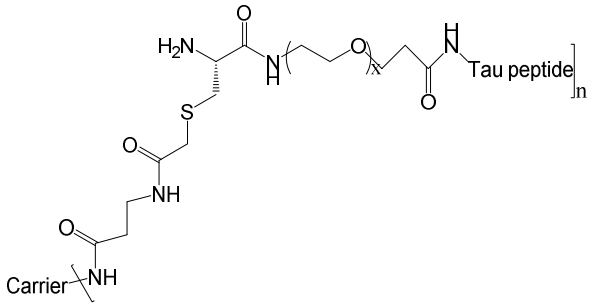
Claims

1. A liposome comprising:
    a. a first tau phosphopeptide;
    b. a helper T-cell epitope;
    c. a lipidated CpG oligonucleotide; and
    d. an adjuvant containing a toll-like receptor 4 ligand;

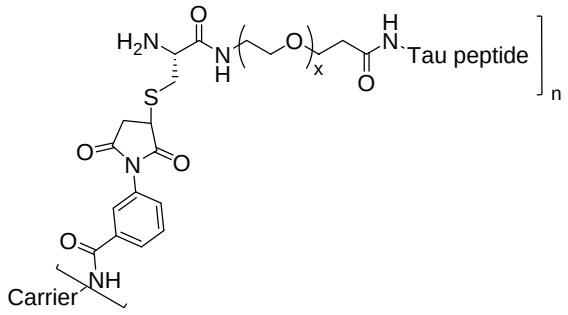
for use in a method of inducing antibodies against at least one of phosphorylated Tau and enriched paired helical filaments (ePHFs) in a subject in need thereof, whereby, in the method

(i) the subject is to be administered a priming composition comprising an immunologically effective amount of the liposome, wherein the tau phosphopeptide is presented on the surface of the liposome, and the priming composition further comprises a pharmaceutically acceptable carrier; and

(ii) the subject is to be administered a first boosting composition comprising an immunologically effective amount of a conjugate comprising a second tau phosphopeptide and an immunogenic carrier conjugated thereto via a linker, the conjugate having the structure of formula (I):



or having the structure of formula (II):



wherein

x is an integer of 0 to 10, preferably 2 to 6, most preferably 3;

n is an integer of 3 to 15, preferably 3 to 12;

Tau peptide represents the second tau phosphopeptide; and

Carrier represents the immunogenic carrier selected from the group consisting of keyhole limpet hemocyanin (KLH), tetanus toxoid, CRM197 and an outer membrane protein mixture from *N. meningitidis* (OMP), or a derivative thereof; and

the first boosting composition further comprises a pharmaceutically acceptable carrier;

wherein the first tau phosphopeptide and the second tau phosphopeptide each independently comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 3 and SEQ ID NO: 5 to SEQ ID NO: 12.

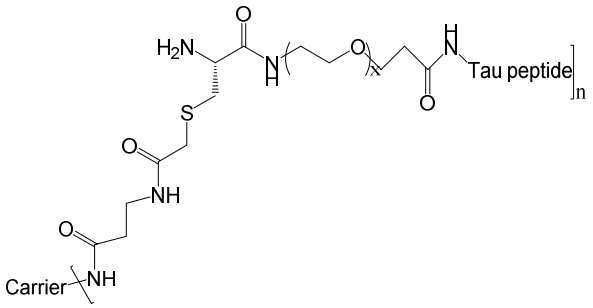
2. Use of a liposome comprising:

a. a first tau phosphopeptide;
b. a helper T-cell epitope;
c. a lipidated CpG oligonucleotide; and
d. an adjuvant containing a toll-like receptor 4 ligand;

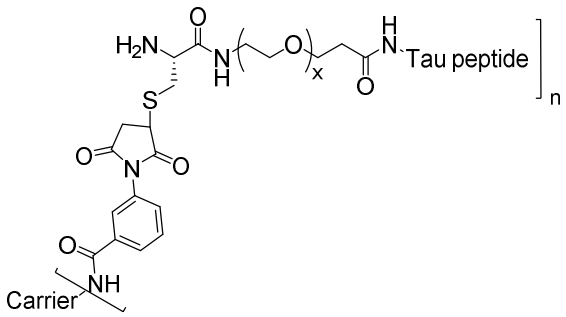
in the manufacture of a medicament for inducing antibodies against at least one of phosphorylated Tau and enriched paired helical filaments (ePHFs) in a subject in need thereof, wherein the liposome is to be administered to the subject in a method whereby:

(i) the subject is to be administered a priming composition comprising an immunologically effective amount of the liposome, wherein the tau phosphopeptide is presented on the surface of the liposome, and the priming composition further comprises a pharmaceutically acceptable carrier; and

(ii) the subject is to be administered a first boosting composition comprising an immunologically effective amount of a conjugate comprising a second tau phosphopeptide and an immunogenic carrier conjugated thereto via a linker, the conjugate having the structure of formula (I):



or having the structure of formula (II):



wherein

x is an integer of 0 to 10, preferably 2 to 6, most preferably 3;

n is an integer of 3 to 15, preferably 3 to 12;

Tau peptide represents the second tau phosphopeptide; and

Carrier represents the immunogenic carrier selected from the group consisting of keyhole limpet hemocyanin (KLH), tetanus toxoid, CRM197 and an outer membrane protein mixture from *N. meningitidis* (OMP), or a derivative thereof; and

the first boosting composition further comprises a pharmaceutically acceptable carrier;

wherein the first tau phosphopeptide and the second tau phosphopeptide each independently comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 3 and SEQ ID NO: 5 to SEQ ID NO: 12.

3. The use of claim 2, wherein:

the liposome comprises:

a. the first tau phosphopeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 27 to SEQ ID NO: 29 and SEQ ID NO: 31 to SEQ ID NO: 38;

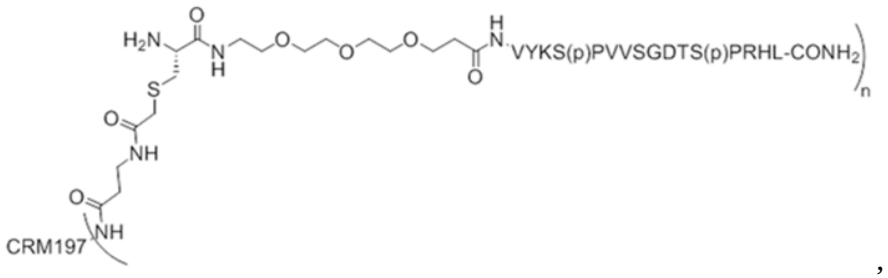
b. the helper T cell epitope having an amino acid sequence selected from the group consisting of SEQ ID NO: 39 to SEQ ID NO: 44, preferably, the helper T cell epitope consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 13 to SEQ ID NO: 17;

c. the lipidated CpG oligonucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NO: 18 to SEQ ID NO: 22, wherein the CpG oligonucleotide comprises one or more phosphorothioate internucleotide linkages, and the CpG oligonucleotide is covalently linked to at least one cholesterol via a linker; and

d. monophosphoryl lipid A (MPLA); and

the conjugate comprises the second tau phosphopeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 3 or SEQ ID NO: 5 to SEQ ID NO: 12 conjugated to CRM197 via the linker.

4. The use of claim 2 or claim 3, wherein the conjugate has the structure of:



,

wherein n is an integer of 3 to 7.

5. Use of a liposome comprising:

a. a first tau phosphopeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 27 to SEQ ID NO: 29 or SEQ ID NO: 31 to SEQ ID NO: 38;

b. a helper T cell epitope having an amino acid sequence selected from the group consisting of SEQ ID NO: 39 to SEQ ID NO: 44, preferably, the helper T cell epitope consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 13 to SEQ ID NO: 17;

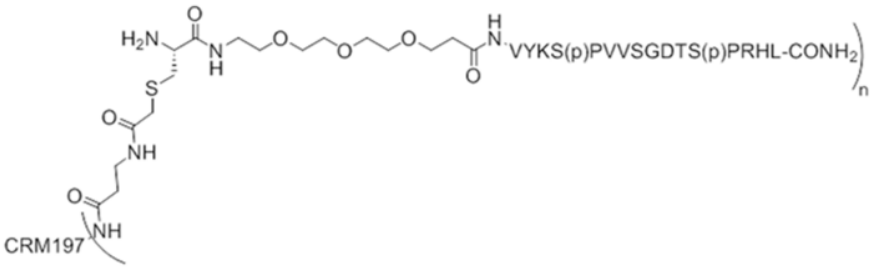
c. a lipidated CpG oligonucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NO: 18 to SEQ ID NO: 22, wherein the CpG oligonucleotide comprises one or more phosphorothioate internucleotide linkages, and the CpG oligonucleotide is covalently linked to at least one cholesterol via a linker; and

d. monophosphoryl lipid A (MPLA);

in the manufacture of a medicament for inducing antibodies against at least one of phosphorylated Tau and enriched paired helical filaments (ePHFs) in a subject in need thereof, wherein the liposome is to be administered to the subject in a method whereby:

(i) the subject is to be administered a priming composition comprising an immunologically effective amount of the liposome, wherein the first tau phosphopeptide is presented on the surface of the liposome, and the priming composition further comprises a pharmaceutically acceptable carrier; and

(ii) the subject is to be administered a first boosting composition comprising an immunologically effective amount of a conjugate comprising a second tau phosphopeptide and an immunogenic carrier conjugated thereto via a linker, the conjugate having the structure of :



,

wherein n is an integer of 3 to 7, and the first boosting composition further comprises a pharmaceutically acceptable carrier.

6. Use of a liposome comprising:

(1) a first tau phosphopeptide having the amino acid sequence of SEQ ID NO:28;

(2) a toll-like receptor 4 agonist comprising monophosphoryl hexa-acyl Lipid A, 3-deacyl;

(3) a helper T-cell epitope comprising the amino acid sequence of SEQ ID NO: 39;

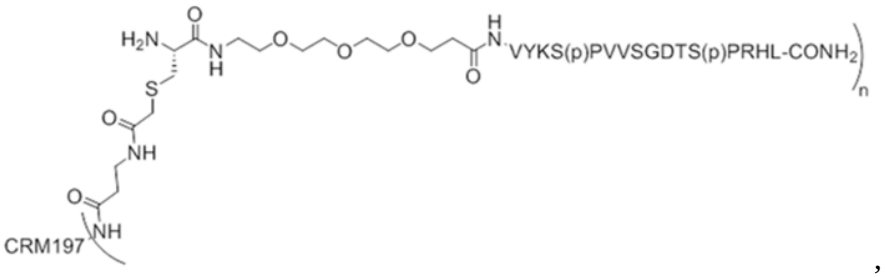
(4) a lipidated CpG oligonucleotide comprising the nucleotide sequence of SEQ ID NO:18; and

(5) at least one lipid selected from the group consisting of 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dimyristoyl-sn-glycero-3-phosphoryl-3'-rac-glycerol (DMPG), and cholesterol,

in the manufacture of a medicament for inducing antibodies against at least one of phosphorylated Tau and enriched paired helical filaments (ePHFs) in a subject in need thereof, wherein the liposome is to be administered to the subject in a method whereby:

(i) the subject is to be administered a priming composition comprising an immunologically effective amount of the liposome comprising: wherein the first tau phosphopeptide is presented on the surface of the liposome, and the priming composition further comprises a pharmaceutically acceptable carrier; and

(ii) the subject is to be administered a first boosting composition comprising an immunologically effective amount of a conjugate comprising a second tau phosphopeptide and an immunogenic carrier conjugated thereto via a linker, the conjugate having the structure of:



,

wherein n is an integer of 3 to 7, and the first boosting composition further comprises a pharmaceutically acceptable carrier.

7. The use of any one of claims 2-6, wherein the first boosting composition is to be administered to the subject at least once after the initial administration of the first boosting composition.

8. The use of any one of claims 2-7, wherein a second boosting composition comprising an immunologically effective amount of the liposome and a pharmaceutically acceptable carrier is to be administered to the subject.

9. The use of claim 8, wherein the second boosting composition is to be administered to the subject at least once after the initial administration of the second boosting composition.

10. Use of a liposome comprising:

(1) a first tau phosphopeptide having the amino acid sequence of SEQ ID NO:28;

(2) a toll-like receptor 4 agonist comprising monophosphoryl hexa-acyl Lipid A, 3-deacyl;

(3) a helper T-cell epitope comprising the amino acid sequence of SEQ ID NO: 39;

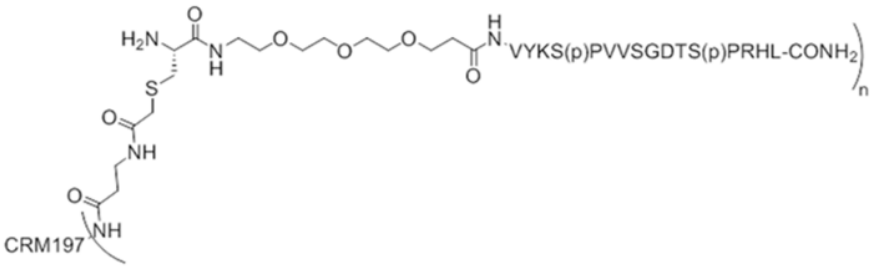
(4) a lipidated CpG oligonucleotide comprising the nucleotide sequence of SEQ ID NO:18; and

(5) at least one lipid selected from the group consisting of 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dimyristoyl-sn-glycero-3-phosphoryl-3'-rac-glycerol (DMPG), and cholesterol,

in the manufacture of a medicament for inducing antibodies against at least one of phosphorylated Tau and enriched paired helical filaments (ePHFs) in a subject in need thereof, wherein the liposome is to be administered to the subject in a method whereby:

(i) the subject is to be administered a priming composition comprising an immunologically effective amount of the liposome, wherein the first tau phosphopeptide is presented on the surface of the liposome, and the priming composition further comprises a pharmaceutically acceptable carrier; and

(ii) the subject is to be administered a first boosting composition comprising an immunologically effective amount of a conjugate comprising a second tau phosphopeptide and an immunogenic carrier conjugated thereto via a linker, the conjugate having the structure of:



,

wherein n is an integer of 3 to 7, and the first boosting composition further comprises a pharmaceutically acceptable carrier; and

(iii) the subject is to be administered the first boosting composition or a second boosting composition comprising an immunologically effective amount of the liposome and a pharmaceutically acceptable carrier.

11. The use of claim 10, wherein (ii) is conducted before (iii).

12. The use of claim 10, wherein (ii) is conducted after (iii).

13. The use of any one of claims 10-12, wherein the first boosting composition that is to be administered to the subject occurs at least once after the initial administration of the first boosting composition.

14. The use of any one of claims 10-13, wherein the second boosting composition is to be administered to the subject at least once.

15. The use of any one of claims 2-14, wherein the subject is in need of a treatment of a neurodegenerative disease or disorder caused by or associated with the formation of neurofibrillary lesions.

16. The use of claim 15, wherein the neurodegenerative disease or disorder is Alzheimer’s Disease, Parkinson’s Disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis, parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, Dementia Lewy Amyotrophic Lateral sclerosis, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease, type C, Pick’s disease, progressive subcortical gliosis, progressive

supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, Myotonic dystrophy, chronic traumatic encephalopathy (CTE), cerebral angiopathy or Lewy body dementia (LBD).

17. The use of claim 16, wherein the subject is in need of a treatment of Alzheimer's Disease, preferably early Alzheimer's Disease, mild cognitive impairment (MCI) due to Alzheimer's Disease, or mild to moderate Alzheimer's Disease.

18. The use of any one of claims 2-17, wherein the immunologically effective amount of the liposome comprises the first tau phosphopeptide at an amount of about 25 nmoles to about 750 nmoles per dose, preferably about 90 nmoles to about 715 nmoles per dose or about 90 nmoles to about 535 nmoles per dose.

19. The use of any one of claims 2-18, wherein the immunologically effective amount of the liposome comprises the first tau phosphopeptide at an amount of about 100 µg to about 2500 µg, preferably about 300 µg to about 2400 µg, such as about 100 µg, about 150 µg, about 200 µg, about 250 µg, about 300 µg, about 400 µg, about 500 µg, about 600 µg, about 700 µg, about 800 µg, about 900 µg, about 1000 µg, about 1100 µg, about 1200 µg, about 1300 µg, about 1400 µg, about 1500 µg, about 1600 µg, about 1700 µg, about 1800 µg, about 1900 µg, about 2000 µg, about 2100 µg, about 2200 µg, about 2300 µg, about 2400 µg, about 2500 µg, or any value in between, per dose.