(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2013 (10.05.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/066731 A3

(51) **International Patent Classification**:
*A61K 39/085* (2006.01)

(21) **International Application Number**:
PCT/US2012/062019

(22) **International Filing Date**:
26 October 2012 (26.10.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/553,589 31 October 2011 (31.10.2011) US

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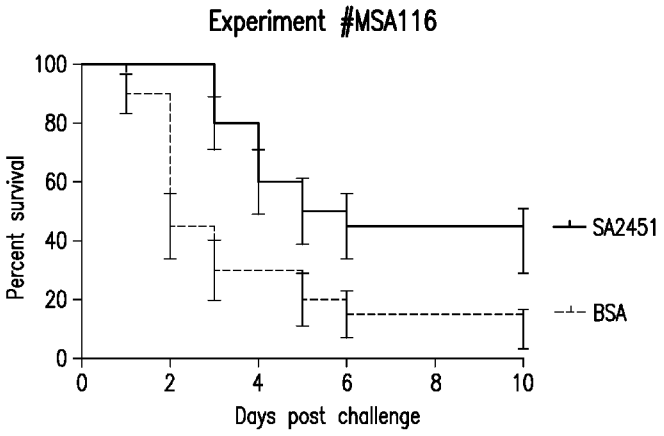
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

*[Continued on next page]*

(54) **Title**: PROTECTIVE VACCINE BASED ON STAPHYLOCOCCUS AUREUS SA2451 PROTEIN




| Log-rank (Mantel-Cox) Test | |
|---|---|
| Chi square | 8.999 |
| df | 1 |
| P value | 0.0027 |
| P value summary | ** |
| Are the survival curves sig different? | Yes |

FIG.4A

(57) **Abstract**: Methods of inducing an immune response to Staphylococcus comprising administering a composition comprising an SA2451 -related polypeptide from Staphylococcus aureus as well as derivatives or fragments thereof are disclosed. Methods of treating and/or reducin the likelihood of a Staphylococcus infection by administering a composition comprising an SA2451 -related polypeptide or an antibody that specifically binds to an SA2451 polypeptide, derivative or fragments thereof are also disclosed. Compositions administered in the methods can include one or more additional antigens.

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**(84) Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**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**:
11 June 2015

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/62019

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/085 (2013.01)
USPC - 424/243.1
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)
USPC: 424/243.1
IPC(8): A61K 39/085 (2013.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/234.1, 184.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ), Google Scholar, Google Patents, PatBase
Search Terms Used: S. aureus, antigen$, 930918?3, SA2451

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 7,608,276 B2 (MASIGNANI et al.) 27 October 2009 (27.10.2009) esp: abstract, col 1, ln 41-44; col 5 ln 10 - col 6 ln 18; col 6 ln 49-50;col 23, ln 21-46; SEQ ID NO: 5282. | 1-3 |
| Y | Sivaraman et al., Genome Sequencing and analysis reveals possible determinants of Staphylococcus aureus nasal carriage. BMC Genomics, 22 September 2008; Vol 9: 433; pg. 1-13. [online]. [Retrieved on 13 December 2012]. Retrieved from the internet <URL: http://www.biomedcentral.com/content/pdf/1471-2164-9-433.pdf> | 1-3 |
| L | Sivaraman Supplementary Information 2 document [online]. [Retrieved on 13 December 2012]. Retrieved from the internet <URL:http://www.biomedcentral.com/content/supplementary/1471-2164-9-433-s2.pdf> esp: abstract, supplementary materials, Table 2. Uploaded in support of Sivaraman above. | 1-3 |
| L | UniProt C8KK51, Glycine betaine/carnitine/choline ABC transporter opuCC. 21 September 2011 (21.09.2011) [online].[Retrieved on 13 December 2012]. Retrieved from the internet <URL: http://www.uniprot.org/uniprot/C8KK51.txt?version=4> Uploaded in support of Sivaraman above. | 1-3 |
| A | Sivaraman et al., Pathogenesis gene families in the common minimal genome of Staphylococcus aureus are hypervariable. FEBS Lett., 17 April 2009, Vol. 583, No. 8, pg. 1304-1308. Entire document. | 1-3 |

☐ 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 |
|---|---|
| 17 February 2013 (17.02.2013) | 05 MAR 2013 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/62019

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☒ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/62019

**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.: 4-9
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. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3, directed to a composition comprising an immunologically effective amount of a polypeptide that is at least 95% identical to SEQ ID NO: 1 or a fragment of the polypeptide and a pharmaceutically acceptable carrier; wherein the polypeptide is not SEQ ID NO: 1.

- Please see extra sheet for continuation -

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.:
1-3: limited to SEQ ID NO: 1

**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.

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US 12/62019

Continuation of Box III: Lack of Unity of Invention

Group II: claims 10-16 and 20, directed to use of a polypeptide that is at least 95% identical to SEQ ID NO: 1 or a fragment of the polypeptide in the manufacture of a medicament for inducing a protective immune response in a patient against S aureus infection.

Group III: claims 17-19, directed to a method of conferring passive immunity to S. aureus infection in a patient comprising administering to the patient one or more antibodies that specifically bind to a polypeptide of SEQ ID NO: 1.

The inventions listed as Groups I - III 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 special technical feature of the Group I claims is a composition comprising an immunologically effective amount of a polypeptide that is at least 95% identical to SEQ ID NO: 1 or a fragment of the polypeptide and a pharmaceutically acceptable carrier; wherein the polypeptide is not SEQ ID NO: 1 - not required by the claims of Groups II or III. The special technical feature of the Group II claims is use of a polypeptide that is at least 95% identical to SEQ ID NO: 1 or a fragment of the polypeptide in the manufacture of a medicament for inducing a protective immune response in a patient against S aureus infection - not required by the claims of Groups I or III. The special technical feature of the Group III claims is a method of conferring passive immunity to S. aureus infection in a patient comprising administering to the patient one or more antibodies that specifically bind to a polypeptide of SEQ ID NO: 1 - not required by the claims of either of Groups I or II. None of these special technical features is common to the other groups, nor do they correspond to special technical features in the other groups. In particular, it should be noted that Group I specifically excludes a polypeptide that is SEQ ID NO: 1, while Group II specifically includes (see claim 11) a polypeptide that is SEQ ID NO: 1.

The only common technical element shared by the above groups is that they are related to SEQ ID NO: 1 in relation to S. aureus infection, and the prevention or treatment thereof. Groups I and II share the common technical element of being related to a polypeptide that is at least 95% identical to SEQ ID NO: 1 or a fragment thereof in an immunogenic composition or medicament. These common technical elements do not represent an improvement over the combined prior art of US 7,608,276 B1 to Masignani et al., in view of the article entitled "Genome Sequencing and analysis reveals possible determinants of Staphylococcus aureus nasal carriage" by Sivaraman et al. (hereinafter "Sivaraman '08) and further in view of UniProtKB Accession C8KK51 by Sivaraman et al. (hereinafter "Sivaraman '51).
Masignani discloses proteins from Staphylococcus aureus including amino acid sequences and corresponding nucleotide sequences; wherein the proteins are useful for vaccines and immunogenic compositions for the prevention or treatment of S. aureus infection (abstract), and compositions (col 23, ln 21-25) comprising said polypeptides and a pharmaceutically acceptable carrier (col 23, ln 45-49), including a polypeptide having SEQ ID NO: 1 (SEQ ID NO: 5282). Although Masignani discloses a polypeptide comprising SEQ ID NO: 1, and immunogenic compositions comprising said polypeptide, the polypeptide is one of a large number of similar polypeptides disclosed at the same time, and there is little motivation for an individual to select this particular polypeptide from those disclosed. However, in a related article, Sivaraman teaches the identification of polypeptides specific for strains of S. aureus in nasal carriage (abstract), including the polypeptide comprising SEQ ID NO: 1 (see suppementary materials, Table 2, as well as Uniprot Accession C8KK51). It would have been obvious to a person of ordinary skill in the art to have selected the polypeptides identified by Sivaraman as targets for the generation of an immunogenic response, in order to enable the elimination of nasal carriage, and subsequent infection or spread of the S. aureus isolates, using immunogenic compositions as disclosed by Masignani, without undue experimentation.

Therefore, the inventions of Groups I-III lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.