

**MULTIEPITOPE VACCINE FOR THE TREATMENT
OF ALZHEIMER'S DISEASE
RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/062,919, filed August 7, 2021, which is incorporated by reference herein in its entirety.

SEQUENCE LISTING STATEMENT

[0002] A computer readable form of the Sequence Listing is filed with this application by electronic submission and is incorporated into this application by reference in its entirety. The Sequence Listing is contained in the ASCII text file created on August 6, 2021, having the file name "20-1085-WO_Sequence-Listing_ST25.txt" and is 191 kb in size.

FIELD

[0003] The disclosure relates to the technical fields of immunology and medicine, and in particular to the treatment of Alzheimer's disease and other diseases of protein misfolding.

BACKGROUND

[0004] Alzheimer's disease (AD) is a progressive disease resulting in senile dementia. Broadly speaking, the disease falls into two categories: late onset, which occurs in old age (65+ years) and early onset, which develops well before the senile period, *i.e.*, between 35 and 60 years. In both types of disease, the pathology is the same, but the abnormalities tend to be more severe and widespread in cases beginning at an earlier age. The disease is characterized by at least two types of lesions in the brain, neurofibrillary tangles and senile plaques. Neurofibrillary tangles are intracellular deposits of microtubule associated tau protein consisting of two filaments twisted about each other in pairs. Senile plaques (*i.e.*, amyloid plaques) are areas of disorganized neuropil up to 150 μm across with extracellular amyloid deposits at the center which are visible by microscopic analysis of sections of brain tissue. The accumulation of amyloid plaques within the central nervous system is also associated with Down's syndrome and other cognitive disorders, Cerebral amyloid angiopathy (CAA), and the ocular disease Age-Related Macular Degeneration.

[0005] A principal constituent of the plaques is a peptide termed A β or β -amyloid peptide. A β peptide is a 4-kDa internal fragment of 38-43 amino acids of a larger transmembrane glycoprotein named amyloid precursor protein (APP). As a result of proteolytic processing of APP by different secretase enzymes, A β is primarily found in both a short form, 40 amino acids in length, and a long form, ranging from 42-43 amino acids in length. Part of the hydrophobic transmembrane domain of APP is found at the carboxy end of A β , and may account for the ability of A β to aggregate into plaques, particularly in the case of the long form. Accumulation of amyloid plaques in the brain eventually leads to neuronal cell death. The cognitive and physical symptoms associated with this type of neural deterioration characterize Alzheimer's disease.

[0006] Another protein reported to occur at increased levels in Alzheimer's patients relative to the general population is tau, the principal constituent of neurofibrillary tangles, which together with amyloid plaques are a hallmark characteristic of Alzheimer's disease. Tau tangles constitute abnormal fibrils measuring 10 nm in diameter occurring in pairs wound in a helical fashion with a regular periodicity of 80 nm. The tau within neurofibrillary tangles is abnormally phosphorylated (hyperphosphorylated) with phosphate groups attached to specific sites on the molecule. Severe involvement of neurofibrillary tangles is seen in the layer II neurons of the entorhinal cortex, the CA1 and subicular regions of the hippocampus, the amygdala, and the deeper layers (layers III, V, and superficial VI) of the neocortex in Alzheimer's disease. Tau pathologies are known to correlate to cognitive decline.

[0007] Alpha-synuclein, a protein found in neurons and other cells, is a major component of pathology that characterizes several neurodegenerative disorders including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, which collectively are termed synucleinopathies. The understanding of the normal physiological function of alpha-synuclein is limited, but evidence indicates that soluble forms of the protein may interact with other proteins and certain intracellular membranes. In synucleinopathies, the alpha-synuclein protein appears to be abnormally aggregated intracellularly, which contributes to disease pathology. There is increasing evidence that certain aggregated forms of alpha-synuclein can be transmitted from neuron to neuron, resulting in a propagation of pathology that causes

neuronal dysfunction and loss. Alpha-synuclein (SNCA) misfolding and aggregation can often be accompanied by β -amyloid deposition in some neurodegenerative diseases, and alpha-synuclein and tau aggregates coexist in several neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.

[0008] Accordingly, there exists the need for new therapies and reagents for the prevention or treatment of Alzheimer's disease, in particular, therapies and reagents capable of causing an immune response to the A β , Tau and alpha-synuclein present in patients.

SUMMARY

[0009] In some embodiments, disclosure is directed to a polypeptide including a first peptide comprising 3-10 amino acids from residues 1-10 or 12-25 of SEQ ID NO:01, a second peptide including 3-13 amino acids from residues 244-400 of SEQ ID NO:02, and a third peptide comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58. In certain embodiments, the polypeptide further comprises a fourth peptide selected from one of: (a) a peptide comprising 3-10 amino acids from residues 1-10 or 12-25 of SEQ ID NO:01; (b) a peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:02; and (c) a peptide comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58. In some embodiments, the first peptide, second peptide, third peptide, and fourth peptide are arranged in any order in the polypeptide. For example, the second peptide may be from the microtubule binding region (MTBR) of tau (residues 244-372 of SEQ ID NO:02). In addition, the first peptide may include an amino acid sequence of one of SEQ ID NOS: 3 to 38 or 1002-1057, the second peptide may include an amino acid sequence of one of SEQ ID NOS: 39 to 57, or 142 to 1000, the third peptide may include an amino acid sequence of one of SEQ ID NOS: 59-129, and the fourth peptide, if present, is one of any one of the amino acid sequences of SEQ ID NO: 3-38, 1002-1057, 39-57, 142 to 1000, and 59-129. For example, the first polypeptide may be DAEFRHD (SEQ ID NO:06), or EFRHDSG (SEQ ID NO:19), the second polypeptide may be 5-10 amino acids, for example QIVYKPV (SEQ ID NO:39), or NIKHVP (SEQ ID NO:57), the third polypeptide may be PDNEAYE (SEQ ID NO:75), or DPDNEAY (SEQ ID NO:69), and the fourth polypeptide, if present, may be NIKHVP (SEQ ID NO:48), or QIVYKPV (SEQ ID NO:39).

[0010] In other embodiments, two or more of the first peptide, the second peptide, and the third peptide, and the fourth peptide, if present, may be linked by a cleavable linker, which may be an amino acid sequence. A cleavable peptide linker, if present, can be 1-10 amino acids in length. In some embodiments, the linker comprises between about 1-10 amino acids, about 1-9 amino acids, about 1-8 amino acids, about 1-7 amino acids, about 1-6 amino acids, about 1-5 amino acids, about 1-4 amino acids, about 1-3 amino acids, about 2 amino acids, or one (1) amino acid. In some embodiments, the cleavable peptide linker is 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9 amino acids, or 10 amino acids. For example, the linker may be arginine-arginine (Arg-Arg), arginine-valine-arginine-arginine (Arg-Val-Arg-Arg (SEQ ID NO:138)), valine-citrulline (Val-Cit), valine-arginine (Val-Arg), valine-lysine (Val-Lys), valine-alanine (Val-Ala), phenylalanine-lysine (Phe-Lys), glycine-alanine-glycine-alanine (Gly-Ala-Gly-Ala; SEQ ID NO:139), Ala-Gly-Ala-Gly (SEQ ID NO:140), or Lys-Gly-Lys-Gly (SEQ ID NO:141). In particular embodiments, the polypeptide may be DAEFRHRRPDNEAYERRQIVYKPVKKC (SEQ ID NO:130), DAEFRHRRQIVYKPVRRPDNEAYEKKC (SEQ ID NO:131), DAEFRHRRPDNEAYERRNIKHVPGKKC (SEQ ID NO:132), DAEFRHRRNIKHVPGRRPDNEAYEKKC (SEQ ID NO:133), DAEFRHRRQIVYKPVRRPDNEAYERRNIKHVPGGC (SEQ ID NO:134), DAEFRHRRDPDNEAYRRNIKHVPGRRQIVYKPVGGC (SEQ ID NO:135), EFRHDSGRRQIVYKPVRRPDNEAYERRNIKHVPGGC (SEQ ID NO:136), EFRHDSGRRDPDNEAYRRNIKHVPGRRQIVYKPVGGC (SEQ ID NO:137), DAEFRHRRDPDNEAYERRENLKHQPGGGC (SEQ ID NO:1058), DAEFRHRRRENLKHQPGRRPDNEAYEGGC (SEQ ID NO:1059), DAEFRHRRPDNEAYERRENLKHQPGGGC (SEQ ID NO:1060), DAEFRHRRRENLKHQPGRRPDNEAYEGGC (SEQ ID NO:1061), DAEFRHRRRSKIGSKDNIKHRRDPDNEAYEGGC (SEQ ID NO:1062), or DAEFRHRRDPDNEAYERRSKIGSKDNIKHGGC (SEQ ID NO:1063).

[0011] In certain embodiments, the polypeptide further comprises a blocked amine at the N-terminus.

[0012] In further embodiments, the polypeptide may include a linker to a carrier at a C-terminal portion of the polypeptide, or at a N-terminal portion of the

polypeptide. A linker, if present, can be 1-10 amino acids in length. In some embodiments, the linker comprises between about 1-10 amino acids, about 1-9 amino acids, about 1-8 amino acids, about 1-7 amino acids, about 1-6 amino acids, about 1-5 amino acids, about 1-4 amino acids, about 1-3 amino acids, about 2 amino acids, or one (1) amino acid. In some embodiments, the linker is 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9 amino acids, or 10 amino acids. For example, the linker may include an amino acid sequence of GG, GGG, AA, AAA, KK, KKK, SS, SSS, GAGA (SEQ ID NO:139), AGAG (SEQ ID NO:140), and KGKG (SEQ ID NO:141). In addition, the linker to the carrier, if present at the C-terminus, may include a C-terminal cysteine (C). For example, the polypeptide may include the amino acid sequence of DAEFRHRRPDNEAYERRQIVYKPVKKC (SEQ ID NO:130), wherein KK and C are independently optional and, if present, KK can be replaced with GG, AA, SS, GAGA (SEQ ID NO:139), AGAG (SEQ ID NO:140), or KGKG (SEQ ID NO:141). Alternatively, the linker to the carrier, if present at the N-terminus, may include a N-terminal cysteine (C). For example, the sequence may be represented as CXX-polypeptide, wherein XX and C are independently optional and, if present, XX can be GG, AA, KK, SS, GAGA (SEQ ID NO:139), AGAG (SEQ ID NO:140), or KGKG (SEQ ID NO:141).

[0013] In other embodiments, the disclosure is directed to an immunotherapy composition including the polypeptides of the disclosure, wherein the polypeptide may be linked to a carrier. The carrier may include serum albumins, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid (TT), diphtheria toxoid (DT), a genetically modified cross-reacting material (CRM) of diphtheria toxin, CRM197, meningococcal outer membrane protein complex (OMPC) and *H. influenzae* protein D (HiD), rEPA (*Pseudomonas aeruginosa* exotoxin A), KLH (keyhole limpet hemocyanin), and flagellin.

[0014] Still further, embodiments of the disclosure are directed to a pharmaceutical formulation includes the polypeptides or the immunotherapy compositions of the disclosure, and including at least one adjuvant. The adjuvant may be aluminum hydroxide, aluminum phosphate, aluminum sulfate, 3 De-O-acylated monophosphoryl lipid A (MPL), QS-21, QS-18, QS-17, QS-7, TQL1055, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), oil in water

emulsions (such as squalene or peanut oil), CpG, polyglutamic acid, polylysine, AddaVax™, MF59®, and combinations thereof. In addition, the formulation may include a liposomal formulation, a diluent, or a multiple antigen presenting system (MAP). The MAP may include one or more of a Lys-based dendritic scaffold, helper T-cell epitopes, immune stimulating lipophilic moieties, cell penetrating peptides, radical induced polymerization, self-assembling nanoparticles as antigen-presenting platforms and gold nanoparticles.

[0015] Still further, embodiments of the disclosure are directed to an immunotherapy composition including a first peptide sequence comprising 3-10 amino acid residues from the first ten or 12 to 25 N-terminal residues of SEQ ID NO:01 and a second peptide sequence comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:02, and a third sequence comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58. The first peptide may include an amino acid sequence of one of SEQ ID NOS: 3 to 38 or SEQ ID NOS:1002 to 1057, and the second peptide may include an amino acid sequence of one of SEQ ID NOS: 39 to 57 or 142-1000, the third peptide sequence may include an amino acid sequence of one of SEQ ID NOS:59-129, and a fourth peptide sequence, if present, is one of any one of the amino acid sequences of SEQ ID NO: 3-38, 1002-1057, 39-57, 142-1000, and 59-129. Each of the first peptide and the second peptide, the third peptide, and the fourth peptide may include a linker to a carrier at a C-terminal portion of the polypeptide, or at a N-terminal portion of the polypeptide. When present, the linker may include an amino acid sequence selected from GG, GGG, AA, AAA, KK, KKK, SS, SSS, GAGA (SEQ ID NO:139), AGAG (SEQ ID NO:140), and KGKG (SEQ ID NO:141), and may include a C-terminal cysteine (C). In some embodiments, where the C-terminal residues in the immunogen are either IVYKPV (SEQ ID NO:194), VYKPV (SEQ ID NO:195), YKPV (SEQ ID NO:196), KPV, or PV the linker is an amino acid linker that does not have a N-terminal glycine (*e.g.*, GG, GAGA (SEQ ID NO:139)). The carrier may include serum albumins, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid (TT), diphtheria toxoid (DT), a genetically modified cross-reacting material (CRM) of diphtheria toxin, CRM197, meningococcal outer membrane protein complex (OMPC) and *H. influenzae* protein D (HiD), rEPA (*Pseudomonas aeruginosa* exotoxin A), KLH (keyhole limpet hemocyanin), and flagellin.

[0016] In addition, the immunotherapy composition may include at least one pharmaceutically acceptable diluent and/or a multiple antigen presenting system (MAP). The MAP may include one or more of a Lys-based dendritic scaffold, helper T-cell epitopes, immune stimulating lipophilic moieties, cell penetrating peptides, radical induced polymerization, self-assembling nanoparticles as antigen-presenting platforms and gold nanoparticles.

[0017] The immunotherapy composition may be included in a pharmaceutical composition including the immunotherapy composition and at least one adjuvant such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, 3 De-O-acylated monophosphoryl lipid A (MPL), QS-21, QS-18, QS-17, QS-7, TQL1055, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), oil in water emulsions (such as squalene or peanut oil), CpG, polyglutamic acid, polylysine, AddaVax™, MF59®, and combinations thereof.

[0018] Embodiments of the disclosure are also directed to nucleic acid sequences encoding the polypeptides and the immunotherapy compositions of the disclosure. The nucleic acids may be included in a nucleic acid immunotherapy composition including the nucleic acid and at least one adjuvant.

[0019] Still further, embodiments of the disclosure are directed to a methods for treating or effecting prophylaxis of Alzheimer's disease in a subject, and methods for inhibiting or reducing aggregation of at least one of A β , tau, and alpha-synuclein in a subject having or at risk of developing Alzheimer's disease. The methods include administering to the subject an immunotherapy composition, a nucleic acids immunotherapy composition, or a pharmaceutical formulation of the disclosure.

[0020] The methods of the disclosure may include repeating the administering at least a second time, at least a third time, at least a fourth time, at least a fifth time, or at least a sixth time, and may include repeating the administering at an interval of about 21 to about 28 days.

[0021] Still further, methods of the disclosure are directed to inducing an immune response in an animal. The methods include administering to the animal a polypeptide, an immunotherapy composition, a pharmaceutical formulation or a nucleic acid immunotherapy composition of the disclosure in a regimen effective to generate an immune response including antibodies that specifically bind to A β , and/or

tau, and/or alpha-synuclein. The immune response may include antibodies that specifically bind to the N-terminal region of A β and/or the microtubule region of tau, and/or the C-terminal region of alpha-synuclein.

[0022] In other embodiments, the disclosure is directed to an immunization kit including an immunotherapy composition of the disclosure and may include an adjuvant, wherein the immunotherapy composition may be in a first container and the adjuvant may be a second container.

[0023] Still further, the disclosure is directed to a kit including a nucleic acid immunotherapy composition of the disclosure and may include an adjuvant. The nucleic acid may be in a first container and the adjuvant may be in a second container.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] **FIG. 1A** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 25 (DAEFRHDDRQIVYKPVRRPDNEAYEKKC; SEQ ID NO:131) on day 0, week 3, and week 7, and serum was collected one week after each injection (i.e., week 1, week 4 and week 8).

[0025] **FIG. 1B** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 27 (DAEFRHDDRNIKHVPGRRPDNEAYEKKC; SEQ ID NO:133) on day 0, week 3, and week 7, and serum was collected one week after each injection (i.e., week 1, week 4 and week 8).

[0026] **FIG. 1C** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 26 (DAEFRHDDRDPNEAYERRNIKHVPGKKC; SEQ ID NO:132) on day 0, week 3, and week 7, and serum was collected one week after each injection (i.e., week 1, week 4 and week 8).

[0027] **FIG. 1D** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide

antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 24 (DAEFRHDDRRPDNEAYERRQIVYKPVKKK; SEQ ID NO:130) on day 0, week 3, and week 7, and serum was collected one week after each injection (i.e., week 1, week 4 and week 8).

[0028] **FIG. 2A** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 25 (DAEFRHDDRRQIVYKPVRRPDNEAYEKKK; SEQ ID NO:131) on day 0, week 3, week 7, and week 11, and serum was collected one week after each injection (i.e., week 1, week 4, week 8, and week 12).

[0029] **FIG. 2B** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 24 (DAEFRHDDRRPDNEAYERRQIVYKPVKKK; SEQ ID NO:130) on day 0, week 3, week 7, and week 11, and serum was collected one week after each injection (i.e., week 1, week 4, week 8, and week 12).

[0030] **FIG. 2C** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 27 (DAEFRHDDRRNIKHVPGRPDNEAYEKKK; SEQ ID NO:133) on day 0, week 3, week 7, and week 11, and serum was collected one week after each injection (i.e., week 1, week 4, week 8, and week 12).

[0031] **FIG. 2D** shows the serum of guinea pigs vaccinated with a tri-peptide immunogen comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Three guinea pigs were injected with Immunogen 26 (DAEFRHDDRRPDNEAYERRNIKHVPGKKK; SEQ ID NO:132) on day 0, week 3, week 7, and week 11, and serum was collected one week after each injection (i.e., week 1, week 4, week 8, and week 12).

[0032] **FIG. 3** shows that the serum of mice vaccinated with one of 4 tri-peptide immunogens each comprising an A β peptide, a Tau peptide and an alpha-synuclein peptide antigen produce titers to A β , Tau, and alpha-synuclein. Four Swiss webster mice per immunogen were injected on day 0 and day 10, and serum was

collected on day 16. Tri 2 is DAEFRHRRDPDNEAYERRENKHKQPGGGC (SEQ ID NO:1058), Tri 1 is DAEFRHRRRENKHKQPGRDPDNEAYEGGC (SEQ ID NO:1059), Tri 4 is DAEFRHRRDPDNEAYERRENKHKQPGGGC (SEQ ID NO:1060), Tri 3 is DAEFRHRRRENKHKQPGRDPDNEAYEGGC (SEQ ID NO:1061) (also see Table 4).

DESCRIPTION

[0033] The disclosure provides peptide compositions and immunotherapy compositions comprising an amyloid-beta (A β) peptide, a tau peptide, and an alpha-synuclein peptide. The disclosure also provides methods of treating or effecting prophylaxis of Alzheimer's disease or other diseases with beta-amyloid deposition in a subject, including methods of clearing and preventing formation of deposits, inhibiting or reducing aggregation of A β and/or tau, and/or alpha-synuclein, blocking the binding and/or uptake of A β and/or tau and/or alpha-synuclein by neurons, inhibiting transmission of tau species between cells, and inhibiting propagation of pathology between brain regions in a subject having or at risk of developing Alzheimer's disease or other diseases containing tau and/or amyloid-beta accumulations. The methods include administering to such patients the compositions comprising an amyloid-beta (A β) peptide, a tau peptide, and an alpha-synuclein peptide.

[0034] A number of terms are defined below. As used herein, the singular forms "a," "an", and "the" include plural referents unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" can include a plurality of compounds, including mixtures thereof.

[0035] Unless otherwise apparent from the context, the term "about" encompasses insubstantial variations, such as values within a standard margin of error of measurement (*e.g.*, SEM) of a stated value. For example the term "about" as used herein when referring to a measurable value such as a parameter, an amount, a temporal duration, can encompass variations of +/-10% or less, +/-5% or less, or +/-1% or less or less of and from the specified value. Designation of a range of values includes all integers within or defining the range, and all subranges defined by integers within the range. As used herein, statistical significance means $p \leq 0.05$.

[0036] Compositions or methods “comprising” or “including” one or more recited elements may include other elements not specifically recited. For example, a composition that “comprises” or “includes” a polypeptide sequence may contain the sequence alone or in combination with other sequences or ingredients.

[0037] An individual is at increased risk of a disease if the subject has at least one known risk-factor (*e.g.*, age, genetic, biochemical, family history, and situational exposure) placing individuals with that risk factor at a statistically significant greater risk of developing the disease than individuals without the risk factor.

[0038] The term “patient” includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment, including treatment naïve subjects. As used herein, the terms “subject” or “patient” refer to any single subject for which treatment is desired, including other mammalian subjects such as, humans, cattle, dogs, guinea pigs, rabbits, and so on. Also intended to be included as a subject are any subjects involved in clinical research trials not showing any clinical sign of disease, or subjects involved in epidemiological studies, or subjects used as controls.

[0039] The term “disease” refers to any abnormal condition that impairs physiological function. The term is used broadly to encompass any disorder, illness, abnormality, pathology, sickness, condition, or syndrome in which physiological function is impaired, irrespective of the nature of the etiology.

[0040] The term “symptom” refers to a subjective evidence of a disease, such as altered gait, as perceived by the subject. A “sign” refers to objective evidence of a disease as observed by a physician.

[0041] As used herein, the terms “treat” and “treatment” refer to the alleviation or amelioration of one or more symptoms or effects associated with the disease, prevention, inhibition or delay of the onset of one or more symptoms or effects of the disease, lessening of the severity or frequency of one or more symptoms or effects of the disease, and/or increasing or trending toward desired outcomes as described herein.

[0042] The terms “prevention”, “prevent”, or “preventing” as used herein refer to contacting (for example, administering) the peptide(s) or immunotherapy compositions of the present disclosure with a subject before the onset of a disease, with or without A β and/or tau pathology already present (primary and secondary

prevention), thereby delaying the onset of clinical symptoms and/or alleviating symptoms of the disease after the onset of the disease, compared to when the subject is not contacted with the peptide or immunotherapy compositions, and does not refer to completely suppressing the onset of the disease. In some cases, prevention may occur for limited time after administration of the peptide or immunotherapy compositions of the present disclosure. In other cases, prevention may occur for the duration of a treatment regimen comprising administering the peptide or immunotherapy compositions of the present disclosure.

[0043] The terms "reduction", "reduce", or "reducing" as used herein refer to decreasing the amount of A β and/or tau and/or alpha-synuclein present in a subject or in tissue of the subject, or suppressing an increase in the amount of A β and/or tau and/or alpha-synuclein present in a subject or in tissue of the subject, which encompasses decreasing or suppressing an increase in (*e.g.*, decreasing the rate of increase) the amount of A β and/or tau and/or alpha-synuclein present, accumulated, aggregated, or deposited in the subject or tissue in the subject. In certain embodiments, the decrease in or suppression of an increase in (*e.g.*, decreasing the rate of increase) the amount of A β and/or tau and/or alpha-synuclein present, accumulated, aggregated, or deposited in the subject refers to an amount of A β and/or tau and/or alpha-synuclein present, accumulated, aggregated, or deposited in the central nervous system (CNS) of the subject. In certain embodiments, the decrease in or suppression of an increase in (*e.g.*, decreasing the rate of increase) the amount of A β and/or tau and/or alpha-synuclein present, accumulated, aggregated, or deposited in the subject refers to an amount of A β and/or tau and/or alpha-synuclein present, accumulated, aggregated, or deposited in the periphery (*e.g.*, peripheral circulatory system) of the subject. In certain embodiments, the decrease in or suppression of an increase in (*e.g.*, decreasing the rate of increase) the amount of A β and/or tau and/or alpha-synuclein present, accumulated, aggregated, or deposited in the subject refers to an amount of A β and/or tau and/or alpha-synuclein present, accumulated, aggregated, or deposited in the brain of the subject. In some embodiments, the A β and/or tau and/or alpha-synuclein reduced is the pathological form(s) of the A β (*e.g.*, extracellular plaque deposits of the β -amyloid peptide (A β), neuritic amyloid plaques), and/or tau (*e.g.*, neurofibrillary tangles of tau, dystrophic neurites), and/or alpha-synuclein (*e.g.*, fibrillar alpha-synuclein inclusions, oligomeric or fibrillar alpha-

synuclein conglomerates, and protofibrillar intermediates of alpha-synuclein oligomers). In yet other embodiments, pathological indicators of neurodegenerative disease and/or synucleinopathies are decreased.

[0044] The terms "epitope" or "antigenic determinant" refers to a site on an antigen to which B and/or T cells respond, or to a site on an antigen to which an antibody binds. Epitopes can be formed both from contiguous amino acids or from noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. *See, e.g.,* Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, Glenn E. Morris, Ed. (1996).

[0045] An "immunogenic agent" or "immunogen" or "antigen" is capable of inducing an immunological response against itself or modified/processed versions of itself upon administration to an animal, optionally in conjunction with an adjuvant. The terms "immunogenic agent" or "immunogen" or "antigen" refer to a compound or composition comprising a peptide, polypeptide or protein which is "antigenic" or "immunogenic" when administered in an appropriate amount (an "immunogenically effective amount"), *i.e.*, capable of inducing, eliciting, augmenting or boosting a cellular and/or humoral immune response and of being recognized by the products of that response (T cells, antibodies). An immunogen can be a peptide, or a combination of two or more same or different peptides, that includes at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 amino acids in a linear or spatial conformation.

[0046] An immunogen may be effective when given alone or in combination, or linked to, or fused to, another substance (which can be administered at one time or over several intervals). An immunogenic agent or immunogen may include an antigenic peptide or polypeptide that is linked to a carrier as described herein.

[0047] A nucleic acid such as DNA or RNA that encodes an antigenic peptide, or polypeptide is referred to as a "DNA [or RNA] immunogen," as the encoded peptide or polypeptide is expressed *in vivo* after administration of the DNA or RNA. The peptide or polypeptide can be recombinantly expressed from a vaccine vector, which can be naked DNA or RNA that comprises the peptide or polypeptide coding sequence operably linked to a promoter, *e.g.*, an expression vector or cassette as described herein.

[0048] The term "adjuvant" refers to a compound that, when administered in conjunction with an antigen, augments the immune response to the antigen, but when administered alone does not generate an immune response to the antigen. Adjuvants can augment an immune response by several mechanisms including lymphocyte recruitment, stimulation of B and/or T cells, and stimulation of macrophages. An adjuvant may be a natural compound, a modified version of or derivative of a natural compound, or a synthetic compound.

[0049] The terms "peptide" and "polypeptide" are used interchangeably herein and refer to a chain of two or more consecutive amino acids. If and when a distinction is made, context makes the meaning clear. For example, if two or more peptides described herein are joined to make a dimeric or multimeric peptide, polypeptide may be used to indicate "poly" or "more than one" peptide.

[0050] The term "pharmaceutically acceptable" means that the carrier, diluent, excipient, adjuvant, or auxiliary is compatible with the other ingredients of a pharmaceutical formulation and not substantially deleterious to the recipient thereof.

[0051] The terms "immunotherapy" or "immune response" refer to the development of a beneficial humoral (antibody mediated) and/or a cellular (mediated by antigen-specific T cells or their secretion products) response directed against an A β and/or tau peptide in a recipient. Such a response can be an active response induced by administration of immunogen (*e.g.* an A β peptide and/or tau peptide and/or alpha-synuclein peptide). A cellular immune response is elicited by the presentation of polypeptide epitopes in association with Class I or Class II MHC molecules to activate antigen-specific CD4⁺ T helper cells and/or CD8⁺ cytotoxic T cells. The response may also involve activation of monocytes, macrophages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils or other components

of innate immunity. The presence of a cell-mediated immunological response can be determined by proliferation assays ($CD4^+$ T cells) or CTL (cytotoxic T lymphocyte) assays. The relative contributions of humoral and cellular responses to the protective or therapeutic effect of an immunogen can be distinguished by separately isolating antibodies and T-cells from an immunized syngeneic animal and measuring protective or therapeutic effect in a second subject.

[0052] Amyloid Beta ($A\beta$)

[0053] $A\beta$ (also referred to herein as beta amyloid peptide or Abeta) peptide is about a 4-kDa internal fragment of 38-43 amino acids of APP ($A\beta$ 39, $A\beta$ 40, $A\beta$ 41, $A\beta$ 42, and $A\beta$ 43). $A\beta$ 40, for example, consists of residues 672-711 of APP and $A\beta$ 42 consists of residues 673-713 of APP. As a result of proteolytic processing of APP by different secretase enzymes *in vivo* or *in situ*, $A\beta$ is found in both a "short form", 40 amino acids in length, and a "long form", ranging from 42-43 amino acids in length. Epitopes or antigenic determinants, as described herein, are located within the N-terminus of the $A\beta$ peptide and include residues within amino acids 1-10 and 12-25 of $A\beta$, for example from residues 1-3, 1-4, 1-5, 1-6, 1-7, or 3-7 of $A\beta$ 42. Additional examples of epitopes or antigenic determinants include residues 2-4, 2-5, 2-6, 2-7, or 2-8 of $A\beta$, residues 3-5, 3-6, 3-7, 3-8, or 3-9 of $A\beta$, or residues 4-7, 4-8, 4-9, or 4-10 of $A\beta$ 42. $A\beta$ residues 12-24, 12-23, 12-22, 13-25, 13-24, 13-23, 13-22, 14-25, 14-24, 14-23, 14-22, 15-25, 15-24, 15-23, or 15-22 of $A\beta$. For example, from residues 12-17, 12-18, 12-19, 12-20, 12-21, 13-17, 13-18, 13-19, 13-20, 13-21, 13-22, 14-17, 14-18, 14-19, 14-20, 14-21, 14-22, 14-23, 15-17, 15-18, 15-19, 15-20, 15-21, 15-22, 15-23, or 15-24 of $A\beta$ 42. Additional examples of epitopes or antigenic determinants include residues 16-18, 16-19, 16-20, 16-21, 16-22, 16-23, 16-24, 16-25, 17-19, 17-20, 17-21, 17-22, 17-23, 17-24 or 17-25 of $A\beta$ 42. Other examples of epitopes or antigenic determinants include residues 18-20, 18-21, 18-22, 18-23, 18-24, 18-25, 19-21, 19-22, 19-23, 19-24, 19-25, 20-22, 20-23, 20-24, 20-25, 21-23, 21-24 or 21-25 of $A\beta$ 42.

[0054] $A\beta$ (Abeta) is the principal component of characteristic plaques of Alzheimer's disease. $A\beta$ is generated by processing of a larger protein APP by two enzymes, termed beta and gamma secretases. Known mutations in APP associated with Alzheimer's disease occur proximate to the site of beta or gamma secretase, or within $A\beta$. Part of the hydrophobic transmembrane domain of APP is found at the

carboxy end of A β , and may account for the ability of A β to aggregate into plaques, particularly in the case of the long form. Accumulation of amyloid plaques in the brain eventually leads to neuronal cell death. The physical symptoms associated with this type of neural deterioration characterize Alzheimer's disease.

[0055] Tau

[0056] Tau is a protein with a molecular weight of about 50,000 that is normally present in nerve axons or the like, and contributes to microtubular stability. The tau proteins (or τ proteins) are a group of six highly-soluble protein isoforms produced by alternative splicing from the gene MAPT (microtubule-associated protein tau). They have roles primarily in maintaining the stability of microtubules in axons and are abundant in the neurons of the central nervous system (CNS). They are less common elsewhere but are also expressed at very low levels in CNS astrocytes and oligodendrocytes. Pathologies and dementias of the nervous system such as Alzheimer's disease and Parkinson's disease are associated with tau proteins that have become hyperphosphorylated insoluble aggregates called neurofibrillary tangles. Pathogenic tau species causes toxic effects through direct binding to cells and/or accumulation inside cells and/or initiation of misfolding processes (seeding) and is can be propagated from one cell to another via cell-to-cell transmission. Toxicity could also happen by neurofibrillary tangles (NFTs), which leads to cell death and cognitive decline. Other tauopathies include, for example, progressive supranuclear palsy, corticobasal syndrome, some frontotemporal dementias, and chronic traumatic encephalopathy.

[0057] Alpha-synuclein

[0058] Alpha-synuclein is a highly conserved protein that is abundant in neurons, especially presynaptic terminals. Aggregated alpha-synuclein proteins form brain lesions that are hallmarks of neurodegenerative synucleinopathies. Furthermore, misfolding and aggregation can often be accompanied by β -amyloid deposition in some neurodegenerative diseases, and alpha-synuclein and tau aggregates coexist in several neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.

[0059] A β /Tau/Alpha-synuclein Polypeptides of an Immunogen

[0060] An agent used for active immunization can induce in a patient an immune response and can serve as an immunotherapy. Agents used for active immunization can be, for example, the same types of immunogens used for generating monoclonal antibodies in laboratory animals, and may include 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 or more contiguous amino acids from a region of A β and/or tau peptide and/or alpha-synuclein peptide. In each of the embodiments of the peptides described herein, the peptides may comprise, consist, or consist essentially of the recited sequences.

[0061] In some embodiments of the disclosure, an A β /tau/alpha-synuclein immunogen can include an A β peptide comprising 3-10 amino acids from residues 1-10 or 12-25 of the N-terminal sequence of A β (SEQ ID NO:01) linked to a tau peptide comprising 3-13 amino acids from residues 244-400 of the long form of tau (SEQ ID NO:02), and an alpha-synuclein peptide comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58. For example, the tau peptide may comprise 3-13 amino acids from the microtubule binding region of tau (residues 344-372 of SEQ ID NO:02).

[0062] In some embodiments of the disclosure, the A β peptide can include 3-10 amino acids from residues 1-10 or 12-25 of DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO:01). For example, the A β peptide is selected from the following:

DAEFRHDSGY	(SEQ ID NO:03),
DAEFRHDSG	(SEQ ID NO:04),
DAEFRHDS	(SEQ ID NO:05),
DAEFRHD	(SEQ ID NO:06),
DAEFRH	(SEQ ID NO:07),
DAEFR	(SEQ ID NO:08),
DAEF	(SEQ ID NO:09),
DAE	(SEQ ID NO:10),
AEFRHDSGY	(SEQ ID NO:11),
AEFRHDSG	(SEQ ID NO:12),
AEFRHDS	(SEQ ID NO:13),
AEFRHD	(SEQ ID NO:14),
AEFRH	(SEQ ID NO:15),

AEFR	(SEQ ID NO:16),
AEF	(SEQ ID NO:17),
EFRHDSGY	(SEQ ID NO:18),
EFRHDSG	(SEQ ID NO:19),
EFRHDS	(SEQ ID NO:20),
EFRHD	(SEQ ID NO:21),
EFRH	(SEQ ID NO:22),
EFR	(SEQ ID NO:23),
FRHDSGY	(SEQ ID NO:24),
FRHDSG	(SEQ ID NO:25),
FRHDS	(SEQ ID NO:26),
FRHD	(SEQ ID NO:27),
FRH	(SEQ ID NO:28),
RHDSGY	(SEQ ID NO:29),
RHDSG	(SEQ ID NO:30),
RHDS	(SEQ ID NO:31),
RHD	(SEQ ID NO:32),
HDSGY	(SEQ ID NO:33),
HDSG	(SEQ ID NO:34),
HDS	(SEQ ID NO:35),
DSGY	(SEQ ID NO:36),
DSG	(SEQ ID NO:37),
SGY	(SEQ ID NO:38),
VHHQKLVFFA	(SEQ ID NO:1002),
VHHQKLVFF	(SEQ ID NO:1003),
VHHQKLVF	(SEQ ID NO:1004),
VHHQKL	(SEQ ID NO:1005),
VHHQKL	(SEQ ID NO:1006),
HHQKLVFFAE	(SEQ ID NO:1007),
HHQKLVFFA	(SEQ ID NO:1008),
HHQKLVFF	(SEQ ID NO:1009),
HHQKLVF	(SEQ ID NO:1010),
HHQKL	(SEQ ID NO:1011),
HHQKL	(SEQ ID NO:1012),

HQKLVFFAED (SEQ ID NO:1013),
HQKLVFFAE (SEQ ID NO:1014),
HQKLVFFA (SEQ ID NO:1015),
HQKLVFF (SEQ ID NO:1016),
HQKLVF (SEQ ID NO:1017),
HQKLV (SEQ ID NO:1018),
HQKL (SEQ ID NO:1019),
QKLVFFAEDV (SEQ ID NO:1020),
QKLVFFAED (SEQ ID NO:1021),
QKLVFFAE (SEQ ID NO:1022),
QKLVFFA (SEQ ID NO:1023),
QKLVFF (SEQ ID NO:1024),
QKLVF (SEQ ID NO:1025),
QKLV (SEQ ID NO:1026),
QKL (SEQ ID NO:1027),
KLVFFAEDVG (SEQ ID NO:1028),
KLVFFAEDV (SEQ ID NO:1029),
KLVFFAED (SEQ ID NO:1030),
KLVFFAE (SEQ ID NO:1031),
KLVFFA (SEQ ID NO:1032),
KLVFF (SEQ ID NO:1033),
KLVF (SEQ ID NO:1034),
KLV (SEQ ID NO:1035),
LVFFAEDVG (SEQ ID NO:1036),
LVFFAEDV (SEQ ID NO:1037),
LVFFAED (SEQ ID NO:1038),
LVFFAE (SEQ ID NO:1039),
LVFFA (SEQ ID NO:1040),
LVFF (SEQ ID NO:1041),
LVF (SEQ ID NO:1042),
VFFAEDVG (SEQ ID NO:1043),
VFFAEDV (SEQ ID NO:1044),
VFFAED (SEQ ID NO:1045),
VFFAE (SEQ ID NO:1046),

VFFA (SEQ ID NO:1047),
 VFF (SEQ ID NO:1048),
 FFAEDVG (SEQ ID NO:1049),
 FFAEDV (SEQ ID NO:1050),
 FFAED (SEQ ID NO:1051),
 FFAE (SEQ ID NO:1052),
 FFA (SEQ ID NO:1053),
 FAEDVG (SEQ ID NO:1054),
 FAEDV (SEQ ID NO:1055),
 FAED (SEQ ID NO:1056), and
 FAE (SEQ ID NO:1057).

[0063] In certain embodiments, the A β peptide is DAEFRHD (SEQ ID NO:06), DAEFR (SEQ ID NO:08) or EFRHD (SEQ ID NO:21).

[0064] The tau peptide can correspond to a peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:02. In some embodiments, the fragment is unphosphorylated. In some embodiments, the fragment is phosphorylated. In some embodiments, the tau peptide comprises an amino acid sequence represented by the consensus motif (Q/E)IVYK(S/P) (SEQ ID NO:996). In some embodiments, the tau peptide comprises an amino acid sequence represented by the consensus motif KXXSXXNX(K/H)H (SEQ ID NO: 995) where X is any amino acid. In some embodiments, the tau peptide is selected from SEQ ID NOS: 146-1000. In some embodiments, the tau peptide is selected from the following:

QIVYKPV (SEQ ID NO:39),
 QIVYKP (SEQ ID NO:40),
 QIVYKSV (SEQ ID NO:41),
 EIVYKSV (SEQ ID NO:42),
 QIVYKS (SEQ ID NO:997),
 EIVYKSP (SEQ ID NO:43),
 EIVYKS (SEQ ID NO:998),
 EIVYKPV (SEQ ID NO:44),
 EIVYKP (SEQ ID NO:999),
 IVYKSPV (SEQ ID NO:45),
 IVYK (SEQ ID NO:46),

CNIKHVPG (SEQ ID NO:1000),
CNIKHVP (SEQ ID NO:47),
NIKHVP (SEQ ID NO:48),
HVPGGG (SEQ ID NO:49),
HVPGG (SEQ ID NO:50),
HKPGGG (SEQ ID NO:51),
HKPGG (SEQ ID NO:52),
KHVPGGG (SEQ ID NO:53),
KHVPGG (SEQ ID NO:54),
HQPGGG (SEQ ID NO:55),
HQPGG (SEQ ID NO:56),
NIKHVPG (SEQ ID NO:57), and
SEQ ID NOs: 146-996.

[0065] The alpha-synuclein peptide can correspond to a peptide comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58. In some embodiments, alpha-synuclein is unphosphorylated. In some embodiments, alpha-synuclein is phosphorylated. In some compositions, the alpha-synuclein peptide is selected from the following:

VDPDNEAYEM (SEQ ID NO:59),
VDPDNEAYE (SEQ ID NO:60),
VDPDNEAY (SEQ ID NO:61),
VDPDNEA (SEQ ID NO:62),
VDPDNE (SEQ ID NO:63),
VDPDN (SEQ ID NO:64),
VDPD (SEQ ID NO:65),
VDP (SEQ ID NO:66),
DPDNEAYEM (SEQ ID NO:67),
DPDNEAYE (SEQ ID NO:68),
DPDNEAY (SEQ ID NO:69),
DPDNEA (SEQ ID NO:70),
DPDNE (SEQ ID NO:71),
DPDN (SEQ ID NO:72),
DPD (SEQ ID NO:73),

PDNEAYEM (SEQ ID NO:74),
PDNEAYE (SEQ ID NO:75),
PDNEAY (SEQ ID NO:76),
PDNEA (SEQ ID NO:77),
PDNE (SEQ ID NO:78),
PDN (SEQ ID NO:79),
DNEAYEM (SEQ ID NO:80),
DNEAYE (SEQ ID NO:81),
DNEAY (SEQ ID NO:82),
DNEA (SEQ ID NO:83),
DNE (SEQ ID NO:84),
NEAYEM (SEQ ID NO:85),
NEAYE (SEQ ID NO:86),
NEAY (SEQ ID NO:87),
NEA (SEQ ID NO:88),
EAYEM (SEQ ID NO:89),
EAYE (SEQ ID NO:90),
EAY (SEQ ID NO:91),
AYEM (SEQ ID NO:92),
AYE (SEQ ID NO:93),
YEM (SEQ ID NO:94),
ATGFVKKDQL (SEQ ID NO:95),
ATGFVKKDQ (SEQ ID NO:96),
ATGFVKKD (SEQ ID NO:97),
ATGFVKK (SEQ ID NO:98),
ATGFVK (SEQ ID NO:99),
ATGFV (SEQ ID NO:100),
ATGF (SEQ ID NO:101),
ATG (SEQ ID NO:102),
TGFVKKDQL (SEQ ID NO:103),
TGFVKKDQ (SEQ ID NO:104),
TGFVKKD (SEQ ID NO:105),
TGFVKK (SEQ ID NO:106),
TGFVK (SEQ ID NO:107),

TGFV (SEQ ID NO:108),
 TGF (SEQ ID NO:109),
 GFVKKDQL (SEQ ID NO:110),
 GFVKKDQ (SEQ ID NO:111),
 GFVKKD (SEQ ID NO:112),
 GFVKK (SEQ ID NO:113),
 GFVK (SEQ ID NO:114),
 GFV (SEQ ID NO:115),
 FVKKDQL (SEQ ID NO:116),
 FVKKDQ (SEQ ID NO:117),
 FVKKD (SEQ ID NO:118),
 FVKK (SEQ ID NO:119),
 FVK (SEQ ID NO:120),
 VKKDQL (SEQ ID NO:121),
 VKKDQ (SEQ ID NO:122),
 VKKD (SEQ ID NO:123),
 VKK (SEQ ID NO:124),
 KKDQL (SEQ ID NO:125),
 KKDQ (SEQ ID NO:126),
 KKD (SEQ ID NO:127),
 KDQL (SEQ ID NO:128), and
 KDQ (SEQ ID NO:129).

In each of these embodiments, the peptide may comprise, consist, or consist essentially of the recited sequences.

[0066] In some embodiments, the A β and/or tau and/or alpha-synuclein peptides are linked to form a multiple A β /tau/alpha-synuclein polypeptide. The A β , tau, and alpha-synuclein peptides can be linked by an intra-peptide linker. For example, a polypeptide linker located between the C-terminal of the first peptide and the N terminal of the second peptide. With or without the intra-peptide linker, the A β peptide and/or the tau peptide and/or the alpha-synuclein peptide may be positioned in a multiple A β /tau/alpha-synuclein polypeptide in any order. For example, the A β peptide may be positioned at the N-terminal portion of the multiple polypeptide and the alpha-synuclein peptide may be positioned at the C-terminal portion of the

multiple polypeptide. Or, the tau peptide may be positioned at the N-terminal portion of the multiple polypeptide and the A β peptide may be positioned at the C-terminal portion of the multiple polypeptide side of the tau peptide. Reference to a first peptide or a second peptide or a third peptide or a fourth peptide herein is not intended to suggest an order of the A β and/or tau and/or alpha-synuclein peptides in the polypeptide of the immunogens.

[0067] In addition, the C-terminal portion of the A β peptide, the tau peptide, the alpha-synuclein, or the multiple A β /tau/alpha-synuclein polypeptide can include a linker for conjugating the peptides or the polypeptide to a carrier. Linkers that couple the peptides or multiple polypeptide to the carrier may include, for example, GG, GGG, KK, KKK, AA, AAA, SS, SSS, GAGA (SEQ ID NO:139), AGAG (SEQ ID NO:140), KGKG (SEQ ID NO:141), and the like between the peptides or dual polypeptide and the carrier and may further include a C-terminal or a N-terminal cysteine to provide a short peptide linker (*e.g.*, G-G-C-, K-K-C-, A-A-C-, or S-S-C-). In some embodiments, where the C-terminal residues in the immunogen are either IVYKPV (SEQ ID NO:194), VYKPV (SEQ ID NO:195), YKPV (SEQ ID NO:196), KPV, or PV the linker is an amino acid linker that does not have a N-terminal glycine (*e.g.*, GG, GAGA (SEQ ID NO:139), and KGKG (SEQ ID NO:141). In some embodiments, the linker comprises an amino acid sequence any one of AA, AAA, KK, KKK, SS, SSS, AGAG (SEQ ID NO:140), GG, GGG, GAGA (SEQ ID NO:139), and KGKG (SEQ ID NO:141). In some embodiments, any of the A β peptide, the tau peptide, the alpha-synuclein peptide and the multiple A β /tau/alpha-synuclein polypeptide may include a C-terminal cysteine without the spacer. In some embodiments, any of the A β peptide, the tau peptide, the alpha-synuclein peptide and the multiple A β /tau/alpha-synuclein polypeptide may include a N-terminal cysteine without the spacer.

[0068] When the A β , tau, and/or alpha-synuclein polypeptides are linked to form a multiple A β /tau/alpha-synuclein polypeptide, the linker may be a cleavable linker. As used herein, the term "cleavable linker" refers to any linker between the antigenic peptides that promotes or otherwise renders the A β peptide, the tau peptide, and/or the alpha-synuclein peptide more susceptible to separation from each other by cleavage (for example, by endopeptidases, proteases, low pH or any other means that may occur within or around the antigen-presenting cell) and, thereby, processing by

the antigen-presenting cell, than equivalent peptides lacking such a cleavable linker. In some compositions, the cleavable linker is a protease-sensitive dipeptide or oligopeptide cleavable linker. In certain embodiments, the cleavable linker is sensitive to cleavage by a protease of the trypsin family of proteases. In some compositions, the cleavable linker comprises an amino acid sequence selected from the group consisting of arginine-arginine (Arg-Arg), arginine-valine-arginine-arginine (Arg-Val-Arg-Arg; SEQ ID NO:138), valine-citrulline (Val-Cit), valine-arginine (Val-Arg), valine-lysine (Val-Lys), valine-alanine (Val-Ala), phenylalanine-lysine (Phe-Lys), glycine-alanine-glycine-alanine (Gly-Ala-Gly-Ala; GAGA (SEQ ID NO:139)), Ala-Gly-Ala-Gly; AGAG (SEQ ID NO:140), and Lys-Gly-Lys-Gly; KGKG (SEQ ID NO:141). In some compositions, the cleavable linker is arginine-arginine (Arg-Arg).

[0069] In some embodiments of the disclosure, the multiple A β /tau/alpha-synuclein polypeptide comprises, consists or consists essentially of an amino acid sequence selected from SEQ ID NOs: 130-137 and SEQ ID NOs: 1058-1063.

[0070] In some embodiments, the multiple A β /tau/alpha-synuclein polypeptide is as follows:

Formula I: [P1]-[CL1]-[P2]-[CL2]-[P3]-[L1]-[Cys];

Formula II: [P1]-[CL1]-[P2]-[CL2]-[P3]-[CL3]-[P4]-[L1]-[Cys];

wherein, each of P1, P2, P3 and P4 may be independently selected from an A β peptide, a tau peptide and an alpha-synuclein peptide, provided that each of an A β peptide, a tau peptide and an alpha-synuclein peptide are selected. In embodiments, the P1 is an A β peptide, for example if the first peptide [P1] is an A β peptide then the second peptide [P2] is a tau peptide, and the third peptide [P3] is an alpha-synuclein peptide, or if [P1] is an A β peptide then [P2] is a tau A β peptide, and the fourth peptide [P4] is a tau peptide, or if [P1] is an A β peptide then [P2] is an alpha-synuclein peptide, and [P3] is a tau peptide, or if [P1] is an A β peptide then [P2] is an alpha-synuclein peptide, [P3] is a tau peptide, and [P4] is a tau peptide, and each of [CL1], [CL2], and [CL3] are cleavable linkers and [L1] is a linker, and [CL1], [CL2], [CL3], [L1], and [Cys] are optional.

[0071] Examples of the A β peptide include any one SEQ ID NOS 3-38 or 1002-1057.

[0072] Examples of the tau peptide include any one of SEQ ID NOS: 39-57, or 142-1000.

[0073] Examples of the alpha-synuclein peptide include any one of SEQ ID NOS: 59-129.

[0074] [CL1], [CL2], and [CL3] are optional, and when present, may be a cleavable linker. A cleavable linker, if present, can be 1-10 amino acids in length. In some embodiments, the linker comprises between about 1-10 amino acids, about 1-9 amino acids, about 1-8 amino acids, about 1-7 amino acids, about 1-6 amino acids, about 1-5 amino acids, about 1-4 amino acids, about 1-3 amino acids, about 2 amino acids, or one (1) amino acid. In some embodiments, the cleavable linker is 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9 amino acids, or 10 amino acids. In some embodiments, the linker may be a cleavable linker having an amino acid sequence selected from the group consisting of arginine-arginine (Arg-Arg), arginine-valine-arginine-arginine (Arg-Val-Arg-Arg; SEQ ID NO:138), valine-citrulline (Val-Cit), valine-arginine (Val-Arg), valine-lysine (Val-Lys), valine-alanine (Val-Ala), phenylalanine-lysine (Phe-Lys), glycine-alanine-glycine-alanine (Gly-Ala-Gly-Ala; SEQ ID NO:139), alanine-glycine-alanine-glycine (Ala-Gly-Ala-Gly; SEQ ID NO:140), and lysine-glycine-lysine-glycine (Lys-Gly-Lys-Gly; SEQ ID NO:141)).

[0075] [L1] is optional, and when present is a linker that couples the polypeptide to a carrier. A linker, if present, can be 1-10 amino acids in length. In some embodiments, the linker comprises between about 1-10 amino acids, about 1-9 amino acids, about 1-8 amino acids, about 1-7 amino acids, about 1-6 amino acids, about 1-5 amino acids, about 1-4 amino acids, about 1-3 amino acids, about 2 amino acids, or one (1) amino acid. In some embodiments, the linker is 1 amino acid, 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, 8 amino acids, 9 amino acids, or 10 amino acids. In some embodiments, the amino acid composition of a linker can mimic the composition of linkers found in natural multidomain proteins, where certain amino acids are overrepresented, underrepresented or equi-represented in natural linkers as compared to their abundance in whole protein. For example, threonine (Thr), serine (Ser), proline (Pro), glycine (Gly), aspartic acid (Asp), lysine (Lys), glutamine (Gln), asparagine (Asn), arginine (Arg), phenylalanine (Phe), glutamic acid (Glu) and alanine (Ala) are

overrepresented in natural linkers. In contrast, isoleucine (Ile), tyrosine (Tyr), tryptophan (Trp), and cysteine (Cys) are underrepresented. In general, overrepresented amino acids were polar uncharged or charged residues, which constitute approximately 50% of naturally encoded amino acids, and Pro, Thr, and Gln were the most preferable amino acids for natural linkers. In some embodiments, the amino acid composition of a linker can mimic the composition of linkers commonly found in recombinant proteins, which can generally be classified as flexible or rigid linkers. For example, flexible linkers found in recombinant proteins are generally composed of small, non-polar (*e.g.* Gly) or polar (*e.g.* Ser or Thr) amino acids whose small size provides flexibility and allows for mobility of the connecting functional domains. The incorporation of, *e.g.*, Ser or Thr can maintain the stability of the linker in aqueous solutions by forming hydrogen bonds with the water molecules, and therefore can reduce interactions between the linker and the immunogens. In some embodiments, a linker comprises stretches of Gly and Ser residues (“GS” linker). An example of a widely used flexible linker is (Gly-Gly-Ser)_n, (Gly-Gly-Gly-Ser)_n (SEQ ID NO:1064) or (Gly-Gly-Gly-Gly-Ser)_n (SEQ ID NO:1065), where *n*=1-3. Adjusting the copy number “*n*” can optimize a linker to achieve sufficient separation of the functional immunogen domains to, *e.g.*, maximize an immunogenic response. Many other flexible linkers have been designed for recombinant fusion proteins that can be used herein. In some embodiments, linkers can be rich in small or polar amino acids such as Gly and Ser but also contain additional amino acids such as Thr and Ala to maintain flexibility, as well as polar amino acids such as Lys and Glu to improve solubility. *See, e.g.*, Chen, X. *et al.*, “Fusion Protein Linkers: Property, Design and Functionality” *Adv Drug Deliv Rev.*, 15; 65(10): 1357–1369 (203). In certain embodiments, when present, the linker can be an amino acid sequence selected from the group consisting of as GG, GGG, KK, KKK, AA, AAA, SS, SSS, G-A-G-A (SEQ ID NO:139), A-G-A-G (SEQ ID NO:140), and K-G-K-G (SEQ ID NO:142).

[0076] [Cys] is optional and can be helpful to conjugate the polypeptide to a carrier. When present, the Cys can be at the C-terminal portion of the polypeptide, or at the N-terminal portion of the polypeptide.

[0077] Examples of multiple A β /tau/alpha-synuclein polypeptide of the disclosure include the following:

Table 1 - Formula I: [P1]-[CL1]-[P2]-[CL2]-[P3]-[L1]-[Cys]

Immunogen Lab ID (SEQ ID NO)	[P1] (SEQ ID NO)	[CL1]	[P2] (SEQ ID NO)	[CL2]	[P3] (SEQ ID NO)	[L1]	Cys
24 (130)	DAEFRHD (06)	RR	PDNEAYE (75)	RR	QIVYKPV (39)	KK	C
25 (131)	DAEFRHD (06)	RR	QIVYKPV (39)	RR	PDNEAYE (75)	KK	C
26 (132)	DAEFRHD (06)	RR	PDNEAYE (75)	RR	NIKHVP (57)	KK	C
27 (133)	DAEFRHD (06)	RR	NIKHVP (57)	RR	PDNEAYE (75)	KK	C
Tri 2 (1058)	DAEFRHD (06)	RR	DPDNEAYE (68)	RR	ENLKHQPG (777)	GG	C
Tri 1 (1059)	DAEFRHD (06)	RR	ENLKHQPG (777)	RR	DPDNEAYE (68)	GG	C
Tri 4 (1060)	DAEFRHD (06)	RR	PDNEAYE (75)	RR	ENLKHQPG (777)	GG	C
Tri 3 (1061)	DAEFRHD (06)	RR	ENLKHQPG (777)	RR	PDNEAYE (75)	GG	C
Tri 5 (1062)	DAEFRHD (06)	RR	SKIGSKDNIKH (986)	RR	DPDNEAYE (68)	GG	C
Tri 6 (1063)	DAEFRHD (06)	RR	DPDNEAYE (68)	RR	SKIGSKDNIKH (986)	GG	C

Table 2 - Formula II: [P1]-[CL1]-[P2]-[CL2]-[P3]-[CL3]-[P4]-[L1]-[Cys]

Immunogen Lab ID (SEQ ID NO)	[P1] (SEQ ID NO)	[CL1]	[P2] (SEQ ID NO)	[CL2]	[P3] (SEQ ID NO)	[CL3]	[P4] (SEQ ID NO)	[L1]	Cys
14 (134)	DAEFRHD (06)	RR	QIVYKPV (39)	RR	PDNEAYE (75)	RR	NIKHVP (48)	GG	C
15 (135)	DAEFRHD (06)	RR	DPDNEAY (69)	RR	NIKHVP (57)	RR	QIVYKPV (39)	GG	C
16 (136)	EFRHDSG (19)	RR	QIVYKPV (39)	RR	PDNEAYE (75)	RR	NIKHVP (48)	GG	C
17 (137)	EFRHDSG (19)	RR	DPDNEAY (69)	RR	NIKHVP (57)	RR	QIVYKPV (39)	GG	C

[0078] Polypeptide Immunogens

[0079] The A β peptide, the tau peptide, the alpha-synuclein, and the multiple A β /tau/alpha-synuclein polypeptide are immunogens in accordance with the disclosure. In some embodiments, the peptides and the multiple A β /tau/alpha-synuclein polypeptide can be linked to a suitable carrier to help elicit an immune response. Accordingly, one or more the peptides and multiple A β /tau/alpha-synuclein polypeptides of the disclosure can be linked to a carrier. For example, each of the A β

peptide, tau peptide, the alpha-synuclein peptide, and the A β /tau/alpha-synuclein polypeptide may be linked to the carrier with or without spacer amino acids (*e.g.*, Gly-Gly, Gly-Gly-Gly, Ala-Ala, Ala-Ala-Ala, Lys-Lys, Lys-Lys-Lys, Ser-Ser, Ser-Ser-Ser, Gly-Ala-Gly-Ala (SEQ ID NO:139), Ala-Gly-Ala-Gly (SEQ ID NO:140), and Lys-Gly-Lys-Gly (SEQ ID NO:141)). In certain embodiments, the multiple A β /tau/alpha-synuclein polypeptide can be linked to a suitable carrier using a C-terminal cysteine to provide a linker between the peptide(s) and the carrier or the multiple A β /tau/alpha-synuclein polypeptide and the carrier. In certain embodiments, the multiple A β /tau/alpha-synuclein polypeptide can be linked to a suitable carrier using an N-terminal cysteine to provide a linker between the peptide(s) and the carrier. In some embodiments, where the C-terminal residues in the immunogen are IVYKPV (SEQ ID NO:194), VYKPV (SEQ ID NO:195), YKPV (SEQ ID NO:196), KPV, or PV the linker is an amino acid linker that does not have a N-terminal glycine (*e.g.*, GG, GAGA (SEQ ID NO:139)).

[0080] Suitable carriers include, but are not limited to serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, or a toxoid from other pathogenic bacteria, such as diphtheria (*e.g.*, CRM197), *E. coli*, cholera, or *H. pylori*, or an attenuated toxin derivative. T cell epitopes are also suitable carrier molecules. Some conjugates can be formed by linking peptide immunogens of the invention to an immunostimulatory polymer molecule (*e.g.*, tripalmitoyl-S-glycerine cysteine (Pam3Cys), mannan (a mannose polymer), or glucan (a β 1-2 polymer)), cytokines (*e.g.*, IL-1, IL-1 alpha and β peptides, IL-2, γ -INF, IL-10, GM-CSF), and chemokines (*e.g.*, MIP1- α and β , and RANTES). Additional carriers include virus-like particles. In some compositions, immunogenic peptides can also be linked to carriers by chemical crosslinking. Techniques for linking an immunogen to a carrier include the formation of disulfide linkages using N-succinimidyl 3-(2-pyridylthio)propionate (SPDP), and succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) (if the peptide lacks a sulfhydryl group, this can be provided by addition of a cysteine residue). These reagents create a disulfide linkage between themselves and peptide cysteine residues on one protein and an amide linkage through the epsilon-amino on a lysine, or other free amino group in other amino acids. In some embodiments, chemical crosslinking can comprise use of SBAP (succinimidyl 3-(bromoacetamido)propionate), which is a

short (6.2 angstrom) cross-linker for amine-to-sulfhydryl conjugation via N-hydroxysuccinimide (NHS) ester and bromoacetyl reactive groups. A variety of such disulfide/amide-forming agents are described by Jansen *et al.*, "Immunotoxins: Hybrid Molecules Combining High Specificity and Potent Cytotoxicity" *Immunological Reviews* 62:185-216 (February 1982). Other bifunctional coupling agents form a thioether rather than a disulfide linkage. Many of these thio-ether-forming agents are commercially available and include reactive esters of 6-maleimidocaproic acid, 2-bromoacetic acid, and 2-iodoacetic acid, 4-(N-maleimido-methyl)cy-clohexane-1-carboxylic acid. The carboxyl groups can be activated by combining them with succinimide or 1-hydroxyl-2-nitro-4-sulfonic acid, sodium salt. Virus-like particles (VLPs), also called pseudovirions or virus-derived particles, represent subunit structures composed of multiple copies of a viral capsid and/or envelope protein capable of self-assembly into VLPs of defined spherical symmetry *in vivo*. (Powilleit, *et al.*, (2007) *PLoS ONE* 2(5):e415.) Alternatively, peptide immunogens can be linked to at least one artificial T-cell epitope capable of binding a large proportion of MHC Class II molecules, such as the pan DR epitope ("PADRE"). Pan DR-binding peptides (PADREs described in US 5,736,142, WO 95/07707, and Alexander, *et al.*, *Immunity*, 1:751-761 (1994).

[0081] Active immunogens can be presented in multimeric form in which multiple copies of an immunogen (peptide or polypeptide) are presented on a carrier as a single covalent molecule. In some embodiments, the carrier includes various forms of the multiple A β /tau/alpha-synuclein polypeptide. For instance, the multiple A β /tau/alpha-synuclein polypeptide of the immunogen can include polypeptides that have the A β antigen, the tau antigen and alpha-synuclein antigen in different orders, or may be present with or without an intrapeptide linker and/or a linker to a carrier.

[0082] In some compositions, the immunogenic peptides can also be expressed as fusion proteins with carriers. In certain compositions, the immunogenic peptides can be linked at the amino terminus, the carboxyl terminus, or internally to the carrier. In some compositions, the carrier is CRM197. In some compositions, the carrier is diphtheria toxoid.

[0083] Nucleic Acids

[0084] The disclosure further provides nucleic acids encoding any of the amyloid-beta (A β) peptides, the tau peptides, and/or the alpha-synuclein peptides as disclosed herein. The nucleic acid immunotherapy compositions, as disclosed herein, comprise, consist of, or consist essentially of, a first nucleic acid sequence encoding an amyloid-beta (A β) peptide, a second nucleic acid sequence encoding a tau peptide, and/or a third nucleic acid sequence encoding an alpha-synuclein peptide as disclosed herein. For example, the A β peptide is a sequence that is 3-10 amino acid residues in length and from the first ten or 12 to 25 N-terminal residues of SEQ ID NO:01, and the tau peptide is a sequence that is 3-13 amino acids in length and from residues 244-400 of SEQ ID NO:02, and the alpha-synuclein peptide is a sequence that is 3-10 amino acids in length and from residues 81-140 of SEQ ID NO:58. Accordingly, a nucleic acid encoding any of SEQ ID NOS: 3-38 or 1002 to 1057 may be combined with a nucleic acid encoding any of SEQ ID NOS: 39-57, or 142-1000, and/or a nucleic acid encoding any of SEQ ID NOS: 59-129 to provide an immunogen and a component of pharmaceutical composition of the disclosure. Likewise, one or more nucleic acids encoding any of A β , tau and alpha-synuclein sequences may include the codons for an RR- N-terminal or -RR C-terminal dipeptide or polypeptide. In certain embodiments, the A β , tau and alpha-synuclein peptide sequences may be encoded by the same nucleic acid sequence or by separate nucleic acid sequences. In some embodiments, the nucleic acid sequences may also encode a linker to a carrier and/or a C-terminal cysteine as described herein. In addition, when a single nucleic acid sequence encodes both peptides, the sequence may also encode an intra-peptide linker as described herein. The nucleic acid compositions described herein (pharmaceutical compositions) can be used in methods for treating or effecting prophylaxis and/or prevention of Alzheimer's disease. In another embodiment, the nucleic acid immunotherapy compositions as disclosed herein provide compositions for reducing pathogenic forms of A β and/or tau and/or alpha-synuclein in the subject and/or in the tissue of the subject. In some embodiments, the A β and/or tau and/or alpha-synuclein reduced by the immunotherapy compositions is the pathological form(s) of the A β (*e.g.* extracellular plaque deposits of the β -amyloid peptide (A β); neuritic amyloid plaques), tau (*e.g.* flame-shaped neurofibrillary tangles of tau; neurofibrillary tangles of tau), and/or alpha-synuclein (*e.g.* oligomeric or fibrillar alpha-synuclein conglomerates and protofibrillar intermediates of alpha-synuclein oligomers). In yet other embodiment, pathological indicators of neurodegenerative disease and/or

synucleinopathies are decreased by the nucleic acid immunotherapy compositions. In another embodiment, the nucleic acid immunotherapy compositions as disclosed herein provide compositions for reducing brain A β , brain tau and brain alpha-synuclein.

[0085] A nucleic acid such as DNA that encodes an immunogen and is used as a vaccine can be referred to as a "DNA immunogen" or "DNA vaccine" as the encoded polypeptides are expressed *in vivo* after administration of the DNA. DNA vaccines are intended to induce antibodies against the proteins of interest they encode in a subject by: integrating DNA encoding the proteins of interest into a vector (a plasmid or virus); administering the vector to the subject; and expressing the proteins of interest in the subject in which the vector has been administered to stimulate the immune system of the subject. A DNA vaccine remains in the body of the subject for a long time after the administration, and continues to slowly produce the encoded proteins. Thus, excessive immune responses can be avoided. DNA vaccines can also be modified using a genetic engineering techniques. Optionally, such nucleic acids further encode a signal peptide and can be expressed with the signal peptide linked to peptide. Coding sequences of nucleic acids can be operably linked with regulatory sequences to ensure expression of the coding sequences, such as a promoter, enhancer, ribosome binding site, transcription termination signal, and the like. The nucleic acids encoding A β , tau, and/or alpha-synuclein can occur in isolated form or can be cloned into one or more vectors. The nucleic acids can be synthesized by, for example, solid state synthesis or PCR of overlapping oligonucleotides. Nucleic acids encoding A β , tau, and/or alpha-synuclein peptides and polypeptides with and without linkers or cleavable linkers and with or without protein based carriers can be joined as one contiguous nucleic acid, *e.g.*, within an expression vector.

[0086] DNA is more stable than RNA, but involves some potential safety risks such as induction of anti-DNA antibodies, thus in some embodiments, the nucleic acid can be RNA. RNA nucleic acid that encodes an immunogen and is used as a vaccine can be referred to as a "RNA immunogen" or "RNA vaccine" or "mRNA vaccine" as the encoded polypeptides are expressed *in vivo* after administration of the RNA. Ribonucleic acid (RNA) vaccines can safely direct a subject's cellular machinery to produce one or more polypeptide(s) of interest. In some embodiments, a RNA vaccine can be a non-replicating mRNA (messenger-RNA) or a virally derived, self-

amplifying RNA. mRNA-based vaccines encode the antigens of interest and contain 5' and 3' untranslated regions (UTRs), whereas self-amplifying RNAs encode not only the antigens, but also the viral replication machinery that enables intracellular RNA amplification and abundant protein expression. *In vitro* transcribed mRNA can be produced from a linear DNA template using a T7, a T3 or an Sp6 phage RNA polymerase. The resulting product can contain an open reading frame that encodes the peptides of interest as disclosed herein, flanking 5'- and 3'-UTR sequences, a 5' cap and a poly(A) tail. In some embodiments, a RNA vaccine can comprise trans-amplifying RNA (for example, *see* Beissert *et al.*, *Molecular Therapy* January 2020 28(1):119-128). In certain embodiments, RNA vaccines encode an A β peptide and a tau peptide as disclosed herein, and are capable of expressing the A β and a tau peptides, in particular if transferred into a cell such as an immature antigen presenting cell. RNA may also contain sequences which encode other polypeptide sequences such as immune stimulating elements. In some embodiments, the RNA of a RNA vaccine can be modified RNA. The term "modified" in the context of the RNA can include any modification of RNA which is not naturally present in RNA. For example, modified RNA can refer to RNA with a 5'-cap; however, RNA may comprise further modifications. A 5'-cap can be modified to possess the ability to stabilize RNA when attached thereto. In certain embodiments, a further modification may be an extension or truncation of the naturally occurring poly(A) tail or an alteration of the 5'- or 3'-untranslated regions (UTR). In some embodiments, the RNA *e.g.* or mRNA vaccine is formulated in an effective amount to produce an antigen specific immune response in a subject. For example, the RNA vaccine formulation is administered to a subject in order to stimulate the humoral and/or cellular immune system of the subject against the A β , tau and alpha synuclein antigens, and thus may further comprise one or more adjuvant(s), diluents, carriers, and/or excipients, and is applied to the subject in any suitable route in order to elicit a protective and/or therapeutic immune reaction against the A β , tau and alpha synuclein antigens.

[0087] Basic texts disclosing general methods of molecular biology, all of which are incorporated by reference, include: Sambrook, J *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Press, Cold Spring Harbor, N.Y., 1989; Ausubel, F M *et al.* *Current Protocols in Molecular Biology*, Vol. 2, Wiley-Interscience, New York, (current edition); Kriegler, *Gene Transfer and*

Expression: A Laboratory Manual (1990); Glover, D M, ed, DNA Cloning: A Practical Approach, vol. I & II, IRL Press, 1985; Albers, B. *et al.*, Molecular Biology of the Cell, 2nd Ed., Garland Publishing, Inc., New York, N.Y. (1989); Watson, J D *et al.*, Recombinant DNA, 2nd Ed., Scientific American Books, New York, 1992; and Old, R W *et al.*, Principles of Gene Manipulation: An Introduction to Genetic Engineering, 2nd Ed., University of California Press, Berkeley, Calif. (1981).

[0088] Techniques for the manipulation of nucleic acids, such as, *e.g.*, generating mutations in sequences, sub-cloning, labeling probes, sequencing, hybridization and the like are well described in the scientific and patent literature. See, *e.g.*, Sambrook, ed., MOLECULAR CLONING: A LABORATORY MANUAL (2ND ED.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989); CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Ausubel, ed. John Wiley & Sons, Inc., New York (1997); LABORATORY TECHNIQUES IN BIOCHEMISTRY AND MOLECULAR BIOLOGY: HYBRIDIZATION WITH NUCLEIC ACID PROBES, Part I. Tijssen, ed. Elsevier, N.Y. (1993).

[0089] Nucleic acids, vectors, capsids, polypeptides, and the like can be analyzed and quantified by any of a number of general means well known to those of skill in the art. These include, *e.g.*, analytical biochemical methods such as NMR, spectrophotometry, radiography, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), and hyperdiffusion chromatography, various immunological methods, *e.g.* fluid or gel precipitin reactions, immunodiffusion, immuno-electrophoresis, radioimmunoassays (RIAs), enzyme-linked immunosorbent assays (ELISAs), immunofluorescence assays, Southern analysis, Northern analysis, dot-blot analysis, gel electrophoresis (*e.g.*, SDS-PAGE), RT-PCR, quantitative PCR, other nucleic acid or target or signal amplification methods, radiolabeling, scintillation counting, and affinity chromatography.

[0090] Pharmaceutical Compositions

[0091] Each of the peptides and immunogens described herein can be presented in a pharmaceutical composition that is administered with pharmaceutically acceptable adjuvants and pharmaceutically acceptable excipients. The adjuvant

increases the titer of induced antibodies and/or the binding affinity of induced antibodies relative to the situation if the peptide were used alone. A variety of adjuvants can be used in combination with an immunogen of the disclosure to elicit an immune response. Some adjuvants augment the intrinsic response to an immunogen without causing conformational changes in the immunogen that affect the qualitative form of the response. An adjuvant may be a natural compound, a modified version of or derivative of a natural compound, or a synthetic compound.

[0092] Some adjuvants include aluminum salts, such as aluminum hydroxide and aluminum phosphate, 3 De-O-acylated monophosphoryl lipid A (MPL™) (*see* GB 2220211 (RIBI ImmunoChem Research Inc., Hamilton, Montana, now part of Corixa). As used herein, MPL refers to natural and synthetic versions of MPL. Examples of synthetic versions include PHAD®, 3D-PHAD® and 3D(6A)-PHAD® (Avanti Polar Lipids, Alabaster, Alabama).

[0093] QS-21 is a triterpene glycoside or saponin isolated from the bark of the Quillaja saponaria Molina tree found in South America (*see* Kensil *et al.*, in Vaccine Design: The Subunit and Adjuvant Approach (eds. Powell & Newman, Plenum Press, NY, 1995)) QS-21 products include Stimulon® (Antigenics, Inc., New York, NY; now Agenus, Inc. Lexington, MA) and QS-21 Vaccine Adjuvant (Desert King, San Diego, CA). QS-21 has been disclosed, characterized, and evaluated in US 5,057,540, and US 8,034,348, the disclosures of which are herein incorporated by reference. Additionally, QS-21 has been evaluated in numerous clinical trials in various dosages. See, NCT00960531 (clinicaltrials.gov/ct2/show/study/NCT00960531), Hüll *et al.*, *Curr Alzheimer Res.* 2017 Jul; 14(7): 696–708 (evaluated 50 mcg of QS-21 in with various doses of vaccine ACC-001); Gilman *et al.*, “Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial” *Neurology*. 2005 May 10; 64(9):1553-62; Wald *et al.*, “Safety and immunogenicity of long HSV-2 peptides complexed with rhHsc70 in HSV-2 seropositive persons” *Vaccine* 2011; 29(47):8520–8529; and Cunningham *et al.*, “Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older.” *NEJM*. 2016 Sep 15; 375(11):1019-32. QS-21 is used in FDA approved vaccines including SHINGRIX. SHINGRIX contains 50 mcg of QS-21. In certain embodiments, the amount of QS-21 is from about 10 µg to about 500 µg.

[0094] TQL1055 is an analogue of QS-21 (Adjuvance Technologies, Lincoln, NE). The semi-synthetic TQL1055 has been characterized in comparison to QS-21 as having high purity, increased stability, decreased local tolerability, decreased systemic tolerability. TQL1055 has been disclosed, characterized, and evaluated in US20180327436 A1, WO2018191598 A1, WO2018200656 A1, and WO2019079160 A1, the disclosures of which are herein incorporated by reference. US20180327436 A1 teaches that 2.5 fold more TQ1055 was superior to 20 µg QS-21 but there was not an improvement over 50 µg TQ1055. However, unlike QS-21 there was no increase in either weight loss or hemolysis of RBC as the TQL1055 dose increased. WO2018200656 A1 teaches that with an optimal amount of TQ1055, one can lower the amount of antigen and achieve superior titers. In certain embodiments, the amount of TQL1055 is from about 10 µg to about 500 µg.

[0095] Other adjuvants are oil in water emulsions (such as squalene or peanut oil), optionally in combination with immune stimulants, such as monophosphoryl lipid A (*see* Stoute *et al.*, *N. Engl. J. Med.* 336, 86-91 (1997)), pluronic polymers, and killed mycobacteria. Ribi adjuvants are oil-in-water emulsions. Ribi contains a metabolizable oil (squalene) emulsified with saline containing Tween 80. Ribi also contains refined mycobacterial products which act as immunostimulants and bacterial monophosphoryl lipid A. Other adjuvants can be CpG oligonucleotides (*see* WO 98/40100), cytokines (*e.g.*, IL-1, IL-1 alpha and β peptides, IL-2, γ-INF, IL-10, GM-CSF), chemokines (*e.g.*, MIP1-α and β, and RANTES), saponins, RNA, and/or TLR agonists (for example, TLR4 agonists such as MPL and synthetic MPL molecules), aminoalkyl glucosaminide phosphate and other TLR agonists. Adjuvants can be administered as a component of a therapeutic composition with an active agent or can be administered separately, before, concurrently with, or after administration of the therapeutic agent.

[0096] In various embodiments of the disclosure, the adjuvant is QS-21 (Stimulon™). In some compositions, the adjuvant is MPL. In certain embodiments, the amount of MPL is from about 10 µg to about 500 µg. In some compositions, the adjuvant is TQL1055. In certain embodiments, the amount of TQL1055 is from about 10 µg to about 500 µg. In some compositions, the adjuvant is QS21. In certain embodiments, the amount of QS21 is from about 10 µg to about 500 µg. In some compositions, the adjuvant is a combination of MPL and QS-21. In some

compositions, the adjuvant is a combination of MPL and TQL1055. In some compositions, the adjuvant can be in a liposomal formulation.

[0097] In addition, some embodiments of the disclosure can comprise a multiple antigen presenting system (MAP). Multiple antigen-presenting peptide vaccine systems have been developed to avoid the adverse effects associated with conventional vaccines (*i.e.*, live-attenuated, killed or inactivated pathogens), carrier proteins and cytotoxic adjuvants. Two main approaches have been used to develop multiple antigen presenting peptide vaccine systems: (1) the addition of functional components, *e.g.*, T-cell epitopes, cell-penetrating peptides, and lipophilic moieties; and (2) synthetic approaches using size-defined nanomaterials, *e.g.*, self-assembling peptides, non-peptidic dendrimers, and gold nanoparticles, as antigen-displaying platforms. Use of a multiple antigenic peptide (MAP) system can improve the sometimes poor immunogenicity of subunit peptide vaccines. In a MAP system, multiple copies of antigenic peptides are simultaneously bound to the α - and ϵ -amino groups of a non-immunogenic Lys-based dendritic scaffold, helping to confer stability from degradation, thus enhancing molecular recognition by immune cells, and induction of stronger immune responses compared with small antigenic peptides alone. In some compositions, the MAP comprises one or more of a Lys-based dendritic scaffold, helper T-cell epitopes, immune stimulating lipophilic moieties, cell penetrating peptides, radical induced polymerization, self-assembling nanoparticles as antigen-presenting platforms and gold nanoparticles.

[0098] Pharmaceutical compositions for parenteral administration are preferably sterile and substantially isotonic and manufactured under GMP conditions. Pharmaceutical compositions can be provided in unit dosage form (*i.e.*, the dosage for a single administration). Pharmaceutical compositions can be formulated using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries. The formulation depends on the route of administration chosen. For injection, the peptides of the disclosure can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline or acetate buffer (to reduce discomfort at the site of injection). The solution can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, peptide compositions can be in lyophilized form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0099] Peptides (and optionally a carrier fused to the peptide(s)) can also be administered in the form of a nucleic acid encoding the peptide(s) and expressed *in situ* in a subject. A nucleic acid segment encoding an immunogen is typically linked to regulatory elements, such as a promoter and enhancer that allow expression of the DNA segment in the intended target cells of a subject. For expression in blood cells, as is desirable for induction of an immune response, promoter and enhancer elements from, for example, light or heavy chain immunoglobulin genes or the CMV major intermediate early promoter and enhancer are suitable to direct expression. The linked regulatory elements and coding sequences are often cloned into a vector.

[00100] DNA and RNA can be delivered in naked form (*i.e.*, without colloidal or encapsulating materials). Alternatively a number of viral vector systems can be used including retroviral systems (see, *e.g.*, Boris-Lawrie and Teumin, *Cur. Opin. Genet. Develop.* 3(1):102-109 (1993)); adenoviral vectors (see, *e.g.*, Bett *et al.*, *J. Virol.* 67(10):5911-21 (1993)); adeno-associated virus vectors (see, *e.g.*, Zhou *et al.*, *J. Exp. Med.* 179(6):1867-75 (1994)), viral vectors from the pox family including vaccinia virus and the avian pox viruses, viral vectors from the alpha virus genus such as those derived from Sindbis and Semliki Forest Viruses (see, *e.g.*, Dubensky *et al.*, *J. Virol.* 70(1):508-519 (1996)), Venezuelan equine encephalitis virus (see US 5,643,576) and rhabdoviruses, such as vesicular stomatitis virus (see WO 96/34625) and papillomaviruses (WO 94/12629; Ohe *et al.*, *Human Gene Therapy* 6(3):325-333 (1995); and Xiao & Brandsma, *Nucleic Acids. Res.* 24(13):2620-2622 (1996)).

[00101] DNA and RNA encoding an immunogen, or a vector containing the same, can be packaged into liposomes, nanoparticles or lipoproteins complexes. Suitable other polymers, include, for example, protamine liposomes, polysaccharide particles, cationic nanoemulsion, cationic polymer, cationic polymer liposome, cationic lipid nanoparticles, cationic lipid, cholesterol nanoparticles, cationic lipid-cholesterol, PEG nanoparticle, or dendrimer nanoparticles. Additional suitable lipids and related analogs are described by US 5,208,036, US 5,264,618, US 5,279,833, and US 5,283,185, each of which are herein incorporated by reference in their entirety. Vectors and DNA encoding an immunogen can also be adsorbed to or associated with particulate carriers, examples of which include polymethyl methacrylate polymers and polylactides and poly(lactide-co-glycolides), (see, *e.g.*, McGee *et al.*, *J. Micro Encap.* Mar-Apr 1997; 14(2):197-210).

[00102] Pharmaceutically acceptable carrier compositions can also include additives, including, but not limited to, water, pharmaceutically acceptable organic solvents, collagen, polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymers, carboxymethylcellulose sodium, sodium polyacrylate, sodium alginate, water-soluble dextran, carboxymethyl starch sodium, pectin, methylcellulose, ethylcellulose, xanthan gum, gum arabic, casein, agar, polyethylene glycol, diglycerine, glycerine, propylene glycol, petrolatum, paraffin, stearyl alcohol, stearic acid, human serum albumin, mannitol, sorbitol, lactose, and surfactants acceptable as pharmaceutical additives.

[00103] Subjects Amenable to Treatment

[00104] The presence of A β plaques and/or neurofibrillary tangles has been found in several diseases including Alzheimer's disease, Down's syndrome, mild cognitive impairment, cerebral amyloid angiopathy, primary age-related tauopathy, postencephalitic parkinsonism, posttraumatic dementia or dementia pugilistica, Pick's disease, type C Niemann-Pick disease, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, argyrophilic grain disease, globular glial tauopathy, amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam, corticobasal degeneration (CBD), dementia with Lewy bodies, Lewy body variant of Alzheimer's disease (LBVAD), chronic traumatic encephalopathy (CTE), globular glial tauopathy (GGT), Parkinson's disease, progressive supranuclear palsy (PSP), dry age-related macular degeneration (AMD), and inclusion-body myositis.

[00105] The compositions and methods of the disclosure can be used in treatment or prophylaxis of any of these diseases. Because of the widespread association between neurological diseases and A β and/or tau and/or alpha-synuclein, the compositions and methods of the disclosure can be used in treatment or prophylaxis of any subject showing elevated levels of A β and/or tau and/or alpha-synuclein (*e.g.*, in the CSF) compared with a mean value in individuals without neurological disease. The compositions and methods of the disclosure can also be used in treatment or prophylaxis of neurological disease in individuals having a mutation in A β and/or tau and/or alpha-synuclein associated with neurological disease. The methods are particularly suitable for treatment or prophylaxis of Alzheimer's disease.

[00106] Subjects amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms, including treatment naïve subjects that have not been previously treated for disease. Subjects at risk of disease include those in an aging population, asymptomatic subjects with A β and/or tau and/or alpha-synuclein pathologies and having a known genetic risk of disease. Such individuals include those having relatives who have experienced this disease, and those whose risk is determined by analysis of genetic or biochemical markers. Genetic markers of risk include mutations in A β and/or tau and/or alpha-synuclein, as well as mutations in other genes associated with neurological disease. For example, the ApoE4 allele in heterozygous and even more so in homozygous form is associated with risk of Alzheimer's disease (AD). Other markers of risk of Alzheimer's disease include mutations in the APP gene, particularly mutations at position 717 and positions 670 and 671 referred to as the Hardy and Swedish mutations respectively, mutations in the presenilin genes, PS1 and PS2, a family history of AD, hypercholesterolemia or atherosclerosis. Individuals presently suffering from Alzheimer's disease can be recognized by PET imaging, from characteristic dementia, as well as the presence of risk factors described above. In addition, a number of diagnostic tests are available for identifying individuals who have AD. These include measurement of CSF or blood tau or phospho-tau and A β 42 levels. Elevated tau or phospho-tau and decreased A β 42 levels signify the presence of AD. Some mutations associated with Parkinson's disease, for example, Ala30Pro or Ala53Thr, or mutations in other genes associated with Parkinson's disease such as leucine-rich repeat kinase (LRRK2 or PARK8). Subjects can also be diagnosed with any of the neurological diseases mentioned above by the criteria of the DSM IV TR.

[00107] In asymptomatic subjects, treatment can begin at any age (*e.g.*, 10, 20, 30, or more). Usually, however, it is not necessary to begin treatment until a subject reaches 20, 30, 40, 50, 60, 70, 80, or 90 years of age. Treatment typically entails multiple dosages over a period of time. Treatment can be monitored by assaying antibody levels over time. If the response falls, a booster dosage is indicated. In the case of potential Down's syndrome patients, treatment can begin antenatally by administering therapeutic agent to the mother or shortly after birth.

[00108] **Methods of Treatments and Uses**

[00109] The disclosure provides methods of inhibiting or reducing aggregation of Abeta and/or tau and/or alpha-synuclein in a subject having or at risk of developing a neurodegenerative disease (*e.g.*, Alzheimer's disease). The methods include administering to the subject the compositions as disclosed herein. A therapeutically effective amount is a dosage that, when given for an effective period of time, achieves the desired immunological or clinical effect. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered at set intervals (*e.g.*, weekly, monthly) or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

[00110] In prophylactic applications, the compositions described herein can be administered to a subject susceptible to, or otherwise at risk of a disease (*e.g.*, Alzheimer's disease) in a regimen (dose, frequency and route of administration) effective to reduce the risk, lessen the severity, or delay the onset of at least one sign or symptom of the disease. In particular, the regimen is effective to inhibit or delay A β plaque formation and/or inhibit or delay tau or phospho-tau and paired filaments and/or alpha-synuclein synucleinopathies formed from it in the brain, and/or inhibit or delay its toxic effects and/or inhibit or delay development of behavioral deficits. In therapeutic applications, the compositions described herein are administered to a subject suspected of, or a patient already suffering from a disease (*e.g.*, Alzheimer's disease) in a regimen (dose, frequency and route of administration) effective to ameliorate or at least inhibit further deterioration of at least one sign or symptom of the disease. In particular, the regimen is preferably effective to reduce or at least inhibit further increase of levels of A β plaques and/or tau, phospho-tau, or paired filaments formed from it, and/or alpha-synuclein synucleinopathies, and associated toxicities and/or behavioral deficits.

[00111] A regimen is considered therapeutically or prophylactically effective if an individual treated achieves an outcome more favorable than the mean outcome in a control population of comparable subjects not treated by methods of the invention, or if a more favorable outcome is demonstrated in treated subjects versus control subjects in a controlled clinical trial (*e.g.*, a phase II, phase II/III or phase III trial) at the $p < 0.05$ or 0.01 or even 0.001 level.

[00112] Effective doses of vary depending on many different factors, such as means of administration, target site, physiological state of the patient, whether the

patient is an ApoE carrier, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic.

[00113] In some embodiments, the effective amount is a total dose of 25 µg to 1000 µg, or 50 µg to 1000 µg. In some embodiments, the effective amount is a total dose of 100 µg. In some embodiments, the effective amount is a dose of 25 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 100 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 400 µg administered to the subject a total of two times. In some embodiments, the effective amount is a dose of 500 µg administered to the subject a total of two times. In some embodiments, a RNA (*e.g.*, mRNA) vaccine is administered to a subject by intradermal, intramuscular injection, or by intranasal administration.

[00114] In some embodiments, the amount of an agent for active immunotherapy varies from 1 to 1,000 micrograms (µg), or from 0.1-500 µg, or from 10 to 500 µg, or from 50 to 250 µg per patient and can be from 1-100 or 1-10 µg per injection for human administration. The timing of injections can vary significantly from once a day, to once a week, to once a month, to once a year, to once a decade. A typical regimen consists of an immunization followed by booster injections at time intervals, such as 6 week intervals or two months. Another regimen consists of an immunization followed by one or more booster injections 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months later. Another regimen entails an injection every two months for life. Alternatively, booster injections can be on an irregular basis as indicated by monitoring of immune response. The frequency of administration may be once or more as long as the side effects are within a clinically acceptable range.

[00115] In some embodiments, the compositions or methods as disclosed herein comprise administering to a subject a nucleic acid vaccine comprising one or more DNA or RNA polynucleotides having an open reading frame encoding a first peptide and a second peptide wherein a dosage of between 10 µg/kg and 400 µg /kg of the nucleic acid vaccine is administered to the subject. In some embodiments the dosage of the RNA polynucleotide is 1-5 µg, 5-10 µg, 10-15 µg, 15-20 µg, 10-25 µg, 20-25 µg, 20-50 µg, 30-50 µg, 40-50 µg, 40-60 µg, 60-80 µg, 60-100 µg, 50-100 µg, 80-120 µg, 40-120 µg, 40-150 µg, 50-150 µg, 50-200 µg, 80-200 µg, 100-200 µg, 120-250 µg, 150-250 µg, 180-280 µg, 200-300 µg, 50-300 µg, 80-300 µg, 100-300 µg,

40-300 µg, 50-350 µg, 100-350 µg, 200-350 µg, 300-350 µg, 320-400 µg, 40-380 µg, 40-100 µg, 100-400 µg, 200-400 µg, or 300-400 µg per dose. In some embodiments, the nucleic acid is administered to the subject by intradermal or intramuscular injection. In some embodiments, the nucleic acid is administered to the subject on day zero. In some embodiments, a second dose of the nucleic acid is administered to the subject on day seven, or fourteen, or twenty one.

[00116] The compositions described herein are preferably administered via a peripheral route (*i.e.*, one in which the administered composition results in a robust immune response and/or the induced antibody population crosses the blood brain barrier to reach an intended site in the brain, spinal cord, or eye). For peripheral diseases, the induced antibodies leave the vasculature to reach the intended peripheral organs. Routes of administration include oral, subcutaneous, intranasal, intradermal, or intramuscular. Some routes for active immunization are subcutaneous and intramuscular. Intramuscular administration and subcutaneous administration can be made at a single site or multiple sites. Intramuscular injection is most typically performed in the arm or leg muscles. In some methods, agents are injected directly into a particular tissue where deposits have accumulated.

[00117] The number of dosages administered can be adjusted to result in a more robust immune response (for example, higher titers). For acute disorders or acute exacerbations of a chronic disorder, between 1 and 10 doses are often sufficient. Sometimes a single bolus dose, optionally in divided form, is sufficient for an acute disorder or acute exacerbation of a chronic disorder. For chronic disorders, a vaccine/immunotherapy as disclosed herein can be administered at regular intervals, *e.g.*, weekly, fortnightly, monthly, quarterly, every six months for at least 1, 5 or 10 years, or the life of the patient.

[00118] An effective amount of a DNA or RNA encoded immunogen can be between about 1 nanogram and about 1 gram per kilogram of body weight of the recipient, or about between about 0.1 µg/kg and about 10 mg/kg, or about between about 1 µg/kg and about 1 mg/kg. Dosage forms suitable for internal administration preferably contain (for the latter dose range) from about 0.1 µg to 100 µg of active ingredient per unit. The active ingredient may vary from 0.5 to 95% by weight based on the total weight of the composition. Alternatively, an effective dose of dendritic cells loaded with the antigen is between about 10^4 and 10^8 cells. Those skilled in the

art of immunotherapy will be able to adjust these doses without undue experimentation.

[00119] The nucleic acid compositions may be administered in a convenient manner, *e.g.*, injection by a convenient and effective route. Routes can include, but are not limited to, intradermal "gene gun" delivery or intramuscular injection. The modified dendritic cells are administered by subcutaneous, intravenous or intramuscular routes. Other possible routes include oral administration, intrathecal, inhalation, transdermal application, or rectal administration.

[00120] Depending on the route of administration, the composition may be coated in a material to protect the compound from the action of enzymes, acids and other natural conditions which may inactivate the compound. Thus, it may be necessary to coat the composition with, or co-administer the composition with, a material to prevent its inactivation. For example, an enzyme inhibitors of nucleases or proteases (*e.g.*, pancreatic trypsin inhibitor, diisopropylfluorophosphate and trasylol) or in an appropriate carrier such as liposomes (including water-in-oil-in-water emulsions) as well as conventional liposomes (Strejan *et al.*, *J. Neuroimmunol* 7(1):27-41, 1984).

[00121] The immunotherapeutic compositions disclosed herein may also be used in combination with other treatments for diseases associated with the accumulation of A β and/or tau and/or alpha-synuclein, for example, anti-A β antibodies such as antibodies that specifically bind to any of the A β epitopes disclosed herein. For example, aducanumab or any of the antibodies disclosed in, for example, U.S. Patent Publication No. 20100202968 and U.S. Patent No. 8,906,367, and/or anti-tau antibodies such as antibodies that specifically bind to any of the tau epitopes disclosed herein, ABBV-8E12, gosuranemab, zagotenemab, RG-6100, BIIB076 or any of the antibodies disclosed in WO2014/165271, US10,501,531, WO2017/191560, US2019/0330314, WO2017/191561, US2019/0330316, WO2017/191559, and WO2018/204546; and/or anti-alpha-synuclein antibodies such as antibodies that specifically bind to any of the alpha-synuclein epitopes disclosed herein, or antibodies and/or other alpha-synuclein binding compounds, such as, PRX002/RO7046015, PRX002/RG7935 (Prasinezumab), NPT200-11/UCB0599, NPT088, BIIB054 (Cinpanemab), ABBV-0805, MEDI-1341, NPT088, Lu AF82422. In some combination therapy methods, the patient receives passive immunotherapy

prior to the active immunotherapy methods disclosed herein. In other methods, the patient receives passive and active immunotherapy during the same period of treatment. Alternatively, patients may receive active immunotherapy prior to passive immunotherapy. Combinations may also include small molecule therapies and non-immunogenic therapies such as RAZADYNE[®] (galantamine), EXELON[®] (rivastigmine), and ARICEPT[®] (donepezil) and other compositions that improve the function of nerve cells in the brain.

[00122] The compositions of the disclosure may be used in the manufacture of medicaments for the treatment regimens described herein.

[00123] Treatment Regimens

[00124] Desired outcomes of the methods of treatment as disclosed herein vary according to the disease and patient profile and are determinable to those skilled in the art. Desired outcomes include an improvement in the patient's health status. Generally, desired outcomes include measurable indices such as reduction or clearance of pathologic amyloid fibrils, decreased or inhibited amyloid aggregation and/or deposition of amyloid fibrils, reduction or clearance of A β plaque formation and/or inhibit or delay tau or phospho-tau and paired filaments and/or decreased alpha-synuclein synucleinopathies, and increased immune response to pathologic and/or aggregated amyloid fibrils. Desired outcomes also include amelioration of amyloid disease-specific symptoms. As used herein, relative terms such as "improve," "increase," or "reduce" indicate values relative to a control, such as a measurement in the same individual prior to initiation of treatment described herein, or a measurement in a control individual or group. A control individual is an individual afflicted with the same amyloid disease as the individual being treated, who is about the same age as the individual being treated (to ensure that the stages of the disease in the treated individual and the control individual are comparable), but who has not received treatment using the disclosed immunotherapy/vaccine formulations. Alternatively, a control individual is a healthy individual, who is about the same age as the individual being treated. Changes or improvements in response to therapy are generally statistically significant and described by a p-value less than or equal to 0.1, less than 0.05, less than 0.01, less than 0.005, or less than 0.001 may be regarded as significant.

[00125] Effective doses of the compositions as disclosed herein, for the treatment of a subject vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, if any, and whether treatment is prophylactic or therapeutic. Treatment dosages can be titrated to optimize safety and efficacy. The amount of immunogen can also depend on whether adjuvant is also administered, with higher dosages being required in the absence of adjuvant. The amount of an immunogen for administration sometimes varies from 1-500 µg per patient and more usually from 5-500 µg per injection for human administration. Occasionally, a higher dose of 1-2 mg per dosage is used. Typically, about 10, 20, 50 or 100 µg is used for each human dosage. The timing of dosages can vary significantly from once a day, to once a year, to once a decade. On any given day that a dosage of immunogen is given, the dosage is greater than 1 µg/patient and usually greater than 10 µg/patient if adjuvant is also administered, and greater than 10 µg/patient and usually greater than 100 µg/patient in the absence of adjuvant. A typical regimen consists of an immunization followed by booster dosage(s) at 6-week intervals. Another regimen consists of an immunization followed by booster dosage(s) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months later. Another regimen entails dosage(s) every two months for life. Alternatively, booster dosage(s) can be on an irregular basis as indicated by monitoring of immune response.

[00126] When administered in combination with a second treatment for Alzheimer's disease, such as, Razadyne® (galantamine), Exelon® (rivastigmine), and Aricept® (donepezil), the second treatment can be administered according to the product label or as necessary in view of the treatment with the compositions of the disclosure.

[00127] Kits

[00128] The disclosure further provides kits (*e.g.*, containers) comprising the compositions disclosed herein and related materials, such as instructions for use (*e.g.*, package insert). The instructions for use may contain, for example, instructions for administration of the compositions and optionally one or more additional agents. The containers of peptide and/or nucleic acid compositions may be unit doses, bulk packages (*e.g.*, multi-dose packages), or sub-unit doses.

[00129] Package insert refers to instructions customarily included in commercial packages of therapeutic products that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Kits can also include a second container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It can also include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[00130] Uses

[00131] Each of the peptides, polypeptides, immunogens, and pharmaceutical compositions described herein may be for use in treating one or more of the diseases as described herein. In addition, each of the peptides, polypeptides, immunogens, and pharmaceutical compositions described herein may be for use in methods for treating one or more of the diseases as described herein. Each of the peptides, polypeptides, immunogens, and pharmaceutical compositions described herein may be used in a method for manufacturing a medicament for treating or use in treating one or more of the diseases as described herein.

[00132] The following are provided for exemplification purposes only and are not intended to limit the scope of the invention described in broad terms above.

[00133] All U.S. and international patent applications identified herein are incorporated by reference in their entirety.

Examples

[00134] Example 1: Animal Immunizations

[00135] Female Swiss Webster mice are injected subcutaneously at two sites with 100 μ l (200 μ l in total) of immunogen on day 0, 14, and 28. Immunogens are prepared by combining 25 μ g of test immunogen and 25 μ g of QS21 adjuvant in 200 μ l phosphate buffered saline (PBS). Mice are bled at least on day 21 and 35 by nicking tails and collecting 50 μ l of blood, followed by processing to serum. The immunogens tested include:

Table 3: Immunogens comprising A β /tau/alpha-synuclein peptides

Immunogen	Immunogen sequence (SEQ ID NO.)
24	DAEFRHRRPDNEAYERRQIVYKPVKKC (SEQ ID NO:130)
25	DAEFRHRRQIVYKPVRRPDNEAYEKKC (SEQ ID NO:131)
26	DAEFRHRRPDNEAYERRNIKHVPGKKC (SEQ ID NO:132)
27	DAEFRHRRNIKHVPGRRPDNEAYEKKC (SEQ ID NO:133)
14	DAEFRHRRQIVYKPVRRPDNEAYERRNIKHVPGGC (SEQ ID NO:134)
15	DAEFRHRRPDNEAYRRNIKHVPGRRQIVYKPVGGC (SEQ ID NO:135)
16	blocked amine-EFRHDSGRRQIVYKPVRRPDNEAYERRNIKHVPGGC (SEQ ID NO:136)
17	blocked amine-EFRHDSGRDPDNEAYRRNIKHVPGRRQIVYKPVGGC (SEQ ID NO:137)
Tri 2	DAEFRHRRDPDNEAYERRENKHPGGGC (SEQ ID NO:1058)
Tri 1	DAEFRHRRRENKHPGRRDPDNEAYEGGC (SEQ ID NO:1059)
Tri 4	DAEFRHRRPDNEAYERRENKHPGGGC (SEQ ID NO:1060)
Tri 3	DAEFRHRRRENKHPGRRPDNEAYEGGC (SEQ ID NO:1061)
Tri 5	DAEFRHRRSKIGSKDNIKHRRDPDNEAYEGGC (SEQ ID NO:1062)
Tri 6	DAEFRHRRDPDNEAYERRSKIGSKDNIKHGGC (SEQ ID NO:1063)

[00136] Immunogens comprise A β /tau/alpha-synuclein peptides, a C-terminal linker, and a C-terminal cysteine, and are coupled through the C-terminal cysteine to CRM-197 with a maleimide linkage.

[00137] Guinea pigs were injected intramuscularly with 50 μ g of a test immunogen, 25 μ g QS21 in 200 μ l of Addavax on day 0, 21, 49 and 77. Bleeds were done starting 7 days post immunization. The immunogens tested are shown in Table 3. The immunogens peptides are coupled through the C-terminal cysteine to CRM-197 with a maleimide linkage.

[00138] Female Guinea Pigs were at least 5 weeks old at the start of the study having an approximate body weight of 350-500g. Appropriate animal housing and research procedures for animal husbandry and care were conducted in an accredited facility in accordance with the guidelines of the U.S. Department of Agriculture's (USDA) and the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

[00139] The immunogen concentration was 0.5 mg/ml. Prior to each administration of the test immunogen, approximately a 3 cm² area on each hind limb was shaved and wiped with ethanol for visualization of the injection site. Each animal received a test immunogen dose of 200 microliters (0.25 micrograms/microliter)

divided into two separate sites each of 100 microliter per injection (*i.e.*, animals received 50 µg of immunogen in 100 µl PBS + 25 µg of QS21 in 100 µl MF59). A 25G-27G needle was inserted intramuscularly into the hind limb, approximately 0.25 - 0.5 cm deep, and injected at 100 microliters per site. Injection sites were rotated each administration between four separate sites per hind limb and separated by at least 2 cm.

[00140] Example 2: Measurement of Antibody Titers

[00141] Whole blood samples were collected into clot activator tubes via jugular vein at 250-350 microliters per collection at weeks 1, 4, 8 and 12 for Guinea pigs and 50 microliters per collection at weeks 1, 3, 7 and 11 by nicking tails for mice. The maximum volume of whole blood was collected into clot activator tubes via cardiac puncture at termination on the final collection week. All blood samples were allowed to clot at room temperature for greater than 30 minutes, centrifuged at ambient temperature (approximately 20-25°C) at 3,000 RPM for 10-15 minutes, and serum supernatant was transferred individually into clean cryovials. Serum supernatant was stored frozen at -80 °C (± 12 °C).

[00142] Aβ Titers (mice)

[00143] 2 µg/ml Aβ 1-28 monomers are coated at coated on to the plate 100 µl per well in PBS and incubated overnight at room temperature. Plates were blocked for 1 hour with 1% BSA in PBS. Plates were aspirated, and to row A 200 µl of 0.1% BSA in PBS Tween was added. In column 1, negative mouse serum was added at 1/100 while the rest of the row contained 1/100 test serums. Rows were serially diluted ½ down the plate giving dilution of 1/100 to 1/12800. Wells were incubated 2 hours at room temperature then were washed. A 1/5000 dilution of anti-mouse IgG HRP in 0.1% BSA in PBS Tween was prepared and then 100 µl added to the washed well. This incubated for 1 hour and was washed. OPD substrate was prepared using Thermo-Fisher OPD tablets at 1 tablet per 10 mL. Thermo-Fisher substrate buffer was added at 1/10, and each well had 100 µl added and was incubated for 15 minutes. 50 µl of 2N H₂SO₄ was added to stop the reaction and plates were read on a Molecular Devices Spectromax at 490 nM. Titer was defined as the dilution giving 50% maximum OD and were extrapolated if it fell between dilutions.

[00144] Tau Titers (mice)

[00145] 2 µg/ml recombinant WT Tau 4R2N was coated on to the plate using 100 µl per well in PBS and incubated overnight at room temperature. Plates were blocked for 1 hour with 1% BSA in PBS. Plates were aspirated and to row A 200 µl of 0.1% BSA in PBS Tween was added. In column 1, negative mouse serum was added at 1/100 while the rest of the row contained 1/100 test sera. Rows were serially diluted ½ down the plate giving dilution of 1/100 to 1/12800. Wells were incubated 2 hours at room temperature then were washed. A 1/5000 dilution of anti-mouse IgG HRP in 0.1% BSA in PBS Tween was prepared and then 100 µl added to the washed well. This reaction mixture was incubated for 1 hour and was washed. OPD substrate was prepared using Thermo-Fisher OPD tablets at 1 tablet per 10 mL. Thermo-Fisher substrate buffer was added at 1/10 and each well had 100 µl added and was incubated for 15 minutes. 50 µl of 2N H₂SO₄ was added to stop the reaction and plates were read at 490 nm on a Molecular Devices Spectromax. Titer was defined as the dilution giving 50% maximum OD measurement and was extrapolated if it fell between dilutions.

[00146] Alpha-synuclein Titers (mice)

[00147] 2 µg/ml recombinant human alpha-synuclein was coated on to the plate 100 µl per well in PBS and incubated overnight at room temperature. Plates were blocked for 1 hour with 1% BSA in PBS. Plates were aspirated and to row A 200 µl of 0.1% BSA in PBS Tween was added. In column 1, negative mouse serum was added at 1/100 while the rest of the row contained 1/100 test serums. Rows were serially diluted ½ down the plate giving dilution of 1/100 to 1/12800. Wells incubated 2 hours at room temperature then were washed and a 1/5000 dilution of anti-mouse IgG HRP in 0.1% BSA in PBS Tween was prepared and then 100 µl added to the washed well. This incubated for 1 hour and was washed. OPD substrate was prepared using Thermo-Fisher OPD tablets at 1 tablet per 10 mL. Thermo-Fisher substrate buffer was added at 1/10 and each well had 100 µl added and was incubated for 15 minutes. 50 µl of 2N H₂SO₄ was added to stop the reaction and plates were read on a Molecular Devices Spectromax at 490 nm. Titer was defined as the dilution giving 50% maximum OD and was extrapolated if it fell between dilutions.

[00148] Aβ Titers (Guinea pig)

[00149] 2 µg/ml Aβ 1-28 monomers were coated onto the plate at 100 µl per well in PBS and incubated overnight at room temperature. Plates were blocked for 1 hour with 1% BSA in PBS. Plates were re-aspirated, and to row A 200 µL of 0.1% BSA in PBS Tween was added. In column 1, negative Guinea Pig serum was added at 1/100 while the rest of the rows contained 1/100 test serums. Rows were serially diluted ½ down the plate giving dilution of 1/100 to 1/12800. Wells incubated 2 hours at room temperature then were washed and a 1/5000 dilution of anti-Guinea Pig IgG HRP in 0.1% BSA in PBS Tween was prepared and then 100 µl added to the washed well. This incubated for 1 hour and was washed. OPD substrate was prepared using Thermo-Fisher OPD tablets at 1 tablet per 10 mL. Thermo-Fisher substrate buffer was added at 1/10 and each well had 100 µl added and was incubated for 15 minutes. 50 µl of 2N H₂SO₄ was added to stop the reaction and plates were read on a Molecular Devices Spectromax at 490 nm. Titer was defined as the dilution giving 50% maximum OD and was extrapolated if it fell between dilutions.

[00150] Tau Titers (Guinea Pig)

[00151] 2 µg/ml recombinant wild-type Tau 4R2N was coated on to the plate at 100 µl per well in PBS and incubated overnight at room temperature. Plates were blocked for 1 hour with 1% BSA in PBS. Plates were aspirated, and to row A 200 µl of 0.1% BSA in PBS Tween was added. In column 1, negative Rabbit serum was added at 1/100 while the rest of the row contained 1/100 test serums. Rows were serially diluted ½ down the plate giving dilution of 1/100 to 1/12800. Wells were incubated 2 hours at room temperature then washed. A 1/5000 dilution of anti-rabbit IgG HRP in 0.1% BSA in PBS Tween was prepared and then 100 µl added to the washed well. This mixture was incubated for 1 hour and then washed. OPD substrate was prepared using Thermo-Fisher OPD tablets at 1 tablet per 10 mL. Thermo-Fisher substrate buffer was added at 1/10 (each well having 100 µl added) and was incubated for 15 minutes. 50 µl of 2N H₂SO₄ was added to stop the reaction and plates were read on a Molecular Devices Spectromax at 490 nm. Titer was defined as the dilution giving 50% maximum OD and was extrapolated if it fell between dilutions.

Table 4. Titers of mice vaccinated with one of 4 tri-peptide immunogens.

Tri 1 immunogen: DAEFRHDDRRENLKHQPGRDPDNEAYEGGC (SEQ ID NO:1059)			
	Aβ titer	Tau titer	AS titer
Mouse 1	20000	100	1000
Mouse 2	12000	25	13000
Mouse 3	5000	100	900
Mouse 4	30000	12000	3300
Tri 2 immunogen: DAEFRHDDRDPDNEAYERRENLKHQPGGGC (SEQ ID NO:1058)			
	Aβ titer	Tau titer	AS titer
Mouse 1	22000	400	1600
Mouse 2	60000	6000	1000
Mouse 3	25000	2200	1200
Mouse 4	50000	6000	3300
Tri 3 immunogen: DAEFRHDDRRENLKHQPGRDPDNEAYEGGC (SEQ ID NO:1061)			
	Aβ titer	Tau titer	AS titer
Mouse 1	4000	25	13500
Mouse 2	8000	600	2000
Mouse 3	12000	25	3200
Mouse 4	10000	25	8000
Tri 4 immunogen: DAEFRHDDRDPDNEAYERRENLKHQPGGGC (SEQ ID NO:1060)			
	Aβ titer	Tau titer	AS titer
Mouse 1	7000	25	15000
Mouse 2	3200	25	7500
Mouse 3	24000	1600	18000
Mouse 4	400	25	18000

[00152] Alpha-synuclein Titers (Guinea pig)

[00153] 2 μ g/ml recombinant human alpha synuclein was coated on to the plate at 100 μ l per well in PBS and incubated overnight at room temperature. Plates were blocked for 1 hour with 1% BSA in PBS. Plates were re-aspirated, and to row A 200 μ l of 0.1% BSA in PBS Tween was added. In column 1, negative Guinea pig serum was added at 1/100, while the rest of the row contained 1/100 test sera. Rows were serially diluted $\frac{1}{2}$ down the plate giving dilution of 1/100 to 1/12800. Wells were incubated 2 hours at room temperature then washed. A 1/5000 dilution of anti-Guinea

Pig IgG HRP in 0.1% BSA in PBS Tween was prepared and then 100 µl added to the washed well. This mixture was incubated for 1 hour and then washed. OPD substrate was prepared using Thermo-Fisher OPD tablets at 1 tablet per 10 mL. Thermo-Fisher substrate buffer was added at 1/10 (each well having 100 µl added) and the mixture was incubated for 15 minutes. 50 µl of 2N H₂SO₄ was added to stop the reaction and plates were read on a Molecular Devices Spectromax at 490 nm. Titer was defined as the dilution giving 50% maximum OD and was extrapolated if it fell between dilutions.

[00154] Example 3: Staining of Alzheimer's brain tissue with sera from animals immunized with Immunogens as disclosed herein.

[00155] Autopsy blocks of fresh frozen human brain tissue (~ 0.5 g) were embedded in optimal cutting temperature compound (OCT compound) and cut using a cryostat to generate 10 µm sections. The sections were placed into a solution of glucose oxidase and beta D-glucose, in the presence of sodium azide, to block endogenous peroxidase. Once tissue sections were prepared, the staining with the specified animal sera from animals immunized with a vaccine as disclosed herein was carried out at two dilutions (1:300 and 1:1500), using a species appropriate secondary antibody and a DAKO DAB Detection Kit as per the manufacturer's instructions. The staining was processed using an automated Leica Bond Stainer. The results indicate whether sera from animals immunized with a vaccine as disclosed herein comprise antibodies specific to Aβ, tau, and/or alpha-synuclein in human brain tissue of Alzheimer's patients.

[00156] Example 4: Serum from vaccinated animals blocks soluble Aβ aggregates from binding to neurons.

[00157] E18 primary rat hippocampal neurons are cultured as described previously (Zago, *et al.* "Neutralization of Soluble, Synaptotoxic Amyloid β Species by Antibodies Is Epitope Specific," *J Neurosci.* 2012 Feb 22; 32(8): 2696–2702). Soluble Aβ aggregate was pre-incubated with or without animal vaccine serum on culture DIV14-21 to block soluble Aβ aggregate from neuritic binding. Animal serum was isolated from animals vaccinated with immunogen peptides as shown in Table 3. Fresh unlabeled, biotinylated or (9:1) soluble Aβ was prepared one day prior and incubated overnight at 4°C. Each diluted serum sample (1:1000, 1:300, and

1:100) and soluble A β solution was prepared at 2x the final concentration in one-half of final treatment volume using NeuroBasal-no phenol red (NB-NPR) medium. This was combined with one-half final volume of 2x soluble A β and with one-half final volume of 2x diluted animal vaccine serum to make up a 1x final concentration in total final treatment volume, which was mixed well and then pre-incubated for 30 minutes at 37°C. E18 neurons were rinsed with NB-NPR at 150 μ L/well before adding binding treatment. Animal serum from vaccinated animals/A β treatment was added to E18 neurons at 60 μ L/well, and then incubated for 30 minutes at 37°C under normal incubator conditions (5% CO₂; 9% O₂). Cells were rinsed twice using 150 μ L/well of NB-NPR, and then fixed in 4% paraformaldehyde in 1x DPBS for 20 minutes. Cells were permeabilized using 0.1 TX-100 for 5 minutes, and blocked using 10% normal goat serum (NGS) for 1 hour at room temperature (RT). Cells were incubated with MAP2 & NeuN primary antibodies in 100 μ L/well, 1x DPBS containing 1% BSA + 1% NGS overnight at 4°C. The next day, cells were rinsed twice in 150 μ L/well 1x DPBS for 5 minutes each wash. Secondary antibodies were added for 1 hour at RT in 100 μ L/well 1x DPBS + 1% BSA + 1% NGS. High-content imaging (HCI) analysis was performed to quantify soluble aggregate A β neuritic binding using Operetta HCI CLS instrument (Perkin Elmer; modified Neurite Outgrowth algorithm: 40x H₂O objective; 40 fields per well; (n=3) per condition; data shown as mean (+/-) SD); MAP2 & NeuN (Abcam) neuronal markers used to each trace neurite tree and count cell body number per optical field; Neuritic A β soluble aggregate spots detected using streptavidin-488 or polyclonal A β antibody (Thermo; Millipore); and data reported as A β soluble aggregate spots/neuron (or as Integrated Intensity)).

[00158] Approximately 80-150 neurons were observed per well for each condition tested. The results indicate whether animal serum from animals vaccinated with the immunogen peptides as disclosed herein comprise antibodies specific to A β that can block soluble A β aggregates from binding to neurons.

[00159] Example 5: Serum from vaccinated animals stains A β plaques and/or Tau pathologies and/or Synucleinopathies in human brain tissue.

[00160] Fresh frozen human brain tissues from autopsied Alzheimer's disease donors or non-diseased controls was embedded in OCT, and cut in a cryostat to generate 10 μ m frozen sections. The tissue sections were incubated in a solution of

glucose oxidase and beta D-glucose, in the presence of sodium azide, to block endogenous peroxidase. The staining with sera from vaccinated animals (animals were vaccinated with the immunogen peptides as disclosed in Table 3) or control animals were then carried out at 1:1000 dilution, in an automated Leica Bond Rx Stainer (Leica Biosystems). Antibody binding was detected using the Bond Polymer Refine Detection Kit (DS9800, Leica Biosystems), which is based on an anti-mouse polymer detection, DAB visualization and hematoxylin nuclear counter-staining. After cover-slipping, the stained tissue slides were digitally imaged with a Hamamatsu NanoZoomer 2.0HT slide scanner (Hamamatsu Corporation) with an NDP.scan, 2.5.85 software. The digitized images were viewed and analyzed using the NDP.view, 2.7.43.0 software.

[00161] Results demonstrate A β plaques and/or tau neurofibrillary tangles, and/or alpha-synuclein based synucleinopathies were identified based on their typical histopathological characteristics. Such pathologies were absent from tissues incubated with control animal serum. Non-diseased tissue had no such pathological staining after incubation with the sera from animals vaccinated with the immunogen peptides as disclosed herein. The immunogens disclosed herein produce A β antibody titers capable of causing phagocytosis of A β , and the synuclein titers are able to prevent the internalization of synuclein soluble aggregates into cells.

[00162] Although various specific embodiments of the present invention have been described herein, it is to be understood that the invention is not limited to those precise embodiments and that various changes or modifications can be affected therein by one skilled in the art without departing from the scope and spirit of the invention.

SEQUENCES

SEQ ID NO:01 - Abeta (Aβ) 1-42

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

SEQ ID NO:02 - TAU (UNIPROTKB - P10636 (*Homo sapiens*))

>P10636-8 (Isoform Tau-F)

10	20	30	40	50
MAEPRQEF	MEDHAGTYGL	GDRKDQGGYT	MHQDQEGDTD	AGLKESPLQT
60	70	80	90	100
PTEDGSEEPG	SETSDAKSTP	TAEDVTAPLV	DEGAPGKQAA	AQPHTIIEG
110	120	130	140	150
TTAEEAGIGD	TPSLEDEAAG	HVTQARMVSK	SKDGTGSDDK	KAKGADGKTK
160	170	180	190	200
IATPRGAAPP	GQKGQANATR	IPAKTPPAPK	TPPSSGEPK	SGDRSGYSSP
210	220	230	240	250
GSPGTPGSRS	RTPSLTPPT	REPKKVAVVR	TPPKSPSSAK	SRLQTAPVPM
260	270	280	290	300
PDLKNVSKI	GSTENLKHQP	GGGKVQIINK	KLDLSNVQSK	CGSKDNIKHV
310	320	330	340	350
PGGGSVQIVY	KPVDLSKVTS	KCGSLGNIHH	KPGGGQVEVK	SEKLDFKDRV
360	370	380	390	400
QSKIGSLDNI	THVPGGGNKK	IETHKLTFRE	NAKAKTDHGA	EIVYKSPVVS
410	420	430	440	
GDTSPRHLSN	VSSTGSIDMV	DSPQLATLAD	EVASASLAKQG	L

A-beta immunogens:

DAEFRHDSGY	(SEQ ID NO:03)
DAEFRHDSG	(SEQ ID NO:04)
DAEFRHDS	(SEQ ID NO:05)
DAEFRHD	(SEQ ID NO:06)
DAEFRH	(SEQ ID NO:07)
DAEFR	(SEQ ID NO:08)
DAEF	(SEQ ID NO:09)
DAE	(SEQ ID NO:10)
AEFRHDSGY	(SEQ ID NO:11)
AEFRHDSG	(SEQ ID NO:12)
AEFRHDS	(SEQ ID NO:13)
AEFRHD	(SEQ ID NO:14)
AEFRH	(SEQ ID NO:15)
AEFR	(SEQ ID NO:16)
AEF	(SEQ ID NO:17)
EFRHDSGY	(SEQ ID NO:18)
EFRHDSG	(SEQ ID NO:19)
EFRHDS	(SEQ ID NO:20)
EFRHD	(SEQ ID NO:21)
EFRH	(SEQ ID NO:22)
EFR	(SEQ ID NO:23)
FRHDSGY	(SEQ ID NO:24)
FRHDSG	(SEQ ID NO:25)
FRHDS	(SEQ ID NO:26)
FRHD	(SEQ ID NO:27)
FRH	(SEQ ID NO:28)

RHDSGY	(SEQ ID NO:29)
RHDSG	(SEQ ID NO:30)
RHDS	(SEQ ID NO:31)
RHD	(SEQ ID NO:32)
HDSGY	(SEQ ID NO:33)
HDSG	(SEQ ID NO:34)
HDS	(SEQ ID NO:35)
DSGY	(SEQ ID NO:36)
DSG	(SEQ ID NO:37)
SGY	(SEQ ID NO:38)
VHHQKLVFFA	(SEQ ID NO:1002)
VHHQKLVFF	(SEQ ID NO:1003)
VHHQKLVF	(SEQ ID NO:1004)
VHHQKLV	(SEQ ID NO:1005)
VHHQKL	(SEQ ID NO:1006)
HHQKLVFFAE	(SEQ ID NO:1007)
HHQKLVFFA	(SEQ ID NO:1008)
HHQKLVFF	(SEQ ID NO:1009)
HHQKLVF	(SEQ ID NO:1010)
HHQKLV	(SEQ ID NO:1011)
HHQKL	(SEQ ID NO:1012)
HQKLVFFAED	(SEQ ID NO:1013)
HQKLVFFAE	(SEQ ID NO:1014)
HQKLVFFA	(SEQ ID NO:1015)
HQKLVFF	(SEQ ID NO:1016)
HQKLVF	(SEQ ID NO:1017)
HQKLV	(SEQ ID NO:1018)
HQKL	(SEQ ID NO:1019)
QKLVFFAEDV	(SEQ ID NO:1020)
QKLVFFAED	(SEQ ID NO:1021)
QKLVFFAE	(SEQ ID NO:1022)
QKLVFFA	(SEQ ID NO:1023)
QKLVFF	(SEQ ID NO:1024)
QKLVF	(SEQ ID NO:1025)
QKLV	(SEQ ID NO:1026)
QKL	(SEQ ID NO:1027)
KLVFFAEDVG	(SEQ ID NO:1028)
KLVFFAEDV	(SEQ ID NO:1029)
KLVFFAED	(SEQ ID NO:1030)
KLVFFAE	(SEQ ID NO:1031)
KLVFFA	(SEQ ID NO:1032)
KLVFF	(SEQ ID NO:1033)
KLVF	(SEQ ID NO:1034)
KLV	(SEQ ID NO:1035)
LVFFAEDVG	(SEQ ID NO:1036)
LVFFAEDV	(SEQ ID NO:1037)
LVFFAED	(SEQ ID NO:1038)
LVFFAE	(SEQ ID NO:1039)
LVFFA	(SEQ ID NO:1040)
LVFF	(SEQ ID NO:1041)
LVF	(SEQ ID NO:1042)

VFFAEDVG	(SEQ ID NO:1043)
VFFAEDV	(SEQ ID NO:1044)
VFFAED	(SEQ ID NO:1045)
VFFAE	(SEQ ID NO:1046)
VFFA	(SEQ ID NO:1047)
VFF	(SEQ ID NO:1048)
FFAEDVG	(SEQ ID NO:1049)
FFAEDV	(SEQ ID NO:1050)
FFAED	(SEQ ID NO:1051)
FFAE	(SEQ ID NO:1052)
FFA	(SEQ ID NO:1053)
FAEDVG	(SEQ ID NO:1054)
FAEDV	(SEQ ID NO:1055)
FAED	(SEQ ID NO:1056)
FAE	(SEQ ID NO:1057)

Tau immunogens:

QIVYKPV	(SEQ ID NO:39)
QIVYKP	(SEQ ID NO:40)
QIVYKSV	(SEQ ID NO:41)
EIVYKSV	(SEQ ID NO:42)
QIVYKS	(SEQ ID NO:997)
EIVYKSP	(SEQ ID NO:43)
EIVYKS	(SEQ ID NO:998)
EIVYKPV	(SEQ ID NO:44)
EIVYKP	(SEQ ID NO:999)
IVYKSPV	(SEQ ID NO:45)
IVYK	(SEQ ID NO:46)
CNIKHVPG	(SEQ ID NO:1000)
CNIKHVP	(SEQ ID NO:47)
NIKHVP	(SEQ ID NO:48)
HVPGGG	(SEQ ID NO:49)
HVPGG	(SEQ ID NO:50)
HKPGGG	(SEQ ID NO:51)
HKPGG	(SEQ ID NO:52)
KHVPGGG	(SEQ ID NO:53)
KHVPGG	(SEQ ID NO:54)
HQPGGG	(SEQ ID NO:55)
HQPGG	(SEQ ID NO:56)
NIKHVPG	(SEQ ID NO:57)
VQIINK	(SEQ ID NO:146)
VQIINKK	(SEQ ID NO:147)
VQIINKKL	(SEQ ID NO:148)
QIINK	(SEQ ID NO:149)
QIINKK	(SEQ ID NO:150)
QIINKKL	(SEQ ID NO:151)
EAAGHVTQC	(SEQ ID NO:152)
EAAGHVTQAR	(SEQ ID NO:153)
AAGHVTQAC	(SEQ ID NO:154)
AGHVTQARC	(SEQ ID NO:155)
AGHVTQAR	(SEQ ID NO:156)

GYTMHQD	(SEQ ID NO:157)
QGGYTMHC	(SEQ ID NO:158)
QGGYTMHQD	(SEQ ID NO:159)
GGYTMHQC	(SEQ ID NO:160)
VPGGGSVQIV	(SEQ ID NO:161)
PGGGSVQIV	(SEQ ID NO:162)
GGGSVQIV	(SEQ ID NO:163)
GGSVQIV	(SEQ ID NO:164)
GSVQIV	(SEQ ID NO:165)
SVQIV	(SEQ ID NO:166)
VQIV	(SEQ ID NO:167)
QIV	(SEQ ID NO:168)
PGGGSVQIVY	(SEQ ID NO:169)
GGGSVQIVY	(SEQ ID NO:170)
GGSVQIVY	(SEQ ID NO:171)
GSVQIVY	(SEQ ID NO:172)
SVQIVY	(SEQ ID NO:173)
VQIVY	(SEQ ID NO:174)
QIVY	(SEQ ID NO:175)
IVY	(SEQ ID NO:176)
GGGSVQIVYK	(SEQ ID NO:177)
GGSVQIVYK	(SEQ ID NO:178)
GSVQIVYK	(SEQ ID NO:179)
SVQIVYK	(SEQ ID NO:180)
VQIVYK	(SEQ ID NO:181)
QIVYK	(SEQ ID NO:182)
VYK	(SEQ ID NO:183)
GGSVQIVYKP	(SEQ ID NO:184)
GSVQIVYKP	(SEQ ID NO:185)
SVQIVYKP	(SEQ ID NO:186)
VQIVYKP	(SEQ ID NO:187)
IVYKP	(SEQ ID NO:188)
VYKP	(SEQ ID NO:189)
YKP	(SEQ ID NO:190)
GSVQIVYKPV	(SEQ ID NO:191)
SVQIVYKPV	(SEQ ID NO:192)
VQIVYKPV	(SEQ ID NO:193)
IVYKPV	(SEQ ID NO:194)
VYKPV	(SEQ ID NO:195)
YKPV	(SEQ ID NO:196)
KPV	(SEQ ID NO:197)
SVQIVYKPWD	(SEQ ID NO:198)
VQIVYKPWD	(SEQ ID NO:199)
QIVYKPWD	(SEQ ID NO:200)
IVYKPWD	(SEQ ID NO:201)
VYKPWD	(SEQ ID NO:203)
YKPWD	(SEQ ID NO:204)
KPWD	(SEQ ID NO:205)
PVD	(SEQ ID NO:206)
VQIVYKPVDL	(SEQ ID NO:207)
QIVYKPVDL	(SEQ ID NO:208)

IVYKPVDL	(SEQ ID NO:209)
VYKPVDL	(SEQ ID NO:210)
YKPVDL	(SEQ ID NO:211)
KPVDL	(SEQ ID NO:212)
PVDL	(SEQ ID NO:213)
VDL	(SEQ ID NO:214)
QIVYKPVDLS	(SEQ ID NO:215)
IVYKPVDLS	(SEQ ID NO:216)
VYKPVDLS	(SEQ ID NO:217)
YKPVDLS	(SEQ ID NO:218)
KPVDLS	(SEQ ID NO:219)
PVDLS	(SEQ ID NO:220)
VDLS	(SEQ ID NO:221)
DLS	(SEQ ID NO:222)
IVYKPVDLSK	(SEQ ID NO:223)
VYKPVDLSK	(SEQ ID NO:224)
YKPVDLSK	(SEQ ID NO:225)
KPVDLSK	(SEQ ID NO:226)
PVDLSK	(SEQ ID NO:227)
VDLSK	(SEQ ID NO:228)
DLSK	(SEQ ID NO:229)
LSK	(SEQ ID NO:230)
VYKPVDLSKV	(SEQ ID NO:231)
YKPVDLSKV	(SEQ ID NO:232)
KPVDLSKV	(SEQ ID NO:233)
PVDLSKV	(SEQ ID NO:234)
VDLSKV	(SEQ ID NO:235)
DLSKV	(SEQ ID NO:236)
LSKV	(SEQ ID NO:237)
SKV	(SEQ ID NO:238)
YKPVDLSKVT	(SEQ ID NO:239)
KPVDLSKVT	(SEQ ID NO:240)
PVDLSKVT	(SEQ ID NO:241)
VDLSKVT	(SEQ ID NO:242)
AKTDHGAEIV	(SEQ ID NO:243)
KTDHGAEIV	(SEQ ID NO:244)
TDHGAEIV	(SEQ ID NO:245)
DHGAEIV	(SEQ ID NO:246)
HGAEIV	(SEQ ID NO:247)
GAEIV	(SEQ ID NO:248)
AEIV	(SEQ ID NO:249)
EIV	(SEQ ID NO:250)
KTDHGAEIVY	(SEQ ID NO:251)
TDHGAEIVY	(SEQ ID NO:252)
DHGAEIVY	(SEQ ID NO:253)
HGAEIVY	(SEQ ID NO:254)
GAEIVY	(SEQ ID NO:255)
AEIVY	(SEQ ID NO:256)
EIVY	(SEQ ID NO:257)
IVY	(SEQ ID NO:258)
TDHGAEIVYK	(SEQ ID NO:259)

DHGAEIVYK	(SEQ ID NO:260)
HGAEIVYK	(SEQ ID NO:261)
GAEIVYK	(SEQ ID NO:262)
AEIVYK	(SEQ ID NO:263)
EIVYK	(SEQ ID NO:264)
IVYK	(SEQ ID NO:265)
DHGAEIVYKS	(SEQ ID NO:266)
HGAEIVYKS	(SEQ ID NO:267)
GAEIVYKS	(SEQ ID NO:268)
AEIVYKS	(SEQ ID NO:269)
EIVYKS	(SEQ ID NO:270)
IVYKS	(SEQ ID NO:271)
VYKS	(SEQ ID NO:272)
YKS	(SEQ ID NO:273)
HGAEIVYKSP	(SEQ ID NO:274)
GAEIVYKSP	(SEQ ID NO:275)
AEIVYKSP	(SEQ ID NO:276)
EIVYKSP	(SEQ ID NO:277)
IVYKSP	(SEQ ID NO:278)
VYKSP	(SEQ ID NO:279)
YKSP	(SEQ ID NO:280)
KSP	(SEQ ID NO:281)
GAEIVYKSPV	(SEQ ID NO:282)
AEIVYKSPV	(SEQ ID NO:283)
EIVYKSPV	(SEQ ID NO:284)
IVYKSPV	(SEQ ID NO:285)
VYKSPV	(SEQ ID NO:286)
YKSPV	(SEQ ID NO:287)
KSPV	(SEQ ID NO:288)
SPV	(SEQ ID NO:289)
AEIVYKSPVV	(SEQ ID NO:290)
EIVYKSPVV	(SEQ ID NO:291)
IVYKSPVV	(SEQ ID NO:292)
VYKSPVV	(SEQ ID NO:293)
YKSPVV	(SEQ ID NO:294)
KSPVV	(SEQ ID NO:295)
SPVV	(SEQ ID NO:296)
PVV	(SEQ ID NO:297)
EIVYKSPVVS	(SEQ ID NO:298)
IVYKSPVVS	(SEQ ID NO:299)
VYKSPVVS	(SEQ ID NO:300)
YKSPVVS	(SEQ ID NO:301)
KSPVVS	(SEQ ID NO:302)
SPVVS	(SEQ ID NO:303)
PVVS	(SEQ ID NO:304)
VVS	(SEQ ID NO:305)
IVYKSPVVSG	(SEQ ID NO:306)
VYKSPVVSG	(SEQ ID NO:307)
YKSPVVSG	(SEQ ID NO:308)
KSPVVSG	(SEQ ID NO:309)
SPVVSG	(SEQ ID NO:310)

PVVSG	(SEQ ID NO:311)
VVSG	(SEQ ID NO:312)
VSG	(SEQ ID NO:313)
VYKSPVVSGD	(SEQ ID NO:314)
YKSPVVSGD	(SEQ ID NO:315)
KSPVVSGD	(SEQ ID NO:316)
SPVVSGD	(SEQ ID NO:317)
PVVSGD	(SEQ ID NO:318)
VVSGD	(SEQ ID NO:319)
VSGD	(SEQ ID NO:320)
SGD	(SEQ ID NO:321)
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KSPVVSGDT	(SEQ ID NO:323)
SPVVSGDT	(SEQ ID NO:324)
PVVSGDT	(SEQ ID NO:325)
VVSGDT	(SEQ ID NO:326)
VSGDT	(SEQ ID NO:327)
SGDT	(SEQ ID NO:328)
GDT	(SEQ ID NO:329)
KSPVVSGDTS	(SEQ ID NO:330)
SPVVSGDTS	(SEQ ID NO:331)
PVVSGDTS	(SEQ ID NO:332)
VVSGDTS	(SEQ ID NO:333)
VSGDTS	(SEQ ID NO:334)
SGDTS	(SEQ ID NO:335)
GDTs	(SEQ ID NO:336)
DTS	(SEQ ID NO:337)
SPVVSGDTSP	(SEQ ID NO:338)
PVVSGDTSP	(SEQ ID NO:339)
VVSGDTSP	(SEQ ID NO:340)
VSGDTSP	(SEQ ID NO:341)
SGDTSP	(SEQ ID NO:342)
GDTSP	(SEQ ID NO:343)
DTSP	(SEQ ID NO:344)
TSP	(SEQ ID NO:345)
PVVSGDTSPR	(SEQ ID NO:346)
VVSGDTSPR	(SEQ ID NO:347)
VSGDTSPR	(SEQ ID NO:348)
SGDTSPR	(SEQ ID NO:349)
GDTSPR	(SEQ ID NO:350)
DTSPR	(SEQ ID NO:351)
TSPR	(SEQ ID NO:352)
SPR	(SEQ ID NO:353)
HQPGGGKVQI	(SEQ ID NO:354)
QPGGGKVQI	(SEQ ID NO:355)
PGGGKVQI	(SEQ ID NO:356)
GGGGKVQI	(SEQ ID NO:357)
GGKVQI	(SEQ ID NO:358)
GKVQI	(SEQ ID NO:359)
KVQI	(SEQ ID NO:360)
VQI	(SEQ ID NO:361)

QPGGGKVQII	(SEQ ID NO:362)
PGGGKVQII	(SEQ ID NO:363)
GGGGKVQII	(SEQ ID NO:365)
GGKVQII	(SEQ ID NO:366)
GKVQII	(SEQ ID NO:367)
KVQII	(SEQ ID NO:368)
VQII	(SEQ ID NO:369)
QII	(SEQ ID NO:370)
PGGGKVQIIN	(SEQ ID NO:371)
GGGGKVQIIN	(SEQ ID NO:372)
GGKVQIIN	(SEQ ID NO:373)
GKVQIIN	(SEQ ID NO:374)
KVQIIN	(SEQ ID NO:375)
VQIIN	(SEQ ID NO:376)
QIIN	(SEQ ID NO:377)
IIN	(SEQ ID NO:378)
GGGGKVQIINK	(SEQ ID NO:379)
GGKVQIINK	(SEQ ID NO:380)
GKVQIINK	(SEQ ID NO:381)
KVQIINK	(SEQ ID NO:382)
IINK	(SEQ ID NO:383)
INK	(SEQ ID NO:384)
GGGGKVQIINKK	(SEQ ID NO:385)
GKVQIINKK	(SEQ ID NO:386)
KVQIINKK	(SEQ ID NO:387)
IINKK	(SEQ ID NO:388)
INKK	(SEQ ID NO:389)
NKK	(SEQ ID NO:390)
GKVQIINKKL	(SEQ ID NO:391)
KVQIINKKL	(SEQ ID NO:392)
IINKKL	(SEQ ID NO:393)
INKKL	(SEQ ID NO:394)
NKKL	(SEQ ID NO:395)
KKL	(SEQ ID NO:396)
KVQIINKKLD	(SEQ ID NO:397)
VQIINKKLD	(SEQ ID NO:398)
QIINKKLD	(SEQ ID NO:399)
IINKKLD	(SEQ ID NO:400)
INKKLD	(SEQ ID NO:401)
NKKLD	(SEQ ID NO:402)
KKLD	(SEQ ID NO:403)
KLD	(SEQ ID NO:404)
VQIINKKLDL	(SEQ ID NO:405)
QIINKKLDL	(SEQ ID NO:406)
IINKKLDL	(SEQ ID NO:407)
INKKLDL	(SEQ ID NO:408)
NKKLDL	(SEQ ID NO:409)
KKLDL	(SEQ ID NO:410)
KLDL	(SEQ ID NO:411)
LDL	(SEQ ID NO:412)
QIINKKLDLS	(SEQ ID NO:413)

IINKKLDLS	(SEQ ID NO:414)
INKKLDLS	(SEQ ID NO:415)
NKKLDLS	(SEQ ID NO:416)
KKLDLS	(SEQ ID NO:417)
KLDLS	(SEQ ID NO:418)
LDLS	(SEQ ID NO:419)
IINKKLDLSN	(SEQ ID NO:420)
INKKLDLSN	(SEQ ID NO:421)
NKKLDLSN	(SEQ ID NO:422)
KKLDLSN	(SEQ ID NO:423)
KLDLSN	(SEQ ID NO:424)
LDLSN	(SEQ ID NO:425)
DLSN	(SEQ ID NO:426)
LSN	(SEQ ID NO:427)
INKKLDLSNV	(SEQ ID NO:428)
NKKLDLSNV	(SEQ ID NO:429)
KKLDLSNV	(SEQ ID NO:430)
KLDLSNV	(SEQ ID NO:431)
LDLSNV	(SEQ ID NO:432)
DLSNV	(SEQ ID NO:433)
LSNV	(SEQ ID NO:434)
SNV	(SEQ ID NO:435)
NKKLDLSNVQ	(SEQ ID NO:436)
KKLDLSNVQ	(SEQ ID NO:437)
KLDLSNVQ	(SEQ ID NO:438)
LDLSNVQ	(SEQ ID NO:439)
DLSNVQ	(SEQ ID NO:440)
LSNVQ	(SEQ ID NO:441)
SNVQ	(SEQ ID NO:442)
NVQ	(SEQ ID NO:443)
KKLDLSNVQS	(SEQ ID NO:444)
KLDLSNVQS	(SEQ ID NO:445)
LDLSNVQS	(SEQ ID NO:446)
DLSNVQS	(SEQ ID NO:447)
LSNVQS	(SEQ ID NO:448)
SNVQS	(SEQ ID NO:449)
NVQS	(SEQ ID NO:450)
VQS	(SEQ ID NO:451)
SKCGSKDNIK	(SEQ ID NO:452)
KCGSKDNIK	(SEQ ID NO:453)
CGSKDNIK	(SEQ ID NO:454)
GSKDNIK	(SEQ ID NO:455)
SKDNIK	(SEQ ID NO:456)
KDNIK	(SEQ ID NO:457)
DNIK	(SEQ ID NO:458)
NIK	(SEQ ID NO:459)
KCGSKDNIKH	(SEQ ID NO:460)
CGSKDNIKH	(SEQ ID NO:461)
GSKDNIKH	(SEQ ID NO:462)
SKDNIKH	(SEQ ID NO:463)
KDNIKH	(SEQ ID NO:464)

DNIKH	(SEQ ID NO:465)
NIKH	(SEQ ID NO:466)
IKH	(SEQ ID NO:467)
CGSKDNIKHV	(SEQ ID NO:468)
GSKDNIKHV	(SEQ ID NO:469)
SKDNIKHV	(SEQ ID NO:470)
KDNIKHV	(SEQ ID NO:471)
DNIKHV	(SEQ ID NO:472)
NIKHV	(SEQ ID NO:473)
IKHV	(SEQ ID NO:474)
KHV	(SEQ ID NO:475)
GSKDNIKHVP	(SEQ ID NO:476)
SKDNIKHVP	(SEQ ID NO:477)
KDNIKHVP	(SEQ ID NO:478)
DNIKHVP	(SEQ ID NO:479)
IKHVP	(SEQ ID NO:480)
KHVP	(SEQ ID NO:481)
HVP	(SEQ ID NO:482)
SKDNIKHVPG	(SEQ ID NO:483)
KDNIKHVPG	(SEQ ID NO:484)
DNIKHVPG	(SEQ ID NO:485)
NIKHVPG	(SEQ ID NO:486)
IKHVPG	(SEQ ID NO:487)
KHVPG	(SEQ ID NO:488)
HVPG	(SEQ ID NO:489)
VPG	(SEQ ID NO:490)
KDNIKHVPGG	(SEQ ID NO:491)
DNIKHVPGG	(SEQ ID NO:492)
NIKHVPGG	(SEQ ID NO:493)
IKHVPGG	(SEQ ID NO:494)
KHVPGG	(SEQ ID NO:495)
VPGG	(SEQ ID NO:496)
PGG	(SEQ ID NO:497)
DNIKHVPGGG	(SEQ ID NO:498)
NIKHVPGGG	(SEQ ID NO:499)
IKHVPGGG	(SEQ ID NO:500)
VPGGG	(SEQ ID NO:501)
PGGG	(SEQ ID NO:502)
GGG	(SEQ ID NO:503)
NIKHVPGGGS	(SEQ ID NO:504)
IKHVPGGGS	(SEQ ID NO:505)
KHVPGGGS	(SEQ ID NO:506)
HVPGGGS	(SEQ ID NO:507)
VPGGGS	(SEQ ID NO:508)
PGGGS	(SEQ ID NO:509)
GGGS	(SEQ ID NO:510)
GGG	(SEQ ID NO:511)
IKHVPGGGSV	(SEQ ID NO:512)
KHVPGGGSV	(SEQ ID NO:513)
HVPGGGSV	(SEQ ID NO:514)
VPGGGSV	(SEQ ID NO:515)

PGGGSV	(SEQ ID NO:516)
GGGSV	(SEQ ID NO:517)
GSV	(SEQ ID NO:518)
GSV	(SEQ ID NO:519)
KHVPGGGSVQ	(SEQ ID NO:520)
HVPGGGSVQ	(SEQ ID NO:521)
VPGGGSVQ	(SEQ ID NO:522)
PGGGSVQ	(SEQ ID NO:523)
GGGSVQ	(SEQ ID NO:524)
GGSVQ	(SEQ ID NO:525)
GSVQ	(SEQ ID NO:526)
SVQ	(SEQ ID NO:527)
HVPGGGSVQI	(SEQ ID NO:528)
VPGGGSVQI	(SEQ ID NO:529)
PGGGSVQI	(SEQ ID NO:530)
GGGSVQI	(SEQ ID NO:531)
GGSVQI	(SEQ ID NO:532)
GSVQI	(SEQ ID NO:533)
SVQI	(SEQ ID NO:534)
GGSVQIVYKS	(SEQ ID NO:535)
GSVQIVYKS	(SEQ ID NO:536)
SVQIVYKS	(SEQ ID NO:537)
VQIVYKS	(SEQ ID NO:538)
QIVYKS	(SEQ ID NO:539)
IVYKS	(SEQ ID NO:540)
VYKS	(SEQ ID NO:541)
YKS	(SEQ ID NO:542)
GSVQIVYKSV	(SEQ ID NO:543)
SVQIVYKSV	(SEQ ID NO:544)
VQIVYKSV	(SEQ ID NO:545)
QIVYKSV	(SEQ ID NO:546)
IVYKSV	(SEQ ID NO:547)
VYKSV	(SEQ ID NO:548)
YKSV	(SEQ ID NO:549)
SVQIVYKSVD	(SEQ ID NO:550)
VQIVYKSVD	(SEQ ID NO:551)
QIVYKSVD	(SEQ ID NO:552)
IVYKSVD	(SEQ ID NO:553)
VYKSVD	(SEQ ID NO:554)
YKSVD	(SEQ ID NO:555)
KSVD	(SEQ ID NO:556)
SVD	(SEQ ID NO:557)
VQIVYKSVDL	(SEQ ID NO:558)
QIVYKSVDL	(SEQ ID NO:559)
IVYKSVDL	(SEQ ID NO:560)
VYKSVDL	(SEQ ID NO:561)
YKSVDL	(SEQ ID NO:562)
KSVDL	(SEQ ID NO:563)
SVDL	(SEQ ID NO:564)
QIVYKSVDLS	(SEQ ID NO:565)
IVYKSVDLS	(SEQ ID NO:566)

VYKSVDLS	(SEQ ID NO:567)
YKSVDLS	(SEQ ID NO:568)
KSVDLS	(SEQ ID NO:569)
SVDLS	(SEQ ID NO:570)
IVYKSVDLSK	(SEQ ID NO:571)
VYKSVDLSK	(SEQ ID NO:572)
YKSVDLSK	(SEQ ID NO:573)
KSVDLSK	(SEQ ID NO:574)
SVDLSK	(SEQ ID NO:364)
VYKSVDLSKV	(SEQ ID NO:575)
YKSVDLSKV	(SEQ ID NO:576)
KSVDLSKV	(SEQ ID NO:577)
SVDLSKV	(SEQ ID NO:578)
YKSVDLSKVT	(SEQ ID NO:579)
KSVDLSKVT	(SEQ ID NO:580)
SVDLSKVT	(SEQ ID NO:581)
DLSKVT	(SEQ ID NO:582)
LSKVT	(SEQ ID NO:583)
SKVT	(SEQ ID NO:584)
KVT	(SEQ ID NO:585)
HGAEIVYKSV	(SEQ ID NO:586)
GAEIVYKSV	(SEQ ID NO:587)
AEIVYKSV	(SEQ ID NO:588)
GAEIVYKSVV	(SEQ ID NO:589)
AEIVYKSVV	(SEQ ID NO:590)
EIVYKSVV	(SEQ ID NO:591)
IVYKSVV	(SEQ ID NO:592)
VYKSVV	(SEQ ID NO:593)
YKSVV	(SEQ ID NO:594)
KSVV	(SEQ ID NO:595)
SVV	(SEQ ID NO:596)
AEIVYKSVVS	(SEQ ID NO:597)
EIVYKSVVS	(SEQ ID NO:598)
IVYKSVVS	(SEQ ID NO:599)
VYKSVVS	(SEQ ID NO:600)
YKSVVS	(SEQ ID NO:601)
KSVVS	(SEQ ID NO:602)
SVVS	(SEQ ID NO:603)
EIVYKSVVSG	(SEQ ID NO:604)
IVYKSVVSG	(SEQ ID NO:605)
VYKSVVSG	(SEQ ID NO:606)
YKSVVSG	(SEQ ID NO:607)
KSVVSG	(SEQ ID NO:608)
SVVSG	(SEQ ID NO:609)
VVSG	(SEQ ID NO:610)
VSG	(SEQ ID NO:611)
IVYKSVVSGD	(SEQ ID NO:612)
VYKSVVSGD	(SEQ ID NO:613)
YKSVVSGD	(SEQ ID NO:614)
KSVVSGD	(SEQ ID NO:615)
SVVSGD	(SEQ ID NO:616)

VVSGD	(SEQ ID NO:617)
VYKSVVSGDT	(SEQ ID NO:618)
YKSVVSGDT	(SEQ ID NO:619)
KSVVSGDT	(SEQ ID NO:620)
SVVSGDT	(SEQ ID NO:621)
YKSVVSGDTS	(SEQ ID NO:622)
KSVVSGDTS	(SEQ ID NO:623)
SVVSGDTS	(SEQ ID NO:624)
YKSVVSGDTS	(SEQ ID NO:625)
KSVVSGDTS	(SEQ ID NO:626)
SVVSGDTS	(SEQ ID NO:627)
VVSGDTS	(SEQ ID NO:628)
KSVVSGDTSP	(SEQ ID NO:629)
SVVSGDTSP	(SEQ ID NO:630)
SVVSGDTSPR	(SEQ ID NO:631)
DHGAEIVYKP	(SEQ ID NO:632)
HGAEIVYKP	(SEQ ID NO:633)
GAEIVYKP	(SEQ ID NO:634)
AEIVYKP	(SEQ ID NO:635)
HGAEIVYKPV	(SEQ ID NO:636)
GAEIVYKPV	(SEQ ID NO:637)
AEIVYKPV	(SEQ ID NO:638)
GAEIVYKPVV	(SEQ ID NO:639)
AEIVYKPVV	(SEQ ID NO:640)
EIVYKPVV	(SEQ ID NO:641)
IVYKPVV	(SEQ ID NO:642)
VYKPVV	(SEQ ID NO:643)
YKPVV	(SEQ ID NO:644)
KPVV	(SEQ ID NO:645)
AEIVYKPVVS	(SEQ ID NO:646)
EIVYKPVVS	(SEQ ID NO:647)
IVYKPVVS	(SEQ ID NO:648)
VYKPVVS	(SEQ ID NO:649)
YKPVVS	(SEQ ID NO:650)
KPVVS	(SEQ ID NO:651)
EIVYKPVVSG	(SEQ ID NO:652)
IVYKPVVSG	(SEQ ID NO:653)
VYKPVVSG	(SEQ ID NO:654)
YKPVVSG	(SEQ ID NO:655)
KPVVSG	(SEQ ID NO:656)
IVYKPVVSGD	(SEQ ID NO:657)
VYKPVVSGD	(SEQ ID NO:658)
YKPVVSGD	(SEQ ID NO:659)
KPVVSGD	(SEQ ID NO:660)
VYKPVVSGDT	(SEQ ID NO:661)
YKPVVSGDT	(SEQ ID NO:662)
KPVVSGDT	(SEQ ID NO:663)
YKPVVSGDTS	(SEQ ID NO:664)
KPVVSGDTS	(SEQ ID NO:665)
PVVSGDTS	(SEQ ID NO:666)
VVSGDTS	(SEQ ID NO:667)

KPVVSGDTSP	(SEQ ID NO:668)
CNIK	(SEQ ID NO:669)
CNIKH	(SEQ ID NO:670)
CNIKHV	(SEQ ID NO:671)
CNIKHVPGG	(SEQ ID NO:672)
CNIKHVPGGG	(SEQ ID NO:673)
CNIKHVPGGGS	(SEQ ID NO:674)
ENLKHQPGGG	(SEQ ID NO:675)
NLKHQPGGG	(SEQ ID NO:676)
LKHQPGGG	(SEQ ID NO:677)
KHQPGGG	(SEQ ID NO:678)
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QPGGG	(SEQ ID NO:680)
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LKHQPGG	(SEQ ID NO:684)
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HQPGG	(SEQ ID NO:686)
QPGG	(SEQ ID NO:687)
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NLKHQPG	(SEQ ID NO:690)
LKHQPG	(SEQ ID NO:691)
KHQPG	(SEQ ID NO:692)
HQPG	(SEQ ID NO:693)
QPG	(SEQ ID NO:694)
TENLKHQP	(SEQ ID NO:695)
ENLKHQP	(SEQ ID NO:696)
NLKHQP	(SEQ ID NO:697)
LKHQP	(SEQ ID NO:698)
KHQP	(SEQ ID NO:699)
HQP	(SEQ ID NO:700)
TENLKHQ	(SEQ ID NO:701)
ENLKHQ	(SEQ ID NO:702)
NLKHQ	(SEQ ID NO:703)
LKHQ	(SEQ ID NO:704)
KHQ	(SEQ ID NO:705)
TENLKH	(SEQ ID NO:706)
ENLKH	(SEQ ID NO:707)
NLKH	(SEQ ID NO:708)
LKH	(SEQ ID NO:709)
TENLK	(SEQ ID NO:710)
ENLK	(SEQ ID NO:711)
NLK	(SEQ ID NO:712)
TENL	(SEQ ID NO:713)
ENL	(SEQ ID NO:714)
TEN	(SEQ ID NO:715)
KDNIKHVPGGG	(SEQ ID NO:716)
KDNI	(SEQ ID NO:717)
KDN	(SEQ ID NO:718)

IKHVGGG	(SEQ ID NO:719)
IKHVGG	(SEQ ID NO:720)
IKHVG	(SEQ ID NO:721)
KHVGGG	(SEQ ID NO:722)
KHVGG	(SEQ ID NO:723)
KHVG	(SEQ ID NO:724)
LGNIHHKPGGG	(SEQ ID NO:725)
GNIHHKPGGG	(SEQ ID NO:726)
NIHHKPGGG	(SEQ ID NO:727)
IHHKPGGG	(SEQ ID NO:728)
HHKPGGG	(SEQ ID NO:729)
KPGGG	(SEQ ID NO:730)
LGNIHHKPGG	(SEQ ID NO:731)
GNIHHKPGG	(SEQ ID NO:732)
NIHHKPGG	(SEQ ID NO:733)
IHHKPGG	(SEQ ID NO:734)
HHKPGG	(SEQ ID NO:735)
KPGG	(SEQ ID NO:736)
LGNIHHKPG	(SEQ ID NO:737)
GNIHHKPG	(SEQ ID NO:738)
NIHHKPG	(SEQ ID NO:739)
IHHKPG	(SEQ ID NO:740)
HHKPG	(SEQ ID NO:741)
HKPG	(SEQ ID NO:742)
KPG	(SEQ ID NO:743)
LGNIHHKP	(SEQ ID NO:744)
GNIHHKP	(SEQ ID NO:745)
NIHHKP	(SEQ ID NO:746)
IHHKP	(SEQ ID NO:747)
HHKP	(SEQ ID NO:748)
HKP	(SEQ ID NO:749)
LGNIHHK	(SEQ ID NO:750)
GNIHHK	(SEQ ID NO:751)
NIHHK	(SEQ ID NO:752)
IHHK	(SEQ ID NO:753)
HHK	(SEQ ID NO:754)
LGNIHH	(SEQ ID NO:755)
GNIHH	(SEQ ID NO:756)
NIHH	(SEQ ID NO:757)
IHH	(SEQ ID NO:758)
LGNIH	(SEQ ID NO:759)
GNIH	(SEQ ID NO:760)
NIH	(SEQ ID NO:761)
LGNI	(SEQ ID NO:762)
GNI	(SEQ ID NO:763)
LGN	(SEQ ID NO:764)
LDNITHVPGGG	(SEQ ID NO:765)
DNITHVPGGG	(SEQ ID NO:766)
NITHVPGGG	(SEQ ID NO:767)
ITHVPGGG	(SEQ ID NO:768)
THVPGGG	(SEQ ID NO:769)

LDNITHVPGG	(SEQ ID NO:770)
DNITHVPGG	(SEQ ID NO:771)
NITHVPGG	(SEQ ID NO:772)
ITHVPGG	(SEQ ID NO:773)
THVPGG	(SEQ ID NO:774)
LDNITHVPG	(SEQ ID NO:775)
DNITHVPG	(SEQ ID NO:776)
NITHVPG	(SEQ ID NO:777)
ITHVPG	(SEQ ID NO:778)
THVPG	(SEQ ID NO:779)
LDNITHVP	(SEQ ID NO:780)
DNITHVP	(SEQ ID NO:781)
NITHVP	(SEQ ID NO:782)
ITHVP	(SEQ ID NO:783)
THVP	(SEQ ID NO:784)
LDNITHV	(SEQ ID NO:785)
DNITHV	(SEQ ID NO:786)
NITHV	(SEQ ID NO:787)
ITHV	(SEQ ID NO:788)
THV	(SEQ ID NO:789)
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DNITH	(SEQ ID NO:791)
NITH	(SEQ ID NO:792)
ITH	(SEQ ID NO:793)
LDNIT	(SEQ ID NO:794)
DNIT	(SEQ ID NO:795)
NIT	(SEQ ID NO:796)
LDNI	(SEQ ID NO:797)
LDN	(SEQ ID NO:798)
KNVKSIGST	(SEQ ID NO:799)
NVKSIGST	(SEQ ID NO:800)
VKSIGST	(SEQ ID NO:801)
KSIGST	(SEQ ID NO:802)
SKIGST	(SEQ ID NO:803)
KIGST	(SEQ ID NO:804)
IGST	(SEQ ID NO:805)
GST	(SEQ ID NO:806)
NVKSIGSTE	(SEQ ID NO:807)
VKSIGSTE	(SEQ ID NO:808)
KSIGSTE	(SEQ ID NO:809)
SKIGSTE	(SEQ ID NO:810)
KIGSTE	(SEQ ID NO:811)
IGSTE	(SEQ ID NO:812)
GSTE	(SEQ ID NO:813)
STE	(SEQ ID NO:814)
VKSIGSTEN	(SEQ ID NO:815)
KSIGSTEN	(SEQ ID NO:816)
SKIGSTEN	(SEQ ID NO:817)
KIGSTEN	(SEQ ID NO:818)
IGSTEN	(SEQ ID NO:819)
GSTEN	(SEQ ID NO:820)

STEN	(SEQ ID NO:821)
KSKIGSTENL	(SEQ ID NO:822)
SKIGSTENL	(SEQ ID NO:823)
KIGSTENL	(SEQ ID NO:824)
IGSTENL	(SEQ ID NO:825)
GSTENL	(SEQ ID NO:826)
STENL	(SEQ ID NO:827)
SKIGSTENLK	(SEQ ID NO:828)
KIGSTENLK	(SEQ ID NO:829)
IGSTENLK	(SEQ ID NO:830)
GSTENLK	(SEQ ID NO:831)
STENLK	(SEQ ID NO:832)
KIGSTENLKH	(SEQ ID NO:833)
IGSTENLKH	(SEQ ID NO:834)
GSTENLKH	(SEQ ID NO:835)
STENLKH	(SEQ ID NO:836)
IGSTENLKHQ	(SEQ ID NO:837)
GSTENLKHQ	(SEQ ID NO:838)
STENLKHQ	(SEQ ID NO:839)
GSTENLKHQP	(SEQ ID NO:840)
STENLKHQP	(SEQ ID NO:841)
STENLKHQPG	(SEQ ID NO:842)
SNVQSKCGSK	(SEQ ID NO:843)
NVQSKCGSK	(SEQ ID NO:844)
VQSKCGSK	(SEQ ID NO:845)
QSKCGSK	(SEQ ID NO:846)
SKCGSK	(SEQ ID NO:847)
KCGSK	(SEQ ID NO:848)
CGSK	(SEQ ID NO:849)
GSK	(SEQ ID NO:850)
NVQSKCGSKD	(SEQ ID NO:851)
VQSKCGSKD	(SEQ ID NO:852)
QSKCGSKD	(SEQ ID NO:853)
SKCGSKD	(SEQ ID NO:854)
KCGSKD	(SEQ ID NO:855)
CGSKD	(SEQ ID NO:856)
GSKD	(SEQ ID NO:857)
SKD	(SEQ ID NO:858)
VQSKCGSKDN	(SEQ ID NO:859)
QSKCGSKDN	(SEQ ID NO:860)
SKCGSKDN	(SEQ ID NO:861)
KCGSKDN	(SEQ ID NO:862)
CGSKDN	(SEQ ID NO:863)
GSKDN	(SEQ ID NO:864)
SKDN	(SEQ ID NO:865)
QSKCGSKDNI	(SEQ ID NO:866)
SKCGSKDNI	(SEQ ID NO:867)
KCGSKDNI	(SEQ ID NO:868)
CGSKDNI	(SEQ ID NO:869)
GSKDNI	(SEQ ID NO:870)
SKDNI	(SEQ ID NO:871)

SKVTSKCGSL	(SEQ ID NO:872)
KVTSKCGSL	(SEQ ID NO:873)
VTSKCGSL	(SEQ ID NO:874)
TSKCGSL	(SEQ ID NO:875)
SKCGSL	(SEQ ID NO:876)
KCGSL	(SEQ ID NO:877)
CGSL	(SEQ ID NO:878)
GSL	(SEQ ID NO:879)
KVTSKCGSLG	(SEQ ID NO:880)
VTSKCGSLG	(SEQ ID NO:881)
TSKCGSLG	(SEQ ID NO:882)
SKCGSLG	(SEQ ID NO:883)
KCGSLG	(SEQ ID NO:884)
CGSLG	(SEQ ID NO:885)
GSLG	(SEQ ID NO:886)
SLG	(SEQ ID NO:887)
VTSKCGSLGN	(SEQ ID NO:888)
TSKCGSLGN	(SEQ ID NO:889)
SKCGSLGN	(SEQ ID NO:890)
KCGSLGN	(SEQ ID NO:891)
CGSLGN	(SEQ ID NO:892)
GSLGN	(SEQ ID NO:893)
SLGN	(SEQ ID NO:894)
TSKCGSLGNI	(SEQ ID NO:895)
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KCGSLGNI	(SEQ ID NO:897)
CGSLGNI	(SEQ ID NO:898)
GSLGNI	(SEQ ID NO:899)
SLGNI	(SEQ ID NO:900)
SKCGSLGNIH	(SEQ ID NO:901)
KCGSLGNIH	(SEQ ID NO:902)
CGSLGNIH	(SEQ ID NO:903)
GSLGNIH	(SEQ ID NO:904)
SLGNIH	(SEQ ID NO:905)
KCGSLGNIHH	(SEQ ID NO:906)
CGSLGNIHH	(SEQ ID NO:907)
GSLGNIHH	(SEQ ID NO:908)
SLGNIHH	(SEQ ID NO:909)
CGSLGNIHHK	(SEQ ID NO:910)
GSLGNIHHK	(SEQ ID NO:911)
SLGNIHHK	(SEQ ID NO:912)
GSLGNIHHKP	(SEQ ID NO:913)
SLGNIHHKP	(SEQ ID NO:914)
SLGNIHHKPG	(SEQ ID NO:915)
DRVQSKIGSL	(SEQ ID NO:916)
RVQSKIGSL	(SEQ ID NO:917)
VQSKIGSL	(SEQ ID NO:918)
QSKIGSL	(SEQ ID NO:919)
SKIGSL	(SEQ ID NO:920)
KIGSL	(SEQ ID NO:921)

IGSL	(SEQ ID NO:922)
RVQSKIGSLD	(SEQ ID NO:923)
VQSKIGSLD	(SEQ ID NO:924)
QSKIGSLD	(SEQ ID NO:925)
SKIGSLD	(SEQ ID NO:926)
KIGSLD	(SEQ ID NO:927)
IGSLD	(SEQ ID NO:928)
GSLD	(SEQ ID NO:929)
SLD	(SEQ ID NO:930)
VQSKIGSLDN	(SEQ ID NO:931)
QSKIGSLDN	(SEQ ID NO:932)
SKIGSLDN	(SEQ ID NO:933)
KIGSLDN	(SEQ ID NO:934)
IGSLDN	(SEQ ID NO:935)
GSLDN	(SEQ ID NO:936)
SLDN	(SEQ ID NO:937)
QSKIGSLDNI	(SEQ ID NO:938)
SKIGSLDNI	(SEQ ID NO:939)
KIGSLDNI	(SEQ ID NO:940)
IGSLDNI	(SEQ ID NO:941)
GSLDNI	(SEQ ID NO:942)
SKIGSLDNIT	(SEQ ID NO:943)
KIGSLDNIT	(SEQ ID NO:944)
IGSLDNIT	(SEQ ID NO:945)
GSLDNIT	(SEQ ID NO:946)
SLDNIT	(SEQ ID NO:947)
KIGSLDNITH	(SEQ ID NO:948)
IGSLDNITH	(SEQ ID NO:949)
GSLDNITH	(SEQ ID NO:950)
SLDNITH	(SEQ ID NO:951)
IGSLDNITHV	(SEQ ID NO:952)
GSLDNITHV	(SEQ ID NO:953)
SLDNITHV	(SEQ ID NO:954)
GSLDNITHVP	(SEQ ID NO:955)
SLDNITHVP	(SEQ ID NO:956)
SLDNITHVPG	(SEQ ID NO:957)
PDLKNVKS	(SEQ ID NO:958)
DLKNVKS	(SEQ ID NO:959)
LKNVSKI	(SEQ ID NO:960)
KNVSKIG	(SEQ ID NO:961)
NVSKIGS	(SEQ ID NO:962)
DLSNVQSK	(SEQ ID NO:963)
LSNVQSKC	(SEQ ID NO:964)
SNVQSKCG	(SEQ ID NO:965)
NVQSKCGS	(SEQ ID NO:966)
VDLSKVTS	(SEQ ID NO:967)
DLSKVTSK	(SEQ ID NO:968)
LSKVTSKC	(SEQ ID NO:969)
SKVTSKCG	(SEQ ID NO:970)
KVTSKCGS	(SEQ ID NO:971)
LDFKDRVQ	(SEQ ID NO:972)

DFKDRVQS (SEQ ID NO:973)
 FKDRVQSK (SEQ ID NO:974)
 KDRVQSKI (SEQ ID NO:975)
 DRVQSKIG (SEQ ID NO:976)
 RVQSKIGS (SEQ ID NO:977)
 SKIGSTENLKH (SEQ ID NO:978)
 SKIGSTENIKH (SEQ ID NO:979)
 SKIGSKDNLKH (SEQ ID NO:980)
 SKIGSKENIKH (SEQ ID NO:981)
 SKIGSLENLKH (SEQ ID NO:982)
 SKIGSLENIKH (SEQ ID NO:983)
 SKIGSTDNLKH (SEQ ID NO:984)
 SKIGSTDNIKH (SEQ ID NO:985)
 SKIGSKDNIKH (SEQ ID NO:986)
 SKIGSLDNLKH (SEQ ID NO:987)
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 SKIGSTGNIKH (SEQ ID NO:990)
 SKIGSKGNLKH (SEQ ID NO:991)
 SKIGSKGNIKH (SEQ ID NO:992)
 SKIGSLGNLKH (SEQ ID NO:993)
 SKIGSLGNIKH (SEQ ID NO:994)

Lys Xaa₁ Xaa₂ Ser Xaa₃ Xaa₄ Asn Xaa₅ Xaa₆ His (SEQ ID NO:995), wherein

Xaa₁ is I or C;
 Xaa₂ is G;
 Xaa₃ is T, K or L;
 Xaa₄ is E, D or G;
 Xaa₅ is L or I;
 Xaa₆ is K, H or T.

(Q/E) IVYK(S/P)

(SEQ ID NO: 996)

alpha-synuclein isoform NACP140 [*Homo sapiens*] (SEQ ID NO:58)

NCBI Reference Sequence: NP_000336.1

1 MDVFMKGLSK AKEGVVAAAE KTKQGVAAEA GKTKEGVLYV GSKTKEGVVH GVATVAEKT
 61 EQVTNVGGAV VTGVTAVAQK TVEGAGSIAA ATGFVKKDQL GKNEEGAPQE GILEDMPVDP
 121 DNEAYEMPSE EGYQDYEPEA

VDPDNEAYEM (SEQ ID NO:59)
 VDPDNEAYE (SEQ ID NO:60)
 VDPDNEAY (SEQ ID NO:61)
 VDPDNEA (SEQ ID NO:62)
 VDPDNE (SEQ ID NO:63)
 VDPDN (SEQ ID NO:64)
 VDPD (SEQ ID NO:65)
 VDP (SEQ ID NO:66)
 DPDNEAYEM (SEQ ID NO:67)
 DPDNEAYE (SEQ ID NO:68)

DPDNEAY	(SEQ ID NO:69)
DPDNEA	(SEQ ID NO:70)
DPDNE	(SEQ ID NO:71)
DPDN	(SEQ ID NO:72)
DPD	(SEQ ID NO:73)
PDNEAYEM	(SEQ ID NO:74)
PDNEAYE	(SEQ ID NO:75)
PDNEAY	(SEQ ID NO:76)
PDNEA	(SEQ ID NO:77)
PDNE	(SEQ ID NO:78)
PDN	(SEQ ID NO:79)
DNEAYEM	(SEQ ID NO:80)
DNEAYE	(SEQ ID NO:81)
DNEAY	(SEQ ID NO:82)
DNEA	(SEQ ID NO:83)
DNE	(SEQ ID NO:84)
NEAYEM	(SEQ ID NO:85)
NEAYE	(SEQ ID NO:86)
NEAY	(SEQ ID NO:87)
NEA	(SEQ ID NO:88)
EAYEM	(SEQ ID NO:89)
EAYE	(SEQ ID NO:90)
EAY	(SEQ ID NO:91)
AYEM	(SEQ ID NO:92)
AYE	(SEQ ID NO:93)
YEM	(SEQ ID NO:94)
ATGFVKKDQL	(SEQ ID NO:95)
ATGFVKKDQ	(SEQ ID NO:96)
ATGFVKKD	(SEQ ID NO:97)
ATGFVKK	(SEQ ID NO:98)
ATGFVK	(SEQ ID NO:99)
ATGFV	(SEQ ID NO:100)
ATGF	(SEQ ID NO:101)
ATG	(SEQ ID NO:102)
TGFVKKDQL	(SEQ ID NO:103)
TGFVKKDQ	(SEQ ID NO:104)
TGFVKKD	(SEQ ID NO:105)
TGFVKK	(SEQ ID NO:106)
TGFVK	(SEQ ID NO:107)
TGFV	(SEQ ID NO:108)
TGF	(SEQ ID NO:109)
GFVKKDQL	(SEQ ID NO:110)
GFVKKDQ	(SEQ ID NO:111)
GFVKKD	(SEQ ID NO:112)
GFVKK	(SEQ ID NO:113)
GFVK	(SEQ ID NO:114)
GFV	(SEQ ID NO:115)
FVKKDQL	(SEQ ID NO:116)
FVKKDQ	(SEQ ID NO:117)
FVKKD	(SEQ ID NO:118)
FVKK	(SEQ ID NO:119)

FVK (SEQ ID NO:120)
 VKKDQL (SEQ ID NO:121)
 VKKDQ (SEQ ID NO:122)
 VKKD (SEQ ID NO:123)
 VKK (SEQ ID NO:124)
 KKDQL (SEQ ID NO:125)
 KKDQ (SEQ ID NO:126)
 KKD (SEQ ID NO:127)
 KDQL (SEQ ID NO:128)
 KDQ (SEQ ID NO:129)

DAEFRHRRPDNEAYERRQIVYKPVKKC (SEQ ID NO:130)
 DAEFRHRRQIVYKPVRRPDNEAYEKKC (SEQ ID NO:131)
 DAEFRHRRPDNEAYERRNIKHVPKKC (SEQ ID NO:132)
 DAEFRHRRNIKHVPGRPDNEAYEKKC (SEQ ID NO:133)
 DAEFRHRRQIVYKPVRRPDNEAYERRNIKHVPGGC (SEQ ID NO:134)
 DAEFRHRRDPDNEAYRRNIKHVPGRQIVYKPVGGC (SEQ ID NO:135)
 EFRHDSGRRQIVYKPVRRPDNEAYERRNIKHVPGGC (SEQ ID NO:136)
 EFRHDSGRRDPDNEAYRRNIKHVPGRQIVYKPVGGC (SEQ ID NO:137)

DAEFRHRRDPDNEAYERRENKHPGGGC (SEQ ID NO:1058)
 DAEFRHRRRENKHPGRDPDNEAYEGGC (SEQ ID NO:1059)
 DAEFRHRRPDNEAYERRENKHPGGGC (SEQ ID NO:1060)
 DAEFRHRRRENKHPGRPDNEAYEGGC (SEQ ID NO:1061)
 DAEFRHRRSKIGSKDNIKHRRDPDNEAYEGGC (SEQ ID NO:1062)
 DAEFRHRRDPDNEAYERRSKIGSKDNIKHGGC (SEQ ID NO:1063)

Arg-Val-Arg-Arg (RVRR; SEQ ID NO:138)
 Gly-Ala-Gly-Ala (GAGA; SEQ ID NO:139)
 Ala-Gly-Ala-Gly (AGAG; SEQ ID NO:140)
 Lys-Gly-Lys-Gly (KGKG; SEQ ID NO:141)

AEFRHDSGC (SEQ ID NO:142)
 DAEFRHDC (SEQ ID NO:143)
 CPDNEAYE (SEQ ID NO:144)
 DPDNEAYC (SEQ ID NO:145)

GGGS (SEQ ID NO:1064)
 GGGGS (SEQ ID NO:1065)

WHAT IS CLAIMED IS:

1. A polypeptide comprising:

- (a) a first peptide comprising 3-10 amino acids from residues 1-10 or 12-25 of SEQ ID NO:01;
 - (b) a second peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:02; and
 - (c) a third peptide comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58;
- wherein the first peptide, second peptide and third peptide are arranged in any order in the polypeptide.

2. The polypeptide of claim 1, further comprising a fourth peptide selected from one of:

- (a) a peptide comprising 3-10 amino acids from residues 1-10 or 12-25 of SEQ ID NO:01;
 - (b) a peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:02; and
 - (c) a peptide comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58;
- wherein the first peptide, second peptide, third peptide, and fourth peptide are arranged in any order in the polypeptide.

3. The polypeptide of claim 1 or claim 2, wherein the second peptide is from the microtubule binding region (MTBR) of tau (residues 244-372 of SEQ ID NO:02).

4. The polypeptide of any of claims 1 to 3, wherein:

- (a) the first peptide comprises an amino acid sequence selected from the group consisting of
 - DAEFRHDSGY (SEQ ID NO:03),
 - DAEFRHDSG (SEQ ID NO:04),
 - DAEFRHDS (SEQ ID NO:05),
 - DAEFRHD (SEQ ID NO:06),

DAEFRH (SEQ ID NO:07),
DAEFR (SEQ ID NO:08),
DAEF (SEQ ID NO:09),
DAE (SEQ ID NO:10),
AEFRHDSGY (SEQ ID NO:11),
AEFRHDSG (SEQ ID NO:12),
AEFRHDS (SEQ ID NO:13),
AEFRHD (SEQ ID NO:14),
AEFRH (SEQ ID NO:15),
AEFR (SEQ ID NO:16),
AEF (SEQ ID NO:17),
EFRHDSGY (SEQ ID NO:18),
EFRHDSG (SEQ ID NO:19),
EFRHDS (SEQ ID NO:20),
EFRHD (SEQ ID NO:21),
EFRH (SEQ ID NO:22),
EFR (SEQ ID NO:23),
FRHDSGY (SEQ ID NO:24),
FRHDSG (SEQ ID NO:25),
FRHDS (SEQ ID NO:26),
FRHD (SEQ ID NO:27),
FRH (SEQ ID NO:28),
RHDSGY (SEQ ID NO:29),
RHDSG (SEQ ID NO:30),
RHDS (SEQ ID NO:31),
RHD (SEQ ID NO:32),
HDSGY (SEQ ID NO:33),
HDSG (SEQ ID NO:34),
HDS (SEQ ID NO:35),
DSGY (SEQ ID NO:36),
DSG (SEQ ID NO:37),
SGY (SEQ ID NO:38),
VHHQKLVFFA (SEQ ID NO:1002),
VHHQKLVFF (SEQ ID NO:1003),

VHHQKLVF (SEQ ID NO:1004),
VHHQKLV (SEQ ID NO:1005),
VHHQKL (SEQ ID NO:1006),
HHQKLVFFAE (SEQ ID NO:1007),
HHQKLVFFA (SEQ ID NO:1008),
HHQKLVFF (SEQ ID NO:1009),
HHQKLVF (SEQ ID NO:1010),
HHQKLV (SEQ ID NO:1011),
HHQKL (SEQ ID NO:1012),
HQKLVFFAED (SEQ ID NO:1013),
HQKLVFFAE (SEQ ID NO:1014),
HQKLVFFA (SEQ ID NO:1015),
HQKLVFF (SEQ ID NO:1016),
HQKLVF (SEQ ID NO:1017),
HQKLV (SEQ ID NO:1018),
HQKL (SEQ ID NO:1019),
QKLVFFAEDV (SEQ ID NO:1020),
QKLVFFAED (SEQ ID NO:1021),
QKLVFFAE (SEQ ID NO:1022),
QKLVFFA (SEQ ID NO:1023),
QKLVFF (SEQ ID NO:1024),
QKLVF (SEQ ID NO:1025),
QKLV (SEQ ID NO:1026),
QKL (SEQ ID NO:1027),
KLVFFAEDVG (SEQ ID NO:1028),
KLVFFAEDV (SEQ ID NO:1029),
KLVFFAED (SEQ ID NO:1030),
KLVFFAE (SEQ ID NO:1031),
KLVFFA (SEQ ID NO:1032),
KLVFF (SEQ ID NO:1033),
KLVF (SEQ ID NO:1034),
KLV (SEQ ID NO:1035),
LVFFAEDVG (SEQ ID NO:1036),
LVFFAEDV (SEQ ID NO:1037),

LVFFAED (SEQ ID NO:1038),
LVFFAE (SEQ ID NO:1039),
LVFFA (SEQ ID NO:1040),
LVFF (SEQ ID NO:1041),
LVF (SEQ ID NO:1042),
VFFAEDVG (SEQ ID NO:1043),
VFFAEDV (SEQ ID NO:1044),
VFFAED (SEQ ID NO:1045),
VFFAE (SEQ ID NO:1046),
VFFA (SEQ ID NO:1047),
VFF (SEQ ID NO:1048),
FFAEDVG (SEQ ID NO:1049),
FFAEDV (SEQ ID NO:1050),
FFAED (SEQ ID NO:1051),
FFAE (SEQ ID NO:1052),
FFA (SEQ ID NO:1053),
FAEDVG (SEQ ID NO:1054),
FAEDV (SEQ ID NO:1055),
FAED (SEQ ID NO:1056), and
FAE (SEQ ID NO:1057);

(b) the second peptide comprises an amino acid sequence selected from the group consisting of

QIVYKPV (SEQ ID NO:39),
QIVYKP (SEQ ID NO:40),
QIVYKSV (SEQ ID NO:41),
EIVYKSV (SEQ ID NO:42),
QIVYKS (SEQ ID NO:997),
EIVYKSP (SEQ ID NO:43),
EIVYKS (SEQ ID NO:998),
EIVYKPV (SEQ ID NO:44),
EIVYKP (SEQ ID NO:999),
IVYKSPV (SEQ ID NO:45),
IVYK (SEQ ID NO:46),
CNIKHVPG (SEQ ID NO:1000),

CNIKHVP (SEQ ID NO:47),
NIKHVP (SEQ ID NO:48),
HVPGGG (SEQ ID NO:49),
HVPGG (SEQ ID NO:50),
HKPGGG (SEQ ID NO:51),
HKPGG (SEQ ID NO:52),
KHVPGGG (SEQ ID NO:53),
KHVPGG (SEQ ID NO:54),
HQPGGG (SEQ ID NO:55),
HQPGG (SEQ ID NO:56),
NIKHVPG (SEQ ID NO:57), and
SEQ ID NOs: 146-996; and

(c) the third peptide comprises an amino acid sequence selected from the group consisting of

VDPDNEAYEM (SEQ ID NO:59),
VDPDNEAYE (SEQ ID NO:60),
VDPDNEAY (SEQ ID NO:61),
VDPDNEA (SEQ ID NO:62),
VDPDNE (SEQ ID NO:63),
VDPDN (SEQ ID NO:64),
VDPD (SEQ ID NO:65),
VDP (SEQ ID NO:66),
DPDNEAYEM (SEQ ID NO:67),
DPDNEAYE (SEQ ID NO:68),
DPDNEAY (SEQ ID NO:69),
DPDNEA (SEQ ID NO:70),
DPDNE (SEQ ID NO:71),
DPDN (SEQ ID NO:72),
DPD (SEQ ID NO:73),
PDNEAYEM (SEQ ID NO:74),
PDNEAYE (SEQ ID NO:75),
PDNEAY (SEQ ID NO:76),
PDNEA (SEQ ID NO:77),
PDNE (SEQ ID NO:78),

PDN (SEQ ID NO:79),
DNEAYEM (SEQ ID NO:80),
DNEAYE (SEQ ID NO:81),
DNEAY (SEQ ID NO:82),
DNEA (SEQ ID NO:83),
DNE (SEQ ID NO:84),
NEAYEM (SEQ ID NO:85),
NEAYE (SEQ ID NO:86),
NEAY (SEQ ID NO:87),
NEA (SEQ ID NO:88),
EAYEM (SEQ ID NO:89),
EAYE (SEQ ID NO:90),
EAY (SEQ ID NO:91),
AYEM (SEQ ID NO:92),
AYE (SEQ ID NO:93),
YEM (SEQ ID NO:94),
ATGFVKKDQL (SEQ ID NO:95),
ATGFVKKDQ (SEQ ID NO:96),
ATGFVKKD (SEQ ID NO:97),
ATGFVKK (SEQ ID NO:98),
ATGFVK (SEQ ID NO:99),
ATGFV (SEQ ID NO:100),
ATGF (SEQ ID NO:101),
ATG (SEQ ID NO:102),
TGFVKKDQL (SEQ ID NO:103),
TGFVKKDQ (SEQ ID NO:104),
TGFVKKD (SEQ ID NO:105),
TGFVKK (SEQ ID NO:106),
TGFVK (SEQ ID NO:107),
TGFV (SEQ ID NO:108),
TGF (SEQ ID NO:109),
GFVKKDQL (SEQ ID NO:110),
GFVKKDQ (SEQ ID NO:111),
GFVKKD (SEQ ID NO:112),

GFVKK (SEQ ID NO:113),
GFVK (SEQ ID NO:114),
GFV (SEQ ID NO:115),
FVKKDQL (SEQ ID NO:116),
FVKKDQ (SEQ ID NO:117),
FVKKD (SEQ ID NO:118),
FVKK (SEQ ID NO:119),
FVK (SEQ ID NO:120),
VKKDQL (SEQ ID NO:121),
VKKDQ (SEQ ID NO:122),
VKKD (SEQ ID NO:123),
VKK (SEQ ID NO:124),
KKDQL (SEQ ID NO:125),
KKDQ (SEQ ID NO:126),
KKD (SEQ ID NO:127),
KDQL (SEQ ID NO:128), and
KDQ (SEQ ID NO:129); and

(d) the fourth peptide, if present, is one of any one of the amino acid sequences of SEQ ID NO: 3-38, 1002-1057, 39-57, 142-1000, and 59-129.

5. The polypeptide of any of claims 1 to 4, wherein two or more of the first peptide, the second peptide, and the third peptide, and the fourth peptide, if present, are each linked by a cleavable linker.

6. The polypeptide of claim 5, wherein each of the cleavable linkers comprise an amino acid sequence.

7. The polypeptide of claim 6, wherein the amino acid sequence of each cleavable linker is independently selected from the group consisting of: arginine-arginine (Arg-Arg), arginine-valine-arginine-arginine (Arg-Val-Arg-Arg; SEQ ID NO:138), valine-citrulline (Val-Cit), valine-arginine (Val-Arg), valine-lysine (Val-Lys), valine-alanine (Val-Ala), phenylalanine-lysine (Phe-Lys), glycine-alanine-glycine-alanine (Gly-Ala-Gly-Ala; SEQ ID NO:139), alanine-glycine-alanine-glycine (Ala-Gly-Ala-Gly; SEQ ID NO:140), and lysine-glycine-lysine-glycine (Lys-Gly-Lys-Gly; SEQ ID NO:141).

8. The polypeptide of any of claims 1 to 7, further comprising a linker to a carrier at either a C-terminal portion of the polypeptide, or a N-terminal portion of the polypeptide.
9. The polypeptide of claim 8, wherein the linker to a carrier comprises an amino acid sequence selected from the group consisting of GG, GGG, AA, AAA, KK, KKK, SS, SSS, GAGA (SEQ ID NO:139), AGAG (SEQ ID NO:140), and KGKG (SEQ ID NO:141).
10. The polypeptide of any of claims 1 to 9, wherein the polypeptide or linker to the carrier, if present, further comprises a C-terminal cysteine (C).
11. The polypeptide of any of claims 1 to 10, wherein the polypeptide further comprises a blocked amine at the N-terminus.
12. The polypeptide of any of claims 2 to 11, wherein any of the first peptide, second peptide, third peptide, or fourth peptide comprises 5-10 amino acids.
13. The polypeptide of any of claims 1 to 12, wherein the first peptide is DAEFRHD (SEQ ID NO:06).
14. The polypeptide of any of claims 1 to 12, wherein the first peptide is EFRHDSG (SEQ ID NO:19).
15. The polypeptide of any of claims 1 to 12, wherein the second peptide comprises the amino acid sequence QIVYKPV (SEQ ID NO:39).
16. The polypeptide of any of claims 1 to 12, wherein the second peptide comprises the amino acid sequence NIKHVPG (SEQ ID NO:57).
17. The polypeptide of any of claims 1 to 12, wherein the third peptide comprises the amino acid sequence PDNEAYE (SEQ ID NO:75).

18. The polypeptide of any of claims 1 to 12, wherein the third peptide comprises the amino acid sequence DPDNEAY (SEQ ID NO:69).

19. The polypeptide of any of claims 1 to 12, wherein the fourth peptide comprises the amino acid sequence NIKHVP (SEQ ID NO:48).

20. The polypeptide of any of claims 1 to 12, wherein the fourth peptide comprises the amino acid sequence QIVYKPV (SEQ ID NO:39).

21. The polypeptide of claim 1, comprising an amino acid sequence of:

DAEFRHDDRRPDNEAYERRQIVYKPVKKC (SEQ ID NO:130);
DAEFRHDDRRQIVYKPVRRPDNEAYEKKC (SEQ ID NO:131);
DAEFRHDDRRPDNEAYERRNIKHVPGKKC (SEQ ID NO:132).
DAEFRHDDRRNIKHVPGRRPDNEAYEKKC (SEQ ID NO:133);
DAEFRHDDRRDPNEAYERRENKHKQPGGGC (SEQ ID NO:1058);
DAEFRHDDRRRENKHKQPGRRDPNEAYEGGC (SEQ ID NO:1059);
DAEFRHDDRRPDNEAYERRENKHKQPGGGC (SEQ ID NO:1060);
DAEFRHDDRRRENKHKQPGRRPDNEAYEGGC (SEQ ID NO:1061);
DAEFRHDDRRSKIGSKDNIKHRRDPNEAYEGGC (SEQ ID NO:1062); or
DAEFRHDDRRDPNEAYERRSKIGSKDNIKHGGC (SEQ ID NO:1063).

22. The polypeptide of claim 2, comprising an amino acid sequence of:

DAEFRHDDRRQIVYKPVRRPDNEAYERRNIKHVPGGC
(SEQ ID NO:134);
DAEFRHDDRRDPNEAYRRNIKHVPGRRQIVYKPVGGC
(SEQ ID NO:135);
EFRHDSGRRQIVYKPVRRPDNEAYERRNIKHVPGGC
(SEQ ID NO:136); or
EFRHDSGRRDPNEAYRRNIKHVPGRRQIVYKPVGGC
(SEQ ID NO:137).

23. The polypeptide of claim 22, wherein the polypeptide is
EFRHDSGRRQIVYKPVRRPDNEAYERRNIKHVPGGC (SEQ ID NO:136), and
further comprises a blocked amine at the N-terminus.

24. The polypeptide of claim 22, wherein the polypeptide is EFRHDSGRRDPDNEAYRRNIKHVPGRRQIVYKPVGGC (SEQ ID NO:137), and further comprising a blocked amine at the N-terminus.

25. An immunotherapy composition, comprising the polypeptide of any of claims 1 to 24, wherein the polypeptide is linked to a carrier.

26. The immunotherapy composition of claim 25, wherein the carrier comprises serum albumins, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid (TT), diphtheria toxoid (DT), a genetically modified cross-reacting material (CRM) of diphtheria toxin, CRM197, meningococcal outer membrane protein complex (OMPC) and *H. influenzae* protein D (HiD), rEPA (*Pseudomonas aeruginosa* exotoxin A), KLH (keyhole limpet hemocyanin), and flagellin.

27. The immunotherapy composition of claim 26, wherein the carrier is CRM197.

28. The immunotherapy composition of claim 26, wherein the carrier is diphtheria toxoid.

29. A pharmaceutical formulation comprising (a) the polypeptide of any one of claims 1 to 24 or the immunotherapy composition of any of claims 25 to 28 and (b) at least one adjuvant.

30. The pharmaceutical formulation of claim 29, wherein the adjuvant is selected from the group consisting of aluminum hydroxide, aluminum phosphate, aluminum sulfate, 3 De-O-acylated monophosphoryl lipid A (MPL), QS-21, TQL1055, QS-18, QS-17, QS-7, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), oil in water emulsions (such as squalene or peanut oil), CpG, polyglutamic acid, polylysine, AddaVax™, MF59®, and combinations thereof.

31. The pharmaceutical formulation of claim 30, wherein the adjuvant is QS-21 or TQL1055.

32. The pharmaceutical formulation of claim 30, wherein the adjuvant is MPL.
33. The pharmaceutical formulation of claim 30, wherein the adjuvant is a combination of MPL and QS-21 or a combination of MPL and TQL1055.
34. The pharmaceutical formulation of any of claims 29 to 33, wherein the adjuvant comprises a liposomal formulation.
35. The pharmaceutical formulation of any of claims 29 to 34, wherein the composition comprises at least one pharmaceutically acceptable diluent.
36. The pharmaceutical formulation of any of claims 29 to 35, comprising a multiple antigen presenting system (MAP).
37. The pharmaceutical formulation of claim 36, wherein the MAP comprises one or more of a Lys-based dendritic scaffold, helper T-cell epitopes, immune stimulating lipophilic moieties, cell penetrating peptides, radical induced polymerization, self-assembling nanoparticles as antigen-presenting platforms and gold nanoparticles.
38. An immunotherapy composition, comprising:
- (a) a first peptide sequence comprising 3-10 amino acid residues from the first ten or 12 to 25 N-terminal residues of SEQ ID NO:01;
 - (b) a second peptide sequence comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:02; and
 - (c) a third peptide sequence comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58.
39. The polypeptide of claim 38, further comprising a fourth peptide sequence selected from one of:
- (a) a peptide comprising 3-10 amino acids from residues 1-10 or 12-25 of SEQ ID NO:01;
 - (b) a peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:02; and

(c) a peptide comprising 3-10 amino acids from residues 81-140 of SEQ ID NO:58.

40. The immunotherapy composition of claim 38 or claim 39, wherein:

(a) the first peptide sequence comprises an amino acid sequence selected from the group consisting of

DAEFRHDSGY (SEQ ID NO:03),
DAEFRHDSG (SEQ ID NO:04),
DAEFRHDS (SEQ ID NO:05),
DAEFRHD (SEQ ID NO:06),
DAEFRH (SEQ ID NO:07),
DAEFR (SEQ ID NO:08),
DAEF (SEQ ID NO:09),
DAE (SEQ ID NO:10),
AEFRHDSGY (SEQ ID NO:11),
AEFRHDSG (SEQ ID NO:12),
AEFRHDS (SEQ ID NO:13),
AEFRHD (SEQ ID NO:14),
AEFRH (SEQ ID NO:15),
AEFR (SEQ ID NO:16),
AEF (SEQ ID NO:17),
EFRHDSGY (SEQ ID NO:18),
EFRHDSG (SEQ ID NO:19),
EFRHDS (SEQ ID NO:20),
EFRHD (SEQ ID NO:21),
EFRH (SEQ ID NO:22),
EFR (SEQ ID NO:23),
FRHDSGY (SEQ ID NO:24),
FRHDSG (SEQ ID NO:25),
FRHDS (SEQ ID NO:26),
FRHD (SEQ ID NO:27),
FRH (SEQ ID NO:28),
RHDSGY (SEQ ID NO:29),
RHDSG (SEQ ID NO:30),

RHDS (SEQ ID NO:31),
RHD (SEQ ID NO:32),
HDSGY (SEQ ID NO:33),
HDSG (SEQ ID NO:34),
HDS (SEQ ID NO:35),
DSGY (SEQ ID NO:36),
DSG (SEQ ID NO:37),
SGY (SEQ ID NO:38),
VHHQKLVFFA (SEQ ID NO:1002),
VHHQKLVFF (SEQ ID NO:1003),
VHHQKLVF (SEQ ID NO:1004),
VHHQKLV (SEQ ID NO:1005),
VHHQKL (SEQ ID NO:1006),
HHQKLVFFAE (SEQ ID NO:1007),
HHQKLVFFA (SEQ ID NO:1008),
HHQKLVFF (SEQ ID NO:1009),
HHQKLVF (SEQ ID NO:1010),
HHQKLV (SEQ ID NO:1011),
HHQKL (SEQ ID NO:1012),
HQKLVFFAED (SEQ ID NO:1013),
HQKLVFFAE (SEQ ID NO:1014),
HQKLVFFA (SEQ ID NO:1015),
HQKLVFF (SEQ ID NO:1016),
HQKLVF (SEQ ID NO:1017),
HQKLV (SEQ ID NO:1018),
HQKL (SEQ ID NO:1019),
QKLVFFAEDV (SEQ ID NO:1020),
QKLVFFAED (SEQ ID NO:1021),
QKLVFFAE (SEQ ID NO:1022),
QKLVFFA (SEQ ID NO:1023),
QKLVFF (SEQ ID NO:1024),
QKLVF (SEQ ID NO:1025),
QKLV (SEQ ID NO:1026),
QKL (SEQ ID NO:1027),

KLVFFAEDVG (SEQ ID NO:1028),
KLVFFAEDV (SEQ ID NO:1029),
KLVFFAED (SEQ ID NO:1030),
KLVFFAE (SEQ ID NO:1031),
KLVFFA (SEQ ID NO:1032),
KLVFF (SEQ ID NO:1033),
KLVF (SEQ ID NO:1034),
KLV (SEQ ID NO:1035),
LVFFAEDVG (SEQ ID NO:1036),
LVFFAEDV (SEQ ID NO:1037),
LVFFAED (SEQ ID NO:1038),
LVFFAE (SEQ ID NO:1039),
LVFFA (SEQ ID NO:1040),
LVFF (SEQ ID NO:1041),
LVF (SEQ ID NO:1042),
VFFAEDVG (SEQ ID NO:1043),
VFFAEDV (SEQ ID NO:1044),
VFFAED (SEQ ID NO:1045),
VFFAE (SEQ ID NO:1046),
VFFA (SEQ ID NO:1047),
VFF (SEQ ID NO:1048),
FFAEDVG (SEQ ID NO:1049),
FFAEDV (SEQ ID NO:1050),
FFAED (SEQ ID NO:1051),
FFAE (SEQ ID NO:1052),
FFA (SEQ ID NO:1053),
FAEDVG (SEQ ID NO:1054),
FAEDV (SEQ ID NO:1055),
FAED (SEQ ID NO:1056), and
FAE (SEQ ID NO:1057);

(b) the second peptide sequence comprises an amino acid sequence
selected from the group consisting of
QIVYKPV (SEQ ID NO:39),
QIVYKP (SEQ ID NO:40),

QIVYKSV (SEQ ID NO:41),
EIVYKSV (SEQ ID NO:42),
QIVYKS (SEQ ID NO:997),
EIVYKSP (SEQ ID NO:43),
EIVYKS (SEQ ID NO:998),
EIVYKPV (SEQ ID NO:44),
EIVYKP (SEQ ID NO:999),
IVYKSPV (SEQ ID NO:45),
IVYK (SEQ ID NO:46),
CNIKHVPG (SEQ ID NO:1000),
CNIKHVP (SEQ ID NO:47),
NIKHVP (SEQ ID NO:48),
HVPGGG (SEQ ID NO:49),
HVPGG (SEQ ID NO:50),
HKPGGG (SEQ ID NO:51),
HKPGG (SEQ ID NO:52),
KHVPGGG (SEQ ID NO:53),
KHVPGG (SEQ ID NO:54),
HQPGGG (SEQ ID NO:55),
HQPGG (SEQ ID NO:56),
NIKHVPG (SEQ ID NO:57), and
SEQ ID NOs: 146-996; and

(c) the third peptide sequence comprises an amino acid sequence selected from the group consisting of

VDPDNEAYEM (SEQ ID NO:59),
VDPDNEAYE (SEQ ID NO:60),
VDPDNEAY (SEQ ID NO:61),
VDPDNEA (SEQ ID NO:62),
VDPDNE (SEQ ID NO:63),
VDPDN (SEQ ID NO:64),
VDPD (SEQ ID NO:65),
VDP (SEQ ID NO:66),
DPDNEAYEM (SEQ ID NO:67),
DPDNEAYE (SEQ ID NO:68),

DPDNEAY (SEQ ID NO:69),
DPDNEA (SEQ ID NO:70),
DPDNE (SEQ ID NO:71),
DPDN (SEQ ID NO:72),
DPD (SEQ ID NO:73),
PDNEAYEM (SEQ ID NO:74),
PDNEAYE (SEQ ID NO:75),
PDNEAY (SEQ ID NO:76),
PDNEA (SEQ ID NO:77),
PDNE (SEQ ID NO:78),
PDN (SEQ ID NO:79),
DNEAYEM (SEQ ID NO:80),
DNEAYE (SEQ ID NO:81),
DNEAY (SEQ ID NO:82),
DNEA (SEQ ID NO:83),
DNE (SEQ ID NO:84),
NEAYEM (SEQ ID NO:85),
NEAYE (SEQ ID NO:86),
NEAY (SEQ ID NO:87),
NEA (SEQ ID NO:88),
EAYEM (SEQ ID NO:89),
EAYE (SEQ ID NO:90),
EAY (SEQ ID NO:91),
AYEM (SEQ ID NO:92),
AYE(SEQ ID NO:93),
YEM (SEQ ID NO:94),
ATGFVKKDQL (SEQ ID NO:95),
ATGFVKKDQ (SEQ ID NO:96),
ATGFVKKD (SEQ ID NO:97),
ATGFVKK (SEQ ID NO:98),
ATGFVK (SEQ ID NO:99),
ATGFV(SEQ ID NO:100),
ATGF (SEQ ID NO:101),
ATG (SEQ ID NO:102),

TGFVKKDQL (SEQ ID NO:103),
TGFVKKDQ (SEQ ID NO:104),
TGFVKKD (SEQ ID NO:105),
TGFVKK (SEQ ID NO:106),
TGFVK (SEQ ID NO:107),
TGFV (SEQ ID NO:108),
TGF (SEQ ID NO:109),
GFVKKDQL (SEQ ID NO:110),
GFVKKDQ (SEQ ID NO:111),
GFVKKD (SEQ ID NO:112),
GFVKK (SEQ ID NO:113),
GFVK (SEQ ID NO:114),
GFV (SEQ ID NO:115),
FVKKDQL (SEQ ID NO:116),
FVKKDQ (SEQ ID NO:117),
FVKKD (SEQ ID NO:118),
FVKK (SEQ ID NO:119),
FVK (SEQ ID NO:120),
VKKDQL (SEQ ID NO:121),
VKKDQ (SEQ ID NO:122),
VKKD (SEQ ID NO:123),
VKK (SEQ ID NO:124),
KKDQL (SEQ ID NO:125),
KKDQ (SEQ ID NO:126),
KKD (SEQ ID NO:127),
KDQL (SEQ ID NO:128), and
KDQ (SEQ ID NO:129) and

(d) the fourth peptide sequence, if present, is one of any one of the amino acid sequences of SEQ ID NO: 3-38, 1002-1057, 39-57, 142-1000, and 59-129; wherein each of the first peptide sequence, the second peptide sequence, the third peptide sequence, and the fourth peptide sequence, if present, may optionally comprise a C-terminal cysteine.

41. The immunotherapy composition of any one of claims 38 to 40, wherein the at least one of the first peptide sequence, the second peptide sequence, the third peptide sequence, and the fourth peptide sequence further comprise a linker to a carrier at either a C-terminal portion of the polypeptide, or a N-terminal portion of the polypeptide.

42. The immunotherapy composition of claim 41, wherein the linker comprises an amino acid sequence selected from the group consisting of GG, GGG, AA, AAA, KK, KKK, SS, SSS, GAGA (SEQ ID NO:139), AGAG (SEQ ID NO:140), and KGKG (SEQ ID NO:141).

43. The immunotherapy composition of claim 42, wherein the linker to the carrier may optionally comprise a C-terminal cysteine (C).

44. The immunotherapy composition of any one of claims 42 to 43, wherein the carrier comprises serum albumins, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid (TT), diphtheria toxoid (DT), a genetically modified cross-reacting material (CRM) of diphtheria toxin, CRM197, meningococcal outer membrane protein complex (OMPC) and *H. influenzae* protein D (HiD), rEPA (*Pseudomonas aeruginosa* exotoxin A), KLH (keyhole limpet hemocyanin), and flagellin.

45. The immunotherapy composition of claim 54, wherein the carrier is CRM197.

46. The immunotherapy composition of claim 54, wherein the carrier is diphtheria toxoid.

47. The immunotherapy composition of any one of claims 38 to 46, further comprising at least one pharmaceutically acceptable diluent.

48. The immunotherapy composition of any one of claims 38 to 47, further comprising a multiple antigen presenting system (MAP).

49. The immunotherapy composition of claim 48, wherein the MAP comprises one or more of a Lys-based dendritic scaffold, helper T-cell epitopes, immune stimulating lipophilic moieties, cell penetrating peptides, radical induced polymerization, self-assembling nanoparticles as antigen-presenting platforms and gold nanoparticles.

50. A pharmaceutical composition comprising the immunotherapy composition of any of claims 38 to 49 and at least one adjuvant.

51. The pharmaceutical composition of claim 50, wherein the adjuvant is selected from the group consisting of aluminum hydroxide, aluminum phosphate, aluminum sulfate, 3 De-O-acylated monophosphoryl lipid A (MPL), QS-21, TQL1055, QS-18, QS-17, QS-7, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), oil in water emulsions (such as squalene or peanut oil), CpG, polyglutamic acid, polylysine, AddaVax™, MF59®, and combinations thereof.

52. The pharmaceutical composition of claim 51, wherein the adjuvant is QS-21 or TQL1055.

53. The pharmaceutical composition of claim 51, wherein the adjuvant is MPL.

54. The pharmaceutical composition of claim 51, wherein the adjuvant is a combination of MPL and QS-21 or a combination of MPL and TQL1055.

55. A nucleic acid comprising a nucleic acid sequence encoding a polypeptide of any one of claims 1 to 24 of the immunotherapy composition of claims 38 to 55.

56. A nucleic acid immunotherapy composition comprising the nucleic acid of claim 55 and at least one adjuvant.

57. A method of treating or effecting prophylaxis of Alzheimer's disease in a subject, comprising administering to the subject the immunotherapy composition of any of claims 25 to 28 and 38 to 49 or the pharmaceutical formulations of any of claims 31 to 37 and 50 to 54.

58. A method of inhibiting or reducing aggregation of at least one of A β , tau, and alpha-synuclein in a subject having or at risk of developing Alzheimer's disease, comprising, administering to the subject the immunotherapy composition of any of claims 25 to 28 and 38 to 49 or the pharmaceutical formulations of any of claims 31 to 37 and 50 to 54.

59. A method of treating or effecting prophylaxis of Alzheimer's disease in a subject, comprising administering to the subject the nucleic acid immunotherapy composition of claim 56.

60. A method of inhibiting or reducing aggregation of at least one of A β , tau, and alpha-synuclein in a subject having or at risk of developing Alzheimer's disease, comprising administering to the subject the nucleic acid immunotherapy composition of claim 56.

61. The method of any of claims 57 to 60, further comprising repeating the administering at least a second time, at least a third time, at least a fourth time, at least a fifth time, or at least a sixth time.

62. The method of claim 61, further comprising repeating the administering at an interval of about 21 to about 28 days.

63. A method of inducing an immune response in an animal, comprising administering to the animal any one of the polypeptide of claims 1 to 21, the immunotherapy composition of claims 25 to 28 and 38 to 49, the pharmaceutical formulations of claims 25 to 37 and 50 to 54 or the nucleic acid immunotherapy composition of claim 62 in a regimen effective to generate an immune response comprising antibodies that specifically bind to A β , tau, and/or alpha-synuclein.

64. The method of claim 63, wherein the immune response comprises antibodies that specifically bind to A β , antibodies that specifically bind to tau, and antibodies that specifically bind to alpha-synuclein.

65. The method of any of claims 63 to 64, wherein the inducing the immune response comprises antibodies that specifically bind to the N-terminal region of A β , the microtubule region of tau, and/or the C-terminal region of alpha-synuclein.

66. An immunization kit comprising the immunotherapy composition of any of claims 25 to 28 and 38 to 49.

67. The kit of claim 66, further comprising an adjuvant.

68. The kit of claim 67, wherein the immunotherapy composition is in a first container and the adjuvant is in a second container.

69. A kit comprising the nucleic acid immunotherapy composition of claim 56.

70. The kit of claim 69, further comprising an adjuvant.

71. The kit of claim 71, wherein the nucleic acid is in a first container and the adjuvant is in a second container.