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(54) **Title:** TAU VACCINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

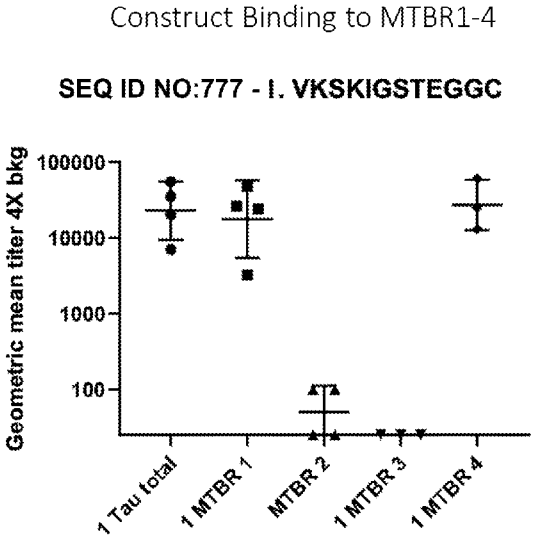

FIG 5A

(57) **Abstract:** The disclosure provides peptides, peptide compositions, immunotherapy compositions, pharmaceutical compositions and nucleic acids comprising one or more tau peptides. The disclosure also provides methods of treating or effecting prophylaxis of Alzheimer's disease or other diseases characterized at least in part by aberrant tau pathology (e.g., aggregation in neurofibrillary tangles) in a subject, including methods of clearing deposits, inhibiting or reducing aggregation of tau, blocking the uptake by neurons, clearing tau, and inhibiting propagation of tau seeds in a subject having or at risk of developing Alzheimer's disease or other diseases containing tau accumulations. The methods include administering to such patients the compositions comprising one or more tau peptides.

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TAU VACCINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/062,971, filed August 7, 2020, 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 file created on May 19, 2021, having the file name "20-1088-WO_Sequence-Listing_ST25.txt" and is 188 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.

[0005] 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.

[0006] 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 tau present in patients.

SUMMARY

[0007] In some embodiments, disclosure is directed to a peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750. For example, the peptide may comprise an amino acid sequence of one of SEQ ID NO:02 to SEQ ID NO:19, SEQ ID NO:25 to SEQ ID NO:320, SEQ ID NO:411, SEQ ID NO:454, SEQ ID NO:456, SEQ ID NO:458 to SEQ ID NO:742, SEQ ID NO:747 to SEQ ID NO:749, or SEQ ID NO:755 to SEQ ID NO:776. In some embodiments, the peptide is from the microtubule binding region (MTBR) of tau (residues 244-372 of SEQ ID NO:01) and, as an example, comprise any one of SEQ ID NO:02 to SEQ ID NO:19, SEQ ID NO:28 to SEQ ID NO:102, SEQ ID NO:185 to SEQ ID NO:320 or SEQ ID NO:458 to SEQ ID NO:742, each optionally further comprising a C-terminal cysteine.

[0008] In some embodiments, the disclosure is directed to a peptide comprising, e.g., 3-13, 7-13, 7-10 or 8 amino acids from residues 244-400 of SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750, further comprising a C-terminal -GGC or -GGGC or an N-terminal CGG- or CGGG-. For example, the peptide can comprise an amino acid sequence of SEQ ID NO:777 to SEQ ID NO:785 or SEQ ID NO:786 to SEQ ID NO:908.

[0009] In some embodiments, the peptide may include a linker to a carrier at a C-terminal portion of the peptide or at a N-terminal portion of the peptide, which may include an amino acid sequence of, for example, AA, AAA, KK, KKK, SS, SSS AGAG, GG, GGG, GAGA, and KGKG. In addition, the linker to the carrier, if present, may include a terminal cysteine (C). As an example of a C-terminal linker, the polypeptide may include the amino acid sequence of NIKHVPG-XXC (SEQ ID NO:05), wherein XX and C are independently optional and, if present, XX can be, for example, AA, KK, SS, AGAG, GG, GAGA, or KGKG. In some embodiments, the peptide further comprises a blocked amine at the N-terminus.

[0010] 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.

[0011] Still further, embodiments of the disclosure are directed to a pharmaceutical compositions comprising the peptides and/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) and synthetic analogs thereof, QS-21, QS-18, QS-17, QS-7, TQL-1055, 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 one or more of 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.

[0012] 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.

[0013] 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.

[0014] Still further, embodiments of the disclosure are directed to methods for treating or effecting prophylaxis of Alzheimer's disease in a subject, and methods for inhibiting or reducing

aggregation of tau in a subject having or at risk of developing Alzheimer's disease. The methods include administrating to the subject an immunotherapy composition, a nucleic acids immunotherapy composition, or a pharmaceutical formulation of the disclosure.

[0015] 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 bimonthly, of about 21 to about 28 days, of about quarterly, of about biannually, or of about annually.

[0016] 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 tau. The immune response may include antibodies that specifically bind to the microtubule region of tau.

[0017] 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.

[0018] 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.

[0019] In each of the embodiments of the peptide described herein, the peptide may comprise, consist, or consist essentially of the recited sequences.

BRIEF DESCRIPTION OF THE FIGURES

[0020] **FIG. 1** shows the results of an experiment comparing the titers of Guinea pig serum for tau single peptide immunogens AGHVTQAR (SEQ ID NO:453), GYTMHQD (SEQ ID NO:454), QIVYKPV (SEQ ID NO:02) and EIVYKSPV (SEQ ID NO:141). All immunogens further comprised a C-terminal linker of GG and a cysteine for coupling to maleimide activated CRM197 carrier. QS21 was utilized as an adjuvant in AddaVax squalene-based oil-in-water nano-emulsion.

[0021] **FIG. 2** shows the results of an experiment measuring the titer of murine serum for tau single peptide immunogen CNIKHVPG (SEQ ID NO:24). The peptide was coupled to maleimide activated CRM197 carrier through the N-terminal cysteine. QS21 was used as an adjuvant.

[0022] **FIG. 3** shows the results of an experiment measuring the titer of murine serum for tau single peptide immunogens described by SEQ ID NO:777 to SEQ ID NO:785 and SEQ ID NO:963 to SEQ ID NO:965.

[0023] **FIG. 4** shows the results of an experiment measuring the titer of murine serum for tau single peptide immunogens described by SEQ ID NO:963, SEQ ID NO:964 and SEQ ID NO:965.

[0024] **FIG. 5(A)-(H)** shows the results of an experiment measuring the binding of various murine sera from animals vaccinated with immunogenic compositions of the disclosure against MTBR1, MTBR2, MTBR3 and MTBR4.

[0025] **FIG. 6** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against VKSKIGSTEGGC (SEQ ID NO:777) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells. For Figures 6-12, filled circles ("neg") are a negative control. Samples labels, e.g., "1.1", "1.2", "1.3" and "1.4" in Figure 6, refer to the peptide construct number ("1"), followed by a period, and a second number, which represents an animal. Thus, Figure 6 illustrates the results of experiments on four mice using construct 1, which corresponds to SEQ ID NO:777.

[0026] **Fig. 7** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against KSKIGSTEGGC (SEQ ID NO:778) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells.

[0027] **FIG. 8** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against SKIGSTENGGC (SEQ ID NO:779) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells.

[0028] **FIG. 9** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against STENLKHQGGC (SEQ ID NO:783) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells.

[0029] **FIG. 10** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against TENLKHQPGGC (SEQ ID NO:784) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells.

[0030] **FIG. 11** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against ENLKHQPGGGC (SEQ ID NO:785) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells.

[0031] **FIG. 12** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against CGGSKIGSKDNIKH (SEQ ID NO:964) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells.

[0032] **FIG. 13** shows the results of an experiment measuring the ability of mouse serum with antibodies raised against CGGSKIGSLDNIKH (SEQ ID NO:965) to block tau binding to heparin as a potential surrogate marker for the ability of the serum to block uptake of tau into cells.

[0033] **FIG. 14** shows staining of Tau pathology in fresh frozen human AD brain tissue (versus normal tissue in the right side panel) using a 1:500 dilution of serum from mice vaccinated with SEQ ID NO:778.

[0034] **FIG. 15** shows staining of Tau pathology in fresh frozen human AD brain tissue (versus normal tissue in the right side panel) using a 1:500 dilution of serum from mice vaccinated with (SEQ ID NO:779).

[0035] **Fig. 16** shows staining of Tau pathology in fresh frozen human AD brain tissue (versus normal tissue in the right side panel) using a 1:500 dilution of serum from mice vaccinated with (SEQ ID NO:784).

[0036] **Fig. 17** shows staining of Tau pathology in fresh frozen human AD brain tissue (versus normal tissue in the right side panel) using a 1:500 dilution of serum from mice vaccinated with (SEQ ID NO:785).

[0037] **Fig. 18** shows staining of Tau pathology in fresh frozen human AD brain tissue (versus normal tissue in the right side panel) using a 1:500 dilution of serum from mice vaccinated with (SEQ ID NO:918).

DESCRIPTION

[0038] The disclosure provides peptide compositions and immunotherapy compositions comprising one or more tau peptides. The disclosure also provides methods of treating or effecting prophylaxis of Alzheimer's disease or other diseases characterized at least in part by aberrant tau pathology (e.g., aggregation in neurofibrillary tangles) in a subject, including methods of clearing and preventing formation of deposits and aggregates, inhibiting or reducing aggregation of tau, blocking the binding and/or uptake of tau 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 accumulations. The methods include administering to such patients the compositions comprising an one or more tau peptides.

[0039] 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.

[0040] 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 $p \leq 0.05$.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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 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.

[0048] The terms "reduction", "reduce", or "reducing" as used herein refer to decreasing the amount of tau present in a subject or in tissue of the subject, or suppressing an increase in the amount of tau present in a subject or in tissue of a subject, which encompasses decreasing or suppressing an increase in (e.g., decreasing the rate of increase) the amount of tau 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 tau present, accumulated, aggregated, or deposited in the subject refers to an amount of tau 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 tau present, accumulated, aggregated, or deposited in the subject refers to an amount of tau 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 tau present, accumulated, aggregated, or deposited in the subject refers to an amount of tau present, accumulated, aggregated, or deposited in the brain of the subject. In some embodiments, the tau reduced is the pathological form(s) of tau (*e.g.*, neurofibrillary tangles of tau, dystrophic neurites). In yet other embodiment, pathological indicators of neurodegenerative disease and/or tauopathies are decreased.

[0049] 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).

[0050] 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 liner or spatial conformation.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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 a tau peptide in a recipient. Such a response can be an active response induced by administration of immunogen (*e.g.* tau peptide(s)). 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.

[0057] **Tau**

[0058] 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 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.

[0059] Peptide Immunogens

[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, 13 or more contiguous amino acids from a region of tau peptide.

[0061] In some embodiments of the disclosure, the immunogen can comprise, consists of, or consists essentially of, a tau peptide comprising 3-13 (e.g., 7-13, 5-10, 7-11, 8) amino acids from residues 244-400 of the long form of tau (SEQ ID NO:01).

[0062] residues 1-150 of full-length tau (SEQ ID NO:750). In some embodiments, the fragment is unphosphorylated. In some embodiments, the fragment is phosphorylated at serine (S), threonine (T), and/or tyrosine (Y) phosphorylation sites.

[0063] In some embodiments, the immunogen comprises, consists of, or consists essentially of, an amino acid sequence represented by the consensus motif (Q/E)IVYK(S/P) (SEQ ID NO:748). In some embodiments, the immunogen comprises an amino acid sequence represented by the consensus motif KXXSXXNX(K/H)H (SEQ ID NO:747) where X is any amino acid. In some embodiments, the immunogen comprises an amino acid sequence represented by the consensus motif SK(I/C)GS (SEQ ID NO:749).

[0064] In some embodiments, the tau peptide comprises, consists of, or consists essentially of, an amino acid sequence selected from the group consisting of any one of SEQ ID NO:02 to SEQ ID NO:19, SEQ ID NO:25 to SEQ ID NO:320, SEQ ID NO:128, SEQ ID NO:411, SEQ ID NO:454, SEQ ID NO:456, SEQ ID NO:458 to SEQ ID NO:742, SEQ ID NO:747 to SEQ ID NO:749, or SEQ ID NO:755 to SEQ ID NO:776. In some embodiments, the immunogen comprises a tau peptide from the microtubule binding region (MTBR) of tau (residues 244-372 of SEQ ID NO:01). In some embodiment, the peptide comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NO:02 to SEQ ID NO:19, SEQ ID NO:28 to SEQ ID NO:102, SEQ ID NO:185 to SEQ ID NO:320, SEQ ID NO:458 to SEQ ID NO:742, or SEQ ID NO:747 to SEQ ID NO:749. In some embodiments, the immunogen can comprise, consists of, or consists essentially of, an amino acid sequence selected from the group consisting of

QIVYKPV (SEQ ID NO:02),
QIVYKP (SEQ ID NO:03),
NIKHVP (SEQ ID NO:04),
NIKHVPG (SEQ ID NO:05),
HVPGGG (SEQ ID NO:06),
HVPGG (SEQ ID NO:07),
HKPGGG (SEQ ID NO:08),
HKPGG (SEQ ID NO:09),
KHVPGGG (SEQ ID NO:10),
KHVPGG (SEQ ID NO:11),
HQPGGG (SEQ ID NO:12),
HQPGG (SEQ ID NO:13),
VQIINK (SEQ ID NO:14),
VQIINKK (SEQ ID NO:15),
VQIINKKL (SEQ ID NO:16),
QIINK (SEQ ID NO:17),
QIINKK (SEQ ID NO:18),
QIINKKL (SEQ ID NO:19),
EIVYKSP (SEQ ID NO:25),

IVYKSPV (SEQ ID NO:26),
IVYK (SEQ ID NO:27),
QIVYKS (SEQ ID NO:325)
EIVYKS (SEQ ID NO:128)
EIVYKP (SEQ ID NO:411)
GYTMHQD (SEQ ID NO:454),
QGGYTMHQD (SEQ ID NO:456),
VKSKIGSTE (SEQ ID NO:589),
KSKIGSTE (SEQ ID NO:590),
SKIGSTEN (SEQ ID NO:598),
KIGSTENL (SEQ ID NO:605),
IGSTENLK (SEQ ID NO:611),
GSTENLKH (SEQ ID NO:616),
STENLKHQ (SEQ ID NO:620),
TENLKHQP (SEQ ID NO:476),
ENLKHQPG (SEQ ID NO:470),
VKSKIGST (SEQ ID NO:582),
PDLKNVKS (SEQ ID NO:755),
DLKNVKSK (SEQ ID NO:756),
LKNVKSKI (SEQ ID NO:757),
KNVKSKIG (SEQ ID NO:758),
NVKSKIGS (SEQ ID NO:759),
NLKHQPGG (SEQ ID NO:465),
LKHQPGGG (SEQ ID NO:460),
LDLSNVQS (SEQ ID NO:760),
DLSNVQSK (SEQ ID NO:761),
LSNVQSKC (SEQ ID NO:762),
SNVQSKCG (SEQ ID NO:763),
NVQSKCGS (SEQ ID NO:764),
VQSKCGSK (SEQ ID NO:626),
QSKCGSKD (SEQ ID NO:634),

SKCGSKDN (SEQ ID NO:642),
KCGSKDNI (SEQ ID NO:649),
CGSKDNIK (SEQ ID NO:258),
GSKDNIKH (SEQ ID NO:653),
SKDNIKHV (SEQ ID NO:271),
KDNIKHVP (SEQ ID NO:278),
DNIKHVPG (SEQ ID NO:285),
NIKHVPGG (SEQ ID NO:292),
IKHVPGGG (SEQ ID NO:297),
VDLSKVTS (SEQ ID NO:765),
DLSKVTSK (SEQ ID NO:766),
LSKVTSKC (SEQ ID NO:767),
SKVTSKCG (SEQ ID NO:768),
KVTSKCGS (SEQ ID NO:769),
VTSKCGSL (SEQ ID NO:770),
TSKCGSLG (SEQ ID NO:666),
SKCGSLGN (SEQ ID NO:674),
KCGSLGNI (SEQ ID NO:681),
CGSLGNIH (SEQ ID NO:687),
GSLGNIHH (SEQ ID NO:692),
SLGNIHHK (SEQ ID NO:696),
LGNIHHKP (SEQ ID NO:524),
GNIHHKPG (SEQ ID NO:518),
NIHHKPGG (SEQ ID NO:513),
IHHKPGGG (SEQ ID NO:508),
LDFKDRVQ (SEQ ID NO:771),
DFKDRVQS (SEQ ID NO:772),
FKDRVQSK (SEQ ID NO:773),
KDRVQSKI (SEQ ID NO:774),
DRVQSKIG (SEQ ID NO:775),
RVQSKIGS (SEQ ID NO:776),

VQSKIGSL (SEQ ID NO:702),
QSKIGSLD (SEQ ID NO:709),
SKIGSLDN (SEQ ID NO:717),
KIGSLDNI (SEQ ID NO:724),
IGSLDNIT (SEQ ID NO:729),
GSLDNITH (SEQ ID NO:734),
SLDNITHV (SEQ ID NO:738),
LDNITHVP (SEQ ID NO:561),
DNITHVPG (SEQ ID NO:555),
NITHVPGG (SEQ ID NO:551), and
ITHVPGGG (SEQ ID NO:547).

[0065] In some embodiments, the immunogen comprises a tau peptide comprising, consisting of, or consisting essentially of, an amino acid sequence selected from the group consisting of any one of SEQ ID NO:20 to SEQ ID NO:24, SEQ ID NO:312 to SEQ ID NO:457,. Each tau sequence optionally further comprising a C-terminal cysteine. In some embodiments, the immunogenic peptide comprises and amino acid sequence selected from the group consisting of

QIVYKSV (SEQ ID NO:20),
EIVYKSV (SEQ ID NO:21),
EIVYKPV (SEQ ID NO:22),
CNIKHVP (SEQ ID NO:23),
CNIKHVPG (SEQ ID NO:24),
EAAGHVTQC (SEQ ID NO:449),
EAAGHVTQAR (SEQ ID NO:450),
AAGHVTQAC (SEQ ID NO:451),
AGHVTQARC (SEQ ID NO:452),
AGHVTQAR (SEQ ID NO:453),
QGGYTMHC (SEQ ID NO:455), and
GGYTMHQC (SEQ ID NO:457).

[0066] In some embodiments, the immunogenic peptide comprises, consists of, or consists essentially of, an amino acid sequence from the MTBR1 region (SEQ ID NO:751) of the long form of tau (SEQ ID NO:01), each with a C-terminal cysteine, -GGC, a C-terminal -GGGC, a N-terminal cysteine, CGG- or a N-terminal CGGG-. Examples include SEQ ID NO:777 to SEQ ID NO:785, SEQ ID NO:786 to SEQ ID NO:793, SEQ ID NO:843 to SEQ ID NO:850, and SEQ ID NO:851 to SEQ ID NO:859. In some embodiments, the peptide includes:

VKSKIGSTEGGC (SEQ ID NO:777),
KSKIGSTEGGC (SEQ ID NO:778),
SKIGSTENGGC (SEQ ID NO:779),
KIGSTENLGGC (SEQ ID NO:780),
IGSTENLKGGC (SEQ ID NO:781),
GSTENLKHGGC (SEQ ID NO:782),
STENLKHQGGC (SEQ ID NO:783),
TENLKHQPGGC (SEQ ID NO:784), and
ENLKHQPGGGC (SEQ ID NO:785).

[0067] In some embodiments, the immunogenic peptide comprises, consists of, or consists essentially of, an amino acid sequence from the MTBR2 region (SEQ ID NO:752) of the long form of tau (SEQ ID NO:01), each with a C-terminal cysteine, -GGC, a C-terminal -GGGC, a N-terminal cysteine, CGG- or a N-terminal CGGG-. Examples include SEQ ID NO:794 to SEQ ID NO:809 and SEQ ID NO:860 to SEQ ID NO:875. In some embodiments, the peptide includes:

VQSKCGSKGGC (SEQ ID NO:799),
QSKCGSKDGGC (SEQ ID NO:800),
SKCGSKDNGGC (SEQ ID NO:801),
KCGSKDNIGGC (SEQ ID NO:802),
CGSKDNIKGGC (SEQ ID NO:803),
GSKDNIKHGGC (SEQ ID NO:804),
SKDNIKHVGGC (SEQ ID NO:805),
KDNIKHVPGGC (SEQ ID NO:806), and
DNIKHVPGGGC (SEQ ID NO:807).

[0068] In some embodiments, the immunogenic peptide comprises, consists of, or consists essentially of, an amino acid sequence from the MTBR3 region (SEQ ID NO:753) of the long form of tau (SEQ ID NO:01), each with a C-terminal cysteine, -GGC, a C-terminal -GGGC, a N-terminal cysteine, CGG- or a N-terminal CGGG-. Examples include SEQ ID NO:810 to SEQ ID NO:825 and SEQ ID NO:876 to SEQ ID NO:891. In some embodiments, the peptide includes:

VTSKCGSLGGC (SEQ ID NO:815),
TSKCGSLGGGC (SEQ ID NO:816),
SKCGSLGNGGC (SEQ ID NO:817),
KCGSLGNIGGC (SEQ ID NO:818),
CGSLGNIHGGC (SEQ ID NO:819),
GSLGNIHHGGC (SEQ ID NO:820),
SLGNIHHKGGC (SEQ ID NO:821),
LGNIHHKPGGC (SEQ ID NO:822), and
GNIHHKPGGGC (SEQ ID NO:823).

[0069] In some embodiments, the immunogenic peptide comprises, consists of, or consists essentially of, an amino acid sequence from the MTBR4 region (SEQ ID NO:754) of the long form of tau (SEQ ID NO:01), each with a C-terminal cysteine, -GGC, a C-terminal -GGGC, a N-terminal cysteine, CGG- or a N-terminal CGGG-. Examples include SEQ ID NO:826 to SEQ ID NO:842 and SEQ ID NO:892 to SEQ ID NO:908. In some embodiments, the peptide includes:

RVQSKIGSGGC (SEQ ID NO:831),
VQSKIGSLGGC (SEQ ID NO:832),
QSKIGSLDGGC (SEQ ID NO:833),
SKIGSLDNGGC (SEQ ID NO:834),
KIGSLDNIGGC (SEQ ID NO:835),
IGSLDNITGGC (SEQ ID NO:836),
GSLDNITHGGC (SEQ ID NO:837),
SLDNITHVGGC (SEQ ID NO:838),
LDNITHVPGGC (SEQ ID NO:839), and

DNITHVPGGGC (SEQ ID NO:840).

[0070] In some embodiments, the immunogenic peptide comprises, consists of, or consists essentially of, 5-13 amino acids from residues 244-400 of SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750, comprising at least one amino acid substitution. In one embodiment, the peptide comprises an amino acid sequence from within the Tau MTBR1 sequence (SEQ ID NO:751) that comprises SKIGSTENLKH (SEQ ID NO:909), and variants thereof. In some embodiments, the at least one amino acid substitutions comprises an isoleucine substitution for a lysine at position 10. In some embodiments, the at least one amino acid substitutions comprises a lysine or leucine substitution for a tyrosine at position 6, and in some embodiments, the at least one amino acid substitutions comprises an aspartic acid or glycine substitution for a glutamic acid at position 7.

[0071] In some embodiments, the peptide comprises an amino acid sequence selected from the group consisting of

SKIGSTENLKH (SEQ ID NO:909),

SKIGSTENIKH (SEQ ID NO:910),

SKIGSKDNLKH (SEQ ID NO:911),

SKIGSKENIKH (SEQ ID NO:912),

SKIGSLENLKH (SEQ ID NO:913),

SKIGSLENIKH (SEQ ID NO:914),

SKIGSTDNLKH (SEQ ID NO:915),

SKIGSTDNIKH (SEQ ID NO:916),

SKIGSKDNLKH (SEQ ID NO:917),

SKIGSKDNIKH (SEQ ID NO:918),

SKIGSLDNLKH (SEQ ID NO:919),

SKIGSLDNIKH (SEQ ID NO:920),

SKIGSTGNLKH (SEQ ID NO:921),

SKIGSTGNIKH (SEQ ID NO:922),

SKIGSKGNLKH (SEQ ID NO:923),

SKIGSKGNIKH (SEQ ID NO:924),

SKIGSLGNLKH (SEQ ID NO:925),

SKIGSLGNIKH (SEQ ID NO:926),

[0072] In some embodiments, the peptide comprises, consists essentially of, or consists of an amino acid sequence selected from the group consisting of SKIGSTDNIKH (SEQ ID NO:916), SKIGSKDNIKH (SEQ ID NO:918), or SKIGSLDNIKH (SEQ ID NO:920).

[0073] In some embodiments, the peptides further comprises, consists essentially of. or consists of, a C-terminal cysteine (-C), -GGC or -GGGC or an N-terminal cysteine (C-), CGG- or CGGG-.

[0074] In some embodiments, the peptide comprises an amino acid sequence selected from the group consisting of

SKIGSTENLKHGGC (SEQ ID NO:927),

SKIGSTENIKHGGC (SEQ ID NO:928),

SKIGSKDNLKHGGC (SEQ ID NO:929),

SKIGSKENIKHGGC (SEQ ID NO:930),

SKIGSLENLKHGGC (SEQ ID NO:931),

SKIGSLENIKHGGC (SEQ ID NO:932),

SKIGSTDNLKHGGC (SEQ ID NO:933),

SKIGSTDNIKHGGC (SEQ ID NO:934),

SKIGSKDNLKHGGC (SEQ ID NO:935),

SKIGSKDNIKHGGC (SEQ ID NO:936),

SKIGSLDNLKHGGC (SEQ ID NO:937),

SKIGSLDNIKHGGC (SEQ ID NO:938),

SKIGSTGNLKHGGC (SEQ ID NO:939),

SKIGSTGNIKHGGC (SEQ ID NO:940),

SKIGSKGNLKHGGC (SEQ ID NO:941),

SKIGSKGNIKHGGC (SEQ ID NO:942),

SKIGSLGNLKHGGC (SEQ ID NO:943),

SKIGSLGNIKHGGC (SEQ ID NO:944),

SKIGSTENLKHGGGC (SEQ ID NO:945),

SKIGSTENIKHGGGC (SEQ ID NO:946),

SKIGSKDNLKHGGGC (SEQ ID NO:947),

SKIGSKENIKHGGGC (SEQ ID NO:948),

SKIGSLENLKHGGGC (SEQ ID NO:949),

SKIGSLENIKHGGGC (SEQ ID NO:950),

SKIGSTDNLKHGGGC (SEQ ID NO:951),

SKIGSTDNIKHGGGC (SEQ ID NO:952),

SKIGSKDNLKHGGGC (SEQ ID NO:953),

SKIGSKDNIKHGGGC (SEQ ID NO:954),

SKIGSLDNLKHGGGC (SEQ ID NO:955),

SKIGSLDNIKHGGGC (SEQ ID NO:956),

SKIGSTGNLKHGGGC (SEQ ID NO:957),

SKIGSTGNIKHGGGC (SEQ ID NO:958),

SKIGSKGNLKHGGGC (SEQ ID NO:959),

SKIGSKGNIKHGGGC (SEQ ID NO:960),

SKIGSLGNLKHGGGC (SEQ ID NO:961),

SKIGSLGNIKHGGGC (SEQ ID NO:962),

CGGSKIGSTDNIKH (SEQ ID NO:963),

CGGSKIGSKDNIKH (SEQ ID NO:964),

CGGSKIGSLDNIKH (SEQ ID NO:965),

CGGGSKIGSTDNIKH (SEQ ID NO:966),

CGGGSKIGSKDNIKH (SEQ ID NO:967), and

CGGGSKIGSLDNIKH (SEQ ID NO:968).

[0075] In some embodiments, the peptide or linker to the carrier, if present, further comprises a C-terminal cysteine (C). In some embodiments, the peptide further comprises a blocked amine at the N-terminus.

[0076] In some embodiments, the immunogen as described herein further comprises a linker to a carrier at a C-terminal portion of the polypeptide. In some embodiments, the immunogen as described herein further comprises a linker to a carrier at a N-terminal portion of the polypeptide. In some embodiments, where the C-terminal residues in the immunogen are either IVYKPV, VYKPV, YKPV, 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:744)).

[0077] 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 one amino acid, two amino acids, three amino acids, four amino acids, five amino acids, six amino acids, seven amino acids, eight amino acids, nine amino acids, or ten amino acids.

[0078] 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. See, e.g., Chen, X. et al., "Fusion Protein Linkers: Property, Design and Functionality" *Adv Drug Deliv Rev.*, 15; 65(10): 1357–1369 (2013).

[0079] In some embodiments, the amino acid composition of a linker can mimic the composition of linkers commonly found in recombinant proteins, which can generally by 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:969), or (Gly-Gly-Gly-Gly-Ser)n (SEQ ID NO:970), 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., *Adv Drug Deliv Rev.*, 15; 65(10): 1357–1369 (2013).

[0080] In some embodiments, a linker to a carrier may be included at the N-terminus of the peptide or polypeptide immunogen.

[0081] In some embodiments, the linker comprises an amino acid sequence of one of AA, AAA, KK, KKK, SS, SSS AGAG, GG, GGG, GAGA, KGKG, (GGS)n, (GGGS)n (SEQ ID NO:969), and (GGGGS)n (SEQ ID NO:970), where n=1-3. In some embodiments, the peptide further comprises a N- or C-terminal cysteine (regardless whether the peptide has a N- or C-terminal cysteine in the sequence identification number, e.g., SEQ ID NO:778 (KSKIGSTEGGC) can have a further C-terminal cysteine to yield KSKIGSTEGGC-C), and some embodiments that comprise a C- or N-terminal linker further comprise a C- or N-terminal

cysteine on the C- or N-terminal end of the linker. In some embodiments, the immunogen peptides further comprise a blocked amine at the N-terminus.

[0082] In some embodiments, the two or more tau peptides are linked to form a tau polypeptide. The one or more tau peptides can be linked by an intra-peptide linker, which linker is as described above and herein. 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 tau polypeptide may be arranged in any order. For example, a specific tau peptide ("tau A") may be positioned at the N-terminal portion of a dual tau polypeptide and the same or a different tau peptide (for this example, a different tau, "tau B") may be positioned at the C-terminal portion of the dual polypeptide. Or, the tau peptides in this example could be arranged in the opposite orientation (tau B N-terminal to tau A). Reference to a first peptide or a second peptide herein is not intended to suggest an order of the tau peptides in embodiments that comprise more than one tau peptide of the immunogens.

[0083] In addition, the C-terminal portion of the tau peptide or tau polypeptide can include a linker for conjugating the peptides or the polypeptide to a carrier, which linker is as described above and herein. In some embodiments, the tau peptide or polypeptide that comprise a linker further comprise a C-terminal cysteine on the C-terminal end of the linker. In some embodiments, the immunogen peptides further comprise a blocked amine at the N-terminus. In some embodiments, any of the tau peptides or polypeptides may include a C-terminal cysteine or a N-terminal cysteine without a linker.

[0084] When the tau peptides are linked to form a tau 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 tau polypeptide 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 embodiments, 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 embodiments, where the C-terminal residues in the immunogen are either IVYKPV (SEQ ID NO:61), VYKPV (SEQ ID

NO:62), YKPV (SEQ ID NO:63), KPV, or PV the cleavable linker is an amino acid linker that does not have a N-terminal glycine (e.g., GAGA). In some embodiments, the cleavable linker comprises an amino acid sequence including arginine-arginine (Arg-Arg), arginine-arginine-valine-arginine (Arg-Val-Arg-Arg; SEQ ID NO:743), Gly-Ala-Gly-Ala (SEQ ID NO:744), Ala-Gly-Ala-Gly (SEQ ID NO:745), Lys-Gly-Lys-Gly (SEQ ID NO:746), valine-citrulline (Val-Cit), valine-arginine (Val-Arg), valine-lysine (Val-Lys), valine-alanine (Val-Ala), and phenylalanine-lysine (Phe-Lys). In some embodiments, the cleavable linker is arginine-arginine (Arg-Arg).

[0085] In some embodiments of the disclosure, the tau polypeptide comprises an amino acid sequence selected from QIVYKPV (SEQ ID NO:02), or NIKHVP (SEQ ID NO:04), or NIKHVPG (SEQ ID NO:05), or EIVYKSV (SEQ ID NO:21), wherein XX is optionally appended to the C-terminal end of SEQ ID NOS:02, 04, 05, or 21, and a cysteine is optionally appended to the C-terminal end of SEQ ID NOS:02, 04, 05 or 21, or if XX is present, to the C-terminal end of the XX. XX can be AA, KK, SS, AGAG (SEQ ID NO:745), and KGKG (SEQ ID NO:746), and in some embodiments GG or GAGA (SEQ ID NO:744).

[0086] In some embodiments, the dual tau polypeptide is as follows:

[first peptide]-[linker 1]-[second peptide]-[linker 2]-[Cys],

wherein, the first peptide is a tau peptide and the second peptide is the same or different tau peptide, each of linker 1, linker 2 and [Cys] is optional, and linker 1 and linker 2 may be the same or different.

[0087] Examples of the tau peptide include any one of SEQ ID NO:02 to SEQ ID NO:742, SEQ ID NO:747 to SEQ ID NO:749, and SEQ ID NO:755 to SEQ ID NO:968.

[0088] **[Linker 1]** is optional, and when present, may be a linker or a cleavable linker, both as described above and herein. **[Linker 2]** is optional, and, when present, comprises a linker as described above and herein. Cys is optional and can be used to conjugate the polypeptide to a carrier.

[0089] In some embodiments, the dual tau polypeptide is as follows:

[Cys]-[linker 1]-[first peptide]-[linker 2]-[second peptide],

wherein, the first peptide is a tau peptide and the second peptide is the same or different tau peptide, each of linker 1, linker 2 and [Cys] is optional, and linker 1 and linker 2 may be the same or different.

[0090] **[Linker 1]** is optional, and when present, may be a linker or a cleavable linker, both as described above and herein. **[Linker 2]** is optional, and, when present, comprises a linker as described above and herein. Cys is optional and can be used to conjugate the polypeptide to a carrier.

[0091] **Peptide-Carrier Immunogens**

[0092] Tau peptides (and polypeptides thereof) are immunogens in accordance with the disclosure. In some embodiments, the peptides described herein can be linked to a suitable carrier to help elicit an immune response. Accordingly, one or more the peptides of the disclosure can be linked to a carrier. For example, the tau peptide may be linked to the carrier with or without a linker as described above and herein and, optionally, a C-terminal cysteine at C-terminal end of the linker or N-terminal cysteine at the N-terminal end of the linker and, if a linker is absent, at the C-terminal end or N-terminal end of the peptide, respectively. For example, each tau peptide may be linked to the carrier with or without spacer amino acids (*e.g.*, Gly-Gly, Ala-Ala, Lys-Lys, Ser-Ser, Gly-Ala-Gly-Ala, Ala-Gly-Ala-Gly, or Lys-Gly-Lys-Gly and, optionally, a C-terminal or N-terminal cysteine to provide a linker between the peptide(s) and the carrier.

[0093] 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-pyridyl-

thio)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 resides 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 (PADRE) are described in US 5,736,142, WO 95/07707, and Alexander J *et al*, Immunity, 1:751-761 (1994).

[0094] Active immunogens can be presented in multimeric form in which multiple copies of an immunogen are presented on a carrier as a single covalent molecule. In some embodiments, the carrier includes various forms of the tau peptide. For instance, the tau peptide of the immunogen can include peptides that have different tau antigens in different orders, or may be present with or without an intrapeptide linker and/or a linker to a carrier.

[0095] 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.

[0096] Nucleic Acids

[0097] The disclosure further provides nucleic acids encoding any of the tau peptides as disclosed herein. The nucleic acid immunotherapy compositions as disclosed herein, comprise, consist of or consisting essentially of a nucleic acid sequence encoding one or more tau peptides as disclosed herein. For example, the tau peptide can comprise a sequence of 3-13 (e.g., 7-13, 5-10, 7-11, 8) amino acids in length and from residues 244-400 of SEQ ID NO:01 or 1-150 of SEQ ID NO:750. Accordingly, and as a non-limiting example, one or more nucleic acids encoding any of SEQ ID NO:02 to SEQ ID NO:742, SEQ ID NO:747 to SEQ ID NO:749, or SEQ ID NO:755 to SEQ ID NO:968 provide an immunogen and pharmaceutical composition of the disclosure. In certain embodiments, the peptide sequences may be encoded by the same or separate nucleic acid sequences. In some embodiments, the nucleic acid sequences may also encode a linker to a carrier and/or a N- or C-terminal cysteine as described herein. In addition, when a single nucleic acid sequence encodes more than one tau peptide, the sequence may also encode a 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 brain tau.

[0098] 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 long after its administration and continues to slowly produce the encoded proteins. Thus, excessive immune responses can be avoided. DNA vaccines can also be modified using 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 tau 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 tau peptide and tau polypeptides with and without linkers and/or cleavable linkers and with or without protein-based carriers can be joined as one contiguous nucleic acid, *e.g.*, within an expression vector.

[0099] DNA is more stable than RNA, but DNA 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 a 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 a tau peptide as disclosed herein, and are capable of expressing the 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., 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 tau 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 tau antigens.

[00100] 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).

[00101] 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).

[00102] 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.

[00103] Pharmaceutical Compositions

[00104] Each of the peptides and immunogens described herein can be presented in a pharmaceutical composition that is often 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.

[00105] 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 (Croda), Alabaster, Alabama).

[00106] 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 S, *et al.*, "Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial", AN1792(QS-21)-201 Study Team.

Neurology. 2005 May 10; 64(9):1553-62; Wald A, *et al.*, "Safety and immunogenicity of long HSV-2 peptides complexed with rhHsc70 in HSV-2 seropositive persons" Vaccine 2011. November 3;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. Vaccine 2011. November 3;29(47):8520–8529. 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.

[00107] 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 US20180327436A1, WO2018191598A1, WO2018200656A1, and WO2019079160A1, the disclosures of which are herein incorporated by reference. US20180327436A1 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. WO2018200656A1 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.

[00108] 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 TLR4 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.

[00109] 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.

[00110] 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 a- 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.

[00111] 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.

[00112] 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.

[00113] 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 Temin, 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)).

[00114] DNA and RNA encoding an immunogen, or a vector containing the same, can be packaged into liposomes, nanoparticles or lipoproteins complexes. Other suitable 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 is herein incorporated by reference in its 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).

[00115] Pharmaceutically acceptable carrier compositions can also include additives, including 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.

[00116] **Subjects Amenable to Treatment**

[00117] The presence of neurofibrillary tangles has been found in several diseases and tauopathies including Alzheimer's disease, Down's syndrome, mild cognitive impairment, 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, ganglioglioma and gangliocytoma, meningioangiomatosis, amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam, subacute sclerosing panencephalitis, 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.

[00118] 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 tau, the compositions and methods of the disclosure can be used in treatment or prophylaxis of any subject showing elevated levels of tau (*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 tau associated with neurological disease. The methods are particularly suitable for treatment or prophylaxis of Alzheimer's disease.

[00119] 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 previous treated for disease. Subjects at risk of disease include those in an aging population, asymptomatic subjects with tau 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 tau, 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 levels. Elevated tau or phospho-tau 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) appear to be associated with some AD. Subjects can also be diagnosed with any of the neurological diseases mentioned above by the criteria of the DSM IV TR.

[00120] 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.

[00121] Methods of Treatments and Uses

[00122] The disclosure provides methods of inhibiting or reducing aggregation of or tau in a subject having or at risk of developing 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.

[00123] 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 tau or phospho-tau and paired filaments, tangles, and/or aggregates formed from them 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 tau or phospho-tau and paired filaments, tangles, and/or aggregates formed from them, associated toxicities and/or behavioral deficits.

[00124] 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.

[00125] 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.

[00126] 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.

[00127] 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, 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.

[00128] 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 peptide and, optionally, 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.

[00129] 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.

[00130] 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. Treatment can be repeated for recurrence of an acute disorder or acute exacerbation.

[00131] 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.

[00132] 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.

[00133] 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).

[00134] The immunotherapeutic compositions disclosed herein may also be used in combination with other treatments for diseases associated with the accumulation of tau, for example, 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, WO2017/191559, WO2017/191560, WO2017/191561, US2019/0330314, US2019/0330316, and WO2018/204546. 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.

[00135] The compositions of the disclosure may be used in the manufacture of medicaments for the treatment regimens described herein.

[00136] **Treatment Regimens**

[00137] 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 tau tangles and/or aggregates, we well as other associated pathologies such as amyloid fibrils, decreased or inhibited amyloid aggregation and/or deposition of amyloid fibrils, and increased immune response to pathologic species, e.g., tau-containing tangles and/or tau-containing aggregates. Desired outcomes also include amelioration of tau 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 disease or tauopathy 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 immunogens. 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.

[00138] 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, 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.

[00139] 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 the product label or as necessary in view of the treatment with the compositions of the disclosure.

[00140] **Kits**

[00141] 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.

[00142] 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.

[00143] The following are provided for exemplification purposes only and are not intended to limit the scope of the invention described in broad terms above. All references cited in this disclosure are incorporated herein by reference.

[00144] Uses

[00145] 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.

[00146] All U.S. and international patent applications identified herein are incorporated by reference in their entirety.

Examples

[00147] **Example 1: Immunogens**

[00148] Immunogens were selected for evaluation in vaccine peptide constructs. Some immunogens comprise a tau peptide comprising 3-10 amino acids from tau. Other immunogens comprise an engineered tau immunogen.

[00149] Engineered Tau Immunogens

[00150] Certain immunogenic peptides were designed and selected to (i) raise antibodies that bind within the within microtubule binding repeats (MTBRs) of human Tau protein, (ii) be less likely to generate an unwanted T cell-mediated autoimmune response, and (iii) be less likely to raise antibodies that would cross-react with other human proteins.

[00151] First, sequence analysis and 3D modeling of Tau MTBRs was conducted to identify amino acid residues that may be important for raising antibodies that bind MTBR. The results of these analyses were used to design synthetic Tau immunogenic peptides with conserved residues and shuffled interspersed residues. Resulting engineered synthetic peptides are listed in Table 1.

Table 1

Engineered Tau immunogenic peptides

Engineered tau immunogenic peptides sequence	**SEQ ID NO:**
SKIGSTENLKH	909
SKIGSTENIKH	910
SKIGSKDNLKH	911

SKIGSKENIKH	912
SKIGSLENLKH	913
SKIGSLENIKH	914
SKIGSTDNLKH	915
SKIGSTDNIKH	916
SKIGSKDNLKH	917
SKIGSKDNIKH	918
SKIGSLDNLKH	919
SKIGSLDNIKH	920
SKIGSTGNLKH	921
SKIGSTGNIKH	922
SKIGSKGNLKH	923
SKIGSKGNIKH	924
SKIGSLGNLKH	925
SKIGSLGNIKH	926

[00152] Next, to assess the potential of an unwanted T cell-mediated autoimmune response, the engineered peptides were subjected to in silico analysis to predict MHC II binding using the IEDB (Immune Epitope Database) from National Institute of Allergy and Infectious Diseases/La Jolla Immunology Institute. MHC class II binding is considered a good indicator of a sequence containing a T-cell epitope. A panel of alleles were used for MHC II binding prediction. Engineered peptides with a predicted half maximal inhibitory concentration (IC50) above a specified cutoff were considered to have a low probability of MHC II binding and were selected for further analysis.

[00153] Finally, the engineered peptides with low predicted MHC II binding were evaluated to predict if the anti-Tau MTBR antibodies that would be raised by the peptides could have unwanted cross-reactivity with other human proteins. Sequences of the engineered peptides were subjected to bioinformatic analysis against a non-redundant human proteome database to determine homology with human proteins. Engineered peptide sequences with low homology to secreted or cell-surface proteins were selected as top candidates to be used as antigens. Top candidate engineered Tau immunogenic peptides are listed in Table 2.

Table 2

Top candidate engineered Tau immunogenic peptides

Engineered tau immunogenic peptides sequence	SEQ ID NO:
SKIGSTDNIKH	916
SKIGSKDNIKH	918
SKIGSLDNIKH	920

[00154] Conjugation. The peptides described in the examples (Biopeptide, San Diego, CA) were coupled to CRM (CRM-bromoacetate, Fina Biosolutions, Rockville, MD) as follows:

[00155] **Example 2: Animal Immunizations**

[00156] Conjugation. The peptides described in the examples (Biopeptide, San Diego, CA) were coupled to CRM (CRM-bromoacetate, Fina Biosolutions, Rockville, MD) as follows:

[00157] 1M Tris HCL (pH 8.0), MilliQ DI water, 50 mM borate, 100 mM NaCl, and 5 mM EDTA pH 8.5 were sterile filtered and degassed. 1 mg of each peptide was dissolved in 0.2 mL of degassed water, then 0.1 mL degassed Tris HCL was added, followed by 0.2 mL of the stock CRM-Bromoacetate (1 mg total) and 0.5 mL of the borate buffer. The peptide mixtures were incubated for 24 hours at 4 degrees on a nutator to provide mixing. Samples were desalted into PBS, and 5 µL was run on a 10% Tris gel to confirm conjugation.

[00158] In certain experiments, female Swiss Webster mice were injected subcutaneously at two sites with 100 µl of test article on day 0, 14, 42 and 70. Test article was prepared by combining 25 µg of test immunogen and 25 µg of QS21 adjuvant in 200 µl phosphate buffered saline (PBS). Mice were bled on day 21, 49 and 77 by nicking tails and collecting 50 µl of blood, followed by processing to serum. The peptides tested included AGHVTQAR (SEQ ID NO:453), GYTMHQD (SEQ ID NO:454), QIVYKPV (SEQ ID NO:02) and EIVYKSPV (SEQ ID NO:141). Immunogens contained one tau peptide, a C-terminal linker and a C-terminal cysteine (i.e., -Gly-Gly-Cys-) and were coupled through the C-terminal cysteine to CRM-197 with a maleimide linkage.

[00159] In certain experiments, immunogen preparation comprised 25 µg of peptide immunogen, 25 µg QS21 and 150 µl of 0.02% Tween 80/PBS. The peptides tested included VKSKIGSTEGGC (SEQ ID NO:777), KSKIGSTEGGC (SEQ ID NO:778), SKIGSTENGGC

(SEQ ID NO:779), KIGSTENLGGC (SEQ ID NO:780), IGSTENLKGGC (SEQ ID NO:781), GSTENLKHGGC (SEQ ID NO:782), STENLKHQGGC (SEQ ID NO:783), TENLKHQPGGC (SEQ ID NO:784), and ENLKHQPGGGC (SEQ ID NO:785). Female Swiss webster mice received 200 µL subcutaneously (four mice per group, each group receiving one immunogen). Mice in these experiments were injected at 0, 4 weeks and 8 weeks with bleeds taken for titer at 5 weeks. Animals were sacrificed and a terminal bleed collected at 9 weeks.

[00160] Guinea pigs were injected intramuscularly with 50 µg of a test immunogen, 25 µg QS21 in 200 µl of Addavax on day 0, 21, 49 and 77. Bleeds were done 7 days post immunization. The peptides tested included AGHVTQAR (SEQ ID NO:453), GYTMHQD (SEQ ID NO:454), QIVYKPV (SEQ ID NO:02) and EIVYKSPV (SEQ ID NO:141). Immunogens contained one tau peptide, a C-terminal linker and a C-terminal cysteine (i.e., -Gly-Gly-Cys-) and were coupled through the C-terminal cysteine to CRM-197 with a maleimide linkage.

[00161] 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.

[00162] The immunogen concentration was 0.5 mg/ml. Prior to each administration of the test immunogen, approximately a 3 cm^2 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 QS-21 in 100 µl Addavax). 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.

[00163] **Example 3: Measurement of Antibody Titers**

[00164] 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 ambient (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).

[00165] Titer on Tau Guinea Pigs

[00166] 2 µg/ml recombinant WT Tau 4R2N 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 Guinnea pig serum was added at a 1/100 dilution while the rest of the row contained 1/100 test serums. Rows were serially diluted by 50% per step down the plate giving dilution of 1/100 to 1/12800. Wells were incubated 2 hours at room temperature and then were 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 incubated for 1 hour and was washed. OPD substrate was prepared using ThermoFisher OPD tablets at 1 tablet per 10 mls. ThermoFisher substrate buffer was added at 1/10 and each well had 100 µl added and was incubated for 15 minutes. 50 µl of 2N H_2SO_4 was added to stop the reaction and plates were read at 490 nm on a Molecular Devices Spectromax. Titer defined as the dilution giving 50% maximum OD and was extrapolated if it fell between dilutions.

[00167] Antibody titers observed in Guinea pigs immunized as described above are shown in Table 3. Immunizations were conducted with QS21 in Addavax. The titers reported are for the bleed after the fourth injection. These results are represented in Figure 1.

Table 3

Antibody titers in Guinea pigs (GP) immunized with tau epitopes.

Tau Epitope in immunogen	SEQ ID	GP 1 Titer	GP 2 Titer	GP 2 Titer
AGHVTQAR	453	1600	3200	1600
GYTMHQD	454	55000	73000	19000
QIVYKPV	02	4000	8500	2000
EIVYSPV	141	7000	2200	2600

[00168] Titers on Tau mouse

[00169] Mouse serum was titered by enzyme-linked immunosorbent assay (ELISA). Plates were coated overnight at 2 µg/mL with recombinant tau (4R2N) in phosphate-buffered saline (PBS) and then blocked for 1 hour with 1% bovine serum albumin (BSA) in PBS. 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 with 0.1% Tween 20 (PBS/BSA/T) was added. Normal mouse serum was used as a negative control while known positive anti-serum from previous mouse studies was used as a positive control at the same dilutions as test serum. In column 1, negative mouse serum and positive mouse serum was added at 1/100 while the rest of the row contained 1/100 test sera. Rows were serially diluted by 50% per step down the plate giving dilution of 1/100 to 1/12800. When needed, due to high titers, 1/3 dilutions were used giving 1/100 to 1/218000 dilutions. Wells were incubated 2 hours at room temperature then were washed with TBS/Tween 20. 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. The reaction mixture was incubated for 1 hour and then washed with TBS/Tween 20. Antibody binding was detected with o-phenylenediamine dihydrochloride (OPD) substrate (Thermo Fisher Scientific, Waltham, MA) following manufacturer's instructions. OPD substrate was prepared using ThermoFisher OPD tablets at 1 tablet per 10 mls. ThermoFisher substrate buffer was added at 1/10 dilution and each well received 100 µl and was incubated for 15 minutes. 50 µl of 2N H_2SO_4 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 in certain experiments. In other experiments, titer was defined as the dilution giving 4X background (defined in graphs and tables); extrapolation was used if it fell in between dilutions.

[00170] Titer results

[00171] Antibody titers observed in mice immunized as described above are shown in Table 4. Immunizations were conducted with QS21. The titers reported are for the bleed after the third injection. These results are represented in Figure 2 (sample 13), Figure 3 (samples 1-12) and Figure 4 (samples 10-12).

Table 4

Antibody titers in mice immunized with tau epitopes.

Tau Epitope in immunogen		mouse 1	mouse 2	mouse 3	mouse 4
1. VKSKIGSTEGGC (SEQ ID NO:777)	QS21 0.02% PS80				
	Bleed 1	7000	55000	35000	20000
	Bleed 2	475	20000	7000	1000
2 KSKIGSTEGGC (SEQ ID NO:778)	QS21 0.02% PS80				
	Bleed 1	30000	20000	10000	15000
	Bleed 2	15000	14000	7000	14500
3 SKIGSTENGGC (SEQ ID NO:779)	QS21 0.02% PS80				
	Bleed 1	40000	35000	15000	35000
	Bleed 2	25000	13000	4000	25000
4. KIGSTENLGGC (SEQ ID NO:780)	QS21 0.02% PS80				
	Bleed 1	6000	3000	1000	dead
	Bleed 2	3200	1600	3200	dead
5. IGSTENLKGGC (SEQ ID NO:781)	QS21 0.02% PS80				
	Bleed 1	25	25	25	dead
	Bleed 2	25	25	25	dead
6. GSTENLKHGGC (SEQ ID NO:782)	QS21 0.02% PS80				
	Bleed 1	200	25	25	12000
	Bleed 2	100	25	25	400
7. STENLKHQGGC (SEQ ID NO:783)	QS21 0.02% PS80				
	Bleed 1	20000	18000	10000	dead
	Bleed 2	25000	5000	7000	dead

8. TENLKHQPGGC (SEQ ID NO:784)	QS21 0.02% PS80				
	Bleed 1	40000	40000	35000	30000
	Bleed 2	22000	28000	20000	25000
9. ENLKHQPGGGC (SEQ ID NO:785)	QS21 0.02% PS80				
	Bleed 1	45000	60000	20000	45000
	Bleed 2	21000	30000	15000	25000
10. CGGSKIGS**T**DNIKH (SEQ ID NO:963)	QS21 0.02% PS80				
	Bleed 1	1000	6400	10000	15000
	Bleed 2	500	2000	3000	20000
11. CGGSKIGS**K**DNIKH (SEQ ID NO:964)	QS21 0.02% PS80				
	Bleed 1	10000	20000	10000	20000
	Bleed 2	10000	7000	3000	20000
12. CGGSKIGS**L**DNIKH (SEQ ID NO:965)	QS21 0.02% PS80				
	Bleed 1	7000	10000	10000	20000
	Bleed 2	3500	2000	4500	15000
13.CNIKHVPG (SEQ ID NO:24)		1000	1300	300	4000

[00172] Figure 3 shows the results with SEQ ID NO:777 through SEQ ID NO:785, and SEQ ID NO:963 to SEQ ID NO:965. Central peptides 4-6 (Fig. 3) did not generate high titers to tau and, thus, were not run in the heparin blocking assay of Example 4.

[00173] **Example 4: Binding of antibody to MTBR1 – MTBR4**

[00174] Certain antibodies that bind to MTBR have been shown to bind to more than one MTBR region due to the homology of the various MTBR regions. Antiserum was titered on all four MTBR regions using peptides of MTBR 1-4 purchased from Anaspec (San Jose, CA).

MTBR peptide 1

QTAPVPMPDLKNVKSKIGSTENLKHQPGGGK (SEQ ID NO:751)

MTBR peptide 2

VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS (SEQ ID NO:752)

MTBR peptide 3

VQIVYKPVDLSKVTSKCGSLGNIHHKPGGGQ (SEQ ID NO:753)

MTBR peptide 4

VEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN (SEQ ID NO:754)

[00175] Mouse serum was again titered by enzyme-linked immunosorbent assay (ELISA). Plates were coated overnight at 2 µg/mL with each the various MTBR peptides in phosphate-buffered saline (PBS) and then blocked 1 hour with 1% bovine serum albumin (BSA) in PBS. Normal mouse serum was used as a negative control. Bleeds were diluted in PBS/0.1% BSA/ 0.1% Tween 20 (PBS/BSA/T) starting at 1/100 and serially diluted 1:2 down the plate. Plates were washed with TBS/Tween 20, and goat anti-mouse immunoglobulin G (IgG) (heavy + light chains) horseradish peroxidase (HRP) (from ThermoFisher) was added at a 1/5000 dilution and incubated for 1 hour at room temperature. Plates were washed in TBS/Tween 20, and antibody binding was detected with o-phenylenediamine dihydrochloride (OPD) substrate (Thermo Fisher Scientific, Waltham, MA) following manufacturer's instructions. Plates were read at 490 nM on a Molecular Devices Spectromax, and titer was defined as the dilution giving 4X background (defined in graphs and tables); extrapolation was used if it fell in between dilutions.

[00176] Peptide binding is showing in Figure 5(A)-5(H). Overall, VKSKIGSTEGGC (SEQ ID NO:777; Fig. 5(A)), KSKIGSTEGGC (SEQ ID NO:778; Fig. 5(B)), SKIGSTENGGC (SEQ ID NO:779; Fig. 5(C)) bound strongly to MTBR 1 and 4. STENLKHQGGC (SEQ ID NO:783; Fig. 5(D)) bound strongly to only MTBR 1. TENLKHQPGGC (SEQ ID NO:784; Fig. 5(E)) bound strongly to MTBR 1 and 2, while ENLKHQPGGGC (SEQ ID NO:785; Fig. 5(F)) bound to all four MTBR.

[00177] **Example 5: Blocking of tau binding to Heparin**

[00178] As a potential surrogate marker for the ability of the serum to block uptake of tau into cells, an ELISA measuring the blocking of tau binding to heparin plates was developed. Recombinant tau was biotinylated in-house. Heparin coated plates (Bioworld, Dublin,OH) were blocked with 2% BSA/PBS for 1 hour. In a separate deep-well polypropylene 96 well plate

(ThermoFisher), serum was diluted from 1/50 to 1/6400 in 2% BSA/PBS, in 60 µl total volume. To this, 60 µl of 200 ng/ml biotinylated tau in 2%BSA/PBS was added for a final concentration of serum 1/100-1/12800, with tau at 100 ng/ml. The mixture of serum and tau was incubated for 2 hours, then 100 µl/well was transferred to the blocked heparin plates and incubated 1 hour. Plates were washed in 0.1% Tween 20/TBS and goat anti-mouse immunoglobulin G (IgG) (heavy + light chains) horseradish peroxidase (HRP) (ThermoFisher) was added at a 1/5000 dilution and incubated for 1 hour at room temperature. Plates were washed in TBS/Tween 20, and 100 µl ThermoFisher TMB was added and incubated for 8 minutes and then stopped with H_2SO_4 and read at 450 nm.

[00179] Figures 6-13 show blocking of tau binding to heparin. Figure 6 shows results for VKSKIGSTEGGC (SEQ ID NO:777); Figure 7 shows results for KSKIGSTEGGC (SEQ ID NO:778); Figure 8 shows results for SKIGSTENGGC (SEQ ID NO:779); Figure 9 shows results for STENLKHQGGC (SEQ ID NO:783); Figure 10 shows results for TENLKHQPGGC (SEQ ID NO:784); Figure 11 shows results for ENLKHQPGGGC (SEQ ID NO:785); Figure 12 shows results for CGGSKIGSKDNIKH (SEQ ID NO:964); and Figure 13 shows results for CGGSKIGSLDNIKH (SEQ ID NO:965).

[00180] Quantitative measurement of the inhibition of tau binding to heparin is shown in Table 5 below.

Table 5

(1) VKSKIGSTEGGC (SEQ ID NO:777), animals 1-4							
dilution	**neg/NMS control**	**1.1**	**1.2**	**1.3**	**1.4**		
100	100.00	52.52	36.48	46.34	58.40		
200	113.45	95.26	52.94	65.31	76.23		
400	111.02	102.94	57.01	82.73	86.02		
800	95.01	129.16	84.63	90.68	86.36		
1600	91.98	121.81	108.05	115.51	114.49		
(2) KSKIGSTEGGC (SEQ ID NO:778), animals 1-4							
dilution	**neg/NMS control**	**2.1**	**2.2**	**2.3**	**2.4**		
100	100.00	37.28	34.00	77.89	18.32		
200	113.45	56.86	45.67	76.90	34.63		

400	111.02	76.47	59.74	81.08	43.94		
800	95.01	94.25	82.62	94.75	64.34		
1600	91.98	109.52	97.98	99.67	76.62		
(3) SKIGSTENGGC (SEQ ID NO:779), animals 1-4							
dilution	**neg/NMS control**	**3.1**	**3.2**	**3.3**	**3.4**		
100	100.000	52.99	42.46	72.94	77.24		
200	115.000	70.24	52.95	72.71	90.63		
400	91.000	67.02	61.32	116.24	106.92		
800	114.000	70.32	69.47	87.73	101.75		
1600	93.000	75.35	72.74	129.27	97.90		
(4) STENLKHQGGC (SEQ ID NO:783), animals 1-3							
dilution	**neg/NMS control**	**7.1**	**7.2**	**7.3**			
100	100.000	74.48	74.48	76.38			
200	115.000	93.77	93.77	93.15			
400	91.000	91.77	91.77	111.09			
800	114.000	99.83	99.83	94.48			
1600	93.000	140.00	140.00	140.00			
(8) TENLKHQPGGC (SEQ ID NO:784), animals 1-4 and (9) ENLKHQPGGGC (SEQ ID NO:785), animals 1-2							
dilution	**neg/NMS control**	**8.1**	**8.2**	**8.3**	**8.4**	**9.1**	**9.2**
100	100.000	44.74	47.87	55.01	38.00	42.14	12.67
200	115.000	60.90	68.96	67.15	54.05	52.02	22.85
400	91.000	93.69	101.92	91.70	62.21	37.51	28.48
800	114.000	81.74	75.99	72.19	60.93	59.88	29.26
1600	93.000	116.63	109.21	111.64	74.37	81.91	51.70
(9) ENLKHQPGGGC (SEQ ID NO:785), animals 3-4 and (11) CGGSKIGSKDNIKH (SEQ ID NO:964), animals 1-4							
dilution	**neg/NMS control**	**9.3**	**9.4**	**11.1**	**11.2**	**11.3**	**11.4**
100	100.00	49.87	33.33	50.19	49.57	69.96	29.61
200	125.44	70.11	55.25	66.19	57.12	80.40	46.60
400	111.94	79.63	62.35	88.92	90.49	95.91	72.05
800	111.72	91.34	77.86	94.14	105.11	104.90	86.62
1600	110.91	100.14	95.96	102.60	114.72	109.67	100.38
(12) CGGSKIGSLDNIKH (SEQ ID NO:965), animals 1-4							

dilution	neg/NMS control	12.1	12.2	12.3	12.4		
100	100.00	55.15	78.01	45.33	46.65		
200	125.44	60.51	76.83	57.06	57.93		
400	111.94	87.44	95.86	59.71	73.17		
800	111.72	93.85	89.73	80.34	67.75		
1600	110.91	100.58	99.20	82.68	83.47		

[00181] Example 6: Staining of Alzheimer's brain tissue with sera from mice and Guinea pigs immunized with vaccines as disclosed herein.

[00182] 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 are placed into a solution of glucose oxidase and beta D-glucose, in the presence of sodium azide, to block endogenous peroxidase.

[00183] Once tissue sections were prepared, the staining with the specified mouse immune sera was carried out at 1:500 in 5% goat serum with 0.25% triton for 1 hour at RT. To image the binding to plagues and tangles, Biotin-SP-Conjugated Goat anti mouse IgG from Jackson (Lot # 115-065-166) at 1:200 dilution was incubated with the sections. A DAKO DAB Detection Kit was used according to the manufacturer's instructions, and staining was processed using an automated Leica Bond Stainer. The results indicate that sera from mice immunized with a vaccine as disclosed herein comprise antibodies specific to tau in human brain tissue of Alzheimer's patients.

[00184] For Guinea pigs immunized with a vaccine as disclosed herein, once tissue sections were prepared, the staining with the specified Guinea pig sera was carried out at two dilutions (1:300 and 1:1500), using a rabbit anti-guinea pig 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 indicated whether sera from Guinea pigs immunized with a vaccine as disclosed herein comprise antibodies specific to tau in human brain tissue of Alzheimer's patients.

[00185] Table 6 shows a summary of the ability of the mouse sera to bind to pathological tau in Alzheimer patient brains. Figures 14-18 are examples of that binding. ND indicates not detected; + signs indicate binding.

Table 6

Ranking of mouse sera binding to pathological Tau in Alzheimer's brain

Construct	Mouse 1	Mouse 2	Mouse 3	Mouse 4
VKSKIGSTEGGC (SEQ ID NO:777)	+	+++	+++	+++
KSKIGSTEGGC (SEQ ID NO:778)	++	+++	++	+
SKIGSTENGGC (SEQ ID NO:779)	+++	+++	+	++
KIGSTENLGGC (SEQ ID NO:780)	+	++	+	ND
IGSTENLKGGC (SEQ ID NO:781)	Astrocyte only	-	-	ND
GSTENLKHGGC (SEQ ID NO:782)	-	-	-	-
STENLKHQGGC (SEQ ID NO:783)	+	-	+	ND
TENLKHQPGGC (SEQ ID NO:784)	+++	+++	++	+++
ENLKHQPGGGC (SEQ ID NO:785)	++ Astrocytes	+++	+++	++
CGGSKIGSTDNIKH (SEQ ID NO:963)	-A	-	-	-
CGGSKIGSKDNIKH (SEQ ID NO:964)	+	-A	-	-A
CGGSKIGSLDNIKH (SEQ ID NO:965)	-A	-A	+	-A
- : negative + : weak ++ : moderate +++ : strong A : astrocyte staining				

[00186] **Example 7: Mice vaccinated with Tau antigens produce titers to Tau.**

[00187] Swiss Webster Female mice are injected on day 0, 14 and 28 with 25 µg of a tau peptide immunogen (e.g., SEQ IDs herein) and 25 µg QS21 (Desert King) in PBS total 200 µl/injection. Each mouse receives 200 µl subcutaneously. Mice are bled on day 21 and 35.

[00188] 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. In addition, in each of the embodiments of the peptide described herein, the peptide may comprise, consist, or consist essentially of the recited sequences.

[00189] In each of the embodiments of the peptide described herein, the peptide may comprise, consist, or consist essentially of the recited sequences. Thus, incorporated in this disclosure (*see* Table 7) are the following sequences that can be part of the compositions comprising, consisting of or consisting essentially of an tau peptide as disclosed herein.

TABLE 7

SEQUENCES

SEQ ID NO:01 - TAU P10636-8

MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
PGGGSVQIVY KPVDLSKVTS KCGSLGNIHH KPGGGQVEVK SEKLDFKDRV QSKIGSLDNI
THVPGGGNKK IETHKLTFRE NAKAKTDHGA EIVYKSPVVS GDTSPRHLSN VSSTGSIDMV
DSPQLATLAD EVSASLAKQG L

QIVYKPV	(SEQ ID NO:02)
QIVYKP	(SEQ ID NO:03)
NIKHVP	(SEQ ID NO:04)
NIKHVPG	(SEQ ID NO:05)
HVPGGG	(SEQ ID NO:06)
HVPGG	(SEQ ID NO:07)
HKPGGG	(SEQ ID NO:08)
HKPGG	(SEQ ID NO:09)
KHVPGGG	(SEQ ID NO:10)
KHVPGG	(SEQ ID NO:11)
HQPGGG	(SEQ ID NO:12)
HQPGG	(SEQ ID NO:13)

VQIINK	(SEQ ID NO:14)
VQIINKK	(SEQ ID NO:15)
VQIINKKL	(SEQ ID NO:16)
QIINK	(SEQ ID NO:17)
QIINKK	(SEQ ID NO:18)
QIINKKL	(SEQ ID NO:19)
QIVYKSV	(SEQ ID NO:20)
EIVYKSV	(SEQ ID NO:21)
EIVYKPV	(SEQ ID NO:22)
CNIKHVP	(SEQ ID NO:23)
CNIKHVPG	(SEQ ID NO:24)
EIVYKSP	(SEQ ID NO:25)
IVYKSPV	(SEQ ID NO:26)
IVYK	(SEQ ID NO:27)
VPGGGSVQIV	(SEQ ID NO:28)
PGGGSVQIV	(SEQ ID NO:29)
GGGSVQIV	(SEQ ID NO:30)
GGSVQIV	(SEQ ID NO:31)
GSVQIV	(SEQ ID NO:32)
SVQIV	(SEQ ID NO:33)
VQIV	(SEQ ID NO:34)
QIV	(SEQ ID NO:35)
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GGGSVQIVY	(SEQ ID NO:37)
GGSVQIVY	(SEQ ID NO:38)
GSVQIVY	(SEQ ID NO:39)
SVQIVY	(SEQ ID NO:40)
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GSVQIVYK	(SEQ ID NO:46)
SVQIVYK	(SEQ ID NO:47)
VQIVYK	(SEQ ID NO:48)
QIVYK	(SEQ ID NO:49)
VYK	(SEQ ID NO:50)
GGSVQIVYKP	(SEQ ID NO:51)
GSVQIVYKP	(SEQ ID NO:52)
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IVYKP	(SEQ ID NO:55)
VYKP	(SEQ ID NO:56)
YKP	(SEQ ID NO:57)
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SVQIVYKPV	(SEQ ID NO:59)

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GAEIV	(SEQ ID NO:108)
AEIV	(SEQ ID NO:109)
EIV	(SEQ ID NO:110)
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GAEIVY	(SEQ ID NO:115)
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EIVY	(SEQ ID NO:117)
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DHGAEIVYK	(SEQ ID NO:119)
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THVP (SEQ ID NO: 565)

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QSKIGSLD (SEQ ID NO: 709)
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GSLD (SEQ ID NO: 713)
SLD (SEQ ID NO: 714)
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SLDN (SEQ ID NO: 721)
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GSLDNI (SEQ ID NO: 726)
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SLDNITH (SEQ ID NO: 735)
IGSLDNITHV (SEQ ID NO: 736)
GSLDNITHV (SEQ ID NO: 737)
SLDNITHV (SEQ ID NO: 738)
GSLDNITHVP (SEQ ID NO: 739)
SLDNITHVP (SEQ ID NO: 740)
SLDNITHVPG (SEQ ID NO: 741)

Lys Xaa_1 Xaa_2 Ser Xaa_3 Xaa_4 Asn Xaa_5 Xaa_6 His (SEQ ID NO: 742),
wherein
Xaa_1 is I or C;
Xaa_2 is G;
Xaa_3 is T, K or L,
Xaa_4 is E, D or G,
Xaa_5 is L or I,

Xaa_6 is K, H or T.

Arg-Val-Arg-Arg (SEQ ID NO: 743),
Gly-Ala-Gly-Ala (SEQ ID NO: 744),
Ala-Gly-Ala-Gly (SEQ ID NO: 745),
Lys-Gly-Lys-Gly (SEQ ID NO: 746),

Lys Xaa_7 Xaa_7 Ser Xaa_7 Xaa_7 Asn Xaa_7 Xaa_8 His (SEQ ID NO: 747),
wherein
Xaa_7 is any amino acid, and
Xaa_8 is K or 543H.

Xaa_9 Ile Val Tyr Lys Xaa_{10} (SEQ ID NO: 748),
wherein
Xaa_9 is Gln or Glu, and
Xaa_{10} is Ser or Pro.

Ser Lys Xaa_{11} Gly Ser (SEQ ID NO: 749),
wherein
Xaa_{11} is I or C.

SEQ ID NO:750 – Tau P10636-1,

MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT
PTEDGSEEPG SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG
TTAEEAGIGD TPSLEDEAAG HVTQEPESGK VVQEGFLREP GPPGLSHQLM
SGMPGAPLLP EGPREATRQP SGTGPEDTEG GRHAPELLKH QLLGDLHQEG
PPLKGAGGKE RPGSKEEVDE DRDVDESSPQ DSPPSKASPA QDGRPPQTAA
REATSIPGFP AEGAIPLPVD FLSKVSTEIP ASEPDGPSVG RAKGQDAPLE
FTFHVEITPN VQKEQAHSEE HLGRAAFPGA PGEGPEARGP SLGEDTKEAD
LPEPSEKQPA AAPRGKPVSR VPQLKARMVS KSKDGTGSDD KKAKTSTRSS
AKTLKNRPCL SPKHPTPGSS DPLIQPSSPA VCPEPPSSPK YVSSVTSRTG
SSGAKEMKLK GADGKTKIAT PRGAAPPGQK GQANATRIPA KTPPAPKTPP
SSGEPPKSGD RSGYSSPGSP GTPGSRSRTP SLPTPPTREP KKVAVVRTPP
KSPSSAKSRL QTAPVPMPDL KNVKSKIGST ENLKHQPGGG KVQIINKKLD
LSNVQSKCGS KDNIKHVPGG GSVQIVYKPV DLSKVTSKCG SLGNIHHKPG
GGQVEVKSEK LDFKDRVQSK IGSLDNITHV PGGGNKKIET HKLTFRENAK
AKTDHGAEIV YKSPVVSGDT SPRHLSNVSS TGSIDMVDSP QLATLADEVS
ASLAKQGL

MTBR peptide 1 (SEQ ID NO: 751):
QTAPVPMPDLKNVKSKIGSTENLKHQPGGGK

MTBR peptide 2, (SEQ ID NO: 752):
VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS

MTBR peptide 3, (SEQ ID NO: 753)

VQIVYKPVDLSKVTSKCGSLGNIHHKPGGGQ

MTBR peptide 4, (SEQ ID NO: 754)
VEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN

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NVKSKIGS	(SEQ ID NO: 759)
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DLSNVQSK	(SEQ ID NO: 761)
LSNVQSKC	(SEQ ID NO: 762)
SNVQSKCG	(SEQ ID NO: 763)
NVQSKCGS	(SEQ ID NO: 764)
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DLSKVTSK	(SEQ ID NO: 766)
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SKVTSKCG	(SEQ ID NO: 768)
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VTSKCGSL	(SEQ ID NO: 770)
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DFKDRVQS	(SEQ ID NO: 772)
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DRVQSKIG	(SEQ ID NO: 775)
RVQSKIGS	(SEQ ID NO: 776)
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IGSTENLKGGC	(SEQ ID NO: 781)
GSTENLKHGGC	(SEQ ID NO: 782)
STENLKHQGGC	(SEQ ID NO: 783)
TENLKHQPGGC	(SEQ ID NO: 784)
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DLKNVKSKGGC	(SEQ ID NO: 788)
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DLSNVQSKGGC	(SEQ ID NO: 795)

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ITHVPGGGGGC (SEQ ID NO: 842)

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LKHQPGGGGGGC (SEQ ID NO: 859)
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DFKDRVQSGGGC (SEQ ID NO: 893)
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CGGSKIGSLDNIKH (SEQ ID NO: 965)
CGGGSKIGSTDNIKH (SEQ ID NO: 966)
CGGGSKIGSKDNIKH (SEQ ID NO: 967)
CGGGSKIGSLDNIKH (SEQ ID NO: 968)
GGGS (SEQ ID NO:969)
GGGGS (SEQ ID NO:970).

WHAT IS CLAIMED IS:

1. A peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750.

2. The peptide of claim 1, wherein the peptide is from the microtubule binding region (MTBR) of tau (residues 244-372 of SEQ ID NO:01).

3. The peptide of claim 1, wherein the peptide comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NO:02 to SEQ ID NO:19, SEQ ID NO:25 to SEQ ID NO:320, SEQ ID NO:411, SEQ ID NO:454, SEQ ID NO:456, SEQ ID NO:458 to SEQ ID NO:742, SEQ ID NO:747 to SEQ ID NO:749, or SEQ ID NO:755 to SEQ ID NO:776.

4. The peptide of claim 3, wherein the peptide comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NO:02 to SEQ ID NO:19, SEQ ID NO:28 to SEQ ID NO:102, SEQ ID NO:185 to SEQ ID NO:320, SEQ ID NO:458 to SEQ ID NO:742, or SEQ ID NO:747 to SEQ ID NO:749.

5. The peptide of any one of claims 1-4, wherein the peptide further comprises a C-terminal cysteine (-C) or an N-terminal cysteine (C-).

6. The peptide of any one of claims 1-4, wherein the peptide further comprises a C-terminal -GGC or -GGGC.

7. The peptide of any one of claims 1-4, wherein the peptide further comprises a N-terminal CGG or CGGG-.

8. The peptide of any one of claims 1-7, wherein the peptide comprises 7-13 amino acids from residues 244-400 of SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750.

9. The peptide of any one of claims 1-7, wherein the peptide comprises 8 amino acids from residues 244-400 of SEQ ID NO:01.

10. The peptide of any one of claims 1-7, wherein the peptide comprises 8 amino acids from residues 1-150 of SEQ ID NO:750.

11. The peptide of any one of claims 1-7, wherein the peptide comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NO:777 to SEQ ID NO:908.

12. A peptide comprising an amino acid sequence selected from the group consisting of any one of SEQ ID NO:20 to SEQ ID NO:24, SEQ ID NO:312 to SEQ ID NO:457, each optionally further comprising a C-terminal cysteine.

13. The peptide of any one of claims 1-7, wherein the peptide comprises an amino acid sequence selected from the group consisting of

QIVYKPV (SEQ ID NO:02),
QIVYKP (SEQ ID NO:03),
NIKHVP (SEQ ID NO:04),
NIKHVPG (SEQ ID NO:05),
HVPGGG (SEQ ID NO:06),
HVPGG (SEQ ID NO:07),
HKPGGG (SEQ ID NO:08),
HKPGG (SEQ ID NO:09),
KHVPGGG (SEQ ID NO:10),
KHVPGG (SEQ ID NO:11),
HQPGGG (SEQ ID NO:12),
HQPGG (SEQ ID NO:13),
VQIINK (SEQ ID NO:14),
VQIINKK (SEQ ID NO:15),
VQIINKKL (SEQ ID NO:16),
QIINK (SEQ ID NO:17),
QIINKK (SEQ ID NO:18),
QIINKKL (SEQ ID NO:19),
EIVYKSP (SEQ ID NO:25),
IVYKSPV (SEQ ID NO:26),
IVYK (SEQ ID NO:27),
QIVYKS (SEQ ID NO:325),
EIVYKS (SEQ ID NO:131),
EIVYKP (SEQ ID NO:411),
GYTMHQD (SEQ ID NO:454),
QGGYTMHQD (SEQ ID NO:456),
VKSKIGSTE (SEQ ID NO:589),
KSKIGSTE (SEQ ID NO:590),
SKIGSTEN (SEQ ID NO:598),
KIGSTENL (SEQ ID NO:605),
IGSTENLK (SEQ ID NO:611),
GSTENLKH (SEQ ID NO:616),
STENLKHQ (SEQ ID NO:620),
TENLKHQP (SEQ ID NO:476),
ENLKHQPG (SEQ ID NO:470),
VKSKIGST (SEQ ID NO:582),
PDLKNVKS (SEQ ID NO:755),
DLKNVKSK (SEQ ID NO:756),
LKNVKSKI (SEQ ID NO:757),
KNVKSKIG (SEQ ID NO:758),
NVKSKIGS (SEQ ID NO:759),
NLKHQPGG (SEQ ID NO:465),
LKHQPGGG (SEQ ID NO:460),

LDLSNVQS (SEQ ID NO:760),
DLSNVQSK (SEQ ID NO:761),

LSNVQSKC (SEQ ID NO:762),
SNVQSKCG (SEQ ID NO:763),
NVQSKCGS (SEQ ID NO:764),
VQSKCGSK (SEQ ID NO:626),
QSKCGSKD (SEQ ID NO:634),
SKCGSKDN (SEQ ID NO:642),
KCGSKDNI (SEQ ID NO:649),
CGSKDNIK (SEQ ID NO:258),
GSKDNIKH (SEQ ID NO:653),
SKDNIKHV (SEQ ID NO:271),
KDNIKHVP (SEQ ID NO:278),
DNIKHVPG (SEQ ID NO:285),
NIKHVPGG (SEQ ID NO:292),
IKHVPGGG (SEQ ID NO:297),
VDLSKVTS (SEQ ID NO:765),
DLSKVTSK (SEQ ID NO:766),
LSKVTSKC (SEQ ID NO:767),
SKVTSKCG (SEQ ID NO:768),
KVTSKCGS (SEQ ID NO:769),
VTSKCGSL (SEQ ID NO:770),
TSKCGSLG (SEQ ID NO:666),
SKCGSLGN (SEQ ID NO:674),
KCGSLGNI (SEQ ID NO:681),
CGSLGNIH (SEQ ID NO:687),
GSLGNIHH (SEQ ID NO:692),
SLGNIHHK (SEQ ID NO:696),
LGNIHHKP (SEQ ID NO:524),
GNIHHKPG (SEQ ID NO:518),
NIHHKPGG (SEQ ID NO:513),
IHHKPGGG (SEQ ID NO:508),
LDFKDRVQ (SEQ ID NO:771),
DFKDRVQS (SEQ ID NO:772),
FKDRVQSK (SEQ ID NO:773),
KDRVQSKI (SEQ ID NO:774),
DRVQSKIG (SEQ ID NO:775),
RVQSKIGS (SEQ ID NO:776),
VQSKIGSL (SEQ ID NO:702),
QSKIGSLD (SEQ ID NO:709),
SKIGSLDN (SEQ ID NO:717),
KIGSLDNI (SEQ ID NO:724),
IGSLDNIT (SEQ ID NO:729),
GSLDNITH (SEQ ID NO:734),
SLDNITHV (SEQ ID NO:738),
LDNITHVP (SEQ ID NO:561),
DNITHVPG (SEQ ID NO:555),
NITHVPGG (SEQ ID NO:551), and

ITHVPGGG (SEQ ID NO:547).

14. The peptide of claim 12, wherein the peptide comprises and amino acid sequence selected from the group consisting of

QIVYKSV (SEQ ID NO:20),
EIVYKSV (SEQ ID NO:21),
EIVYKPV (SEQ ID NO:22),
CNIKHVP (SEQ ID NO:23),
CNIKHVPG (SEQ ID NO:24),
EAAGHVTQC (SEQ ID NO:449),
EAAGHVTQAR (SEQ ID NO:450),
AAGHVTQAC (SEQ ID NO:451),
AGHVTQARC (SEQ ID NO:452),
AGHVTQAR (SEQ ID NO:453),
QGGYTMHC (SEQ ID NO:455), and
GGYTMHQC (SEQ ID NO:457).

15. The peptide of either one of claims 13 or 14, wherein the peptide further comprises a C-terminal cysteine (-C), -GGC or -GGGC or an N-terminal cysteine (C-), CGG- or CGGG-.

16. The peptide of claim 13, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VKSKIGSTE (SEQ ID NO:589),
KSKIGSTE (SEQ ID NO:590),
SKIGSTEN (SEQ ID NO:598),
KIGSTENL (SEQ ID NO:605),
IGSTENLK (SEQ ID NO:611),
GSTENLKH (SEQ ID NO:616),
STENLKHQ (SEQ ID NO:620),
TENLKHQP (SEQ ID NO:476), and
ENLKHQPG (SEQ ID NO:470).

17. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VKSKIGSTEGGC (SEQ ID NO:777),
KSKIGSTEGGC (SEQ ID NO:778),
SKIGSTENGGC (SEQ ID NO:779),
KIGSTENLGGC (SEQ ID NO:780),
IGSTENLKGGC (SEQ ID NO:781),
GSTENLKHGGC (SEQ ID NO:782),
STENLKHQGGC (SEQ ID NO:783),
TENLKHQPGGC (SEQ ID NO:784),
ENLKHQPGGGC (SEQ ID NO:785),
VKSKIGSTGGC (SEQ ID NO:786),
PDLKNVKSGGC (SEQ ID NO:787),
DLKNVKSKGGC (SEQ ID NO:788),

LKNVKSKIGGC (SEQ ID NO:789),
KNVKSKIGGGC (SEQ ID NO:790),
NVKSKIGSGGC (SEQ ID NO:791),
NLKHQPGGGGC (SEQ ID NO:792), and
LKHQPGGGGGC (SEQ ID NO:793).

18. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

LDLSNVQSGGC (SEQ ID NO:794),
DLSNVQSKGGC (SEQ ID NO:795),
LSNVQSKCGGC (SEQ ID NO:796),
SNVQSKCGGGC (SEQ ID NO:797),
NVQSKCGSGGC (SEQ ID NO:798),
VQSKCGSKGGC (SEQ ID NO:799),
QSKCGSKDGGC (SEQ ID NO:800),
SKCGSKDNGGC (SEQ ID NO:801),
KCGSKDNIGGC (SEQ ID NO:802),
CGSKDNIKGGC (SEQ ID NO:803),
GSKDNIKHGGC (SEQ ID NO:804),
SKDNIKHVGGC (SEQ ID NO:805),
KDNIKHVPGGC (SEQ ID NO:806),
DNIKHVPGGGC (SEQ ID NO:807),
NIKHVPGGGGC (SEQ ID NO:808), and
IKHVPGGGGGC (SEQ ID NO:809),

19. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VDLSKVTSGGC (SEQ ID NO:810),
DLSKVTSKGGC (SEQ ID NO:811),
LSKVTSKCGGC (SEQ ID NO:812),
SKVTSKCGGGC (SEQ ID NO:813),
KVTSKCGSGGC (SEQ ID NO:814),
VTSKCGSLGGC (SEQ ID NO:815),
TSKCGSLGGGC (SEQ ID NO:816),
SKCGSLGNGGC (SEQ ID NO:817),
KCGSLGNIGGC (SEQ ID NO:818),
CGSLGNIHGGC (SEQ ID NO:819),
GSLGNIHHGGC (SEQ ID NO:820),
SLGNIHHKGGC (SEQ ID NO:821),
LGNIHHKPGGC (SEQ ID NO:822),
GNIHHKPGGGC (SEQ ID NO:823),
NIHHKPGGGGC (SEQ ID NO:824), and
IHHKPGGGGGC (SEQ ID NO:825),

20. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

LDFKDRVQGGC (SEQ ID NO:826),
DFKDRVQSGGC (SEQ ID NO:827),
FKDRVQSKGGC (SEQ ID NO:828),
KDRVQSKIGGC (SEQ ID NO:829),
DRVQSKIGGGC (SEQ ID NO:830),
RVQSKIGSGGC (SEQ ID NO:831),
VQSKIGSLGGC (SEQ ID NO:832),
QSKIGSLDGGC (SEQ ID NO:833),
SKIGSLDNGGC (SEQ ID NO:834),
KIGSLDNIGGC (SEQ ID NO:835),
IGSLDNITGGC (SEQ ID NO:836),
GSLDNITHGGC (SEQ ID NO:837),
SLDNITHVGGC (SEQ ID NO:838),
LDNITHVPGGC (SEQ ID NO:839),
DNITHVPGGGC (SEQ ID NO:840),
NITHVPGGGGC (SEQ ID NO:841), and
ITHVPGGGGGC (SEQ ID NO:842).

21. The peptide of claim 17, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VKSKIGSTEGGC (SEQ ID NO:777),
KSKIGSTEGGC (SEQ ID NO:778),
SKIGSTENGGC (SEQ ID NO:779),
KIGSTENLGGC (SEQ ID NO:780),
IGSTENLKGGC (SEQ ID NO:781),
GSTENLKHGGC (SEQ ID NO:782),
STENLKHQGGC (SEQ ID NO:783),
TENLKHQPGGC (SEQ ID NO:784), and
ENLKHQPGGGC (SEQ ID NO:785).

22. The peptide of claim 18, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VQSKCGSKGGC (SEQ ID NO:799),
QSKCGSKDGGC (SEQ ID NO:800),
SKCGSKDNGGC (SEQ ID NO:801),
KCGSKDNIGGC (SEQ ID NO:802),
CGSKDNIKGGC (SEQ ID NO:803),
GSKDNIKHGGC (SEQ ID NO:804),
SKDNIKHVGGC (SEQ ID NO:805),
KDNIKHVPGGC (SEQ ID NO:806), and
DNIKHVPGGGC (SEQ ID NO:807).

23. The peptide of claim 19, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VTSKCGSLGGC (SEQ ID NO:815),
TSKCGSLGGGC (SEQ ID NO:816),

SKCGSLGNGGC (SEQ ID NO:817),
KCGSLGNIGGC (SEQ ID NO:818),
CGSLGNIHGGC (SEQ ID NO:819),
GSLGNIHHGGC (SEQ ID NO:820),
SLGNIHHKGGC (SEQ ID NO:821),
LGNIHHKPGGC (SEQ ID NO:822), and
GNIHHKPGGGC (SEQ ID NO:823).

24. The peptide of claim 20, wherein the peptide comprises an amino acid sequence selected from the group consisting of

RVQSKIGSGGC (SEQ ID NO:831),
VQSKIGSLGGC (SEQ ID NO:832),
QSKIGSLDGGC (SEQ ID NO:833),
SKIGSLDNGGC (SEQ ID NO:834),
KIGSLDNIGGC (SEQ ID NO:835),
IGSLDNITGGC (SEQ ID NO:836),
GSLDNITHGGC (SEQ ID NO:837),
SLDNITHVGGC (SEQ ID NO:838),
LDNITHVPGGC (SEQ ID NO:839), and
DNITHVPGGGC (SEQ ID NO:840).

25. The peptide of claim 21, comprising an amino acid sequence of KSKIGSTEGGC (SEQ ID NO:778).

26. The peptide of claim 21, comprising an amino acid sequence of SKIGSTENGGC (SEQ ID NO:779).

27. The peptide of claim 21, comprising an amino acid sequence of TENLKHQPGGC (SEQ ID NO:784).

28. The peptide of claim 21, comprising an amino acid sequence of ENLKHQPGGGC (SEQ ID NO:785).

29. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VKSKIGSTEGGGC (SEQ ID NO:851),
PDLKNVKSGGGC (SEQ ID NO:852),
DLKNVKSKGGGC (SEQ ID NO:853),
LKNVKSKIGGGC (SEQ ID NO:854),
KNVKSKIGGGGC (SEQ ID NO:855),
NVKSKIGSGGGC (SEQ ID NO:856),
VKSKIGSTEGGGC (SEQ ID NO:843),
KSKIGSTEGGGC (SEQ ID NO:844),
SKIGSTENGGGC (SEQ ID NO:845),
KIGSTENLGGGC (SEQ ID NO:846),

IGSTENLKGGGC (SEQ ID NO:847),
GSTENLKHGGGC (SEQ ID NO:848),
STENLKHQGGGC (SEQ ID NO:849),
TENLKHQPGGGC (SEQ ID NO:850),
ENLKHQPGGGGC (SEQ ID NO:857),
NLKHQPGGGGGC (SEQ ID NO:858), and
LKHQPGGGGGGC (SEQ ID NO:859).

30. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

LDLSNVQSGGGC (SEQ ID NO:860),
DLSNVQSKGGGC (SEQ ID NO:861),
LSNVQSKCGGGC (SEQ ID NO:862),
SNVQSKCGGGGC (SEQ ID NO:863),
NVQSKCGSGGGC (SEQ ID NO:864),
VQSKCGSKGGGC (SEQ ID NO:865),
QSKCGSKDGGGC (SEQ ID NO:866),
SKCGSKDNGGGC (SEQ ID NO:867),
KCGSKDNIGGGC (SEQ ID NO:868),
CGSKDNIKGGGC (SEQ ID NO:869),
GSKDNIKHGGGC (SEQ ID NO:870),
SKDNIKHVGGGC (SEQ ID NO:871),
KDNIKHVPGGGC (SEQ ID NO:872),
DNIKHVPGGGGC (SEQ ID NO:873),
NIKHVPGGGGGC (SEQ ID NO:874), and
IKHVPGGGGGGC (SEQ ID NO:875).

31. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VDLSKVTSGGGC (SEQ ID NO:876),
DLSKVTSKGGGC (SEQ ID NO:877),
LSKVTSKCGGGC (SEQ ID NO:878),
SKVTSKCGGGGC (SEQ ID NO:879),
KVTSKCGSGGGC (SEQ ID NO:880),
VTSKCGSLGGGC (SEQ ID NO:881),
TSKCGSLGGGGC (SEQ ID NO:882),
SKCGSLGNGGGC (SEQ ID NO:883),
KCGSLGNIGGGC (SEQ ID NO:884),
CGSLGNIHGGGC (SEQ ID NO:885),
GSLGNIHHGGGC (SEQ ID NO:886),
SLGNIHHKGGGC (SEQ ID NO:887),
LGNIHHKPGGGC (SEQ ID NO:888),
GNIHHKPGGGGC (SEQ ID NO:889),
NIHHKPGGGGGC (SEQ ID NO:890), and
IHHKPGGGGGGC (SEQ ID NO:891).

32. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

LDFKDRVQGGGC (SEQ ID NO:892),
DFKDRVQSGGGC (SEQ ID NO:893),
FKDRVQSKGGGC (SEQ ID NO:894),
KDRVQSKIGGGC (SEQ ID NO:895),
DRVQSKIGGGGC (SEQ ID NO:896),
RVQSKIGSGGGC (SEQ ID NO:897),
VQSKIGSLGGGC (SEQ ID NO:898),
QSKIGSLDGGGC (SEQ ID NO:899),
SKIGSLDNGGGC (SEQ ID NO:900),
KIGSLDNIGGGC (SEQ ID NO:901),
IGSLDNITGGGC (SEQ ID NO:902),
GSLDNITHGGGC (SEQ ID NO:903),
SLDNITHVGGGC (SEQ ID NO:904),
LDNITHVPGGGC (SEQ ID NO:905),
DNITHVPGGGGC (SEQ ID NO:906),
NITHVPGGGGGC (SEQ ID NO:907), and
ITHVPGGGGGGC (SEQ ID NO:908).

33. The peptide of claim 11, wherein the peptide comprises an amino acid sequence selected from the group consisting of

CGGGSKIGSTDNIKH (SEQ ID NO:966),
CGGGSKIGSKDNIKH (SEQ ID NO:967),
CGGGSKIGSLDNIKH (SEQ ID NO:968),
CGGSKIGSTDNIKH (SEQ ID NO:963),
CGGSKIGSKDNIKH (SEQ ID NO:964),
CGGSKIGSLDNIKH (SEQ ID NO:965).

34. The peptide of claim 29, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VKSKIGSTEGGGC (SEQ ID NO:843),
KSKIGSTEGGGC (SEQ ID NO:844),
SKIGSTENGGGC (SEQ ID NO:845),
KIGSTENLGGGC (SEQ ID NO:846),
IGSTENLKGGGC (SEQ ID NO:847),
GSTENLKHGGGC (SEQ ID NO:848),
STENLKHQGGGC (SEQ ID NO:849),
TENLKHQPGGGC (SEQ ID NO:850), and
ENLKHQPGGGGC (SEQ ID NO:857).

35. The peptide of claim 30, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VQSKCGSKGGGC (SEQ ID NO:865),
QSKCGSKDGGGC (SEQ ID NO:866),
SKCGSKDNGGGC (SEQ ID NO:867),

KCGSKDNIGGGC (SEQ ID NO:868),
CGSKDNIKGGGC (SEQ ID NO:869),
GSKDNIKHGGGC (SEQ ID NO:870),
SKDNIKHVGGGC (SEQ ID NO:871),
KDNIKHVPGGGC (SEQ ID NO:872), and
DNIKHVPGGGGC (SEQ ID NO:873).

36. The peptide of claim 31, wherein the peptide comprises an amino acid sequence selected from the group consisting of

VTSKCGSLGGGC (SEQ ID NO:881),
TSKCGSLGGGGC (SEQ ID NO:882),
SKCGSLGNGGGC (SEQ ID NO:883),
KCGSLGNIGGGC (SEQ ID NO:884),
CGSLGNIHGGGC (SEQ ID NO:885),
GSLGNIHHGGGC (SEQ ID NO:886),
SLGNIHHKGGGC (SEQ ID NO:887),
LGNIHHKPGGGC (SEQ ID NO:888), and
GNIHHKPGGGGC (SEQ ID NO:889).

37. The peptide of claim 32, wherein the peptide comprises an amino acid sequence selected from the group consisting of

RVQSKIGSGGGC (SEQ ID NO:897),
VQSKIGSLGGGC (SEQ ID NO:898),
QSKIGSLDGGGC (SEQ ID NO:899),
SKIGSLDNGGGC (SEQ ID NO:890),
KIGSLDNIGGGC (SEQ ID NO:891),
IGSLDNITGGGC (SEQ ID NO:892),
GSLDNITHGGGC (SEQ ID NO:893),
SLDNITHVGGGC (SEQ ID NO:894),
LDNITHVPGGGC (SEQ ID NO:895), and
DNITHVPGGGGC (SEQ ID NO:896).

38. The peptide of claim 33, comprising an amino acid sequence of CGGGSKIGSKDNIKH (SEQ ID NO:967).

39. The peptide of claim 33, comprising an amino acid sequence of CGGSKIGSKDNIKH (SEQ ID NO:964).

40. The peptide of claim 34, comprising an amino acid sequence of VKSKIGSTEGGGC (SEQ ID NO:843).

41. The peptide of claim 34, comprising an amino acid sequence of KSKIGSTEGGGC (SEQ ID NO:844).

42. The peptide of claim 34, comprising an amino acid sequence of SKIGSTENGGGC (SEQ ID NO:845).

43. The peptide of claim 34, comprising an amino acid sequence of KIGSTENLGGGC (SEQ ID NO:846).

44. The peptide of claim 34, comprising an amino acid sequence of IGSTENLKGGGC (SEQ ID NO:847).

45. The peptide of claim 34, comprising an amino acid sequence of GSTENLKHGGGC (SEQ ID NO:848).

46. The peptide of claim 34, comprising an amino acid sequence of STENLKHQGGGC (SEQ ID NO:849).

47. The peptide of claim 34, comprising an amino acid sequence of TENLKHQPGGGC (SEQ ID NO:850).

48. The peptide of claim 34, comprising an amino acid sequence of ENLKHQPGGGGC (SEQ ID NO:857).

49. The peptide of claim 13, comprising an amino acid sequence of QIINK (SEQ ID NO:17).

50. The peptide of claim 13, comprising an amino acid sequence of QIVYKPV (SEQ ID NO:02).

51. The peptide of claim 13, comprising an amino acid sequence of NIKHVP (SEQ ID NO:04).

52. The peptide of claim 13, comprising an amino acid sequence of NIKHVPG (SEQ ID NO:05).

53. The peptide of claim 14, comprising an amino acid sequence of EIVYKSV (SEQ ID NO:21).

54. The peptide of claim 16, comprising an amino acid sequence of VKSKIGSTE (SEQ ID NO:589).

55. The peptide of claim 16, comprising an amino acid sequence of KSKIGSTE (SEQ ID NO:590).

56. The peptide of claim 16, comprising an amino acid sequence of SKIGSTEN (SEQ ID NO:598).

57. The peptide of claim 16, comprising an amino acid sequence of KIGSTENL (SEQ ID NO:605).

58. The peptide of claim 16, comprising an amino acid sequence of IGSTENLK (SEQ ID NO:611).

59. The peptide of claim 16, comprising an amino acid sequence of GSTENLKH (SEQ ID NO:616).

60. The peptide of claim 16, comprising an amino acid sequence of STENLKHQ (SEQ ID NO:620).

61. The peptide of claim 16, comprising an amino acid sequence of TENLKHQP (SEQ ID NO:476).

61. The peptide of claim 16, comprising an amino acid sequence of ENLKHQPG (SEQ ID NO:470).

62. A peptide comprising 5-13 amino acids from residues 244-400 of SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750, comprising at least one amino acid substitution.

63. The peptide of claim 62, comprising an amino acid sequence of SKIGSTENLKH (SEQ ID NO:909)

64. The peptide of claim 63, wherein one of the at least one amino acid substitutions comprises an isoleucine substitution for a lysine at position 10.

65. The peptide of either one of claims 63 or 64, wherein one of the at least one amino acid substitutions comprises a lysine or leucine substitution for a tyrosine at position 6.

66. The peptide of any one of claims 63-65, wherein one of the at least one amino acid substitutions comprises an aspartic acid or glycine substitution for a glutamic acid at position 7.

67. The peptide of claim 62, wherein the peptide comprises an amino acid sequence selected from the group consisting of

SKIGSTENLKH (SEQ ID NO:909),
SKIGSTENIKH (SEQ ID NO:910),
SKIGSKDNLKH (SEQ ID NO:911),
SKIGSKENIKH (SEQ ID NO:912),
SKIGSLENLKH (SEQ ID NO:913),
SKIGSLENIKH (SEQ ID NO:914),
SKIGSTDNLKH (SEQ ID NO:915),
SKIGSTDNIKH (SEQ ID NO:916),
SKIGSKDNLKH (SEQ ID NO:917),
SKIGSKDNIKH (SEQ ID NO:918),
SKIGSLDNLKH (SEQ ID NO:919),
SKIGSLDNIKH (SEQ ID NO:920),
SKIGSTGNLKH (SEQ ID NO:921),
SKIGSTGNIKH (SEQ ID NO:922),
SKIGSKGNLKH (SEQ ID NO:923),
SKIGSKGNIKH (SEQ ID NO:924),
SKIGSLGNLKH (SEQ ID NO:925),

SKIGSLGNIKH (SEQ ID NO:926).

68. The peptide of claim 67, wherein the peptide comprises an amino acid sequence selected from the group consisting of SKIGSTDNIKH (SEQ ID NO:916), SKIGSKDNIKH (SEQ ID NO:918), or SKIGSLDNIKH (SEQ ID NO:920).

69. The peptide of any one of claims 62-68, wherein the peptide further comprises a C-terminal cysteine (-C), -GGC or -GGGC or an N-terminal cysteine (C-), CGG- or CGGG-.

70. The peptide of claim 69, wherein the peptide comprises an amino acid sequence selected from the group consisting of

SKIGSTENLKHGGC (SEQ ID NO:927),
SKIGSTENIKHGGC (SEQ ID NO:928),
SKIGSKDNLKHGGC (SEQ ID NO:929),
SKIGSKENIKHGGC (SEQ ID NO:930),
SKIGSLENLKHGGC (SEQ ID NO:931),
SKIGSLENIKHGGC (SEQ ID NO:932),
SKIGSTDNLKHGGC (SEQ ID NO:933),
SKIGSTDNIKHGGC (SEQ ID NO:934),
SKIGSKDNLKHGGC (SEQ ID NO:935),
SKIGSKDNIKHGGC (SEQ ID NO:936),
SKIGSLDNLKHGGC (SEQ ID NO:937),
SKIGSLDNIKHGGC (SEQ ID NO:938),
SKIGSTGNLKHGGC (SEQ ID NO:939),
SKIGSTGNIKHGGC (SEQ ID NO:940),
SKIGSKGNLKHGGC (SEQ ID NO:941),
SKIGSKGNIKHGGC (SEQ ID NO:942),
SKIGSLGNLKHGGC (SEQ ID NO:943),
SKIGSLGNIKHGGC (SEQ ID NO:944),
SKIGSTENLKHGGGC (SEQ ID NO:945),
SKIGSTENIKHGGGC (SEQ ID NO:946),
SKIGSKDNLKHGGGC (SEQ ID NO:947),
SKIGSKENIKHGGGC (SEQ ID NO:948),
SKIGSLENLKHGGGC (SEQ ID NO:949),
SKIGSLENIKHGGGC (SEQ ID NO:950),
SKIGSTDNLKHGGGC (SEQ ID NO:951),
SKIGSTDNIKHGGGC (SEQ ID NO:952),
SKIGSKDNLKHGGGC (SEQ ID NO:953),
SKIGSKDNIKHGGGC (SEQ ID NO:954),
SKIGSLDNLKHGGGC (SEQ ID NO:955),
SKIGSLDNIKHGGGC (SEQ ID NO:956),
SKIGSTGNLKHGGGC (SEQ ID NO:957),
SKIGSTGNIKHGGGC (SEQ ID NO:958),
SKIGSKGNLKHGGGC (SEQ ID NO:959),
SKIGSKGNIKHGGGC (SEQ ID NO:960),
SKIGSLGNLKHGGGC (SEQ ID NO:961),

SKIGSLGNIKHGGGC (SEQ ID NO:962),
CGGSKIGSTDNIKH (SEQ ID NO:963),
CGGSKIGSKDNIKH (SEQ ID NO:964),
CGGSKIGSLDNIKH (SEQ ID NO:965),
CGGGSKIGSTDNIKH (SEQ ID NO:966),
CGGGSKIGSKDNIKH (SEQ ID NO:967), and
CGGGSKIGSLDNIKH (SEQ ID NO:968).

71. The peptide of any one of claims 1-70, further comprising a linker to a carrier at a C-terminal portion of the peptide or at a N-terminal portion of the peptide.

72. The peptide of claim 71, wherein the linker comprises an amino acid sequence.

73. The peptide of claim 72, wherein the linker amino acid sequence 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.

74. The peptide of claim 72, wherein the linker comprises an amino acid sequence selected from the group consisting of AA, AAA, KK, KKK, SS, SSS AGAG, GG, GGG, GAGA, KGKG, (GGS)n, (GGGS)n, and (GGGGS)n, where n=1-3.

75. The peptide of any one of claims 1 to 74, wherein the peptide or linker to the carrier, if present, further comprises a C-terminal cysteine (C).

76. The peptide of any one of claims 1 to 75, wherein the peptide further comprises a blocked amine at the N-terminus.

77. An immunotherapy composition, comprising one or more of the peptides of any of claims 1 to 76.

78. The immunotherapy composition of claim 77, wherein the one or more peptides further comprises a linker to a carrier at a C-terminal portion of the peptide.

79. The immunotherapy composition of claim 78, wherein the linker to the carrier comprises an amino acid sequence selected from the group consisting of AA, AAA, KK, KKK, SS, SSS AGAG, GG, GGG, GAGA, KGKG, (GGS)n, (GGGS)n, and (GGGGS)n, where n=1-3.

80. The immunotherapy composition of either one of claims 78 or 79, 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.

81. The immunotherapy composition of claim 80, wherein the carrier is CRM197.

82. The immunotherapy composition of claim 81, wherein the carrier is diphtheria toxoid.

83. The immunotherapy composition of any one of claims 77 to 82, further comprising at least one pharmaceutically acceptable diluent.

84. The immunotherapy composition of any one of claims 77 to 83, further comprising a multiple antigen presenting system (MAP).

85. The immunotherapy composition of claim 84, 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.

86. A pharmaceutical composition comprising (a) one or more of the peptides of any of claims 1 to 76 or (b) the immunotherapy composition of any of claims 77 to 85 and at least one adjuvant.

87. The pharmaceutical composition of claim 86, 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, TQL-1055, 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.

88. The pharmaceutical composition of claim 87, wherein the adjuvant is QS-21 or TQL-1055.

89. The pharmaceutical composition of claim 87, wherein the adjuvant is MPL.

90. The pharmaceutical composition of claim 87, wherein the adjuvant is a combination of MPL and QS-21 or a combination of MPL and TQL-1055.

91. The pharmaceutical composition of any of claims 86 to 90, wherein the adjuvant comprises a liposomal formulation.

92. The pharmaceutical composition of any of claims 86 to 91, wherein the composition comprises at least one pharmaceutically acceptable diluent.

93. The pharmaceutical formulation of any of claims 86 to 92, comprising a multiple antigen presenting system (MAP).

94. The pharmaceutical formulation of claim 93, 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.

95. A nucleic acid comprising a nucleic acid sequence encoding a peptide of any one of claims 1 to 76 or the immunotherapy composition of claims 77 to 85.

96. A nucleic acid immunotherapy composition comprising the nucleic acid of claim 95 and at least one adjuvant.

97. A method of treating or effecting prophylaxis of Alzheimer's disease in a subject, comprising administrating to the subject the immunotherapy composition of any of claims 77 to 85 or the pharmaceutical compositions of any of claims 86 to 94.

98. A method of inhibiting or reducing aggregation of tau in a subject having or at risk of developing Alzheimer's disease, comprising, administering to the subject the immunotherapy composition of any of claims 77 to 85 or the pharmaceutical formulations of any of claims 86 to 94.

99. A method of treating or effecting prophylaxis of Alzheimer's disease in a subject, comprising administrating to the subject the nucleic acid immunotherapy composition of claim 95 or 96.

100. A method of inhibiting or reducing aggregation of tau in a subject having or at risk of developing Alzheimer's disease, comprising administering to the subject the nucleic acid immunotherapy composition of claim 96 or 96.

101. The method of any of claims 97 to 100, 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.

102. The method of claim 101, further comprising repeating the administering at an interval of about 21 to about 28 days.

103. A method of inducing an immune response in an animal, comprising administering to the animal any one of the peptide of claims 1 to 76, the immunotherapy composition of claims 77 to 85, the pharmaceutical formulations of claims 86 to 94 or the nucleic acid immunotherapy composition of claims 95 to 96 in a regimen effective to generate an immune response comprising antibodies that specifically bind to tau.

104. The method of claim 103, wherein the immune response comprises antibodies that specifically bind to tau.

105. The method of any of claims 103 to 104, wherein the inducing the immune response comprises antibodies that specifically bind to the microtubule region of tau.

106. An immunization kit comprising the immunotherapy composition of any of claims 77 to 85.

107. The kit of claim 106, further comprising an adjuvant.

108. The kit of claim 107, wherein the immunotherapy composition is in a first container and the adjuvant is in a second container.

109. A kit comprising the nucleic acid immunotherapy composition of claim 96.

110. The kit of claim109, further comprising an adjuvant.

111. The kit of claim 110, wherein the nucleic acid is in a first container and the adjuvant is in a second container.

Tau Epitope Titers in Guinea pigs after four injections

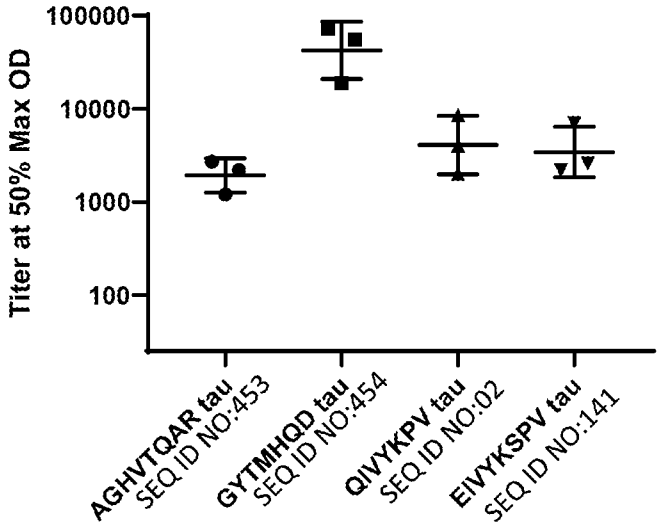

FIG 1

Titer in mice to full length tau from a tau epitope after three injections

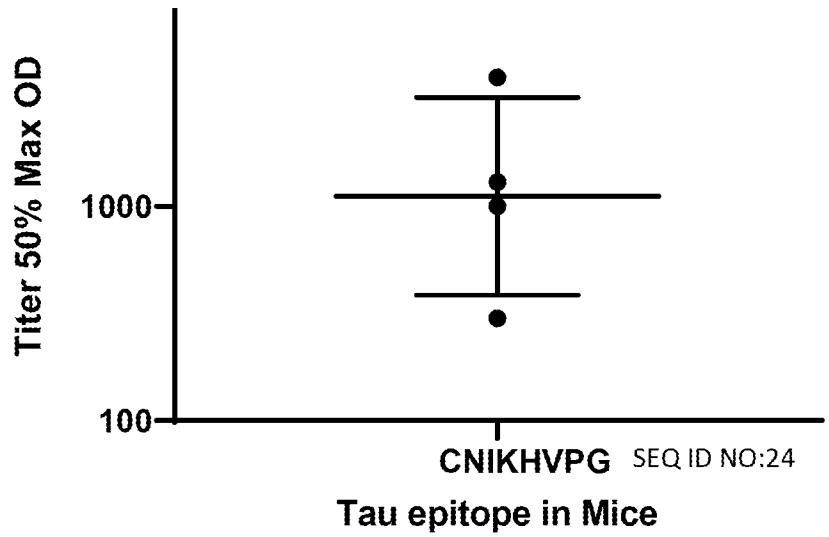

FIG 2

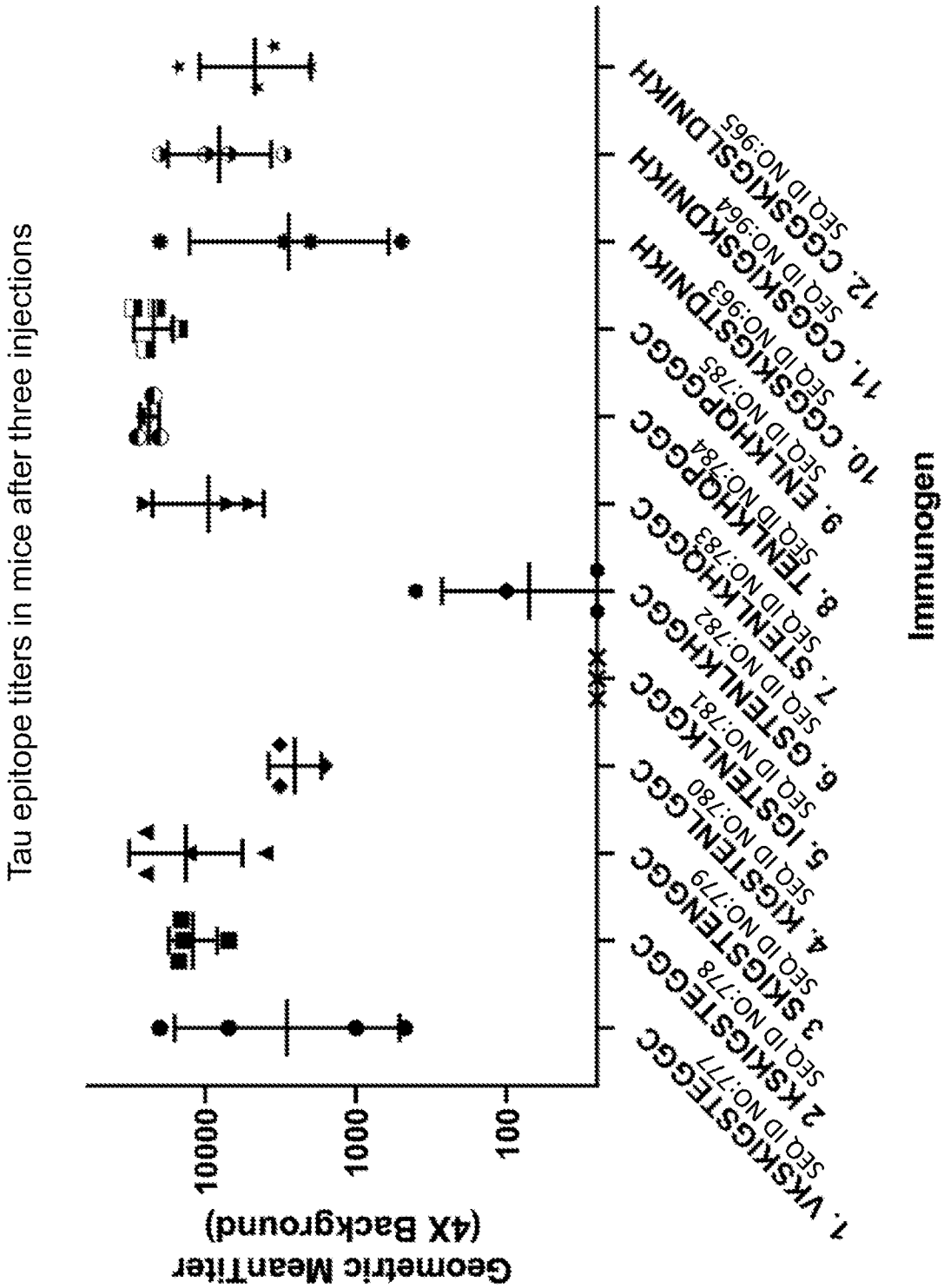
Tau epitope titers in mice after three injections
Geometric Mean Titer
(4X Background)
10000
1000
100
1. VKSKIGSTEGGC SEQ ID NO:777
2 KSKIGSTEGGC SEQ ID NO:778
3 SKIGSTENGGC SEQ ID NO:779
4. KIGSTENLGGC SEQ ID NO:780
5. IGSTENLKGGC SEQ ID NO:781
6. GSTENLKHGGC SEQ ID NO:782
7. STENLKHQGGC SEQ ID NO:783
8. TENLKHQPGGC SEQ ID NO:784
9. ENLKHQPGGGC SEQ ID NO:785
10. CGGSKIGSTDNIKH SEQ ID NO:963
11. CGGSKIGSKDNIKH SEQ ID NO:964
12. CGGSKIGSLDNIKH SEQ ID NO:965
Immunogen

FIG 3

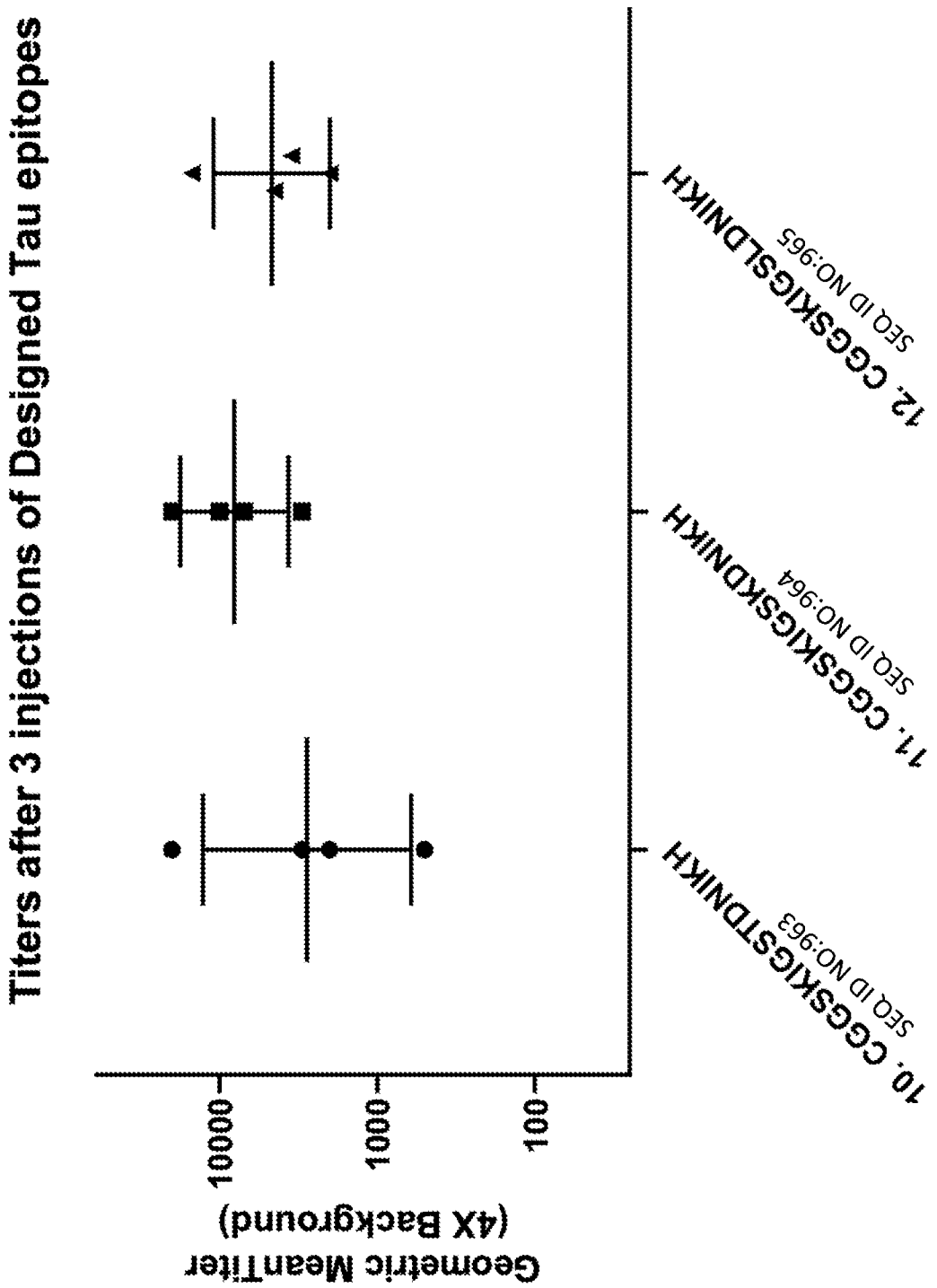
Titers after 3 injections of Designed Tau epitopes
Geometric MeanTiter
(4X Background)
10000
1000
100
10. CGGSKIGSTDNIKH
SEQ ID NO:963
11. CGGSKIGSKDNIKH
SEQ ID NO:964
12. CGGSKIGSLDNIKH
SEQ ID NO:965
Immunogen

FIG 4

Construct Binding to MTBR1-4

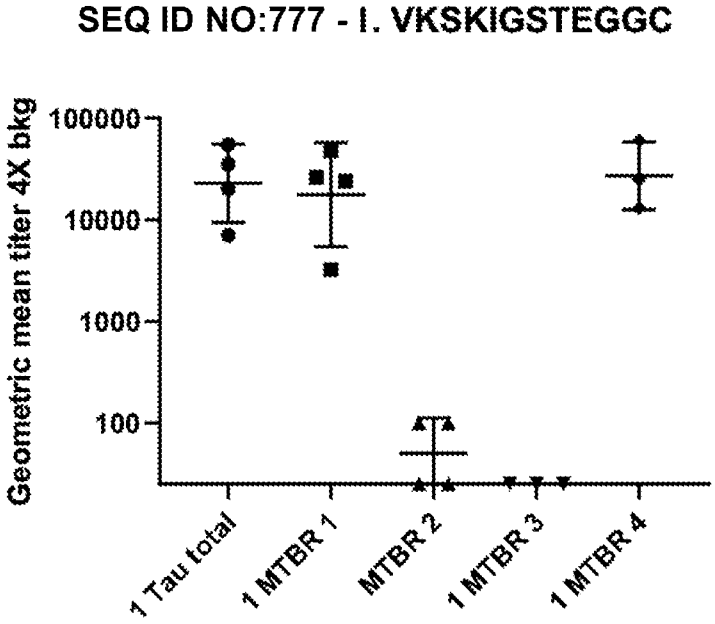

FIG 5A

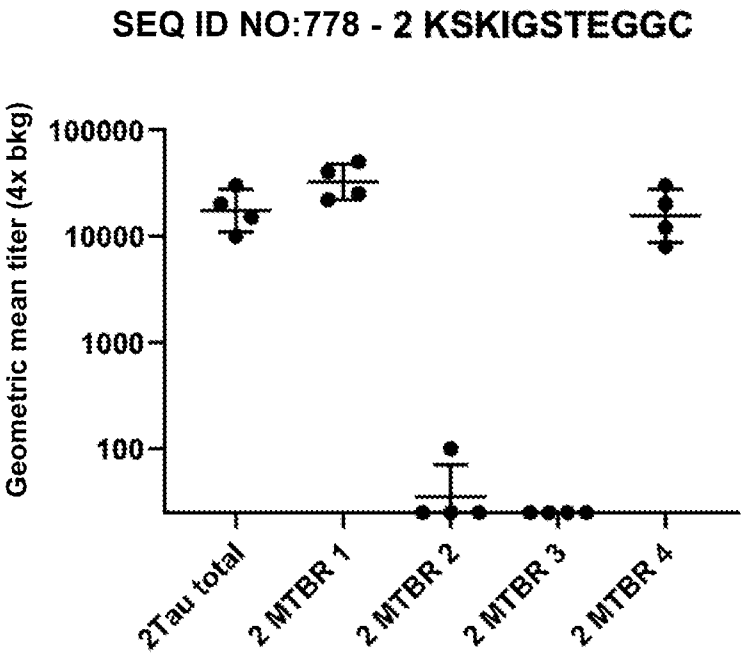

FIG 5B

Construct Binding to MTBR1-4

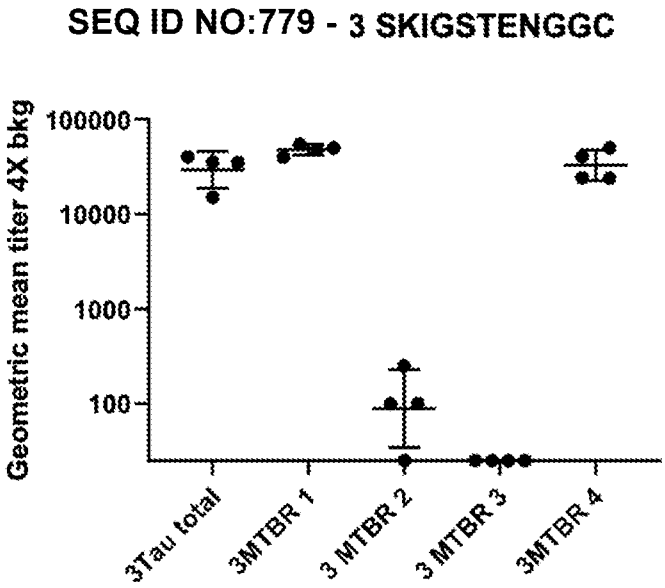

FIG 5C

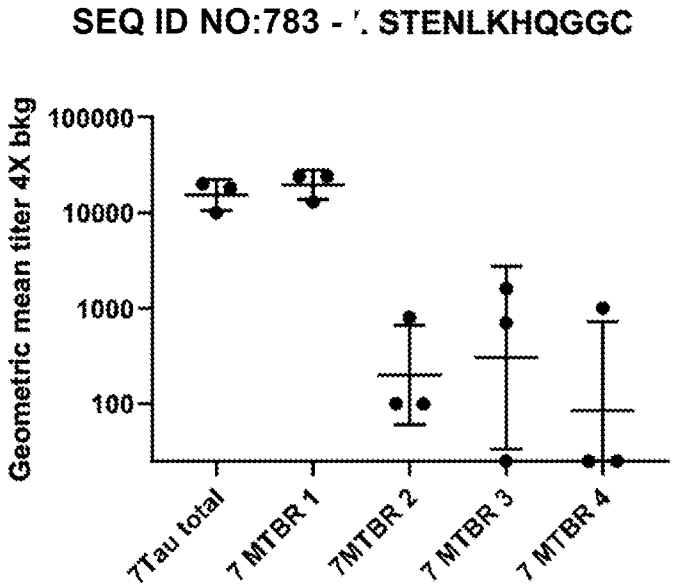

FIG 5D

Construct Binding to MTBR1-4

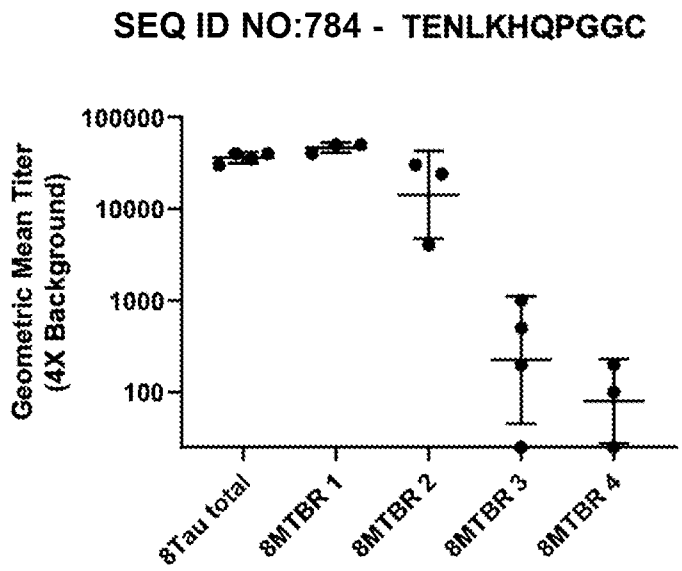

FIG 5E

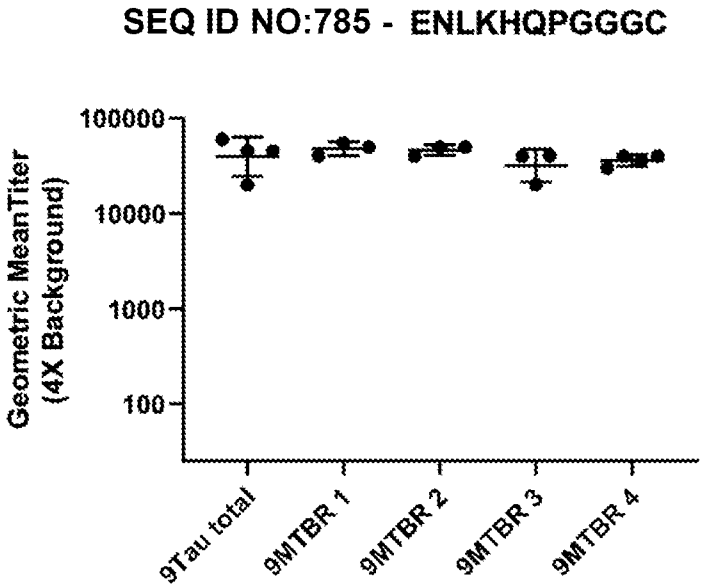

FIG 5F

Construct Binding to MTBR1-4

SEQ ID NO:964 - CGGSKIGSKDNIKH

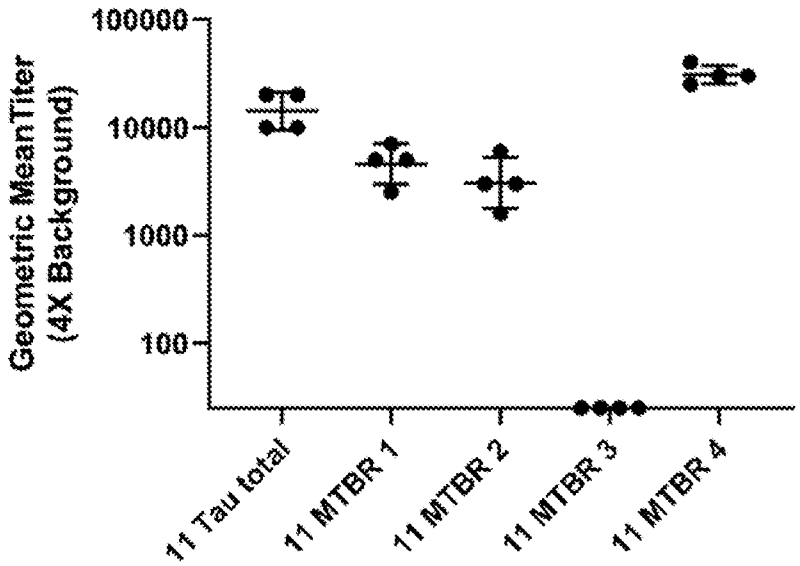

FIG 5G

SEQ ID NO:965 - CGGSKIGSLDNIKH

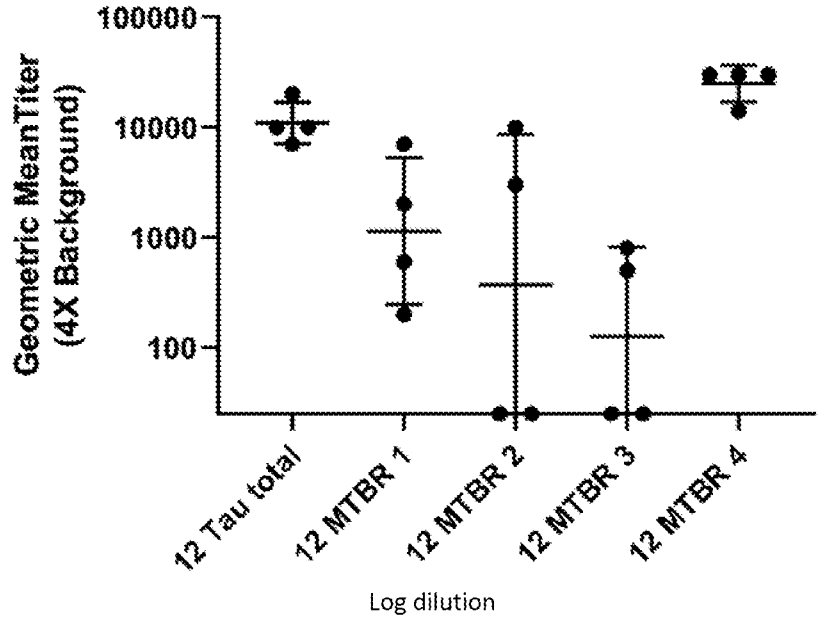

FIG 5H

Competition of tau from binding to heparin

SEQ ID NO:777 VKSKIGSTEGGC immunized mice ability to inhibit Tau binding to heparin

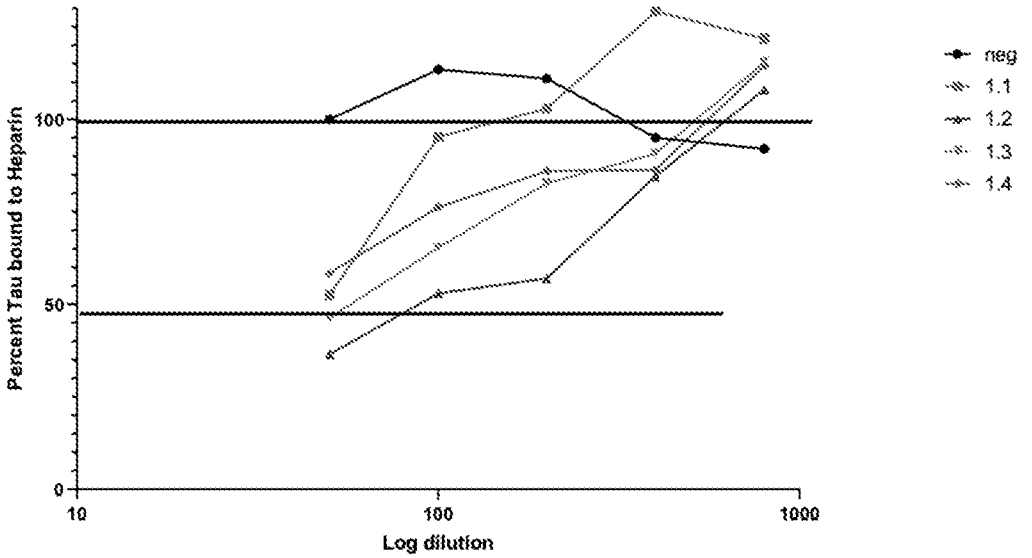

FIG 6

SEQ ID NO:778 KSKIGSTEGGC immunized mice ability to inhibit Tau binding to heparin

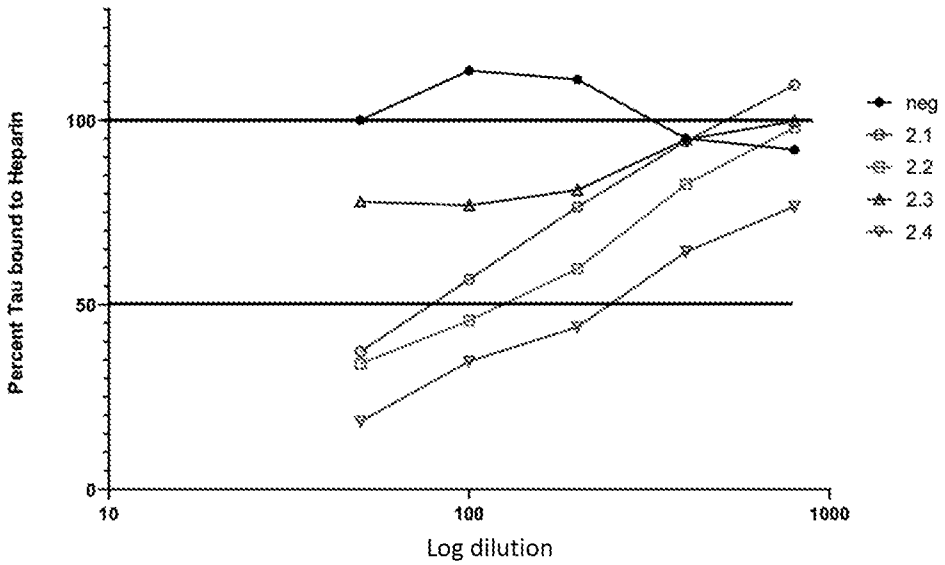

FIG 7

Competition of tau from binding to heparin

SEQ ID NO:779 SKIGSTENGGC immunized mice ability to inhibit Tau binding to heparin

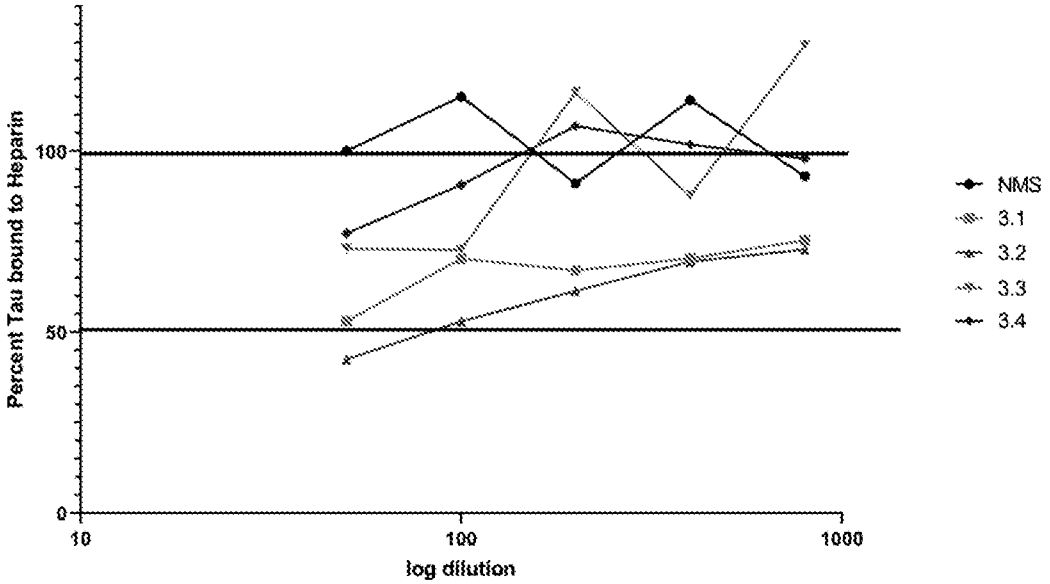

FIG. 8

SEQ ID NO:783 STENLKHQGGC immunized mice ability to inhibit Tau binding to heparin

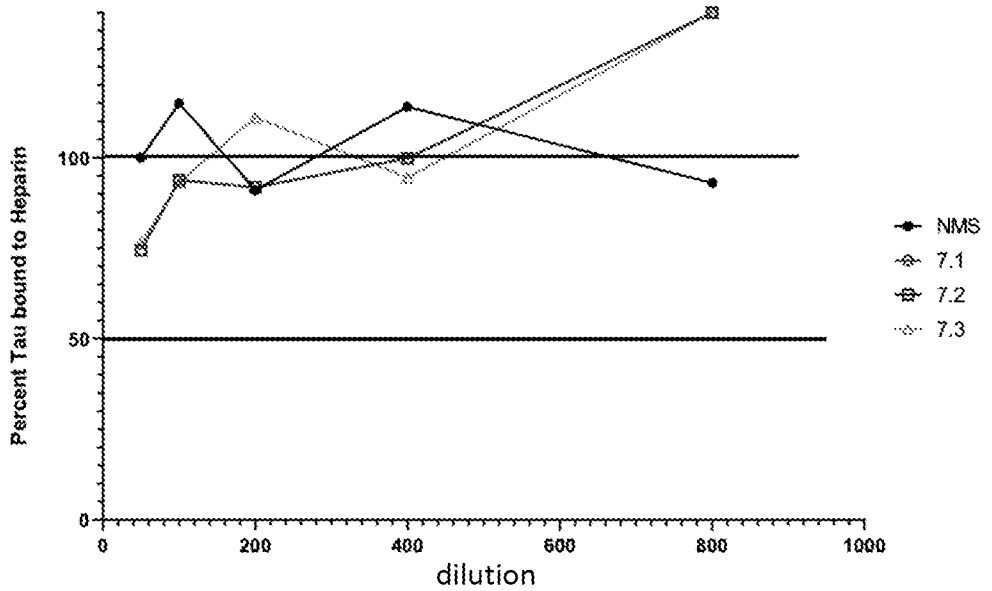

FIG 9

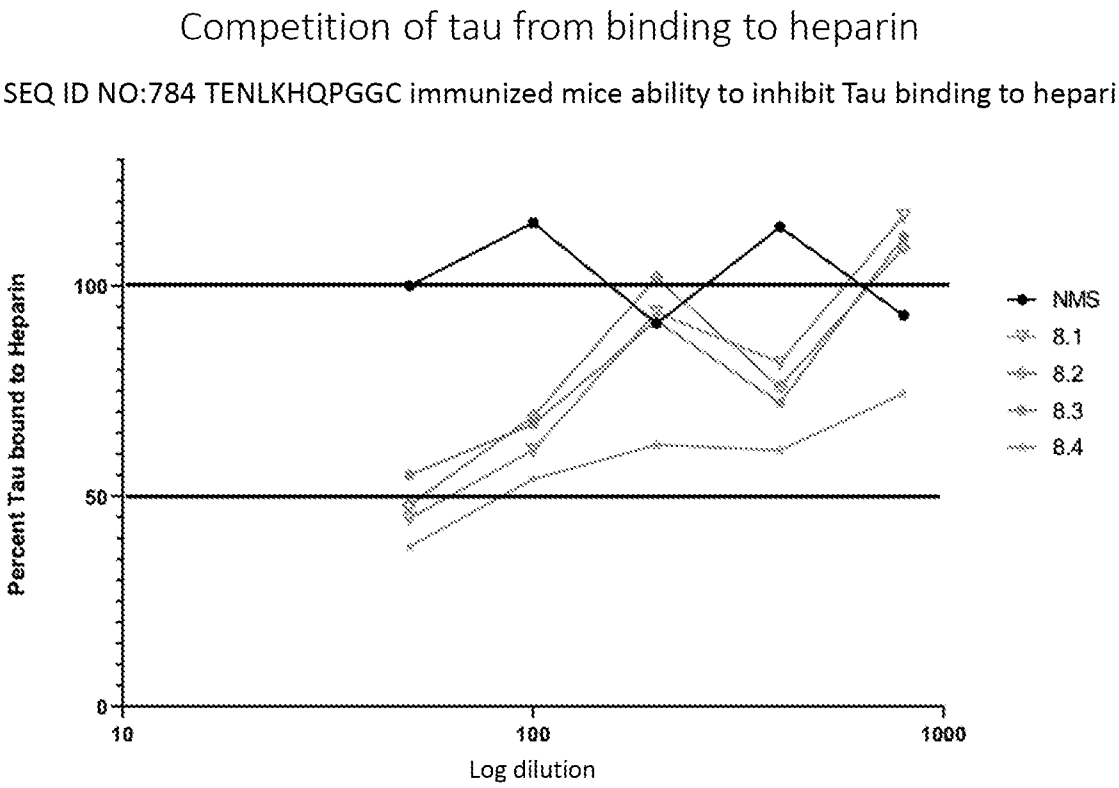
Competition of tau from binding to heparin
SEQ ID NO:784 TENLKHQPGGC immunized mice ability to inhibit Tau binding to heparin
Percent Tau bound to Heparin
100
50
0
10
100
1000
Log dilution
NMS
8.1
8.2
8.3
8.4

FIG 10

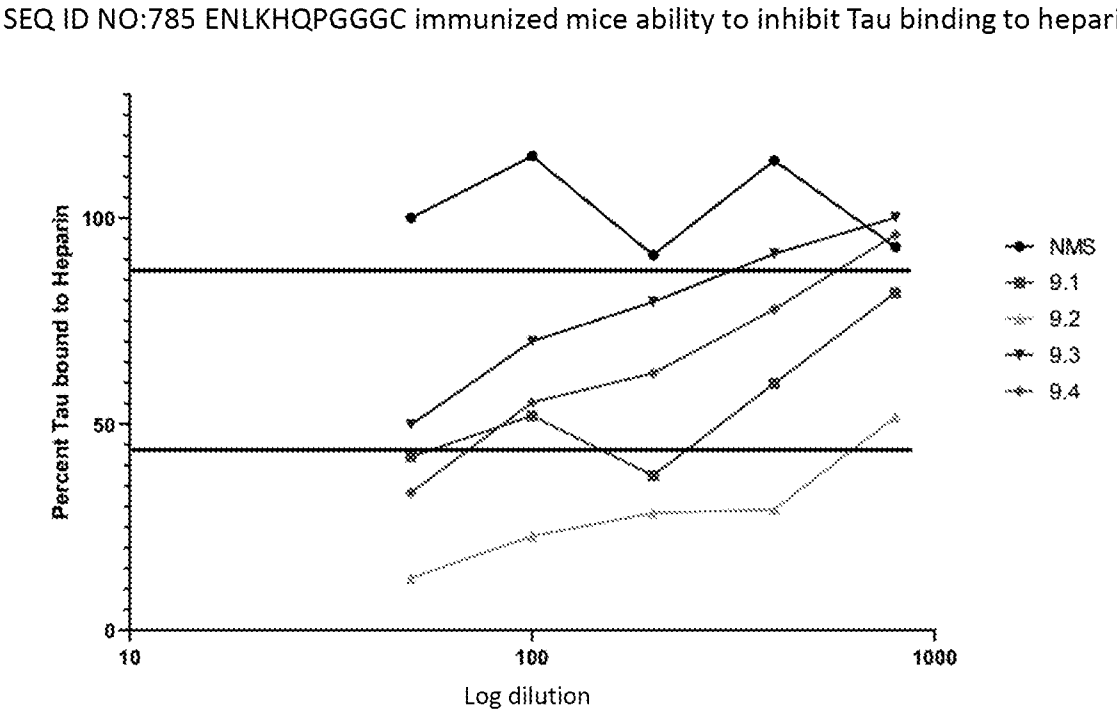
SEQ ID NO:785 ENLKHQPGGGC immunized mice ability to inhibit Tau binding to heparin
Percent Tau bound to Heparin
100
50
0
10
100
1000
Log dilution
NMS
9.1
9.2
9.3
9.4

FIG 11

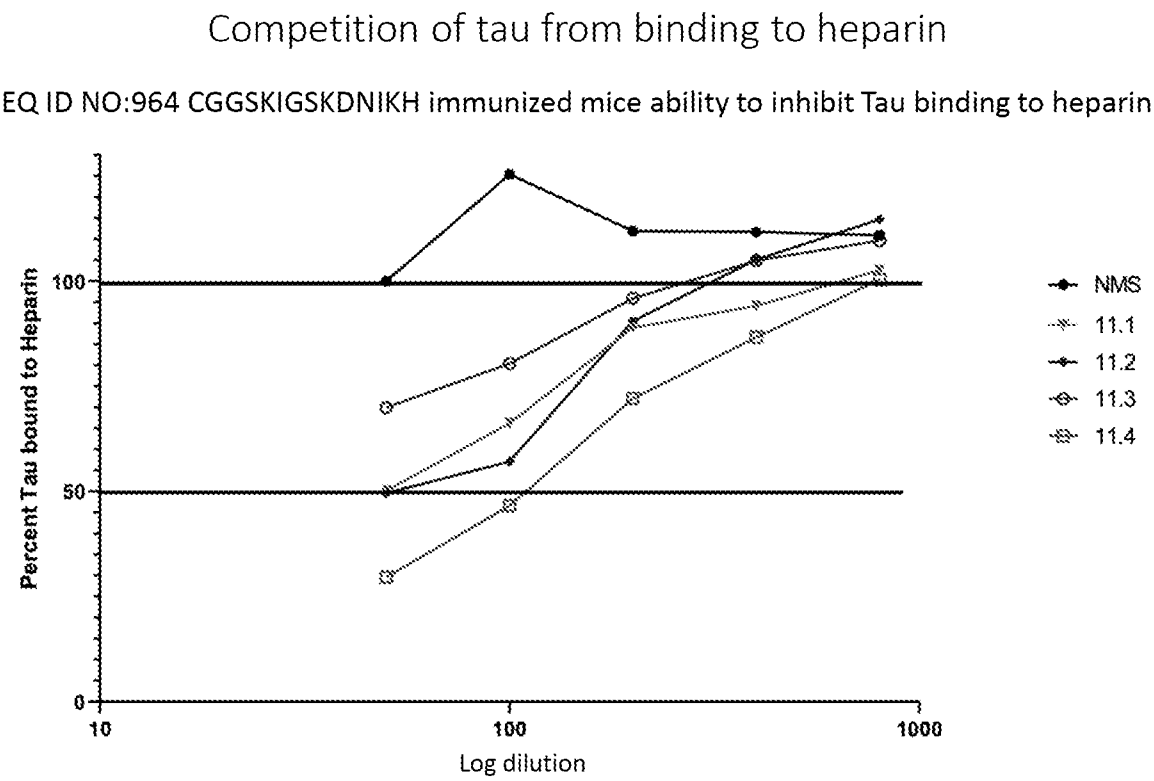
Competition of tau from binding to heparin
SEQ ID NO:964 CGGSKIGSKDNIKH immunized mice ability to inhibit Tau binding to heparin
Percent Tau bound to Heparin
100
50
0
10
100
1000
Log dilution
NMS
11.1
11.2
11.3
11.4

FIG 12

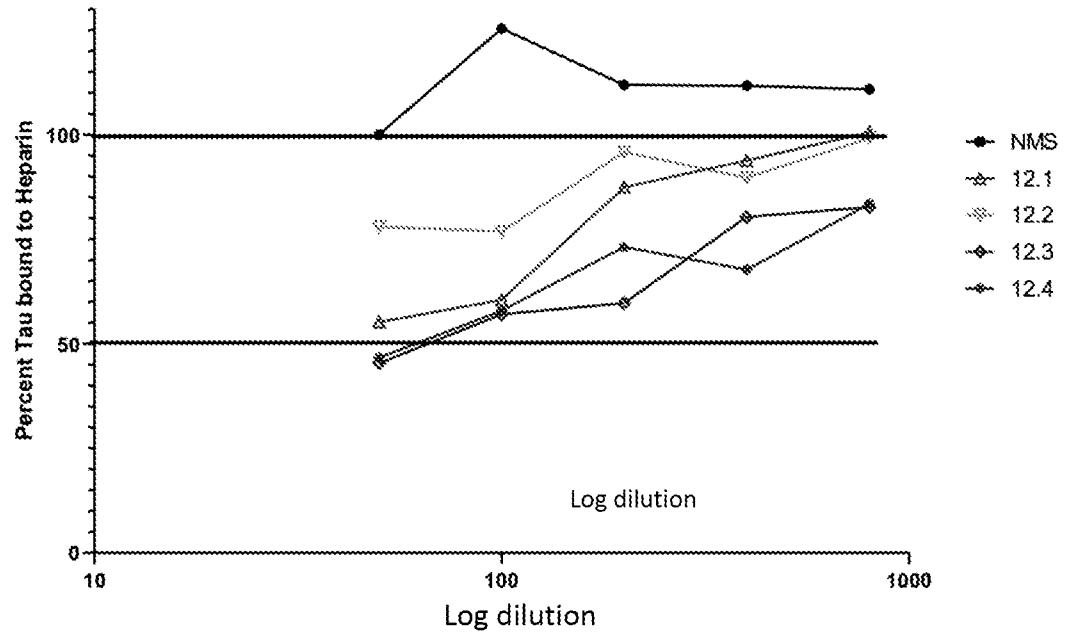
SEQ ID NO:965 CGGSKIGSLDNIKH immunized mice ability to inhibit Tau binding to heparin
Percent Tau bound to Heparin
100
50
0
10
100
1000
Log dilution
Log dilution
NMS
12.1
12.2
12.3
12.4

FIG 13

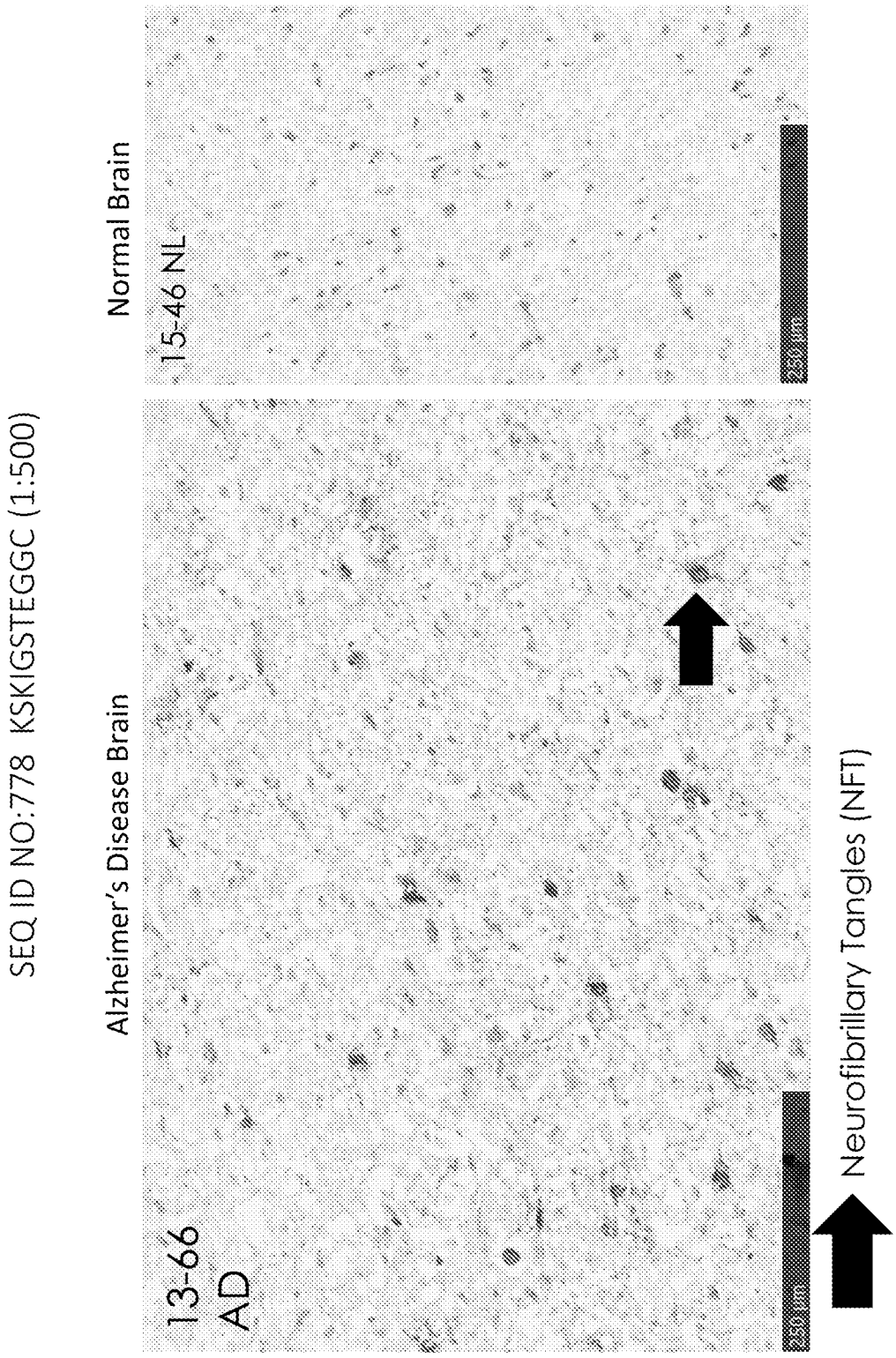
SEQ ID NO:778 KSKIGSTEGGC (1:500)
Alzheimer's Disease Brain
13-66
AD
250 um
Neurofibrillary Tangles (NFT)
Normal Brain
15-46 NL
250 um

FIG 14

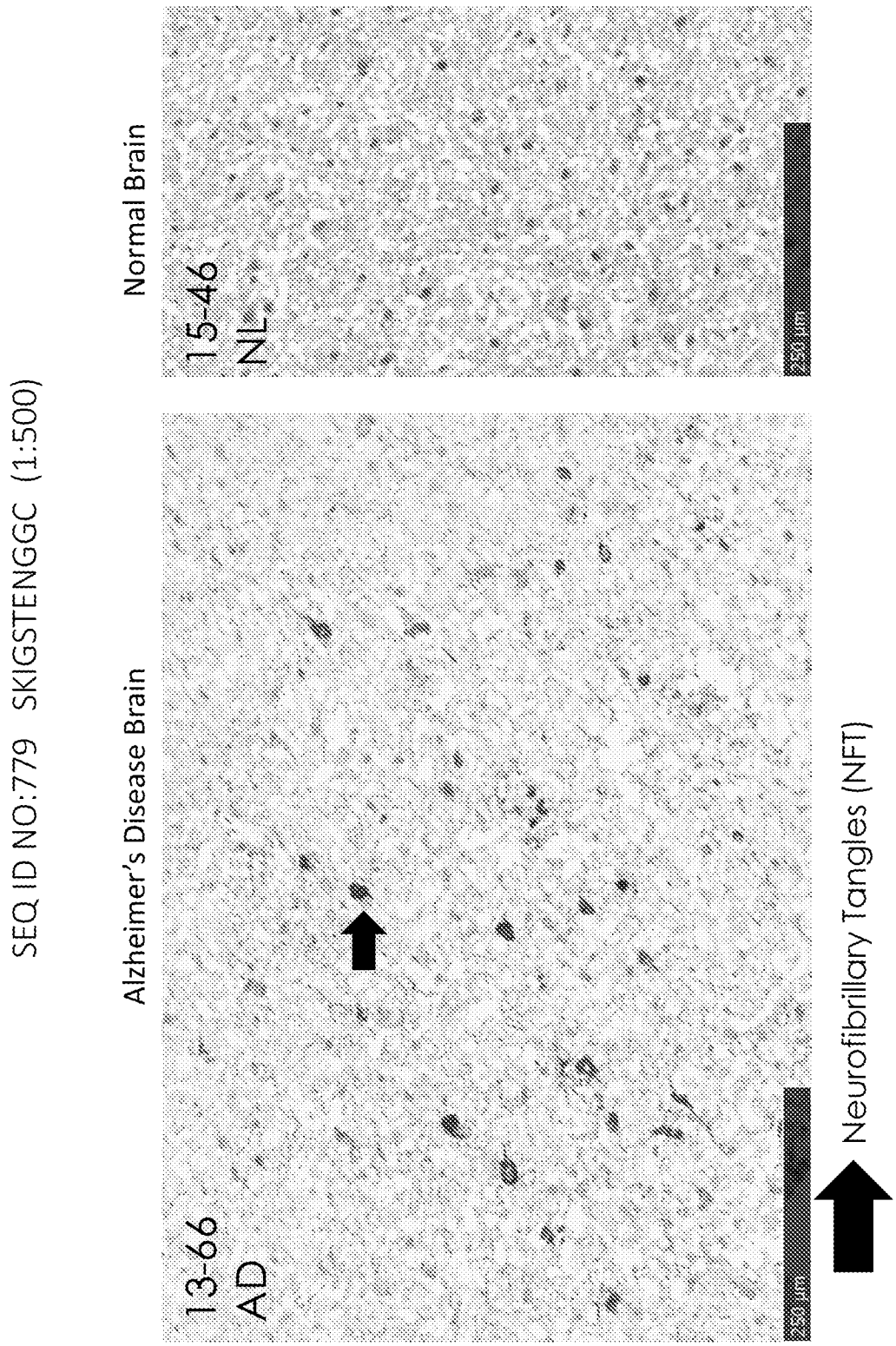
SEQ ID NO:779 SKIGSTENGGC (1:500)
Alzheimer's Disease Brain
13-66
AD
Normal Brain
15-46
NL
250 um
Neurofibrillary Tangles (NFT)

FIG 15

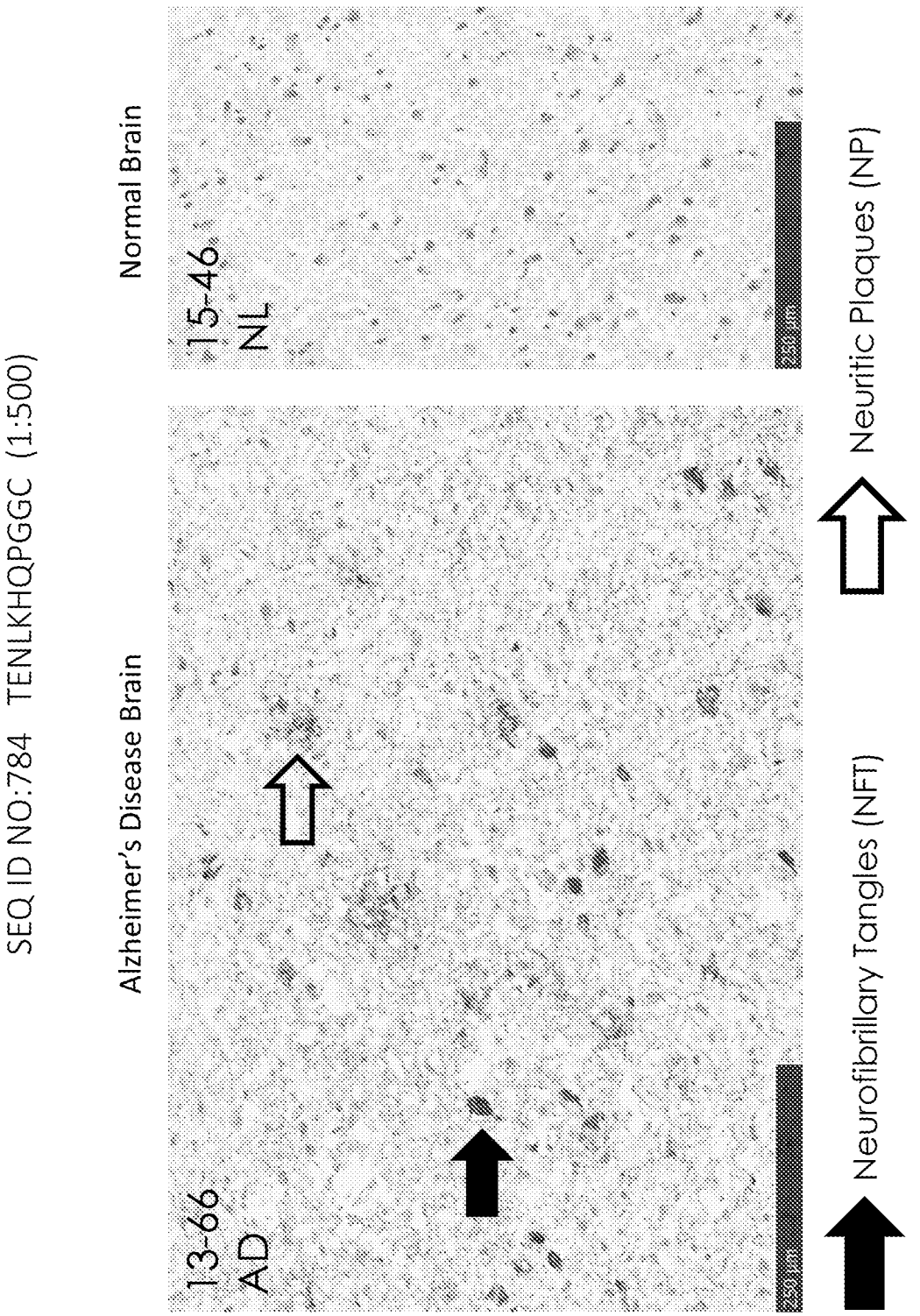
SEQ ID NO:784 TENLKHQPGGC (1:500)
Alzheimer's Disease Brain
Normal Brain
13-66
AD
15-46
NL
250 µm
250 µm
Neurofibrillary Tangles (NFT)
Neuritic Plaques (NP)

FIG 16

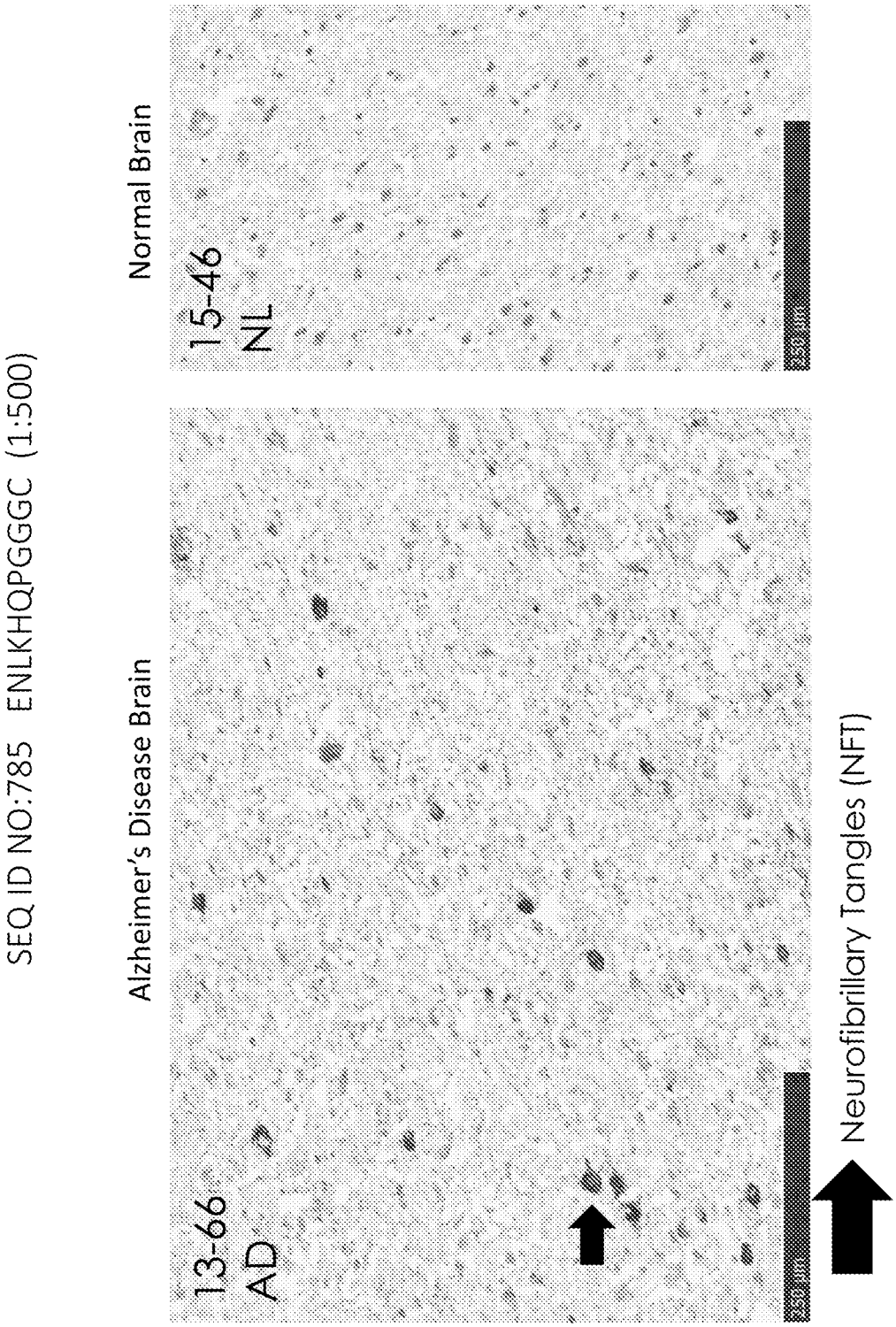
SEQ ID NO:785 ENLKHQPGGGC (1:500)
Alzheimer's Disease Brain
Normal Brain
13-66
AD
15-46
NL
250 um
250 um
Neurofibrillary Tangles (NFT)

FIG 17

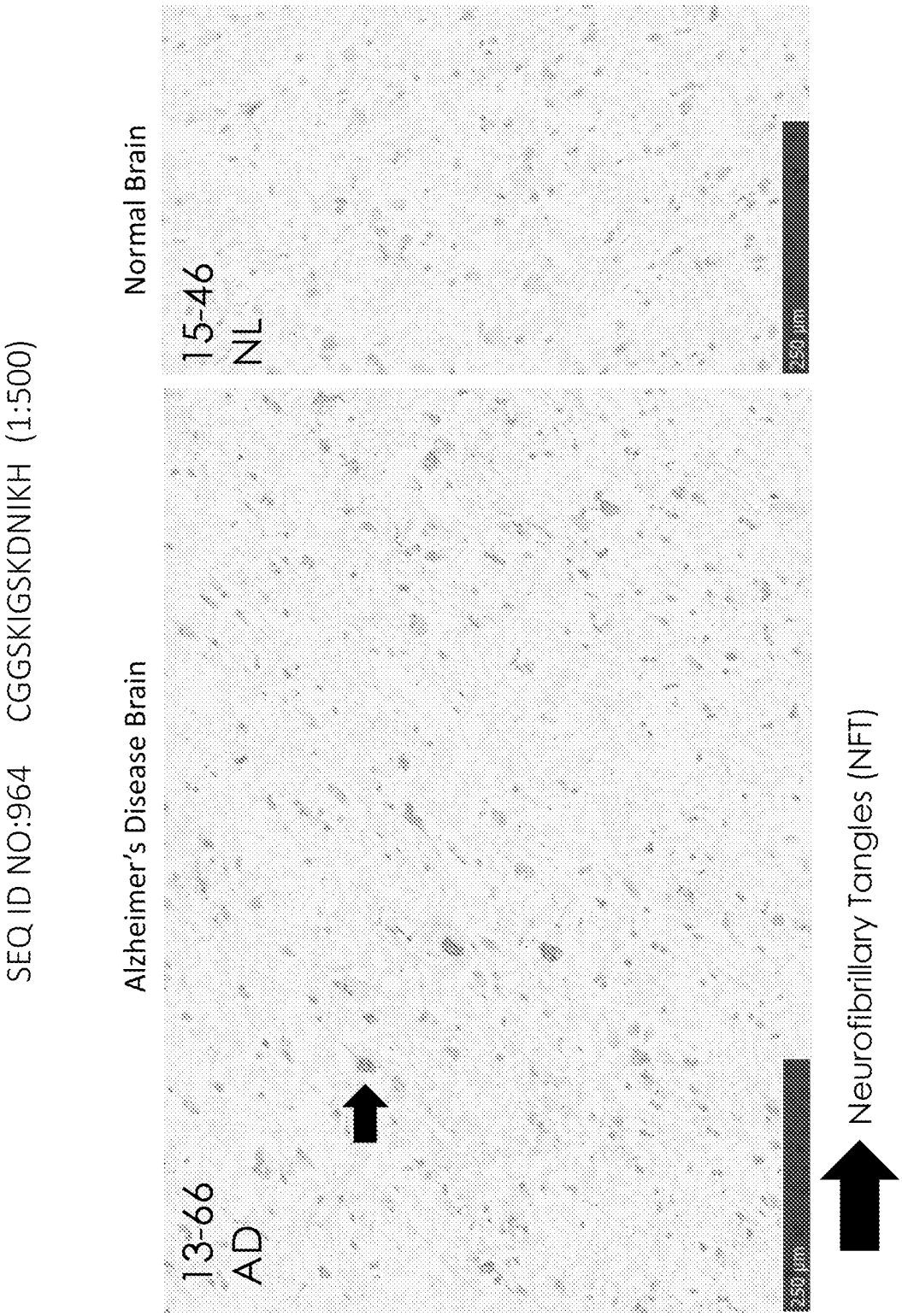
SEQ ID NO:964 CGGSKIGSKDNIKH (1:500)
Alzheimer's Disease Brain
Normal Brain
13-66
AD
15-46
NL
250 µm
250 µm
Neurofibrillary Tangles (NFT)

FIG 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/33189

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61P 25/28; A61P 37/04; A61K 39/00 (2021.01)

CPC - C07K 14/4711; A61K 2039/6037; A61K 39/0007; A61K 2039/55566; A61K 2039/64

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2016/0318975 A1 (TOAGOSEI CO. LTD. et al.) 3 November 2016 (03.11.2016) para [0110], [0115]; claim 1	1-4, 62 -- 5-7
Y	WO 2015/165961 A1 (AFFIRIS AG) 5 November 2015 (05.11.2015) pg 1, para 1; pg 8, para 3; pg 16, para 4-5; pg 17, para 2	5-7

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2021	NOV 12 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/33189

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

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

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

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

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/33189

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-11, 13, 15-52, 54-60, 61A, 61B, 66, 69-111
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Continued on Supplemental Page

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7 and 62 limited to SEQ ID NO: 2

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/33189

Continued from Box No. III Observations where unity of invention is lacking

Group I+: Claims 1-7, 12, 14, 53, 62-65 and 67-68 directed to an isolated (immunogenic) tau peptide. The tau peptide composition will be searched to the extent that the peptide is from the microtubule binding region (MTBR) of tau (residues 244-372 of applicant SEQ ID NO:01, a splicing isoform of human tau), and comprises SEQ ID NO: 2 (QIVYKPV), and further comprises C-terminal amino acids GGC. It is believed that claims 1-7 and 62 limited to said peptide encompass this first named invention, and thus these claims will be searched without fee to the extent that the peptide encompass the sequence QIVYKPVGGC. Additional tau peptides will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected tau peptides. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a tau peptide comprising 5-13 amino acids from residues 244-400 of SEQ ID NO:01, comprising SEQ ID NO: 9009 (SKIGSTENLKH) comprising an isoleucine amino acid substitution at position 10 (SKIGSTENLIH)(claims 62-64 and 67).

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

No technical features are shared between the peptide amino acid sequences of Group I+, accordingly, these groups lack unity a priori.

Additionally, even if the inventions listed as Group I+ were considered to share technical features, these shared technical features are previously disclosed by the prior art, as further discussed below.

Common Technical Features

The inventions of Group I+ share the technical feature of a tau peptide of 3-13 amino acids from residues 244-400 crf SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750 (i.e., splicing isoforms of human tau protein, instant specification, para [0058]), which may comprise one or more amino acid substitutions relative to SEQ ID NOs 1 and 750. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by US 2016/0318975 A1 to Toagosei Co. Ltd. et al. (hereinafter 'Toagosei')

Toagosei discloses a peptide comprising 3-13 amino acids from residues 244-400 of SEQ ID NO:01 or from residues 1-150 of SEQ ID NO:750 (para [0115] - "The amino acid sequence of SEQ ID NO:71 corresponds to an amino acid sequence comprising a total of 11 amino acid residues that is a partial amino acid sequence of a tau protein."; SEQ ID NO: 71 of Toagosei, consisting of 11 residues, exhibits 100% identity with residues 305-315 of SEQ ID NO: 01 of the instant application", para [0020] "a peptide ...comprising an amino acid sequence represented by any of SEQ ID NOS: 6 to 74, or a modified amino acid sequence formed by substitution, deletion and/or addition of 1, 2 or 3 amino acid residues in any of these amino acid sequences.").

As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions.

Group I+ therefore lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

Item 4, continued: claims 8-11, 13, 15-52, 54-60, 61A, 61B, 66, 69-111 are not drafted in accordance with the second and third sentences of Rule 6.4(a) regarding multiply dependent claims.

Note: There are two claims numbered 61. For the purposes of this application, the first is referred to as claim "61A" and the second is referred to as claim "61B".