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[Continued on next page]

(54) Title: ANTIBODIES THAT SPECIFICALLY BIND STAPHYLOCOCCUS AUREUS ALPHA TOXIN AND METHODS OF USE

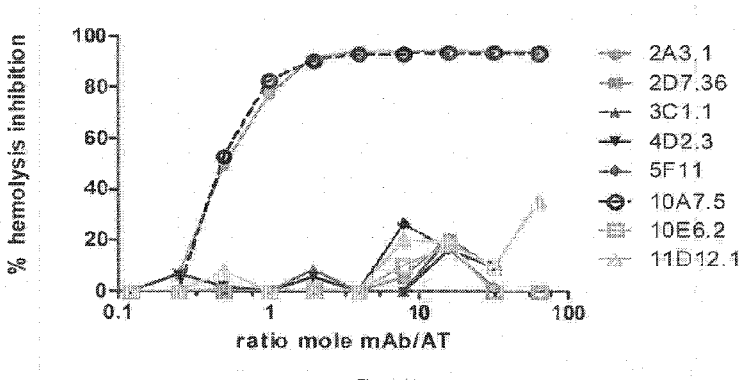

Figure 1A

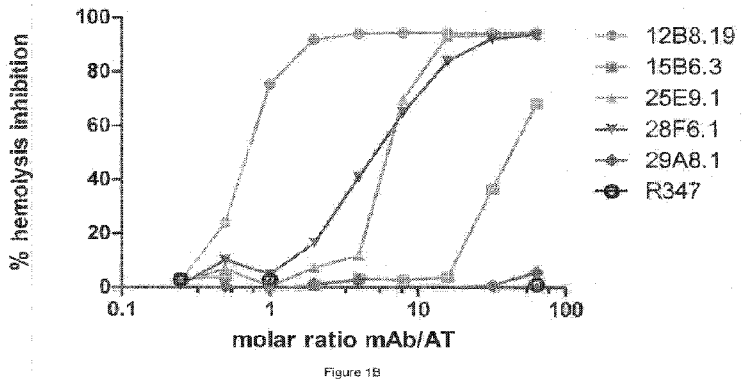

Figure 1B

(57) Abstract: The disclosure provides compositions, methods of manufacture and methods of use of antibodies and fragments that bind Staphylococcus aureus alpha toxin. More specifically, the disclosure provides VH CDR and VL CDR region sequences of antibodies or antigen-binding fragments. Method of preventing, treating or managing a condition associated with Staphylococcus aureus infection using the antibodies are also disclosed.

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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, 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.

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4 October 2012

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PCT/US 12/24201

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12P 21/08; C07K 16/00; A61K 39/40; A61K 39/085 (2012.01)
USPC - 530/388.4; 530/389.5, 530/391.7; 424/150.1,424/165.1; 424/237.1
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)
IPC(8) - C12P 21/08; C07K 16/00; A61K 39/40; A61K 39/085; A61K 38/00; A61K 38/04 (2012.01)
USPC - 530/388.4; 530/389.5, 530/391.7; 424/150.1,424/165.1; 424/237.1; 530/324; 530/327; 530/300; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C12P 21/08; C07K 16/00; A61K 39/40; A61K 39/085; A61K 38/00; A61K 38/04 (2012.01) - see keyword below
USPC - 530/388.4; 530/389.5, 530/391.7; 424/150.1,424/165.1; 424/237.1; 530/324; 530/327; 530/300; 530/350 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: antibody, isolated, purified, specific, bind, Staphylococcus aureus, alpha toxin, CDR, heavy chain, light chain, monoclonal, mAb, infection, oligomerization, affinity, constant, Kd, cytolytic, activity, cytokine, infiltration, hemolysis, assay, inhibit

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0053235 A1 (TAYLOR et al.) 26 February 2009 (26.02.2009), Abstract, para [0002], [0004], [0016], [0019], [0035], [0067], [0103], [0113], [0125], and [0139]	1-13, 23-24
A	US 2005/0226876 A1 (GRAUS et al.) 13 October 2005 (13.10.2005), para [0030], and SEQ ID NO: 29	1-8, 13, 23-24
A	US 2009/0155164 A1 (BRASEL et al.) 18 June 2009 (18.06.2009), Abstract, para [0006], [0009], [0013], and SEQ ID NO: 156	1-8, 13, 23-24
A	CN 1513874 A (LIANG et al.) 21 July 2004 (21.07.2004), Abstract; and Fig 4, VH1 SARSFab20, amino acid residues 100-110	1-8, 13, 23-24
A	US 2003/0226155 A1 (SADEGHI et al.) 04 December 2003 (04.12.2003), Abstract, para [0010], and Table 3, SEQ ID NO: 66 and SEQ ID NO: 68	3-4, 13, 23-24
A	US 2006/0093610 A1 (LANG et al.) 04 May 2006 (04.05.2006), para [0009], and SEQ ID NO: 2	3-4, 13, 23-24
A	WO 2010/003108 A2 (LOFQUIST et al.) 07 January 2010 (07.01.2010), para [0033], [0059], [00174], [00253], and SEQ ID NO:376	9-13, 23-24
A	US 2008/0152587 A1 (ZHOU et al.) 26 June 2008 (26.06.2008), Abstract, para [0003], [0115], and SEQ ID NO: 70	9-13, 23-24
A	EP 2,208,787 A1 (PATRICE et al.) 21 July 2010 (21.07.2010), para [0007], [0027], [0061], [0102], [0104], and SEQ ID NO: 1	1-13, 23-24

☒ 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
09 July 2012 (09.07.2012)	27 JUL 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: 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/US 12/24201

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.: 84
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:
Claim 84 is an omnibus type claim, and is not drafted in accordance with PCT Rule 6.2(a). The claim is indefinite as it is unclear what is included or excluded.

3. ☒ Claims Nos.: 14-22, 25-44, 48, 54-68, 73-74, 77-78, 80
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 1-13, 23-24, drawn to a purified/isolated antibody or fragment of an antibody, wherein the antibody or the fragment immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide and comprises: VH CDR1, VH CDR2 and VH CDR3. The first named invention (claims 1-13, 23-24) is directed to an antibody having VH CDR1, VH CDR2 and VH CDR3 represented by SEQ ID NOs: 7, 8 and 9, including heavy chain variable sequence having SEQ ID NO: 20, and wherein the antibody further comprising VL CDR1, VL CDR2, and VL CDR3 represented by SEQ ID NOs: 1,2,3, including light chain variable sequence having SEQ ID NO: 19 (Specification: Table 7, pg 104, mAB 2A3.1). **********Continued in the 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.:
1-13, 23-24, limited to an antibody having VH CDRs1-3, represented by SEQ ID NOs: 7, 8 and 9, including SEQ ID NOs: 20, 1 -3, and 19.

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 12/24201

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BHAKDI et al. Alpha-Toxin of Staphylococcus aureus. Microbiol Rev. 1991, Vol. 55(4), p. 733-51. Entire documentation	1-13, 23-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/24201

Continuation of:
Box No III (unity of invention is lacking)

(Continuation of Group I+) Applicant is invited to elect an additional set of SEQ ID NOs representing VH CDRs 1-3 and VL CDRs 1-3 as well as SEQ ID NOs of associated heavy chain and light chain variable sequences, or/and a specified SEQ ID NO(s) for CDR(s) comprising (a) specified amino acid substitution(s) at (a) specified position(s), or/and (a) sequence(s) that is (are) at least 90% identical to SEQ ID NO(s) representing heavy chain or/and light chain variable sequences with (a) specified amino acid substitution(s) at (a) specified CDR(s) in the sequence(s), to be searched, by paying additional fee for each set of election. The scope of each claim will be searched will depend upon the election.

Group II, claims 45-47, 49-53, 79, drawn to a method for preventing, treating or managing a skin infection condition in a subject, or a method for preventing, treating or managing a condition associated with Staphylococcus aureus infection, comprising: administering an antibody or antigen-binding fragment thereof that immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide to a subject, as indicated in claim 45, 49, or 51.

Group III, claims 69-72, 75-76, 81-83, drawn to an isolated antibody or antigen-binding fragment thereof that immunospecifically binds to a fragment of the Staphylococcus aureus alpha toxin of SEQ ID NO: 39, or a method of inhibiting the formation of alpha toxin oligomers comprising contacting an alpha toxin monomer with an isolated antibody or antigen-binding fragment thereof that immunospecifically binds to a Staphylococcus aureus alpha toxin, wherein the antibody or antigen-binding fragment is in contact with one or more residues of SEQ ID NO: 39.

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:

Groups I+- II do not include the inventive concept of an isolated antibody or antigen-binding fragment thereof that immunospecifically binds to a fragment of the Staphylococcus aureus alpha toxin of SEQ ID NO: 39, as required by Group III.

Groups I+ do not include the inventive concept of administering an antibody or antigen-binding fragment thereof that immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide to a subject, as required by Groups II and III.

Groups II and III do not include the inventive concept of HV CDRs1-3, comprising SEQ ID NOs: 7-9, etc. as required by Group I+.

Furthermore, among Group I+, an antibody comprising heavy chain CDRs and light chain CDRs represented by a set of SEQ ID NOs, is structurally different from an antibody comprising heavy chain and light chain CDRs represented by a different set of SEQ ID NOs. Therefore, the antibodies are functionally different from each other including binding specificity to different epitopes or binding affinities to the same epitope. Furthermore, each set of CDR regions with (an) amino acid substitution(s), will further alter the antibody structure in variable regions and influence the antibody binding specificity and affinity to the specified antigen, without specifying the position(s) for amino acid substitution(s), the resulting antibody is unpredictable.

The inventions of Groups I+ through III share the technical feature of an antibody or fragment of an antibody, wherein the antibody or the fragment immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide, and the inventions of Group I+ further share the technical feature of wherein the antibody comprising CDR regions. However, these shared technical features do not represent a contribution over prior art as being anticipated by US 2009/0053235 A1 to TAYLOR et al. (hereinafter 'Taylor'), as follows:

Taylor discloses an antibody or fragment of an antibody, wherein the antibody or the fragment immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide (Abstract - 'Antibody compositions comprising antibodies to alpha-toxin'; para [0016] - 'antibody that specifically binds to an S. aureus alpha-toxin antigen'; para [0002] - 'compositions and methods for treating and preventing Staphylococcus aureus (S. aureus)'). Taylor further discloses wherein the antibody comprising CDR regions (para [0067] - 'An alpha-toxin antibody or bacterial antigen antibody in accordance with the invention may be a murine, human or humanized antibody. A humanized antibody is a recombinant protein in which the CDRs of an antibody from one species; e.g., a rodent, .. are transferred from the heavy and light variable chains of the rodent antibody into human heavy and light variable domains'). Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Groups II and III further share the technical feature of preventing or treating a condition associated with Staphylococcus aureus infection, comprising: administering an antibody or antigen-binding fragment thereof that immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide to a subjec. However, this shared technical feature does not represent a contribution over prior art. Specifically, Taylor further discloses a method of preventing or treating a condition associated with Staphylococcus aureus infection, comprising: administering an antibody or antigen-binding fragment thereof that immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide to a subject (para [0002] - methods for treating and preventing Staphylococcus aureus (S. aureus) and other bacterial infections'; Abstract - 'Antibody compositions comprising antibodies to alpha-toxin'; para [0019] - ' treating or preventing S. aureus infection, comprising administering to a subject in need thereof any of the aforementioned antibody compositions'). Furthermore, EP 2,208,787 A1 to PATRICE et al. also discloses a method of preventing or treating a condition associated with Staphylococcus aureus infection, comprising: administering an antibody or antigen-binding fragment thereof that immunospecifically binds to a Staphylococcus aureus alpha toxin polypeptide to a subject (para [0102] - 'antibody compositions suitable for administration,...that neutralizes infection and/or provides protection against infection'; para [0104] - 'an antibody that specifically binds to an S. aureus alpha-hemolysin antigen'), wherein the antibody is generated using peptide generated from an alpha toxin that has the sequence that is 100% identical to the claimed SEQ ID NO: 39 (para [0061] - 'the recombinant single-chain alpha-hemolysin polypeptide may be used for the... antibodies against a disease caused by Staphylococcus, wherein 'alpha-hemolysin' is an alpha-toxin; para [0007] - 'Staphylococcal alpha-hemolysin (HA) ... This toxin'; para [0027] - 'single-chain alpha-hemolysin polypeptide,... the wild-type sequence SEQ ID NO: 1', wherein SEQ ID NO: 1 is 100% identical to the claimed SEQ ID NO: 39; please also see Taylor: para [0004] - 'important virulence factor is alpha-toxin (alpha-hemolysin)'). Without a shared special technical feature, the inventions lack unity with one another. **********Continued in the next extra sheet**********

Continuation of:
The previous extra sheet - Box No III (unity of invention is lacking)

The inventions of Groups I+ further share an antibody or fragment comprising 1, 2, or 3 amino acid residue substitutions in VH CDR 1-3 represented by SEQ ID NOs 7-9, respectively, or an antibody that is at least 90% identical to SEQ ID NO: 20 or SEQ ID NO: 19. However, without specifying amino acid(s) for substitution at specified position(s) in (a) specified CDR(s), the resulted substitution sequences will share little function similarity when substituting different numbers of amino acids at the different positions in different CDR regions. Specifically, US 2005/0226876 A1 to GRAUS et al. discloses a VH CDR1 sequence (para [0030] - 'the variable heavy chain comprises CDR sequences CDR1, ... selected from the group consisting of SEQ ID NOs: 29', which is 100% identical to the claimed SEQ ID NO: 7 (VH CDR1), the antibody is specific binding to a different antigen P-selectin (para [0030] - 'an antibody binding to P-selectin... CDR1, ... SEQ ID NOs: 29'). Furthermore, US 2009/0155164 A1 to BRASEL et al. discloses VH CDR2 sequences (para [0009] - 'a CDRH2 selected from the group consisting of SEQ ID NOs:148-164'), wherein SEQ ID NO: 156 is 100% identical to the claimed SEQ ID NO: 8 (VH CDR2), the antibody is specific for binding to c-fms (Abstract - 'Antigen binding proteins that bind to human c -fms protein are provided...The antigen binding proteins can inhibit binding of c-fms to CSF-1'; para [0013] - 'an isolated antigen binding protein is provided that specifically binds to an epitope containing the c-fms'; para [0006] - 'the c-fms proto-oncogene ... known as M-CSFR, CSF-1R or CD115'). In addition, US 2008/0152587 A1 to ZHOU et al. discloses an antibody heavy chain variable sequence (Table 18, SEQ ID NO: 70), which is 92.1% identical to the claimed SEQ ID NO: 20, with CDR1 region that is 100% identical the CDR1 of the claimed SEQ ID NO: 20, and only one mismatch between CDR2 regions in both sequences, the antibody is specific for binding to urokinase-type plasminogen activator receptor (uPAR) (para [0115] - 'Table 1. This table reports the identification number of eachanti-uPAR antibody, along with the SEQ ID number of the variable domain of the corresponding heavy chain'; Table 1 - SEQ ID NO: 2; Table 18 - SEQ ID NO: 70, SEQ ID NO: 2; para [0003] - 'urokinase-type plasminogen activator receptor (uPAR)'). Moreover, WO 2010/003108 A2 to LOFQUIST et al. discloses antibodies' light chain sequences specific to IL6 IL6R or IL6xR (para [0059] - 'VL domains specific for IL6, IL6R or IL6xR are set fourth in SEQ ID NOS:....373-434'), wherein SEQ ID NO: 376 (107 a.a) comprising a region between amino acid residues 2-107, that is 100% identical to the claimed SEQ ID NO: 19. Since an antibody comprising the same CDR region(s) with different combination of other CDR regions, can bind to different antigens, without specified specific amino acid(s) for substitution(s) at specific site(s) for each CDR, the binding specificity of the resulting antibodies are unpredictable. Without a shared special technical feature, the inventions lack unity with one another.

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

Note re item 4: Claims 14-22, 25-44, 48, 54-68, 73-74, 77-78, 80 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

Note re item 4: Claim 84 is an omnibus type claim, and is not drafted in accordance with PCT Rule 6.2(a). The claim is indefinite as it is unclear what is included or excluded.