr Cys Arg Tyr Gly
65          70          75          80

Phe Ile Glu Gly His Val Val Ile Pro Arg Ile His Pro Asn Ser Ile
85          90          95

Cys Ala Ala Asn Asn Thr Gly Val Tyr Ile Leu Thr Ser Asn Thr Ser
100         105         110

Gln Tyr Asp Thr Tyr Cys Phe Asn Ala Ser Ala Pro Pro Glu Glu Asp
115         120         125

Cys Thr Ser Val Thr Asp Leu Pro Asn Ala Phe Asp Gly Pro Ile Thr
130         135         140

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Ile Thr Ile Val Asn Arg Asp Gly Thr Arg Tyr Val Gln Lys Gly Glu
145                      150                      155                      160

Tyr Arg Thr Asn Pro Glu Asp Ile Tyr Pro Ser Asn Pro Thr Asp Asp
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Asp Val Ser Ser Gly Ser Ser Ser Glu Arg Ser Ser Thr Ser Gly Gly
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Tyr Ile Phe Tyr Thr Phe Ser Thr Val His Pro Ile Pro Asp Glu Asp
195                      200                      205

Ser Pro Trp Ile Thr Asp Ser Thr Asp Arg Ile Pro Ala Thr Thr Thr
210                      215                      220

Ser Ser Asn Thr Ile Ser Ala Gly Trp Glu Pro Asn Glu Glu Asn Glu
225                      230                      235                      240

Asp Glu Arg Asp Arg His Leu Ser Phe Ser Gly Ser Gly Ile Asp Asp
                      245                      250                      255

Asp Glu Asp Phe Ile Ser Ser Thr Ile Ser Thr Thr Pro Arg Ala Phe
260                      265                      270

Asp His Thr Lys Gln Asn Gln Asp Trp Thr Gln Trp Asn Pro Ser His
275                      280                      285

Ser Asn Pro Glu Val Leu Leu Gln Thr Thr Thr Arg Met Thr Ala Asp
290                      295                      300

Val Asp Arg Asn Gly Thr Thr Ala Tyr Glu Gly Asn Trp Asn Pro Glu
305                      310                      315                      320

Ala His Pro Pro Leu Ile His His Glu His His Glu Glu Glu Glu Thr
325                      330                      335

Pro His Ser Thr Ser Thr Ile Gln Ala Thr Pro Ser Ser Thr Thr Glu
340                      345                      350

Glu Thr Ala Thr Gln Lys Glu Gln Trp Phe Gly Asn Arg Trp His Glu
355                      360                      365

Gly Tyr Arg Gln Thr Pro Arg Glu Asp Ser His Ser Thr Thr Gly Thr
370                      375                      380

Ala Ala Ala Ser Ala His Thr Ser His Pro Met Gln Gly Arg Thr Thr
385                      390                      395                      400

Pro Ser Pro Glu Asp Ser Ser Trp Thr Asp Phe Phe Asn Pro Ile Ser
405                      410                      415

His Pro Met Gly Arg Gly His Gln Ala Gly Arg Arg Met Asp Met Asp
420                      425                      430

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Ser Ser His Ser Thr Thr Leu Gln Pro Thr Ala Asn Pro Asn Thr Gly
 435 440 445
 Leu Val Glu Asp Leu Asp Arg Thr Gly Pro Leu Ser Met Thr Thr Gln
 450 455 460
 Gln Ser Asn Ser Gln Ser Phe Ser Thr Ser His Glu Gly Leu Glu Glu
 465 470 475 480
 Asp Lys Asp His Pro Thr Thr Ser Thr Leu Thr Ser Ser Asn Arg Asn
 485 490 495
 Asp Val Thr Gly Gly Arg Arg Asp Pro Asn His Ser Glu Gly Ser Thr
 500 505 510
 Thr Leu Leu Glu Gly Tyr Thr Ser His Tyr Pro His Thr Lys Glu Ser
 515 520 525
 Arg Thr Phe Ile Pro Val Thr Ser Ala Lys Thr Gly Ser Phe Gly Val
 530 535 540
 Thr Ala Val Thr Val Gly Asp Ser Asn Ser Asn Val Asn Arg Ser Leu
 545 550 555 560
 Ser Gly Asp Gln Asp Thr Phe His Pro Ser Gly Gly Ser His Thr Thr
 565 570 575
 His Gly Ser Glu Ser Asp Gly His Ser His Gly Ser Gln Glu Gly Gly
 580 585 590
 Ala Asn Thr Thr Ser Gly Pro Ile Arg Thr Pro Gln Ile Pro Glu Trp
 595 600 605
 Leu Ile Ile Leu Ala Ser Leu Leu Ala Leu Ala Ile Leu Ala Val
 610 615 620
 Cys Ile Ala Val Asn Ser Arg Arg Arg Cys Gly Gln Lys Lys Lys Leu
 625 630 635 640
 Val Ile Asn Ser Gly Asn Gly Ala Val Glu Asp Arg Lys Pro Ser Gly
 645 650 655
 Leu Asn Gly Glu Ala Ser Lys Ser Gln Glu Met Val His Leu Val Asn
 660 665 670
 Lys Glu Ser Ser Glu Thr Pro Asp Gln Phe Met Thr Ala Asp Glu Thr
 675 680 685
 Arg Asn Leu Gln Asn Val Asp Met Lys Ile Gly Val
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<210> 12

<211> 531

<212> DNA

<213> Homo sapiens

<400> 12

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<210> 13

<211> 678

<212> DNA

<213> Homo sapiens

<400> 13

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agttatcctg gggcatacag ccataccatt ctgaaggtgt cttatctcct ctgatctaga    180
gagcaccatg aagcttctca cgggcctggt tttctgctcc ttggtcctgg gtgtcagcag    240
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<210> 14

<211> 122

<212> PRT

<213> Homo sapiens

<400> 14

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

Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
35          40          45

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Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
 50 55 60

Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asp Ala Arg
 65 70 75 80

Glu Asn Ile Gln Arg Phe Phe Gly His Gly Ala Glu Asp Ser Leu Ala
 85 90 95

Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 100 105 110

Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 115 120

<210> 15

<211> 607

<212> DNA

<213> Mus musculus

<400> 15

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<210> 16

<211> 2053

<212> DNA

<213> Homo sapiens

<400> 16

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tgtcagcagc cgaagcttct tttcgttctt tggcgaggct tttgatgggg ctggggacat	180
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ggagatggta tgataggact cctggacacc ccagacatca atcaaaacac cacagacaag	840
aagggtgtgga tacaaaaact agcagttaga agaaataata gaaaatgaac tccaactact	900
tctgaaaaaa aagtaatgag ggcaattaat acattgaaga aagcctcaat aagtacaaca	960
gtgtagtact gacttatata tagaaaaaac ctgatcagtg gaaccaaata ctcagaatta	1020
gacataagtg catatgagaa ttttgtatgt gataaagggt gtatgttaac gtattaagta	1080
aaagacggac tattcaacaa atgggattgg tacaactggg tgaccatcta aaataacatc	1140
atgttgaaaa cactactgtat atattacggg aggacaaatt ccaaataatgc taaatattta	1200
taaacaaata aggaaaatga taataataat attaacatta tctggtgaat ccatggaaaa	1260
ttcttttata gcccaaagta gggaaagctg caacaacaag gatggaactg gaggtcatta	1320
tgctaagtga aatcattcag gaacagaaag acaaacatca catgttctca cttattttgtg	1380
ggatctaaaa atcaaaacaa ttgaattcat ggagatagag aatagaagga tggttaccag	1440
aggctgggaa gggtagtggg gaggggggga gtgaggggag gtgaggatgg ttaatgagta	1500
ccaaaaaaat acttagaatg aataagagct agtattttgat agcacaaagg gggactatag	1560
tcagtaataa tttagctgta cattgtaaaa taacaaaaag agtataattg gattatttgt	1620
aacacaaagg ataaatgctt gaggggatgg ataccaatt ttccatgatg tgattattgc	1680
gcattgcatg gctgtaccaa aatatctcat gtaccccata attatataca cctactatgt	1740
accacaaaaa aattttttaa aaggaatgaa ataaaaacat ttgagttaa gaaaaccaca	1800
aaaaaacaaa gtagggaaag ctcttcaaat actatgaaat tgagaagaca actaaagaaa	1860
atattaataa agacaagaac ataaataatt tctttggcag aacataagcc atcataatca	1920
gaagataaat aagctgggaa aaatatttgt aactcatatc ctagataaca tactcathtt	1980
ccctgtatat aaaaagtttc tctaattgtg taaataaaaa cacaataaac cagtaaaaaa	2040
tgaaaaaaaa aaa	2053

<210> 17

<211> 594

<212> DNA

<213> Homo sapiens

<400> 17

aggctcacta taaatagcag ccacctctcc ctggcagaca gggacccgca gctcagctac	60
agcacagatc agcaccatga agcttctcac gggcctggtt ttctgctcct tggctctgag	120
tgtcagcagc cgaagcttct ttctgttctt tggcgaggct tttgatgggg ctggggacat	180

```

gtggagagcc tactctgaca tgagagaagc caattacatc ggctcagaca aatacttcca      240
tgctcggggg aactatgatg ctgccaaaag gggacctggg ggtgcctggg ctgcagaagt      300
gatcagcaat gccagagaga atatccagag actcacaggc cgtggtgcgg aggactcgct      360
ggccgatcag gctgccaata aatggggcag gagtggcaga gacccaatc acttccgacc      420
tgctggcctg cctgagaaat actgagcttc ctcttcaatc tgctctcagg agacctggct      480
atgaggccct cggggcaggg atacaaagt agtgaggtct atgtccagag aagctgagat      540
atggcatata ataggcatct aataaatgct taagaggtgg aatttggtga aaca          594

```

<210> 18

<211> 122

<212> PRT

<213> Homo sapiens

<400> 18

```

Met Lys Leu Leu Thr Gly Leu Val Phe Cys Ser Leu Val Leu Gly Val
1           5           10          15

```

```

Ser Ser Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala
          20           25           30

```

```

Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
          35           40           45

```

```

Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
50           55           60

```

```

Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asp Ala Arg
65           70           75           80

```

```

Glu Asn Ile Gln Arg Phe Phe Gly His Gly Ala Glu Asp Ser Leu Ala
          85           90           95

```

```

Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
          100          105          110

```

```

Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
          115          120

```

<210> 19

<211> 610

<212> DNA

<213> Mus musculus

<400> 19

```

atagaccacc agatctgccc aggagacacc agcaggatga agctactcac cagcctggtc      60
ttctgctccc tgctcctggg agtctgccat ggagggtttt ttcatattat tggggaggct      120
ttccaagggg ctggagacat gtggcgagcc tacactgaca tgaaggaagc tggctggaaa      180
gatggagaca aatacttcca tgctcggggg aactatgatg ctgccaaaag gggctccggg      240
ggagtctggg ctgctgagaa aatcagtgat gcaagagaga gctttcagga attcttcggc      300

```

```

agaggacacg aggacaccat ggctgaccag gaagccaaca gacatggccg cagtggcaaa    360
gaccccaatt actacagacc tcctggactg cctgccaaat actgagagtc ctctattag    420
ttcagaaggc tgtgttgggg tcctgagggg ggggtctggg ctctctatct aggaacactg    480
aagatgctct ctggggcaac atagtatacc tctcatgtgt gtatcccaca agggtttcag    540
aatggagtta ctcgagcagt agtaactgct tgaggaggag agggtaataa acaggaactt    600
ggaagtggat                                     610

```

<210> 20

<211> 675

<212> DNA

<213> Homo sapiens

<400> 20

```

ggatttaaaa ccgttctccc attaatgcca aagccagcag aggtaccaac tatagctcca    60
cggccagaag ataccagcag ctctgccttt actgaaattt catctggaga aaggtccaca    120
gcacaatgag gcttttcaca ggcattgttt tctgctcctt ggtcatggga gtcaccagtg    180
aaagctggcg ttcgtttttc aaggaggctc tccaaggggt tggggacatg ggcagagcct    240
attgggacat aatgatatcc aatcaccaaa attcaaacag atatctctat gctcggggaa    300
actatgatgc tgcccaaaga ggacctgggg gtgtctgggc tgctaaactc atcagccgtt    360
ccagggtcta tcttcagggg ttaatagact gctatttatt tggaacagc agcactgtat    420
tgaggagctc gaagtccaac gagaaagctg aggaatgggg ccggagtggc aaagaccccg    480
accgcttcag acctgacggc ctgcctaaga aatactgagc ttctgctcc tctgctctca    540
gggaaactgg gctgtgagcc acacacttct cccccagac agggacacag ggtcactgag    600
ctttgtgtcc ccaggaactg gtatagggca cctagagggt ttcaataaat gtttgtcaaa    660
ttgaaaaaaaa aaaaaa                                     675

```

<210> 21

<211> 130

<212> PRT

<213> Homo sapiens

<400> 21

```

Met Arg Leu Phe Thr Gly Ile Val Phe Cys Ser Leu Val Met Gly Val
1           5           10          15

Thr Ser Glu Ser Trp Arg Ser Phe Phe Lys Glu Ala Leu Gln Gly Val
20          25          30

Gly Asp Met Gly Arg Ala Tyr Trp Asp Ile Met Ile Ser Asn His Gln
35          40          45

Asn Ser Asn Arg Tyr Leu Tyr Ala Arg Gly Asn Tyr Asp Ala Ala Gln
50          55          60

Arg Gly Pro Gly Gly Val Trp Ala Ala Lys Leu Ile Ser Arg Ser Arg

```

Arg Gly Leu Gly Gly Val Asp Ala Ala Lys Leu Ile Val Arg Val Arg
65 70 75 80

Val Tyr Leu Gln Gly Leu Ile Asp Cys Tyr Leu Phe Gly Asn Ser Ser
85 90 95

Thr Val Leu Glu Asp Ser Lys Ser Asn Glu Lys Ala Glu Glu Trp Gly
100 105 110

Arg Ser Gly Lys Asp Pro Asp Arg Phe Arg Pro Asp Gly Leu Pro Lys
115 120 125

Lys Tyr
130

<210> 22

<211> 147

<212> PRT

<213> Homo sapiens

<400> 22

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

Val Ser Glu Ala Gly Pro Thr Gly Thr Gly Glu Ser Lys Cys Pro Leu
20 25 30

Met Val Lys Val Leu Asp Ala Val Arg Gly Ser Pro Ala Ile Asn Val
35 40 45

Ala Val His Val Phe Arg Lys Ala Ala Asp Asp Thr Trp Glu Pro Phe
50 55 60

Ala Ser Gly Lys Thr Ser Glu Ser Gly Glu Leu His Gly Leu Thr Thr
65 70 75 80

Glu Glu Glu Phe Val Glu Gly Ile Tyr Lys Val Glu Ile Asp Thr Lys
85 90 95

Ser Tyr Trp Lys Ala Leu Gly Ile Ser Pro Phe His Glu His Ala Glu
100 105 110

Val Val Phe Thr Ala Asn Asp Ser Gly Pro Arg Arg Tyr Thr Ile Ala
115 120 125

Ala Leu Leu Ser Pro Tyr Ser Tyr Ser Thr Thr Ala Val Val Thr Asn
130 135 140

Pro Lys Glu
145

<210> 23

<211> 938

<212> DNA

<213> Homo sapiens

<400> 23

```

gttgactaag tcaataatca gaatcagcag gtttgcaagc agattggcag ggataagcag      60
cctagctcag gagaagttag tataaaagcc ccaggctggg agcagccatc acagaagtc      120
actcattctt ggcaggatgg cttctcatcg tctgctcctc ctctgccttg ctggactgg      180
atgtgtgtct gaggctggcc ctacgggcac cgggtgaatcc aagtgtcctc tgatggtcaa      240
agttctagat gctgtccgag gcagtcctgc catcaatgtg gccgtgcatg tgttcagaaa      300
ggctgctgat gacacctggg agccatttgc ctctgggaaa accagttagt ctggagagct      360
gcatgggctc acaactgagg aggaatttgt agaagggata taaaagtgg aaatagacac      420
caaactctac tggaaggcac ttggcatctc ccattccat gagcatgcag aggtggtatt      480
cacagccaac gactccggcc cccgccgcta caccattgcc gccctgctga gccctactc      540
ctattccacc acggtgtgct tcaccaatcc caaggaatga gggacttctc ctccagtgg      600
cctgaaggac gagggatggg atttcatgta accaagagta ttccattttt actaaagcag      660

tgttttcacc tcatatgcta tgtagaagt ccaggcagag acaataaaac attcctgtga      720
aaggcacttt tcattccact ttaacttgat tttttaaat cccttattgt cccttccaaa      780
aaaaagagaa tcaaaatttt acaaagaatc aaaggaattc tagaaagtat ctgggcagaa      840
cgctaggaga gatccaaatt tccattgtct tgcaagcaaa gcacgtatta aatatgatct      900
gcagccatta aaaagacaca ttctgtaaaa aaaaaaaaa      938

```

<210> 24

<211> 147

<212> PRT

<213> Mus musculus

<400> 24

```

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

Val Ser Glu Ala Gly Pro Ala Gly Ala Gly Glu Ser Lys Cys Pro Leu
      20              25              30

Met Val Lys Val Leu Asp Ala Val Arg Gly Ser Pro Ala Val Asp Val
      35              40              45

Ala Val Lys Val Phe Lys Lys Thr Ser Glu Gly Ser Trp Glu Pro Phe
      50              55              60

Ala Ser Gly Lys Thr Ala Glu Ser Gly Glu Leu His Gly Leu Thr Thr
      65              70              75              80

Asp Glu Lys Phe Val Glu Gly Val Tyr Arg Val Glu Leu Asp Thr Lys
      85              90              95

Ser Tyr Trp Lys Thr Leu Gly Ile Ser Pro Phe His Glu Phe Ala Asp
      100             105             110

Val Val Phe Thr Ala Asn Asp Ser Gly His Arg His Tyr Thr Ile Ala

```

115 120 125

Ala Leu Leu Ser Pro Tyr Ser Tyr Ser Thr Thr Ala Val Val Ser Asn

130 135 140

Pro Gln Asn
145

<210> 25
<211> 1237
<212> DNA
<213> Mus musculus

<400> 25						
ctaattctccc	taggcaaggt	tcatatttgt	gtaggttact	tatttctcctt	ttgttgacta	60
agtcaataat	cagaatcagc	aggtttggag	tcagcttggc	agggatcagc	agcctggggt	120
ggaaggaggg	ggtataaaaag	ccccttcacc	aggagaagcc	gtcacacaga	tccacaagct	180
cctgacagga	tggcttccct	tcgactcttc	ctcctttgcc	tcgctggact	ggtatttgtg	240
tctgaagctg	gccccgcggg	tgctggagaa	tccaaatgtc	ctctgatggg	caaagtccctg	300
gatgctgtcc	gaggcagccc	tgctgtagac	gtggctgtaa	aagtgttcaa	aaagacctct	360
gagggatcct	gggagccctt	tgcctctggg	aagaccgcgg	agtctggaga	gctgcacggg	420
ctcaccacag	atgagaagtt	tgtagaagga	gtgtacagag	tagaactgga	caccaaactc	480
tactggaaga	cacttggcat	ttccccgttc	catgaattcg	cggatgtggg	tttcacagcc	540
aacgactctg	gccatcgcca	ctacaccatc	gcagccctgc	tcagcccata	ctcctacagc	600
accacggctg	tcgtcagcaa	cccccagaat	tgagagactc	agcccaggag	gaccaggatc	660
ttgccaaaagc	agtagcatcc	cattttgtacc	aaaacagtgt	tcttgctcta	taaaccgtgt	720
tagcagctca	ggaagatgcc	gtgaagcatt	cttattaaac	cacctgctat	ttcattcaaa	780
ctgtgtttct	tttttatttc	ctcatttttc	tcccctgctc	ctaaaacca	aaatcttcta	840
aagaattcta	gaaggtatgc	gatcaaaactt	tttaaagaaa	gaaaatactt	tttgactcat	900
ggtttaaagg	catcctttcc	atcttgggga	ggtcatgggt	gctcctggca	acttgcttga	960
ggaagatagg	tcagaaagca	gagtggacca	accgttcaat	gtttttacaag	caaacatac	1020
actaagcatg	gtctgtagct	attaaaaagca	cacaatctga	agggtcttag	atgcacagta	1080
gtgttttccc	agagcatgtt	caaaagccct	gggttcaatc	acaatactga	aaagtaggcc	1140
aaaaaacatt	ctgaaaatga	aatatttggg	ttttttttta	taacctttag	tgactaaata	1200
aagacaaatc	taagagacta	aaaaaaaaaa	aaaaaaa			1237

<210> 26
<211> 4563
<212> PRT
<213> Homo sapiens

<400> 26
Met Asp Pro Pro Arg Pro Ala Leu Leu Ala Leu Leu Ala Leu Pro Ala
1 5 10 15

Leu Leu Leu Leu Leu Leu Ala Gly Ala Arg Ala Glu Glu Glu Met Leu
 20 25 30

Glu Asn Val Ser Leu Val Cys Pro Lys Asp Ala Thr Arg Phe Lys His
 35 40 45

Leu Arg Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu Ser Ser Ser Gly Val
 50 55 60

Pro Gly Thr Ala Asp Ser Arg Ser Ala Thr Arg Ile Asn Cys Lys Val
 65 70 75 80

Glu Leu Glu Val Pro Gln Leu Cys Ser Phe Ile Leu Lys Thr Ser Gln
 85 90 95

Cys Thr Leu Lys Glu Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu
 100 105 110

Leu Lys Lys Thr Lys Asn Ser Glu Glu Phe Ala Ala Ala Met Ser Arg
 115 120 125

Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly Lys Gln Val Phe Leu Tyr
 130 135 140

Pro Glu Lys Asp Glu Pro Thr Tyr Ile Leu Asn Ile Lys Arg Gly Ile
 145 150 155 160

Ile Ser Ala Leu Leu Val Pro Pro Glu Thr Glu Glu Ala Lys Gln Val
 165 170 175

Leu Phe Leu Asp Thr Val Tyr Gly Asn Cys Ser Thr His Phe Thr Val
 180 185 190

Lys Thr Arg Lys Gly Asn Val Ala Thr Glu Ile Ser Thr Glu Arg Asp
 195 200 205

Leu Gly Gln Cys Asp Arg Phe Lys Pro Ile Arg Thr Gly Ile Ser Pro
 210 215 220

Leu Ala Leu Ile Lys Gly Met Thr Arg Pro Leu Ser Thr Leu Ile Ser
 225 230 235 240

Ser Ser Gln Ser Cys Gln Tyr Thr Leu Asp Ala Lys Arg Lys His Val
 245 250 255

Ala Glu Ala Ile Cys Lys Glu Gln His Leu Phe Leu Pro Phe Ser Tyr
 260 265 270

Lys Asn Lys Tyr Gly Met Val Ala Gln Val Thr Gln Thr Leu Lys Leu
 275 280 285

Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe Phe Gly Glu Gly Thr Lys
 290 295 300

Lys Met Gly Leu Ala Phe Glu Ser Thr Lys Ser Thr Ser Pro Pro Lys
 305 310 315 320

Gln Ala Glu Ala Val Leu Lys Thr Leu Gln Glu Leu Lys Lys Leu Thr
 325 330 335

Ile Ser Glu Gln Asn Ile Gln Arg Ala Asn Leu Phe Asn Lys Leu Val
 340 345 350

Thr Glu Leu Arg Gly Leu Ser Asp Glu Ala Val Thr Ser Leu Leu Pro
 355 360 365

Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu Gln Ala Leu Val Gln
 370 375 380

Cys Gly Gln Pro Gln Cys Ser Thr His Ile Leu Gln Trp Leu Lys Arg
 385 390 395 400

Val His Ala Asn Pro Leu Leu Ile Asp Val Val Thr Tyr Leu Val Ala
 405 410 415

Leu Ile Pro Glu Pro Ser Ala Gln Gln Leu Arg Glu Ile Phe Asn Met
 420 425 430

Ala Arg Asp Gln Arg Ser Arg Ala Thr Leu Tyr Ala Leu Ser His Ala
 435 440 445

Val Asn Asn Tyr His Lys Thr Asn Pro Thr Gly Thr Gln Glu Leu Leu
 450 455 460

Asp Ile Ala Asn Tyr Leu Met Glu Gln Ile Gln Asp Asp Cys Thr Gly
 465 470 475 480

Asp Glu Asp Tyr Thr Tyr Leu Ile Leu Arg Val Ile Gly Asn Met Gly
 485 490 495

Gln Thr Met Glu Gln Leu Thr Pro Glu Leu Lys Ser Ser Ile Leu Lys
 500 505 510

Cys Val Gln Ser Thr Lys Pro Ser Leu Met Ile Gln Lys Ala Ala Ile
 515 520 525

Gln Ala Leu Arg Lys Met Glu Pro Lys Asp Lys Asp Gln Glu Val Leu
 530 535 540

Leu Gln Thr Phe Leu Asp Asp Ala Ser Pro Gly Asp Lys Arg Leu Ala
 545 550 555 560

Ala Tyr Leu Met Leu Met Arg Ser Pro Ser Gln Ala Asp Ile Asn Lys
 565 570 575

Ile Val Gln Ile Leu Pro Trp Glu Gln Asn Glu Gln Val Lys Asn Phe
 580 585 590

Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser Glu Glu Leu Asp Ile
 595 600 605

Gln Asp Leu Lys Lys Leu Val Lys Glu Ala Leu Lys Glu Ser Gln Leu
 610 615 620

Pro Thr Val Met Asp Phe Arg Lys Phe Ser Arg Asn Tyr Gln Leu Tyr
 625 630 635 640

Lys Ser Val Ser Leu Pro Ser Leu Asp Pro Ala Ser Ala Lys Ile Glu
 645 650 655

Gly Asn Leu Ile Phe Asp Pro Asn Asn Tyr Leu Pro Lys Glu Ser Met
 660 665 670

Leu Lys Thr Thr Leu Thr Ala Phe Gly Phe Ala Ser Ala Asp Leu Ile
 675 680 685

Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro Thr Leu Glu Ala Leu
 690 695 700

Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val Asn Lys Ala Leu Tyr
 705 710 715 720

Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser Lys Val Leu Val Asp
 725 730 735

His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu Gln Asp Met Val Asn
 740 745 750

Gly Ile Met Leu Ser Val Glu Lys Leu Ile Lys Asp Leu Lys Ser Lys
 755 760 765

Glu Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile Leu Gly Glu Glu Leu
 770 775 780

Gly Phe Ala Ser Leu His Asp Leu Gln Leu Leu Gly Lys Leu Leu Leu
 785 790 795 800

Met Gly Ala Arg Thr Leu Gln Gly Ile Pro Gln Met Ile Gly Glu Val
 805 810 815

Ile Arg Lys Gly Ser Lys Asn Asp Phe Phe Leu His Tyr Ile Phe Met
 820 825 830

Glu Asn Ala Phe Glu Leu Pro Thr Gly Ala Gly Leu Gln Leu Gln Ile
 835 840 845

Ser Ser Ser Gly Val Ile Ala Pro Gly Ala Lys Ala Gly Val Lys Leu
 850 855 860

Glu Val Ala Asn Met Gln Ala Glu Leu Val Ala Lys Pro Ser Val Ser
 865 870 875 880

Val Glu Phe Val Thr Asn Met Gly Ile Ile Ile Pro Asp Phe Ala Arg
 885 890 895

Ser Gly Val Gln Met Asn Thr Asn Phe Phe His Glu Ser Gly Leu Glu
 900 905 910

Ala His Val Ala Leu Lys Ala Gly Lys Leu Lys Phe Ile Ile Pro Ser
 915 920 925

Pro Lys Arg Pro Val Lys Leu Leu Ser Gly Gly Asn Thr Leu His Leu
 930 935 940

Val Ser Thr Thr Lys Thr Glu Val Ile Pro Pro Leu Ile Glu Asn Arg
 945 950 955 960

Gln Ser Trp Ser Val Cys Lys Gln Val Phe Pro Gly Leu Asn Tyr Cys
 965 970 975

Thr Ser Gly Ala Tyr Ser Asn Ala Ser Ser Thr Asp Ser Ala Ser Tyr
 980 985 990

Tyr Pro Leu Thr Gly Asp Thr Arg Leu Glu Leu Glu Leu Arg Pro Thr
 995 1000 1005

Gly Glu Ile Glu Gln Tyr Ser Val Ser Ala Thr Tyr Glu Leu Gln
 1010 1015 1020

Arg Glu Asp Arg Ala Leu Val Asp Thr Leu Lys Phe Val Thr Gln
 1025 1030 1035

Ala Glu Gly Ala Lys Gln Thr Glu Ala Thr Met Thr Phe Lys Tyr
 1040 1045 1050

Asn Arg Gln Ser Met Thr Leu Ser Ser Glu Val Gln Ile Pro Asp
 1055 1060 1065

Phe Asp Val Asp Leu Gly Thr Ile Leu Arg Val Asn Asp Glu Ser
 1070 1075 1080

Thr Glu Gly Lys Thr Ser Tyr Arg Leu Thr Leu Asp Ile Gln Asn
 1085 1090 1095

Lys Lys Ile Thr Glu Val Ala Leu Met Gly His Leu Ser Cys Asp
 1100 1105 1110

Thr Lys Glu Glu Arg Lys Ile Lys Gly Val Ile Ser Ile Pro Arg
 1115 1120 1125

Leu Gln Ala Glu Ala Arg Ser Glu Ile Leu Ala His Trp Ser Pro
 1130 1135 1140

Ala Lys Leu Leu Leu Gln Met Asp Ser Ser Ala Thr Ala Tyr Gly
 1145 1150 1155

Ser Thr Val Ser Lys Arg Val Ala Trp His Tyr Asp Glu Glu Lys
 1160 1165 1170

Ile Glu Phe Glu Trp Asn Thr Gly Thr Asn Val Asp Thr Lys Lys
 1175 1180 1185

Met Thr Ser Asn Phe Pro Val Asp Leu Ser Asp Tyr Pro Lys Ser
 1190 1195 1200

Leu His 1205	Met Tyr Ala Asn Arg 1210	Leu Leu Asp His Arg 1215	Val Pro Gln
Thr Asp 1220	Met Thr Phe Arg His 1225	Val Gly Ser Lys Leu 1230	Ile Val Ala
Met Ser 1235	Ser Trp Leu Gln Lys 1240	Ala Ser Gly Ser Leu 1245	Pro Tyr Thr
Gln Thr 1250	Leu Gln Asp His Leu 1255	Asn Ser Leu Lys Glu 1260	Phe Asn Leu
Gln Asn 1265	Met Gly Leu Pro Asp 1270	Phe His Ile Pro Glu 1275	Asn Leu Phe
Leu Lys 1280	Ser Asp Gly Arg Val 1285	Lys Tyr Thr Leu Asn 1290	Lys Asn Ser
Leu Lys 1295	Ile Glu Ile Pro Leu 1300	Pro Phe Gly Gly Lys 1305	Ser Ser Arg
Asp Leu 1310	Lys Met Leu Glu Thr 1315	Val Arg Thr Pro Ala 1320	Leu His Phe
Lys Ser 1325	Val Gly Phe His Leu 1330	Pro Ser Arg Glu Phe 1335	Gln Val Pro
Thr Phe 1340	Thr Ile Pro Lys Leu 1345	Tyr Gln Leu Gln Val 1350	Pro Leu Leu
Gly Val 1355	Leu Asp Leu Ser Thr 1360	Asn Val Tyr Ser Asn 1365	Leu Tyr Asn
Trp Ser 1370	Ala Ser Tyr Ser Gly 1375	Gly Asn Thr Ser Thr 1380	Asp His Phe
Ser Leu 1385	Arg Ala Arg Tyr His 1390	Met Lys Ala Asp Ser 1395	Val Val Asp
Leu Leu 1400	Ser Tyr Asn Val Gln 1405	Gly Ser Gly Glu Thr 1410	Thr Tyr Asp
His Lys 1415	Asn Thr Phe Thr Leu 1420	Ser Cys Asp Gly Ser 1425	Leu Arg His
Lys Phe 1430	Leu Asp Ser Asn Ile 1435	Lys Phe Ser His Val 1440	Glu Lys Leu
Gly Asn 1445	Asn Pro Val Ser Lys 1450	Gly Leu Leu Ile Phe 1455	Asp Ala Ser
Ser Ser 1460	Trp Gly Pro Gln Met 1465	Ser Ala Ser Val His 1470	Leu Asp Ser
Lys Lys 1475	Lys Gln His Leu Phe 1480	Val Lys Glu Val Lys 1485	Ile Asp Gly

Gln Phe	Arg Val Ser Ser Phe	Tyr Ala Lys Gly Thr	Tyr Gly Leu
1490	1495	1500	
Ser Cys	Gln Arg Asp Pro Asn	Thr Gly Arg Leu Asn	Gly Glu Ser
1505	1510	1515	
Asn Leu	Arg Phe Asn Ser Ser	Tyr Leu Gln Gly Thr	Asn Gln Ile
1520	1525	1530	
Thr Gly	Arg Tyr Glu Asp Gly	Thr Leu Ser Leu Thr	Ser Thr Ser
1535	1540	1545	
Asp Leu	Gln Ser Gly Ile Ile	Lys Asn Thr Ala Ser	Leu Lys Tyr
1550	1555	1560	
Glu Asn	Tyr Glu Leu Thr Leu	Lys Ser Asp Thr Asn	Gly Lys Tyr
1565	1570	1575	
Lys Asn	Phe Ala Thr Ser Asn	Lys Met Asp Met Thr	Phe Ser Lys
1580	1585	1590	
Gln Asn	Ala Leu Leu Arg Ser	Glu Tyr Gln Ala Asp	Tyr Glu Ser
1595	1600	1605	
Leu Arg	Phe Phe Ser Leu Leu	Ser Gly Ser Leu Asn	Ser His Gly
1610	1615	1620	
Leu Glu	Leu Asn Ala Asp Ile	Leu Gly Thr Asp Lys	Ile Asn Ser
1625	1630	1635	
Gly Ala	His Lys Ala Thr Leu	Arg Ile Gly Gln Asp	Gly Ile Ser
1640	1645	1650	
Thr Ser	Ala Thr Thr Asn Leu	Lys Cys Ser Leu Leu	Val Leu Glu
1655	1660	1665	
Asn Glu	Leu Asn Ala Glu Leu	Gly Leu Ser Gly Ala	Ser Met Lys
1670	1675	1680	
Leu Thr	Thr Asn Gly Arg Phe	Arg Glu His Asn Ala	Lys Phe Ser
1685	1690	1695	
Leu Asp	Gly Lys Ala Ala Leu	Thr Glu Leu Ser Leu	Gly Ser Ala
1700	1705	1710	
Tyr Gln	Ala Met Ile Leu Gly	Val Asp Ser Lys Asn	Ile Phe Asn
1715	1720	1725	
Phe Lys	Val Ser Gln Glu Gly	Leu Lys Leu Ser Asn	Asp Met Met
1730	1735	1740	
Gly Ser	Tyr Ala Glu Met Lys	Phe Asp His Thr Asn	Ser Leu Asn
1745	1750	1755	
Ile Ala	Gly Leu Ser Leu Asp	Phe Ser Ser Lys Leu	Asp Asn Ile
1760	1765	1770	

1760					1765					1770				
Tyr	Ser	Ser	Asp	Lys	Phe	Tyr	Lys	Gln	Thr	Val	Asn	Leu	Gln	Leu
1775						1780					1785			
Gln	Pro	Tyr	Ser	Leu	Val	Thr	Thr	Leu	Asn	Ser	Asp	Leu	Lys	Tyr
1790						1795					1800			
Asn	Ala	Leu	Asp	Leu	Thr	Asn	Asn	Gly	Lys	Leu	Arg	Leu	Glu	Pro
1805						1810					1815			
Leu	Lys	Leu	His	Val	Ala	Gly	Asn	Leu	Lys	Gly	Ala	Tyr	Gln	Asn
1820						1825					1830			
Asn	Glu	Ile	Lys	His	Ile	Tyr	Ala	Ile	Ser	Ser	Ala	Ala	Leu	Ser
1835						1840					1845			
Ala	Ser	Tyr	Lys	Ala	Asp	Thr	Val	Ala	Lys	Val	Gln	Gly	Val	Glu
1850						1855					1860			
Phe	Ser	His	Arg	Leu	Asn	Thr	Asp	Ile	Ala	Gly	Leu	Ala	Ser	Ala
1865						1870					1875			
Ile	Asp	Met	Ser	Thr	Asn	Tyr	Asn	Ser	Asp	Ser	Leu	His	Phe	Ser
1880						1885					1890			
Asn	Val	Phe	Arg	Ser	Val	Met	Ala	Pro	Phe	Thr	Met	Thr	Ile	Asp
1895						1900					1905			
Ala	His	Thr	Asn	Gly	Asn	Gly	Lys	Leu	Ala	Leu	Trp	Gly	Glu	His
1910						1915					1920			
Thr	Gly	Gln	Leu	Tyr	Ser	Lys	Phe	Leu	Leu	Lys	Ala	Glu	Pro	Leu
1925						1930					1935			
Ala	Phe	Thr	Phe	Ser	His	Asp	Tyr	Lys	Gly	Ser	Thr	Ser	His	His
1940						1945					1950			
Leu	Val	Ser	Arg	Lys	Ser	Ile	Ser	Ala	Ala	Leu	Glu	His	Lys	Val
1955						1960					1965			
Ser	Ala	Leu	Leu	Thr	Pro	Ala	Glu	Gln	Thr	Gly	Thr	Trp	Lys	Leu
1970						1975					1980			
Lys	Thr	Gln	Phe	Asn	Asn	Asn	Glu	Tyr	Ser	Gln	Asp	Leu	Asp	Ala
1985						1990					1995			
Tyr	Asn	Thr	Lys	Asp	Lys	Ile	Gly	Val	Glu	Leu	Thr	Gly	Arg	Thr
2000						2005					2010			
Leu	Ala	Asp	Leu	Thr	Leu	Leu	Asp	Ser	Pro	Ile	Lys	Val	Pro	Leu
2015						2020					2025			
Leu	Leu	Ser	Glu	Pro	Ile	Asn	Ile	Ile	Asp	Ala	Leu	Glu	Met	Arg
2030						2035					2040			
Asp	Ala	Val	Glu	Lys	Pro	Gln	Glu	Phe	Thr	Ile	Val	Ala	Phe	Val
2045						2050					2055			

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Lys Tyr Asp Lys Asn Gln Asp Val His Ser Ile Asn Leu Pro Phe
2060                               2065                               2070

Phe Glu Thr Leu Gln Glu Tyr Phe Glu Arg Asn Arg Gln Thr Ile
2075                               2080                               2085

Ile Val Val Leu Glu Asn Val Gln Arg Asn Leu Lys His Ile Asn
2090                               2095                               2100

Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala Ala Leu Gly Lys Leu
2105                               2110                               2115

Pro Gln Gln Ala Asn Asp Tyr Leu Asn Ser Phe Asn Trp Glu Arg
2120                               2125                               2130

Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala Leu Thr Lys Lys
2135                               2140                               2145

Tyr Arg Ile Thr Glu Asn Asp Ile Gln Ile Ala Leu Asp Asp Ala
2150                               2155                               2160

Lys Ile Asn Phe Asn Glu Lys Leu Ser Gln Leu Gln Thr Tyr Met
2165                               2170                               2175

Ile Gln Phe Asp Gln Tyr Ile Lys Asp Ser Tyr Asp Leu His Asp
2180                               2185                               2190

Leu Lys Ile Ala Ile Ala Asn Ile Ile Asp Glu Ile Ile Glu Lys
2195                               2200                               2205

Leu Lys Ser Leu Asp Glu His Tyr His Ile Arg Val Asn Leu Val
2210                               2215                               2220

Lys Thr Ile His Asp Leu His Leu Phe Ile Glu Asn Ile Asp Phe
2225                               2230                               2235

Asn Lys Ser Gly Ser Ser Thr Ala Ser Trp Ile Gln Asn Val Asp
2240                               2245                               2250

Thr Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln
2255                               2260                               2265

Leu Lys Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly
2270                               2275                               2280

Lys Leu Lys Gln His Ile Glu Ala Ile Asp Val Arg Val Leu Leu
2285                               2290                               2295

Asp Gln Leu Gly Thr Thr Ile Ser Phe Glu Arg Ile Asn Asp Val
2300                               2305                               2310

Leu Glu His Val Lys His Phe Val Ile Asn Leu Ile Gly Asp Phe
2315                               2320                               2325

Glu Val Ala Glu Lys Ile Asn Ala Phe Arg Ala Lys Val His Glu
2330                               2335                               2340

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Leu Ile	Glu Arg Tyr Glu Val	Asp Gln Gln Ile Gln	Val Leu Met
2345	2350	2355	
Asp Lys	Leu Val Glu Leu Ala	His Gln Tyr Lys Leu	Lys Glu Thr
2360	2365	2370	
Ile Gln	Lys Leu Ser Asn Val	Leu Gln Gln Val Lys	Ile Lys Asp
2375	2380	2385	
Tyr Phe	Glu Lys Leu Val Gly	Phe Ile Asp Asp Ala	Val Lys Lys
2390	2395	2400	
Leu Asn	Glu Leu Ser Phe Lys	Thr Phe Ile Glu Asp	Val Asn Lys
2405	2410	2415	
Phe Leu	Asp Met Leu Ile Lys	Lys Leu Lys Ser Phe	Asp Tyr His
2420	2425	2430	
Gln Phe	Val Asp Glu Thr Asn	Asp Lys Ile Arg Glu	Val Thr Gln
2435	2440	2445	
Arg Leu	Asn Gly Glu Ile Gln	Ala Leu Glu Leu Pro	Gln Lys Ala
2450	2455	2460	
Glu Ala	Leu Lys Leu Phe Leu	Glu Glu Thr Lys Ala	Thr Val Ala
2465	2470	2475	
Val Tyr	Leu Glu Ser Leu Gln	Asp Thr Lys Ile Thr	Leu Ile Ile
2480	2485	2490	
Asn Trp	Leu Gln Glu Ala Leu	Ser Ser Ala Ser Leu	Ala His Met
2495	2500	2505	
Lys Ala	Lys Phe Arg Glu Thr	Leu Glu Asp Thr Arg	Asp Arg Met
2510	2515	2520	
Tyr Gln	Met Asp Ile Gln Gln	Glu Leu Gln Arg Tyr	Leu Ser Leu
2525	2530	2535	
Val Gly	Gln Val Tyr Ser Thr	Leu Val Thr Tyr Ile	Ser Asp Trp
2540	2545	2550	
Trp Thr	Leu Ala Ala Lys Asn	Leu Thr Asp Phe Ala	Glu Gln Tyr
2555	2560	2565	
Ser Ile	Gln Asp Trp Ala Lys	Arg Met Lys Ala Leu	Val Glu Gln
2570	2575	2580	
Gly Phe	Thr Val Pro Glu Ile	Lys Thr Ile Leu Gly	Thr Met Pro
2585	2590	2595	
Ala Phe	Glu Val Ser Leu Gln	Ala Leu Gln Lys Ala	Thr Phe Gln
2600	2605	2610	

Thr	Pro	Asp	Phe	Ile	Val	Pro	Leu	Thr	Asp	Leu	Arg	Ile	Pro	Ser
2615						2620					2625			
Val	Gln	Ile	Asn	Phe	Lys	Asp	Leu	Lys	Asn	Ile	Lys	Ile	Pro	Ser
2630						2635					2640			
Arg	Phe	Ser	Thr	Pro	Glu	Phe	Thr	Ile	Leu	Asn	Thr	Phe	His	Ile
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Pro	Ser	Phe	Thr	Ile	Asp	Phe	Val	Glu	Met	Lys	Val	Lys	Ile	Ile
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Arg	Thr	Ile	Asp	Gln	Met	Leu	Asn	Ser	Glu	Leu	Gln	Trp	Pro	Val
2675						2680					2685			
Pro	Asp	Ile	Tyr	Leu	Arg	Asp	Leu	Lys	Val	Glu	Asp	Ile	Pro	Leu
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Ala	Arg	Ile	Thr	Leu	Pro	Asp	Phe	Arg	Leu	Pro	Glu	Ile	Ala	Ile
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Pro	Glu	Phe	Ile	Ile	Pro	Thr	Leu	Asn	Leu	Asn	Asp	Phe	Gln	Val
2720						2725					2730			
Pro	Asp	Leu	His	Ile	Pro	Glu	Phe	Gln	Leu	Pro	His	Ile	Ser	His
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Thr	Ile	Glu	Val	Pro	Thr	Phe	Gly	Lys	Leu	Tyr	Ser	Ile	Leu	Lys
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Ile	Gln	Ser	Pro	Leu	Phe	Thr	Leu	Asp	Ala	Asn	Ala	Asp	Ile	Gly
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Asn	Gly	Thr	Thr	Ser	Ala	Asn	Glu	Ala	Gly	Ile	Ala	Ala	Ser	Ile
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Thr	Ala	Lys	Gly	Glu	Ser	Lys	Leu	Glu	Val	Leu	Asn	Phe	Asp	Phe
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Gln	Ala	Asn	Ala	Gln	Leu	Ser	Asn	Pro	Lys	Ile	Asn	Pro	Leu	Ala
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Leu	Lys	Glu	Ser	Val	Lys	Phe	Ser	Ser	Lys	Tyr	Leu	Arg	Thr	Glu
2825						2830					2835			
His	Gly	Ser	Glu	Met	Leu	Phe	Phe	Gly	Asn	Ala	Ile	Glu	Gly	Lys
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Ser	Asn	Thr	Val	Ala	Ser	Leu	His	Thr	Glu	Lys	Asn	Thr	Leu	Glu
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Asp Phe 2900	Ser Ser Gln Ala	Asp 2905	Leu Arg Asn Glu	Ile 2910	Lys Thr Leu
Leu Lys 2915	Ala Gly His Ile	Ala 2920	Trp Thr Ser Ser	Gly 2925	Lys Gly Ser
Trp Lys 2930	Trp Ala Cys Pro	Arg 2935	Phe Ser Asp Glu	Gly 2940	Thr His Glu
Ser Gln 2945	Ile Ser Phe Thr	Ile 2950	Glu Gly Pro Leu	Thr 2955	Ser Phe Gly
Leu Ser 2960	Asn Lys Ile Asn	Ser 2965	Lys His Leu Arg	Val 2970	Asn Gln Asn
Leu Val 2975	Tyr Glu Ser Gly	Ser 2980	Leu Asn Phe Ser	Lys 2985	Leu Glu Ile
Gln Ser 2990	Gln Val Asp Ser	Gln 2995	His Val Gly His	Ser 3000	Val Leu Thr
Ala Lys 3005	Gly Met Ala Leu	Phe 3010	Gly Glu Gly Lys	Ala 3015	Glu Phe Thr
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Asn Ile 3110	Met Glu Ala His	Val 3115	Gly Ile Asn Gly	Glu 3120	Ala Asn Leu
Asp Phe 3125	Leu Asn Ile Pro	Leu 3130	Thr Ile Pro Glu	Met 3135	Arg Leu Pro
Tyr Thr 3140	Ile Ile Thr Thr	Pro 3145	Pro Leu Lys Asp	Phe 3150	Ser Leu Trp
Glu Lys 3155	Thr Gly Leu Lys	Glu 3160	Phe Leu Lys Thr	Thr 3165	Lys Gln Ser
Phe Asp 3170	Leu Ser Val Lys	Ala 3175	Gln Tyr Lys Lys	Asn 3180	Lys His Arg

His Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu Phe Ile Ser
3185 3190 3195

Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn
3200 3205 3210

Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile
3215 3220 3225

Lys Phe Asp Lys Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro
3230 3235 3240

Arg Thr Phe Gln Ile Pro Gly Tyr Thr Val Pro Val Val Asn Val
3245 3250 3255

Glu Val Ser Pro Phe Thr Ile Glu Met Ser Ala Phe Gly Tyr Val
3260 3265 3270

Phe Pro Lys Ala Val Ser Met Pro Ser Phe Ser Ile Leu Gly Ser
3275 3280 3285

Asp Val Arg Val Pro Ser Tyr Thr Leu Ile Leu Pro Ser Leu Glu
3290 3295 3300

Leu Pro Val Leu His Val Pro Arg Asn Leu Lys Leu Ser Leu Pro
3305 3310 3315

Asp Phe Lys Glu Leu Cys Thr Ile Ser His Ile Phe Ile Pro Ala
3320 3325 3330

Met Gly Asn Ile Thr Tyr Asp Phe Ser Phe Lys Ser Ser Val Ile
3335 3340 3345

Thr Leu Asn Thr Asn Ala Glu Leu Phe Asn Gln Ser Asp Ile Val
3350 3355 3360

Ala His Leu Leu Ser Ser Ser Ser Ser Val Ile Asp Ala Leu Gln
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Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg Gly Leu
3380 3385 3390

Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val Glu Gly
3395 3400 3405

Ser His Asn Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu Val
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Ser Val Ala Thr Thr Thr Lys Ala Gln Ile Pro Ile Leu Arg Met
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Asn Phe Lys Gln Glu Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr
3440 3445 3450

Val Ser Ser Ser Met Glu Phe Lys Tyr Asp Phe Asn Ser Ser Met

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Glu Ser	Leu Thr Ser Tyr	Phe	Ser Ile Glu Ser	Ser Thr Lys Gly
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Asp Val	Lys Gly Ser Val	Leu	Ser Arg Glu Tyr	Ser Gly Thr Ile
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Ala Ser	Glu Ala Asn Thr	Tyr	Leu Asn Ser Lys	Ser Thr Arg Ser
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Ser Val	Lys Leu Gln Gly	Thr	Ser Lys Ile Asp	Asp Ile Trp Asn
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Leu Glu	Val Lys Glu Asn	Phe	Ala Gly Glu Ala	Thr Leu Gln Arg
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Ile Tyr	Ser Leu Trp Glu	His	Ser Thr Lys Asn	His Leu Gln Leu
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Glu Gly	Leu Phe Phe Thr	Asn	Gly Glu His Thr	Ser Lys Ala Thr
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Leu Glu	Leu Ser Pro Trp	Gln	Met Ser Ala Leu	Val Gln Val His
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Ala Ser	Gln Pro Ser Ser	Phe	His Asp Phe Pro	Asp Leu Gly Gln
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Glu Val	Ala Leu Asn Ala	Asn	Thr Lys Asn Gln	Lys Ile Arg Trp
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Lys Asn	Glu Val Arg Ile	His	Ser Gly Ser Phe	Gln Ser Gln Val
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Glu Leu	Ser Asn Asp Gln	Glu	Lys Ala His Leu	Asp Ile Ala Gly
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Ser Leu	Glu Gly His Leu	Arg	Phe Leu Lys Asn	Ile Ile Leu Pro
3665		3670		3675
Val Tyr	Asp Lys Ser Leu	Trp	Asp Phe Leu Lys	Leu Asp Val Thr
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Thr Ser	Ile Gly Arg Arg	Gln	His Leu Arg Val	Ser Thr Ala Phe
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Val Tyr	Thr Lys Asn Pro	Asn	Gly Tyr Ser Phe	Ser Ile Pro Val
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Lys Val	Leu Ala Asp Lys	Phe	Ile Ile Pro Gly	Leu Lys Leu Asn
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Asp Leu	Asn Ser Val Leu	Val	Met Pro Thr Phe	His Val Pro Phe

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

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Ser Leu Lys Asp Asn Val 4070	Pro Lys Ala Thr Gly 4075	Val Leu Tyr Asp 4080
Tyr Val Asn Lys Tyr His 4085	Trp Glu His Thr Gly 4090	Leu Thr Leu Arg 4095
Glu Val Ser Ser Lys Leu 4100	Arg Arg Asn Leu Gln 4105	Asn Asn Ala Glu 4110
Trp Val Tyr Gln Gly Ala 4115	Ile Arg Gln Ile Asp 4120	Asp Ile Asp Val 4125
Arg Phe Gln Lys Ala Ala 4130	Ser Gly Thr Thr Gly 4135	Thr Tyr Gln Glu 4140
Trp Lys Asp Lys Ala Gln 4145	Asn Leu Tyr Gln Glu 4150	Leu Leu Thr Gln 4155
Glu Gly Gln Ala Ser Phe 4160	Gln Gly Leu Lys Asp 4165	Asn Val Phe Asp 4170
Gly Leu Val Arg Val Thr 4175	Gln Glu Phe His Met 4180	Lys Val Lys His 4185
Leu Ile Asp Ser Leu Ile 4190	Asp Phe Leu Asn Phe 4195	Pro Arg Phe Gln 4200
Phe Pro Gly Lys Pro Gly 4205	Ile Tyr Thr Arg Glu 4210	Glu Leu Cys Thr 4215
Met Phe Ile Arg Glu Val 4220	Gly Thr Val Leu Ser 4225	Gln Val Tyr Ser 4230
Lys Val His Asn Gly Ser 4235	Glu Ile Leu Phe Ser 4240	Tyr Phe Gln Asp 4245
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Glu Val Leu Arg Asn Leu 4295	Gln Asp Leu Leu Gln 4300	Phe Ile Phe Gln 4305
Leu Ile Glu Asp Asn Ile 4310	Lys Gln Leu Lys Glu 4315	Met Lys Phe Thr 4320

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Asp Tyr	Ile Pro Tyr Val	Phe Lys Leu Leu Lys Glu	Asn Leu Cys		
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Leu Asn	Leu His Lys Phe Asn	Glu Phe Ile Gln Asn	Glu Leu Gln		
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Glu Ala	Ser Gln Glu Leu Gln	Gln Ile His Gln Tyr	Ile Met Ala		
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Leu Arg	Glu Glu Tyr Phe Asp	Pro Ser Ile Val Gly	Trp Thr Val		
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Lys Tyr	Tyr Glu Leu Glu Glu	Lys Ile Val Ser Leu	Ile Lys Asn		
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Leu Leu	Val Ala Leu Lys Asp	Phe His Ser Glu Tyr	Ile Val Ser		
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Ala Ser	Asn Phe Thr Ser Gln	Leu Ser Ser Gln Val	Glu Gln Phe		
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Leu His	Arg Asn Ile Gln Glu	Tyr Leu Ser Ile Leu	Thr Asp Pro		
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Ser Asp	Tyr His Gln Gln Phe	Arg Tyr Lys Leu Gln	Asp Phe Ser		
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Asp Gln	Leu Ser Asp Tyr Tyr	Glu Lys Phe Ile Ala	Glu Ser Lys		
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Arg Leu	Ile Asp Leu Ser Ile	Gln Asn Tyr His Thr	Phe Leu Ile		
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<211> 14121

<212> DNA

<213> Homo sapiens

<400> 27

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Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly Lys Gln Ile Val Leu Tyr
130         135         140

Pro Asp Lys Asp Glu Pro Lys Tyr Ile Leu Asn Ile Lys Arg Gly Ile
145         150         155         160

Tyr Ser Ala Tyr Tyr Val Phe Phe Glu Thr Glu Glu Tyr Glu Glu Glu
165         170         175         180

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Ile Ser Ala Leu Leu Val Pro Pro Glu Thr Glu Glu Asp Gln Gln Glu
      165                      170                      175

Leu Phe Leu Asp Thr Val Tyr Gly Asn Cys Ser Thr Gln Val Thr Val
      180                      185                      190

Asn Ser Arg Lys Gly Thr Val Pro Thr Glu Met Ser Thr Glu Arg Asn
      195                      200                      205

Leu Gln Gln Cys Asp Gly Phe Gln Pro Ile Ser Thr Ser Val Ser Pro
      210                      215                      220

Leu Ala Leu Ile Lys Gly Leu Val His Pro Leu Ser Thr Leu Ile Ser
      225                      230                      235                      240

Ser Ser Gln Thr Cys Gln Tyr Thr Leu Asp Pro Lys Arg Lys His Val
      245                      250                      255

Ser Glu Ala Val Cys Asp Glu Gln His Leu Phe Leu Pro Phe Ser Tyr
      260                      265                      270

Lys Asn Lys Tyr Gly Ile Met Thr Arg Val Thr Gln Lys Leu Ser Leu
      275                      280                      285

Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe Phe Ser Glu Gly Thr Asn
      290                      295                      300

Arg Met Gly Leu Ala Phe Glu Ser Thr Lys Ser Thr Ser Ser Pro Lys
      305                      310                      315                      320

Gln Ala Asp Ala Val Leu Lys Thr Leu Gln Glu Leu Lys Lys Leu Ser
      325                      330                      335

Ile Ser Glu Gln Asn Ala Gln Arg Ala Asn Leu Phe Asn Lys Leu Val
      340                      345                      350

Thr Glu Leu Arg Gly Leu Thr Gly Glu Ala Ile Thr Ser Leu Leu Pro
      355                      360                      365

Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu Gln Ala Leu Val Gln
      370                      375                      380

Cys Gly Gln Pro Gln Cys Tyr Thr His Ile Leu Gln Trp Leu Lys Thr
      385                      390                      395                      400

Glu Lys Ala His Pro Leu Leu Val Asp Ile Val Thr Tyr Leu Met Ala
      405                      410                      415

Leu Ile Pro Asn Pro Ser Thr Gln Arg Leu Gln Glu Ile Phe Asn Thr
      420                      425                      430

Ala Lys Glu Gln Gln Ser Arg Ala Thr Leu Tyr Ala Leu Ser His Ala
      435                      440                      445

Val Asn Ser Tyr Phe Asp Val Asp His Ser Arg Ser Pro Val Leu Gln
      450                      455                      460

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100          150          200
Asp Ile Ala Gly Tyr Leu Leu Lys Gln Ile Asp Asn Glu Cys Thr Gly
465          470          475          480

Asn Glu Asp His Thr Phe Leu Ile Leu Arg Val Ile Gly Asn Met Gly
          485          490          495

Arg Thr Met Glu Gln Val Met Pro Ala Leu Lys Ser Ser Val Leu Ser
          500          505          510

Cys Val Arg Ser Thr Lys Pro Ser Leu Leu Ile Gln Lys Ala Ala Leu
          515          520          525

Gln Ala Leu Arg Lys Met Glu Leu Glu Asp Glu Val Arg Thr Ile Leu
530          535          540

Phe Asp Thr Phe Val Asn Gly Val Ala Pro Val Glu Lys Arg Leu Ala
545          550          555          560

Ala Tyr Leu Leu Leu Met Lys Asn Pro Ser Ser Ser Asp Ile Asn Lys
          565          570          575

Ile Ala Gln Leu Leu Gln Trp Glu Gln Ser Glu Gln Val Lys Asn Phe
          580          585          590

Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser Glu Glu Leu Tyr Val
          595          600          605

Gln Asp Leu Lys Val Leu Ile Lys Asn Ala Leu Glu Asn Ser Gln Phe
610          615          620

Pro Thr Ile Met Asp Phe Arg Lys Phe Ser Arg Asn Tyr Gln Ile Ser
625          630          635          640

Lys Ser Ala Ser Leu Pro Met Phe Asp Pro Val Ser Val Lys Ile Glu
          645          650          655

Gly Asn Leu Ile Phe Asp Pro Ser Ser Tyr Leu Pro Arg Glu Ser Leu
          660          665          670

Leu Lys Thr Thr Leu Thr Val Phe Gly Leu Ala Ser Leu Asp Leu Phe
          675          680          685

Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro Thr Leu Glu Ala Leu
690          695          700

Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val Asn Lys Ala Leu Tyr
705          710          715          720

Trp Val Asn Gly Arg Val Pro Asp Gly Val Ser Lys Val Leu Val Asp
          725          730          735

His Phe Gly Tyr Thr Thr Asp Gly Lys His Glu Gln Asp Met Val Asn
          740          745          750

Gly Ile Met Pro Ile Val Asp Lys Leu Ile Lys Asp Leu Lys Ser Lys
755          760          765

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155	160	165
Glu Ile Pro Glu Ala Arg Ala Tyr Leu Arg Ile Leu Gly Lys Glu Leu 770	775	780
Ser Phe Val Arg Leu Gln Asp Leu Gln Val Leu Gly Lys Leu Leu Leu 785	790	800
Ser Gly Ala Gln Thr Leu Gln Gly Ile Pro Gln Met Val Val Gln Ala 805	810	815
Ile Arg Glu Gly Ser Lys Asn Asp Leu Phe Leu His Tyr Ile Phe Met 820	825	830
Asp Asn Ala Phe Glu Leu Pro Thr Gly Ala Gly Leu Gln Leu Gln Val 835	840	845
Ser Ser Ser Gly Val Phe Thr Pro Gly Ile Lys Ala Gly Val Arg Leu 850	855	860
Glu Leu Ala Asn Ile Gln Ala Glu Leu Val Ala Lys Pro Ser Val Ser 865	870	875
Leu Glu Phe Val Thr Asn Met Gly Ile Ile Ile Pro Asp Phe Ala Lys 885	890	895
Ser Ser Val Gln Met Asn Thr Asn Phe Phe His Glu Ser Gly Leu Glu 900	905	910
Ala Arg Val Ala Leu Lys Ala Gly Gln Leu Lys Val Ile Ile Pro Ser 915	920	925
Pro Lys Arg Pro Val Lys Leu Phe Ser Gly Ser Asn Thr Leu His Leu 930	935	940
Val Ser Thr Thr Lys Thr Glu Val Ile Pro Pro Leu Val Glu Asn Arg 945	950	955
Gln Ser Trp Ser Thr Cys Lys Pro Leu Phe Thr Gly Met Asn Tyr Cys 965	970	975
Thr Thr Gly Ala Tyr Ser Asn Ala Ser Ser Thr Glu Ser Ala Ser Tyr 980	985	990
Tyr Pro Leu Thr Gly Asp Thr Arg Tyr Glu Leu Glu Leu Arg Pro Thr 995	1000	1005
Gly Glu Val Glu Gln Tyr Ser Ala Thr Ala Thr Tyr Glu Leu Leu 1010	1015	1020
Lys Glu Asp Lys Ser Leu Val Asp Thr Leu Lys Phe Leu Val Gln 1025	1030	1035
Ala Glu Gly Val Gln Gln Ser Glu Ala Thr Val Leu Phe Lys Tyr 1040	1045	1050
Asn Arg Arg Ser Arg Thr Leu Ser Ser Glu Val Leu Ile Pro Gly 1055	1060	1065

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Phe Asp Val Asn Phe Gly Thr Ile Leu Arg Val Asn Asp Glu Ser
1070                               1075                               1080

Ala Lys Asp Lys Asn Thr Tyr Lys Leu Ile Leu Asp Ile Gln Asn
1085                               1090                               1095

Lys Lys Ile Thr Glu Val Ser Leu Val Gly His Leu Ser Tyr Asp
1100                               1105                               1110

Lys Lys Gly Asp Gly Lys Ile Lys Gly Val Val Ser Ile Pro Arg
1115                               1120                               1125

Leu Gln Ala Glu Ala Arg Ser Glu Val His Thr His Trp Ser Ser
1130                               1135                               1140

Thr Lys Leu Leu Phe Gln Met Asp Ser Ser Ala Thr Ala Tyr Gly
1145                               1150                               1155

Ser Thr Ile Ser Lys Arg Val Thr Trp Arg Tyr Asp Asn Glu Ile
1160                               1165                               1170

Ile Glu Phe Asp Trp Asn Thr Gly Thr Asn Val Asp Thr Lys Lys
1175                               1180                               1185

Val Ala Ser Asn Phe Pro Val Asp Leu Ser His Tyr Pro Arg Met
1190                               1195                               1200

Leu His Glu Tyr Ala Asn Gly Leu Leu Asp His Arg Val Pro Gln
1205                               1210                               1215

Thr Asp Val Thr Phe Arg Asp Met Gly Ser Lys Leu Ile Val Ala
1220                               1225                               1230

Thr Asn Thr Trp Leu Gln Met Ala Thr Arg Gly Leu Pro Tyr Pro
1235                               1240                               1245

Gln Thr Leu Gln Asp His Leu Asn Ser Leu Ser Glu Leu Asn Leu
1250                               1255                               1260

Leu Lys Met Gly Leu Ser Asp Phe His Ile Pro Asp Asn Leu Phe
1265                               1270                               1275

Leu Lys Thr Asp Gly Arg Val Lys Tyr Thr Met Asn Arg Asn Lys
1280                               1285                               1290

Ile Asn Ile Asp Ile Pro Leu Pro Leu Gly Gly Lys Ser Ser Lys
1295                               1300                               1305

Asp Leu Lys Met Pro Glu Ser Val Arg Thr Pro Ala Leu Asn Phe
1310                               1315                               1320

Lys Ser Val Gly Phe His Leu Pro Ser Arg Glu Val Gln Val Pro
1325                               1330                               1335

Thr Phe Thr Ile Pro Lys Thr His Gln Leu Gln Val Pro Leu Leu

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1340	1345	1350
Gly Val 1355	Leu Asp Leu Ser Thr 1360	Asn Val Tyr Ser Asn 1365
Trp Ser 1370	Ala Ser Tyr Thr Gly 1375	Gly Asn Thr Ser Arg 1380
Ser Leu 1385	Gln Ala Gln Tyr Arg 1390	Met Lys Thr Asp Ser 1395
Leu Phe 1400	Ser Tyr Ser Val Gln 1405	Gly Ser Gly Glu Thr 1410
Ser Lys 1415	Asn Thr Phe Thr Leu 1420	Ser Cys Asp Gly Ser 1425
Lys Phe 1430	Leu Asp Ser Lys Phe 1435	Lys Val Ser His Val 1440
Gly Asn 1445	Ser Pro Val Ser Lys 1450	Gly Leu Leu Thr Phe 1455
Ser Ala 1460	Leu Gly Pro Gln Met 1465	Ser Ala Thr Val His 1470
Lys Lys 1475	Lys Gln His Leu Tyr 1480	Val Lys Asp Ile Lys 1485
Gln Phe 1490	Arg Ala Ser Ser Phe 1495	Tyr Ala Gln Gly Lys 1500
Ser Cys 1505	Glu Arg Asp Val Thr 1510	Thr Gly Gln Leu Ser 1515
Asn Met 1520	Arg Phe Asn Ser Thr 1525	Tyr Phe Gln Gly Thr 1530
Val Gly 1535	Met Tyr Gln Asp Gly 1540	Ala Leu Ser Ile Thr 1545
Asp Leu 1550	Gln Asp Gly Ile Phe 1555	Lys Asn Thr Ala Ser 1560
Glu Asn 1565	Tyr Glu Leu Thr Leu 1570	Lys Ser Asp Ser Ser 1575
Glu Asn 1580	Phe Ala Ala Ser Asn 1585	Lys Leu Asp Val Thr 1590
Gln Ser 1595	Ala Leu Leu Arg Ser 1600	Glu His Gln Ala Asn 1605
Leu Arg 1610	Leu Val Thr Leu Leu 1615	Ser Gly Ser Leu Thr 1620

Val	Glu	Leu	Asn	Ala	Asp	Ile	Leu	Gly	Thr	Asp	Lys	Ile	Asn	Thr
1625						1630				1635				
Gly	Ala	His	Lys	Ala	Thr	Leu	Lys	Ile	Ala	Arg	Asp	Gly	Leu	Ser
1640						1645				1650				
Thr	Ser	Ala	Thr	Thr	Asn	Leu	Lys	Tyr	Ser	Pro	Leu	Leu	Leu	Glu
1655						1660				1665				
Asn	Glu	Leu	Asn	Ala	Glu	Leu	Gly	Leu	Ser	Gly	Ala	Ser	Met	Lys
1670						1675				1680				
Leu	Ser	Thr	Asn	Gly	Arg	Phe	Lys	Glu	His	His	Ala	Lys	Phe	Ser
1685						1690				1695				
Leu	Asp	Gly	Arg	Ala	Ala	Leu	Thr	Glu	Val	Ser	Leu	Gly	Ser	Ile
1700						1705				1710				
Tyr	Gln	Ala	Met	Ile	Leu	Gly	Ala	Asp	Ser	Lys	Asn	Ile	Phe	Asn
1715						1720				1725				
Phe	Lys	Leu	Ser	Arg	Glu	Gly	Leu	Arg	Leu	Ser	Asn	Asp	Leu	Met
1730						1735				1740				
Gly	Ser	Tyr	Ala	Glu	Met	Lys	Leu	Asp	His	Thr	His	Ser	Leu	Asn
1745						1750				1755				
Ile	Ala	Gly	Leu	Ser	Leu	Asp	Phe	Phe	Ser	Lys	Met	Asp	Asn	Ile
1760						1765				1770				
Tyr	Ser	Gly	Asp	Lys	Phe	Tyr	Lys	Gln	Asn	Phe	Asn	Leu	Gln	Leu
1775						1780				1785				
Gln	Pro	Tyr	Ser	Phe	Ile	Thr	Thr	Leu	Ser	Asn	Asp	Leu	Arg	Tyr
1790						1795				1800				
Gly	Ala	Leu	Asp	Leu	Thr	Asn	Asn	Gly	Arg	Phe	Arg	Leu	Glu	Pro
1805						1810				1815				
Leu	Lys	Leu	Asn	Val	Gly	Gly	Asn	Phe	Lys	Gly	Thr	Tyr	Gln	Asn
1820						1825				1830				
Asn	Glu	Leu	Lys	His	Ile	Tyr	Thr	Ile	Ser	Tyr	Thr	Asp	Leu	Val
1835						1840				1845				
Val	Ala	Ser	Tyr	Arg	Ala	Asp	Thr	Val	Ala	Lys	Val	Gln	Gly	Val
1850						1855				1860				
Glu	Phe	Ser	His	Arg	Leu	Asn	Ala	Asp	Ile	Glu	Gly	Leu	Thr	Ser
1865						1870				1875				
Ser	Val	Asp	Val	Thr	Thr	Ser	Tyr	Asn	Ser	Asp	Pro	Leu	His	Phe
1880						1885				1890				
Asn	Asn	Val	Phe	His	Phe	Ser	Leu	Ala	Pro	Phe	Thr	Leu	Gly	Ile
1895						1900				1905				

Asp Thr 1910	His Thr Ser Gly 1915	Asp Gly Lys Leu Ser Phe 1920	Trp Gly Glu
His Thr 1925	Gly Gln Leu Tyr Ser 1930	Lys Phe Leu Leu Lys 1935	Ala Glu Pro
Leu Ala 1940	Leu Ile Val Ser His 1945	Asp Tyr Lys Gly Ser 1950	Thr Ser His
Ser Leu 1955	Pro Tyr Glu Ser Ser 1960	Ile Ser Thr Ala Leu 1965	Glu His Thr
Val Ser 1970	Ala Leu Leu Thr Pro 1975	Ala Glu Gln Thr Ser 1980	Thr Trp Lys
Phe Lys 1985	Thr Lys Leu Asn Asp 1990	Lys Val Tyr Ser Gln 1995	Asp Phe Glu
Ala Tyr 2000	Asn Thr Lys Asp Lys 2005	Ile Gly Val Glu Leu 2010	Ser Gly Arg
Ala Asp 2015	Leu Ser Gly Leu Tyr 2020	Ser Pro Ile Lys Leu 2025	Pro Phe Phe
Tyr Ser 2030	Glu Pro Val Asn Val 2035	Leu Asn Gly Leu Glu 2040	Val Asn Asp
Ala Val 2045	Asp Lys Pro Gln Glu 2050	Phe Thr Ile Ile Ala 2055	Val Val Lys
Tyr Asp 2060	Lys Asn Gln Asp Val 2065	His Thr Ile Asn Leu 2070	Pro Phe Phe
Lys Ser 2075	Leu Pro Asp Tyr Leu 2080	Glu Arg Asn Arg Arg 2085	Gly Met Ile
Ser Leu 2090	Leu Glu Ala Met Arg 2095	Gly Glu Leu Gln Arg 2100	Leu Ser Val
Asp Gln 2105	Phe Val Arg Lys Tyr 2110	Arg Ala Ala Leu Ser 2115	Arg Leu Pro
Gln Gln 2120	Ile His His Tyr Leu 2125	Asn Ala Ser Asp Trp 2130	Glu Arg Gln
Val Ala 2135	Gly Ala Lys Glu Lys 2140	Ile Thr Ser Phe Met 2145	Glu Asn Tyr
Arg Ile 2150	Thr Asp Asn Asp Val 2155	Leu Ile Ala Ile Asp 2160	Ser Ala Lys
Ile Asn 2165	Phe Asn Glu Lys Leu 2170	Ser Gln Leu Glu Thr 2175	Tyr Ala Ile
Gln Phe 2180	Asp Gln Tyr Ile Lys 2185	Asp Asn Tyr Asp Pro 2190	His Asp Leu

Lys Arg Thr Ile Ala Glu Ile Ile Asp Arg Ile Ile Glu Lys Leu
 2195 2200 2205
 Lys Ile Leu Asp Glu Gln Tyr His Ile Arg Val Asn Leu Ala Lys
 2210 2215 2220
 Ser Ile His Asn Leu Tyr Leu Phe Val Glu Asn Val Asp Leu Asn
 2225 2230 2235
 Gln Val Ser Ser Ser Asn Thr Ser Trp Ile Gln Asn Val Asp Ser
 2240 2245 2250
 Asn Tyr Gln Val Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln Leu
 2255 2260 2265
 Arg Thr Gln Ile Gln Asn Ile Asp Ile Gln Gln Leu Ala Ala Glu
 2270 2275 2280
 Val Lys Arg Gln Met Asp Ala Ile Asp Val Thr Met His Leu Asp
 2285 2290 2295
 Gln Leu Arg Thr Ala Ile Leu Phe Gln Arg Ile Ser Asp Ile Ile
 2300 2305 2310
 Asp Arg Val Lys Tyr Phe Val Met Asn Leu Ile Glu Asp Phe Lys
 2315 2320 2325
 Val Thr Glu Lys Ile Asn Thr Phe Arg Val Ile Val Arg Glu Leu
 2330 2335 2340
 Ile Glu Lys Tyr Glu Val Asp Gln His Ile Gln Val Leu Met Asp
 2345 2350 2355
 Lys Ser Val Glu Leu Ala His Arg Tyr Ser Leu Ser Glu Pro Leu
 2360 2365 2370
 Gln Lys Leu Ser Asn Val Leu Gln Arg Ile Glu Ile Lys Asp Tyr
 2375 2380 2385
 Tyr Glu Lys Leu Val Gly Phe Ile Asp Asp Thr Val Glu Trp Leu
 2390 2395 2400
 Lys Ala Leu Ser Phe Lys Asn Thr Ile Glu Glu Leu Asn Arg Leu
 2405 2410 2415
 Thr Asp Met Leu Val Lys Lys Leu Lys Ala Phe Asp Tyr His Gln
 2420 2425 2430
 Phe Val Asp Lys Thr Asn Ser Lys Ile Arg Glu Met Thr Gln Arg
 2435 2440 2445
 Ile Asn Ala Glu Ile Gln Ala Leu Lys Leu Pro Gln Lys Met Glu
 2450 2455 2460
 Ala Leu Lys Leu Leu Val Glu Asn Phe Lys Thr Thr Val Ser Asn

Ala Leu	Lys Leu Leu Val	Glu Asp Phe Lys Ile Ile	Val Ser Asn
2465		2470	2475
Ser Leu	Glu Arg Leu Lys Asp	Thr Lys Val Thr Val	Val Ile Asp
2480		2485	2490
Trp Leu	Gln Asp Ile Leu Thr	Gln Met Lys Asp His	Phe Gln Asp
2495		2500	2505
Thr Leu	Glu Asp Val Arg Asp	Arg Ile Tyr Gln Met	Asp Ile Gln
2510		2515	2520
Arg Glu	Leu Glu His Phe Leu	Ser Leu Val Asn Gln	Val Tyr Ser
2525		2530	2535
Thr Leu	Val Thr Tyr Met Ser	Asp Trp Trp Thr Leu	Thr Ala Lys
2540		2545	2550
Asn Ile	Thr Asp Phe Ala Glu	Gln Tyr Ser Ile Gln	Asn Trp Ala
2555		2560	2565
Glu Ser	Ile Lys Val Leu Val	Glu Gln Gly Phe Ile	Val Pro Glu
2570		2575	2580
Met Gln	Thr Phe Leu Trp Thr	Met Pro Ala Phe Glu	Val Ser Leu
2585		2590	2595
Arg Ala	Leu Gln Glu Gly Asn	Phe Gln Thr Pro Val	Phe Ile Val
2600		2605	2610
Pro Leu	Thr Asp Leu Arg Ile	Pro Ser Ile Arg Ile	Asn Phe Lys
2615		2620	2625
Met Leu	Lys Asn Ile Lys Ile	Pro Leu Arg Phe Ser	Thr Pro Glu
2630		2635	2640
Phe Thr	Leu Leu Asn Thr Phe	His Val His Ser Phe	Thr Ile Asp
2645		2650	2655
Leu Leu	Glu Ile Lys Ala Lys	Ile Ile Arg Thr Ile	Asp Gln Ile
2660		2665	2670
Leu Ser	Ser Glu Leu Gln Trp	Pro Leu Pro Glu Met	Tyr Leu Arg
2675		2680	2685
Asp Leu	Asp Val Val Asn Ile	Pro Leu Ala Arg Leu	Thr Leu Pro
2690		2695	2700
Asp Phe	His Val Pro Glu Ile	Thr Ile Pro Glu Phe	Thr Ile Pro
2705		2710	2715
Asn Val	Asn Leu Lys Asp Leu	His Val Pro Asp Leu	His Ile Pro
2720		2725	2730
Glu Phe	Gln Leu Pro His Leu	Ser His Thr Ile Glu	Ile Pro Ala
2735		2740	2745
Phe Glv	Lvs Leu His Ser Ile	Leu Lvs Ile Gln Ser	Pro Leu Phe

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2750          2755          2760
Ile Leu Asp Ala Asn Ala Asn Ile Gln Asn Val Thr Thr Ser Gly
2765          2770          2775

Asn Lys Ala Glu Ile Val Ala Ser Val Thr Ala Lys Gly Glu Ser
2780          2785          2790

Gln Phe Glu Ala Leu Asn Phe Asp Phe Gln Ala Gln Ala Gln Phe
2795          2800          2805

Leu Glu Leu Asn Pro His Pro Pro Val Leu Lys Glu Ser Met Asn
2810          2815          2820

Phe Ser Ser Lys His Val Arg Met Glu His Glu Gly Glu Ile Val
2825          2830          2835

Phe Asp Gly Lys Ala Ile Glu Gly Lys Ser Asp Thr Val Ala Ser
2840          2845          2850

Leu His Thr Glu Lys Asn Glu Val Glu Phe Asn Asn Gly Met Thr
2855          2860          2865

Val Lys Val Asn Asn Gln Leu Thr Leu Asp Ser His Thr Lys Tyr
2870          2875          2880

Phe His Lys Leu Ser Val Pro Arg Leu Asp Phe Ser Ser Lys Ala
2885          2890          2895

Ser Leu Asn Asn Glu Ile Lys Thr Leu Leu Glu Ala Gly His Val
2900          2905          2910

Ala Leu Thr Ser Ser Gly Thr Gly Ser Trp Asn Trp Ala Cys Pro
2915          2920          2925

Asn Phe Ser Asp Glu Gly Ile His Ser Ser Gln Ile Ser Phe Thr
2930          2935          2940

Val Asp Gly Pro Ile Ala Phe Val Gly Leu Ser Asn Asn Ile Asn
2945          2950          2955

Gly Lys His Leu Arg Val Ile Gln Lys Leu Thr Tyr Glu Ser Gly
2960          2965          2970

Phe Leu Asn Tyr Ser Lys Phe Glu Val Glu Ser Lys Val Glu Ser
2975          2980          2985

Gln His Val Gly Ser Ser Ile Leu Thr Ala Asn Gly Arg Ala Leu
2990          2995          3000

Leu Lys Asp Ala Lys Ala Glu Met Thr Gly Glu His Asn Ala Asn
3005          3010          3015

Leu Asn Gly Lys Val Ile Gly Thr Leu Lys Asn Ser Leu Phe Phe
3020          3025          3030

Ser Ala Gln Pro Phe Glu Ile Thr Ala Ser Thr Asn Asn Glu Gly
3035          3040          3045

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3035	3040	3045
Asn Leu Lys Val Gly Phe Pro Leu Lys Leu Thr Gly Lys Ile Asp 3050 3055 3060		
Phe Leu Asn Asn Tyr Ala Leu Phe Leu Ser Pro Arg Ala Gln Gln 3065 3070 3075		
Ala Ser Trp Gln Ala Ser Thr Arg Phe Asn Gln Tyr Lys Tyr Asn 3080 3085 3090		
Gln Asn Phe Ser Ala Ile Asn Asn Glu His Asn Ile Glu Ala Ser 3095 3100 3105		
Ile Gly Met Asn Gly Asp Ala Asn Leu Asp Phe Leu Asn Ile Pro 3110 3115 3120		
Leu Thr Ile Pro Glu Ile Asn Leu Pro Tyr Thr Glu Phe Lys Thr 3125 3130 3135		
Pro Leu Leu Lys Asp Phe Ser Ile Trp Glu Glu Thr Gly Leu Lys 3140 3145 3150		
Glu Phe Leu Lys Thr Thr Lys Gln Ser Phe Asp Leu Ser Val Lys 3155 3160 3165		
Ala Gln Tyr Lys Lys Asn Ser Asp Lys His Ser Ile Val Val Pro 3170 3175 3180		
Leu Gly Met Phe Tyr Glu Phe Ile Leu Asn Asn Val Asn Ser Trp 3185 3190 3195		
Asp Arg Lys Phe Glu Lys Val Arg Asn Asn Ala Leu His Phe Leu 3200 3205 3210		
Thr Thr Ser Tyr Asn Glu Ala Lys Ile Lys Val Asp Lys Tyr Lys 3215 3220 3225		
Thr Glu Asn Ser Leu Asn Gln Pro Ser Gly Thr Phe Gln Asn His 3230 3235 3240		
Gly Tyr Thr Ile Pro Val Val Asn Ile Glu Val Ser Pro Phe Ala 3245 3250 3255		
Val Glu Thr Leu Ala Ser Ser His Val Ile Pro Thr Ala Ile Ser 3260 3265 3270		
Thr Pro Ser Val Thr Ile Pro Gly Pro Asn Ile Met Val Pro Ser 3275 3280 3285		
Tyr Lys Leu Val Leu Pro Pro Leu Glu Leu Pro Val Phe His Gly 3290 3295 3300		
Pro Gly Asn Leu Phe Lys Phe Phe Leu Pro Asp Phe Lys Gly Phe 3305 3310 3315		

Asn Thr Ile Asp Asn Ile Tyr Ile Pro Ala Met Gly Asn Phe Thr
 3320 3325 3330
 Tyr Asp Phe Ser Phe Lys Ser Ser Val Ile Thr Leu Asn Thr Asn
 3335 3340 3345
 Ala Gly Leu Tyr Asn Gln Ser Asp Ile Val Ala His Phe Leu Ser
 3350 3355 3360
 Ser Ser Ser Phe Val Thr Asp Ala Leu Gln Tyr Lys Leu Glu Gly
 3365 3370 3375
 Thr Ser Arg Leu Met Arg Lys Arg Gly Leu Lys Leu Ala Thr Ala
 3380 3385 3390
 Val Ser Leu Thr Asn Lys Phe Val Lys Gly Ser His Asp Ser Thr
 3395 3400 3405
 Ile Ser Leu Thr Lys Lys Asn Met Glu Ala Ser Val Arg Thr Thr
 3410 3415 3420
 Ala Asn Leu His Ala Pro Ile Phe Ser Met Asn Phe Lys Gln Glu
 3425 3430 3435
 Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr Val Ser Ser Ser Ile
 3440 3445 3450
 Glu Leu Asn Tyr Asp Phe Asn Ser Ser Lys Leu His Ser Thr Ala
 3455 3460 3465
 Thr Gly Gly Ile Asp His Lys Phe Ser Leu Glu Ser Leu Thr Ser
 3470 3475 3480
 Tyr Phe Ser Ile Glu Ser Phe Thr Lys Gly Asn Ile Lys Ser Ser
 3485 3490 3495
 Phe Leu Ser Gln Glu Tyr Ser Gly Ser Val Ala Asn Glu Ala Asn
 3500 3505 3510
 Val Tyr Leu Asn Ser Lys Gly Thr Arg Ser Ser Val Arg Leu Gln
 3515 3520 3525
 Gly Ala Ser Lys Val Asp Gly Ile Trp Asn Val Glu Val Gly Glu
 3530 3535 3540
 Asn Phe Ala Gly Glu Ala Thr Leu Gln Arg Ile Tyr Thr Thr Trp
 3545 3550 3555
 Glu His Asn Met Lys Asn His Leu Gln Val Tyr Ser Tyr Phe Phe
 3560 3565 3570
 Thr Lys Gly Lys Gln Thr Cys Arg Ala Thr Leu Glu Leu Ser Pro
 3575 3580 3585
 Trp Thr Met Ser Thr Leu Leu Gln Val His Val Ser Gln Leu Ser
 3590 3595 3600

Ser	Leu	Leu	Asp	Leu	His	His	Phe	Asp	Gln	Glu	Val	Ile	Leu	Lys
3605						3610					3615			
Ala	Asn	Thr	Lys	Asn	Gln	Lys	Ile	Ser	Trp	Lys	Gly	Gly	Val	Gln
3620						3625					3630			
Val	Glu	Ser	Arg	Val	Leu	Gln	His	Asn	Ala	Gln	Phe	Ser	Asn	Asp
3635						3640					3645			
Gln	Glu	Glu	Ile	Arg	Leu	Asp	Leu	Ala	Gly	Ser	Leu	Asp	Gly	Gln
3650						3655					3660			
Leu	Trp	Asp	Leu	Glu	Ala	Ile	Phe	Leu	Pro	Val	Tyr	Gly	Lys	Ser
3665						3670					3675			
Leu	Gln	Glu	Leu	Leu	Gln	Met	Asp	Gly	Lys	Arg	Gln	Tyr	Leu	Gln
3680						3685					3690			
Ala	Ser	Thr	Ser	Leu	Leu	Tyr	Thr	Lys	Asn	Pro	Asn	Gly	Tyr	Leu
3695						3700					3705			
Leu	Ser	Leu	Pro	Val	Gln	Glu	Leu	Ala	Asp	Arg	Phe	Ile	Ile	Pro
3710						3715					3720			
Gly	Ile	Lys	Leu	Asn	Asp	Phe	Ser	Gly	Val	Lys	Ile	Tyr	Lys	Lys
3725						3730					3735			
Leu	Ser	Thr	Ser	Pro	Phe	Ala	Leu	Asn	Leu	Thr	Met	Leu	Pro	Lys
3740						3745					3750			
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Thr Asp 3950	Phe His Leu Tyr Tyr 3955	Lys Glu Asp Lys Thr 3960	Ser Leu Ser
Ala Ser 3965	Ala Ala Ser Ser Thr 3970	Ile Gly Thr Val Gly 3975	Leu Asp Ser
Ser Thr 3980	Asp Asp Gln Ser Val 3985	Glu Leu Asn Val Tyr 3990	Phe His Pro
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Glu Glu 4025	Glu Ala Ala Ser Arg 4030	Leu Leu Gly Ser Leu 4035	Lys Ser Asn
Val Pro 4040	Lys Ala Ser Lys Ala 4045	Ile Tyr Asp Tyr Ala 4050	Asn Lys Tyr
His Leu 4055	Glu Tyr Val Ser Ser 4060	Glu Leu Arg Lys Ser 4065	Leu Gln Val
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Phe Gln 4085	Arg Val Ala Arg Asp 4090	Thr Tyr Gln Asn Leu 4095	Tyr Glu Glu
Met Leu 4100	Ala Gln Lys Ser Leu 4105	Ser Ile Pro Glu Asn 4110	Leu Lys Lys
Arg Val 4115	Leu Asp Ser Ile Val 4120	His Val Thr Gln Lys 4125	Tyr His Met
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ctattcaagt ttttctccc agatttcaag ggattcaaca ctattgaca tatttatatt	10080
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- - - - -
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aaaaaaaaa a 13931

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**ISOLEREDE CD44-POLYPEPTIDER OG ANVENDELSER HERAF
PATENTKRAV**

1. Isoleret polypeptid, der består af SEQ ID NR: 1.
2. Isoleret polypeptid, der er modificeret med end-capping, der består af SEQ ID NR: 1, hvor det modificerede polypeptid omfatter en anti-inflammatorisk aktivitet.
3. Polypeptidet, der er modificeret med end-capping ifølgekrav 2, hvor end-cappingen omfatter en N-terminus end-capping.
4. Polypeptidet, der er modificeret med end-capping ifølge krav 3, hvor N-terminus end-cappingen omfatter acetyl.
5. Polipeptidet, der er modificeret med end-capping ifølge et hvilket som helst af kravene 2-4, hvor end-cappingen omfatter en C-terminus end-capping.
6. Polypeptidet, der er modificeret med end-capping ifølge krav 5, hvor C-terminus end-cappingen omfatter et amid.
7. Polypeptidet, der er modificeret med end-capping ifølge krav 2, er som fremsat i SEQ ID NR: 4.
8. Stofsammensætning, der omfatter det isolerede polypeptid ifølge et hvilket som helst af kravene 1-7 og en ikke-proteinholdig andel bundet til det isolerede polypeptid.
9. Det isolerede polypeptid eller stofsammensætningen ifølge et hvilket som helst af kravene 2-6 og 8, hvor den anti-inflammatoriske aktivitet ikke forudsætter vaccination eller slimhindetolerance, eller hvor peptidet er i stand til binde et protein udvalgt fra gruppen bestående af serum-amyloid A, transthyretin og apolipoprotein B.
10. Det isolerede polypeptid eller stofsammensætningen ifølge et hvilket som helst af kravene 1-9 til brug i behandlingen af inflammatorisk sygdom.
11. Det isolerede polypeptid eller sammensætningen ifølge krav 10, hvor den

inflammatoriske sygdom er udvalgt fra gruppen, der består af rheumatoid arthritis, psoriasis arthritis, Alzheimers sygdom, cancer og kardiovaskulær sygdom.

12. Det isolerede polypeptid eller sammensætningen ifølge krav 10, hvor den inflammatoriske sygdom er rheumatoid arthritis.

13. Det isolerede polypeptid eller sammensætningen ifølge krav 10, hvor den inflammatoriske sygdom er multipel sklerose.

14. Det isolerede polypeptid eller sammensætningen ifølge krav 10, hvor den inflammatoriske sygdom er gastrointestinal sygdom.

15. Det isolerede polypeptid eller sammensætningen ifølge krav 10, hvor den inflammatoriske sygdom er valgt fra gruppen, der består af kronisk inflammatorisk tarmsygdom, cøliaki, colitis, ileitis og Chrohns sygdom.

DRAWINGS

FIG. 1

5-Mer peptide stability

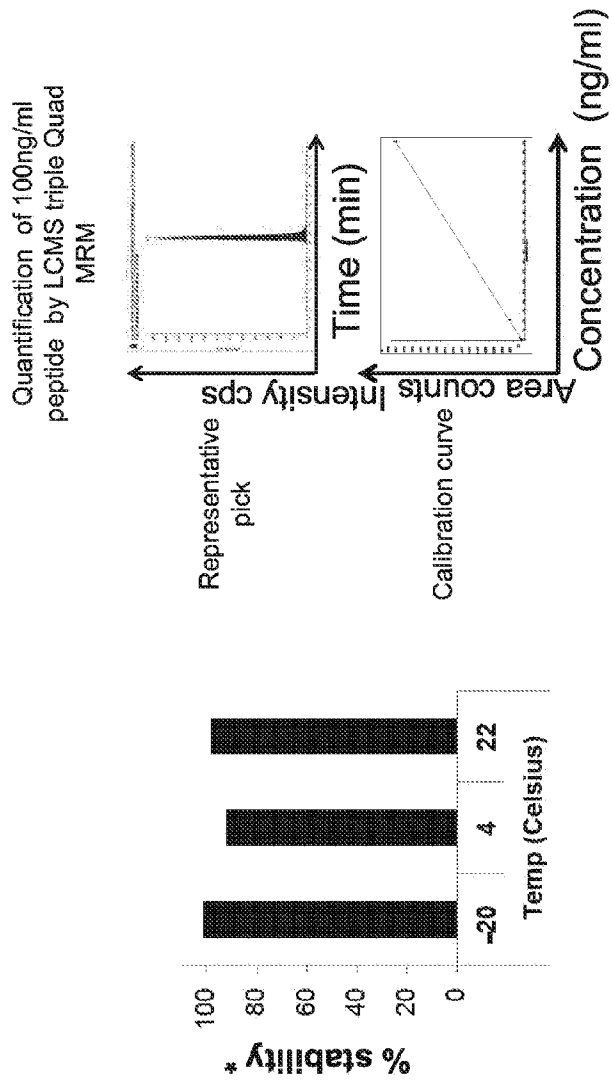


FIG. 2A

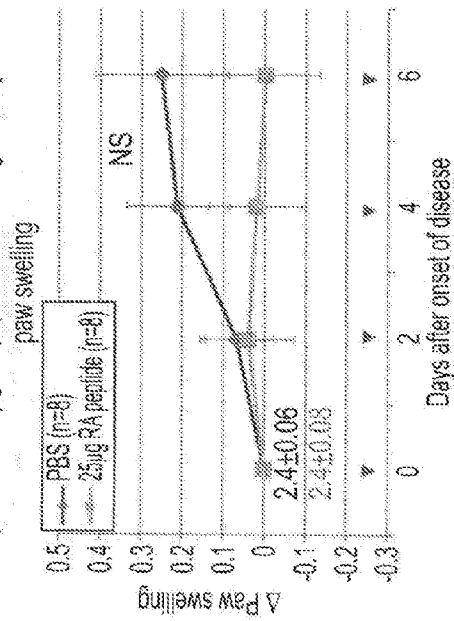
Injection of 25 μ g RA peptide does not significantly affect

FIG. 2B

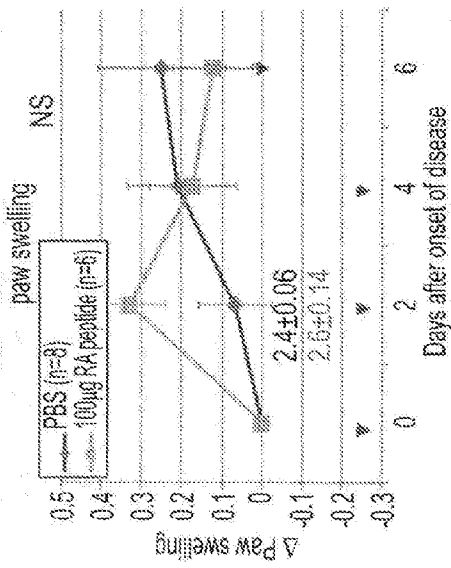
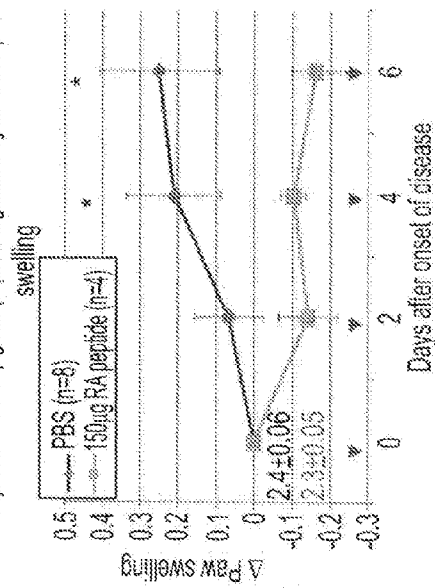
Injection of 100 μ g RA peptide does not significantly affectInjection of 150 μ g RA peptide significantly reduces paw

FIG. 2C

FIG. 3A

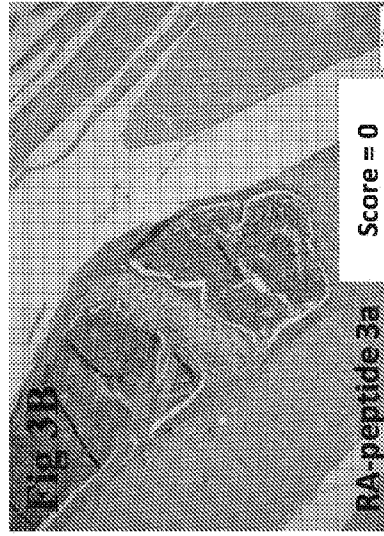
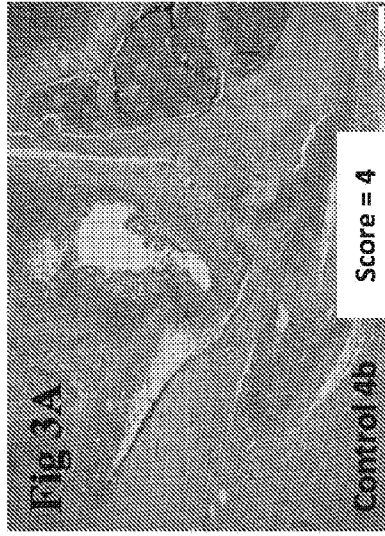


FIG. 3B

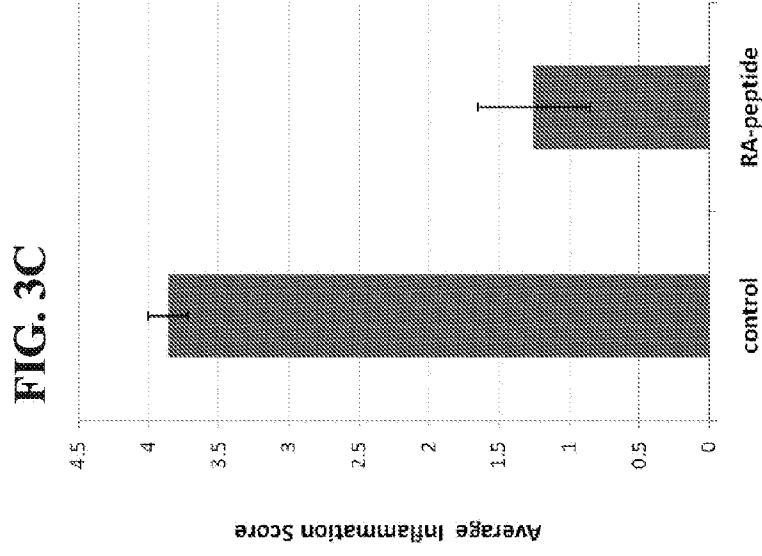


FIG. 4

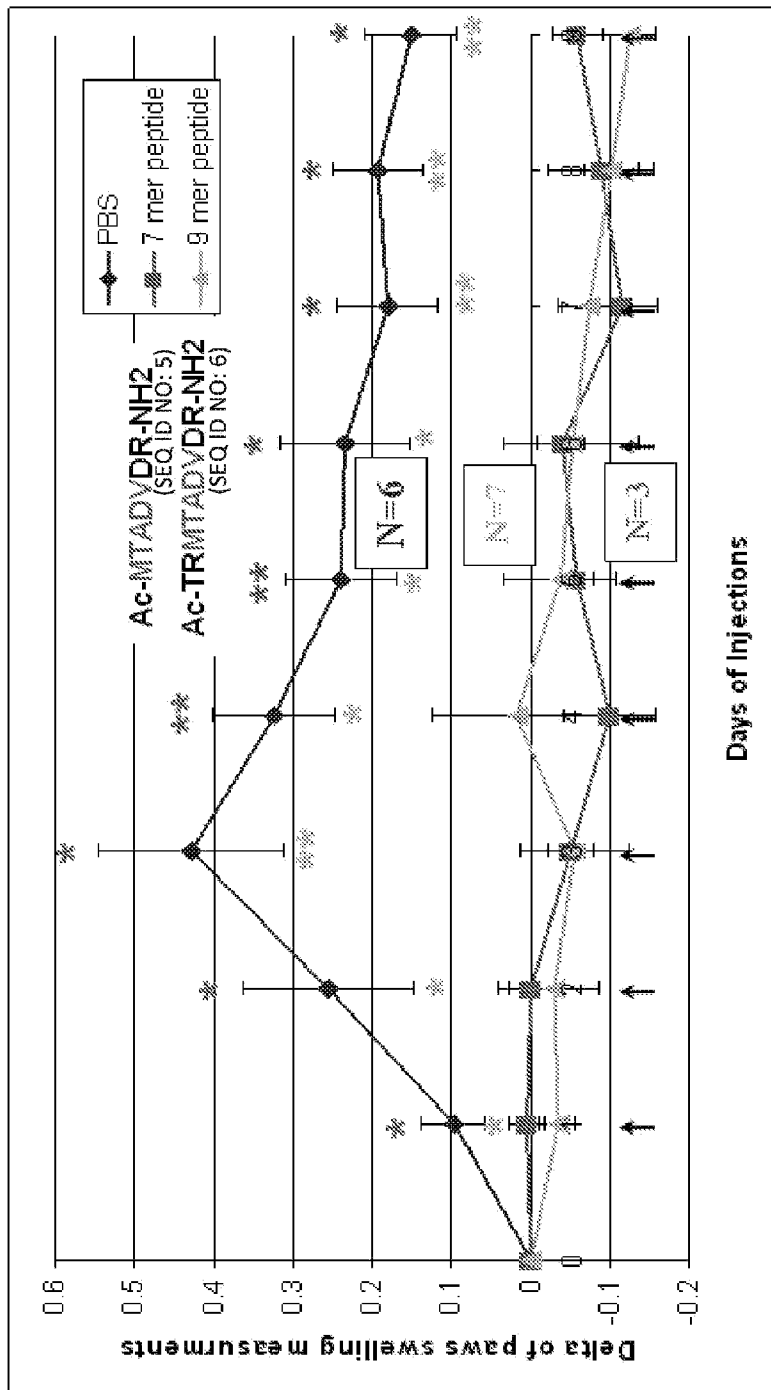
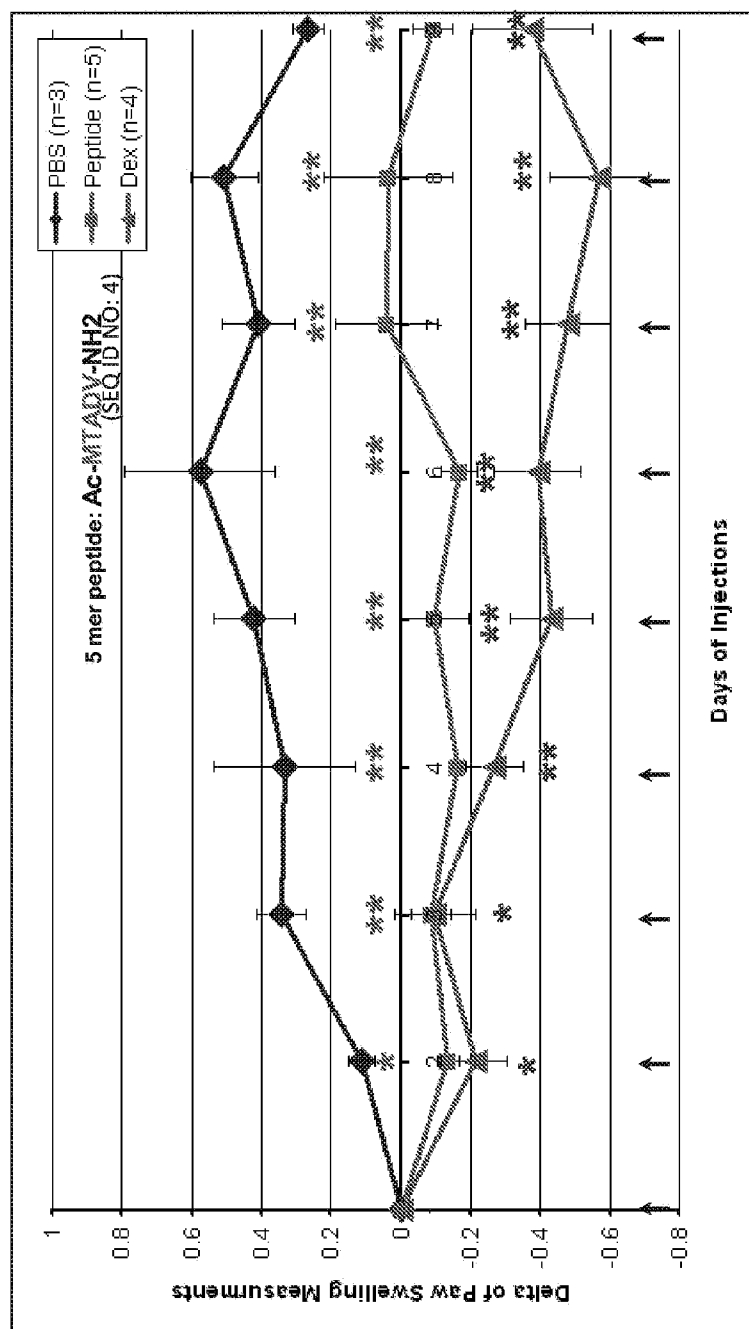


FIG. 5A



PBS vs. Peptide: $P < 0.05 = *$
 $P < 0.001 = **$
 PBS vs. Dex: $P < 0.05 = *$
 $P < 0.001 = **$

FIG. 5B

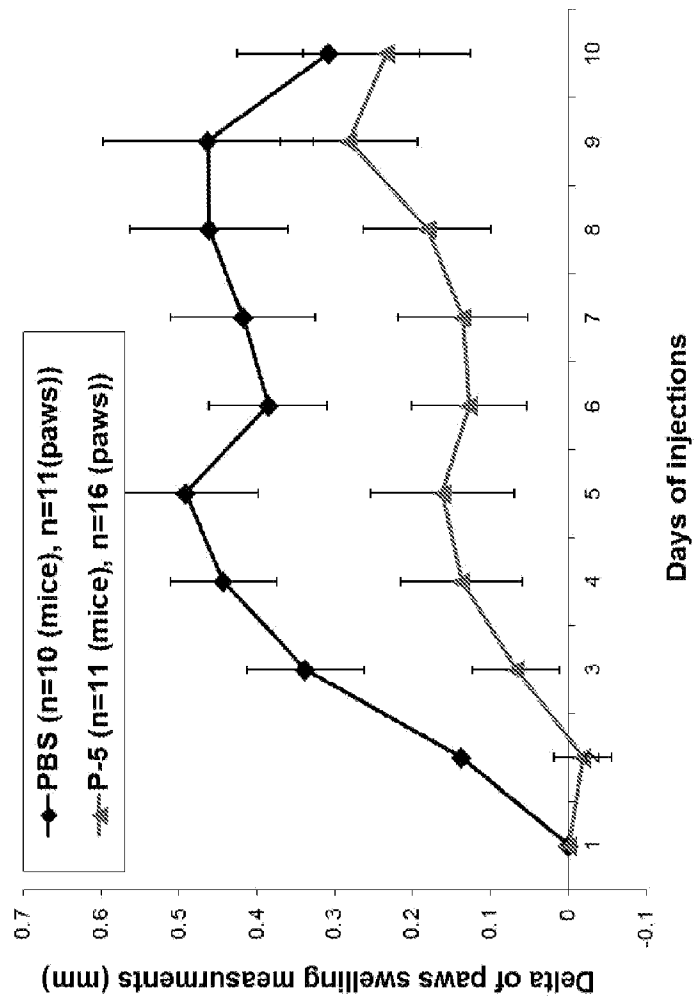


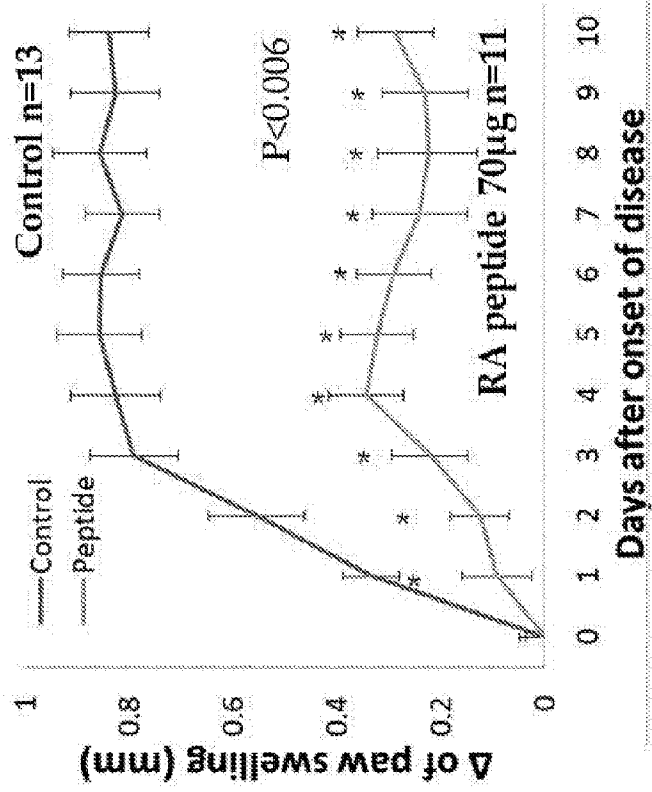
FIG. 6

FIG. 7A

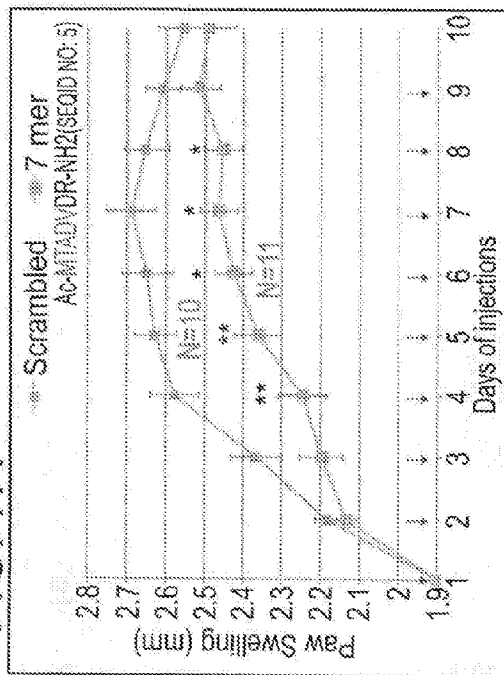


FIG. 7B

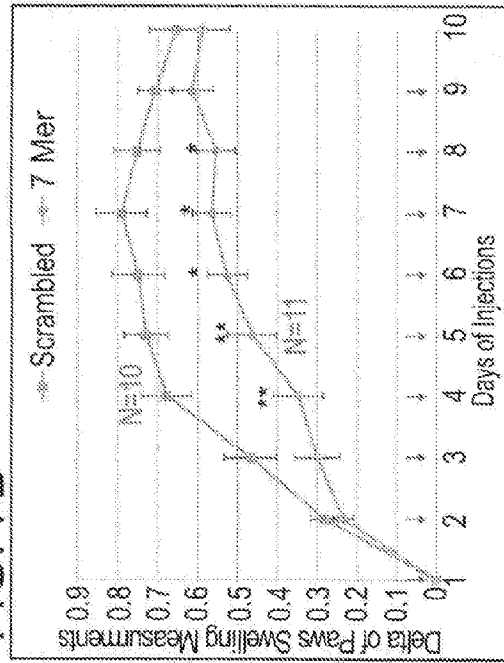


FIG. 7C

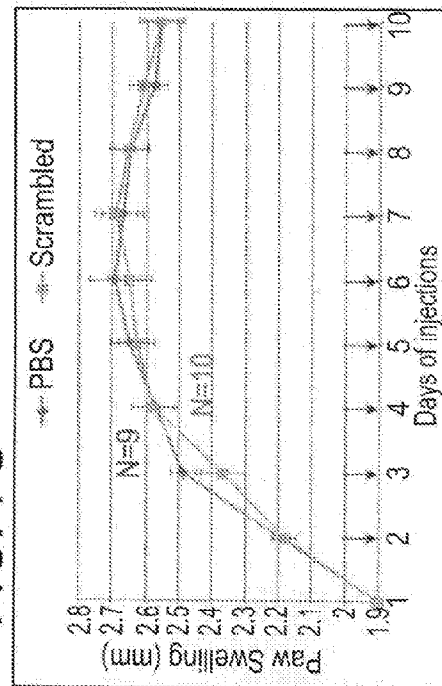


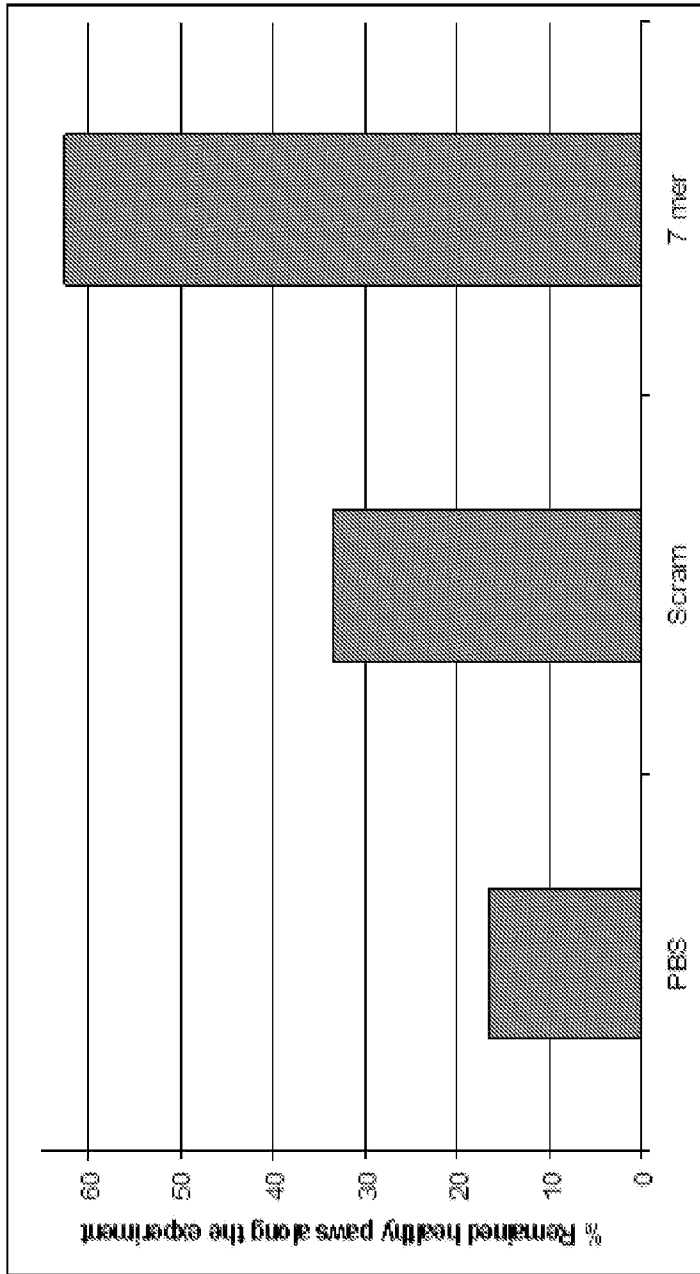
FIG. 8

FIG. 9A

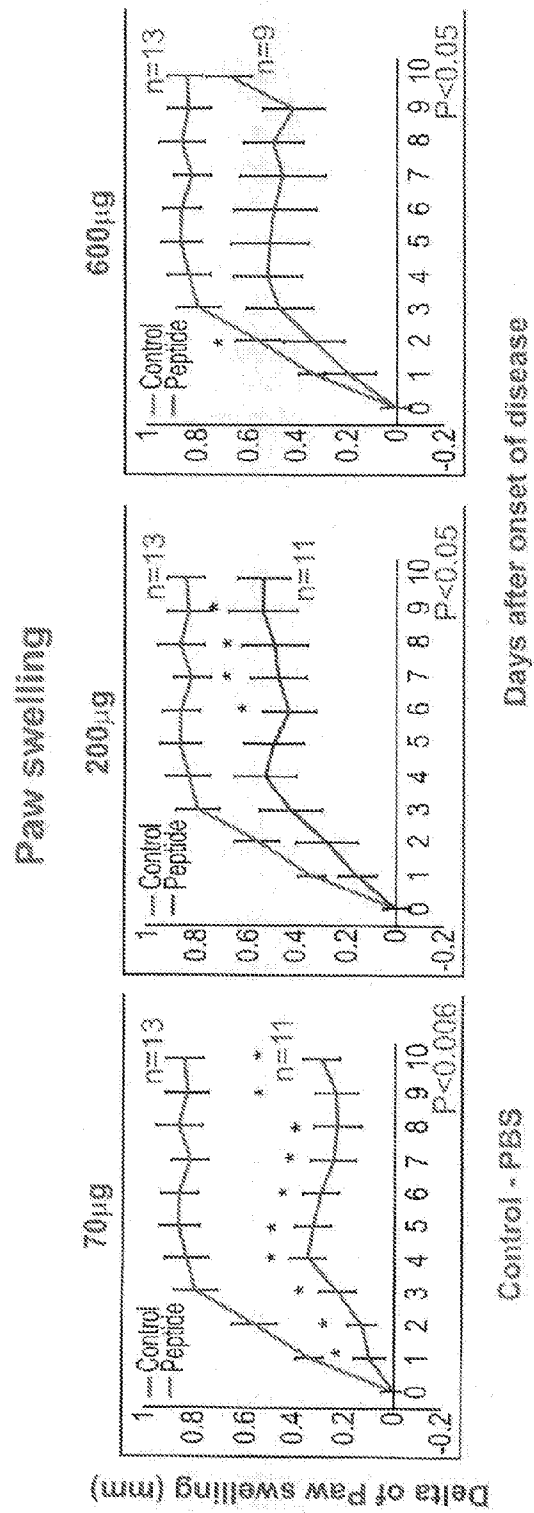


FIG. 9B

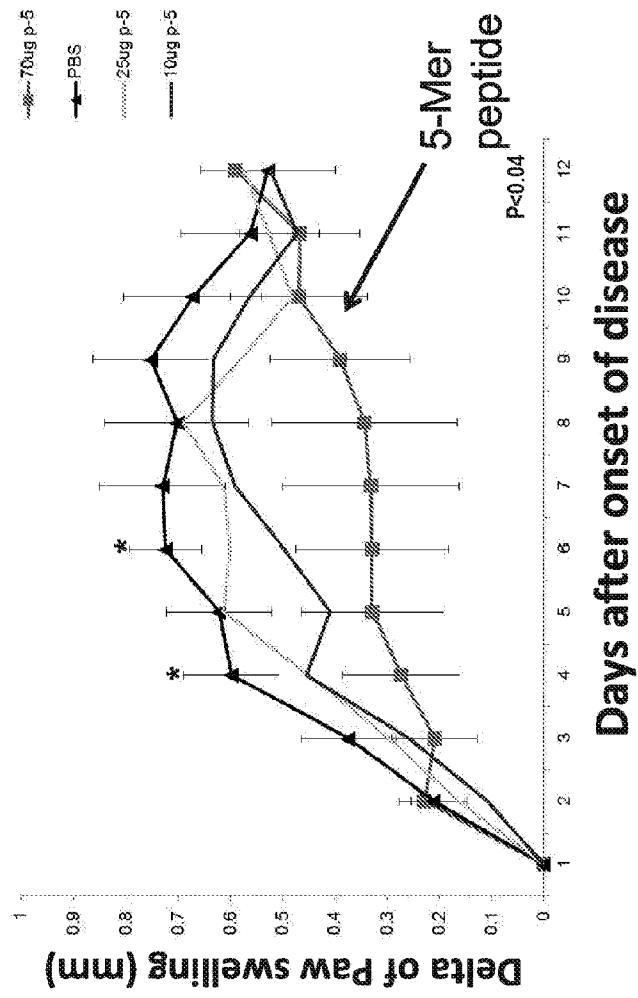


FIG. 10

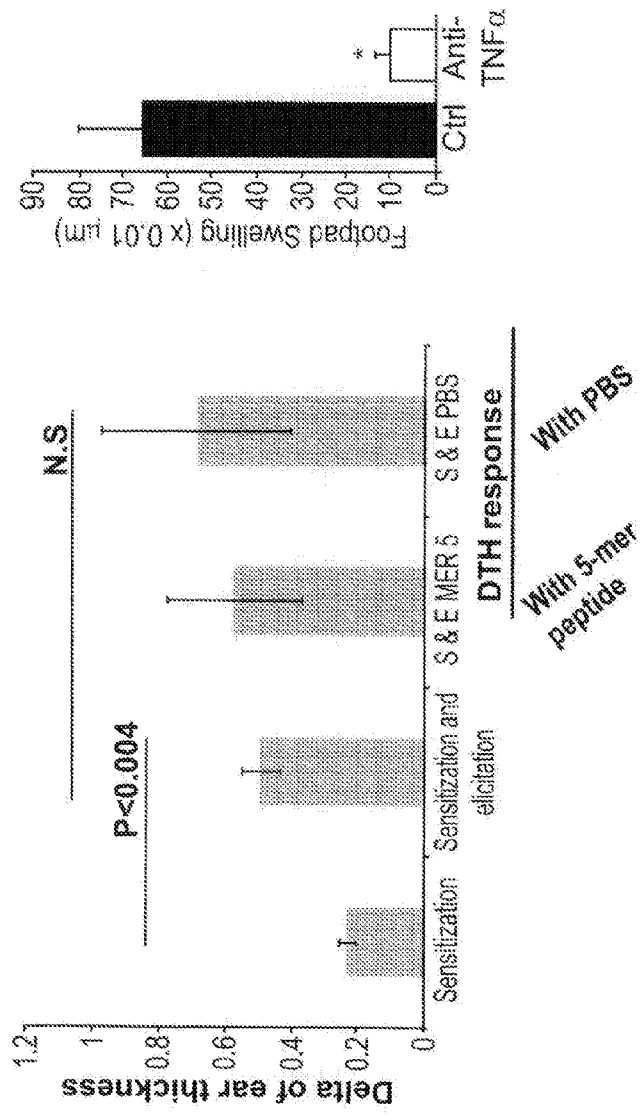


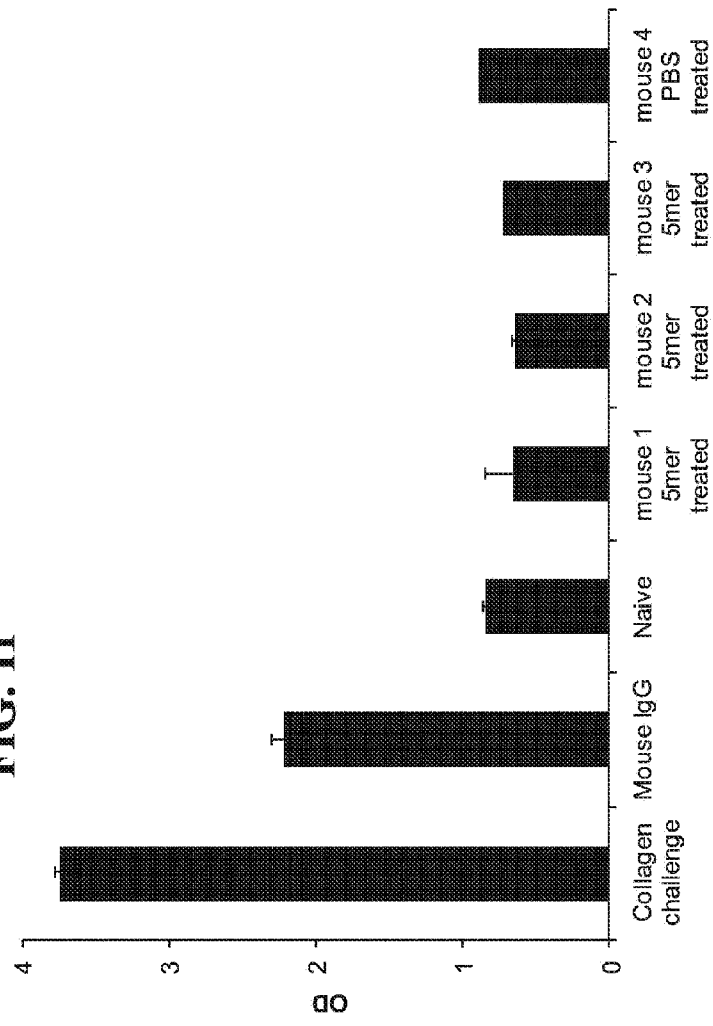
FIG. 11

FIG. 12

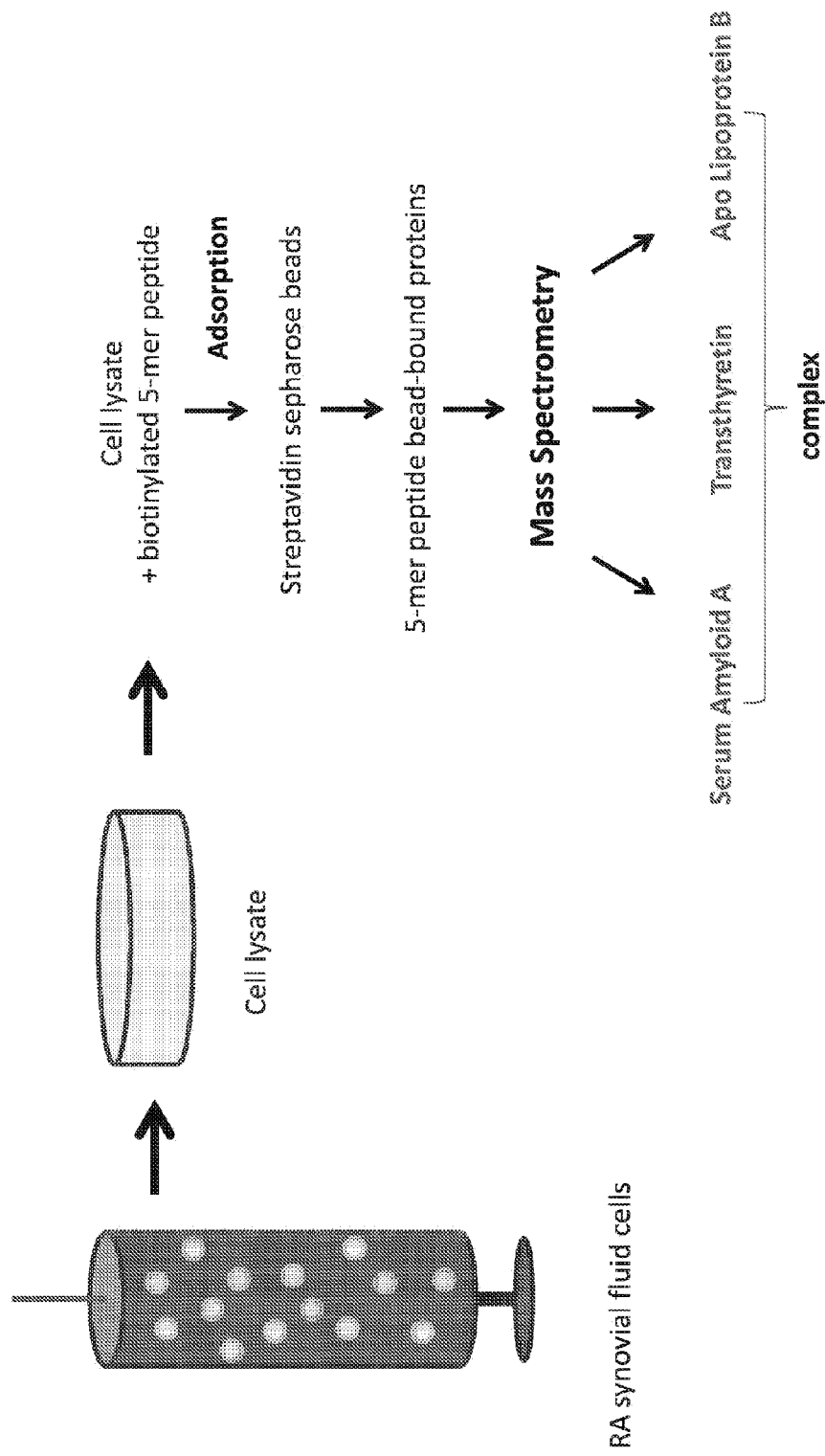


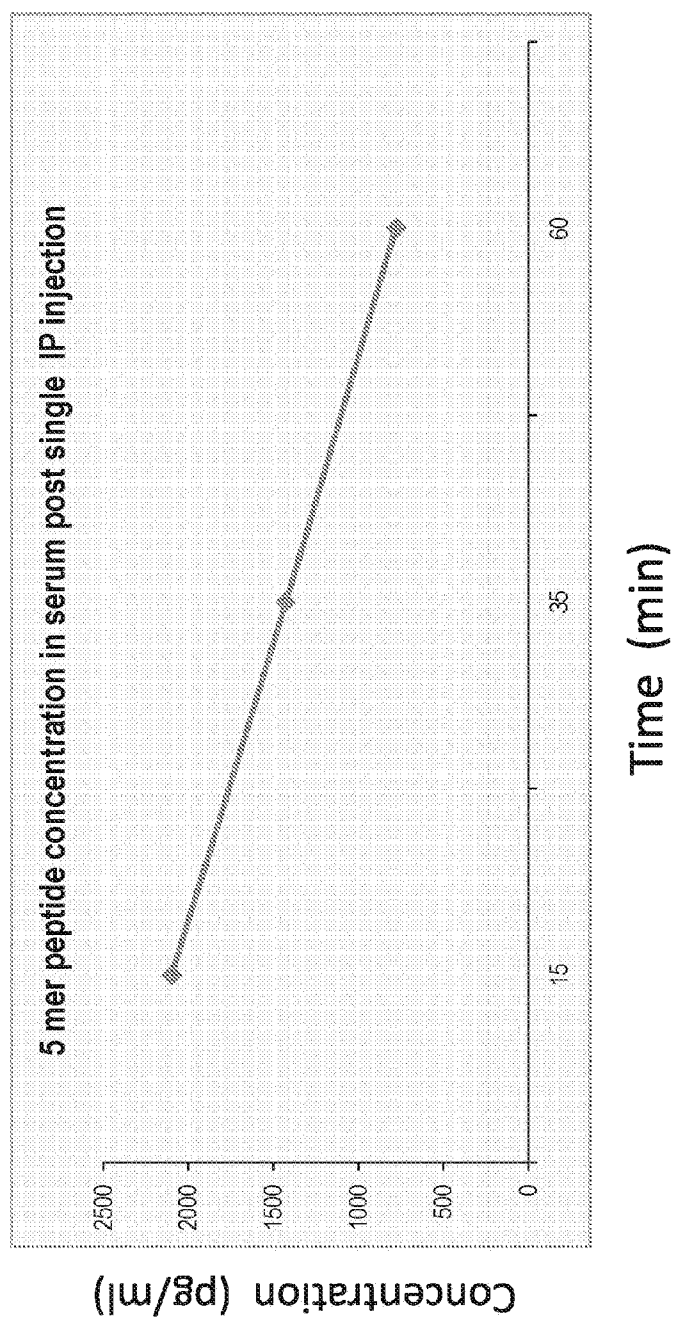
FIG. 13

FIG. 14

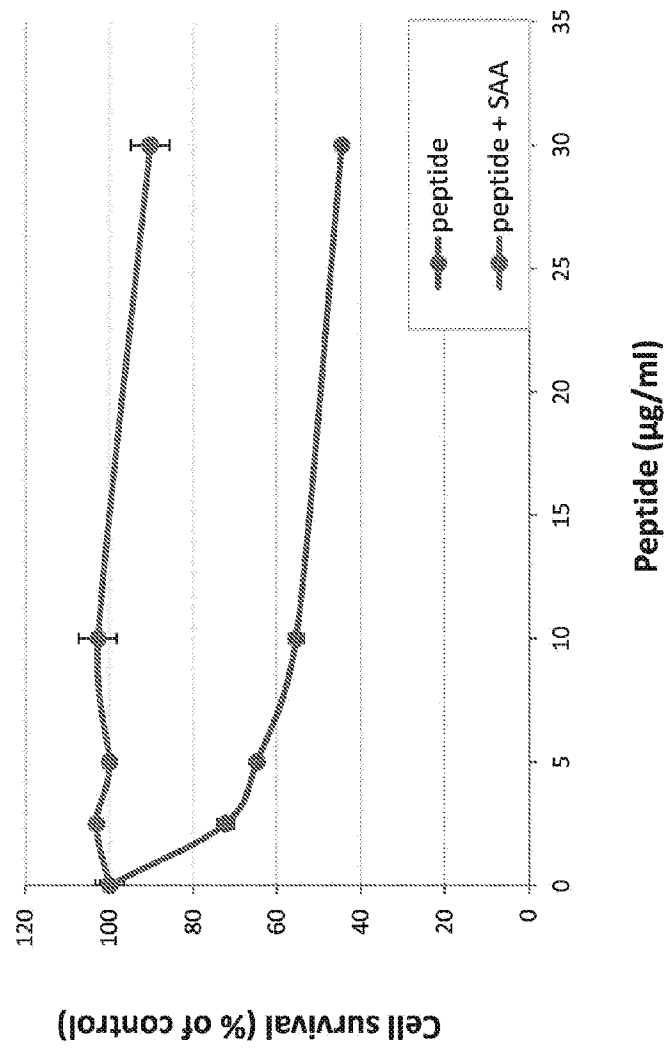


FIG. 15

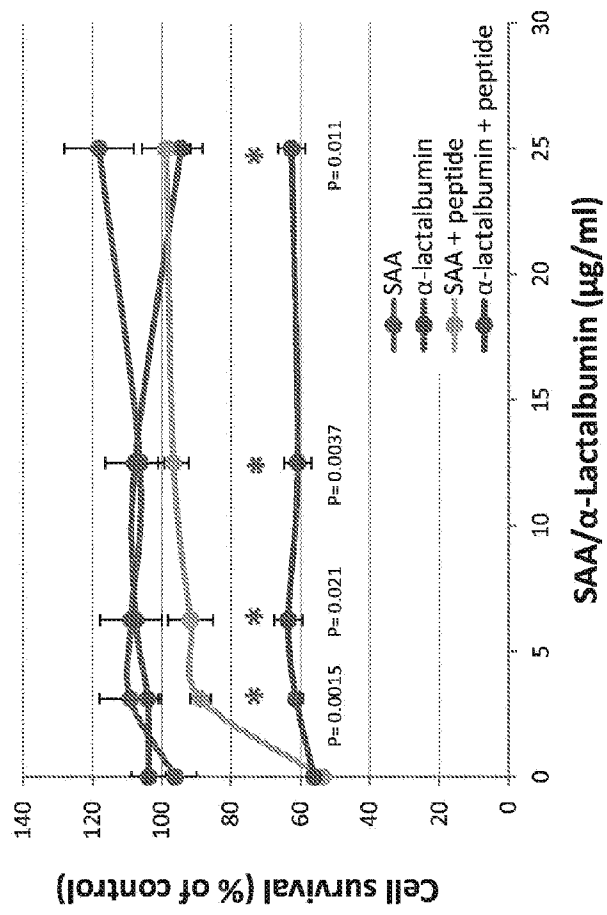


FIG. 16

