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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMMUNOGENIC PEPTIDE COMPOSITION FOR THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: The present invention relates to a composition comprising a peptide immunogen useful for the prevention and treatment of Alzheimer’s Disease. More particularly, the peptide immunogen comprises a main functional/regulatory site, an N-terminal fragment of Amyloid (Ab) peptide linked to a helper T cell epitope (Th) having multiple class II MHC binding motifs. The peptide immunogen elicit a site-directed immune response against the main functional/regulatory site of the Ab peptide and generate antibodies, which are highly cross-reactive to the soluble Ab1-42 peptide and the amyloid plaques formed in the brain of Alzheimer's Disease patients. The antibodies elicited being cross reactive to the soluble Ab1-42 peptide, promote fibril disaggregation and inhibit fibrillar aggregation leading to immunoneutralization of the "soluble Ab-derived toxins"; and being cross-reactive to the amyloid plaques, accelerate the clearance of these plaques from the brain. Thus, the composition of the invention comprising the peptide immunogen is useful for the prevention and treatment of Alzheimer's Disease.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07K 5/00
US CL. : 530/300; 424/184.1
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)
U.S. : 530/300; 424/184.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEQ ID NO:1, 52-54, 65, Author search

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, CAPLUS, Genbank, Biosys

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 5,759,551 A (LADD et al. 02 June 1998 (02.06.1998), SEQ ID NO:s:2, 10, 18, 32, 60, 66-68, 92-94, see entire document, especially Abstract, column 3, lines 30-38, column 4, lines 19-38, Figure 5, 10-12, 24, 27, 33, column 9-10, column 12, lines 16-57, column 13-14, column 16, line 45-column 17, line15, column 18, lines 23-55, especially lines 33-37, column 19-20 Treatment of non-insulin diabetes by Amylin based immunochemistry, Example 6, 19, and Tables 10-12.</td>
<td>1-80</td>
</tr>
<tr>
<td>Y</td>
<td>US 6,228,987 B1 (WANG et al.) 08 May 2001 (08.05.2001), see entire document, especially SEQ ID NO:23-25.</td>
<td>1-80</td>
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<tr>
<td>Y</td>
<td>US 5,750,349 A (SUZUKI et al.) 12 May 1998 (12.05.1998), see entire document.</td>
<td>1-80</td>
</tr>
<tr>
<td>Y</td>
<td>WO 99/27944 A1 (ATHENA NEUROSCIENCES, INC.) 10 June 1999 (10.06.1999), see entire document.</td>
<td>1-80</td>
</tr>
<tr>
<td>Y</td>
<td>WO 01/18169 A2 (RAMOT UNIVERSITYAUTHORITY FOR APPLIED RESEARCH &amp; INDUSTRIAL DEVELOPMENT LTD.) 15 March 2001 (15.03.2001), see entire document.</td>
<td>1-80</td>
</tr>
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</table>

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

Date of the actual completion of the international search

Date of mailing of the international search report
30 SEP 2004

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Form PCT/ISA/210 (second sheet) (July 1998)
### INTERNATIONAL SEARCH REPORT

#### C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tbody>
<tr>
<td>Y</td>
<td>FRENKEL, D. Immunization against Alzheimer’s Beta-amyloid plaques via EFRH phage administration. PNAS. October 2000, Vol. 97, No. 21, pages 11455-11459.</td>
<td>1-80</td>
</tr>
<tr>
<td>Y</td>
<td>WO 94/28412 (THE MIRIAM HOSPITAL) 08 December 1994 (08.12.1994), pages 10-2, Examples pp. 23-24, Abeta 1-28 and 1-10, mAb 10H3, SEQ ID NO’s:7-10, Example 6, p. 29-30, claims 1-15, Figure 1.</td>
<td>1-80</td>
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Form PCT/ISA/210 (second sheet) (July 1998)
BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING
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 examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-80 drawn to the extent of the first appearing special technical feature peptides comprising respectively the Th epitope of SEQ ID NO:1 shared with SEQ ID NO's:52-54, and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65 and first method of use in a method of preventing or treating Alzheimer’s Disease and producing antibodies.

Groups II-XXVI (2-26), claim(s) 1-40 drawn to the extent of the second to twenty sixth appearing special technical feature peptides comprising respectively the Th epitope of SEQ ID NO's:2-26 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XXVII (27), claim(s) 1-40 drawn to the extent of the twenty seventh appearing special technical feature peptides comprising respectively the shared Th epitope of SEQ ID NO's:27 and 30 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XXVIII-XXIX (28-29), claim(s) 1-40 drawn to the extent of the twenty eighth to twenty ninth appearing special technical feature peptides comprising respectively the Th epitope of SEQ ID NO's:28-29 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XXX-XXXVI (30-36), claim(s) 1-40 drawn to the extent of the thirtieth to thirty sixth appearing special technical feature peptides comprising respectively the Th epitope of SEQ ID NO's:31-37 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XXXVII-XXXVI (37), claim(s) 1-40 drawn to the extent of the thirty seventh appearing special technical feature peptides comprising respectively the shared Th epitope of SEQ ID NO's:38 and 41 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XXXVIII-XXXIX (38-39), claim(s) 1-40 drawn to the extent of the thirty eighth to thirty ninth appearing special technical feature peptides comprising respectively the Th epitopes of SEQ ID NO's:39-40 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XL-XLI (40-42), claim(s) 1-40 drawn to the extent of the fortieth to forty second appearing special technical feature peptides comprising respectively the Th epitopes of SEQ ID NO's:42-44 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XLIII (43), claim(s) 1-40 drawn to the extent of the forty third appearing special technical feature peptides comprising respectively the shared Th epitopes of SEQ ID NO's:45 and 50 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XLIV-XLVII (44-47), claim(s) 1-40 drawn to the extent of the forty fourth to forty seventh appearing special technical feature peptides comprising respectively the Th epitopes of SEQ ID NO's:46-49 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group XLVIII (48), claim(s) 1-40 drawn to the extent of the forty eighth appearing special technical feature peptides comprising respectively the Th epitope of SEQ ID NO:51 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

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Group ILIII (49-53), claim(s) 1-40 drawn to the extent of the forty ninth to fifty third appearing special technical feature peptides comprising respectively the Th epitopes of SEQ ID NO:55-59 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65.

Group LIV (54), claim(s) 1-40 drawn to the extent of the fifty fourth appearing special technical feature peptides comprising respectively the shared Th epitopes of SEQ ID NO:60-61 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65

Group LV (55), claim(s) 1-40 drawn to the extent of the fifty fifth appearing special technical feature peptides comprising respectively the Th epitopes of SEQ ID NO:62 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65

Group LVI (56), claim(s) 1-40 drawn to the extent of the fifty sixth appearing special technical feature peptides comprising respectively the shared Th epitopes of SEQ ID NO:63-64 and an N-terminal fragment of Abeta peptide consisting of 10-28 residues wherein each fragment comprises amino acid 1 of SEQ ID NO:65

Groups LXVII-CXII (57-112), claim(s) 41-80 drawn to the extent of a method of preventing or treating Alzheimer's Disease and producing antibodies via administration of the second to fifty seventh appearing special technical feature peptides.

The inventions listed as Groups I-CXII 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: The peptide of SEQ ID NO:1 lacks unity in view of Efim Ladd et al., US 5,759,551 issued June 2, 1998, see in particular SEQ ID NO:10. The peptide of SEQ ID NO:65 lacks unity in view of Glenner and Wong., Biochem. Biophys. Res. Comm., 1984, 120:885-890 and Glenner and Wong, Biochem. Biophys. Res. Comm., 1984, 122:1131-1135. In addition, the N-terminal fragment of 10-28 residues of Abeta that includes the first residue lacks unity in view of Hanan and Solomon, Int. J. Exp. Clin. Investigat., 3:130-133, 1996(a), Solomon et al., PNAS 93:452-455, 1996(b) and Solomon et al., PNAS 94:4109-4112, 1997. Further, the special technical features each lack common structure and function. In particular, the Thelper cell epitopes differ in primary amino acid sequence and specificity in production and binding of antibodies. The Thelper cell epitopes also differ in their pathogen of origin, i.e., HBs, FF, TT, MVP, DT, PF, SM, TraT, HBe, and CTP as disclosed and thus differentially stimulate immune responses. In addition, while the N-terminal fragments share in common amino acids 1-10 of Abeta, the N-terminal fragments differ in length and hence in full length sequence. Further, the different fragments ranging from 10-28 amino acids in length differ in their ability to stimulate B-cell responses, react with antibodies and ability to stimulate disaggregation as noted in Hanan and Solomon, Solomon 1996(a) and Solomon 1996(b). While this literature supports a lack of unity between the N-terminal fragments, no further division is set forth on this basis. The methods are characterized by administration of the unique special technical feature peptides corresponding to unique Th epitopes that differentially stimulate antibody responses and binding to antibodies. The methods thus lack unity as they each use the different special technical features as noted in Groups I-56 as set forth above. Thus, the inventions lack unity and are separable as set forth above.
INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

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

2. □ Claim 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. □ Claim Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

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 an additional fee, this Authority did not invite payment of any additional fee.

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.: 1-80 in part drawn to the extent of SEQ ID NO’s: 1, and 52-54

Remark on Protest □ The additional search fees were accompanied by the applicant’s protest.
□ No protest accompanied the payment of additional search fees.