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the Holy and Undivided Trinity of Queen Eliza, behth Near
Dublin, Trinity College, Dublin 2 (IE).

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(74) Agent: **SCHULMAN, Aaron, B.**; Larson & Taylor, PLC,
Suite 900, 1199 North Fairfax Street, Alexandria, VA
22314 (US).

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(71) Applicants: **INHIBITEX, INC.** [US/US]; 8995 West-
side Parkway, Alpharetta, GA (US). **THE PROVOST
FELLOWS AND SCHOLARS OF THE COLLEGE
OF THE HOLY AND UNDIVIDED TRINITY OF
QUEENS ELIZABETH NEAR DUBLIN** [IE/IE];
Trinity College, Dublin 2 (IE). **UNIVERSITA' DEGLI
STUDI DI PAVIA** [IT/IT]; Strada Nuova, 65, I-27100
Pavia (IT).

(72) Inventors: **FOSTER, Timothy, J.**; 70 Coolamber Park,
Templeogue, Dublin 16 (IE). **ROCHE, Fiona**; C/o The
Provost Fellows and Scholars of the Colleg, e of the Holy
and Undivided Trinity of Queen Eliza, beth near Dublin,
Trinity College, Dublin 2 (IE). **PATTI, Joseph, M.**; 6680
Stratford Place, Cumming, GA 30040 (US). **HUTCHINS,
Jeff, T.**; 1120 Quail Run Lane, Cumming, GA 30041 (US).
SPEZIALE, Pietro; c/o Universita' Degli Strudi Di Pavia,
Strada Nuova, 65, I-27100 Pavia (IT). **PALLEN, Mark**;
C/o The Provost Fellows and Scholars of the Colleg, e of

(54) Title: CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES WHICH RECOGNIZE SURFACE PRO-
TEINS FROM COAGULASE-NEGATIVE STAPHYLOCOCCI AND STAPHYLOCOCCUS AUREUS

(57) Abstract: Polyclonal and monoclonal antibodies which are cross-reactive to both coagulase-positive staphylococcus bacteria, such as *S. hemolyticus*, are provided which can recognize surface proteins from both coagulase-positive and coagulase negative staph bacteria. The antibodies may be generated from surface proteins that have been isolated on the basis of characteristics that may be common between *S. aureus* and coagulase-negative staphylococci, and these recombinant surface proteins are used to generate the antibodies of the invention. There is also provided vaccines and methods which utilize these proteins and antibodies for the treatment or protection against a wide variety of staphylococcal infections.



WO 2002/102829 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19220

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01 N 33/569; C12 N 5/06, 5/16; C07 K 16/00
US CL : 435/7.33, 326, 332, 530/388.2, 388.4

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. : 435/7.33, 326, 332, 530/388.2, 388.4

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.
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q9L470, 100% identical to SEQ.ID.NO: 21, SEQ.ID.NO: 19.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QY4, 99.8% identical to SEQ.ID.NO: 18.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QZ2, 97.4% identical to SEQ.ID.NO: 16.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99XE9, 92 % identical to SEQ.ID.NO: 12.	1-16, 19 and 21

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

☐ See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

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Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer

Padmavathi v Baskar

Telephone No. (703)308-0196

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99UX5, 97.8 % identical to SEQ.ID.NO: 10.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99UX4, 98.8 % identical to SEQ.ID.NO: 8.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q931P4 96.7 % identical to SEQ.ID.NO: 6 and Accession number Q99TD3, 96.6 % identical to SEQ.ID.NO: 6	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QY4, 98.6 % identical to SEQ.ID.NO: 4.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99TB0, 91.6 % identical to SEQ.ID.NO: 2.	1-16, 19 and 21
Y	OHLSEN. K. et al Effects of subinhibitory concentrations of antibiotics on alpha-toxin (hla) gene expression of methicillin-sensitive and methicillin-resistant Staphylococcus aureus isolates. Antimicrob Agents Chemother, November 1998 , Vol 42, No.11, pages 2817-2823.	1-16, 19 and 21

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19220

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.: Please See Continuation Sheet
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.

INTERNATIONAL SEARCH REPORT

PCT/US02/19220

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions 1-58 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.

Groups 1-21 Claim(s) 1-14, 16, 19, 21 and 15, drawn to an isolated antibodies that bind to SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19, 21, nucleic acid sequence encoding amino acid sequences SEQ.ID.NOS: 1, 3, 5,7,9, 11, 13, 15, 20 and the nucleic sequences coding for the A domain of the Aap protein or degenerate.

Groups 22-33 Claims 20 and 22 drawn to fragment of the DsqA protein and a vaccine comprising a protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21

Groups 34-45 Claim 17 drawn to a method for treating or preventing S.aureus infection using antibodies that bind to SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21.

Groups 46-57 Claim 18 drawn to a method inducing an immune response using protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21.

The inventions listed as Groups 1-58 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 1, claim(s) 1-14, 16, 19, 21 and 15, claim(s) 1-14, 16, 19, 21 drawn to an isolated antibodies that bind to SEQ.ID.NOS: 2, diagnostic kit comprising antibody to SEQ.ID.NOS: 2, pharmaceutical composition comprising said antibody and a method of diagnosing S.aureus infection using said antibody which is the first product and first product of use.

Pursuant to PCT Rule 13.2 the ISA/US considers that where multiple products, processes and methods are claimed, the main invention shall consists of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly the main invention (Group 1) comprises the first product and a method of use.

Further pursuant to PCT Rule 13.2 the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention. Therefore, the groups of inventions below do not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

Groups 2-21 drawn to different isolated antibodies that bind to SEQ.ID.NOS: 4, 6,8,10, 12, 14, 16, 17, 18, 19, 21, nucleic acid sequence encoding amino acid sequences SEQ.ID.NOS: 1, 3, 5,7,9, 11, 13, 15, 20 and the nucleic sequences coding for the A domain of the Aap protein or degenerate that are different to each other and lack the same or corresponding special technical features because each antibody bind to a protein having a specific amino acid sequence. They are structurally different to each other since each sequence has been identified with a specific sequence identification number that contains specific amino acids. In the instant case the different inventions represent structurally different antibodies that bind to different polypeptides. Therefore, where structural identity is required, such as for expression, the different sequences have different effects. Thus, each sequence is unique and lacks the same or corresponding special technical features.

Groups 22-33 drawn to fragment of the DsqA protein and a vaccine comprising a protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19, and 21. These proteins are different to each other and lack the same or corresponding special technical features because each protein contains a specific amino acid sequence. They are structurally different to each other since each sequence has been identified with a specific sequence identification number that contains specific amino acids. In the instant case the different inventions represent structurally different proteins. Therefore, where structural identity is required, such as for expression, the different sequences have different effects. Thus, each sequence is unique and lacks the same or corresponding special technical features

INTERNATIONAL SEARCH REPORT

PCT/US02/19220

Groups 34-45 and 46-57 are different methods utilizing different products of antibodies or proteins that are unique and lack the same or corresponding special technical features that result in a different outcome such as preventing an infection with antibody or inducing an immune response with specific protein. These methods are different to each other in utilizing different reagents such as different polypeptides and antibodies as discussed above and thus lack the same or special technical features as explained above.

Continuation of Box II Item 3:

1-16, 19 and 21 with respect to SEQ.ID.NOS: 2, 4, 6, 8, 10, 12,16, 18, 19 and 21

Continuation of B. FIELDS SEARCHED Item 3:

SEQ.ID.NOS: 2, 4, 6, 8, 10, 12, 14, 16, 19, 17, 18 and 21 searched on MEDLINE, STN, A -GENSEQ, N-GENSEQ,EST, DERWENT, SWISS-PROT, PIR, USPTOWEST, SWISSPTREMBL, GENEMBL, PUBLISHED APPLICATIONS AND ISSUED PATENTS