and formulations thereof for cost effective treatment of patients suffering tauopathies.

References:

1. "Tau protein," Wikipedia, The Free Encyclopedia, website address: en.wikipedia.org/wiki/Tau_protein (accessed September 29, 2017).
2. Fitzpatrick, AWP, et al., "Cryo-EM structures of Tau filaments from Alzheimer's disease", *Nature*, 547(7662):185-190 (2017).

SUMMARY

In one aspect, the present disclosure refers to a Tau peptide immunogen construct can be represented by the formulae:

$$(Th)_m–(A)_n–(\text{Tau fragment})–X$$

or

$$(\text{Tau fragment})–(A)_n–(Th)_m–X$$

wherein

Th is a heterologous T helper epitope selected from the group consisting of SEQ ID NOs: 33 and 35;

A is a heterologous spacer;

(Tau fragment) is a B cell epitope is selected from the group consisting of SEQ ID NOs: 1-15, 18-21 and 101-124;

X is an α-COOH or α-$CONH_2$ of an amino acid;

m is from 1 to 4; and

n is from 0 to 10.

In another aspect, the present disclosure refers to a Tau peptide immunogen construct comprising: a B cell epitope is selected from the group consisting of SEQ ID NOs: 1-15, 18-21 and 101-124; a T helper epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: ~~22-50~~33 and 35; and an optional heterologous spacer selected from the group consisting of an amino acid, Lys-, Gly-, Lys-Lys-Lys-, (α, ε-N)Lys, and ε-N-Lys-Lys-Lys-Lys (SEQ ID NO: 102), wherein the B cell epitope is covalently linked to the T helper epitope directly or through the optional heterologous spacer.

In yet another aspect, the present disclosure refers to a composition comprising a peptide immunogen construction as disclosed herein.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising:a. a peptide immunogen construct as disclosed herein; and b. a pharmaceutically acceptable delivery vehicle and/or adjuvant.

~~In yet another aspect, the present disclosure refers to an isolated antibody or epitope binding fragment thereof that specifically binds to the B cell epitope of the Tau peptide~~

~~immunogen construct as disclosed herein.~~

~~In yet another aspect, the present disclosure refers to a composition comprising the isolated antibody or epitope binding fragment thereof as disclosed herein.~~

The present disclosure is directed to individual peptide immunogen constructs targeting portions of the Tau protein for the treatment and/or prevention of tauopathies. The present disclosure is also directed to compositions containing the peptide immunogen constructs, methods of making and using the peptide immunogen constructs, and antibodies produced by the peptide immunogen constructs.

The disclosed peptide immunogen constructs contain about 15 or more amino acids. The peptide immunogen constructs contain a B cell epitope from portions of the longest isoform of the human Tau protein (GenBank: AGF19246.1) having the amino acid sequence of SEQ ID NO: 100 shown in **Table 8**. The B cell epitope can be linked to a heterologous T helper cell (Th) epitope derived from pathogen proteins through an optional heterologous spacer. The disclosed peptide immunogen constructs stimulate the generation of highly specific antibodies directed against Tau. The disclosed peptide immunogen constructs can be used as an immunotherapy for patients suffering from tauopathies.

The B cell epitope portion of the peptide immunogen constructs have amino acid sequences from the full-length Tau protein (SEQ ID NO: 100). In some examples, the B cell epitope has a sequence containing any of SEQ ID NOs: 1-21 and 101-124 as shown in **Table 1**.

The peptide immunogen constructs of the present disclosure can contain a heterologous Th epitope amino acid sequence derived from a pathogenic protein (e.g., SEQ ID NOs: 22 to 50) as shown in **Table 2**. In certain examples, the heterologous Th epitope is derived from natural pathogens, such as Diphtheria Toxin (SEQ ID NO: 26), Plasmodium Falciparum (SEQ ID NO: 27), Cholera Toxin (SEQ ID NO: 29). In other examples, the heterologous Th epitope is an idealized artificial Th epitope derived from Measles Virus Fusion protein (MVF 1 to 5) or Hepatitis B Surface Antigen (HBsAg 1 to 3) in the form of either single sequence or combinatorial sequences (e.g., SEQ ID NOs: 33, 32, and 34).

In some examples, the peptide immunogen constructs contain a B cell epitope from Tau linked to a heterologous T helper cell (Th) epitope through an optional heterologous spacer. In certain examples, the peptide immunogen constructs contain a B cell antigenic site having

CLAIMS

1. A Tau peptide immunogen construct is represented by the formulae:

$$(Th)_m–(A)_n–(\text{Tau fragment})–X$$

or

$$(\text{Tau fragment})–(A)_n–(Th)_m–X$$

wherein

Th is a heterologous T helper epitope selected from the group consisting of SEQ ID NOs: 33 and 35;

A is a heterologous spacer;

(Tau fragment) is a B cell epitope is selected from the group consisting of SEQ ID NOs: 1-15, 18-21 and 101-124;

X is an α-COOH or α-$CONH_2$ of an amino acid;

m is from 1 to 4; and

n is from 0 to 10.

~~2. The Tau peptide immunogen construct according to any of claim 1, wherein the Th epitope is selected from the group consisting of SEQ ID NOs: 22-50.~~

~~3~~2. The Tau peptide immunogen construct according to claim 1, wherein the peptide immunogen construct is selected from the group consisting of SEQ ID NOs: 51-65, 68-71 and 125-155.

~~4~~3. A Tau peptide immunogen construct comprising:

a B cell epitope is selected from the group consisting of SEQ ID NOs: 1-15, 18-21 and 101-124;

a T helper epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: ~~22-50~~33 and 35; and

an optional heterologous spacer selected from the group consisting of an amino acid, Lys-, Gly-, Lys-Lys-Lys-, (α, ε-N)Lys, and ε-N-Lys-Lys-Lys-Lys ~~(SEQ ID NO: 102)~~,

wherein the B cell epitope is covalently linked to the T helper epitope directly or through the optional heterologous spacer.

~~5. The Tau peptide immunogen construct of claim 4, wherein the T helper epitope is selected from the group consisting of SEQ ID NOs: 22-50.~~

~~6~~4. The Tau peptide immunogen construct of claim ~~4~~3, wherein the optional heterologous spacer is (α, ε-N)Lys or ε-N-Lys-Lys-Lys-Lys ~~(SEQ ID NO: 102)~~.

~~7~~5. The Tau peptide immunogen construct of claim ~~4~~3, wherein the T helper epitope is covalently linked to the amino terminus of the B cell epitope.

~~8~~6. The Tau peptide immunogen construct of claim ~~4~~3, wherein the T helper epitope is covalently linked to the amino terminus of the B cell epitope through the optional heterologous spacer.

~~9~~7. A composition comprising a peptide immunogen construction according to any of claims 1 to ~~4~~3.

~~10~~8. A pharmaceutical composition comprising:

a. a peptide immunogen construct according to any of claims 1 to ~~3~~2; and

b. a pharmaceutically acceptable delivery vehicle and/or adjuvant.

~~11~~9. The pharmaceutical composition of claim ~~10~~8, wherein

a. the Tau peptide immunogen construct is selected from the group consisting of SEQ ID NOs: 51-65, 68-71 and 125-155; and

b. the Tau peptide immunogen construct is mixed with an CpG oligodeoxynucleotide (ODN) to form a stabilized immunostimulatory complex.

~~12. An isolated antibody or epitope binding fragment thereof that specifically binds to the B cell epitope of the Tau peptide immunogen construct according to any of claims 1 – 8.~~

~~13. The isolated antibody or epitope binding fragment thereof according to claim 12 bound to the Tau peptide immunogen construct.~~

~~14. A composition comprising the isolated antibody or epitope binding fragment thereof according to any of claims 12 – 13.~~