

target, the Th response is provided by coupling the target to a carrier protein. The disadvantages of this technique are many. It is difficult to manufacture well-defined, safe, and effective peptide-carrier protein conjugates for the following reasons:

[0005] a. Chemical coupling are random reactions introducing heterogeneity of size and composition, e.g., conjugation with glutaraldehyde (Borras-Cuesta et al., Eur J Immunol, 1987; 17: 1213-1215);

[0006] b. the carrier protein introduces a potential for undesirable immune responses such as allergic and autoimmune reactions (Bixler et al., WO 89/06974);

[0007] c. the large peptide-carrier protein elicits irrelevant immune responses predominantly misdirected to the carrier protein rather than the target site (Cease et al., Proc Natl Acad Sci USA, 1987; 84: 4249-4253); and

[0008] d. the carrier protein also introduces a potential for epitopic suppression in a host which had previously been immunized with an immunogen comprising the same carrier protein. When a host is subsequently immunized with another immunogen wherein the same carrier protein is coupled to a different hapten, the resultant immune response is enhanced for the carrier protein but inhibited for the hapten (Schutze et al., J Immunol, 1985; 135: 2319-2322).

[0009] To avoid the risks described above, it is desirable to elicit T cell help without the use of traditional carrier proteins.

INCORPORATION BY REFERENCE

[0010] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

BRIEF DESCRIPTION OF THE DRAWING

[0011] Figure 1: Detection of promiscuous and artificial Th peptide responsive T cells in naïve Peripheral blood mononuclear cells of normal donors.

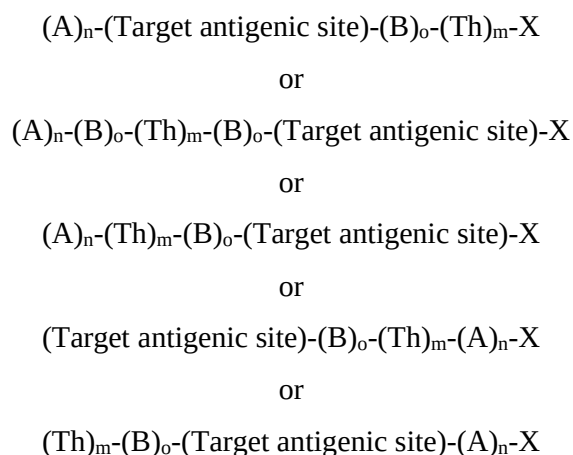
SUMMARY

[0011a] In one aspect, the present disclosure refers to use of a peptide in the manufacture of a medicament for treating a condition, wherein the peptide comprises a T helper cell epitope and an antigen-presenting epitope, wherein the peptide produces an immunogenic inflammatory response that is at least about 3-fold lower than an immunogenic inflammatory response of a positive control, wherein the peptide is to be administered to a subject in need thereof.

[0012] The present disclosure provides promiscuous artificial T helper cell (Th) epitopes that can be used to produce peptide immunogens that are capable of stimulating functional site-directed antibody responses for therapeutic effects. The disclosed artificial Th epitopes can be linked to a synthetic peptide B cell epitope (“target antigenic site”), through an optional spacer, to produce an immunogenic peptide. The immunogenic peptides can also comprise other components, including a general immune stimulator sequence.

[0013] The artificial Th epitope imparts to the peptide immunogen the capability to induce a strong T helper cell-mediated immune response with the production of a high level of antibodies directed against the “target antigenic site.” The present disclosure further provides for the advantageous replacement of carrier proteins and pathogen-derived T helper cell sites in established peptide immunogens with artificial Th epitopes designed specifically to improve their immunogenicity. The short peptide immunogens with the artificial Th epitopes of the present disclosure elicit a high level of antibodies targeted to specific target antigenic site B cell epitopes without causing a significant inflammatory response.

[0014] The artificial Th epitopes of the present disclosure can be linked to target antigenic sites and optionally to an immunostimulatory sequence. The immunogenic peptides of the present disclosure may be represented by the formulae:



wherein:

each A is independently an amino acid;

each B is independently an amino acid, $\text{-NHCH(X)CH}_2\text{SCH}_2\text{CO-}$, $\text{-NHCH(X)CH}_2\text{SCH}_2\text{CO}(\epsilon\text{N})\text{Lys-}$, $\text{-NHCH(X)CH}_2\text{S-succinimidyl}(\epsilon\text{N})\text{Lys-}$, or $\text{-NHCH(X)CH}_2\text{S-(succinimidyl)-}$;

each Th is independently an artificial Th cell epitope, an analog, or segment thereof;

Target antigenic site is a B cell epitope, a peptide hapten, or an immunologically reactive analogue thereof;

X is an amino acid, $\alpha\text{-COOH}$, or -CONH_2 ;

n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

m is 1, 2, 3, or 4; and

o is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[0015] An example of a peptide hapten as a target antigenic site is amino acids 1-14 of the beta-amyloid ($\text{A}\beta$) protein ($\text{A}\beta_{1-14}$) (SEQ ID NO: 56).

[0016] The compositions of the present disclosure comprise peptides capable of evoking antibody responses in an immunized host to a desired target antigenic site. The target antigenic site may be derived from pathogenic organisms and normally immunosilent self-antigens and tumor-associated targets.

[0017] Accordingly, the compositions of the present disclosure are useful in many diverse medical and veterinary applications. These include vaccines to provide protective immunity from infectious disease, immunotherapies for the treatment of disorders resulting from the malfunction of normal physiological processes, immunotherapies for the treatment of cancer, and agents to desirably intervene in and modify normal physiological processes.

[0018] Some of the targets antigens that may be covalently linked to the Th epitopes of the present disclosure include portions of: beta-amyloid (A β) for the treatment of Alzheimer's Disease, alpha-synuclein (α -Syn) for the treatment of Parkinson's Disease, the extracellular membrane-proximal domain of membrane-bound IgE (or IgE EMPD) for the treatment of allergic disease, Tau for the treatment of tauopathies including Alzheimer's Disease, and Interleukin-31 (IL-31) for the treatment of atopic dermatitis, to name a few. More specifically, A β ₁₋₁₄ (as described in U.S. Patent No. 9,102,752), α -Syn₁₂₆₋₁₃₅ (as described in U.S. Provisional Application No. 62/521,287), IgE EMPD₁₋₃₉ (as described in International PCT Application No. PCT/US2017/069174), Tau₃₇₉₋₄₀₈ (as described in U.S. Provisional Application No. 62/578,124), and IL-31₉₇₋₁₄₄ (as described in U.S. Provisional Application No. 62/597,130).

[0019] In some examples, the disclosure provides a method of treating a condition comprising administering a peptide to a subject in need thereof, wherein the peptide comprises a T helper cell epitope and an antigen-presenting epitope, wherein the peptide produces an immunogenic inflammatory response that is at least about 3-fold lower than an immunogenic inflammatory response of a positive control.

DETAILED DESCRIPTION

[0020] The present disclosure provides promiscuous artificial T helper cell (Th) epitopes that can be used to produce peptide immunogens that are capable of stimulating functional site-directed antibody responses for therapeutic effects. The disclosed artificial Th epitopes can be linked to a synthetic peptide B cell epitope ("target antigenic site"), through an optional spacer, to produce an immunogenic peptide.

[0021] The artificial Th epitope imparts to the peptide immunogen the capability to induce a strong T helper cell-mediated immune response with the production of a high level of antibodies directed against the "target antigenic site." The present invention further provides for the advantageous replacement of carrier proteins and pathogen-derived T helper cell sites in

CLAIMS

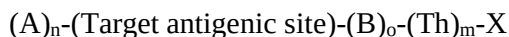
1. Use of a peptide in the manufacture of a medicament for treating a condition, wherein the peptide comprises a T helper cell epitope and an antigen-presenting epitope, wherein the peptide produces an immunogenic inflammatory response that is at least about 3-fold lower than an immunogenic inflammatory response of a positive control, wherein the peptide is to be administered to a subject in need thereof.
2. The use according to claim 1, wherein
 - (a) the antigen-presenting epitope is a B cell epitope or a peptide hapten and
 - (b) the T helper cell epitope is a Th1 epitope or Th2 epitope.
3. The use according to any one of claims 1 or 2, wherein the T helper cell epitope is an artificial T cell epitope.
4. The use according to any one of claims 1 to 3, wherein the T helper cell epitope is selected from the group consisting of SEQ ID NOs: 1-52.
5. The use according to any one of claims 1 to 4, wherein the T helper cell epitope and the antigen-presenting epitope are covalently linked.
6. The use according to any one of claims 1 to 5, wherein the T helper cell epitope is attached to the antigen-presenting epitope through a spacer.
7. The use according to claim 6, wherein the spacer is Gly-Gly, (ϵ -N)Lys, or any one of SEQ ID NOs: 53-55.
8. The use according to any one of claims 1 to 7, wherein the immunologic inflammatory response is measured in peripheral blood mononuclear cells or isolated peripheral blood mononuclear cells.
9. The use according to any one of claims 1 to 8, wherein the immunologic inflammatory response is an increase in cytokine concentration.

10. The use according to claim 9, wherein the increase in cytokine concentration is an increase in concentration of IL-2, IL-6, IL-10, INF- γ , or TNF- α .

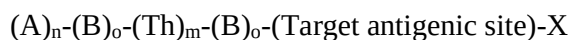
11. The use according to any one of claims 1 to 10, wherein the positive control is a phytohaemagglutinin mitogen.

12. The use according to any one of claims 1 to 11, wherein to be administered comprises to be administered about 150 μg to about 750 μg of the peptide.

13. The use according to any one of claims 1 to 12, wherein the peptide is of the formula:



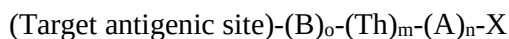
or



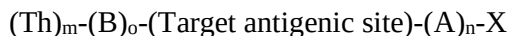
or



or



or



wherein:

- A is an amino acid or an immunostimulatory sequence;
- B is at least one amino acid, -NHCH(X)CH₂SCH₂CO-, -NHCH(X)CH₂SCH₂CO(ϵ N)Lys-, -NHCH(X)CH₂S-succinimidyl(ϵ N)Lys-, or -NHCH(X)CH₂S-(succinimidyl)-;
- Th is a helper T cell epitope, an analog, or a segment thereof;
- Target antigenic site is a B cell epitope or an immunologically reactive analogue thereof;
- X is an amino acid α -COOH, -CONH₂;
- n is from 1 to about 10;

- m is from 1 to about 4; and
- o is from 0 to about 10.

14. The use according to any one of claims 1 to 13, wherein the peptide produces an immunogenic inflammatory response in the subject that is less than about 3-fold higher than an immunogenic inflammatory response of a negative control.