a life-long exposure to antigens leads to a shrinkage of the naive T-cell pool in elderly persons and consequently to limitations in the host's ability to respond to new antigens. This is particularly disturbing when old individuals contract newly emerging diseases, such as the severe acute respiratory syndrome (SARS), which killed 50% of infected persons over 50 years of age. Additionally, the naive T-cells found in old age have resided for decades in the periphery and have been exposed to a series of factors, such as oxidative stress and limited concentrations of survival factors, that may have a negative impact on cell function. Naïve CD4+ T cells from aged animals, compared with cells from young mice, produce significantly less IL-2, expand poorly and give rise to fewer effectors, with a less activated phenotype and reduced ability to produce cytokines. However, newly generated CD4+ T cells in old animals respond strongly to antigens in vivo and in vitro, are able to expand, produce IL-2 and exhibit cognate helper function. Thus, age-related defects in response to antigenic stimulation may, at least in part, be due to the chronological age of CD4+ T cells.

Memory CD4+ T cells are pivotal in controlling humoral and cellular responses, and so their longevity and response to vaccination are critical for the maintenance of protective immunity. Memory T cells generated from aged naive T cells survive and persist well in vivo but they are markedly defective in their proliferation and cytokine secretion during recall responses, whereas memory cells generated in young individuals retain function for extended periods of time as their host ages. These data, from animal studies, have recently been confirmed in humans. Healthy elderly individuals are able to mount a CD4+ T-cell response comparable to that observed in younger individuals when vaccinated against influenza, but they exhibit an impaired long-term CD4+ T-cell immune response to the influenza vaccine.

T-cell deficiencies do, however, not only occur as a consequence of ageing, but can also be found in immunosuppressed patients or in patients who suffer from certain diseases such as, for example, HIV, cancer or other malignancies.

SUMMARY OF THE INVENTION

In a particular ~~embodiment~~example of the present ~~invention~~disclosure an antigenic composition has been generated comprising a palmitoylated peptide presented on liposomes combined with MPLA, which vaccine is T-cell independent. The peptide is in beta-sheet conformation. This vaccine induces rapid and strong antibody responses. It is not dependent on another carrier protein and can

induce antibody responses in the absence of T cells, as demonstrated by antibody induction in nude mice. Finally, it induces a strong and effective antibody response in elderly mice despite the T cell deficiency at this old age (Miller R.A, et all, 1996; Adolfsson O, et all, 2001; Linton P.J., et all 1996).

Summary of characteristics of the vaccine

- Specific conformation (beta-sheet)
- Strong response (1000000 ng/ml at 7 days after immunization)
- Fast rapid response (7 days after first immunization)
- No need for T cell help
- No need for carrier protein
- Effectiveness in elderly mice, despite T cell deficiencies at this old age

Aβ antigenic compositions known in the prior art, such as AN1792 from the company Elan Inc (CA; USA), are usually typical T-dependent antigens (Aβ1-42) administered with a strong Th1 driving adjuvant (QS21). An initial study of AN1792 in Alzheimer's disease patients showed promising efficacy, with a slower rate of cognitive decline in patients who had received vaccination than in placebo-treated patients (Gilman et al. 2005). However 6% of treated patients developed meningoencephalitis a reaction considered to be due to a T-cell-mediated response against full length Aβ1-42 (Orgogozo et al. 2003). Although reversible in most patients this inflammatory response led to discontinuation of the clinical trial.

What is therefore needed, are methods wherein the use of an antigen, such as, for example, an anti-Aβ antigen or an anti-tau antigen, induces an antibody response through direct activation of B-cells in the absence of antigen-specific, i.e. Aβ –or tau-specific, T cells for the treatment, alleviation of the symptoms, delaying onset or prevention of diseases and disorders, such as diseases and disorders which are caused by or associated with amyloid or amyloid-like proteins including amyloidosis, a group of disorders and abnormalities associated with amyloid protein such as Alzheimer's Disease, or diseases and disorders which are caused by or associated with protein tau including tauopathies, in patients with a T-cell deficiency, particularly patients which are depleted of CD4 T-cells. Particularly, palmitoylated Aβ peptide or tau peptide presented by liposomes in combination with MPLA induce Aβ specific antibodies without the need for T cells help and without the need for a carrier protein providing T cell help.

The present ~~invention~~disclosure provides a method for the therapeutic and diagnostic use in the treatment, alleviation of the symptoms or prevention of diseases

and disorders comprising administering to a patient a T-cell independent antigenic composition comprising a modified antigen, wherein said antigen is presented in a highly repetitive array on the surface of a liposome. In particular, said diseases and disorders are caused by or associated with amyloid or amyloid-like proteins including amyloidosis, a group of disorders and abnormalities associated with amyloid protein such as Alzheimer's Disease, or diseases and disorders which are caused by or associated with protein tau including tauopathies, in a patient, particularly an immune tolerant patient, particular in a patient suffering from a T-cell deficiency, particularly a T-cell deficiency which is caused by a depletion within said patients of CD4 T-cells and/or a reduced expression of CD14 and/or the CD40L on CD4 T-cells such as, for example, an immunocompromised patient or a patient having an autoimmune disease.

Moreover, it was now surprisingly found within the scope of the present ~~invention~~disclosure that diseases in patients, which are in need of a T-cell independent immune response, particularly in immune tolerant patients, particularly in patients suffering from a T-cell immunodeficiency disease, can be avoided in an individual, particularly animal or human, wherein the individual can be either vaccinated before the onset of the disease, such as, for example, an amyloid- or tau protein-associated disease or, in case of suffering from an amyloid-or tau protein-associated disease or condition, the individual can be treated by the method described herein.

The technical problem underlying the present ~~invention~~disclosure is the provision of a method for the therapeutic and diagnostic use of an antigenic composition in the treatment, alleviation of the symptoms or prevention of diseases and disorders in a patient, particularly a patient in need of a T-cell independent immune response such as, for example, an immune tolerant patient or a T-cell activated patient, wherein a T-cell independent immune response is induced in the treated individual. In particular, diseases and disorders to be treated within the scope of the present ~~invention~~disclosure are, for example, diseases and disorders which are caused by or associated with amyloid or amyloid-like proteins including amyloidosis, a group of disorders and abnormalities associated with amyloid protein such as Alzheimer's Disease, or diseases and disorders which are caused by or associated with protein tau including tauopathies.

The technical problem is solved by the provision of the embodiments characterized in the claims.

The present ~~invention~~disclosure thus relates in ~~a first embodiment~~one example to an antigenic composition comprising a modified antigen for inducing a T-cell independent immune response upon treatment of a disease, condition or disorder in a patient, particularly an animal or human patient, particularly a patient in need of such a T-cell independent response such as, for example, an immune tolerant patient or a T-cell activated patient wherein said antigen is presented on the surface of a liposome.

In one ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure as described herein is effective as an immune stimulant.

In a specific ~~embodiment~~example of the ~~invention~~disclosure, said antigen is a peptide antigen, which is presented in a highly repetitive array on the surface of the liposome. In a further specific ~~embodiment~~example, said antigen does not contain a T-cell epitope.

In one ~~embodiment~~example of the ~~invention~~disclosure, the antigenic composition of the ~~invention~~disclosure as described herein is used for treating an immune tolerant patient or a T-cell activated patient, particularly a immunocompromised patient, particularly a patient suffering from an autoimmune disease, particularly a patient who suffers from a T-cell deficiency, particularly a T-cell deficiency, which is caused by a depletion within said patients of CD4 T-cells and/or a reduced expression of CD14 and/or the CD40L on CD4 T-cells.

In one ~~embodiment~~example, the ~~invention~~disclosure relates to the antigenic composition of the ~~invention~~disclosure and as described herein, wherein said T-cell deficiency is caused by age, immunosuppression or disease, particularly a disease selected from the group of HIV, cancer or other malignancies including, for example, inflammatory diseases which are treated with immunosuppressive and chemotherapeutic compounds, respectively, leading to an immune-suppressed status of the patients such as, for example, Rheumatoid Arthritis; Psoriasis, Systemic Lupus Erythrematosis, Wegener`s Granulamatosis, etc.

In one ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure and as described herein comprises a conformational antigen, wherein all or part of said antigen is in a beta-sheet conformation. In a specific ~~embodiment~~example, said antigenic peptide is modified such that it is capable of maintaining and stabilizing a defined conformation of the antigen, particularly a conformation which is characterized by a balanced proportion of random coil, α-helical and β-sheet portions. This defined conformation leads to the induction of a strong and highly specific immune response, particularly a T-cell independent immune response, upon introduction into an animal or a human.

In particular, the antigenic composition of the ~~invention~~disclosure and as described herein may comprise a conformational antigen, wherein more than 30%, particularly more than 40%, particularly more than 50%, particularly more than 60%, particularly more than 70%, particularly more than 80%, particularly more than 90%, particularly more than 95% and up to 100% is in a beta-sheet conformation.

In one ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure and as described herein comprises a peptide antigen, which is modified by a lipophilic or hydrophobic moiety, particularly a fatty acid, a triglyceride, a diglyceride, a steroid, a sphingolipid, a glycolipid or a phospholipid that facilitates insertion into the lipid bilayer of the liposome.

In a specific ~~embodiment~~example, the the lipophilic or hydrophobic moiety is a fatty acid, particularly a fatty acid with a carbon back bone of at least 10 carbon atoms, particularly a palmitic acid.

In another specific ~~embodiment~~example of the ~~invention~~disclosure, the antigenic composition of the ~~invention~~disclosure and as described herein comprises a peptide antigen comprising two palmitic acid moieties, particularly four palmitic acid moieties.

In still another specific ~~embodiment~~example of the ~~invention~~disclosure, the dimension of the lipophilic or hydrophobic moiety in combination with the overall net charge of the antigenic peptide and of the carrier/adjuvant to which the peptide becomes attached to, incorporated or reconstituted in, is such that the antigenic peptide is exposed, stabilized and presented in a highly biologically active conformation, which allows the immune system of the target organism to freely interact with the antigenic determinants contained in the antigenic construct in its exposed, stabilized and highly biologically active conformation, which leads to a strong immune response.

In one ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure and as described herein, comprises a liposome preparation and an adjuvant, particularly lipid A, particularly detoxified lipid A, such as monophosphoryl or diphosphoryl lipid A or alum.

In one ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure and as described herein, comprises an antigenic construct, particularly an Aβ antigenic construct, comprising a single or repetitive Aβ peptide fragment derived from the N-terminus of the Aβ peptide.

In a specific ~~embodiment~~example of the ~~invention~~disclosure, the N-terminus of the Aβ peptide comprises

a) Aβ 1-30;

b) Aβ 1-20; or

c) Aβ 1-16;

In another specific ~~embodiment~~example of the ~~invention~~disclosure, the Aβ peptide fragment comprises between

a) 4 and 20 amino acids;

b) 5 and 16 amino acids;

c) 6 and 12 amino acids; or

d) 4 and 8 amino acids.

In still another specific ~~embodiment~~example of the ~~invention~~disclosure, the Aβ peptide fragment is

a) $A\beta_{1-15;}$

b) $A\beta_{1-16;}$

c) $A\beta_{1-5.}$

In one ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure and as described herein comprises an antigenic construct comprising an antigenic peptide, which is a phospho-peptide mimicking a major pathological phospho-epitope of protein tau, particularly a human protein tau.

In a specific ~~embodiment~~example of the ~~invention~~disclosure, said tau protein has an amino acid sequence identity to

a) SEQ ID NO: 2 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 2, wherein the amino acid residue corresponding to amino acid residue 18 ($P\text{-}Tyr_{18}$) of SEQ ID NO: 2 is phosphorylated (T1);

b) SEQ ID NO: 3 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 3, wherein at least one, particularly at least 2 of amino acid residues corresponding to amino acid residues 212 ($P\text{-}Thr_{212}$) and 214 ($P\text{-}Ser_{214}$) of SEQ ID NO: 3 are phosphorylated;

c) SEQ ID NO: 4 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 4, wherein at least one, particularly at least 2 of amino acid residues corresponding to amino acid residues 202 ($P\text{-}Ser_{202}$) and 205 ($P\text{-}Thr_{205}$) of SEQ ID NO: 4 are phosphorylated;

d) SEQ ID NO: 5 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 5, wherein at least one, but especially all of amino acid residues corresponding to amino acid residues 396 ($P\text{-}Ser_{396}$) and 404 ($P\text{-}Ser_{404}$) of SEQ ID NO: 5 are phosphorylated;

e) SEQ ID NO: 6 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 6, wherein at least one, but especially all of amino acid residues corresponding to amino acid residues 404 (P-Ser_{404}) and 409 (P-Ser_{409}) of SEQ ID NO: 6 are phosphorylated;

f) SEQ ID NO: 7 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 7, wherein at least one, particularly at least 2, particularly a least 3, but especially all of amino acid residues corresponding to amino acid residues 202 (P-Ser_{202}), 205 (P-Thr_{205}), 212 (P-Thr_{212}), and 214 (P-Ser_{214}) of SEQ ID NO: 7 are phosphorylated.

In another specific ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure and as described herein comprises a tau protein, which has an amino acid sequence of

a) SEQ ID NO: 2;
b) SEQ ID NO: 3;
c) SEQ ID NO: 4;
d) SEQ ID NO: 5;
e) SEQ ID NO: 6; or
f) SEQ ID NO: 7.

In still another ~~embodiment~~example, the ~~invention~~disclosure relates to the antigenic composition of any of the previously described embodiments comprising a modified antigen for use in the treatment of a disease, condition or disorder in a patient, particularly an animal or human patient, particularly a patient in need of a T-cell independent response such as, for example, an immune tolerant patient or a T-cell activated patient, particularly a immunocompromised patient, particularly a patient suffering from an autoimmune disease, particularly a patient who suffers from a T-cell deficiency, particularly a T-cell deficiency, which is caused by a depletion within said patients of CD4 T-cells and/or a reduced expression of CD14 and/or the CD40L on CD4 T-cells, to overcome or reduce immune tolerance in said patient, wherein said antigen is presented in a highly repetitive array on the surface of a liposome and wherein said patient is suffering from a disease or disorder which is caused by or associated with amyloid or amyloid-like proteins.

In still another ~~embodiment~~example, the ~~invention~~disclosure relates to the antigenic composition of any of the previously described embodiments comprising a modified antigen for use in the treatment of a disease, condition or disorder in a patient, particularly an animal or human patient, particularly a patient in need of a T-

cell independent response such as, for example, an immune tolerant patient or a T-cell activated patient, particularly a immunocompromised patient, particularly a patient suffering from an autoimmune disease, particularly a patient who suffers from a T-cell deficiency, particularly a T-cell deficiency, which is caused by a depletion within said patients of CD4 T-cells and/or a reduced expression of CD14 and/or the CD40L on CD4 T-cells, to overcome or reduce immune tolerance in said patient, wherein said antigen is presented in a highly repetitive array on the surface of a liposome and wherein said patient is suffering from a disease or disorder which is caused by or associated with tau or tau-like proteins.

In a specific ~~embodiment~~example of the ~~invention~~disclosure, the amyloid-associated disease or disorder is characterized by a loss of cognitive memory capacity in an individual, particularly animal or human.

In another specific ~~embodiment~~example of the ~~invention~~disclosure, said disease is a disease or disorder is a neurological disease or disorder, particularly a disease or disorder from the amyloidosis group, particularly a disease or disorder selected from the group consisting of Alzheimer's Disease (AD), mild cognitive impairment (MCI), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, stroke, traumatic brain injury, macular degeneration and glaucoma.

In a specific ~~embodiment~~example, said disease is Alzheimer's disease.

In still another specific ~~embodiment~~example of the ~~invention~~disclosure, the tau-associated disease or disorder is a neurodegenerative disorder, particularly a neurodegenerative disease or disorder, which is caused by or associated with the formation of neurofibrillary lesions.

In a specific ~~embodiment~~example of the ~~invention~~disclosure, neurodegenerative disease or disorder is a tauopathy, particularly selected from the group consisting of Alzheimer's disease, Creutzfeldt-Jakob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker *disease, inclusion-body myositis, and 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, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to

chromosome 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.

In a specific embodiment of the invention, said neurodegenerative disorder is Alzheimer's disease.

In one ~~aspect of the invention~~example, the antigenic composition of any of the previously described ~~embodiments~~examples does not show any adverse inflammatory effects.

In one aspect, there is provided the use of an antigenic composition comprising a conformational antigen all or part of which comprises a biologically active conformation, which antigen is modified by a lipophilic or hydrophobic moiety that facilitates insertion into the lipid bilayer of a liposome carrier/adjuvant and presented in a highly repetitive array on the surface of a liposome, in the manufacture of a medicament for inducing a T-cell independent immune response in a population of patients suffering from T-cell deficiency, wherein the antigenic composition comprising modified antigen is to be administered to the patient in need thereof, and wherein the modified antigen is a peptide fragment derived from an amyloid protein or amyloid-like protein.

In one ~~embodiment~~example, the ~~invention~~disclosure relates to a method of using an antigenic composition comprising a modified antigen according to any of the previously described ~~embodiments~~examples for the preparation of a medicament for inducing a T-cell independent immune response upon treatment of a disease, condition or disorder in a patient, particularly an animal or human patient, particularly a patient in need of such a T-cell independent response, wherein said antigen is presented on the surface of a liposome, particularly in a highly repetitive array.

In one ~~embodiment~~example of the ~~invention~~disclosure said antigenic composition is effective as an immune stimulant.

In another aspect, there is provided a method of using an antigenic composition comprising a conformational antigen all or part of which comprises a biologically active conformation, which antigen is modified by a lipophilic or hydrophobic moiety that facilitates insertion into the lipid bilayer of a liposome carrier/adjuvant and presented in a highly repetitive array on the surface of a liposome for the preparation of a medicament for use in inducing a T-cell independent immune response in a population of patients suffering from T-cell deficiency, wherein said antigenic composition comprising the modified antigen is to be administered to the patient in need thereof, and wherein the modified antigen is a peptide fragment derived from an amyloid protein or amyloid-like protein.

In yet another aspect, there is provided the use of an antigenic composition comprising a conformational antigen all or part of which comprises a biologically active conformation, which antigen is modified by a lipophilic or hydrophobic moiety that facilitates insertion into the lipid bilayer of a liposome carrier/adjuvant and presented in a highly repetitive array on the surface of a liposome in the manufacture of a medicament for inducing a T-cell independent immune response in a population of patients suffering from T-cell deficiency, wherein the antigenic composition comprising the modified antigen is to be administered to the patient in need thereof, and wherein the modified antigen is a peptide fragment derived from an amyloid protein or amyloid-like protein.

In one ~~embodiment~~example, the ~~invention~~disclosure relates to a method of using an antigenic composition comprising a modified antigen according to any of the previously described embodiments for the preparation of a medicament for use in the treatment of an immune tolerant patient or a T-cell activated patient, particularly an animal or a human, particularly a immunocompromised patient, particularly a patient suffering from an autoimmune disease, particularly a patient who suffers from a T-cell deficiency, particularly a T-cell deficiency, which is caused by a depletion within said patients of CD4 T-cells and/or a reduced expression of CD14 and/or the CD40L on CD4 T-cells, to overcome or reduce immune tolerance in said patient or to avoid an overstimulation of the T-cell response in said patient, wherein said antigen is presented in a highly repetitive array on the surface of a liposome.

Also comprised by the present ~~invention~~disclosure is a method for inducing a T-cell independent immune response upon treatment of a disease, condition or disorder in a patient, particularly an animal or human patient, particularly a patient in need of such a T-cell independent response, wherein said antigen is presented on the surface of a liposome, particularly in a highly repetitive array.

In one ~~embodiment~~example of the ~~invention~~disclosure said antigenic composition is effective as an immune stimulant.

Also comprised by the present ~~invention~~disclosure is a method for overcoming or reducing an immune tolerance in an immune tolerant patient or to avoid an overstimulation of the T-cell response in a T-cell activated patient, upon treatment of a disease or disorder in said patient, particularly an animal or a human patient, particularly a immunocompromised patient, particularly a patient suffering from an autoimmune disease, particularly a patient who suffers from a T-cell deficiency, particularly a T-cell deficiency, which is caused by a depletion within said patients of CD4 T-cells and/or a reduced expression of CD14 and/or the CD40L on CD4 T-cells, comprising administering to said patient an antigenic composition comprising a modified antigen according to any of the previously described embodiments, wherein said antigen is presented in a highly repetitive array on the surface of a liposome; and optionally the further step of determining the immune response in said individual by measuring the antibody concentration of IgG and/or IgM.

The present ~~invention~~disclosure further relates in another ~~embodiment~~example to a method for the treatment, alleviation of the symptoms or prevention of a disease or condition, particularly an amyloid- or tau-protein associated disease or condition, in an immune tolerant patient or a T-cell activated patient, particularly an animal or human, which patient suffers from a T-cell deficiency, particularly a T-cell deficiency caused by a depletion of T-cells, particularly of CD4 T cells such as, for example, an immunocompromised patient or a patient having an autoimmune disease, comprising administering to said patient an antigenic composition comprising a modified antigen according to any of the previously described embodiments, wherein said antigen is presented in a highly repetitive array on the surface of a liposome and wherein a T-cell independent immune response is induced in the treated patient.

The present ~~invention~~disclosure thus further relates to a method for inducing a T-cell independent immune response in an immune tolerant patient or a T-cell activated patient, particularly to a method for the treatment, alleviation of the symptoms, delaying onset or prevention of a disease or disorder in such an immune tolerant patient or a T-cell activated patient, which disease or disorder is caused by or associated with amyloid or amyloid-like proteins including amyloidosis, a group of disorders and abnormalities associated with amyloid protein such as Alzheimer's Disease, or diseases and disorders which are caused by or associated with protein tau including tauopathies, in an individual, particularly animal or human, particularly an animal or human who is depleted of T-cells, particularly of CD4 T-cells such as, for example, an

immunocompromised patient or a patient having an autoimmune disease, comprising the following steps (a) administration of an antigenic construct, particularly an antigenic construct comprising a T-independent antigen, to said individual; and (b) determination of the immune response in said individual, particularly by measuring the antibody concentration of IgG.

In a particular ~~embodiment~~example of the ~~invention~~disclosure, said individual is an elderly human patient depleted of T-cells, particularly of CD4 T cells, particularly an immunocompromised patient or a patient having an autoimmune disease.

In another embodiment of the invention, said individual is an immunosuppressed human patient, who is depleted of T-cells, particularly of CD4 T cells.

In still another ~~embodiment~~example of the ~~invention~~disclosure, said individual is a human patient, who is depleted of T-cells, particularly of CD4 T cells and suffers from an immunodeficiency disease, particularly from HIV.

In still another ~~embodiment~~example of the ~~invention~~disclosure, said individual is a human patient, who has cancer or another malignancy and is depleted of T-cells, particularly of CD4 T cells.

In still another ~~embodiment~~example of the ~~invention~~disclosure, said individual is a human patient, who is depleted of T-cells, particularly of CD4 T cells and suffers from an autoimmune disease.

The present ~~invention~~disclosure further relates in another ~~embodiment~~example to a method for inducing a T-cell independent immune response, particularly an Aβ immune response or a tau-related immune response, in an individual, particularly an animal or human, particularly an individual in need of such a T-cell independent Aβ immune response, particularly an immune tolerant individual or patient, who is depleted of T-cells, particularly of CD4 T cells such as, for example, an immunocompromised patient or a patient having an autoimmune disease, comprising the following steps (a) administration of an antigenic construct, particularly an Aβ- or tau-related antigenic construct, particularly an Aβ- or tau-related antigenic construct comprising a T-independent antigen, to said individual; and (b) determination of the immune response in said individual, particularly by measuring the antibody concentration of IgG.

In another ~~embodiment~~example, the ~~invention~~disclosure relates to a method according to the previously described ~~embodiment~~example, wherein said Aβ- or tau-related antigen induces an antibody response in the absence of T helper cells *in vivo*.

In another ~~embodiment~~example of the present ~~invention~~disclosure a method according to any of the previously described ~~embodiments~~examples is provided, wherein said Aβ- or tau-related immune response is an IgG response.

In one ~~embodiment~~example as described herein a method according to any of the previously described ~~embodiments~~examples is provided, wherein the immune tolerant individual or patient or the T-cell activated patient, particularly animal or human, particularly an animal or human who is depleted of T-cells, particularly of CD4 T cells, does not show any adverse inflammatory effect.

In another ~~embodiment~~example of the present ~~invention~~disclosure, a method according to any of the previously described embodiments is provided, wherein the immune tolerant individual or patient, particularly animal or human, is T-cell deficient, particularly CD4 T cell deficient such as, for example, an *immunocompromised patient or a patient having an autoimmune disease.*

In a further ~~embodiment~~example, a method according to any of the previously described embodiments is provided, wherein the Aβ antigenic construct comprises a single or repetitive Aβ peptide fragment derived from the N-terminus of the Aβ peptide.

In another ~~embodiment~~example of the present ~~invention~~disclosure, a method according to any of the previously described embodiments is provided, wherein the N-terminus of the Aβ peptide comprises Aβ 1-30; Aβ 1-20; or Aβ 1-16.

In a further ~~embodiment~~example, a method according to any of the previously described ~~embodiments~~examples is provided, wherein the Aβ peptide fragment comprises between 4 and 20 amino acids; between 5 and 16 amino acids; between 6 and 12 amino acids; or between 4 and 8 amino acids.

In particular, the present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous embodiment, wherein said Aβ peptide fragment is $A\beta_{1-15;}$ $A\beta_{1-16;}$ or $A\beta_{1-5}$.

In one ~~embodiment~~example, the ~~invention~~disclosure relates to a method according to any of the previously described embodiment, wherein the antigenic composition comprises an antigenic construct comprising an antigenic peptide, which is a phospho-peptide mimicking a major pathological phospho-epitope of protein tau, particularly a human protein tau.

In a specific ~~embodiment~~example of the ~~invention~~disclosure, said tau protein has an amino acid sequence identity to

a) SEQ ID NO: 2 of at least 95%, and has substantially the same *immunogenic activity as said antigenic peptide of SEQ ID NO: 2, wherein the* amino acid residue corresponding to amino acid residue 18 ($P\text{-}Tyr_{18}$) of SEQ ID NO: 2 is phosphorylated (T1);

b) SEQ ID NO: 3 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 3, wherein at least one, particularly at least 2 of amino acid residues corresponding to

amino acid residues 212 (P-Thr_{212}) and 214 (P-Ser_{214}) of SEQ ID NO: 3 are phosphorylated;

c) SEQ ID NO: 4 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 4, wherein at least one, particularly at least 2 of amino acid residues corresponding to amino acid residues 202 (P-Ser_{202}) and 205 (P-Thr_{205}) of SEQ ID NO: 4 are phosphorylated;

d) SEQ ID NO: 5 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 5, wherein at least one, but especially all of amino acid residues corresponding to amino acid residues 396 (P-Ser_{396}) and 404 (P-Ser_{404}) of SEQ ID NO: 5 are phosphorylated;

e) SEQ ID NO: 6 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 6, wherein at least one, but especially all of amino acid residues corresponding to amino acid residues 404 (P-Ser_{404}) and 409 (P-Ser_{409}) of SEQ ID NO: 6 are phosphorylated;

f) SEQ ID NO: 7 of at least 95%, and has substantially the same immunogenic activity as said antigenic peptide of SEQ ID NO: 7, wherein at least one, particularly at least 2, particularly a least 3, but especially all of amino acid residues corresponding to amino acid residues 202 (P-Ser_{202}), 205 (P-Thr_{205}), 212 (P-Thr_{212}), and 214 (P-Ser_{214}) of SEQ ID NO: 7 are phosphorylated.

In another specific ~~embodiment~~example, the antigenic composition of the ~~invention~~disclosure and as described herein comprises a tau protein, which has an amino acid sequence of

a) SEQ ID NO: 2;
b) SEQ ID NO: 3;
c) SEQ ID NO: 4;
d) SEQ ID NO: 5;
e) SEQ ID NO: 6; or
f) SEQ ID NO: 7.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any of the preceding ~~embodiments~~examples, wherein the antigen, particularly the Aβ- or tau-peptide antigen is presented reconstituted in a carrier such as, for example, a vesicle, a particulate body or molecule.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any of the preceding ~~embodiments~~examples, wherein the antigen, particularly the Aβ- or tau-peptide antigen is presented reconstituted in a liposome.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any of the preceding ~~embodiments~~examples, wherein the antigen, particularly the Aβ- or tau-peptide antigen is modified by a lipophilic or hydrophobic moiety that facilitates insertion into the lipid bilayer of the liposome carrier/adjuvant.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous ~~embodiment~~example, wherein the dimension of the lipophilic or hydrophobic moiety in combination with the overall net charge of the antigenic peptide and of the carrier/adjuvant to which the peptide becomes attached to, incorporated or reconstituted in is such that the antigenic peptide is exposed, stabilized and presented in a highly biologically active conformation, which allows the immune system of the target organism to freely interact with the antigenic determinants contained in the antigenic construct in its exposed, stabilized and highly biologically active conformation, which leads to a strong immune response.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any of the previous ~~embodiments~~examples, wherein the lipophilic or hydrophobic moiety is a fatty acid, a triglycerides or a phospholipid, particularly a fatty acid with a carbon back bone of at least 10 carbon atoms, particularly a palmitic acid.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous ~~embodiment~~example, wherein the antigen, particularly the Aβ- or tau-peptide antigen comprises two palmitic acid moieties, particularly four palmitic acid moieties.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any of the previous ~~embodiments~~examples, wherein the liposome preparation contains an adjuvant, particularly lipid A, particularly detoxified lipid A, such as monophosphoryl or diphosphoryl lipid A or alum.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any one of the preceding ~~embodiments~~examples, wherein the amyloid associated disease or condition is one selected from the group consisting of diseases including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), including diseases or conditions characterized by a loss of cognitive memory capacity such as, for example, mild cognitive impairment (MCI), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia

complex; as well as other diseases which are based on or associated with amyloid-like proteins such as progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, stroke, traumatic brain injury, all ocular diseases and others, including macular degeneration and glaucoma, but particularly Alzheimer's Disease.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous ~~embodiment~~example, wherein the amyloid-associated condition is characterized by a loss of cognitive memory capacity in an individual, particularly an immune tolerant individual or patient or a T-cell activated patient, particularly animal or human.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous ~~embodiment~~example, wherein treatment of an immune tolerant individual or patient or a T-cell activated patient, particularly animal or human, suffering from an amyloid-associated condition characterized by a loss of cognitive memory capacity leads to an increase in the retention of cognitive memory capacity, particularly to a complete restoration of cognitive memory capacity.

In still another specific ~~embodiment~~example of the ~~invention~~disclosure relates to a method according to any one of the preceding ~~embodiments~~examples, wherein the tau-associated disease or disorder is a neurodegenerative disorder, particularly a neurodegenerative disease or disorder, which is caused by or associated with the formation of neurofibrillary lesions, particularly a tauopathy, particularly a tauopathy selected from the group consisting of Alzheimer's disease, Creutzfeldt-Jakob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, and 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, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to chromosome 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, but particularly Alzheimer's disease.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to the use of an antigen, particularly an Aβ peptide antigen or a tau peptide antigen as described in any of the preceding ~~embodiments~~examples for inducing a T-cell independent immune response, particularly an Aβ-related or tau-related immune response in an individual, particularly animal or human, particularly an animal or human who is depleted of T-cells, particularly of CD4 T cells.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method for the treatment, alleviation of the symptoms or prevention of disease or condition, particularly an amyloid- or tau-protein associated disease or condition in an individual, particularly an immune tolerant individual or patient or a T-cell activated patient, comprising administering to said individual or patient, particularly animal or human, particularly an animal or human who is depleted of T-cells, particularly of CD4 T cells, suffering from such a disease or condition, an antigenic construct, particularly an Aβ or tau antigenic construct, as claimed in any of the preceding embodiments, or a T-cell independent antigenic composition comprising said antigenic construct, wherein a T-cell independent immune response, particularly the Aβ or tau immune response, is induced in the treated individual.

In a particular ~~embodiment~~example of the ~~invention~~disclosure, said individual is an elderly human patient depleted of T-cells, particularly of CD4 T cells,

In another ~~embodiment~~example of the ~~invention~~disclosure, said individual is an immunosuppressed human patient, who is depleted of T-cells, particularly of CD4 T cells.

In still another ~~embodiment~~example of the ~~invention~~disclosure, said individual is a human patient, who is depleted of T-cells, particularly of CD4 T cells and suffers from an immunodeficiency disease, particularly from HIV.

In still another ~~embodiment~~example of the ~~invention~~disclosure, said individual is a human patient, who has cancer or another malignancy and is depleted of T-cells, particularly of CD4 T cells.

In still another ~~embodiment~~example of the ~~invention~~disclosure, said individual is a human patient who exhibits T-cell activation and where a further stimulation of the T-cell response would cause a medical risk.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any o f the previous ~~embodiments~~examples, wherein no adverse inflammatory effect is induced.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous ~~embodiment~~example, wherein administration of said antigen, particularly of an Aβ or tau-antigenic construct results mainly in the generation

of antibodies of non-inflammatory subtypes, particularly of the non-inflammatory Th2 subtype, particularly of isotype IgG1 and IgG2b.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous ~~embodiments~~examples, wherein administration of said Aβ antigenic construct results mainly in the generation of antibodies of the T-cell independent IgG subclass, particularly of the IgG3 isotype.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to the previous ~~embodiment~~example wherein administration of said Aβ antigenic construct does not lead to a significant increase in inflammation markers in the brain, particularly markers selected from the group consisting of IL-1 β, IL-6, IFN-γ and TNF α.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any of the preceding ~~embodiments~~examples, wherein administration of said Aβ antigenic construct leads to a significant decrease of insoluble, plaque-related- Aβ1-40 and Aβ1-42 in the brain.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to ~~embodiment~~example (49), wherein administration of said Aβ antigenic construct leads to a significant reduction in the level of soluble Aβ1-42 in the brain.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method according to any of the preceding ~~embodiments~~examples, wherein the amyloid associated disease or condition is one selected from the group consisting of diseases including, but not limited to, neurological disorders such as Alzheimer's Disease (AD), including diseases or conditions characterized by a loss of cognitive memory capacity such as, for example, mild cognitive impairment (MCI), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; as well as other diseases which are based on or associated with amyloid-like proteins such as progressive supranuclear palsy, multiple sclerosis; Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, ALS (amyotropic lateral sclerosis), Adult Onset Diabetes; senile cardiac amyloidosis; endocrine tumors, stroke, traumatic brain injury, all ocular diseases and others, including macular degeneration and glaucoma, particularly Alzheimer's Disease.

The present ~~invention~~disclosure relates in another ~~embodiment~~example to a method for the treatment, alleviation of the symptoms or prevention of disease or condition, particularly tau-protein associated disease or condition in an individual, particularly an immune tolerant individual or patient, or a T-cell activated patient, according to any of the preceding ~~embodiments~~examples, wherein the tau-associated disease or disorder is a neurodegenerative disorder, particularly a

residues corresponding to amino acid residues 202 (P-Ser_{202}), 205 (P-Thr_{205}), 212 (P-Thr_{212}), and 214 (P- Ser_{214}) of SEQ ID NO: 7 are phosphorylated.

32. The use of claim 25, wherein said tau protein has an amino acid sequence of SEQ ID NO: 2.

33. The use of claim 25, wherein said tau protein has an amino acid sequence of SEQ ID NO: 3.

34. The use of claim 25, wherein said tau protein has an amino acid sequence of SEQ ID NO: 4.

35. The use of claim 25, wherein said tau protein has an amino acid sequence of SEQ ID NO: 5.

36. The use of claim 25 wherein said tau protein has an amino acid sequence of SEQ ID NO: 6.

37. The use of claim 25, wherein said tau protein has an amino acid sequence of SEQ ID NO: 7.

38. The use of any of claims 20 - 23, wherein said patient is suffering from a disease or disorder which is caused by or associated with amyloid or amyloid-like proteins.

39. The use according to claim 38, wherein the amyloid- associated disease or disorder is characterized by a loss of cognitive memory capacity in an individual, particularly animal or human.

40. The use of claim 39, wherein said disease is a disease or disorder from the amyloidosis group.

41. The use of claim 40, wherein said disease is a neurological disorder.

42. The use of claim 41, wherein said disease is a disease or disorder selected from the group consisting of Alzheimer's Disease (AD), mild cognitive impairment (MCI), Lewy body dementia, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type); the Guam Parkinson-Dementia complex; progressive supranuclear palsy, multiple sclerosis; Creutzfeldt-Jacob~~Creutzfeld-Jacob~~ disease, Parkinson's disease, HIV- related dementia, ALS (amyotropic lateral sclerosis), senile cardiac amyloidosis; endocrine tumors, stroke, and glaucoma.

43. The use of claim 42, wherein said disease is Alzheimer's disease.

44. The use of any of claims 24 - 37, wherein said patient is suffering from a disease or disorder which is caused by or associated with tau or tau-like proteins.

45. The use according to claim 44, wherein the tau- associated disease or disorder is a neurodegenerative disorder.

46. The use of claim 45, wherein said neurodegenerative disease or disorder is caused by or associated with the formation of neurofibrillary lesions.

47. The use according to claim 46, wherein neurodegenerative disease or disorder is a tauopathy.

48. The use of claim 47, wherein said neurodegenerative disease or disorder is one selected from the group consisting of Alzheimer's disease, Creutzfeldt-Jakob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Straussler-Scheinker disease, inclusion- body myositis, and prion protein cerebral amyloid angiopathy, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism linked to chromosome 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.

49. The use of claim 48, wherein said neurodegenerative disorder is Alzheimer's disease.

50. The use of any of the preceding claims, wherein the individual, particularly animal or human does not show any adverse inflammatory effect.

51. A method of using an antigenic composition comprising a conformational antigen all or part of which comprises a biologically active conformation, which antigen is modified by a lipophilic or hydrophobic moiety that facilitates insertion into the lipid bilayer of a liposome carrier/adjuvant and presented in a highly repetitive array on the surface of a liposome for the preparation of a medicament for use in inducing a T-cell independent immune response in a population of patients suffering from T-cell deficiency, wherein said antigenic composition comprising the modified antigen is to

be administered to the patient in need thereof, and wherein the modified antigen is a peptide fragment derived from an amyloid protein or amyloid-like protein.

52. Use of an antigenic composition comprising a conformational antigen all or part of which comprises a biologically active conformation, which antigen is modified by a lipophilic or hydrophobic moiety that facilitates insertion into the lipid bilayer of a liposome carrier/adjuvant and presented in a highly repetitive array on the surface of a liposome in the manufacture of a medicament for inducing a T-cell independent immune response in a population of patients suffering from T-cell deficiency, wherein the antigenic composition comprising the modified antigen is to be administered to the patient in need thereof, and wherein the modified antigen is a peptide fragment derived from an amyloid protein or amyloid-like protein.

53. The use of claim 52 further comprising the step of determining the immune response in said individual by measuring the antibody concentration of IgG and/or IgM.