

	Espacio reservado para el adhesivo de radicación
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DIRECCIÓN DE NUEVAS CREACIONES
Procedimiento acelerado de exámenes de patente (PPH)

1	NÚMERO DE SOLICITUD ANTE LA SIC	NC2016/0005707		
2	OFICINA DE PRIMERA PRESENTACIÓN (OPP) ☐	USPTO ☒	OEPM ☐	
3	OFICINA DE EXAMEN ANTERIOR (OEA) ☐	JAPON ☐	KR Sur ☐	
4	PPH – PCT ☐	JAPON ☐	KR Sur ☐	
5	PROSUR: AR ☐ CH ☐ EC ☐ PY ☐ PE ☐ UR ☐ BR ☐	6	Alianza del Pacifico (AdP) : MX ☐ CH ☐ PE ☐	
7	NÚMERO DE SOLICITUD O PUBLICACIÓN DE LA SOLICITUD (OPP) ☐ X NÚMERO DE SOLICITUD EN OFICINA DE EXAMEN ANTERIOR (OEA): ☐ NÚMERO DE SOLICITUD PCT: ☐	1. 14/729,260		
8	☐ REPRESENTANTE LEGAL X APODERADO			
APELLIDOS JARAMILLO CAMPUZANO		NOMBRES MAURICIO		IDENTIFICACIÓN C.C.80.421.942 T.P.74.555 del C.S.J.
DIRECCIÓN Calle 67 No. 7 – 35, oficina 1204		No. TELÉFONO 3192900		
CIUDAD Bogotá		CORREO ELECTRÓNICO patentes@gpzlegal.com		
PAÍS Colombia		No. RADICACIÓN O PROTOCOLO DE PODER GENERAL		
9	CONDICIONES PARA ACCEDER A ESTE PROCESO:			
9.1. DATOS DE PRIORIDAD ☐ SI ☐ NO				
(33) PAÍS DE ORIGEN		CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. ESTADOS UNIDOS DE AMÉRICA		US	62/007,242	03 jun 2014
2. ESTADOS UNIDOS DE AMÉRICA		US	62/115,665	13 feb 2015
3. ESTADOS UNIDOS DE AMÉRICA		US	62/041,423	25 ago 2014
9.2. DATOS SOLICITUD INTERNACIONAL PCT ☐ SI ☐ NO				
Solicitud Internacional No.		PCT/US2015/033902		Fecha 03 jun 2015
Publicación Internacional No.		WO/2015/187779		Fecha 10 dic 2015
*El solicitante presenta una copia de la(s) reivindicación(es) patentable(s) u otorgable(s) de la solicitud de la Oficina de Primera Presentación que profirió el examen de patentabilidad, junto con una traducción al castellano. X SI ☐ NO				
*El solicitante presenta los resultados de búsqueda de la Oficina de Examen Anterior, junto con una traducción al castellano X SI ☐ NO				
REQUISITOS PARA EL RECONOCIMIENTO DE LOS RESULTADOS DE EXÁMENES DE PATENTABILIDAD EFECTUADOS A SOLICITUDES EXTRANJERAS				
Para que la Superintendencia de Industria y Comercio pueda reconocer los resultados de exámenes de patentabilidad producidos por otras Oficinas de Propiedad Industrial se debe cumplir con las siguientes condiciones:				
(a) Al momento de solicitar el examen de patentabilidad, si el solicitante pide que se reconozcan exámenes de patentabilidad de otras oficinas extranjeras, deberá aportar junto con el pago de la tasa correspondiente, los siguientes anexos:				
(i) Copia de las resoluciones, fallos o decisiones que han sido relevantes para la determinación de la patentabilidad de la(s) solicitud(es) en la Oficina que haya proferido el examen de patentabilidad que contienen reivindicaciones patentables u otorgables que son la base de la petición, y si es del caso, su traducción al castellano. X SI ☐ NO				
(ii) Copia de todas las reivindicaciones determinadas como patentables u otorgables en la Oficina que profirió el examen de patentabilidad y, si es del caso, su traducción al castellano. X SI ☐ NO				
(iii) Copia de los antecedentes, información o documentos citados por el examinador de la Oficina de Primera Presentación del examen de patentabilidad, en las resoluciones, fallos o decisiones correspondientes, incluyendo la literatura no patente. Los documentos de patente deberán presentarse siempre y cuando no estén disponibles para la Superintendencia de Industria y Comercio mediante el simple acceso a bases de datos gratuitas. ☐ SI X NO				
(iv) Una tabla de correspondencias de las reivindicaciones que han sido determinadas como patentables u otorgables en la solicitud de la Oficina que haya proferido el examen de patentabilidad. X SI ☐ NO				
10	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)			



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9	TABLA DE CORRESPONDENCIA DE REIVINDICACIONES		
Reivindicaciones en la solicitud en Colombia		Reivindicaciones otorgables en la solicitud internacional	Explicación sobre la suficiente correspondencia ó Comentarios que explican la correspondencia
1. Una composición farmacéutica que comprende un portador farmacéuticamente aceptable y un anticuerpo monoclonal purificado, en donde el anticuerpo monoclonal se une específicamente a Staphylococcus aureus, y es capaz de desplazar inmunoglobulinas IgG humanas unidas a SpA en Staphylococcus aureus, en donde el anticuerpo comprende un dominio variable de cadena pesada que comprende un CDR1, un CDR2 y un CDR3 de SEQ ID NO: 2, 3 y 4, respectivamente, y un dominio variable de cadena ligera que comprende un CDR1, un CDR2 y un CDR3 de SEQ ID NO: 7, 8 y 9, respectivamente.		1. Una composición farmacéutica que comprende un portador farmacéuticamente aceptable y un anticuerpo monoclonal purificado que comprende un dominio variable de cadena pesada que comprende un CDR1, CDR2 y CDR3 de SEQ ID NO: 2, 3 y 4, respectivamente, y un dominio variable de cadena ligera que comprende un CDR1, CDR2 y CDR3 de SEQ ID NO: 7, 8 y 9, respectivamente, en donde el anticuerpo monoclonal se une específicamente a la proteína A (SpA) de Staphylococcus aureus con un KD de menos de 1X10-10 M por medio de su paratopo de región Fab, en donde el anticuerpo monoclonal es capaz de desplazar inmunoglobulinas humanas IgG unidas a SpA en bacterias Staphylococcus aureus por medio de sus regiones Fc.	Las secuencias de aminoácidos de los dominios variables de las cadenas pesada y ligera (características técnicas esenciales del anticuerpo monoclonal de la composición farmacéutica que se reivindica) corresponden exactamente a las secuencias de aminoácidos de los dominios variables de las cadenas pesada y ligera del anticuerpo comprendido en la composición farmacéutica de la patente estadounidense concedida.
2. La composición farmacéutica según la reivindicación 1, en donde el dominio variable de cadena pesada comprende SEQ ID NO: 5 y el dominio variable de cadena ligera comprende SEQ ID NO: 10.		5. La composición farmacéutica de la reivindicación 1, en donde el dominio variable de cadena pesada comprende la SEQ ID NO: 5 y el dominio variable de cadena ligera comprende la SEQ ID NO: 10.	Las secuencias de aminoácidos son del todo equivalentes.
3. La composición farmacéutica según cualquiera de las reivindicaciones precedentes, en donde el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado.		3. La composición farmacéutica de la reivindicación 1, en donde el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado. 7. La composición farmacéutica de la reivindicación 5, en donde el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado.	La reivindicación 3 especifica la composición de acuerdo con cualquiera de las reivindicaciones 1 y 2, mencionando que el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado. Esta reivindicación es equivalente a las reivindicaciones concedidas 3 y 7 de la patente estadounidense, las cuales dependen de las reivindicaciones 1 y 5, respectivamente.

Notice of Allowability	Application No. 14/729,260	Applicant(s) SIMARD, JOHN	
	Examiner Padma V. Baskar	Art Unit 1645	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 04/01/2016.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 6,13-15,17 and 19-21. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. ☐ Notice of References Cited (PTO-892) | 5. ☒ Examiner's Amendment/Comment |
| 2. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date <u>02/26/2016</u> | 6. ☒ Examiner's Statement of Reasons for Allowance |
| 3. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. ☐ Other _____. |
| 4. ☒ Interview Summary (PTO-413),
Paper No./Mail Date <u>04/25/2016</u> . | |

Art Unit: 1645

Detailed Action

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.
2. Applicants response filed on 04/01/2016 is acknowledged and entered. Claims 6-11 and 13-18 are pending.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 02/26/2016 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner and a signed copy is attached to this office action.

Examiner's amendment

4. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with applicant's representative Stanley A. Kim on 4/25/16 and the application has been amended as follows:

Claims 7-12, 16 and 18 are canceled.

Claim 6 (currently amended): A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a purified monoclonal antibody comprising a heavy chain variable domain comprising a CDR1, CDR2, and CDR3 of SEQ ID NO: 2, 3, and 4, respectively, and a light chain variable domain comprising a CDR1, CDR2, and CDR3 of SEQ ID NO: 7, 8, and 9, respectively, wherein the monoclonal antibody ~~which~~ specifically binds *Staphylococcus aureus* protein A (SpA) with a K_D of less than 1×10^{-10} M via its Fab region paratope, wherein the monoclonal antibody is able to displace human IgG immunoglobulins bound to SpA on *Staphylococcus aureus* bacteria via their Fc regions.

Claim 13 (previously presented): The pharmaceutical composition of claim 6, wherein the monoclonal antibody is able to mediate opsonization of SpA-expressing *Staphylococcus aureus* bacteria in the presence of at least 1 mg/ml of IgG immunoglobulins which bind SpA via their Fc regions.

Claim 14 (previously presented): The pharmaceutical composition of claim 6, wherein the monoclonal antibody is a human or humanized IgG3 monoclonal antibody.

Art Unit: 1645

Claim 15 (previously presented): The pharmaceutical composition of claim 6, wherein the monoclonal antibody specifically binds to the amino acid sequence SEQ ID NO: 1 : ~~KPGKEDNKKPGKEDGNKPGK~~ (SEQ ID NO: 1).

Claim 17 (currently amended): The pharmaceutical composition of claim 6, wherein the ~~monoclonal antibody comprises a heavy chain variable domain comprising~~ comprises SEQ ID NO: 5 and ~~[[a]] the light chain variable domain comprising~~ comprises SEQ ID NO: 10.

Claim 19 (new): The pharmaceutical composition of claim 17, wherein the monoclonal antibody is able to mediate opsonization of SpA-expressing *Staphylococcus aureus* bacteria in the presence of at least 1 mg/ml of IgG immunoglobulins which bind SpA via their Fc regions.

Claim 20 (new): The pharmaceutical composition of claim 17, wherein the monoclonal antibody is a human or humanized IgG3 monoclonal antibody.

Claim 21 (new): The pharmaceutical composition of claim 17, wherein the monoclonal antibody specifically binds to the amino acid sequence SEQ ID NO: 1 : ~~KPGKEDNKKPGKEDGNKPGK~~ (SEQ ID NO: 1).

Reasons for Allowance

5. The following is an examiner's statement of reasons for allowance:

The claimed invention is drawn to a novel pharmaceutical composition comprising a monoclonal antibody (PA8-G3, example 1) having a heavy chain variable domain SEQ ID NO: 5 (CDR1-3 set forth as SEQ.ID.NO: 2-4 respectively) and a light chain variable domain SEQ ID NO: 10 (CDR1-3 set forth as SEQ.ID.NO: 7-9 respectively) that specifically binds *Staphylococcus aureus* protein A (SpA) SEQ.ID.NO:1. The claimed monoclonal antibody is able to mediate opsonization of SpA-expressing *Staphylococcus aureus* bacteria as shown in example 2. The instant invention is novel and nonobvious because there is no prior art which teaches the monoclonal antibody referred to PA8-G3 (example 1). The specification meets 35 U.S.C. 112, first paragraph, requirements because it contains an adequate written description of the invention that enables one of ordinary skill in the art to make and use the invention. The specification also sets forth the best mode to carry out the invention. The claims also meet 35 U.S.C. 112, second paragraph, requirements because the claims point out and distinctly claim the invention.

Conclusion

6. Claims 6, 13-15, 17 and 19-21 are allowed and are renumbered as 1-8 respectively.

Art Unit: 1645

Correspondence

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma V. Baskar whose telephone number is (571)272-0853. The Examiner can normally be reached on Mon-Fri 9:00 A.M- 5:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571- 272- 0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
/Padma Baskar/
Padma Baskar, Ph.D (Microbiology and Immunology)
Primary Examiner, Art Unit 1645



US009416172B2

(12) **United States Patent**
Simard

(10) **Patent No.:** **US 9,416,172 B2**

(45) **Date of Patent:** **Aug. 16, 2016**

(54) **COMPOSITIONS AND METHODS FOR
TREATING AND PREVENTING
STAPHYLOCOCCUS AUREUS INFECTIONS**

(71) Applicant: **XBiotech, Inc.**, Vancouver (CA)

(72) Inventor: **John Simard**, Austin, TX (US)

(73) Assignee: **XBIOTECH, INC.**, Vancouver (CA)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/729,260**

(22) Filed: **Jun. 3, 2015**

(65) **Prior Publication Data**

US 2015/0344548 A1 Dec. 3, 2015

Related U.S. Application Data

(60) Provisional application No. 62/007,242, filed on Jun.
3, 2014, provisional application No. 62/041,423, filed
on Aug. 25, 2014, provisional application No.
62/115,665, filed on Feb. 13, 2015.

(51) **Int. Cl.**

A61K 39/40 (2006.01)
C07K 16/12 (2006.01)
A61K 38/12 (2006.01)
A61K 38/14 (2006.01)
A61K 39/00 (2006.01)

(52) **U.S. Cl.**

CPC **C07K 16/1271** (2013.01); **A61K 38/14**
(2013.01); **A61K 39/40** (2013.01); **A61K**
2039/505 (2013.01); **C07K 2317/21** (2013.01);
C07K 2317/24 (2013.01); **C07K 2317/30**
(2013.01); **C07K 2317/34** (2013.01); **C07K**
2317/56 (2013.01); **C07K 2317/565** (2013.01);
C07K 2317/732 (2013.01); **C07K 2317/76**
(2013.01); **C07K 2317/92** (2013.01)

(58) **Field of Classification Search**

CPC **C07K 16/1271**; **C07K 2317/92**; **C07K**
2317/30; **C07K 2317/21**; **C07K 2317/56**;
C07K 2317/24; **C07K 2317/565**; **A61K**
2039/505

See application file for complete search history.

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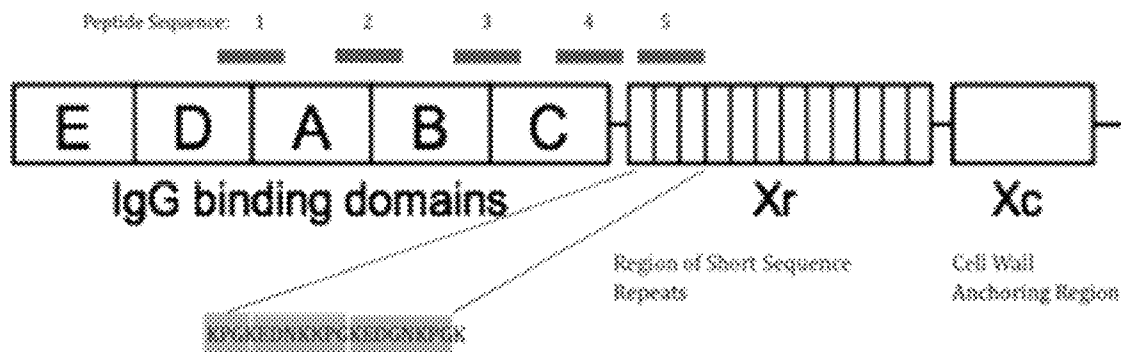
Primary Examiner — Padma V Baskar

(74) Attorney, Agent, or Firm — Stanley A. Kim

(57) **ABSTRACT**

Antibodies having Fab regions that specifically bind to *Sta-
phylococcus aureus* protein A are capable of mediating
opsinization of *Staphylococcus aureus* bacteria despite their
expression of antibody-neutralizing protein A. These anti-
bodies and antigen-binding fragments thereof can be used in
methods of treating and/or preventing *Staphylococcus aureus*
infections.

8 Claims, 5 Drawing Sheets



(56)

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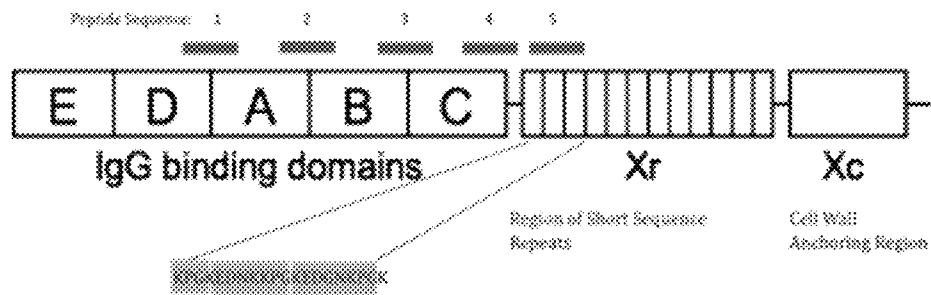


FIG. 1

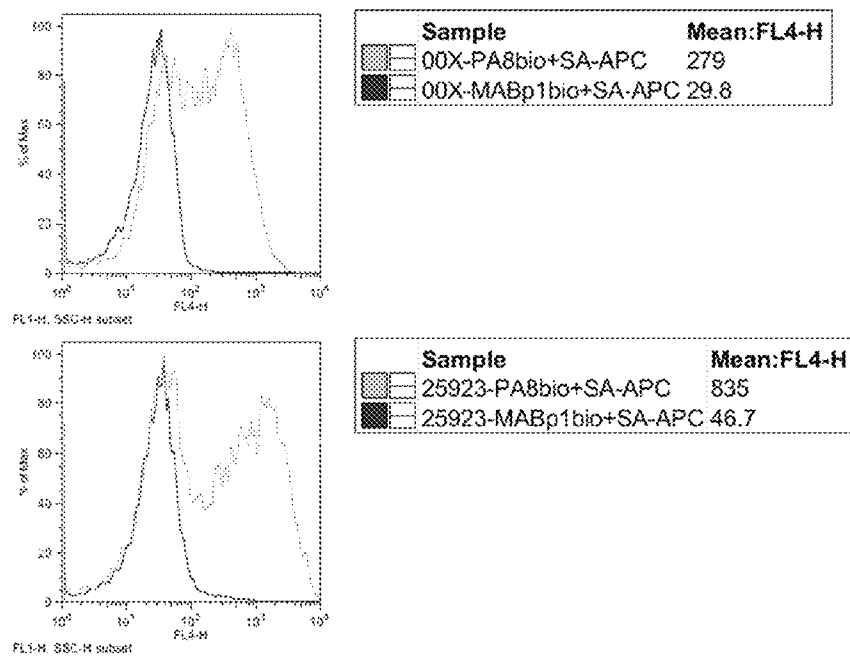


FIG. 2

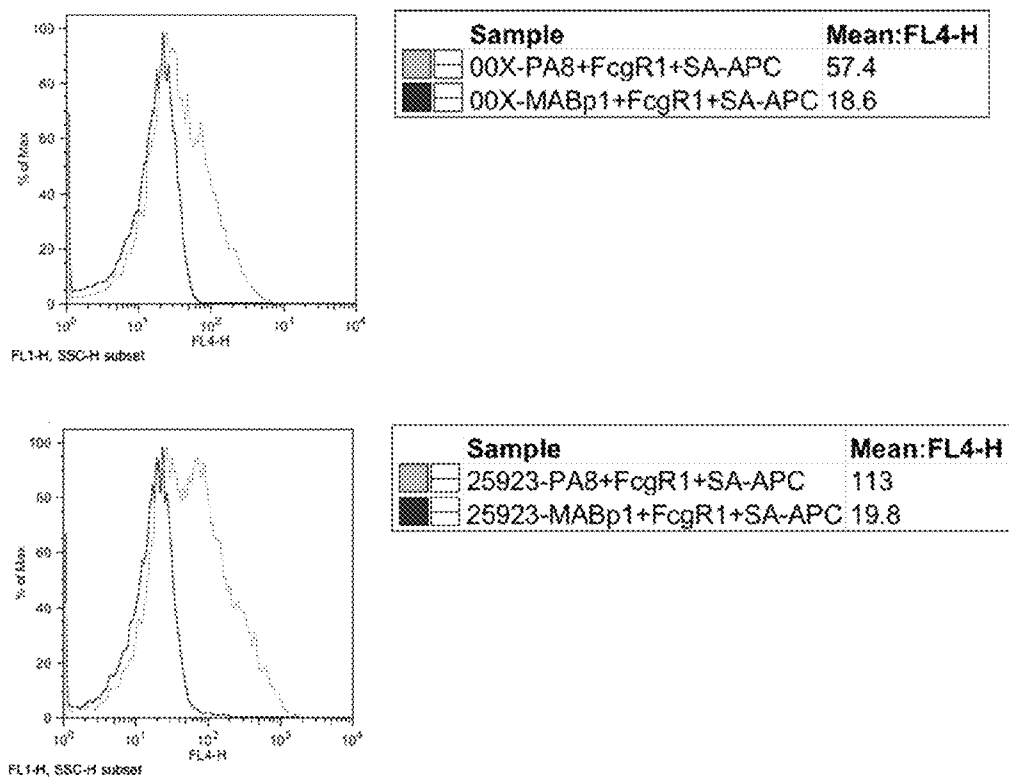


Fig. 3

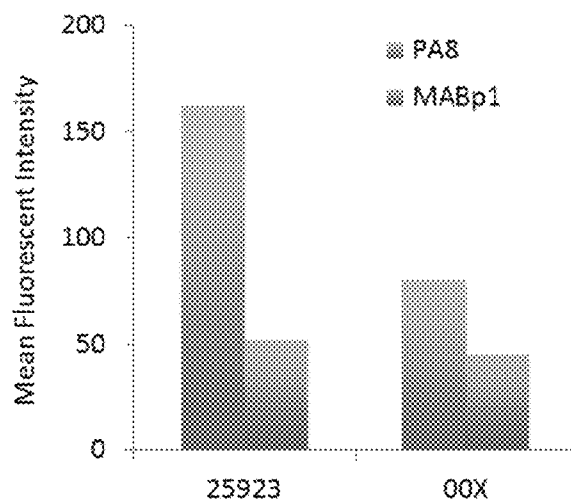


FIG. 4

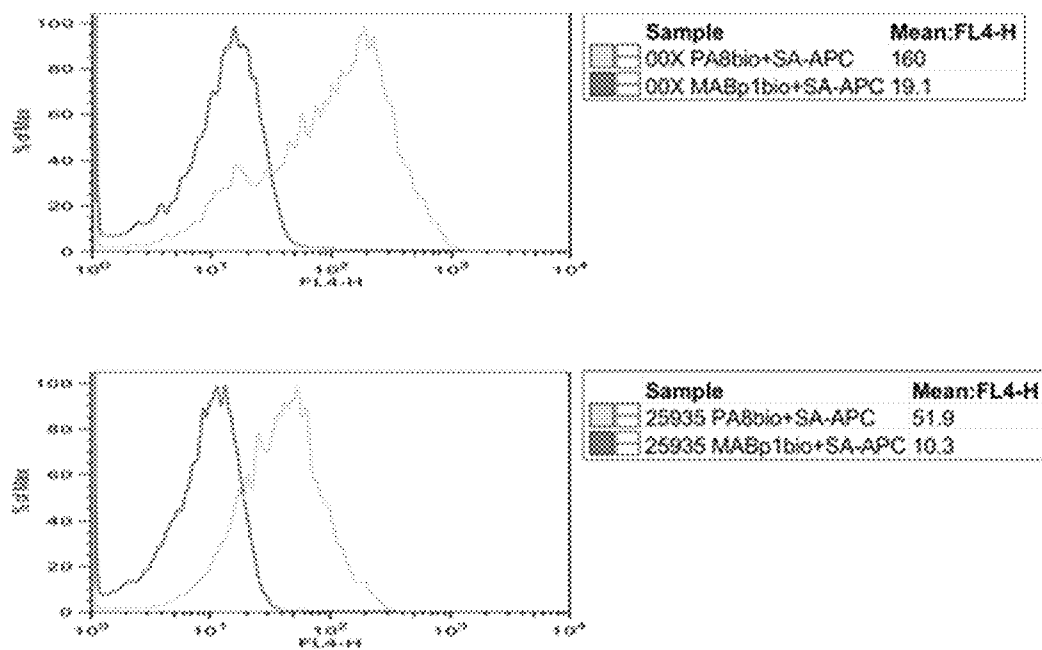


FIG. 5

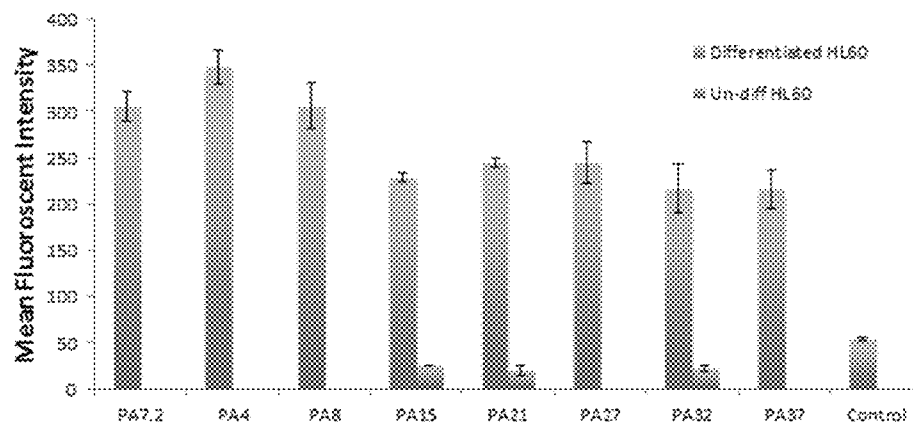


FIG. 6

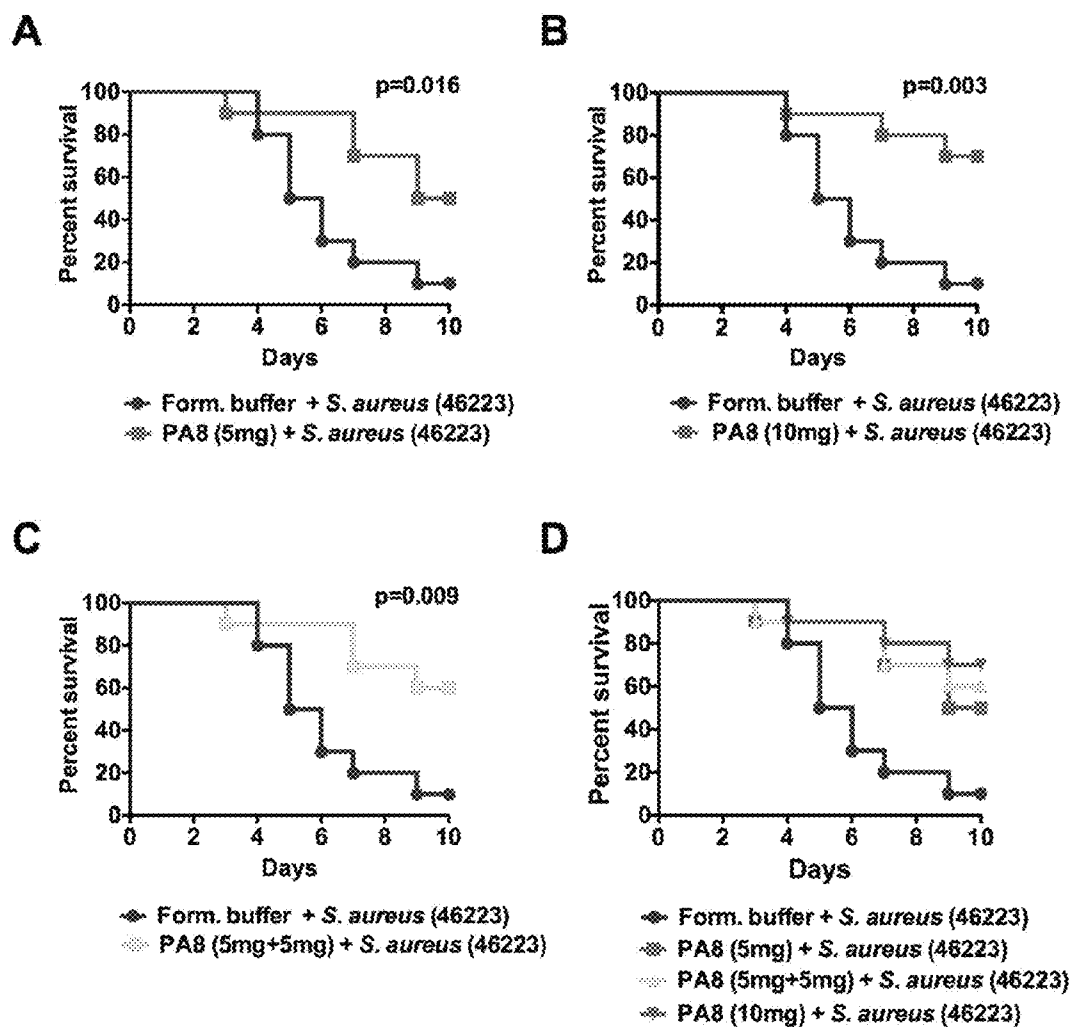


FIG. 7

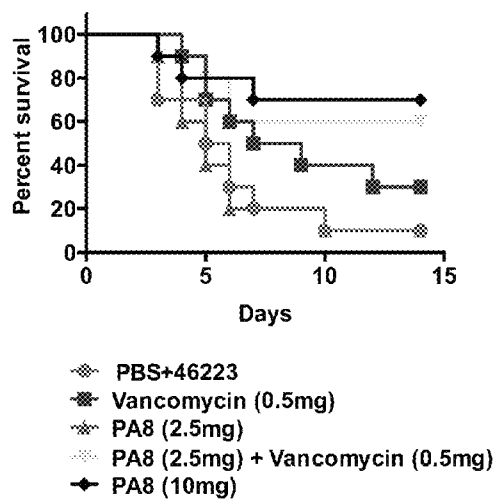


FIG. 8A

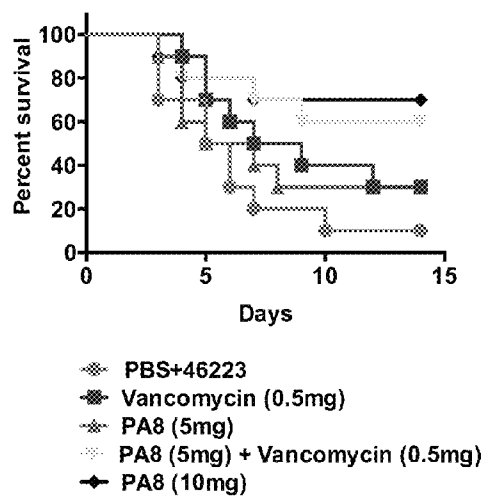


FIG. 8B

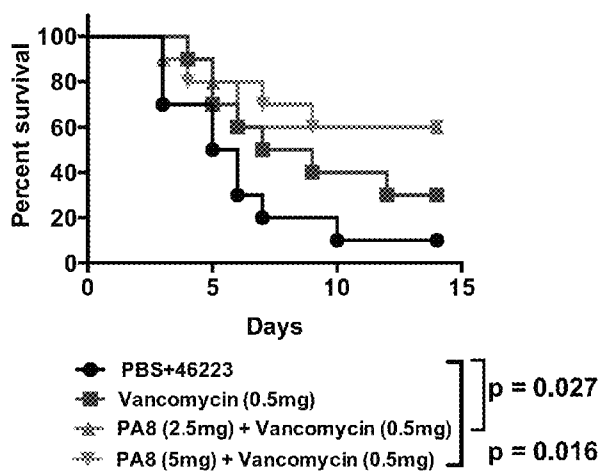


FIG. 8C

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COMPOSITIONS AND METHODS FOR TREATING AND PREVENTING STAPHYLOCOCCUS AUREUS INFECTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. provisional patent application No. 62/007,242 filed on Jun. 3, 2014, U.S. provisional patent application No. 62/041,423 filed on Aug. 25, 2014, and U.S. provisional patent application No. 62/115,665 filed on Feb. 13, 2015.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 28, 2015, is named 5407-0233_SL.txt and is 83,034 bytes in size.

FIELD OF INVENTION

The invention relates generally to methods of medical treatment, immunology, and microbiology. More particularly, the invention relates to compositions and methods for treating and preventing *Staphylococcus aureus* infections.

BACKGROUND

Staphylococcus aureus (SA) is a substantial cause of sickness and death in both humans and animals. Infection with these gram-positive cocci often results in the development of a superficial abscess. Other cases of SA infection can be much more serious. For example, intrusion of SA into the lymphatics and blood can lead to a systemic infection which in turn can cause complications such as endocarditis, arthritis, osteomyelitis, pneumonia, septic shock and even death. Hospital-acquired SA infection is common and particularly problematic with SA being the most frequent cause of hospital-acquired surgical site infections and pneumonia, and the second most frequent cause of cardiovascular and blood-stream infections. Antibiotic administration has been and remains the standard treatment for SA infections. Unfortunately, the use of antibiotics has also fueled the development of antibiotic resistance in SA. Notably, methicillin-resistant SA (MRSA) has evolved the ability to resist beta-lactam antibiotics such as penicillin and cephalosporins. More alarmingly, SA resistant to antibiotics of last resort such as vancomycin and linezolid have recently emerged. Therefore a new approach for preventing and treating SA infections is needed.

SUMMARY

It was discovered that certain antibodies (Abs) having Fab region paratopes that specifically bind to SA protein A (SpA) are capable of mediating opsonization of SA bacteria despite SA's expression of antibody (Ab)-neutralizing SpA. Previous Ab-based strategies for treating or preventing SA infections showed promise in pre-clinical and early stage clinical trials, but failed to meet endpoints in phase III trials. Perhaps explaining these results, previous strategies did not address the Ab-neutralizing property of SpA. SpA is a heavily expressed cell wall-associated protein that binds most immunoglobulins (Igs) via their Fc (effector) regions. SpA binds to human antibodies of subclasses IgG1, IgG2, and IgG4 via

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their Fc region with a KD of about 1×10^{-9} M, and thereby acts as an Fc region anchor that orients the effector portion of an immunoglobulin (Ig) away from Fc-interacting immune effectors such as complement and Fc receptor (FcR)-bearing phagocytes. Accordingly, most Abs specific for SA antigens are "sequestered" from immune effectors in this manner. In addition, because SpA is so highly expressed on the cell wall of SA (estimated 7% of the cell wall), it mediates the formation of a shield of Igs covering the cell wall. This shield sterically hinders Abs specific for cell wall antigens from binding their targets and mediating opsonophagocytosis of the bacteria. The formation of an Ig shield was not previously appreciated as a virulence factor. Thus the discovery that SA-binding Abs having Fab regions that specifically bind SpA while permitting their Fc regions to still interact with FcRs on immune effector cells and/or activate complement by binding C1q despite the Fc-neutralizing ability of SpA and the formation of an Ig shield was a significant step over other anti-SA Ab-based approaches. Preferred versions of such Abs are capable of displacing Igs already bound to SpA by their Fc regions.

As examples of the foregoing, described herein are isolated or purified antibodies (particularly human IgG3 antibodies which have Fc regions with low or no affinity for SpA such as one with the allotype having arginine at amino acid position 435; Stapleton et al., Nature Communications 2, Article number: 599, 2011) having Fab regions that can specifically bind a target epitope of SpA on a SA bacterium while their Fc regions are still able to interact with an FcR (e.g., soluble recombinant or native on immune effector cells)—despite the Fc-binding property of SpA and steric hindrance of the target epitope by Igs bound to SpA via their Fc region. Also provided herein are pharmaceutical compositions that contain at least one of these antibodies and a pharmaceutically acceptable carrier (e.g., a non-natural pharmaceutically acceptable carrier). Further provided are methods of treating a subject having a SA infection or reducing the risk of developing a SA infection in a subject that include administering a therapeutically effective amount of any of the pharmaceutical compositions described herein or any of the antibodies or antigen-binding fragments described herein to a subject in need thereof.

As used herein, the word "a" or "an" before a noun represents one or more of the particular noun. For example, the phrase "an antibody" represents "one or more antibodies."

By the term "antibody" or "Ab" is meant any immunoglobulin (e.g., human, cartilaginous fish, or camelid antibodies) or conjugate thereof, that specifically binds to an antigen (e.g., an SpA antigen such as SEQ ID NO: 1 or an antigenic fragment of SEQ ID NO: 1). A wide variety of Abs are known by those skilled in the art. Non-limiting examples of Abs include: monoclonal Abs (e.g., including full-length Abs), polyclonal Abs, multi-specific Abs (e.g., bi-specific Abs), dual variable domain Abs, single-chain Abs (e.g., single-domain Abs, camelid Abs, and cartilaginous fish Abs), chimeric (e.g., humanized, such as humanized IgG3) Abs, and human Abs (e.g., human IgG3 Abs). The term antibody also includes Ab conjugates (e.g., an Ab conjugated to a stabilizing protein, a label, or a therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art)).

By the term "antigen-binding fragment" is meant any portion of a full-length Ab that contains at least one variable domain ((e.g., a variable domain of a mammalian (e.g., human, mouse, rat, rabbit, or goat) heavy or light chain immunoglobulin), a camelid variable antigen-binding domain (VHH), or a cartilaginous fish immunoglobulin new antigen receptor (Ig-NAR) domain) that is capable of specifically

binding to an antigen. For example, an antigen-binding fragment described herein can include at least part of an Ab Fc region that is sufficient to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC) in a mammal (e.g., a human) and/or is conjugated to a therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art). Non-limiting examples of Ab fragments include Fab, Fab', F(ab')₂, Fv fragments, diabodies, linear antibodies, and multi-specific Ab formed from Ab fragments. Additional Ab fragments containing at least one camelid VHH domain or at least one cartilaginous fish Ig-NAR domain include mini-bodies, micro-antibodies, subnano-antibodies, and nano-antibodies, and any of the other forms of Abs described in U.S. Patent Application Publication No. 2010/0092470. An antigen binding fragment can be, e.g., an antigen-binding fragment of human or humanized IgG1, IgG2, IgG3 IgG4, IgD, IgA, IgE, or IgM.

By the term "human antibody" is meant an Ab that is encoded by a nucleic acid (e.g., rearranged human immunoglobulin heavy or light chain locus) present in the genome of a human. In some embodiments, a human Ab is produced in a mammalian (e.g., human) cell culture. In some embodiments, a human Ab is produced in a non-human cell (e.g., a Chinese hamster ovary cell line or a mouse or hamster cell line). In some embodiments, a human Ab is produced in a bacterial or yeast cell. A human Ab can include a conjugated therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art). A human Ab can be human IgG1, IgG2, IgG4, IgD, IgA, IgE, or IgM, and is preferably human IgG3. By the term "true human antibody" is meant an Ab with heavy and light chain variable regions that are naturally present in the serum of a human being.

By the term "humanized antibody" is meant an Ab which contains mostly sequences of a human Ab but also includes minimal sequences derived from a non-human (e.g., mouse, rat, rabbit, or goat) Ig. In non-limiting examples, humanized Abs are human Abs (recipient Ab) in which hypervariable region residues of the recipient Ab are replaced by hypervariable region residues from a non-human species Ab (donor Ab), e.g., mouse, rat, rabbit, or goat Ab having the desired specificity, affinity, and capacity. In some embodiments, the Fv framework residues of the human Ig are replaced by corresponding non-human residues. In some embodiments, humanized Abs may contain residues which are not found in the recipient Ab or in the donor Ab. These modifications can be made to further refine Ab performance.

In some embodiments, the humanized Ab will contain substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops (complementary determining regions) correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin sequence. The humanized antibody can also contain at least a portion of an Ig constant region (Fc region), typically, that of a human Ig (e.g., human IgG3). Humanized Abs can be produced by molecular biology methods that are well known in the art. Non-limiting examples of methods for generating humanized Abs are described herein. A humanized antibody can include a conjugated therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art).

By the term "single-chain antibody" is meant a single polypeptide that contains at least one variable binding domain (e.g., a variable domain of a mammalian heavy or light chain Ig, a camelid variable antigen-binding domain (VHH), or a cartilaginous fish (e.g., shark) immunoglobulin new antigen receptor (Ig-NAR) domain) that is capable of specifically

binding to an antigen. Non-limiting examples of single-chain Abs are described herein, and are known in the art (see, for example, the antibodies described in U.S. Patent Publication No. 2010/0092470). A single-domain antibody can include a conjugated therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art).

An Ab or antigen-binding fragment thereof "specifically binds" or "binds specifically" to a particular antigen, e.g., SpA (such as an epitope comprising SEQ ID NO: 1 or an antigenic fragment of SEQ ID NO: 1), when it binds to that antigen, but recognizes and binds to a lesser extent (e.g., does not recognize and bind) to other molecules in a sample. In some embodiments, an Ab or an antigen-binding fragment thereof selectively binds to an epitope with an affinity (K_D) equal to or less than 1×10^{-10} M (e.g., less than 1×10^{-11} M or less than 1×10^{-12} M) in phosphate buffered saline (e.g., as determined by surface plasmon resonance). The ability of an Ab or antigen-binding fragment to specifically bind a protein epitope may be determined using any of the methods known in the art or those methods described herein.

By the term "complementarity determining region" or "CDR" is meant a region within an Ig (heavy or light chain Ig) that forms part of an antigen-binding site (paratope) in an Ab or antigen-binding fragment thereof. As is known in the art, a heavy chain Ig normally contains three CDRs: CDR1, CDR2, and CDR3, respectively, and a light chain Ig normally contains three CDRs: CDR1, CDR2, and CDR3. In any Ab or antigen-binding fragment thereof, the three CDRs from the heavy chain Ig and the three CDRs from the light chain Ig together form an antigen-binding site in the Ab or antigen-binding fragment thereof. The Kabat Database is one system used in the art to number CDR sequences present in a light chain Ig or a heavy chain Ig.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic diagram of SpA showing the different domains and the location of each of five antigenic peptides. The sequence of antigenic peptide #5 is shown (SEQ ID NO: 1).

FIG. 2 is a set of two graphs showing a histogram of the fluorescence of SA clinical isolate 00X (top) and SA strain ATCC #25923 (bottom) incubated with biotinylated PA8-G3 Ab (light line) or control biotinylated anti-interleukin-1 alpha Ab (MABp1) (dark line), and then incubated with streptavidin-APC.

FIG. 3 is a set of two graphs showing a histogram of the fluorescence of clinical isolate 00X (top) and strain ATCC #25923 (bottom) incubated with unlabeled PA8-G3 Ab (light line) or unlabeled MABp1 Ab (dark line), followed by biotinylated recombinant Fcγ receptor 1, and then incubated with streptavidin-APC.

FIG. 4 is graph of the mean fluorescent intensity of differentiated HL60 cells (using fluorescence cell sorting) following co-incubation with PA8-G3 Ab opsonized with pH-rod-green labeled strain ATCC #25923 or clinical isolate 00X.

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Similar samples incubated with a control Ab MABp1, instead of PA8-G3 Ab were used as a negative control.

FIG. 5 is a set of two graphs showing the fluorescence intensity of clinical isolate 00X (top) or ATCC #25923 (bottom) pre-incubated with human sera for 15 minutes prior to the addition of biotinylated PA8-G3 Ab or negative control MABp1 Ab, and then incubated with streptavidin APC.

FIG. 6 is a graph showing the mean fluorescent intensity of differentiated or undifferentiated HL-60 cells after co-incubation with pH-rodo-green labeled SA and one of the following unlabeled Abs: PA7.2-G3, PA4-G3, PA8-G3, PA15-G3, PA21-G3, PA27-G3, PA32-G3, PA37-G3, or MABp1. The MABp1 Ab samples were used as a negative control.

FIG. 7A-D are graphs showing that administration of mAb PA8 enhances the survival of murine subjects infected with *S. aureus*.

FIGS. 8 A-C are graphs showing the synergy between PA8-G3 and vancomycin.

DETAILED DESCRIPTION

Described herein are methods and compositions for treating a subject having a SA infection or reducing the risk of developing a SA infection in a subject.

Antibodies and Antigen-Binding Fragments Thereof

Described herein are purified or isolated (e.g., at least 90%, 92%, 94%, 95%, 96%, 97%, 98%, or 99% pure by weight) Abs (e.g., preferably true human, human, or humanized IgG3s) that bind to SpA and are capable of mediating opsonization of SA bacteria despite SA's expression of antibody (Ab)-neutralizing SpA. Preferred such Abs bind to the peptide of SEQ ID NO:1 with a sufficient binding affinity to displace human IgG immunoglobulins (e.g., one or more of IgG1, IgG2, and IgG4) bound to SpA via their Fc region. Preferred Abs can bind to SpA via their Fab region paratopes with a K_D of less than 1×10^{-10} M (e.g., less than 1×10^{-11} M, less than 1×10^{-12} M, less than 0.5×10^{-12} M, or less than 1×10^{-13} M) under physiological conditions (e.g., phosphate buffered saline) (e.g., as determined using surface plasmon resonance or Bio-Layer Interferometry using recombinant SpA). For example, the Abs described herein that bind to SpA via their Fab regions with a K_D of between 1×10^{-10} M and 0.5×10^{-12} M, between 1×10^{-11} M and 0.5×10^{-12} M, between 1×10^{-11} M and 0.2×10^{-12} M (e.g., under physiological conditions, e.g., phosphate buffered saline, e.g., as measured using surface plasmon resonance using recombinant SpA) are preferred. Those Abs or antigen-binding fragments described herein preferably are able to displace human Abs (e.g., one or more of IgG1, IgG2, and IgG4) bound to SpA in the cell wall of a SA bacterium via their Fc regions. Also provided herein are purified or isolated (e.g., at least 90%, 92%, 94%, 95%, 96%, 97%, 98%, or 99% pure by weight) mAbs (e.g., preferably true human, human, or humanized IgG3s) that specifically bind *Staphylococcus aureus* protein A (SpA) with a K_D of less than 1×10^{-10} M via their Fab region paratopes, wherein the mAbs are able to mediate opsonization of SpA-expressing *Staphylococcus aureus* bacteria in the presence of at least 1 mg/ml (e.g., at least 1, 2, 3, 4, 5, 10, 25, 50, or 100 mg/ml, or the amount normally contained in human serum) of IgG immunoglobulins which bind SpA via their Fc regions.

The purified or isolated Abs provided herein might bind to an epitope present in the extracellular domain (e.g., present in the X_R repeat region and one or more of the IgG binding domains) of SpA. Non-limiting examples of an antigen that can be specifically recognized by any of the Abs (or antigen-

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binding fragments thereof) provided herein include: 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acids of SEQ ID NO: 1 (e.g., a fragment starting at amino acid position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 of SEQ ID NO: 1); 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 contiguous amino acids of SEQ ID NO: 82 (e.g., a fragment starting at amino acid position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 of SEQ ID NO: 82); 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 contiguous amino acids of SEQ ID NO: 83 (e.g., a fragment starting at amino acid position 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 of SEQ ID NO: 83); 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 contiguous amino acids of SEQ ID NO: 84 (e.g., a fragment starting at amino acid position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 of SEQ ID NO: 84); 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acids of SEQ ID NO: 85 (e.g., a fragment starting at amino acid position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 of SEQ ID NO: 85); or 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acids from amino acid positions 1 to 20, 10 to 30, 20 to 40, 30 to 50, 40 to 60, 50 to 70, 60 to 80, 70 to 90, 80 to 100, 90 to 110, 100 to 120, 110 to 130, 120 to 140, 130 to 150, 140 to 160, 150 to 170, 160 to 180, 170 to 190, 180 to 200, 190 to 210, 200 to 220, 210 to 230, 220 to 240, 230 to 250, 240 to 260, 250 to 270, 260 to 280, 270 to 290, 280 to 300, 290 to 310, 300 to 320, 310 to 330, 320 to 340, 330 to 350, 340 to 360, 350 to 370, 360 to 380, 370 to 390, 380 to 400, 390 to 410, 400 to 420, 410 to 430, 420 to 440, or 430 or to 450 of SEQ ID NO: 86. Examples of other antigens include similar fragments of SpAs having amino acids sequences differing from that of SEQ ID NO:86.

Methods for determining the ability of an Ab or antigen-binding fragment thereof to bind to a target protein (e.g., SpA or a portion thereof) can be performed using methods known in the art. Non-limiting examples of such methods include competitive binding assays using Abs known to bind the target protein (e.g., SpA), enzyme-linked immunosorbent assays, BioCoRE®, affinity columns, immunoblotting, or protein array technology. In some embodiments, the binding activity of the Ab or antigen-binding fragment thereof is determined by contacting a SA bacterium with the Ab or antigen-binding fragment thereof. Exemplary methods for determining the ability of an Ab or antigen-binding fragment to displace human Abs (e.g., one or more of IgG1, IgG2, and IgG4) bound to SpA in the cell wall of a SA bacterium are described in the Examples section below. Additional methods for determining the ability of an Ab or antigen-binding fragment to displace human Abs (e.g., one or more of IgG1, IgG2, and IgG4) bound to SpA in the cell wall of a SA bacterium are known in the art.

An Ab can be, e.g., a mAb, a multi-specific Ab (e.g., a bispecific Ab), a chimeric Ab (e.g., a humanized Ab, such as a humanized IgG Ab), a human Ab, or a fragment of any of the foregoing. For example, an Ab can be a human or humanized monoclonal IgG3 Ab. An Ab can also be a single-chain Ab (e.g., a single-domain Ab), such as a single-chain camelid or cartilaginous fish (e.g., shark) Ab, or a single-chain Ab that contains at least one camelid variable antigen-binding domain (VHH) or at least one cartilaginous fish (e.g., shark) immunoglobulin new antigen receptor (Ig-NAR) domain (see, for example, the Abs described in U.S. Patent Publication No. 2010/0092470). An Ab can be a whole Ab molecule or an Ab multimer.

The term Ab also includes Ab conjugates (e.g., an Ab conjugated to a stabilizing protein, a label, or a therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art)). An Ab provided herein can, for example,

include a Fc domain or part of a Fc domain that is sufficient to mediate Ab-dependent cell-mediated cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC) in a mammal (e.g., a human), and/or is conjugated to a therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art). An Ab can be, e.g., a human or humanized IgG1, IgG2, IgG4, IgD, IgA, IgE, or IgM, and is preferably a human or humanized IgG3.

An antigen-binding fragment described herein can, e.g., include at least part of a Fc domain that is sufficient to mediate Ab-dependent cell-mediated cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC) in a mammal (e.g., a human) and/or is conjugated to a therapeutic agent (e.g., any of the therapeutic agents described herein or known in the art). Non-limiting examples of Ab fragments include Fab, Fab', F(ab')₂, single-chain Fvs (scFvs), Fv fragments, fragments containing either a variable light or variable heavy chain domain, diabodies, linear Abs, and multi-specific Abs formed from Ab fragments. Additional Ab fragments containing at least one camelid VHH domain or at least one cartilaginous fish Ig-NAR domain include mini-bodies, micro-Abs, subnano-Abs, and nano-Abs, and any of the other forms of Abs described in U.S. Patent Application Publication No. 2010/0092470.

The Abs or antigen-binding fragments thereof can be of any type (e.g., human or humanized IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., human or humanized IgG1 (e.g., IgG1a or IgG1b), IgG2 (e.g., IgG2a or IgG2b), IgG3 (e.g., IgG3a or IgG3b), IgG4 (e.g., IgG4a or IgG4b), IgA1, and IgA2 or subclass, although those with an Fc binding affinity for SpA is low (e.g., having a K_D of greater than 1×10^{-7} M, 1×10^{-6} M, 1×10^{-5} M, 1×10^{-4} M, or 1×10^{-3} M; or having a K_D greater than that of SpA for the Fc region of a human IgG1) under physiological conditions (e.g., phosphate buffered saline) (e.g., as determined using surface plasmon resonance using recombinant SpA) are preferred. An antigen binding fragment can be, e.g., an antigen-binding fragment of human or humanized IgG1 (e.g., IgG1a or IgG1b), IgG2 (e.g., IgG2a or IgG2b), IgG4 (e.g., IgG4a or IgG4b), IgD, IgA (e.g., IgA1 or IgA2), IgE, or IgM, and is preferably a fragment of human or humanized IgG3 (e.g., IgG3a or IgG3b). Amino acid mutations may be introduced into the constant region of these IgG subclasses. Amino acid mutations that can be introduced may be, for example, those that enhance binding to Fc receptors (as described in, e.g., *Proc. Natl. Acad. Sci. U.S.A.* 103(11): 4005-4010, 2006; *MAbs* 1(6): 572-579, 2009; US 2010/0196362; US 2013/0108623; US 2014/0171623; US 2014/0093496; and US 2014/0093959), or enhance or decrease binding to FcRn (as described in, e.g., *J. Biol. Chem.* 276(9): 6591-6604, 2001; *Int Immunol.* 18(12):1759-1769, 2006; and *J. Biol. Chem.* 281(33):23514-23524, 2006).

Two types of H chains are heterologously associated to produce a bispecific Ab. The knobs-into-holes technology (as described in, e.g., *J. Immunol. Methods* 248(1-2):7-15, 2001; and *J. Biol. Chem.* 285(27): 20850-20859, 2010), the electrostatic repulsion technology (as described in, e.g., WO 06/106905), the SEEDbody technology (as described in, e.g., *Protein Eng. Des. Sel.* 23(4):195-202, 2010), and such may be used for heterologous association of two types of H chains via a CH3 domain. Any of the antibodies described herein may be those with a modified or deficient sugar chain. Examples of antibodies having modified sugar chains include glycosylation-engineered antibodies (as described in, e.g., WO 99/54342), antibodies with defucosylated sugar chains (as described in, e.g., WO 00/61739, WO 02/31140, WO 06/067847, and WO 06/067913), and antibodies having a sugar chain with bisecting GlcNAc (as described in, e.g., WO

02/79255). Known examples of methods for producing sugar chain-deficient IgG antibodies include the method of introducing a mutation to asparagine at EU numbering position 297 in the heavy chain (*J. Clin. Pharmacol.* 50(5): 494-506, 2010), and the method of producing IgG using *E. coli* (*J. Immunol. Methods* 263(1-2):133-147, 2002; and *J. Biol. Chem.* 285(27):20850-20859, 2010). Furthermore, heterogeneity accompanying deletion of C-terminal lysine in IgG, and heterogeneity accompanying mispairing of disulfide bonds in the hinge region of IgG2 can be decreased by introducing amino acid deletions/substitutions (as described in, e.g., WO 09/041613). Any of the Abs or antigen-binding fragments described herein includes at least one (e.g., one, two, three, four, five, or six) amino acids (e.g., an added, inserted, or substituted amino acid, e.g., not within a CDR) that are not present in a corresponding human Ab. Any of the Abs or antigen-binding fragments described herein can also have at least one amino acid deleted (e.g., as compared to a corresponding human Ab), e.g., a deletion from the N- or C-terminus of a light or heavy chain, or a deletion of an amino acid from a constant domain (e.g., Fc domain).

SpA, or fragment thereof (e.g., at least 7, 8, 9, or 10 continuous amino acids of SEQ ID NO: 1 (e.g., starting at amino acid position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 of SEQ ID NO: 1), or all of SEQ ID NO: 1) can be used as an immunogen to generate Abs using standard techniques for polyclonal and monoclonal Ab preparation. Ab fragments can be generated from monoclonal Abs using well-known methods in the art.

An immunogen typically is used to prepare Abs by immunizing a suitable subject (e.g., rabbit, goat, mouse, or other mammal). An appropriate immunogenic preparation can contain, for example, a recombinantly expressed or a chemically synthesized polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent.

As an alternative to preparing monoclonal Ab-secreting hybridomas, a monoclonal Ab directed against a polypeptide can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an Ab phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP* Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening an Ab display library can be found in, for example, U.S. Pat. No. 5,223,409; WO 92/18619; WO 91/17271; WO 92/2079; WO 92/15679; WO 93/01288; WO 92/01047; WO 92/09690; WO 90/02809; Fuchs et al., *Bio/Technology* 9:1370-1372, 1991; Hay et al., *Hum. Antibod. Hybridomas* 3:81-85, 1992; Huse et al., *Science* 246:1275-1281, 1989; Griffiths et al., *EMBO J.* 12:725-734, 1993.

Additional methods for isolating and sequencing a human Ab (e.g., human IgG3) that binds specifically to a SpA epitope (e.g., an epitope located or defined within the polypeptide of SEQ ID NO: 1) are described in the Examples section below. Additional general methods for making Abs and antigen-binding fragments are described in U.S. Patent Application Publication No. 2011/0059085.

In some embodiments, Abs or antigen-binding fragments provided herein are human or humanized Abs (e.g., human or humanized IgG3 Abs). In some embodiments, a humanized Ab is a human Ab that has been engineered to contain at least one complementary determining region (CDR) present in a non-human Ab (e.g., a rat, mouse, rabbit, or goat Ab). In some

embodiments, a humanized Ab or fragment thereof can contain all three CDRs of a light chain of a human or non-human Ab that specifically binds to a SpA epitope (e.g., an epitope located or defined within the polypeptide of SEQ ID NO: 1). In some embodiments, the humanized Ab or fragment thereof can contain all three CDRs of a heavy chain of a human or non-human Ab that specifically binds to a SpA epitope (e.g., an epitope located or defined within the polypeptide of SEQ ID NO: 1). In some embodiments, the humanized Ab or fragment thereof can contain all three CDRs of a heavy chain and all three CDRs of a light chain of a non-human or human monoclonal Ab that specifically binds to a SpA epitope (e.g., an epitope located or defined within the polypeptide of SEQ ID NO: 1).

Abs of the invention may also include multimeric forms of Abs. For example, Abs of the invention may take the form of Ab dimers, trimers, or higher-order multimers of monomeric immunoglobulin molecules. Dimers of whole immunoglobulin molecules or of F(ab')₂ fragments are tetravalent, whereas dimers of Fab fragments or scFv molecules are bivalent. Individual monomers within an Ab multimer may be identical or different, i.e., they may be heteromeric or homomeric Ab multimers. For example, individual Abs within a multimer may have the same or different binding specificities.

Multimerization of Abs may be accomplished through natural aggregation of Abs or through chemical or recombinant linking techniques known in the art. For example, some percentage of purified Ab preparations (e.g., purified IgG1 molecules) spontaneously form protein aggregates containing Ab homodimers and other higher-order Ab multimers. Alternatively, Ab homodimers may be formed through chemical linkage techniques known in the art. For example, heterobifunctional crosslinking agents including, but not limited to, SMCC (succinimidyl 4-(maleimidomethyl)cyclohexane-1-carboxylate) and SATA (N-succinimidyl S-acetylthioacetate) (available, for example, from Pierce Biotechnology, Inc. (Rockford, Ill.)) can be used to form Ab multimers. An exemplary protocol for the formation of Ab homodimers is given in Ghetie et al. (*Proc. Natl. Acad. Sci. U.S.A.* 94: 7509-7514, 1997). Ab homodimers can be converted to Fab'₂ homodimers through digestion with pepsin. Another way to form Ab homodimers is through the use of the autophilic T15 peptide described in Zhao et al. (*J. Immunol.* 25:396-404, 2002).

Alternatively, Abs can be made to multimerize through recombinant DNA techniques. IgM and IgA naturally form Ab multimers through the interaction with the mature J chain polypeptide. Non-IgA or non-IgM molecules, such as IgG molecules, can be engineered to contain the J chain interaction domain of IgA or IgM, thereby conferring the ability to form higher order multimers on the non-IgA or non-IgM molecules (see, for example, Chintalacharuvu et al., *Clin. Immunol.* 101:21-31, 2001, and Frigerio et al., *Plant Physiol.* 123:1483-1494, 2000). IgA dimers are naturally secreted into the lumen of mucosa-lined organs. This secretion is mediated through interaction of the J chain with the polymeric IgA receptor (pIgR) on epithelial cells. If secretion of an IgA form of an Ab (or of an Ab engineered to contain a J chain interaction domain) is not desired, it can be greatly reduced by expressing the Ab molecule in association with a mutant J chain that does not interact well with pIgR (Johansen et al., *J. Immunol.*, 167:5185-192, 2001). ScFv dimers can also be formed through recombinant techniques known in the art; an example of the construction of scFv dimers is given in Goel et al. (*Cancer Res.* 60:6964-71, 2000). Ab multimers may be purified using any suitable method known in the art, including, but not limited to, size exclusion chromatography.

Any of the Abs or antigen-binding fragments described herein may be conjugated to a stabilizing molecule (e.g., a molecule that increases the half-life of the Ab or antigen-binding fragment thereof in a feline or in solution). Non-limiting examples of stabilizing molecules include: a polymer (e.g., a polyethylene glycol) or a protein (e.g., serum albumin, such as feline serum albumin). Any of the Abs or antigen-binding fragments described herein may be conjugated to a label (e.g., a fluorophore, radioisotope, or luminescent molecule) or a therapeutic agent (e.g., a cytotoxic agent or a radioisotope). Exemplary methods for attaching a label or therapeutic agent to an Ab are described in U.S. Patent Application No. 2013/0224228. Non-limiting examples of cytotoxic agents include agent known to induce cell death of microbe (e.g., a gram positive bacterium, such as *Staphylococcus aureus*). Non-limiting examples of cytotoxic agents that can be conjugated to any of the Abs or antigen-binding fragments provided herein include: linezolid, erythromycin, mupirocin, ertapenem, doripenem, imipenem, cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cephalothin, cephalixin, ceflacor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, clindamycin, lincomycin, daptomycin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, penicillin G, temocillin, ticarcillin, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilamide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole, sulfonamidochrysoidine, demeclocycline, doxycycline, minocycline, oxytetracycline, and tetracycline.

For example, an Ab (e.g., a human or humanized monoclonal IgG3) or antigen-binding fragment thereof (e.g., a fragment of a human or humanized monoclonal IgG3) provided herein that specifically binds to SpA can include:

(i) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 2, 3, and 4, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 7, 8, and 9, respectively;

(ii) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 12, 13, and 14, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 17, 18, and 19, respectively;

(iii) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 22, 23, and 24, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 27, 28, and 29, respectively;

(iv) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 32, 33, and 34, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 37, 38, and 39, respectively;

(v) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 42, 43, and 44, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 47, 48, and 49, respectively;

(vi) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 52, 53, and 54, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 57, 58, and 59, respectively;

(vii) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 62, 63, and 64, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 67, 68, and 69, respectively; or

(viii) a heavy chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 72, 73, and 74, respectively, and/or a light chain comprising a CDR1, CDR2, and CDR3 of SEQ ID NOs: 77, 78, and 79, respectively.

In some examples, any of the Abs provided herein has: an Ab heavy chain including SEQ ID NO: 6 and/or a light chain including SEQ ID NO: 11; an Ab heavy chain including SEQ ID NO: 16 and/or a light chain including SEQ ID NO: 21; an Ab heavy chain including SEQ ID NO: 26 and/or a light chain including SEQ ID NO: 31; an Ab heavy chain including SEQ ID NO: 36 and/or a light chain including SEQ ID NO: 41; an Ab heavy chain including SEQ ID NO: 46 and/or a light chain including SEQ ID NO: 51; an Ab heavy chain including SEQ ID NO: 56 and/or a light chain including SEQ ID NO: 61; an Ab heavy chain including SEQ ID NO: 66 and/or a light chain including SEQ ID NO: 71; or an Ab heavy chain including SEQ ID NO: 76 and/or a light chain including SEQ ID NO: 81.

In additional examples, any of the Abs (e.g., a human or humanized IgG3) or antigen-binding fragments (e.g., an antigen-binding fragment of a human or humanized IgG3) provided herein might bind to SpA with a K_D of less than 1×10^{-10} M (e.g., less than 1×10^{-11} M or less than 1×10^{-12} M) and/or be capable of displacing human Abs (e.g., one or more of IgG1, IgG2, and IgG4) bound to SpA, where the antigen or antigen-binding fragment has a set of six CDRs has no more than one, two, three, four, five, or six total amino acid substitutions (e.g., conservative amino acid substitutions) in the set (the entire set) of six CDRs selected from the group consisting of:

- (i) SEQ ID NOs: 2, 3, 4, 7, 8, and 9;
- (ii) SEQ ID NOs: 12, 13, 14, 17, 18, and 19;
- (iii) SEQ ID NOs: 22, 23, 24, 27, 28, and 29;
- (iv) SEQ ID NOs: 32, 33, 34, 37, 38, and 39;
- (v) SEQ ID NOs: 42, 43, 44, 47, 48, and 49;
- (vi) SEQ ID NOs: 52, 53, 54, 57, 58, and 59;
- (vii) SEQ ID NOs: 62, 63, 64, 67, 68, and 69; or
- (viii) SEQ ID NOs: 72, 73, 74, 77, 78, and 79.

For example, an Ab (e.g., a human or humanized IgG3) or an antigen-binding fragment (e.g., an antigen-binding fragment of a human or humanized IgG3) provided herein can include a set of six CDRs that has no more than one, two, three, or four total amino acid substitutions in the set (the entire set) of six CDRs of SEQ ID NOs: 2, 3, 4, 7, 8, and 9. For example, an Ab (e.g., a human or humanized IgG3) or antigen-binding fragment (e.g., an antigen binding fragment of a human or humanized IgG3) provided herein can comprise or consist of:

- (i) a set of six CDRs of SEQ ID NOs: 2, 3, 4, 7, 8, and 9;
- (ii) a set of six CDRs of SEQ ID NOs: 12, 13, 14, 17, 18, and 19;
- (iii) a set of six CDRs of SEQ ID NOs: 22, 23, 24, 27, 28, and 29;
- (iv) a set of six CDRs of SEQ ID NOs: 32, 33, 34, 37, 38, and 39;
- (v) a set of six CDRs of SEQ ID NOs: 42, 43, 44, 47, 48, and 49;
- (vi) a set of six CDRs of SEQ ID NOs: 52, 53, 54, 57, 58, and 59;
- (vii) a set of six CDRs of SEQ ID NOs: 62, 63, 64, 67, 68, and 69; or
- (viii) a set of six CDRs of SEQ ID NOs: 72, 73, 74, 77, 78, and 79.

In additional examples, an Ab (e.g., a human or humanized monoclonal IgG3) or antigen-binding fragment (e.g., an antigen-binding fragment of a human or humanized IgG3) provided herein that specifically binds to SpA includes a variable domain selected from the group of: (i) a variable domain comprising or consisting of SEQ ID NO: 5; (ii) a variable domain comprising or consisting of SEQ ID NO: 10; (iii) a variable domain comprising or consisting of SEQ ID NO: 15; (iv) a variable domain comprising or consisting of SEQ ID NO: 20; (v) a variable domain comprising or consisting of SEQ ID NO: 25; (vi) a variable domain comprising or consisting of SEQ ID NO: 30; (vii) a variable domain comprising or consisting of SEQ ID NO: 35; (viii) a variable domain comprising or consisting of SEQ ID NO: 40; (ix) a variable domain comprising or consisting of SEQ ID NO: 45; (x) a variable domain comprising or consisting of SEQ ID NO: 50; (xi) a variable domain comprising or consisting of SEQ ID NO: 55; (xii) a variable domain comprising or consisting of SEQ ID NO: 60; (xiii) a variable domain comprising or consisting of SEQ ID NO: 65; (xiv) a variable domain comprising or consisting of SEQ ID NO: 70; (xv) a variable domain comprising or consisting of SEQ ID NO: 75; or (xvi) a variable domain comprising or consisting of SEQ ID NO: 80. For example, an Ab (e.g., a human or humanized monoclonal IgG3) or antigen-binding fragment (e.g., an antigen-binding fragment of a human or humanized IgG3) can include (i) a variable domain comprising or consisting of SEQ ID NO: 5 and/or a variable domain comprising or consisting of SEQ ID NO: 10; (ii) a variable domain comprising or consisting of SEQ ID NO: 15 and/or a variable domain comprising or consisting of SEQ ID NO: 20; (iii) a variable domain comprising or consisting of SEQ ID NO: 25 and/or a variable domain comprising or consisting of SEQ ID NO: 30; (iv) a variable domain comprising or consisting of SEQ ID NO: 35 and/or a variable domain comprising or consisting of SEQ ID NO: 40; (v) a variable domain comprising or consisting of SEQ ID NO: 45 and/or a variable domain comprising or consisting of SEQ ID NO: 50; (vi) a variable domain comprising or consisting of SEQ ID NO: 55 and/or a variable domain comprising or consisting of SEQ ID NO: 60; (vii) a variable domain comprising or consisting of SEQ ID NO: 65 and/or a variable domain comprising or consisting of SEQ ID NO: 70; or a variable domain comprising or consisting of SEQ ID NO: 75 and/or a variable domain comprising or consisting of SEQ ID NO: 80.

Some embodiments of any of the Abs (e.g., human or humanized monoclonal IgG3) or antigen-binding fragments (e.g., an antigen-binding fragment of a human or humanized IgG3) described herein have one or more (e.g., one, two, three, or four) of the following activities: specifically bind to SpA in a strain of MRSA; specifically bind to an epitope defined by SEQ ID NO: 1; bind to SpA with a K_D of less than 1×10^{-10} M (e.g., less than 1×10^{-11} M or less than 1×10^{-12}); and displace human Abs bound to SpA in the cell wall of a *Staphylococcus aureus* bacterium (e.g., a MRSA bacterium).

Pharmaceutical Compositions

Provided herein are pharmaceutical compositions containing at least one pharmaceutically acceptable carrier (e.g., a non-natural pharmaceutically acceptable carrier) and at least one (e.g., two, three, or four) of any of the Abs or antigen-binding fragments provided herein. Non-limiting examples of pharmaceutically acceptable carriers include sterilized water, physiological saline, stabilizers, excipients, antioxidants (e.g., ascorbic acid), buffers (e.g., phosphate, citrate, histidine, and other organic acids), antiseptics, surfactants

(e.g., PEG and Tween), chelating agents (e.g., EDTA or EGTA), and binders. Additional examples of pharmaceutically acceptable carriers also include low-molecular-weight polypeptides, proteins (e.g., serum albumin and gelatin), amino acids (e.g., glycine, glutamine, asparagine, glutamic acid, aspartic acid, methionine, arginine, and lysine), sugars and carbohydrates (e.g., polysaccharides and monosaccharides), and sugar alcohols (e.g., mannitol and sorbitol). When preparing an aqueous solution for injection, physiological saline and isotonic solutions comprising glucose and other adjuvants such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride may be used, and if necessary, in combination with appropriate solubilizers, such as alcohol (e.g., ethanol), polyalcohols (e.g., propylene glycol and PEG), and non-ionic surfactants (e.g., polysorbate 80, polysorbate 20, poloxamer 188, and HCO-50). By mixing hyaluronidase into the formulation, a larger fluid volume can be administered subcutaneously (see, e.g., *Expert. Opin. Drug. Deliv.* 4(4): 427-440, 2007).

The Abs and antigen-binding fragments provided herein may, e.g., be encapsulated in microcapsules (e.g., those made of hydroxymethylcellulose, gelatin, and poly(methyl-metacrylate)), or incorporated as components of colloidal drug delivery systems (e.g., liposomes, albumin microspheres, microemulsion, nanoparticles, and nanocapsules) (see, for example, "Remington's Pharmaceutical Science 16th edition", Oslo Ed. (1980)). Methods for preparing the pharmaceutical compositions as controlled-release pharmaceutical agents are also well-known, and such methods may be applied to the Abs and antigen-binding fragments of the present invention (see, e.g., Langer et al., *J. Biomed. Mater. Res.* 15: 267-277, 1981; Langer, *Chemtech.* 12: 98-105, 1982; U.S. Pat. No. 3,773,919; European Patent Application Publication No. EP 58,481; Sidman et al., *Biopolymers* 22: 547-556, 1983; and EP 133,988).

The pharmaceutical compositions provided herein can be formulated for intravenous, intraarterial, intradermally, subcutaneous, intramuscular, intraperitoneal, or oral administration.

The dose of a pharmaceutical composition of the present invention may be appropriately determined by considering the dosage form, method of administration, patient age and body weight, symptoms of the patient, severity of the SA infection, or level of risk of SA infection. Generally, the daily dose for an adult can be, e.g., between 0.1 mg to 10,000 mg at once or in several portions. The dose can be, e.g., 0.2 to 10,000 mg/day (e.g., 1-10 g/day, 2-8 g/day, 1-5 g/day, 0.5 to 2.5 g/day, 0.5 to 500 mg/day, 1 to 300 mg/day, 3 to 100 mg/day, or 5 to 50 mg/day). These doses may vary, depending on the patient body weight and age, and the method of administration; however, selection of suitable dosage is well within the purview of those skilled in the art. Similarly, the dosing period may be appropriately determined depending on the therapeutic progress.

Any of the pharmaceutical compositions provided herein can further include one or more additional antimicrobial agents. Non-limiting examples of such antimicrobial agents include: linezolid, erythromycin, mupirocin, ertapenem, doripenem, imipenem, cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalothin, cephalixin, ceflacor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, televancin, clindamycin, lincomycin, daptomycin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin

G, penicillin V, piperacillin, penicillin G, temocillin, ticarcillin, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilamide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole, sulfonamidochrysoidine, demeclocycline, doxycycline, minocycline, oxytetracycline, and tetracycline.

Methods of Treating a Subject Having a *S. aureus* Infection or Reducing the Risk of Developing a *S. Aureus* Infection in a Subject

Also provided are methods of treating a subject having a SA infection (e.g., MRSA infection, SA bacteremia, SA skin infection, SA mastitis, SA cellulitis or folliculitis, or SA-involved wound infections, abscesses, osteomyelitis, endocarditis, pneumonia, septic shock, food poisoning, or toxic shock syndrome) that include administering to a subject (e.g., a human being or another mammal such as a bovine, ovine, canine, feline, equine, hircine, leporine, porcine, or avian) in need thereof a therapeutically effective amount of at least one of any of the pharmaceutical compositions provided herein or at least one of any of the Abs or antigen-binding fragments provided herein. In some examples, the subject has been diagnosed or identified as having a SA infection (e.g., a MRSA infection). Some embodiments further include (prior to the administering step) a step of diagnosing, identifying, or selecting subject having or as having a SA infection (e.g., a MRSA or VRSA infection). In some examples, the SA infection is a nosocomial infection. In some examples, the subject has previously been treated with an antibacterial treatment and the prior treatment was unsuccessful.

Also provided are methods of reducing a subject's risk of developing a SA infection (e.g., a MRSA infection) that include administering to the subject an effective amount of at least one of any of the pharmaceutical compositions provided herein or at least one of any of the Abs or antigen-binding fragments provided herein. In some embodiments, the SA infection is a nosocomial infection. Some embodiments further include prior to administering selecting or identifying a subject as having an increased risk of developing a SA infection (e.g., a MRSA infection). For example, the subject can be a medical professional (e.g., a physician, a nurse, a laboratory technician, or a physician's assistant) (e.g., a medical professional in physical contact with a subject having a SA infection (e.g., a MRSA infection)). A subject in these methods can also be a subject admitted to a hospital or inpatient treatment (e.g., a nursing home) that contains (has admitted) at least one other subject having a SA infection (e.g., a MRSA infection). The subject may be a hospitalized patient such as one in the intensive care unit, an immunocompromised patient, and a patient who has undergone or will undergo a surgical procedure (e.g., cardiac surgery).

In any of the methods provided herein, the subject can be a male or a female. For example, the subject can be an infant, a toddler, an adolescent, a teenager, or an adult (e.g., at least 18 years old, at least 20 years old, at least 25 years old, at least 30 years old, at least 35 years old, at least 40 years old, at least 45 years old, at least 50 years old, at least 55 years old, at least 60 years old, at least 65 years old, at least 70 years old, at least 75 years old, at least 80 years old, at least 85 years old, at least 90 years old, at least 95 years old, or at least 100 years old). In some examples, the subject has a suppressed or weakened immune system (e.g., humoral or cellular immune system).

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In some examples, the at least one pharmaceutical composition provided herein or at least one Ab or antigen-binding fragment provided herein is administered by intravenous, intraarterial, intradermally, subcutaneous, intramuscular, intraperitoneal, or oral administration. For example, in methods of reducing the risk of developing a SA infection, the subject is administered at least one of the pharmaceutical compositions provided herein or at least one of the Abs or antigen-binding fragments provided herein prior to or shortly after coming into physical contact with a subject identified, diagnosed, having, or suspected of having SA infection (e.g., a MRSA infection).

In any of the methods described herein, the subject is administered at least one (e.g., two, three, four, five, six, seven, eight, nine, or ten) dose(s) of any of the pharmaceutical compositions provided herein or at least one (e.g., two, three, four, five, six, seven, eight, nine, or ten) dose(s) of any of the Abs or antigen-binding fragments provided herein. A subject can be administered two or more doses of any of the pharmaceutical compositions or at least two doses of any of the Abs or antigen-binding fragments provided herein at a frequency of at least one dose every month (e.g., at least two doses every month, at least three doses every month, at least four doses every month, at least one dose a week, at least two doses a week, at least three doses a week, at least four doses a week, at least five doses a week, at least one dose a day, at least two doses a day, or at least three doses a day).

Some embodiments further include co-administering to a subject and Ab described herein and one or more additional antimicrobial agents. Non-limiting examples of such antimicrobial agents include: linezolid, erythromycin, mupirocin, ertapenem, doripenem, imipenem, cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalothin, cephalixin, ceflaxor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, televancin, clindamycin, lincomycin, daptomycin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, penicillin G, temocillin, ticarcillin, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilamide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole, sulfonamidochrysoidine, demeclocycline, doxycycline, minocycline, oxytetracycline, and tetracycline. Additional examples of therapeutic agents that can be included in any of the pharmaceutical compositions provided herein are one or more Abs described in U.S. Patent Application Publication No. 2011/0059085.

Kits

Also provided herein are kits containing at least one (e.g., two, three, four, or five) of any of the Abs or antigen-binding fragments provided herein. In some examples, the kits can contain a recombinant SpA or a peptide comprising or consisting of SEQ ID NO: 1 or an antigenic fragment of SEQ ID NO: 1 (e.g., at least 7 contiguous amino acids of SEQ ID NO: 1 (e.g., starting at amino acids position 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 of SEQ ID NO: 1)). In some examples, the at least one Ab or antigen-binding fragment is attached to a solid substrate (e.g., a well, a chip, a film, a bead, or a chromatog-

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raphy resin). Such kits can include commercial packaging and/or printed information about the Abs and methods of their use.

EXAMPLES

Example 1

Generation of Human Abs that Specifically Bind to SpA and Displace Human IgG Immunoglobulins Bound to SpA Via their Fc Region

Human IgG3 Abs that bind to a SpA epitope were generated as described below. Five synthesized peptides covering the IgG-binding and Xr repeat sequences in SpA were used to screen for anti-peptide Abs in the blood of 311 healthy adult volunteers. The five synthesized peptides from SpA used for screening had the sequences indicated as: SEQ ID NOs: 82, 83, 84, 85, and 1 (peptides 1, 2, 3, 4, and 5, respectively). About 4% of the healthy subjects had greater than 10-fold higher levels of anti-peptide (anti-SpA) Abs over background (hereafter called "positive donors") as determined using an enzyme-linked immunosorbent assay (ELISA). Plasma from these positive donors was obtained and used to isolate true human Abs that bind specifically to a peptide covering the IgG-binding and Xr repeat sequences of SpA using the methods described in U.S. Patent Application Publication No. 2013/0018173. In sum, Abs of interest were isolated using antigen affinity chromatography, and de novo sequenced using mass spectrometry. In parallel, the Abs were isotyped using a human isotyping kit.

One of the isolated Abs was identified as being in the VH3 subfamily and having an IgG2 heavy chain and VK1 light chain. B-cells were isolated from the donor blood using a kit obtained from STEMCELL Technologies, Inc. Their RNA was extracted using a Trizol extraction protocol, and cDNA was generated using SuperScript III. Leader-specific primers were used to amplify the corresponding heavy and light chains of the Ab and a "directed" ScFv library was generated. The library was panned against wildtype SpA antigen for 7 rounds. The clones were screened using direct and sandwich ELISA with wildtype SpA. The selected clones were sequenced, and the heavy and light chains were cloned into vectors with an IgG3 constant (Fc) region (one that lacks the SpA recognition site in the Fab regions). The vectors were transfected into CHO cell lines, and high producing clones were picked. The purified Abs were tested for anti-SpA activity. The clones were scaled up for large-scale production, and the produced Abs were purified and used for further analyses. Examples of eight such Abs are described below:

PA8-G3 Ab

Heavy chain variable domain of SEQ ID NO: 5.

Heavy chain CDRs 1, 2, and 3 of SEQ ID NOs: 2, 3, and 4, respectively.

Heavy chain of SEQ ID NO: 6.

Light chain variable domain of SEQ ID NO: 10.

Light chain CDRs 1, 2, and 3 of SEQ ID NO: 7, 8, and 9, respectively.

Light chain of SEQ ID NO: 11.

PA4-G3 Ab

Heavy chain variable domain of SEQ ID NO: 15.

Heavy chain CDRs 1, 2, and 3 of SEQ ID NOs: 12, 13, and 14, respectively.

Heavy chain of SEQ ID NO: 16.

Light chain variable domain of SEQ ID NO: 20.

Light chain CDRs 1, 2, and 3 of SEQ ID NOs: 17, 18, and 19, respectively.

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Light chain of SEQ ID NO: 21.
 PA7.2-G3 Ab
 Heavy chain variable domain of SEQ ID NO: 25.
 Heavy chain CDRs 1, 2, and 3 of SEQ ID NOs: 22, 23, and 24, respectively.
 Heavy chain of SEQ ID NO: 26.
 Light chain variable domain of SEQ ID NO: 30.
 Light chain CDRs 1, 2, and 3 of SEQ ID NOs: 27, 28, and 29, respectively.
 Light chain of SEQ ID NO: 31.
 PA15-G3 Ab
 Heavy chain variable domain of SEQ ID NO: 35.
 Heavy chain CDRs 1, 2, and 3 of SEQ ID NOs: 32, 33, and 34, respectively.
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 Heavy chain of SEQ ID NO: 46.
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 Light chain CDRs 1, 2, and 3 of SEQ ID NOs: 47, 48, and 49, respectively.
 Light chain of SEQ ID NO: 51.
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 Heavy chain variable domain of SEQ ID NO: 55.
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 Heavy chain of SEQ ID NO: 56.
 Light chain variable domain of SEQ ID NO: 60.
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 Light chain of SEQ ID NO: 61.
 PA32-G3 Ab
 Heavy chain variable domain of SEQ ID NO: 65.
 Heavy chain CDRs 1, 2, and 3 of SEQ ID NOs: 62, 63, and 64, respectively.
 Heavy chain of SEQ ID NO: 66.
 Light chain variable domain of SEQ ID NO: 70.
 Light chain CDRs 1, 2, and 3 of SEQ ID NO: 67, 68, and 69, respectively.
 Light chain of SEQ ID NO: 71.
 PA37-G3 Ab
 Heavy chain variable domain of SEQ ID NO: 75.
 Heavy chain CDRs 1, 2, and 3 of SEQ ID NOs: 72, 73, and 74, respectively.
 Heavy chain of SEQ ID NO: 76.
 Light chain variable domain of SEQ ID NO: 80.
 Light chain CDRs 1, 2, and 3 of SEQ ID NOs: 77, 78, and 79, respectively.
 Light chain of SEQ ID NO: 81.

A set of experiments was performed to determine whether the PA8-G3 Ab would be capable of binding to SpA on the cell wall of SA. In these experiments, SA strains ATCC #25923 or clinical isolate 00X were incubated either with (i) biotinylated PA8-G3, and then streptavidin-APC to fluorescently quantify the amount of biotin-PA-G3 bound on the SA surface (FIG. 2) or (ii) purified unlabeled PA8-G3 Ab, followed by biotinylated recombinant Fc γ receptor 1, and then streptavidin-APC to fluorescently quantify the amount of PA8-G3 bound to the SA surface that would lead to phagocytosis (i.e., have free Fc regions available to bind the recombinant Fc γ receptor 1) (FIG. 3). An anti-interleukin-1 α Ab

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(MABp1) was used as a negative control in these experiments. The data in FIG. 2 show that PA8-G3 binds to SpA in the cell wall of SA and the data in FIG. 3 indicate that the bound PA8-G3 Ab had its Fc regions available to interact with FcR suggesting that the Ab would be able to mediate opsonophagocytosis of SA in human subjects (as opposed to having its Fc regions bound to SpA and not able to engage FcRs and therefore mediate opsonophagocytosis of the bacteria).

A further set of experiments was performed to test whether binding of PA8-G3 Ab to the surface of SA would be recognized by the Fc γ receptors on phagocytes. In these experiments, two different strains of pH-rodo-green labeled *S. aureus* (clinical isolate 00X or ATCC #25923) were incubated with either unlabeled PA8-G3 Ab or a control Ab (MABp1), and then incubated with differentiated HL-60 cells. The resulting fluorescence of the HL-60 cells was determined using fluorescence-assisted cell sorting (FACS). The data show that PA8-G3 binds to the cell wall of both SA strains and mediates phagocytosis through the Fc γ receptors on the surface of HL-60 cells (FIG. 4). The successful phagocytosis by differentiated HL-60 cells of *S. aureus* bound to PA8-G3 was also evident from fluorescence microscopy experiments.

Surface plasmon resonance was used to determine the binding kinetics of PA8-G3 to SpA. In these experiments, PA8-G3 Ab was immobilized using anti-human capture sensor and commercial wildtype SpA. These data show that PA8-G3 has a K_D of 5.38 pM. This affinity is approximately 1000-fold higher than the nanomolar affinity of human serum IgG1, IgG2, and IgG4 to SpA.

An additional set of experiments was performed to determine whether PA8-G3 Ab would be able to successfully compete for binding to SpA with human IgG bound to SpA through their Fc receptor. In these experiments, two different *S. aureus* strains were pre-incubated with human sera (which contains a high concentration of Igs which bind SpA via their Fc regions) for 15 minutes prior to incubation with biotinylated PA8-G3 Ab or biotinylated MABp1-IgG3 Ab (isotype-matched negative control), then treated with streptavidin APC, and then fluorescence was determined by flow cytometry. The data show that PA8-G3 Ab was able to bind SpA having human IgG Abs bound to SpA by their Fc domain (FIG. 5).

In another set of experiments, PA8-G3 antibody was shown to compete with MABp1-IgG1 (which binds SpA via its Fc region) binding on SpA-coated beads. Pre-incubating the SpA beads with PA8-G3 reduced later added MABp1-IgG1 binding by 80.3%. Conversely, with SpA beads pre-incubated with MABp1-IgG1, later added PA8-G3 bound greater than >30% of the SpA beads surfaces within 15 minutes, whereas later added MABp1-IgG3 (isotype-matched negative control having the Fab of MABp1 and a human IgG3 Fc) did not significantly bind to SpA beads pre-incubated with MABp1-IgG1.

An additional set of experiments was performed to test the ability of additional anti-SpA Abs to promote phagocytosis of SA by differentiated HL-60 cells. In these experiments, differentiated HL-60 cells were co-incubated with pH-rodo-green labeled *S. aureus* and one of the following Abs: PA7.2-G3, PA4-G3, PA8-G3, PA15-G3, PA21-G3, PA27-G3, PA32-G3, PA37-G3, or MABp1. MABp1 was used as a negative control in these experiments. The data show that all of the tested anti-SpA Abs were able to promote opsonization and phagocytosis of *S. aureus* by differentiated HL-60 cells (FIG. 6).

Additional Bio-Layer Interferometry (using done using a ForteBio Octet Red 96 instrument) experiments were performed to determine the K_D of seven additional anti-SpA Abs

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(performed using 20 nM antigen). The resulting data showed that PA7.2-G3 has a K_D of less than 1×10^{-12} M, PA4-G3 has a K_D of 5.38×10^{-12} M, PA15-G3 has a K_D of less than 1×10^{-12} M, PA21-G3 has a K_D of less than 1×10^{-12} M, PA27-G3 has a K_D of less than 1×10^{-12} M, PA32-G3 has a K_D of less than 1×10^{-12} M, and PA37-G3 has a K_D of less than 1×10^{-12} M.

In sum, the data show that the Abs provided herein can bind with very high affinity to SpA in the cell wall of SA, promote phagocytosis by immune cells, and are capable of doing so in the presence of human IgGs bound to SpA by their Fc domain.

Example 2

In Vivo Survival Study of Monoclonal Antibody PA8 in Mice Bacteremia/Sepsis Model

Survival of mice from *S. aureus* bacteremia was examined using prophylactic doses of PA8 (the monoclonal antibody termed PA8-G3 described in Example 1).

Female Balb/C mice (6-8 weeks of age) were purchased from Charles River Laboratory, NIH, Maryland. Upon arrival, the mice were examined, group housed (10/cage) in cages with absorbent bedding. All mice were placed under the required husbandry standards found in the NIH Guide for the Care and Use of Laboratory Animals.

The protective efficacy of PA8 was investigated in the SA sepsis model induced by intravenous injections (i.v.) of 2×10^7 CFUs of MRSA strain NR-46223. Mice were treated intravenously with PA8 at specific doses (5 mg or 10 mg) 3 h prior to MRSA infection or two doses of 5 mg each at day 0 and 3. Control mice were treated with formulation buffer only. The mice were followed for 10 days (twice per day) at which point all remaining mice were sacrificed.

Three hours after the PA8/formulation buffer (0.1 ml) i.v. administration, the mice were challenged with a single intravenous (IV) injection of *S. aureus* strain NR-46223 (2×10^7 CFU in 0.1 ml). One set of mice was given two doses of 5 mg each at day 0 and 3. Significant differences in the relative survival times between treatment groups were detected. Referring to FIG. 7A-D, passive administration of single dose of 5 mg (A) or 10 mg (B), or two doses of 5 mg at day 0 & day 3 (C), of mAb PA8 (intravenously) enhances the survival of BALB/c mice significantly higher than formulation buffer

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treatment in dose dependent manner (10 mice per group) with *Staphylococcus aureus* sepsis (induced by intravenous injection of 2×10^7 colony-forming units of methicillin-resistant *S. aureus* strain NR-46223). Section (D) shows the survival using all different treatment in one graph. Fifty percent ($\frac{5}{10}$) of the mice survived that received 5 mg of Mab PA8 ($p=0.016$), sixty percent that received two doses of 5 mg each ($p=0.09$), and seventy percent ($\frac{7}{10}$) that received 10 mg of mAb PA8 ($p=0.003$) compared to 10% ($\frac{1}{10}$) of mice that received formulation buffer ($\frac{1}{10}$) survived the bacterial challenge with *S. aureus* NR-46223. Statistical analysis of the animal data was conducted using Kaplan-Meier Survival Analysis with a Mantel-Cox (logrank) test. These results clearly indicate that PA8 provides a significant level of protection against lethal infection with *S. aureus* MRSA strain.

Example 3

Female Balb/C mice (10 per group) from Charles River Laboratory were injected with 0.5 mg of vancomycin via intraperitoneal route, along with different sub-optimal doses of PA8-G3 (0 mg, 2.5 mg and 5 mg via intravenous route) two hours prior to infection with MRSA (NR 46223 at 3×10^7 CFU i.v.). The mice were observed for 14 days. Referring to FIGS. 8A-C, at day 14, only 10% of the PBS treated mice survived, 30% of the vancomycin treated mice survived. However, when 2.5 mg of PA8-G3 was injected along with vancomycin treatment, then 60% of the animals survived ($p=0.027$), and when 5 mg of PA8-G3 was injected with vancomycin, then 60% of the animals survived and those mice that died lived longer than the lower dosage ($p=0.016$). This data indicates that sub-efficacious doses of PA8-G3 can rescue animals from SA mediated bacteremia, when co-treated with sub-optimal dose of vancomycin. Statistical analysis of the animal data was conducted using Kaplan-Meier Survival Analysis with a Mantel-Cox (logrank) test.

Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

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<220> FEATURE:

<223> OTHER INFORMATION: Antigenic Peptide #5

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Lys Pro Gly Lys
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<212> TYPE: PRT

<213> ORGANISM: *Homo sapiens*

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<220> FEATURE:
<223> OTHER INFORMATION: PA8-G3 Heavy Chain CDR1

<400> SEQUENCE: 2

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<210> SEQ ID NO 3
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA8-G3 Heavy Chain CDR2

<400> SEQUENCE: 3

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Gly

<210> SEQ ID NO 4
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA8-G3 Heavy Chain CDR3

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<210> SEQ ID NO 5
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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: PA8-G3 Heavy Chain Variable Domain

<400> SEQUENCE: 5

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1             5             10             15

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20            25            30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35            40            45

Ser Ser Ile Thr Gly Ser Gly Arg Ser Thr Phe Tyr Ala Asp Ser Val
50            55            60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Thr Asn Thr Leu Ser
65            70            75            80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85            90            95

Ala Arg Ser Pro Ala Asp Ile Val Thr Gly Tyr Tyr Pro Trp Trp Phe
100           105           110

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115           120           125

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		20						25					30			
Gly	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
		35					40					45				
Ser	Ser	Ile	Thr	Gly	Ser	Gly	Arg	Ser	Thr	Phe	Tyr	Ala	Asp	Ser	Val	
	50					55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Thr	Asn	Thr	Leu	Ser	
65					70				75					80		
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
			85						90					95		
Ala	Arg	Ser	Pro	Ala	Asp	Ile	Val	Thr	Gly	Tyr	Tyr	Pro	Trp	Trp	Phe	
		100						105					110			
Asp	Leu	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	
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Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	
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Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	
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Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	
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Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	
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225				230						235					240	
Glu	Pro	Lys	Ser	Cys	Asp	Thr	Pro	Pro	Pro	Cys	Pro	Arg	Cys	Pro	Glu	
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Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	
	370					375					380					
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	
385				390						395					400	
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	
			405					410						415		

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Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 420 425 430

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 435 440 445

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 450 455 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe Ser Cys
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 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
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<210> SEQ ID NO 8
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 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA8-G3 Light Chain CDR2

<400> SEQUENCE: 8

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<210> SEQ ID NO 9
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 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
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<400> SEQUENCE: 9

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 1 5

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 <220> FEATURE:
 <223> OTHER INFORMATION: PA8-G3 Light Chain Variable Domain

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Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
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Ala Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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1 5 10 15

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20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
35 40 45

Ala Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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Phe Asn Arg Gly Glu Cys
210

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<212> TYPE: PRT
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<223> OTHER INFORMATION: PA4-G3 Heavy Chain CDR1

<400> SEQUENCE: 12

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<213> ORGANISM: Homo sapiens

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<223> OTHER INFORMATION: PA4-G3 Heavy Chain CDR2

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Gly

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<223> OTHER INFORMATION: PA4-G3 Heavy Chain CDR3

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20           25           30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35           40           45

Ser Ala Ile Thr Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50           55           60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65           70           75           80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85           90           95

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100          105          110

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115

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20           25           30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35           40           45

Ser Ala Ile Thr Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50           55           60

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Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	305	310	315	320
Gln	Phe	Lys	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	325	330	335	
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Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	370	375	380	
Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	385	390	395	400
Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	405	410	415	
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Ser	Gly	420	425	430	
Gln	Pro	Glu	Asn	Asn	Tyr	Asn	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	435	440	445	
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	450	455	460	
Gln	Gln	Gly	Asn	Ile	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	465	470	475	480
Asn	Arg	Phe	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						

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485

490

<210> SEQ ID NO 17
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA4-G3 Light Chain CDR1

<400> SEQUENCE: 17

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
 1 5 10

<210> SEQ ID NO 18
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA4-G3 Light Chain CDR2

<400> SEQUENCE: 18

Ala Ala Ser Ser Leu Gln Ser
 1 5

<210> SEQ ID NO 19
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA4-G3 Light Chain CDR3

<400> SEQUENCE: 19

Gln Gln Ser Tyr Ser Thr Pro Trp Thr
 1 5

<210> SEQ ID NO 20
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA4-G3 Light Chain Variable Domain

<400> SEQUENCE: 20

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
 20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Trp
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 21
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA4-G3 Light Chain

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<400> SEQUENCE: 21

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 22

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA7.2-G3 Heavy Chain CDR1

<400> SEQUENCE: 22

Asn Tyr Ala Met Ser
1 5

<210> SEQ ID NO 23

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA7.2-G3 Heavy Chain CDR2

<400> SEQUENCE: 23

Thr Ile Ser Gly Ser Asp Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 24

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

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<223> OTHER INFORMATION: PA7.2-G3 Heavy Chain CDR3

<400> SEQUENCE: 24

Val Gly Leu Ser Ala Pro Val Thr Phe Phe Asp Phe
1 5 10

<210> SEQ ID NO 25

<211> LENGTH: 121

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA7.2-G3 Heavy Chain Variable Domain

<400> SEQUENCE: 25

Glu Val Gln Leu Val Glu Ser Arg Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Asp Gly Gly Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gly Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Glu Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Leu Ser Ala Pro Val Thr Phe Phe Asp Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 26

<211> LENGTH: 498

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA7.2-G3 Heavy Chain

<400> SEQUENCE: 26

Glu Val Gln Leu Val Glu Ser Arg Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Asp Gly Gly Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gly Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Glu Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Leu Ser Ala Pro Val Thr Phe Phe Asp Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val

[illegible]

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

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<210> SEQ ID NO 28
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA7.2-G3 Light Chain CDR2

<400> SEQUENCE: 28

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 29
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA7.2-G3 Light Chain CDR3

<400> SEQUENCE: 29

Gln Gln Ser Tyr Arg Thr Pro Phe Ser
1 5

<210> SEQ ID NO 30
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA7.2-G3 Light Chain Variable Domain

<400> SEQUENCE: 30

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Pro Phe
85 90 95

Ser Phe Gly Gln Gly Thr Asp Leu Asp Leu Lys Arg
100 105

<210> SEQ ID NO 31
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA7.2-G3 Light Chain

<400> SEQUENCE: 31

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Pro Phe
 85 90 95
 Ser Phe Gly Gln Gly Thr Asp Leu Asp Leu Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 32
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Heavy Chain CDR1

<400> SEQUENCE: 32

Thr Phe Ala Met Asn
 1 5

<210> SEQ ID NO 33
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Heavy Chain CDR2

<400> SEQUENCE: 33

Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
 1 5 10 15

Gly

<210> SEQ ID NO 34
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Heavy Chain CDR3

<400> SEQUENCE: 34

Asp Phe Asn Trp Asp Ser Gly Thr Met Asp Leu
 1 5 10

<210> SEQ ID NO 35
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Heavy Chain Variable Domain

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<400> SEQUENCE: 35

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Arg Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Leu Thr Phe Ser Thr Phe
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Asp Phe Asn Trp Asp Ser Gly Thr Met Asp Leu Trp Gly Gln
 100 105 110
 Gly Thr Thr Val Thr Val Ser Pro
 115 120

<210> SEQ ID NO 36

<211> LENGTH: 497

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA15-G3 Heavy Chain

<400> SEQUENCE: 36

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Arg Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Leu Thr Phe Ser Thr Phe
 20 25 30
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Asp Phe Asn Trp Asp Ser Gly Thr Met Asp Leu Trp Gly Gln
 100 105 110
 Gly Thr Thr Val Thr Val Ser Pro Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asn His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Leu Lys Thr Pro Leu
 210 215 220

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Gly Asp Thr Thr His Thr Cys Pro Arg Cys Pro Glu Pro Lys Ser Cys
 225 230 235 240
 Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu Pro Lys Ser Cys Asp
 245 250 255
 Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr
 260 265 270
 Pro Pro Pro Cys Pro Arg Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 275 280 285
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 290 295 300
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 305 310 315 320
 Pro Glu Val Gln Phe Lys Trp Tyr Val Asp Gly Val Glu Val His Asn
 325 330 335
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Phe Arg Val
 340 345 350
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 355 360 365
 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 370 375 380
 Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 385 390 395 400
 Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 405 410 415
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 420 425 430
 Ser Ser Gly Gln Pro Glu Asn Asn Tyr Asn Thr Thr Pro Pro Met Leu
 435 440 445
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 450 455 460
 Ser Arg Trp Gln Gln Gly Asn Ile Phe Ser Cys Ser Val Met His Glu
 465 470 475 480
 Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 485 490 495

Lys

<210> SEQ ID NO 37
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Light Chain CDR1

<400> SEQUENCE: 37

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
 1 5 10

<210> SEQ ID NO 38
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Light Chain CDR2

<400> SEQUENCE: 38

Ala Ala Ser Ser Leu Gln Ser
 1 5

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<210> SEQ ID NO 39
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Light Chain CDR3

<400> SEQUENCE: 39

Gln Gln Ser Tyr Ser Thr Pro Tyr Thr
 1 5

<210> SEQ ID NO 40
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Light Chain Variable Domain

<400> SEQUENCE: 40

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 41
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA15-G3 Light Chain

<400> SEQUENCE: 41

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala

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130	135	140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
145	150	155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
	165	170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
	180	185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
	195	200 205
Phe Asn Arg Gly Glu Cys		
210		

<210> SEQ ID NO 42
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA21-G3 Heavy Chain CDR1

<400> SEQUENCE: 42

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 43
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA21-G3 Heavy Chain CDR2

<400> SEQUENCE: 43

Gly Ile Ser Gly Asp Ala Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 44
 <211> LENGTH: 13
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA21-G3 Heavy Chain CDR3

<400> SEQUENCE: 44

Val Met Asn Tyr Tyr Gly Pro Gly Ser Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 45
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA21-G3 Heavy Chain Variable Domain

<400> SEQUENCE: 45

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Asp Ala Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Met Asn Tyr Tyr Gly Pro Gly Ser Ala Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 46
<211> LENGTH: 499
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA21-G3 Heavy Chain

<400> SEQUENCE: 46

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Asp Ala Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Met Asn Tyr Tyr Gly Pro Gly Ser Ala Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Leu Lys Thr
210 215 220

Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys Pro Glu Pro Lys
225 230 235 240

Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu Pro Lys Ser
245 250 255

Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu Pro Lys Ser Cys
260 265 270

Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Ala Pro Glu Leu Leu Gly
275 280 285

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
290 295 300

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Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
305 310 315 320

Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr Val Asp Gly Val Glu Val
325 330 335

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Phe
340 345 350

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
355 360 365

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
370 375 380

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
385 390 395 400

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
405 410 415

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
420 425 430

Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn Tyr Asn Thr Thr Pro Pro
435 440 445

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
450 455 460

Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe Ser Cys Ser Val Met
465 470 475 480

His Glu Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser
485 490 495

Pro Gly Lys

<210> SEQ ID NO 47
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA21-G3 Light Chain CDR1

<400> SEQUENCE: 47

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 48
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA21-G3 Light Chain CDR2

<400> SEQUENCE: 48

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 49
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA21-G3 Light Chain CDR3

<400> SEQUENCE: 49

Gln Gln Ser Tyr Ser Thr Pro Ile Thr
1 5

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<210> SEQ ID NO 50
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA21-G3 Light Chain Variable Domain

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<400> SEQUENCE: 50

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
          20             25             30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35             40             45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
          50             55             60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
        65             70             75             80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
          85             90             95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
          100             105

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<210> SEQ ID NO 51
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA21-G3 Light Chain

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<400> SEQUENCE: 51

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
          20             25             30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35             40             45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
          50             55             60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
        65             70             75             80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Ile
          85             90             95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
          100             105             110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
          115             120             125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
          130             135             140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
          145             150             155             160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
          165             170             175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
          180             185             190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
          195             200             205

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Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 52
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Heavy Chain CDR1

<400> SEQUENCE: 52

Lys Tyr Gly Met Ser
1 5

<210> SEQ ID NO 53
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Heavy Chain CDR2

<400> SEQUENCE: 53

Thr Ile Ser Gly Ser Gly Phe Thr Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 54
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Heavy Chain CDR3

<400> SEQUENCE: 54

Asp Gly Trp Asp Tyr Glu Asp Phe Phe Gly Ser
1 5 10

<210> SEQ ID NO 55
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Heavy Chain Variable Domain

<400> SEQUENCE: 55

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Phe Thr Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Phe Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Gly Trp Asp Tyr Glu Asp Phe Phe Gly Ser Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

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<210> SEQ ID NO 56
<211> LENGTH: 497
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA27-G3 Heavy Chain

<400> SEQUENCE: 56
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1          5          10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Tyr
20          25          30
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45
Ser Thr Ile Ser Gly Ser Gly Phe Thr Thr Tyr Tyr Ala Asp Ser Val
50          55          60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Phe Lys Asn Thr Leu Tyr
65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95
Ala Lys Asp Gly Trp Asp Tyr Glu Asp Phe Phe Gly Ser Trp Gly Gln
100         105         110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115         120         125
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Gly Gly Thr Ala Ala
130         135         140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145         150         155         160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165         170         175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180         185         190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asn His Lys
195         200         205
Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Leu Lys Thr Pro Leu
210         215         220
Gly Asp Thr Thr His Thr Cys Pro Arg Cys Pro Glu Pro Lys Ser Cys
225         230         235         240
Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu Pro Lys Ser Cys Asp
245         250         255
Thr Pro Pro Pro Cys Pro Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr
260         265         270
Pro Pro Pro Cys Pro Arg Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
275         280         285
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
290         295         300
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
305         310         315         320
Pro Glu Val Gln Phe Lys Trp Tyr Val Asp Gly Val Glu Val His Asn
325         330         335
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Phe Arg Val
340         345         350
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
355         360         365
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys

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370	375	380
Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
385	390	395 400
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
	405	410 415
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
	420	425 430
Ser Ser Gly Gln Pro Glu Asn Asn Tyr Asn Thr Thr Pro Pro Met Leu		
	435	440 445
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
	450	455 460
Ser Arg Trp Gln Gln Gly Asn Ile Phe Ser Cys Ser Val Met His Glu		
465	470	475 480
Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
	485	490 495

Lys

<210> SEQ ID NO 57
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Light Chain CDR1

<400> SEQUENCE: 57

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> SEQ ID NO 58
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Light Chain CDR2

<400> SEQUENCE: 58

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 59
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Light Chain CDR3

<400> SEQUENCE: 59

Gln Gln Ser Tyr Ala Phe Pro Tyr Thr
1 5

<210> SEQ ID NO 60
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Light Chain Variable Domain

<400> SEQUENCE: 60

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

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Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Thr Asn Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Ser Tyr Ala Phe Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 61
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA27-G3 Light Chain

<400> SEQUENCE: 61

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Thr Asn Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Gly Thr Tyr Tyr Cys Gln Gln Ser Tyr Ala Phe Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 62
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Heavy Chain CDR1

<400> SEQUENCE: 62

Asp Tyr Tyr Met Asp

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1 5

<210> SEQ ID NO 63
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Heavy Chain CDR2

<400> SEQUENCE: 63

Ser Ile Lys Ala Asp Gly Ser Glu Thr His Tyr Val Asp Ser Val Lys
 1 5 10 15

Gly

<210> SEQ ID NO 64
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Heavy Chain CDR3

<400> SEQUENCE: 64

Asp Pro Gly Arg Arg Phe Asp Tyr
 1 5

<210> SEQ ID NO 65
 <211> LENGTH: 117
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Heavy Chain Variable Domain

<400> SEQUENCE: 65

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ala Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asp Tyr
 20 25 30

Tyr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
 35 40 45

Ala Ser Ile Lys Ala Asp Gly Ser Glu Thr His Tyr Val Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Gly Arg Asp Pro Gly Arg Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> SEQ ID NO 66
 <211> LENGTH: 494
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Heavy Chain

<400> SEQUENCE: 66

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ala Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asp Tyr
 20 25 30

Tyr	Met	Asp	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Pro	Glu	Trp	Val
		35					40					45			
Ala	Ser	Ile	Lys	Ala	Asp	Gly	Ser	Glu	Thr	His	Tyr	Val	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Val	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Gly	Arg	Asp	Pro	Gly	Arg	Arg	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu
			100					105					110		
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
		115					120					125			
Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
	130					135					140				
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145					150					155					160
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
				165					170					175	
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
			180					185					190		
Leu	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
		195					200					205			
Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Leu	Lys	Thr	Pro	Leu	Gly	Asp	Thr
	210					215					220				
Thr	His	Thr	Cys	Pro	Arg	Cys	Pro	Glu	Pro	Lys	Ser	Cys	Asp	Thr	Pro
225					230					235					240
Pro	Pro	Cys	Pro	Arg	Cys	Pro	Glu	Pro	Lys	Ser	Cys	Asp	Thr	Pro	Pro
				245					250					255	
Pro	Cys	Pro	Arg	Cys	Pro	Glu	Pro	Lys	Ser	Cys	Asp	Thr	Pro	Pro	Pro
			260					265					270		
Cys	Pro	Arg	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe
		275					280					285			
Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro
	290					295					300				
Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val
305					310					315					320
Gln	Phe	Lys	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr
				325					330					335	
Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val
			340					345					350		
Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys
		355				360						365			
Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser
	370					375					380				
Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln						

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Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 450 455 460

Gln Gln Gly Asn Ile Phe Ser Cys Ser Val Met His Glu Ala Leu His
 465 470 475 480

Asn Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 485 490

<210> SEQ ID NO 67
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Light Chain CDR1

<400> SEQUENCE: 67

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
 1 5 10

<210> SEQ ID NO 68
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Light Chain CDR2

<400> SEQUENCE: 68

Ala Ala Ser Ser Leu Gln Ser
 1 5

<210> SEQ ID NO 69
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Light Chain CDR3

<400> SEQUENCE: 69

Gln Gln Ser Tyr Ser Thr Pro Tyr Thr
 1 5

<210> SEQ ID NO 70
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA32-G3 Light Chain Variable Domain

<400> SEQUENCE: 70

Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

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<210> SEQ ID NO 71
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA32-G3 Light Chain

<400> SEQUENCE: 71

Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20             25             30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35             40             45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50             55             60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65             70             75             80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85             90             95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100            105            110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115            120            125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130            135            140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145            150            155            160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165            170            175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180            185            190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195            200            205
Phe Asn Arg Gly Glu Cys
210

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<210> SEQ ID NO 72
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA37-G3 Heavy Chain CDR1

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<400> SEQUENCE: 72

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Ser Tyr Ala Met Asn
1             5

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<210> SEQ ID NO 73
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: PA37-G3 Heavy Chain CDR2

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<400> SEQUENCE: 73

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Ala Ile Ser Gly Ser Gly Asp Ile Thr His Tyr Ala Asp Ser Val Lys
1             5             10             15

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Gly

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<210> SEQ ID NO 74
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA37-G3 Heavy Chain CDR3

<400> SEQUENCE: 74

Gly Pro Trp Leu Ala Pro Gly Gly Trp Phe Asp Pro
 1 5 10

<210> SEQ ID NO 75
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA37-G3 Heavy Chain Variable Domain

<400> SEQUENCE: 75

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Arg Arg Leu Ser Cys Ala Thr Ser Gly Leu Ser Phe Ser Ser Tyr
 20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Asp Ile Thr His Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Leu Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Gly Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Gly Pro Trp Leu Ala Pro Gly Gly Trp Phe Asp Pro Trp Gly
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 76
 <211> LENGTH: 498
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <223> OTHER INFORMATION: PA37-G3 Heavy Chain

<400> SEQUENCE: 76

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Arg Arg Leu Ser Cys Ala Thr Ser Gly Leu Ser Phe Ser Ser Tyr
 20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Asp Ile Thr His Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Leu Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Gly Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Gly Pro Trp Leu Ala Pro Gly Gly Trp Phe Asp Pro Trp Gly
 100 105 110

Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
115						120						125			
Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Gly	Gly	Thr	Ala
130						135						140			
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
145						150						160			
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
			165						170			175			
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
			180						185			190			
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asn	His
			195						200			205			
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Leu	Lys	Thr	Pro
210						215						220			
Leu	Gly	Asp	Thr	Thr	His	Thr	Cys	Pro	Arg	Cys	Pro	Glu	Pro	Lys	Ser
225						230						240			
Cys	Asp	Thr	Pro	Pro	Pro	Cys	Pro	Arg	Cys	Pro	Glu	Pro	Lys	Ser	Cys
			245						250			255			
Asp	Thr	Pro	Pro	Pro	Cys	Pro	Arg	Cys	Pro	Glu	Pro	Lys	Ser	Cys	Asp
			260						265			270			
Thr	Pro	Pro	Pro	Cys	Pro	Arg	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly
275						280						285			
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
290						295						300			
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
305						310						315			
Asp	Pro	Glu	Val	Gln	Phe	Lys	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
			325						330			335			
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Phe	Arg
340									345			350			
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
355						360						365			
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
370						375						380			
Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
385						390						395			
Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
			405						410			415			
Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
420									425			430			
Glu	Ser	Ser	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Asn	Thr	Thr	Pro	Pro	Met
435						440						445			
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp
450						455						460			
Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Ile	Phe	Ser	Cys	Ser	Val	Met	His
465						470						475			
Glu	Ala	Leu	His	Asn	Arg	Phe	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro
			485						490			495			
Gly	Lys														

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<210> SEQ ID NO 77
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<220> FEATURE:

<223> OTHER INFORMATION: PA37-G3 Light Chain CDR1

<400> SEQUENCE: 77

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
 1 5 10

<210> SEQ ID NO 78

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA37-G3 Light Chain CDR2

<400> SEQUENCE: 78

Ala Ala Ser Ser Leu Gln Ser
 1 5

<210> SEQ ID NO 79

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA37-G3 Light Chain CDR3

<400> SEQUENCE: 79

Gln Gln Ser Tyr Ser Thr Pro Tyr Thr
 1 5

<210> SEQ ID NO 80

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA37-G3 Light Chain Variable Domain

<400> SEQUENCE: 80

Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 81

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<223> OTHER INFORMATION: PA37-G3 Light Chain

<400> SEQUENCE: 81

Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr

-continued

20	25	30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
35	40	45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr		
85	90	95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala		
100	105	110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		
115	120	125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
130	135	140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
145	150	155
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
165	170	175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
180	185	190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
195	200	205
Phe Asn Arg Gly Glu Cys		
210		

<210> SEQ ID NO 82
 <211> LENGTH: 21
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus aureus
 <220> FEATURE:
 <223> OTHER INFORMATION: Antigenic Peptide #1

<400> SEQUENCE: 82

Gly Glu Ala Lys Lys Leu Asn Glu Ser Gln Ala Pro Lys Ala Asp Asn
1 5 10 15
Asn Phe Asn Lys Glu
20

<210> SEQ ID NO 83
 <211> LENGTH: 16
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus aureus
 <220> FEATURE:
 <223> OTHER INFORMATION: Antigenic Peptide #2

<400> SEQUENCE: 83

Pro Asn Leu Asn Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys
1 5 10 15

<210> SEQ ID NO 84
 <211> LENGTH: 21
 <212> TYPE: PRT
 <213> ORGANISM: Staphylococcus aureus
 <220> FEATURE:
 <223> OTHER INFORMATION: Antigenic Peptide #3

<400> SEQUENCE: 84

Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys Ala Asp Asn
1 5 10 15

-continued

Lys Phe Asn Lys Glu
20

<210> SEQ ID NO 85
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus
<220> FEATURE:
<223> OTHER INFORMATION: Antigenic Peptide #4

<400> SEQUENCE: 85

Lys Glu Ile Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro
1 5 10 15

Lys Glu Glu Asp
20

<210> SEQ ID NO 86
<211> LENGTH: 520
<212> TYPE: PRT
<213> ORGANISM: Staphylococcus aureus
<220> FEATURE:
<223> OTHER INFORMATION: Protein A

<400> SEQUENCE: 86

Met Met Thr Leu Gln Ile His Thr Gly Gly Ile Asn Leu Lys Lys Lys
1 5 10 15

Asn Ile Tyr Ser Ile Arg Lys Leu Gly Val Gly Ile Ala Ser Val Thr
20 25 30

Leu Gly Thr Leu Leu Ile Ser Gly Gly Val Thr Pro Ala Ala Asn Ala
35 40 45

Ala Gln His Asp Glu Ala Gln Gln Asn Ala Phe Tyr Gln Val Leu Asn
50 55 60

Met Pro Asn Leu Asn Ala Asp Gln Arg Asn Gly Phe Ile Gln Ser Leu
65 70 75 80

Lys Asp Asp Pro Ser Gln Ser Ala Asn Val Leu Gly Glu Ala Gln Lys
85 90 95

Leu Asn Asp Ser Gln Ala Pro Lys Ala Asp Ala Gln Gln Asn Asn Phe
100 105 110

Asn Lys Asp Gln Gln Ser Ala Phe Tyr Glu Ile Leu Asn Met Pro Asn
115 120 125

Leu Asn Glu Ala Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp
130 135 140

Pro Ser Gln Ser Thr Asn Val Leu Gly Glu Ala Lys Lys Leu Asn Glu
145 150 155 160

Ser Gln Ala Pro Lys Ala Asp Asn Asn Phe Asn Lys Glu Gln Gln Asn
165 170 175

Ala Phe Tyr Glu Ile Leu Asn Met Pro Asn Leu Asn Glu Glu Gln Arg
180 185 190

Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn
195 200 205

Leu Leu Ser Glu Ala Lys Lys Leu Asn Glu Ser Gln Ala Pro Lys Ala
210 215 220

Asp Asn Lys Phe Asn Lys Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu
225 230 235 240

His Leu Pro Asn Leu Asn Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser
245 250 255

Leu Lys Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu Ala Glu Ala Lys

-continued

260	265	270
Lys Leu Asn Asp Ala Gln Ala Pro Lys Ala Asp Asn Lys Phe Asn Lys		
275	280	285
Glu Gln Gln Asn Ala Phe Tyr Glu Ile Leu His Leu Pro Asn Leu Thr		
290	295	300
Glu Glu Gln Arg Asn Gly Phe Ile Gln Ser Leu Lys Asp Asp Pro Ser		
305	310	315
Val Ser Lys Glu Ile Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln		
325	330	335
Ala Pro Lys Glu Glu Asp Asn Asn Lys Pro Gly Lys Glu Asp Asn Asn		
340	345	350
Lys Pro Gly Lys Glu Asp Asn Asn Lys Pro Gly Lys Glu Asp Asn Asn		
355	360	365
Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp Asn Lys		
370	375	380
Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp Asn Lys		
385	390	395
Lys Pro Gly Lys Glu Asp Gly Asn Lys Pro Gly Lys Glu Asp Gly Asn		
405	410	415
Lys Pro Gly Lys Glu Asp Gly Asn Gly Val His Val Val Lys Pro Gly		
420	425	430
Asp Thr Val Asn Asp Ile Ala Lys Ala Asn Gly Thr Thr Ala Asp Lys		
435	440	445
Ile Ala Ala Asp Asn Lys Leu Ala Asp Lys Asn Met Ile Lys Pro Gly		
450	455	460
Gln Glu Leu Val Val Asp Lys Lys Gln Pro Ala Asn His Ala Asp Ala		
465	470	475
Asn Lys Ala Gln Ala Leu Pro Glu Thr Gly Glu Glu Asn Pro Phe Ile		
485	490	495
Gly Thr Thr Val Phe Gly Gly Leu Ser Leu Ala Leu Gly Ala Ala Leu		
500	505	510
Leu Ala Gly Arg Arg Arg Glu Leu		
515	520	

What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a purified monoclonal antibody comprising a heavy chain variable domain comprising a CDR1, CDR2, and CDR3 of SEQ ID NO: 2, 3, and 4, respectively, and a light chain variable domain comprising a CDR1, CDR2, and CDR3 of SEQ ID NO: 7, 8, and 9, respectively, wherein the monoclonal antibody specifically binds *Staphylococcus aureus* protein A (SpA) with a K_D of less than 1×10^{-10} M via its Fab region paratope, wherein the monoclonal antibody is able to displace human IgG immunoglobulins bound to SpA on *Staphylococcus aureus* bacteria via their Fc regions.

2. The pharmaceutical composition of claim 1, wherein the monoclonal antibody is able to mediate opsonization of SpA-expressing *Staphylococcus aureus* bacteria in the presence of at least 1 mg/ml of IgG immunoglobulins which bind SpA via their Fc regions.

3. The pharmaceutical composition of claim 1, wherein the monoclonal antibody is a human or humanized IgG3 monoclonal antibody.

4. The pharmaceutical composition of claim 1, wherein the monoclonal antibody specifically binds to the amino acid sequence SEQ ID NO: 1.

5. The pharmaceutical composition of claim 1, wherein the heavy chain variable domain comprises SEQ ID NO: 5 and the light chain variable domain comprises SEQ ID NO: 10.

6. The pharmaceutical composition of claim 5, wherein the monoclonal antibody is able to mediate opsonization of SpA-expressing *Staphylococcus aureus* bacteria in the presence of at least 1 mg/ml of IgG immunoglobulins which bind SpA via their Fc regions.

7. The pharmaceutical composition of claim 5, wherein the monoclonal antibody is a human or humanized IgG3 monoclonal antibody.

8. The pharmaceutical composition of claim 5, wherein the monoclonal antibody specifically binds to the amino acid sequence SEQ ID NO: 1.

* * * * *

1. Una composición farmacéutica que comprende un portador farmacéuticamente aceptable y un anticuerpo monoclonal purificado que comprende un dominio variable de cadena pesada que comprende un CDR1, CDR2 y CDR3 de SEQ ID NO: 2, 3 y 4, respectivamente, y un dominio variable de cadena ligera que comprende un CDR1, CDR2 y CDR3 de SEQ ID NO: 7, 8 y 9, respectivamente, en donde el anticuerpo monoclonal se une específicamente a la proteína A (SpA) de *Staphylococcus aureus* con un K_D de menos de 1×10^{-10} M por medio de su paratopo de región Fab, en donde el anticuerpo monoclonal es capaz de desplazar inmunoglobulinas humanas IgG unidas a SpA en bacterias *Staphylococcus aureus* por medio de sus regiones Fc.
2. La composición farmacéutica de la reivindicación 1, en donde el anticuerpo monoclonal es capaz de mediar la opsonización de bacterias *Staphylococcus aureus* que expresan SpA en la presencia de al menos 1 mg/ml de inmunoglobulinas IgG que se unen a SpA mediante sus regiones Fc.
3. La composición farmacéutica de la reivindicación 1, en donde el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado.
4. La composición farmacéutica de la reivindicación 1, en donde el anticuerpo monoclonal se une específicamente a la secuencia de aminoácidos SEQ ID NO: 1.
5. La composición farmacéutica de la reivindicación 1, en donde el dominio variable de cadena pesada comprende la SEQ ID NO: 5 y el dominio variable de cadena ligera comprende la SEQ ID NO: 10.
6. La composición farmacéutica de la reivindicación 5, en donde el anticuerpo monoclonal es capaz de mediar la opsonización de bacterias

Staphylococcus aureus que expresan SpA en la presencia de al menos 1 mg/ml de inmunoglobulinas IgG que se unen a Spa mediante sus regiones Fc.

7. La composición farmacéutica de la reivindicación 5, en donde el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado.
8. La composición farmacéutica de la reivindicación 5, en donde el anticuerpo monoclonal se une específicamente a la secuencia de aminoácidos SEQ ID NO:1.

Solicitud/Número de Control: 14/729,260

Unidad de Arte: 1645

Acción Detallada

1. La presente solicitud, presentada el o después del 16 de marzo de 2013, se está examinando bajo las provisiones de primer inventor en presentar de la AIA.
2. La respuesta del solicitante, presentada el 04/01/2016, es reconocida e introducida. Las reivindicaciones 6-11 y 13-18 están bajo trámite.

Declaración de divulgación de información

3. Las declaraciones de divulgación de información (IDS, por sus siglas en inglés), presentadas el 02/26/2016 se encuentran en cumplimiento de las provisiones de 37 CFR 1.97. De acuerdo con esto, la declaración de divulgación de información está siendo considerado por el examinador y se anexa una copia firmada a esta acción oficial.

Modificaciones del examinador

4. A continuación, aparece una modificación hecha por el examinador al expediente. Si los cambios y/o adiciones son inaceptables para el solicitante, se puede presentar una modificación como establece el 37 CFR 1.312. Para asegurar la consideración de la modificación, se debe presentar antes del pago de la tasa de concesión.

Autorización para esta modificación del examinador se dio en una llamada telefónica con el representante del solicitante, Stanley A. Kim el 4/25/16 y la solicitud se modificó como sigue:

Reivindicaciones 7-12, 16 y 18 son eliminadas.

Reivindicación 6 (actualmente modificada): Una composición farmacéutica que comprende un portador farmacéuticamente aceptable y un anticuerpo

monoclonal purificado que comprende un dominio variable de cadena pesada que comprende un CDR1, CDR2 y CDR3 de SEQ ID NO: 2, 3 y 4, respectivamente, y un dominio variable de cadena ligera que comprende un CDR1, CDR2 y CDR3 de SEQ ID NO: 7, 8 y 9, respectivamente, en donde el anticuerpo monoclonal ~~el cual~~ se une específicamente a la proteína A (SpA) de *Staphylococcus aureus* con un K_D de menos de 1×10^{-10} M por medio de su paratopo de región Fab, en donde el anticuerpo monoclonal es capaz de desplazar inmunoglobulinas humanas IgG unidas a SpA en bacterias *Staphylococcus aureus* por medio de sus regiones Fc.

Reivindicación 13 (presentada anteriormente): La composición farmacéutica de la reivindicación 1, en donde el anticuerpo monoclonal es capaz de mediar la opsonización de bacterias *Staphylococcus aureus* que expresan SpA en la presencia de al menos 1 mg/ml de inmunoglobulinas IgG que se unen a SpA mediante sus regiones Fc.

Reivindicación 14 (presentada anteriormente): La composición farmacéutica de la reivindicación 1, en donde el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado.

Reivindicación 15 (presentada anteriormente): La composición farmacéutica de la reivindicación 1, en donde el anticuerpo monoclonal se une específicamente a la secuencia de aminoácidos SEQ ID NO: 1: ~~KPGKEDNKKPGKEDGNKPGK~~ (SEQ ID NO: 1).

Reivindicación 17 (actualmente modificada): La composición farmacéutica de la reivindicación 6, en donde ~~el anticuerpo monoclonal comprende~~ el dominio variable de cadena pesada ~~comprendiendo~~ comprende la SEQ ID NO: 5 y el dominio variable de cadena ligera ~~comprendiendo~~ comprende la SEQ ID NO: 10.

Reivindicación 19 (nueva): La composición farmacéutica de la reivindicación 17, en donde el anticuerpo monoclonal es capaz de mediar la opsonización de bacterias *Staphylococcus aureus* que expresan SpA en la presencia de al

menos 1 mg/ml de inmunoglobulinas IgG que se unen a Spa mediante sus regiones Fc.

Reivindicación 20 (nueva): La composición farmacéutica de la reivindicación 17, en donde el anticuerpo monoclonal es un anticuerpo monoclonal IgG3 humano o humanizado.

Reivindicación 21 (nueva): La composición farmacéutica de la reivindicación 17, en donde el anticuerpo monoclonal se une específicamente a la secuencia de aminoácidos SEQ ID NO: 1: ~~KPGKEDNKKPGKEDGNKPGK (SEQ ID NO: 1)~~.

Razones para la concesión

5. La siguiente es la declaración del examinador para la concesión: La invención reivindicada se dirige a una composición farmacéutica novedosa que comprende un anticuerpo monoclonal (PA8-G3, ejemplo 1) que tiene un dominio variable de cadena pesada de SEQ ID NO: 5 (CDR1-3 de SEQ ID NO: 2-4 respectivamente) y un dominio variable de cadena ligera de SEQ ID NO: 10 (CDR1-3 de SEQ ID NO: 7-9 respectivamente) que se une específicamente a la proteína A de *Staphylococcus aureus* (SpA) de SEQ ID NO: 1. El anticuerpo monoclonal que se reivindica es capaz de mediar la opsonización de bacterias *Staphylococcus aureus* que expresan la SpA como se muestra en el ejemplo 2. La presente invención es novedosa y no resulta obvia porque no existe arte previo que enseñe el anticuerpo monoclonal referido como PA8-G3 (ejemplo 1). La descripción cumple con los requisitos del 35 U.S.C. 112, primer párrafo, porque contiene una descripción adecuada de la invención que permite que la persona ordinariamente versada en la materia puede reproducir y usar la invención. La descripción también muestra la mejor manera de llevar a cabo la invención. Las reivindicaciones también cumplen con los requisitos del 35 U.S.C. 112, segundo párrafo, porque indican y distintamente reivindican la invención.

Conclusión

6. Las reivindicaciones 6, 13-15, 17 y 19-21 son otorgadas y reenumeradas como 1-8 respectivamente.

Correspondencia

7. Cualquier duda relacionada con esta comunicación o con comunicaciones previas del examinador deben dirigirse a Padma V. Baskar cuyo número de teléfono es (571)272-0853. El examinador puede normalmente ser contactado de Lunes a Viernes 9:00AM-5:30PM.

Si los intentos de contactar al examinador telefónicamente no son exitosos, el supervisor del examinador, Gary Nickol puede ser contactado en 571-272-0835 ext. 77. El número de fax de la organización donde se encuentra asignada esta solicitud es el 571-273-8300.

Información relacionada con el estado de la solicitud puede ser obtenida del sistema PAIR. Información del estado de solicitudes publicadas puede ser obtenido tanto del PAIR Privado o el PAIR público. Información del estado de patentes sin publicar puede ser consultada sólo a través del PAIR privado. Para más información acerca del sistema PAIR, ver <http://pair-direct.uspto.gov>. Si tiene preguntas para acceder al sistema PAIR privado, contacte el Centro de Negocios Electrónicos (EBC) en 866-217-9197 (gratis). Si requiere asistencia del Representante de servicio al cliente de la USPTO o acceder al sistema de información automatizado, llame al 800-786-9199 (EN USA O CANADÁ) o 571-272-1000.

Respetuosamente,

/Padma Baskar/

Padma Baskar, Ph.D (Microbiología e Inmunología)

Examinador Primario, Unidad de Arte 1645