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Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
22 March 2012

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(54) Title: MODIFIED FORMS OF PNEUMOCOCCAL SURFACE IMMUNOGENIC PROTEIN B (PSIPB)

(57) Abstract: The present invention relates to modified forms of the protein Pneumococcal surface immunogenic protein B (PsipB) derived from Streptococcus pneumonia (S. pneumoniae). The modified PsipB polypeptides and fragments have enhanced immunogenicity, stability at physiological pH formulation and formulation properties as compared to wild type PsipB. The invention further provides immunogenic compositions and vaccines comprising the modified PsipB polypeptides and fragments, and use thereof in methods for eliciting protective immunity to S. pneumoniae.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 11/00295

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00; A61K 38/16 (2011.01)
USPC - 514/1.6; 514/21.2
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)
USPC - 514/1.6, 514/21.2

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)
PubWEST (PGPB,USPT,EPAB,JPAB); Google Scholar: pneumococcal surface protein, pneumococcal surface immunogenic protein, streptococc$, pneumococc$, protein, polypeptide, vaccin$, immunogen$, cysteine, substitution, mutation, PsipB, PspB, amino acid substitution, mutation, pH, stability, physiological

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0148470 A1 (MIZRACHI-NEBENZAHL) 11 June 2009 (11.06.2009) Abstract, SEQ ID NO:34, Claim 6, para [0015], [0017], [0032], [0071], [0075]	1-5, 7-10, 21-23, 33
Y	US 2004/0223976 A1 (BIANCHI et al.) 11 November 2004 (11.11.2004) Claim 22, Abstract, para [0024], [0026], [0074]	1-5, 7-10, 21-23
Y	US 2004/0115199 A1 (HAKIER et al.) 17 June 2004 (17.06.2004) Abstract, para [0110], [0213], [0216]	33
Y	US 2010/0081151 A1 (FARIAS-EISNER et al.) 01 April 2010 (01.04.2010) para [0089]	4-5, 7-8, 22
Y	US 2003/0059438 A1 (BRILES et al.) 27 March 2003 (27.03.2003) para [0038]	9-10

☐ Further documents are listed in the continuation of Box C. ☐

* 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 but 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

Date of the actual completion of the international search	Date of mailing of the international search report
02 December 2011 (02.12.2011)	12 DEC 2011

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 11/00295

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

2. ☐ Claims 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. ☒ Claims Nos.: 12-13, 24-27, 29, 31-32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
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.

Group I+: claims 1-11, 21-23, 33, drawn to a modified PsipB polypeptide or fragment comprising at least ammo acid residues 48-112 of SEQ ID NO: 1 or of a sequence having at least 95% homology to SEQ ID NO: 1 and comprising an amino acid substitution of at least one cysteine residue naturally present in a wild type PsipB polypeptide. The first invention is restricted to the Cys66Ala substitution and SEQ ID NO: 13. Should an additional fee(s) be paid, Applicant is invited to elect an additional substitution(s) and/or SEQ ID NO(s) to be searched. The exact claims searched will depend on Applicant's election.
[NOTE: Claims 6 and 11 were excluded from the search, because they are drawn to a non-elected subject matter.]

----------Please see Extra 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 additional fees, this Authority did not invite payment of additional fees.

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.:
1-5, 7-10, 21-23 and 33, restricted to the Cys66Ala substitution and SEQ ID NO: 13

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

********** Supplemental Box **********

Continuation of Box III: Observations where unity of invention is lacking

Group II+: claims 14-20, 28, 30, drawn to an isolated polynucleotide sequence encoding a modified PsipB polypeptide or fragment, wherein the modified PsipB polypeptide or fragment encoded by the polynucleotide has an amino acid residue other than cysteine at a position corresponding to a position of the wild type PsipB polypeptide of SEQ ID NO: 1. The first invention of Group II+ is restricted to the Cys66Ala substitution and SEQ ID NO: 13. Should an additional fee(s) be paid, Applicant is invited to elect an additional substitution(s) and/or SEQ ID NO(s) to be searched. The exact claims searched will depend on Applicant's election.

The inventions listed as Groups I+ and II+ 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 inventions of Group I+ do not include the inventive concept of an isolated polynucleotide sequence encoding a modified PsipB polypeptide or fragment, as required by Group II+.

The inventions of Groups I+ and II+ share the technical feature of a modified PsipB polypeptide or fragment comprising at least ammo acid residues 48-112 of SEQ ID NO: 1 or of a sequence having at least 95% homology to SEQ ID NO: 1 and comprising an amino acid substitution of at least one cysteine residue naturally present in a wild type PsipB polypeptide. However, this shared technical feature does not represent a contribution over prior art as being obvious over US 2009/0148470 A1 to Mizrachi (hereinafter 'Mizrachi') in view of US 2010/0068228 A1 to Sette et al. (hereinafter 'Sette') as follows:

Mizrachi discloses a modified PsipB polypeptide or fragment (para [0015]; [0017]) comprising at least ammo acid residues 48-112 of SEQ ID NO: 1 or of a sequence having at least 95% homology to SEQ ID NO: 1 (i.e., whole gene) (para [0075]; Claim 6; SEQ ID NO:34).
Mizrachi does not specifically disclose the modified polypeptide comprising an amino acid substitution of at least one cysteine residue naturally present in a wild type PsipB polypeptide.
Mizrachi does further disclose use of the polypeptide in vaccines (Abstract).
Sette discloses modified polypeptides for use in vaccines in which cysteine residues are replaced by alpha amino-butyric acid residues to reduce crosslinking that interferes with binding (Abstract; para [0159]-[0160]). It would have been obvious to a person skilled it the art to substitute alpha amino-butyric acid residues for cysteine residues, as disclosed by Sette, in the PsipB polypeptide of Mizrachi, to improve the binding capacity of PsipB, because Sette discloses increasing binding by substitution of cysteine residues in proteins for use in vaccines is beneficial. As said modified PsipB polypeptide would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

The inventions of Group II+ share the technical feature of an isolated polynucleotide sequence encoding a modified PsipB polypeptide. However, this shared technical feature does not represent a contribution over prior art as being obvious over Mizrachi in view of Sette as follows:

Mizrachi discloses an isolated polynucleotide sequence (para [0069]; [0075]) encoding a modified PsipB polypeptide or fragment (para [0017]; [0048]) and the wild type PsipB polypeptide of SEQ ID NO: 1 (SEQ ID NO:34; claim 6) having cysteine residues at positions 66, 72 and 84 (SEQ ID NO:34).
Mizrachi does not specifically disclose that said modified PsipB polypeptide or fragment has cysteine at a position selected from the group consisting of position 66, position 72, position 84, substituted by another amino acid.
Mizrachi does further disclose use of the polypeptide in vaccines (Abstract).
Sette discloses modified polypeptides for use in vaccines in which cysteine residues are replaced by alpha amino-butyric acid residues to reduce crosslinking that interferes with binding (Abstract; para [0159]- [0160]). It would have been obvious to a person skilled it the art to substitute alpha amino-butyric acid residues for cysteine residues, as disclosed by Sette, in the PsipB polypeptide of Mizrachi at one or more of amino acid positions 66, 72 and 84, to improve the binding capacity of PsipB, because Sette discloses increasing binding by substitution of cysteine residues in proteins for use in vaccines is beneficial. As said isolated polynucleotide sequence encoding a modified PsipB polypeptide would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ and II+ is the specific cystein substitution(s) recited therein. The inventions do not share a special technical feature, because 1) Mizrachi discloses the wild type PsipB polypeptide of SEQ ID NO: 1 (SEQ ID NO:34; claim 6), and 2) therefore, no significant structural similarities can readily be ascertained among the substitutions. Without a shared special technical feature, the inventions lack unity with one another.

Another special technical feature of the inventions listed as Group I+ and II+ is the specific amino acid sequence(s) recited therein. The inventions do not share a special technical feature, because Mizrachi discloses the wild type PsipB polypeptide of SEQ ID NO: 1 (SEQ ID NO:34; claim 6), thereby disclosing the common structural core shared by the variant sequences. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ and II+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.