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(54) Title: REPLIKIN PEPTIDES IN RAPID REPLICATION OF GLIOMA CELLS AND IN INFLUENZA EPIDEMICS

(57) Abstract: Peptides of influenza virus hemagglutinin protein and *Plasmodium falciparum* malaria antigen, antibodies specific for the peptides, influenza vaccines, malaria vaccines and methods of stimulating the immune response of a subject to produce antibodies to influenza virus or malaria are disclosed. Also disclosed are methods for formulating vaccines for influenza virus.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/08990

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 38/00; C07K 14/11
US CL : 530/300, 387.1, 389.1, 424/204.1; 514/2
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, 387.1, 389.1, 424/204.1; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GAO et al. Identification and characterization of T helper epitopes in the nucleoprotein of influenza A virus. J Immunol. 01 November 1989, Vol. 143, No. 9, pages 3007-3014, see Figure 1, first line, right hand side sequenc(ERR...), 3008, column 1, Viruses and Other Ag and Immunization.	1-9, 11, 13-16
X	SHI et al., Immunogenicity and in vitro protective efficacy of a recombinant multistage Plasmodium falciparum candidate vaccine. Proc. Natl. Acad. Sci., USA. February 1999, Vol. 96, No. 4, pages 1615-1620, see Table 1 and page 1616, Materials and Methods.	32-43

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/08990

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.: 10,12,17-31 and 44-48
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:
Please See Continuation Sheet

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.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box I Reason 2:
Claims 10, 12, and 17 contain the limitation "at least two consecutive years, including the current year" and this is not searchable because the current year changes. Claims 18-23 are drawn to algorithms and are not searchable as written. Claims 24-31 are a product and method of using depending on the method of claim 23 and cannot be searched because the product is not determined. Claims 44 and 45 are not searchable because it is not known the correlation between replikin and microorganism and it is also not known what is indicated by such a finding. Claims 46-48 are not searchable because it is not known what the result is or what the enzyme is.

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) 1,2, 9, 11, 15, and 16, drawn to an influenza peptide, and method of using.

Group II, claim(s) 3- 8, drawn to an antibody or cocktail of antibodies against inflenza.

Group III, claim(s) 13, drawn to an antisense nucleic acid complementary to the sequence of an influenza HN mRNA.

Group IV, claim(s) 14, drawn to an antisense nucleic acid complementary to the sequence of an influenza HN genome.

Group V, claim(s) 32- 37, drawn to a malerial vaccine comprising a P. falciparum replikin.

Group VI, claim(s) 38- 40, drawn to an antibody that binds to a P. falciparum replikin.

Group VII, claim(s) 41- 43, drawn to a method to stimulate the immune system of a subject.

The inventions listed as Groups I-VII 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:

Group I is directed to an isolated influenza virus peptide (an isolated influenza peptide having about 7-50 residues comprising at least one lysine located 6 to 10 residues away from a second lysine[symbol=k], one histidine residue[h], and at least 6% lysine), which is the first product. However, because Gao et al. (Identification and characterization of T helper epitopes in the nucleoprotein of influenza A virus. Journal of Immunology 1989 Vol. 143, pages 3007-3014) disclose a peptide that meets the limitations of claim 1 (an isolated influenza peptide having about 7-50 residues comprising at least one lysine located 6 to 10 residues away from a second lysine[symbol=k], one histidine residue[h], and at least 6% lysine (a 20-mer peptide shown in Figure 1, top line, right side (ERRNKYLEEHPSAGKDPKKT)), no special technical feature exists for Group I as defined by PCT Rule 13.2, because it does not define a contribution over the prior art. The technical features of Groups II-XIV are drawn to products and methods having different goals, method steps and starting materials, which do not require each other for their practice and do not share the same or a corresponding technical feature. Groups II-IV relate to influenza antibodies and nucleic acid (different products), not an influenza peptide which is the first named product. Groups V-VII do not relate to the influenza peptide product of Group I. Groups V-VII are drawn to P. falciparum peptide and antibodies and a method of using. Shi et al.(Immunogenicity and in vitro protective efficacy of a recombinant multistage Plasmodium falciparum candidate vaccine. 1999 PNAS Vol. 96, No. 4, pages 1615-1620) teach a peptide (Table 1, tenth from the top, GNAEKYDKMDEPQHYGKS) that meets the limitation of Group V (a P. falciparum peptide with the same residue requirements as Group I except that it is not an influenza peptide). Note that PCT Rule 13 does not provide for multiple products or methods within a single application. Because the technical feature of Group I is not a special technical feature, unity of invention is lacking.

Continuation of B. FIELDS SEARCHED Item 3:
Sequence search of replikin motif, WEST, MEDLINE
terms- influenza, p falciparum, replication