

TREATMENT OF POLYBACTERIALS INFECTIONS

FIELD

- [0001]** The technology relates to the use of anti-bacterial antibodies or antigen-binding fragments thereof for the treatment and prevention of infections including polybacterial infections.

BACKGROUND

- [0002]** Opportunistic infections are infections that are more frequent and/or more severe as a result of a particularly suitable environment such as a weakened immune system. They frequently present in hospitalized and/or immunosuppressed patients. Often times, opportunistic infections are polymicrobial, i.e., involving multiple infectious agents. Two important opportunistic bacteria are *Staphylococcus aureus* and *Pseudomonas aeruginosa*.
- [0003]** *Staphylococcus aureus* (*S. aureus*) is a Gram-positive, facultatively aerobic, clump-forming cocci bacterium that commonly colonizes the nose and skin of healthy humans. Approximately 20-30% of the population is colonized with *S. aureus* at any given time. Mucosal and epidermal barriers (skin) normally protect against *S. aureus* infections, but opportunistic *S. aureus* infections can become serious, causing a variety of diseases or conditions, non-limiting examples of which include bacteremia, cellulitis, eyelid infections, food poisoning, joint infections, skin infections, scalded skin syndrome, toxic shock syndrome, pneumonia, osteomyelitis, endocarditis, meningitis, and abscess formation.
- [0004]** *Pseudomonas aeruginosa* (*P. aeruginosa*) is a Gram-negative bacterium that causes both acute and chronic infections. *P. aeruginosa* is a common cause of hospital-acquired infections in the Western world. It is a frequent causative agent of bacteremia in burn victims and immune compromised individuals. It is also the most common cause of nosocomial Gram-negative pneumonia, especially in mechanically ventilated patients, and is the most prevalent pathogen in the lungs of individuals with cystic fibrosis.
- [0005]** Infections with bacteria such as *S. aureus* and *P. aeruginosa* are associated with increased morbidity and mortality, and *S. aureus* and *P. aeruginosa* are commonly isolated from the same patient. In view of this, as well as the fact that multidrug

resistance is increasing, there is a need for novel strategies for preventing and treating bacterial infections including polybacterial infections.

BRIEF SUMMARY

[0006] Methods of preventing and treating polybacterial infections comprising administering an effective amount of an antibody or antigen-binding fragment thereof that specifically binds to an epitope produced by at least one of the bacterium in the polybacterial infection are provided herein. For example, an antibody that specifically binds to *Staphylococcus aureus* alpha toxin can be administered to a patient with a polybacterial infection comprising *Staphylococcus aureus* and *Pseudomonas aeruginosa* to inhibit the growth of *Pseudomonas aeruginosa*.

[0007] In certain aspects, a method of treating or preventing a polybacterial infection in a patient comprises administering an antibody or antigen-binding fragment thereof that specifically binds to a *Staphylococcus aureus* (*S. aureus*) antigen, wherein the polybacterial infection comprises *S. aureus* and at least one other bacterium. In certain aspects, the *S. aureus* potentiates the growth of the at least one other bacterium in the patient. In certain aspects, the administration inhibits the growth of the at least one other bacterium. In certain aspects, the at least one other bacterium is *Pseudomonas*. In certain aspects, the *Pseudomonas* is *Pseudomonas aeruginosa* (*P. aeruginosa*).

[0008] In certain aspects, a method of treating or preventing a polybacterial infection in a patient comprises administering an antibody or antigen-binding fragment thereof that specifically binds to a *P. aeruginosa* antigen, wherein the polybacterial infections comprises *P. aeruginosa* and at least one other bacterium. In certain aspects, the *P. aeruginosa* potentiates the growth of the at least one other bacterium. In certain aspects, the administration inhibits the growth of the at least one other bacterium. In certain aspects, the at least one other bacterium is *Staphylococcus*. In certain aspects, the *Staphylococcus* is *S. aureus*.

[0009] In certain aspects, a method of inhibiting the growth of *P. aeruginosa* in a patient comprises administering to the patient an antibody or antigen-binding fragment thereof that specifically binds to a *S. aureus* antigen.

[0010] In certain aspects, a method of reducing *S. aureus* colony forming units (CFU) in a patient comprises administering to the patient an antibody or antigen-binding fragment thereof that specifically binds to a *Pseudomonas aeruginosa* antigen.

[0011] In certain aspects, an antibody or antigen-binding fragment thereof specifically binds to a *S. aureus* antigen, and the *S. aureus* antigen is alpha toxin. In certain aspects, the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin binds to the same alpha toxin epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:20 and 19; SEQ ID NOs: 22 and 21; SEQ ID NOs:24 and 23; SEQ ID NOs:26 and 25; SEQ ID NOs:28 and 27; SEQ ID NOs:29 and 30; SEQ ID NOs:31 and 32; SEQ ID NOs:33 and 34; SEQ ID NOs:35 and 36; SEQ ID NOs:37 and 38; SEQ ID NOs:39 and 40; SEQ ID NOs:41 and 42; SEQ ID NOs:43 and 44; SEQ ID NOs:45 and 46; SEQ ID NOs:47 and 48; SEQ ID NOs:49 and 46; SEQ ID NOs:50 and 46; SEQ ID NOs:50 and 51; or SEQ ID NOs:67 and 51. In certain aspects, the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin is an antibody or antigen-binding fragment thereof comprising (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO:7, 10, 13, or 57; (b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO:8, 11, 14, 17, 58, or 63; (c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO:9, 12, 15, 18, 16, 53, 54, 55, 66, 59, 60, or 64; (d) a VL CDR1 comprising the amino acid sequence of SEQ ID NO:1 or 4; (e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:2, 5, 61, or 65; and (f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:3, 6, 52, 56, or 62. In certain aspects, the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of SEQ ID NOs:7, 8, 9, 1, 2, and 3; SEQ ID NOs:10, 11, 12, 1, 2, and 3; SEQ ID NOs:13, 14, 15, 4, 5, and 6; SEQ ID NOs:7, 17, 18, 1, 2, and 3; SEQ ID NOs:7, 8, 16, 1, 2, and 52; SEQ ID NOs:7, 8, 53, 1, 2, and 52; SEQ ID NOs: 7, 8, 54, 1, 2, and 52; SEQ ID NOs:7, 8, 55, 1, 2, and 56; SEQ ID NOs:7, 8, 55, 1, 2, and 52; SEQ ID NOs:7, 8, 66, 1, 2, and 52; SEQ ID NOs:7, 8, 53, 1, 2, and 56; SEQ ID NOs:57, 58, 59, 1, 2, and 56; SEQ ID NOs:7, 8, 60, 1, 61, and 62; SEQ ID NOs:57, 63, 59, 1, 2, and 56; SEQ ID NOs:57, 63, 64, 1, 2, and 56; SEQ ID NOs:57, 63, 64, 1, 65, and 62; or SEQ ID NOs:57, 58, 59, 1, 65, and 67. In certain aspects, the VH and the VL of the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha comprise to the amino acid sequences of SEQ ID NOs:20 and 19;

SEQ ID NOs: 22 and 21; SEQ ID NOs:24 and 23; SEQ ID NOs:26 and 25; SEQ ID NOs:28 and 27; SEQ ID NOs:29 and 30; SEQ ID NOs:31 and 32; SEQ ID NOs:33 and 34; SEQ ID NOs:35 and 36; SEQ ID NOs:37 and 38; SEQ ID NOs:39 and 40; SEQ ID NOs:41 and 42; SEQ ID NOs:43 and 44; SEQ ID NOs:45 and 46; SEQ ID NOs:47 and 48; SEQ ID NOs:49 and 46; SEQ ID NOs:50 and 46; SEQ ID NOs:50 and 51; or SEQ ID NOs:67 and 51.

[0012] In certain aspects, the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin binds to the same alpha toxin epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:45 and 46. In certain aspects, the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:57, 58, 59, 1, 2, and 56, respectively. In certain aspects, the VH and VL of the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin comprise the amino acid sequences of SEQ ID NOs:45 and 46. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:68 and a light chain comprising the amino acid sequence of SEQ ID NO:69.

[0013] In certain aspects, an antibody or antigen-binding fragment thereof specifically binds to a *P. aeruginosa* antigen, and the *P. aeruginosa* antigen is Psl, PcrV, or both Psl and PcrV. In certain aspects, the antibody or antigen-binding fragment thereof binds to *P. aeruginosa* Psl and PcrV.

[0014] In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen binds to the same *P. aeruginosa* Psl epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:79 and 72. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen binds to the same *P. aeruginosa* PcrV epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen binds to the same *P. aeruginosa* Psl epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:79 and 72 and binds to the same *P. aeruginosa* PcrV epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82.

[0015] In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen binds to the same *P. aeruginosa* Psl epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:96 and 97. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen binds to the same *P. aeruginosa* PcrV epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:98 and 99. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen binds to the same *P. aeruginosa* Psl epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:96 and 97 and binds to the same *P. aeruginosa* PcrV epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:98 and 99.

[0016] In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:73, 74, 80, 76, 77, and 78 or SEQ ID NOs: 73, 74, 94, 76, 77, and 95. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:83, 84, 85, 86, 87, and 88. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen (e.g., Psl and PcrV) comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:73, 74, 80, 76, 77, and 78 or SEQ ID NOs: 73, 74, 94, 76, 77, and 95 and comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:83, 84, 85, 86, 87, and 88. In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:73, 74, 80, 76, 77, and 78 or SEQ ID NOs: 73, 74, 94, 76, 77, and 95 are in an ScFv. In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:83, 84, 85, 86, 87, and 88 are in an ScFv. In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:83, 84, 85, 86, 87, and 88 are in an IgG. In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:73, 74, 80, 76, 77, and 78 or SEQ ID NOs: 73, 74, 94, 76, 77, and 95 are in an IgG.

- [0017]** In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the VH sequence of SEQ ID NO:79 and the VL sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the VH sequence of SEQ ID NO:81 and the VL sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen (e.g., Psl and PcrV) comprises the VH sequence of SEQ ID NO:79, the VL sequence of SEQ ID NO:72, the VH sequence of SEQ ID NO:81, and the VL sequence of SEQ ID NO:82. In certain aspects, the VH sequence of SEQ ID NO:79 and the VL sequence of SEQ ID NO:72 are in an ScFv. In certain aspects, the VH sequence of SEQ ID NO:81 and the VL sequence of SEQ ID NO:82 are in an ScFv. In certain aspects, the VH sequence of SEQ ID NO:81 and the VL sequence of SEQ ID NO:82 are in an IgG. In certain aspects, the VH sequence of SEQ ID NO:79 and the VL sequence of SEQ ID NO:72 are in an IgG. In certain aspects, the IgG contains the YTE mutations.
- [0018]** In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the amino acid sequence of SEQ ID NO:89. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen the amino acid sequence of SEQ ID NO:90. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the amino acid sequence of SEQ ID NO:91.
- [0019]** In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:93 and a light chain comprising the amino acid sequence of SEQ ID NO:92.
- [0020]** In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the VH sequence of SEQ ID NO:96 and the VL sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen comprises the VH sequence of SEQ ID NO:98 and the VL sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen (e.g., Psl and PcrV) comprises the VH sequence of SEQ ID NO:96, the VL sequence of SEQ ID NO:97, the VH sequence of SEQ ID NO:98, and the VL sequence of SEQ ID NO:99. In certain aspects, the VH sequence of SEQ ID NO:96 and the VL sequence of SEQ ID

NO:97 are in an ScFv. In certain aspects, the VH sequence of SEQ ID NO:98 and the VL sequence of SEQ ID NO:99 are in an ScFv. In certain aspects, the VH sequence of SEQ ID NO:98 and the VL sequence of SEQ ID NO:99 are in an IgG. In certain aspects, the VH sequence of SEQ ID NO:96 and the VL sequence of SEQ ID NO:97 are in an IgG. In certain aspects, the IgG contains the YTE mutations.

- [0021] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:101 and a light chain comprising the amino acid sequence of SEQ ID NO:100.
- [0022] In certain aspects, the antibody or antigen-binding fragment thereof (e.g., an antibody or antigen-binding fragment thereof that binds to an *S. aureus* antigen or an antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen) is administered for two or more prevention or treatment cycles.
- [0023] In certain aspects, the methods provided herein comprise administering an antibody or antigen-binding fragment thereof (e.g., an antibody or antigen-binding fragment thereof that binds to an *S. aureus* antigen or an antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen) and administering a second anti-bacterial agent.
- [0024] In certain aspects, the polybacterial infection is an ocular infection, a lung infection, a burn infection, a wound infection, a surgical wound infection, a skin infection, a soft tissue infection, a blood infection, a bone infection, or a combination of two or more of said infections.
- [0025] In certain aspects, the patient has acute pneumonia, burn injury, corneal infection, cystic fibrosis, ventilator-associated pneumonia, a skin infection, a wound infection, or a combination thereof.
- [0026] In certain aspects, the patient is hospitalized.
- [0027] In certain aspects, the methods provided herein comprise administering an antibody or antigen-binding fragment thereof (e.g., an antibody or antigen-binding fragment thereof that binds to an *S. aureus* antigen or an antibody or antigen-binding fragment thereof that binds to a *P. aeruginosa* antigen) and result in the outcomes shown in Figures 1-10 and described in Examples 1-4.

BRIEF DESCRIPTION OF THE FIGURES

- [0028] **Figure 1** shows the survival of mice inoculated with *Pseudomonas aeruginosa* strain 6077 (**A**) or *Staphylococcus aureus* strain SF8300 (**B**).
- [0029] **Figure 2A** shows the survival of mice inoculated with *P. aeruginosa* ("PA 6077"), *S. aureus* ("SA SF8300") ("Combo Infection"). **Figure 2B** shows the colony forming units (CFU) of *P. aeruginosa* ("PA CFU") and *S. aureus* ("SA CFU") from the lungs of mice inoculated with *P. aeruginosa* and/or *S. aureus*.
- [0030] **Figure 3** shows the CFU of *P. aeruginosa* ("PA Counts") and *S. aureus* ("SA Counts") measured in mice inoculated with *P. aeruginosa* ("PA"), *S. aureus* ("SA"), or both (SA+PA).
- [0031] **Figure 4** shows the CFU per mL of lung homogenate in inoculated mice. Mice were inoculated with wild-type *S. aureus* ("SA SF8300 WT") alone (circles) or in combination with *P. aeruginosa* ("PA 6077") (triangles), where levels of *S. aureus* were measured at 4, 8, 24 and 48 hours post-inoculation. Mice were also inoculated with *P. aeruginosa* ("PA 6077") alone (squares) or in combination with wild-type *S. aureus* ("SA SF8300 WT"), where levels of *P. aeruginosa* ("PA") were measured at 4, 8, 24 and 48 hours post-inoculation.
- [0032] **Figure 5** shows the survival of mice inoculated with wild-type *S. aureus* ("SA SF8300 WT"), *S. aureus* containing a deletion in the gene encoding for alpha toxin ("SA SF8300 Δ hla"), *P. aeruginosa* ("PA 6077"), or a combination thereof.
- [0033] **Figure 6A** shows the survival of mice that received *S. aureus* alpha toxin ("AT"), *P. aeruginosa* ("PA 6077"), *P. aeruginosa* in combination with alpha toxin, or *P. aeruginosa* in combination with alpha toxin and an anti-alpha toxin antibody (LC10). **Figure 6B** also shows the survival of mice that received *S. aureus* alpha toxin ("AT"), and *P. aeruginosa* ("PA 6077"), and also shows the survival of mice that received wild-type *S. aureus* ("SA SF8300 WT"), wild-type *S. aureus* ("SA SF8300 WT") in combination with *P. aeruginosa* ("PA 6077"), or *P. aeruginosa* ("PA 6077") with a cell pellet obtained from heat-killed *S. aureus* ("SA HK Cells") or supernatant obtained from heat-killed *S. aureus* ("SA HK SUP").
- [0034] **Figure 7** shows the level of *P. aeruginosa* in mice treated with *P. aeruginosa* ("PA 6077") alone or in combination with wild-type *S. aureus* ("SA SF8300 WT"), *S.*

aureus containing a deletion in the gene encoding for alpha toxin ("SA SF8300 Δhla "), alpha toxin (AT), or both alpha toxin and the anti-alpha toxin antibody LC10.

[0035] **Figure 8** shows the survival of mice that received either a control antibody ("R347"), an anti-*S. aureus* alpha toxin antibody ("LC10"), an anti-*P. aeruginosa* antibody ("3902"), or a combination of an anti-*S. aureus* alpha toxin antibody ("LC10") and an anti-*P. aeruginosa* antibody ("3902"), and were then inoculated with *S. aureus* ("SA") and *P. aeruginosa* ("PA").

[0036] **Figure 9** shows the survival of mice that received a combination of 15 mg/kg anti-*S. aureus* alpha toxin antibody ("LC10") and 1 mg/kg anti-*P. aeruginosa* antibody ("3902") or 15 mg/kg control antibody ("R347") 48 hours before, 24 hours before, or 1 hour after inoculation with *S. aureus* ("SA") and *P. aeruginosa* ("PA").

[0037] **Figure 10** shows the levels of *S. aureus* ("SA CFU") and *P. aeruginosa* ("PA CFU") in mice receiving either 15 mg/kg anti-*S. aureus* alpha toxin antibody ("LC10"), 1 mg/kg anti-*P. aeruginosa* antibody ("3902"), or 15 mg/kg control antibody ("R347").

[0038] **Figure 11(A)** shows that LC10 reduces pulmonary CFU and dissemination. A) Groups of mice were injected with LC10 (□), or the iso-type control IgG (○) and challenged intranasally 24 h later with 1e5 CFU of *P.aeruginosa* and 5e7 CFU *S.aureus*, or *P.aeruginosa* + AT. Lungs and spleens were removed at the indicated times for CFU determination. **Figure 11(B)** *S. aureus* bacterial burden in the spleens of mice in the mono (Sa) or co-infected (Sa + Pa (Sa)) mice at the indicated time points following intranasal challenge as described above. **Figure 11(C)** Numbers of *P. aeruginosa* recovered from distal organs at 24 and 48 h in mono infection, co-infection and co-infection combined with prophylaxis using LC10.

[0039] **Figure 12** shows that α -Toxin also potentiates *Klebsiella pneumoniae* and *Acinetobacter baumannii* virulence in lung infection model. A) Groups of mice were infected intranasally with *K. pneumoniae* 5e1 (■), *K. pneumoniae* 5e1 + *S. aureus* (5e7) (△), *K. pneumoniae* 5e1 + AT (●), *S. aureus* (△). Survival was monitored for 7 days B) Animals were injected with LC10 (△), or the iso-type IgG (▲) and challenged intranasally 24 h later as described above with *K. pneumoniae* + *S. aureus*, or *K. pneumoniae* + AT LC10 (○), or the iso-type IgG (●). CFU recovery from the lungs (C) and spleens (D) 24 h post-challenge. E) Groups of mice were infected intranasally with *A. baumannii* (8e5) (■), *A. baumannii* 8e5 + *S. aureus* (5e7) (△), *A. baumannii* 8e5 + AT

(●), *S. aureus* (△). Animals were injected with LC10 (△), or the iso-type IgG (▲) and challenged intranasally 24 h later with *A. baumannii* + *S. aureus*, or *A. baumannii* + AT LC10 (○), or the iso-type IgG (●). CFU recovery from the lungs (F) and spleens (G) 24 h post-challenge.

DETAILED DESCRIPTION

[0040] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "an antibody or antigen-binding fragment thereof" is understood to represent one or more antibodies or antigen-binding fragments thereof. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0041] The term "antibody" means an immunoglobulin molecule that recognizes and specifically binds to a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing through at least one antigen recognition site within the variable region of the immunoglobulin molecule. As used herein, the term "antibody" encompasses intact polyclonal antibodies, intact monoclonal antibodies, antibody fragments (such as Fab, Fab', F(ab')₂, and Fv fragments), single chain Fv (scFv) mutants, multispecific antibodies such as bispecific antibodies generated from at least two intact antibodies, chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antigen determination portion of an antibody, and any other modified immunoglobulin molecule comprising an antigen recognition site so long as the antibodies exhibit the desired biological activity. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well known subunit structures and three-dimensional configurations. Antibodies can be naked or conjugated to other molecules such as toxins, radioisotopes, etc.

[0042] The term "antibody fragment" refers to a portion of an intact antibody and refers to the antigenic determining variable regions of an intact antibody. Examples of antibody fragments include, but are not limited to Fab, Fab', F(ab')₂, and Fv fragments, linear

antibodies, single chain antibodies, and multispecific antibodies formed from antibody fragments.

[0043] A "monoclonal antibody" refers to a homogeneous antibody population involved in the highly specific recognition and binding of a single antigenic determinant, or epitope. This is in contrast to polyclonal antibodies that typically include different antibodies directed against different antigenic determinants.

[0044] The term "monoclonal antibody" encompasses both intact and full-length monoclonal antibodies as well as antibody fragments (such as Fab, Fab', F(ab')₂, Fv), single chain (scFv) mutants, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antigen recognition site. Furthermore, "monoclonal antibody" refers to such antibodies made in any number of ways including, but not limited to, by hybridoma, phage selection, recombinant expression, and transgenic animals.

[0045] The term "humanized antibody" refers to an antibody derived from a non-human (*e.g.*, murine) immunoglobulin, which has been engineered to contain minimal non-human (*e.g.*, murine) sequences. Typically, humanized antibodies are human immunoglobulins in which residues from the complementary determining region (CDR) are replaced by residues from the CDR of a non-human species (*e.g.*, mouse, rat, rabbit, or hamster) that have the desired specificity, affinity, and capability (Jones *et al.*, 1986, *Nature*, 321:522-525; Riechmann *et al.*, 1988, *Nature*, 332:323-327; Verhoeven *et al.*, 1988, *Science*, 239:1534-1536). In some instances, the Fv framework region (FW) residues of a human immunoglobulin are replaced with the corresponding residues in an antibody from a non-human species that has the desired specificity, affinity, and capability.

[0046] The humanized antibody can be further modified by the substitution of additional residues either in the Fv framework region and/or within the replaced non-human residues to refine and optimize antibody specificity, affinity, and/or capability. In general, the humanized antibody will comprise substantially all of at least one, and typically two or three, variable domains containing all or substantially all of the CDR regions that correspond to the non-human immunoglobulin whereas all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody can also comprise at least a portion of an immunoglobulin constant region or

domain (Fc), typically that of a human immunoglobulin. Examples of methods used to generate humanized antibodies are described in U.S. Pat. Nos. 5,225,539 or 5,639,641.

[0047] A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. The variable regions of the heavy and light chain each consist of four framework regions (FW) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FW regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (*i.e.*, Kabat *et al.* Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda Md.)); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Al-lazikani *et al.* (1997) *J. Molec. Biol.* 273:927-948)). In addition, combinations of these two approaches are sometimes used in the art to determine CDRs.

[0048] The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat *et al.*, Sequences of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)).

[0049] The amino acid position numbering as in Kabat, refers to the numbering system used for heavy chain variable domains or light chain variable domains of the compilation of antibodies in Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991). Using this numbering system, the actual linear amino acid sequence can contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FW or CDR of the variable domain. For example, a heavy chain variable domain can include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.*, residues 82a, 82b, and 82c, *etc.* according to Kabat) after heavy chain FW residue 82.

Table 1

Loop	Kabat	AbM	Chothia
L1	L24-L34	L24-L34	L24-L34
L2	L50-L56	L50-L56	L50-L56
L3	L89-L97	L89-L97	L89-L97
H1	H31-H35B	H26-H35B (Kabat Numbering)	H26-H32..34
H1	H31-H35	H26-H35 (Chothia Numbering)	H26-H32
H2	H50-H65	H50-H58	H52-H56
H3	H95-H102	H95-H102	H95-H102

[0050] The Kabat numbering of residues can be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence. Chothia refers instead to the location of the structural loops (Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software.

[0051] As used herein the Fc region includes the polypeptides comprising the constant region of an antibody excluding the first constant region immunoglobulin domain. Thus Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, and the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM Fc can include the J chain. For IgG, Fc comprises immunoglobulin domains Cgamma2 and Cgamma3 (Cγ2 and Cγ3) and the hinge between Cgamma1 (Cγ1) and Cgamma2 (Cγ2). Although the boundaries of the Fc region can vary, the human IgG heavy chain Fc region is usually defined to comprise residues C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index as set forth in Kabat (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). Fc can refer to this region in isolation, or this region in the context

of an antibody, antibody fragment, or Fc fusion protein. Polymorphisms have been observed at a number of different Fc positions, including but not limited to positions 270, 272, 312, 315, 356, and 358 as numbered by the EU index, and thus slight differences between the presented sequence and sequences in the prior art may exist.

[0052] The term "human antibody" means an antibody produced by a human or an antibody having an amino acid sequence corresponding to an antibody produced by a human made using any technique known in the art. This definition of a human antibody includes intact or full-length antibodies, fragments thereof, and/or antibodies comprising at least one human heavy and/or light chain polypeptide such as, for example, an antibody comprising murine light chain and human heavy chain polypeptides.

[0053] The term "chimeric antibodies" refers to antibodies wherein the amino acid sequence of the immunoglobulin molecule is derived from two or more species. Typically, the variable region of both light and heavy chains corresponds to the variable region of antibodies derived from one species of mammals (*e.g.*, mouse, rat, rabbit, etc.) with the desired specificity, affinity, and capability while the constant regions are homologous to the sequences in antibodies derived from another (usually human) to avoid eliciting an immune response in that species.

[0054] "Binding affinity" generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present disclosure.

[0055] The term "bispecific antibody" as used herein refers to an antibody that has binding sites for two different antigens within a single antibody molecule. It will be appreciated that other molecules in addition to the canonical antibody structure can be constructed with two binding specificities. It will further be appreciated that antigen

binding by bispecific antibodies can be simultaneous or sequential. Triomas and hybrid hybridomas are two examples of cell lines that can secrete bispecific antibodies. Bispecific antibodies can also be constructed by recombinant means.

[0056] By "specifically binds," it is generally meant that an antibody binds to an epitope via its antigen binding domain, and that the binding entails some complementarity between the antigen binding domain and the epitope. According to this definition, an antibody is said to "specifically bind" to an epitope when it binds to that epitope, via its antigen binding domain more readily than it would bind to a random, unrelated epitope. The term "specificity" is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody "A" may be deemed to have a higher specificity for a given epitope than antibody "B," or antibody "A" may be said to bind to epitope "C" with a higher specificity than it has for related epitope "D."

[0057] By "preferentially binds," it is meant that the antibody specifically binds to an epitope more readily than it would bind to a related, similar, homologous, or analogous epitope. Thus, an antibody which "preferentially binds" to a given epitope would more likely bind to that epitope than to a related epitope, even though such an antibody may cross-react with the related epitope.

[0058] An antibody is said to "competitively inhibit" binding of a reference antibody to a given epitope if it preferentially binds to that epitope to the extent that it blocks, to some degree, binding of the reference antibody to the epitope. Competitive inhibition may be determined by any method known in the art, for example, competition ELISA assays. An antibody may be said to competitively inhibit binding of the reference antibody to a given epitope by at least 90%, at least 80%, at least 70%, at least 60%, or at least 50%.

[0059] The term "YTE" mutations refers to a combination of the three mutations, M252Y, S254T, and T256E, wherein the numbering is according to the EU index as set forth in Kabat, introduced into the heavy chain of an IgG. See U.S. Patent No. 7,658,921, which is herein incorporated by reference in its entirety.

[0060] Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder, e.g., infection. Thus, those in need of treatment include those already diagnosed with or suspected of having the disorder. In certain embodiments, a subject is successfully "treated" for a microbial

infection according to the methods of the present disclosure if the patient shows one or more of the following: a reduction in the symptoms of microbial infection, a reduction in the number or a complete absence of the microbe in the patient (e.g., as assessed using a sample obtained from the patient), reduction in the amount or complete absence of an indicator of the microbe (e.g., alpha toxin of *S. aureus*) in the patient, and/or a reduction in the severity and/or frequency of a symptom or symptoms of the infection.

[0061] Prophylactic or preventative measures refer to measures that prevent and/or slow the development of a targeted pathologic condition or disorder, e.g., infection. Thus, those in need of prophylactic or preventative measures include those prone to have the disorder and those in whom the disorder is to be prevented.

[0062] The term "pharmaceutical formulation" "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. The formulation can be sterile.

[0063] An "effective amount" of an antibody or immunoconjugate as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" can be determined empirically and in a routine manner, in relation to the stated purpose.

[0064] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

Anti-*Staphylococcus* Antibodies and Antigen-Binding Fragments Thereof

[0065] In certain aspects, the antibody or antigen-binding fragment thereof for use according to the methods provided herein specifically binds to a *Staphylococcus* antigen (e.g., polypeptide and/or carbohydrate).

[0066] In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., polypeptide and/or carbohydrate). *S. aureus* expresses a number of virulence factors, including capsular polysaccharides and protein toxins. One virulence factor often associated with *S. aureus* infection that is the major cytotoxic agent is alpha toxin (also known as alpha-hemolysin or Hla), a pore-forming and hemolytic exoprotein produced by most pathogenic strains of *S. aureus*. The toxin forms heptameric pores in membranes of susceptible cells such as white blood cells,

platelets, erythrocytes, peripheral blood monocytes, macrophages, keratinocytes, fibroblasts and endothelial cells. Alpha toxin pore formation often leads to cell dysfunction or lysis. Accordingly, in certain aspects, the antibody or antigen-binding fragment thereof specifically binds to *Staphylococcus aureus* alpha toxin. In certain aspects, the *S. aureus* alpha toxin comprises the amino acid sequence of SEQ ID NO:70.

[0067] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin is an antibody or an antigen-binding fragment thereof disclosed in US 2014/0072577 (which is herein incorporated by reference in its entirety). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin is an antibody or an antigen-binding fragment thereof disclosed in WO 2012/109285 (which is herein incorporated by reference in its entirety).

[0068] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin binds to the same alpha toxin epitope as 2A3.1, 10A7.5, 12B8.19, 28F6.1, 25E9.1, QD20, QD33, QD37, QD3, QD4, QD23, QD32, 2A3GL, LC10, TVES, 3H7KAD, LC9, LC4, or LC5 (listed in Table 2 below). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin binds to the same alpha toxin epitope as LC10. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin competitively inhibits the binding of 2A3.1, 10A7.5, 12B8.19, 28F6.1, 25E9.1, QD20, QD33, QD37, QD3, QD4, QD23, QD32, 2A3GL, LC10, TVES, 3H7KAD, LC9, LC4, or LC5 to *S. aureus* alpha toxin. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin competitively inhibits the binding of LC10 to *S. aureus* alpha toxin.

Table 2: Anti-Alpha Toxin Antibody Sequence SEQ ID NOs

Antibody	VL	VL CDR1	VL CDR2	VL CDR3	VH	VH CDR1	VH CDR2	VH CDR3
2A3.1	19	1	2	3	20	7	8	9
10A7.5	21	1	2	3	22	10	11	12
12B8.19	23	1	2	3	24	10	11	12
28F6.1	25	4	5	6	26	13	14	15
25E9.1	27	1	2	3	28	7	17	18
QD20	30	1	2	52	29	7	8	16
QD33	32	1	2	52	31	7	8	53
QD37	34	1	2	52	33	7	8	54
QD3	36	1	2	56	35	7	8	55
QD4	38	1	2	52	37	7	8	55
QD23	40	1	2	52	39	7	8	66
QD32	42	1	2	56	41	7	8	53
2A3GL	44	1	2	3	43	7	8	9
LC10	46	1	2	56	45	57	58	59
TVES	48	1	61	62	47	7	8	60
3H7KAD	46	1	2	56	49	57	63	59
LC9	46	1	2	56	50	57	63	64
LC4	51	1	65	62	50	57	63	64
LC5	51	1	65	62	67	57	58	59

[0069] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin binds to the same alpha toxin epitope as an antibody comprising the heavy chain variable region (VH) and light chain variable region (VL) sequences of SEQ ID NOs:20 and 19; SEQ ID NOs: 22 and 21; SEQ ID NOs:24 and 23; SEQ ID NOs:26 and 25; SEQ ID NOs:28 and 27; SEQ ID NOs:29 and 30; SEQ ID NOs:31 and 32; SEQ ID NOs:33 and 34; SEQ ID NOs:35 and 36; SEQ ID NOs:37 and 38; SEQ ID NOs:39 and 40; SEQ ID NOs:41 and 42; SEQ ID NOs:43 and 44; SEQ ID NOs:45 and 46; SEQ ID NOs:47 and 48; SEQ ID NOs:49 and 46; SEQ ID NOs:50 and 46; SEQ ID NOs:50 and 51; or SEQ ID NOs:67 and 51. In certain aspects, the

antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin binds to the same alpha toxin epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:45 and 46.

[0070] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:20 and 19; SEQ ID NOs:22 and 21; SEQ ID NOs:24 and 23; SEQ ID NOs:26 and 25; SEQ ID NOs:28 and 27; SEQ ID NOs:29 and 30; SEQ ID NOs:31 and 32; SEQ ID NOs:33 and 34; SEQ ID NOs:35 and 36; SEQ ID NOs:37 and 38; SEQ ID NOs:39 and 40; SEQ ID NOs:41 and 42; SEQ ID NOs:43 and 44; SEQ ID NOs:45 and 46; SEQ ID NOs:47 and 48; SEQ ID NOs:49 and 46; SEQ ID NOs:50 and 46; SEQ ID NOs:50 and 51; or SEQ ID NOs:67 and 51 to *S. aureus* alpha toxin. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:45 and 46 to *S. aureus* alpha toxin.

[0071] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin is an antibody or antigen-binding fragment thereof comprising (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO:7, 10, 13, or 57; (b) a VH CDR2 comprising the amino acid sequence of SEQ ID NO:8, 11, 14, 17, 58, or 63; (c) a VH CDR3 comprising the amino acid sequence of SEQ ID NO:9, 12, 15, 18, 16, 53, 54, 55, 59, 60, 64, or 66; (d) a VL CDR1 comprising the amino acid sequence of SEQ ID NO:1 or 4; (e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:2, 5, 61, or 65; and (f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:3, 6, 52, 56, or 62.

[0072] In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 comprise the amino acid sequences of SEQ ID NOs:7, 8, 9, 1, 2, and 3; SEQ ID NOs:10, 11, 12, 1, 2, and 3; SEQ ID NOs:13, 14, 15, 4, 5, and 6; SEQ ID NOs:7, 17, 18, 1, 2, and 3; SEQ ID NOs:7, 8, 16, 1, 2, and 52; SEQ ID NOs:7, 8, 53, 1, 2, and 52; SEQ ID NOs:7, 8, 54, 1, 2, and 52; SEQ ID NOs:7, 8, 55, 1, 2, and 56; SEQ ID NOs:7, 8, 55, 1, 2, and 52; SEQ ID NOs:7, 8, 66, 1, 2, and 52; SEQ ID NOs:7, 8, 53, 1, 2, and 56; SEQ ID NOs:57, 58, 59, 1, 2, and 56; SEQ ID NOs:7, 8, 60, 1, 61, and 62; SEQ ID NOs:57, 63, 59, 1, 2, and 56; SEQ ID NOs:57, 63, 64, 1, 2, and 56; SEQ ID NOs:57, 63,

64, 1, 65, and 62; or SEQ ID NOs:57, 58, 59, 1, 65, and 67. In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 correspond to the amino acid sequences of SEQ ID NOs:57, 58, 59, 1, 2, and 56.

[0073] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises VH having at least 75% identity to the amino acid sequence of SEQ ID NO:20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, or 67 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:19, 21, 23, 25, 27, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 or 51. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, or 67 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:19, 21, 23, 25, 27, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 or 51. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, or 67 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:19, 21, 23, 25, 27, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 or 51. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, or 67 and comprises VL having at least 90% identity to the amino acid sequence of SEQ ID NO:19, 21, 23, 25, 27, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 or 51. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, or 67 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:19, 21, 23, 25, 27, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 or 51. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, or 67 and comprises a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:19, 21, 23, 25, 27, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 or 51. In

certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, or 67 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:19, 21, 23, 25, 27, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 or 51.

[0074] In certain aspects, the VH and VL correspond to the amino acid sequences of SEQ ID NOs:20 and 19; SEQ ID NOs: 22 and 21; SEQ ID NOs:24 and 23; SEQ ID NOs:26 and 25; SEQ ID NOs:28 and 27; SEQ ID NOs:29 and 30; SEQ ID NOs:31 and 32; SEQ ID NOs:33 and 34; SEQ ID NOs:35 and 36; SEQ ID NOs:37 and 38; SEQ ID NOs:39 and 40; SEQ ID NOs:41 and 42; SEQ ID NOs:43 and 44; SEQ ID NOs:45 and 46; SEQ ID NOs:47 and 48; SEQ ID NOs:49 and 46; SEQ ID NOs:50 and 46; SEQ ID NOs:50 and 51; or SEQ ID NOs:67 and 51. In certain aspects, the VH and VL correspond to the amino acid sequences of SEQ ID NOs:45 and 46.

[0075] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:68 and a light chain comprising the amino acid sequence of SEQ ID NO:69 (i.e., MEDI4893).

[0076] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin binds to a fragment of the *S. aureus* alpha toxin of SEQ ID NO:70 comprising (a) amino acids 261-272 of SEQ ID NO:70; (b) amino acids 173-201 of SEQ ID NO:70; (c) amino acids 261-272 of SEQ ID NO:70 and amino acids 173-201 of SEQ ID NO:70; or (d) amino acids 248-277 of SEQ ID NO:70. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin binds to a fragment of the *S. aureus* alpha toxin of SEQ ID NO:70 consisting of (a) amino acids 261-272 of SEQ ID NO:70; (b) amino acids 173-201 of SEQ ID NO:70; (c) amino acids 261-272 of SEQ ID NO:70 and amino acids 173-201 of SEQ ID NO:70; or (d) amino acids 248-277 of SEQ ID NO:70.

[0077] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin (a) has an affinity constant (K_D) for alpha toxin of about 13 nM or less; (b) binds to alpha toxin monomers, but does not inhibit binding of alpha toxin to alpha toxin receptor; (c) inhibits the formation of alpha toxin oligomers by at least 50%, 60%, 70%, 80%, 90%, or 95%; (d) reduces alpha toxin cytolytic activity by

at least 50%, 60%, 70%, 80%, 90%, or 95% (e.g., as determined by cell lysis and hemolysis assays); (e) reduces cell infiltration and pro-inflammatory cytokine release; or (f) a combination thereof.

[0078] In certain embodiments, an antibody or antigen-binding fragment thereof as described herein specifically binds to an *S. aureus* epitope (e.g., alpha toxin) with an affinity characterized by a dissociation constant (KD) no greater than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

[0079] In certain embodiments, an anti-alpha toxin antibody or antigen-binding fragment alters the biological properties of alpha toxin, alpha toxin expressing cells, or other bacterial cells. In certain aspects, an anti-alpha toxin antibody or antigen-binding fragment neutralizes the biological activity of alpha toxin by binding to the polypeptide and inhibiting the assembly of alpha toxin monomers into a transmembrane pore (e.g., alpha toxin heptamer). Neutralization assays can be performed using methods known in the art using, in some circumstances, commercially available reagents. Neutralization of alpha toxin often is measured with an IC₅₀ of 1×10^{-6} M or less, 1×10^{-7} M or less, 1×10^{-8} M or less, 1×10^{-9} M or less, 1×10^{-10} M or less and 1×10^{-11} M or less. In certain embodiments, an anti-alpha toxin antibody or fragment neutralizes the ability of alpha toxin to oligomerize and form a transmembrane pore. The term "inhibitory concentration 50%" (abbreviated as "IC₅₀") represents the concentration of an inhibitor (e.g., an anti-alpha toxin antibody or fragment provided herein) that is required for 50% inhibition of a given activity of the molecule the inhibitor targets (e.g., alpha toxin oligomerization to form a transmembrane pore heptamer complex). A lower IC₅₀ value generally corresponds to a more potent inhibitor.

[0080] In certain embodiments, an anti-alpha toxin antibody or fragment inhibits one or more biological activities of alpha toxin. The term "inhibition" as used herein, refers to any statistically significant decrease in biological activity, including full blocking of the activity. For example, "inhibition" can refer to a decrease of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% in biological activity. In certain embodiments, an anti-alpha toxin antibody or fragment inhibits one or more biological activities of alpha toxin by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%.

- [0081] In certain aspects, an anti-alpha toxin antibody or fragment can deplete alpha toxin secreted by pathogenic *S. aureus*. In certain aspects, an anti-alpha toxin antibody or fragment may achieve at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or about 100% depletion of alpha toxin secreted by *S. aureus*.
- [0082] In certain embodiments, an anti-alpha toxin antibody or fragment can inhibit *in vitro* stimulated alpha toxin activity (e.g., receptor binding, oligomerization) and/or proliferation of cells expressing or secreting alpha toxin. An anti-alpha toxin antibody or fragment sometimes inhibits *in vitro* alpha toxin activity, *S. aureus* pathogenicity by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50% or at least about 75%. Methods for measuring cell proliferation, pathogenicity, and alpha hemolysin activity are known in the art.
- [0083] In certain embodiments, an anti-alpha toxin antibody or antigen-binding fragment can inhibit the expression of one or more inducible genes that responds directly or indirectly to the environment created by *S. aureus* infection and/or alpha toxin expression and function. In specific embodiments, an anti-alpha toxin antibody or antigen-binding fragment inhibits the expression of one or more inducible genes that responds directly or indirectly to the environment created by *S. aureus* infection and/or alpha toxin expression and function by at least 20%, by at least 30%, by at least 40%, by at least 50%, by at least 60%, by at least 70%, by at least 80%, by at least 90%, by at least 100%, by at least 120%, by at least 140%, by at least 160%, by at least 180%, or by at least 200%

Anti-*Pseudomonas* Antibodies and Antigen-Binding Fragments Thereof

- [0084] In certain aspects, the antibody or antigen-binding fragment thereof for use according to the methods provided herein specifically binds to a *Pseudomonas* antigen (e.g., polypeptide and/or carbohydrate). In certain aspects, the antibody or antigen-binding fragment thereof binds to a *Pseudomonas fluorescens*, *Pseudomonas putida*, *Pseudomonas alcaligenes*, or *Pseudomonas aeruginosa* antigen (e.g., polypeptide and/or carbohydrate). In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., polypeptide and/or carbohydrate).

- [0085] In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to *P. aeruginosa* Psl exopolysaccharide. Psl exopolysaccharide is a repeating pentasaccharide polymer consisting of D-mannose, L-rhamnose, and D-glucose. Psl is reported to be anchored to the surface of *P. aeruginosa* and is thought to be important in facilitating colonization of host tissues and in establishing/maintaining biofilm formation.
- [0086] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl is an antibody or an antigen-binding fragment thereof disclosed in WO 2012/170807, WO 2013/070615, or WO 2014/074528 (each of which is herein incorporated by reference in its entirety).
- [0087] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl binds to the same *P. aeruginosa* Psl epitope as Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD (as disclosed in WO 2012/170807, which is herein incorporated by reference in its entirety). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl competitively inhibits the binding of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD to *P. aeruginosa* Psl.
- [0088] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl is an antibody or antigen-binding fragment thereof comprising VH CDR1, VH CDR2, VH, VL CDR1, VL CDR2, and VL CDR3 sequences comprising the VH CDR1, VH CDR2, VH, VL CDR1, VL CDR2, and VL CDR3 sequences of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD.
- [0089] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a heavy chain variable domain (VH) and a light chain variable region (VL) having at least 75% identity to the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH and a VL having at least 80% identity to the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to

P. aeruginosa Psl comprises a VH and a VL having at least 85% identity to the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH and a VL having at least 90% identity to the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH and a VL having at least 95% identity to the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH and a VL having at least 98% identity to the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH and a VL having at least 99% identity to the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH and a VL having the sequences of the VH and VL of Cam-003, Cam-004, Cam-005, WapR-001, WapR-002, WapR-003, WapR-004, WapR-007, WapR-016, or WapR-004RAD.

[0090] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl binds to the same *P. aeruginosa* Psl epitope as WapR-004, WapR-004RAD, or Ps10096. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* competitively inhibits the binding of WapR-004, WapR-004RAD, or Ps10096 to *P. aeruginosa* Psl. The sequences of the WapR-004, WapR-004RAD, and Ps10096 are provided in Table 3 below.

Table 3: Anti-*P. aeruginosa* Psl Antibody Sequence SEQ ID NOs

Antibody	VL	VL CDR1	VL CDR2	VL CDR3	VH	VH CDR1	VH CDR2	VH CDR3
WapR-004	72	76	77	78	71	73	74	75
WapR-004RAD	72	76	77	78	79	73	74	80
Ps10096	97	76	77	95	96	73	74	94

[0091] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl binds to the same epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:71 and 72; SEQ ID NOs:79 and 72; or SEQ ID NOs:96 and 97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl binds to the same epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:79 and 72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl binds to the same epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:96 and 97.

[0092] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:71 and 72; SEQ ID NOs:79 and 72; or SEQ ID NOs:96 and 97 to *P. aeruginosa* Psl. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl toxin competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:79 and 72 to *P. aeruginosa* Psl. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl toxin competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:96 and 97 to *P. aeruginosa* Psl.

[0093] In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 correspond to the amino acid sequences of SEQ ID NOs:73, 74, 75, 76, 77, and 78; or SEQ ID NOs:73, 74, 80, 76, 77, and 78. In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 correspond to the amino

acid sequences of SEQ ID NOs:73, 74, 80, 76, 77, and 78. In certain aspects, the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 correspond to the amino acid sequences of SEQ ID NOs:73, 74, 94, 76, 77, and 95.

[0094] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:71 or 79 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the VH and VL comprise the amino acid sequences of SEQ ID

NOs:71 and 72; or SEQ ID NOs:79 and 72. In certain aspects, the VH and VL comprise the amino acid sequences of SEQ ID NOs:79 and 72.

[0095] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the VH and VL comprise the amino acid sequences of SEQ ID NOs:96 and 97.

[0096] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl is a germ-line optimized Wap-004-RAD. In certain aspects, the germ-line optimized Wap-004-RAD is Psl0096, Psl0170, Psl0225, Psl0304, Psl0337, Psl0348, Psl0567, Psl0573, Psl0574, Psl0582, Psl0584, Psl0585, Psl0588, or Psl0589 (as described in WO 2014/074528, which is herein incorporated by reference in its entirety). In certain aspects, the germ-line optimized Wap-004-RAD is Psl0096, Psl0225, Psl0337, Psl0567, or Psl0588. In certain aspects, the germ-line optimized Wap-004-RAD is Psl0096.

[0097] In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to *P. aeruginosa* PcrV. PcrV is a relatively conserved component of the type III secretion system. PcrV appears to be an integral component of the translocation apparatus of the type III secretion system mediating the delivery of the type III secretory toxins into target eukaryotic cells. Active and passive immunization against PcrV improve acute lung injury and mortality of mice infected with cytotoxic *P. aeruginosa*. The major effect of immunization against PcrV is due to the blockade of translocation of the type III secretory toxins into eukaryotic cells. In certain aspects, the *P. aeruginosa* PcrV comprises the amino acid sequence of GenBank Accession No. AAC45935 or AAO91771.

[0098] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV is an antibody or an antigen-binding fragment thereof disclosed in WO 2013/070615 or WO 2014/074528 (which are herein incorporated by reference in their entireties).

[0099] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV binds to the same *P. aeruginosa* PcrV epitope as 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR (as provided in WO 2013/070615 and/or WO 2014/074528, each of which is herein incorporated by reference in its entirety). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* competitively inhibits the binding of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR to *P. aeruginosa* PcrV.

[0100] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV is an antibody or antigen-binding fragment thereof comprising VH CDR1, VH CDR2, VH, VL CDR1, VL CDR2, and VL CDR3

sequences comprising the VH CDR1, VH CDR2, VH, VL CDR1, VL CDR2, and VL CDR3 sequences of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR.

[0101] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having at least 75% identity to the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having at least 80% identity to the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having at least 85% identity to the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having at least 90% identity to the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having at least 95% identity to the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having at least 98% identity to the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having at least 99% identity to the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR.

[0102] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH and a VL having the sequences of the VH and VL of 29D2, V2L2, V2L2-GL, V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR.

[0103] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV binds to the same *P. aeruginosa* PcrV epitope as V2L2. In certain aspects, the antibody or antigen-binding fragment thereof that

specifically binds to *P. aeruginosa* competitively inhibits the binding of V2L2 to *P. aeruginosa* PcrV. The sequences of V2L2 and V2L2-MD are provided in Table 4 below.

Table 4: Anti-*P. aeruginosa* PcrV Antibody Sequence SEQ ID NOs

Antibody	VL	VL CDR1	VL CDR2	VL CDR3	VH	VH CDR1	VH CDR2	VH CDR3
V2L2	82	86	87	88	81	83	84	85
V2L2-MD	99	86	87	88	98	83	84	85

[0104] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV binds to the same PcrV epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82 or SEQ ID NOs: 98 and 99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82 or SEQ ID NOs: 98 and 99 to *P. aeruginosa* PcrV.

[0105] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV is an antibody or antigen-binding fragment thereof comprising the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:83-88.

[0106] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises

a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the VH and VL comprise the amino acid sequences of SEQ ID NOs:81 and 82.

[0107] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or

antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the VH and VL comprise the amino acid sequences of SEQ ID NOs:98 and 99.

[0108] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV is a germ-line optimized V2L2. In certain aspects, the germ-line optimized V2L2 is V2L2 germlined Mab (V2L2-GL), or a V2L2-GL optimized Mab (e.g., V2L2-P4M, V2L2-MFS, V2L2-MD, or V2L2-MR) (as described in WO 2014/074528, which is herein incorporated by reference in its entirety).

[0109] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* PcrV can disrupt the activity of the type III toxin secretion system.

[0110] In certain aspects, the antibody or antigen-binding fragment thereof is a bispecific antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV is an antibody or an antigen-binding fragment thereof disclosed in WO 2013/070615 and/or WO 2014/074528 (which are herein incorporated by reference in their entireties).

[0111] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV binds to the same Psl epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:79 and 72 or SEQ ID NOs: 96 and 97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV binds to the same PcrV epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82 or SEQ ID NOs: 98 and 99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV binds to the same Psl epitope as an antibody comprising the VH and VL sequences corresponding of SEQ ID NOs:79 and 72

or SEQ ID NOs: 96 and 97 and to the same PcrV epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82 or SEQ ID NOs: 98 and 99.

[0112] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:79 and 72 or SEQ ID NOs: 96 and 97 to *P. aeruginosa* Psl. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82 or SEQ ID NOs: 98 and 99 to *P. aeruginosa* PcrV. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:79 and 72 or SEQ ID NOs: 96 and 97 to *P. aeruginosa* Psl and competitively inhibits the binding of an antibody comprising the VH and VL sequences of SEQ ID NOs:81 and 82 or SEQ ID NOs: 98 and 99 to *P. aeruginosa* PcrV.

[0113] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:73, 74, 80, 76, 77, and 78 or SEQ ID NOs: 73, 74, 94, 76, 77, and 95. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:83-88. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs:73, 74, 80, 76, 77, and 78 or SEQ ID NOs: 73, 74, 94, 76, 77, and 95 and VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences that correspond to the amino acid sequences of SEQ ID NOs:83-88.

[0114] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:79 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 80% identity to the amino acid sequence of

SEQ ID NO:79 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:79 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:79 and comprises a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:79 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:79 and comprises a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:79 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:72. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH and a VL having the amino acid sequences of SEQ ID NOs:79 and 72.

[0115] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL

having at least 85% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:96 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:97. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH and a VL having the amino acid sequences of SEQ ID NOs:96 and 97.

[0116] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 90% identity to the amino

acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:81 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH and a VL having the amino acid sequences of SEQ ID NOs:81 and 82.

[0117] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 85% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 85% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:99. In

certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:98 and comprises a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH and a VL having the amino acid sequences of SEQ ID NOs:98 and 99.

[0118] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:79, a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:81, a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:72, and a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:79, a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:81, a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:72, and a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:79, a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:81, a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:72, and a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:79, a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:81, a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:72, and a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment

thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:79, a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:81, a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:72, and a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:79, a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:81, a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:72, and a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:82. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH comprising the amino acid sequence of SEQ ID NO:79, a VH comprising the amino acid sequence of SEQ ID NO:81, a VL comprising the amino acid sequence of SEQ ID NO:72, and a VL comprising the amino acid sequence of SEQ ID NO:82.

[0119] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:96, a VH having at least 75% identity to the amino acid sequence of SEQ ID NO:98, a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:97, and a VL having at least 75% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:96, a VH having at least 80% identity to the amino acid sequence of SEQ ID NO:98, a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:97, and a VL having at least 80% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:96, a VH having at least 90% identity to the amino acid sequence of SEQ ID NO:98, a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:97, and a VL having at least 90% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to

P. aeruginosa Psl and PcrV comprises a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:96, a VH having at least 95% identity to the amino acid sequence of SEQ ID NO:98, a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:97, and a VL having at least 95% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:96, a VH having at least 98% identity to the amino acid sequence of SEQ ID NO:98, a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:97, and a VL having at least 98% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:96, a VH having at least 99% identity to the amino acid sequence of SEQ ID NO:98, a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:97, and a VL having at least 99% identity to the amino acid sequence of SEQ ID NO:99. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a VH comprising the amino acid sequence of SEQ ID NO:96, a VH comprising the amino acid sequence of SEQ ID NO:98, a VL comprising the amino acid sequence of SEQ ID NO:97, and a VL comprising the amino acid sequence of SEQ ID NO:99.

[0120] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises an ScFv comprising the VH and VL sequences of the WapR-004RAD (SEQ ID NOs:79 and 72) and/or V2L2 antibody (SEQ ID NOs:81 and 82). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises an ScFv comprising the VH and VL sequences of WapR-004RAD (SEQ ID NOs:79 and 72) and V2L2 IgG. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises an ScFv comprising the VH and VL sequences of V2L2 (SEQ ID NOs:81 and 82) and WapR-004RAD IgG. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of WapR-004RAD (i.e., SEQ ID NOs:73, 74, 80,

76, 77, and 78, respectively). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of V2L2 (i.e., SEQ ID NOs:83, 84, 85, 86, 87, and 88, respectively). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of WapR-004RAD (i.e., SEQ ID NOs:73, 74, 80, 76, 77, and 78, respectively) and the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of V2L2 (i.e., SEQ ID NOs:83, 84, 85, 86, 87, and 88, respectively). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the amino acids of SEQ ID NO:89 (W4-RAD ScFv in Bs3), SEQ ID NO:90 (W4-RAD ScFv-V2L2 in Bs2), or SEQ ID NO:91 (W4-RAD ScFv in Bs4).

[0121] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the amino acid sequence of SEQ ID NO:92 (the light chain of Bs4-V2L2-2C). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the amino acid sequence of SEQ ID NO:93 (the heavy chain of Bs4-V2L2-2C). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the amino acid sequence of SEQ ID NO:92 (the light chain of Bs4-V2L2-2C) and the amino acid sequence of SEQ ID NO:93 (the heavy chain of Bs4-V2L2-2C).

[0122] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV is Bs2-V2L2, Bs3-V2L2, Bs4-V2L2, Bs2-V2L2-2C, Bs3-V2L2-2C, Bs4-V2L2-2C (also referred to as Bs4-WT), Bs4-V2L2-2C-YTE, or Bs2-W4-RAD-2C (as disclosed in WO 2013/070615 or WO 2014/074528, which are herein incorporated by reference in their entireties).

[0123] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises an ScFv comprising the VH and VL sequences of Psl0096 (SEQ ID NOs:96 and 97) and/or V2L2-MD (SEQ ID NOs:98 and 99). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises an ScFv comprising the VH

and VL sequences of Psl0096 (SEQ ID NOs:96 and 97) and V2L2-MD IgG. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises an ScFv comprising the VH and VL sequences of V2L2-MD (SEQ ID NOs:98 and 99) and Psl0096 IgG. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of Psl0096 (i.e., SEQ ID NOs:73, 74, 94, 76, 77, and 95, respectively). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of V2L2-MD (i.e., SEQ ID NOs:83, 84, 85, 86, 87, and 88, respectively). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of Psl0096 (i.e., SEQ ID NOs:73, 74, 94, 76, 77, and 95, respectively) and the VH-CDR1, VH-CDR2, VH-CDR3, VL-CDR1, VL-CDR2, and VL-CDR3 sequences of V2L2-MD (i.e., SEQ ID NOs:83, 84, 85, 86, 87, and 88, respectively).

[0124] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV is a BS4-GLO (as described in WO 2014/074528, which is herein incorporated by reference in its entirety). In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises anti-Psl scFv Psl0096 and anti-PcrV V2L2-MD VH and VL. In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises an anti-PcrV ScFv and an anti-Psl VH and VL.

[0125] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *P. aeruginosa* Psl and PcrV comprises a light chain comprising the amino acid sequence of SEQ ID NO:100 and a heavy chain comprising the amino acid sequence of SEQ ID NO:101.

[0126] In certain embodiments, an antibody or antigen-binding fragment thereof as described herein specifically binds to an *P. aeruginosa* epitope (e.g., Psl, PcrV, or Psl and PcrV) with an affinity characterized by a dissociation constant (KD) no greater than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, or less.

6 M , $5 \times 10^{-7} \text{ M}$, 10^{-7} M , $5 \times 10^{-8} \text{ M}$, 10^{-8} M , $5 \times 10^{-9} \text{ M}$, 10^{-9} M , $5 \times 10^{-10} \text{ M}$, 10^{-10} M , $5 \times 10^{-11} \text{ M}$, 10^{-11} M , $5 \times 10^{-12} \text{ M}$, 10^{-12} M , $5 \times 10^{-13} \text{ M}$, 10^{-13} M , $5 \times 10^{-14} \text{ M}$, 10^{-14} M , $5 \times 10^{-15} \text{ M}$, or 10^{-15} M .

[0127] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds to *Pseudomonas* Psl and/or PcrV, (a) inhibits attachment of *Pseudomonas aeruginosa* to epithelial cells, (b) promotes, mediates, or enhances opsonophagocytic killing (OPK) of *P. aeruginosa*, (c) inhibits attachment of *P. aeruginosa* to epithelial cells, and/or (d) disrupts the activity of the type III toxin secretion system.

Pharmaceutical Compositions

[0128] In certain embodiments, an anti-*Staphylococcus* and/or anti-*Pseudomonas* antibody or antigen-binding fragment provided herein can be formulated with a pharmaceutically acceptable carrier as pharmaceutical (therapeutic) compositions, and can be administered by a variety of methods known in the art. The route and/or mode of administration may vary depending upon the desired results. As used herein, the pharmaceutical formulations comprising an anti-*Staphylococcus* and/or anti-*Pseudomonas* antibody or antigen-binding fragment are referred to as formulations of the technology. The term "pharmaceutically acceptable carrier" means one or more non-toxic materials that do not interfere with the effectiveness of the biological activity of the active ingredients. Such preparations routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic agents. Such pharmaceutically acceptable preparations also routinely contain compatible solid or liquid fillers, diluents or encapsulating substances which are suitable for administration into a human. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being comingled with the antibodies and antigen-binding fragments thereof of the present technology, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

[0129] Therapeutic compositions of the present technology can be formulated for a particular dosage. Dosage regimens can be adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus can be administered, several divided doses can be administered over time or the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0130] Therapeutic compositions of the present technology can be formulated for particular routes of administration, such as oral, nasal, pulmonary, topical (including buccal and sublingual), rectal, vaginal, and/or parenteral administration. The formulations can conveniently be presented in unit dosage form and can be prepared by any methods known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect.

Treatment and Prevention Methods

[0131] As provided herein, polybacterial infections can be treated or prevented by administering an antibody or an antigen-binding fragment thereof that binds to an epitope of at least one bacterium in the polybacterial infection.

[0132] Accordingly, certain aspects are directed to methods of treating or preventing a polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *Staphylococcus aureus* antigen, wherein the polybacterial infection comprises *S. aureus* and at least one other bacterium. One embodiment is directed to a method of treating or preventing a polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *Staphylococcus aureus* antigen, wherein the polybacterial infection comprises *S. aureus*

and at least one other bacterium, wherein the *S. aureus* potentiates the growth of the at least one other bacterium. In one embodiment, *S. aureus* alpha toxin potentiates the growth of the at least one other bacterium. Administration of the anti-*S.aureus* antibody or antigen-binding fragment thereof (e.g., an anti-alpha toxin antibody or antigen-binding fragment thereof) can inhibit the growth of at least one other bacterium. Administration of the anti-*S.aureus* antibody or antigen-binding fragment thereof (e.g., an anti-alpha toxin antibody or antigen-binding fragment thereof) can increase survival. Administration of the anti-*S.aureus* antibody or antigen-binding fragment thereof (e.g., an anti-alpha toxin antibody or antigen-binding fragment thereof) can decrease mortality.

[0133] One embodiment is directed to a method of treating or preventing a polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *Staphylococcus aureus* antigen, wherein the polybacterial infection comprises *S. aureus* and *Pseudomonas* (e.g., *P. aeruginosa*). One embodiment is directed to a method of treating or preventing a polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *Staphylococcus aureus* antigen, wherein the polybacterial infection comprises *S. aureus* and *Pseudomonas* (e.g., *P. aeruginosa*), wherein the *S. aureus* potentiates the growth of the *Pseudomonas* (e.g., *P. aeruginosa*). In one embodiment, *S. aureus* alpha toxin potentiates the growth of the *Pseudomonas* (e.g., *P. aeruginosa*). Administration of the anti-*S. aureus* antibody or antigen-binding fragment thereof (e.g., an anti-alpha toxin antibody or antigen-binding fragment thereof) can inhibit the growth of the *Pseudomonas* (e.g., *P. aeruginosa*). Administration of the anti-*S. aureus* antibody or antigen-binding fragment thereof (e.g., an anti-alpha toxin antibody or antigen-binding fragment thereof) can increase survival. Administration of the anti-*S. aureus* antibody or antigen-binding fragment thereof (e.g., an anti-alpha toxin antibody or antigen-binding fragment thereof) can decrease mortality.

[0134] Certain aspects are directed to methods of treating or preventing a polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *Pseudomonas aeruginosa* antigen, wherein the polybacterial infection comprises *P. aeruginosa* and at least one other bacterium. One embodiment is directed to a method of treating or preventing a

polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *P. aeruginosa* antigen, wherein the polybacterial infection comprises *P. aeruginosa* and at least one other bacterium, wherein the *P. aeruginosa* potentiates the growth of the at least one other bacterium. Administration of the anti-*P. aeruginosa* antibody or antigen-binding fragment (e.g., an antibody or antigen-binding fragment thereof that binds to Psl, PcrV, or Psl and PcrV) thereof can inhibit the growth of at least one other bacterium. Administration of the anti-*P. aeruginosa* antibody or antigen-binding fragment (e.g., an antibody or antigen-binding fragment thereof that binds to Psl, PcrV, or Psl and PcrV) thereof can increase survival. Administration of the anti-*P. aeruginosa* antibody or antigen-binding fragment (e.g., an antibody or antigen-binding fragment thereof that binds to Psl, PcrV, or Psl and PcrV) thereof can decrease mortality.

[0135] One embodiment is directed to a method of treating or preventing a polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *P. aeruginosa* antigen, wherein the polybacterial infection comprises *P. aeruginosa* and *Staphylococcus* (e.g., *S. aureus*). One embodiment is directed to a method of treating or preventing a polybacterial infection in a patient in need thereof comprising administering to the patient, an antibody or antigen-binding fragment thereof that specifically binds to a *P. aeruginosa* antigen, wherein the polybacterial infection comprises *P. aeruginosa* and *Staphylococcus* (e.g., *S. aureus*), wherein the *P. aeruginosa* potentiates the growth of the *Staphylococcus* (e.g., *S. aureus*). Administration of the anti-*P. aeruginosa* antibody or antigen-binding fragment thereof (e.g., an antibody or antigen-binding fragment thereof that binds to Psl, PcrV, or Psl and PcrV) can inhibit the growth of the *Staphylococcus* (e.g., *S. aureus*). Administration of the anti-*P. aeruginosa* antibody or antigen-binding fragment thereof (e.g., an antibody or antigen-binding fragment thereof that binds to Psl, PcrV, or Psl and PcrV) can increase survival. Administration of the anti-*P. aeruginosa* antibody or antigen-binding fragment thereof (e.g., an antibody or antigen-binding fragment thereof that binds to Psl, PcrV, or Psl and PcrV) can decrease mortality.

[0136] Certain aspects are directed to methods of inhibiting the growth of *Pseudomonas* (e.g., *P. aeruginosa*) in a patient comprising administering an antibody or antigen-binding fragment thereof to a patient in need thereof, wherein the antibody or antigen-binding

fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin). In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) inhibits the growth of *Pseudomonas* (e.g., *P. aeruginosa*) by 25%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) inhibits the growth of *Pseudomonas* (e.g., *P. aeruginosa*) by 50%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) inhibits the growth of *Pseudomonas* (e.g., *P. aeruginosa*) by 75%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) inhibits the growth of *Pseudomonas* (e.g., *P. aeruginosa*) by 80%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) inhibits the growth of *Pseudomonas* (e.g., *P. aeruginosa*) by 85%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) inhibits the growth of *Pseudomonas* (e.g., *P. aeruginosa*) by 90%.

[0137] The number of colony forming units (CFU) in a samples obtained from a patient with a polybacterial infection can provide an indication of the severity of the infection. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 50%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 75%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 80%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 85%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases

Pseudomonas (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 90%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 95%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 96%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 97%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 98%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) decreases *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient by at least 99%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Staphylococcus aureus* antigen (e.g., alpha toxin) eliminates *Pseudomonas* (e.g., *P. aeruginosa*) CFU in a sample obtained from a patient.

[0138] Certain aspects are directed to methods of inhibiting the growth of *Staphylococcus* (e.g., *S. aureus*) in a patient comprising administering an antibody or antigen-binding fragment thereof to a patient in need thereof, wherein the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV). In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) inhibits growth of *Staphylococcus* (e.g., *S. aureus*) by 25%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) inhibits growth of *Staphylococcus* (e.g., *S. aureus*) by 50%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) inhibits growth of *Staphylococcus* (e.g., *S. aureus*) by 75%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas*

aeruginosa antigen (e.g., Pcs1, PcrV, or Psl and PcrV) inhibits growth of *Staphylococcus* (e.g., *S. aureus*) by 80%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) inhibits growth of *Staphylococcus* (e.g., *S. aureus*) by 85%. In certain aspects, the antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) inhibits growth of *Staphylococcus* (e.g., *S. aureus*) by 90%.

[0139] In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 50%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 75%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 80%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 85%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 90%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 95%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 96%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases

Staphylococcus (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 97%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 98%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) decreases *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient by at least 99%. In certain aspects, administration of an antibody or antigen-binding fragment thereof specifically binds to a *Pseudomonas aeruginosa* antigen (e.g., Pcs1, PcrV, or Psl and PcrV) eliminates *Staphylococcus* (e.g., *S. aureus*) CFU in a sample obtained from a patient.

[0140] In certain aspects, the polybacterial infection is an ocular infection, a lung infection, a burn infection, a wound infection, a surgical wound infection, a skin infection, a soft tissue infection, a blood infection, a bone infection, or a combination of two or more of said infections.

[0141] In certain aspects, the patient suffers from acute pneumonia, burn injury, corneal infection, cystic fibrosis, ventilator-associated pneumonia, a skin infection, a wound infection, or a combination thereof.

[0142] Methods of preparing and administering anti-bacterial antibodies or antigen-binding fragments thereof (e.g. anti-*Staphylococcus*, anti-*S. aureus*, anti-alpha toxin, anti-*Pseudomonas*, anti-*P. aeruginosa*, anti-Psl, anti-PcrV, or anti-Psl and PcrV antibodies, or antigen-binding fragments thereof) are well known to or are readily determined by those skilled in the art. The route of administration of the anti-bacterial antibodies or antigen-binding fragments thereof can be, for example, oral, parenteral, by inhalation or topical. The term parenteral as used herein includes, e.g., intravenous, intraarterial, intraperitoneal, intramuscular, or subcutaneous administration. A suitable form for administration would be a solution for injection, in particular for intravenous or intraarterial injection or drip. However, in other methods compatible with the teachings herein, anti-bacterial antibodies or antigen-binding fragments thereof can be delivered directly to the site of the adverse cellular population e.g., infection thereby increasing the exposure of the diseased tissue to the therapeutic agent. For example, anti-bacterial

antibodies or antigen-binding fragment thereof can be directly administered to ocular tissue, burn injury, or lung tissue.

[0143] Anti-bacterial antibodies or antigen-binding fragments thereof (e.g. anti-*Staphylococcus*, anti-*S. aureus*, anti-alpha toxin, anti-*Pseudomonas*, anti-*P. aeruginosa*, anti-Psl, anti-PcrV, or anti-Psl and PcrV antibodies, or antigen-binding fragments thereof) can be administered in a pharmaceutically effective amount for the *in vivo* treatment of polybacterial infections (e.g., infections comprising *Staphylococcus* and/or *Pseudomonas* bacteria). In this regard, it will be appreciated that the antibodies or antigen-binding fragments thereof are formulated so as to facilitate administration and promote stability of the active agent.

[0144] In certain embodiments, anti-bacterial antibodies or antigen-binding fragments thereof (e.g. anti-*Staphylococcus*, anti-*S. aureus*, anti-alpha toxin, anti-*Pseudomonas*, anti-*P. aeruginosa*, anti-Psl, anti-PcrV, or anti-Psl and PcrV antibodies or antigen-binding fragments thereof) can be used in combination with other anti-bacterial agents such as antibiotics. Antibiotics include, for example, beta-lactam antibiotics (such as cephalexin), sulfa drugs (like co-trimoxazole/trimethoprim-sulfamethoxazole), tetracyclines (like doxycycline and minocycline), clindamycin, vancomycin, linezolid, daptomycin, teicoplanin, quinupristin/dalfopristin (synercid), tigecycline, ciprofloxacin, meropenem, tobramycin, and aztreonam. In certain embodiments, the antibiotic is ciprofloxacin.

Examples

Example 1: *Staphylococcus aureus* potentiates infection with *Pseudomonas aeruginosa*

[0145] Mice were inoculated with either *Pseudomonas aeruginosa* strain 6077 or *Staphylococcus aureus* strain SF8300 and their survival was assessed. Mice (n=10) were briefly anesthetized in 3% isoflurane/O₂, and 50 µl of bacteria (at various concentrations) was deposited on the tip of the nares. Mortality was monitored for seven days. As shown in Figure 1A, all mice treated with 7.5e4 colony forming units (CFU) of *P. aeruginosa* survived over the seven day period, but no mice treated with 8.00e5 CFU survived. In addition, all mice treated with 1.25e8 CFU *S. aureus* survived over the seven day period, but no mice treated with either 2.25e8 or 3.25e8 CFU *S. aureus* survived (Figure 1B).

[0146] In order to investigate, co-infection kinetics, mice were inoculated with a mixture of *P. aeruginosa* and *S. aureus* at a final concentration of 5.5×10^7 CFU per mouse of *S. aureus* and 1.1×10^5 CFU per mouse of *P. aeruginosa*. Mortality was monitored for seven days. As shown in Figure 1, these doses were well below the lethal doses when administered individually. Therefore, the majority of the mice treated with either *P. aeruginosa* or *S. aureus* survived (Figure 2A). However, none of the mice treated with the combination survived (Figure 2A).

[0147] *P. aeruginosa* and *S. aureus* colonization in the mice was also examined. In these experiments, mice were inoculated with a combination of *P. aeruginosa* and *S. aureus* as described above, and five mice/group were euthanized at various times. Their lungs were removed, and following homogenization in 1 mL phosphate buffered saline (PBS), aliquots were plated on mannitol-salt agar in order to quantitate *S. aureus* or on pseudomonas isolation agar in order to quantitate *P. aeruginosa*. Levels of *P. aeruginosa* were significantly higher in mice inoculated with both *P. aeruginosa* and *S. aureus* than in mice inoculated with only *P. aeruginosa* (Figure 2B). In addition, levels of *P. aeruginosa* were significantly higher in mice inoculated with both *P. aeruginosa* and *S. aureus* than in mice inoculated with only *P. aeruginosa* at both 24 hours and 36 hours post-inoculation (Figure 3). In an additional experiment, colonization in mice inoculated with 6.1×10^7 CFU *S. aureus* and/or 1.3×10^5 CFU *P. aeruginosa* was also examined. In these experiments, levels of *S. aureus* were significantly higher in mice inoculated with both *P. aeruginosa* and *S. aureus* than in mice inoculated with only *S. aureus* 48 hours post-inoculation (Figure 4).

[0148] These data demonstrate that *S. aureus* potentiates growth of *P. aeruginosa*. Furthermore, these data also demonstrate that *S. aureus* and *P. aeruginosa* combination of normally sub-lethal challenge doses increase lethality in a lung infection model. A summary of titration of *P. aeruginosa* and *S. aureus* challenge doses in a lung co-infection model is shown below where the intranasal challenge involved the *P. aeruginosa* strain: 6077 (exoU) : LD100 = $\sim 1 \times 10^6$ and the *S. aureus* strain: SF8300 (cMRSA) : LD100 = $\sim 2 \times 10^8$.

<i>P. aeruginosa</i>	<i>S. aureus</i>	Survival
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challenge (CFU/mouse)	challenge (CFU/mouse)	(7 days)
1e5	0	100%
0	5e7	80-100%
1e5	5e7	0-10%
1e5	2.5e7	40%
1e4	5e7	100%
1e3	5e7	100%
1e2	5e7	100%

Example 2: *S. aureus* alpha toxin potentiates infection with *P. aeruginosa*

[0149] In order to determine if *S. aureus* alpha toxin was necessary for *S. aureus* to potentiate *P. aeruginosa* growth, experiments were conducted with an *S. aureus* strain containing a deletion in the gene encoding for alpha toxin (also known as alpha-hemolysin (*hla*)). In these experiments, mice were inoculated with either wild-type (WT) or mutant (Δhla) *S. aureus* alone (single infection) or in combination with *P. aeruginosa* (mixed infection). Levels of *S. aureus* and *P. aeruginosa* were then measured at 24 hours and 36 hours after inoculation. *S. aureus* levels were lower in mice receiving inoculations with *S. aureus* lacking alpha toxin (Δhla) than with wild-type *S. aureus*. In addition, *P. aeruginosa* levels were lower in mice receiving inoculations with *S. aureus* lacking alpha toxin (Δhla) than with wild-type *S. aureus*.

[0150] The effect of *S. aureus* alpha toxin on the survival of mice was also evaluated. Mice were inoculated with 1e8 CFU wild-type *S. aureus*, 1e8 CFU *S. aureus* lacking alpha toxin, 1e5 CFU *P. aeruginosa*, or a combination thereof. As shown in Figure 5, none of the mice that received both wild-type *S. aureus* and *P. aeruginosa* survived. On the other hand all of the mice that received either *P. aeruginosa* or *S. aureus* lacking alpha toxin survived (Figure 5). Notably, a greater number of mice that received *S. aureus* lacking alpha toxin in combination with *P. aeruginosa* survived than mice that received wild-type *S. aureus* in combination with *P. aeruginosa* (Figure 5).

- [0151] In order to determine if *S. aureus* alpha toxin is sufficient to potentiate the growth of *P. aeruginosa*, mice were inoculated with 1e5 CFU *P. aeruginosa*, 0.1 µg alpha toxin, or a combination thereof. Those mice inoculated with only *P. aeruginosa* or alpha toxin survived, but many mice inoculated with the combination did not (Figure 6A). Thus, native alpha toxin enhances mortality when combined with *P. aeruginosa*. Administration of an anti-alpha toxin antibody, LC10, 24 hours prior to the inoculation was sufficient to reverse this effect. Mice receiving the combination of *P. aeruginosa* and alpha toxin after receiving LC10 survived (Figure 6A).
- [0152] Additional experiments demonstrated that heat-killed *S. aureus* were not able to potentiate growth of *P. aeruginosa*. Mice inoculated with 1e5 CFU *P. aeruginosa* in combination with either the cell pellet or supernatant obtained from heat-killed *S. aureus* survived (Figure 6B).
- [0153] Analysis of *P. aeruginosa* levels in treated mice revealed similar results. In particular, mice inoculated with 1e5 CFU *P. aeruginosa* alone showed low levels of *P. aeruginosa* growth (Figure 7). However, co-inoculating with any of 1e8 CFU *S. aureus*, 1e8 CFU *S. aureus* lacking alpha toxin, or 0.1 mg alpha toxin increased *P. aeruginosa* (Figure 7). Administration of 15 mg/kg of LC10 along with the 0.1 mg alpha toxin prevented the increase in *P. aeruginosa* (Figure 7).
- [0154] These data indicate that the alpha toxin of *S. aureus* is important for the ability of *S. aureus* to potentiate growth of *P. aeruginosa* and is sufficient to potentiate growth of *P. aeruginosa*. Moreover, an anti-*S. aureus* alpha toxin antibody suppresses the alpha toxin-mediated *P. aeruginosa* growth.

Example 3: The combination of anti-alpha toxin and anti-*P. aeruginosa* antibodies promotes survival in a *S. aureus* and *P. aeruginosa* polymicrobial infection model

- [0155] In order to determine if antibodies could increase survival of mice co-inoculated with *P. aeruginosa* and *S. aureus*, mice were given 15 mg/kg LC10 (an anti-*S. aureus* alpha toxin antibody) in combination with 1 mg/kg MEDI3902 (a bispecific antibody that binds to *P. aeruginosa* Psl and PcrV), or 15 mg/kg isotype control antibody (R347). The antibodies were administered 24 hours prior to inoculation with 1e5 CFU *P. aeruginosa* and/or 1e8 CFU *S. aureus*. Mice inoculated with only *S. aureus* or *P. aeruginosa*

survived (Figure 8). However, mice inoculated with both *S. aureus* and *P. aeruginosa* did not survive when they received the control antibody (Figure 8). Administration of the LC10 and MEDI3902 antibodies was able to rescue mice receiving both *S. aureus* and *P. aeruginosa* (Figure 8).

[0156] Similar experiments were performed in which the amounts of *S. aureus* and *P. aeruginosa* in the inoculations were varied. The inoculations contained 5×10^7 CFU *S. aureus* and 1.1×10^5 CFU *P. aeruginosa*. The combination of LC10 and MEDI3902 antibodies dramatically increased survival of mice over seven days as compared to the control antibody (R347).

[0157] In order to assess the important of the timing of administration of the protective anti-*S. aureus* and *P. aeruginosa* antibodies, mice were given 15 mg/kg LC10 and 1 mg/kg MEDI3902 or 15 mg/kg R347 at three different times: 48-hours prior to inoculation, 24-hours prior to inoculation, or 1 hour after inoculation. All mice were inoculated with 5×10^7 - 1×10^8 CFU *S. aureus* and 5×10^4 CFU *P. aeruginosa*. Administration at any of the three times tested was sufficient to increase survival of mice over seven days as compared to administration of the control antibody (Figure 9).

[0158] These data demonstrate that the combination of anti-*S. aureus* and *P. aeruginosa* antibodies prevents infections by mixed *S. aureus* and *P. aeruginosa* colonies.

Example 4: Anti-alpha toxin antibody is sufficient to inhibit the growth *P. aeruginosa* in a *S. aureus* and *P. aeruginosa* co-infection model

[0159] In order to examine the effects of individual antibodies on the growth of mixed colonies of *S. aureus* and *P. aeruginosa*, mice were given either (i) a combination of 15 mg/kg LC10 and 1 mg/kg MEDI3902, (ii) 15 mg/kg LC10, (iii) 1 mg/kg MEDI3902, or (iv) 15 mg/kg control antibody (R347). The antibodies were administered 24 hours before the mice were inoculated with 5×10^7 CFU *S. aureus* and 1×10^5 CFU *P. aeruginosa*. Lungs were harvested 24 hours after infection, and the homogenates were plated on selective agar to assess *S. aureus* and *P. aeruginosa* growth. Surprisingly, administration of the anti-*S. aureus* alpha toxin antibody decreased both *S. aureus* and *P. aeruginosa* growth, and administration of the anti-*P. aeruginosa* antibody decreased both *S. aureus* and *P. aeruginosa* growth (Figure 10).

- [0160] These data demonstrate that anti-*S. aureus* alpha toxin antibodies can inhibit growth of *P. aeruginosa* in a mixed colony containing both *S. aureus* and *P. aeruginosa*. In addition, anti-*P. aeruginosa* antibodies reduce *S. aureus* CFU in an *S. aureus*/*P. aeruginosa* co-infection model.

Example 5: Proliferation and systemic dissemination of *P. aeruginosa* correlates with AT dependent loss of airway barrier integrity

- [0161] AT binding to its receptor, ADAM10, on epithelial cell surface results in vascular leakage due to reorganization of junctional proteins and cell lysis (Bubeck Nat Med ADAM10 gp junction). Epithelial necrosis was observed in lung sections from mice infected with *S. aureus* or treated with AT. Additionally, an increase in airway hemoglobin was observed in mice infected with *S. aureus* or AT, indicating the presence of red blood cells. Therefore we hypothesized that AT may promote Gram-negative dissemination by perturbation of the epithelial barrier. In the mixed-infection with either *S. aureus* or purified AT, the spleen contained significantly larger numbers of *P. aeruginosa* in comparison to animals infected with *P. aeruginosa* alone (Fig. 11A). There was no difference in *S. aureus* bacterial burden in the spleens of mice in the mono or co-infected mouse groups (Fig. 11B). Prophylaxis with LC10 significantly decreased the numbers of *P. aeruginosa* recovered from distal organs at 24 and 48 h (Fig Fig. 11C). These data demonstrate that AT promotes systemic dissemination of *P. aeruginosa* during a mixed infection.

Example 6: *S. aureus* AT potentiates infection with diverse Gram-negative bacteria

- [0162] To determine if the effect of AT is specific to *P. aeruginosa* or could be observed during SA co-infection with other Gram-negative organisms, SA co-infections were performed with either *K. pneumoniae* or *A. baumannii*. Sub-lethal IN challenge doses of 5×10^1 CFU/mouse *K. pneumoniae* or 1×10^6 CFU/mouse *A. baumannii* (1/20 and 1/10 LD₁₀₀ respectively) with 5×10^7 CFU/mouse *S. aureus* resulted in 90-100% lethality and increased Gram-negative bacterial burden in the lung and distal tissues compared to Gram-negative mono-infections (Figs 12B,C,E,F). Similar to results with Pa, LC10 prophylaxis and co-infection with Δhla prevented lethality and reduced Gram-negative bacterial burden suggesting AT plays a key role in the potentiation of co-infections with these pathogens

as well. Consistent with this hypothesis, co-administration of a sub-lethal AT dose along with either Kp or Ab was sufficient to potentiate growth of the Gram-negative pathogen and, to induce a lethal infection. These data show that *S. aureus* AT expression potentiates respiratory infection with a range of Gram-negative opportunistic bacterial pathogens.

* * *

[0163] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific aspects of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

[0164] Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

[0165] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications can be practiced within the scope of the appended claims.

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 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 17
 Val Ile Asp Thr Ala Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys Gly
 1 5 10 15

<210> 18
 <211> 14
 <212> PRT

63
AT 10W01 (1)

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 18

Asp Arg Tyr Ser Gly Asn Phe His Tyr Asn Gly Met Asp Val
1 5 10

<210> 19

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 19

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

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

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

<210> 20

<211> 122

<212> PRT

64
AT 10W01 (1)

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20

Glu 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 Ser Tyr
20 25 30

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

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

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

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

Arg Asp Asn Tyr Ser Ser Thr Gly Gly Tyr Tyr Gly Met Asp Val Trp
100 105 110

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

<210> 21

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 21

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

65
AT 10W01 (1)

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

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

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

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

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

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

<210> 22
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 22
Glu 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 Arg Tyr
20 25 30

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

Ser Val Ile Gly Thr Asp Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
50 55 60

Gly Arg Phe Ile Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu

[illegible]

67
AT 10W01 (1)

<210> 24
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 24
Glu 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 Arg Tyr
20 25 30

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

Ser Val Ile Gly Thr Asp Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
50 55 60

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

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

Arg Asp Arg Tyr Ser Ser Ser Asn His Tyr Asn Gly Met Asp Val Trp
100 105 110

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

<210> 25
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

68
AT 10W01 (1)

<400> 25

Ala 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 Gly Ile Arg Asn Asp
20 25 30

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

Tyr Asp 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 Leu Gln Asp Tyr Asn Tyr Pro Trp
85 90 95

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

<210> 26

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 26

Glu Val Gln Leu Leu 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 Ser Tyr
20 25 30

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

Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

[illegible]

70
AT 10W01 (1)

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

<210> 28
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 28
Glu 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 Thr Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

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

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

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

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

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

<210> 29
<211> 122
<212> PRT
<213> Artificial Sequence

71
AT 10W01 (1)

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29

Glu 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 Ser Tyr
20 25 30

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

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

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

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

Arg Asp Arg Tyr Ser Pro Thr Gly His Tyr Met Gly Met Asp Val Trp
100 105 110

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

<210> 30

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 30

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp

72
AT 10W01 (1)
25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Thr Tyr Trp Thr
85 90 95

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

```
<210> 31
<211> 122
<212> PRT
<213> Artificial Sequence
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73
AT 10W01 (1)

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

Arg Asp Arg Tyr Ser Arg Thr Gly His Tyr Met Gly Met Asp Val Trp
100 105 110

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

<210> 32

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 32

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Thr Tyr Trp Thr
85 90 95

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

<210> 33

74
AT 10W01 (1)

<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 33
Glu 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 Ser Tyr
20 25 30

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

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

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

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

Arg Asp Arg Tyr Ser Arg Thr Gly His Tyr Met Gly Met Ser Leu Trp
100 105 110

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

<210> 34
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 34
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly

1 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
 AT 10W01 (1)
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Thr Tyr Trp Thr
 Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

<210> 35

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 35

Glu 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 Ser Tyr
 20 25 30

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

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

76
AT 10W01 (1)

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

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

Arg Asp Asn Tyr Ser Arg Thr Gly His Tyr Met Gly Met Asp Val Trp
100 105 110

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

<210> 36
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 36
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Lys Gln Tyr Ala Asp Tyr Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

77
10W01 (1)

```
<210> 37
<211> 122
<212> PRT
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 37
Glu 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 Ser Tyr
20 25 30

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

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

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

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

Arg Asp Asn Tyr Ser Arg Thr Gly His Tyr Met Gly Met Asp Val Trp
100 105 110

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

```
<210> 38
<211> 106
<212> PRT
<213> Artificial Sequence
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<220>
<223> Description of Artificial Sequence: Synthetic

78
AT 10W01 (1)

polypeptide

<400> 38

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Thr Tyr Trp Thr
85 90 95

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

<210> 39

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 39

Glu 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 Ser Tyr
20 25 30

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

79
AT 10W01 (1)

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

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

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

Arg Asp Arg Tyr Ser Pro Thr Gly His Tyr Met Gly Met Ser Leu Trp
100 105 110

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

<210> 40

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 40

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Thr Tyr Trp Thr

80
AT 10W01 (1)
85 90 95

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

<210> 41
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 41
Glu 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 Ser Tyr
20 25 30

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

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

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

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

Arg Asp Arg Tyr Ser Arg Thr Gly His Tyr Met Gly Met Asp Val Trp
100 105 110

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

<210> 42
<211> 106
<212> PRT

81
AT 10W01 (1)

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 42

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Lys Gln Tyr Ala Asp Tyr Trp Thr
85 90 95

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

<210> 43

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 43

Glu 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 Ser Tyr
20 25 30

82
AT 10W01 (1)

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

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

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

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

Arg Asp Asn Tyr Ser Ser Thr Gly Gly Tyr Tyr Gly Met Asp Val Trp
100 105 110

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

<210> 44
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 44
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

83																	
10W01 (1)																	
65	70							AT	75							80	
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Trp	Thr		
				85					90				95				
Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys								
				100					105								
<210> 45																	
<211> 122																	
<212> PRT																	
<213> Artificial Sequence																	
<220>																	
<223> Description of Artificial Sequence: Synthetic polypeptide																	
<400> 45																	
Glu	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	Ser	His		
			20					25				30					
Asp	Met	His	Trp	Val	Arg	Gln	Ala	Thr	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40				45						
Ser	Gly	Ile	Gly	Thr	Ala	Gly	Asp	Thr	Tyr	Tyr	Pro	Asp	Ser	Val	Lys		
		50					55				60						
Gly	Arg	Phe	Thr	Ile	Ser	Arg	Glu	Asn	Ala	Lys	Asn	Ser	Leu	Tyr	Leu		
65					70				75				80				
Gln	Met	Asn	Ser	Leu	Arg	Ala	Gly	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala		
				85					90				95				
Arg	Asp	Arg	Tyr	Ser	Pro	Thr	Gly	His	Tyr	Tyr	Gly	Met	Asp	Val	Trp		
			100					105				110					
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser								
				115					120								

84
AT 10W01 (1)

<210> 46
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 46
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Lys Gln Tyr Ala Asp Tyr Trp Thr
85 90 95

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

<210> 47
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 47
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

85
AT 10W01 (1)

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

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

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

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

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

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

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

<210> 48
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 48
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

Tyr Lys Ala Ser Ser Leu Lys Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 86
AT 10W01 (1)
60

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

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

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

<210> 49

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 49

Glu 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 Ser His
20 25 30

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

Ser Gly Ile Gly Thr Arg Gly Asp Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

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

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

Arg Asp Arg Tyr Ser Pro Thr Gly His Tyr Tyr Gly Met Asp Val Trp
100 105 110

87
AT 10W01 (1)

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

<210> 50
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 50
Glu 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 Ser His
20 25 30

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

Ser Gly Ile Gly Thr Arg Gly Asp Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

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

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

Arg Asp Lys Tyr Ser Pro Thr Gly His Tyr Tyr Gly Met Asp Val Trp
100 105 110

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

<210> 51
<211> 106
<212> PRT
<213> Artificial Sequence

88
AT 10W01 (1)

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 51

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

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

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

<210> 52

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 52

Gln Gln Tyr Asp Thr Tyr Trp Thr
1 5

<210> 53

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 53

Asp Arg Tyr Ser Arg Thr Gly His Tyr Met Gly Met Asp Val
1 5 10

<210> 54

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 54

Asp Arg Tyr Ser Arg Thr Gly His Tyr Met Gly Met Ser Leu
1 5 10

<210> 55

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 55

Asp Asn Tyr Ser Arg Thr Gly His Tyr Met Gly Met Asp Val
1 5 10

<210> 56

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 56

Lys Gln Tyr Ala Asp Tyr Trp Thr
1 5

<210> 57

90
AT 10W01 (1)

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 57
Ser His Asp Met His
1 5

<210> 58
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 58
Gly Ile Gly Thr Ala Gly Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly
1 5 10 15

<210> 59
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 59
Asp Arg Tyr Ser Pro Thr Gly His Tyr Tyr Gly Met Asp Val
1 5 10

<210> 60
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 60
Asp Asn Tyr Ser Pro Thr Gly Gly Tyr Tyr Gly Met Asp Val

1 5 AT 91 10W01 (1)
10

<210> 61
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 61
Lys Ala Ser Ser Leu Lys Ser
1 5

<210> 62
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 62
Gln Gln Tyr Glu Ser Tyr Trp Thr
1 5

<210> 63
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 63
Gly Ile Gly Thr Arg Gly Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly
1 5 10 15

<210> 64
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

92
AT 10W01 (1)

peptide

<400> 64

Asp Lys Tyr Ser Pro Thr Gly His Tyr Tyr Gly Met Asp Val
1 5 10

<210> 65

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 65

Lys Ala Ser Ser Leu Val Lys
1 5

<210> 66

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 66

Asp Arg Tyr Ser Pro Thr Gly His Tyr Met Gly Met Ser Leu
1 5 10

<210> 67

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 67

Glu 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 Ser His
20 25 30

93
AT 10W01 (1)

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

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

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

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

Arg Asp Arg Tyr Ser Pro Thr Gly His Tyr Tyr Gly Met Asp Val Trp
100 105 110

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

<210> 68
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 68
Glu 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 Ser His
20 25 30

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

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

Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu

									AT	94 10W01 (1) 75								
65					70													80
Gln	Met	Asn	Ser	Leu	Arg	Ala	Gly	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala			
				85					90					95				
Arg	Asp	Arg	Tyr	Ser	Pro	Thr	Gly	His	Tyr	Tyr	Gly	Met	Asp	Val	Trp			
			100					105					110					
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro			
		115					120					125						
Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	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	Ile	Cys	Asn	Val	Asn			
		195					200					205						
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser			
	210					215					220							
Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu			
225					230					235					240			
Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu			
				245					250					255				
Tyr	Ile	Thr	Arg	Glu	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser			
			260					265					270					
His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu			

275
 280
AT
95
10W01 (1)
285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 290
 295
300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 305
 310
315
320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 325
 330
335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 340
 345
350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
 355
 360
365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 370
 375
380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 385
 390
395
400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 405
 410
415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 420
 425
430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 435
 440
445

Ser Pro Gly Lys
 450

<210> 69
 <211> 212
 <212> PRT
 <213> Artificial Sequence

96
AT 10W01 (1)

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 69

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr 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 Trp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Lys Gln Tyr Ala Asp Tyr Trp Thr
85 90 95

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

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

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

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

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

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

97
AT 10W01 (1)

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

Asn Arg Gly Glu
210

<210> 70
<211> 293
<212> PRT
<213> Staphylococcus aureus

<400> 70
Ala Asp Ser Asp Ile Asn Ile Lys Thr Gly Thr Thr Asp Ile Gly Ser
1 5 10 15

Asn Thr Thr Val Lys Thr Gly Asp Leu Val Thr Tyr Asp Lys Glu Asn
20 25 30

Gly Met His Lys Lys Val Phe Tyr Ser Phe Ile Asp Asp Lys Asn His
35 40 45

Asn Lys Lys Leu Leu Val Ile Arg Thr Lys Gly Thr Ile Ala Gly Gln
50 55 60

Tyr Arg Val Tyr Ser Glu Glu Gly Ala Asn Lys Ser Gly Leu Ala Trp
65 70 75 80

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

Gln Ile Ser Asp Tyr Tyr Pro Arg Asn Ser Ile Asp Thr Lys Glu Tyr
100 105 110

Met Ser Thr Leu Thr Tyr Gly Phe Asn Gly Asn Val Thr Gly Asp Asp
115 120 125

Thr Gly Lys Ile Gly Gly Leu Ile Gly Ala Asn Val Ser Ile Gly His
130 135 140

Thr Leu Lys Tyr Val Gln Pro Asp Phe Lys Thr Ile Leu Glu Ser Pro

AT 98
10W01 (1)
145 150 155 160

Thr Asp Lys Lys Val Gly Trp Lys Val Ile Phe Asn Asn Met Val Asn
165 170 175

Gln Asn Trp Gly Pro Tyr Asp Arg Asp Ser Trp Asn Pro Val Tyr Gly
180 185 190

Asn Gln Leu Phe Met Lys Thr Arg Asn Gly Ser Met Lys Ala Ala Asp
195 200 205

Asn Phe Leu Asp Pro Asn Lys Ala Ser Ser Leu Leu Ser Ser Gly Phe
210 215 220

Ser Pro Asp Phe Ala Thr Val Ile Thr Met Asp Arg Lys Ala Ser Lys
225 230 235 240

Gln Gln Thr Asn Ile Asp Val Ile Tyr Glu Arg Val Arg Asp Asp Tyr
245 250 255

Gln Leu His Trp Thr Ser Thr Asn Trp Lys Gly Thr Asn Thr Lys Asp
260 265 270

Lys Trp Thr Asp Arg Ser Ser Glu Arg Tyr Lys Ile Asp Trp Glu Lys
275 280 285

Glu Glu Met Thr Asn
290

<210>	71
<211>	119
<212>	PRT
<213>	Artificial

<220>
<223> WapR-004 VH

<400> 71

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

99
AT 10W01 (1)

Thr Leu Ser Leu Thr Cys Asn Val Ala Gly Gly Ser Ile Ser Pro Tyr
20 25 30

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

Gly Tyr Ile His Ser Ser Gly Tyr Thr Asp Tyr Asn Pro Ser Leu Lys
50 55 60

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

His Val Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Asp Trp Asp Leu Leu His Ala Leu Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 72
<211> 107
<212> PRT
<213> Artificial

<220>
<223> WapR-004 & WarR-004RAD VL

<400> 72

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

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

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

Tyr Gly Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60 65 70 75 80 85 90 95 100
 AT 10W01 (1)
 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 Phe Pro Leu
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105

101
AT 10W01 (1)
Gly Asp Trp Asp Leu Leu His Ala Leu Asp Ile
1 5 10

<210> 76
<211> 11
<212> PRT
<213> Artificial

<220>
<223> WapR-004 & WapR-004RAD VLCDR1

<400> 76

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

<210> 77
<211> 7
<212> PRT
<213> Artificial

<220>
<223> WapR-004 & WapR-004RAD VLCDR2

<400> 77

Gly Ala Ser Asn Leu Gln Ser
1 5

<210> 78
<211> 6
<212> PRT
<213> Artificial

<220>
<223> WapR-004 & WapR-004RAD VLCDR3

<400> 78

Tyr Ser Phe Pro Leu Thr
1 5

<210> 79
<211> 119
<212> PRT
<213> Artificial

<220>

102
AT 10W01 (1)

<223> WapR-004RAD VH

<400> 79

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

Thr Leu Ser Leu Thr Cys Asn Val Ala Gly Gly Ser Ile Ser Pro Tyr
20 25 30

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

Gly Tyr Ile His Ser Ser Gly Tyr Thr Asp Tyr Asn Pro Ser Leu Lys
50 55 60

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

His Val Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Ala Asp Trp Asp Leu Leu His Ala Leu Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 80

<211> 11

<212> PRT

<213> Artificial

<220>

<223> WapR-004RAD VHCDR3

<400> 80

Ala Asp Trp Asp Leu Leu His Ala Leu Asp Ile
1 5 10

<210> 81

<211> 124

103
AT 10W01 (1)

<212> PRT
<213> Artificial

<220>
<223> V2L2 VH

<400> 81

Glu Met Gln Leu Leu 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 Ser Tyr
20 25 30

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

Ser Ala Ile Thr Ile Ser Gly Ile Thr Ala Tyr Tyr Thr 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 Gly Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Glu Glu Phe Leu Pro Gly Thr His Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 82
<211> 107
<212> PRT
<213> Artificial

<220>
<223> V2L2 VL

<400> 82

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

104
AT 10W01 (1)

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 Leu Val Ile
35 40 45

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

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

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

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

<210> 83
<211> 5
<212> PRT
<213> Artificial

<220>
<223> V2L2 VHCDR1

<400> 83

Ser Tyr Ala Met Asn
1 5

<210> 84
<211> 17
<212> PRT
<213> Artificial

<220>
<223> V2L2 VHCDR2

<400> 84

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

105
AT 10W01 (1)

Gly

<210> 85
<211> 15
<212> PRT
<213> Artificial

<220>
<223> V2L2 VHCDR3

<400> 85

Glu	Glu	Phe	Leu	Pro	Gly	Thr	His	Tyr	Tyr	Tyr	Gly	Met	Asp	Val
1				5					10					15

<210> 86
<211> 11
<212> PRT
<213> Artificial

<220>
<223> V2L2 VLCDR1

<400> 86

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

<210> 87
<211> 7
<212> PRT
<213> Artificial

<220>
<223> V2LC VLCDR2

<400> 87

Ser	Ala	Ser	Thr	Leu	Gln	Ser
1				5		

<210> 88
<211> 9
<212> PRT
<213> Artificial

106
AT 10W01 (1)

<220>

<223> V2L2 VLCDR3

<400> 88

Leu Gln Asp Tyr Asn Tyr Pro Trp Thr
1 5

<210> 89

<211> 256

<212> PRT

<213> Artificial

<220>

<223> W4-RAD scFv sequence in BS3 vector

<400> 89

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

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
20 25 30

Asn Val Ala Gly Gly Ser Ile Ser Pro Tyr Tyr Trp Thr Trp Ile Arg
35 40 45

Gln Pro Pro Gly Lys Cys Leu Glu Leu Ile Gly Tyr Ile His Ser Ser
50 55 60

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

Gly Asp Thr Ser Lys Lys Gln Phe Ser Leu His Val Ser Ser Val Thr
85 90 95

Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala Arg Ala Asp Trp Asp Leu
100 105 110

Leu His Ala Leu Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
130 135 140

107
AT 10W01 (1)

Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu
145 150 155 160

Ser Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln
165 170 175

Ser Ile Arg Ser His Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
180 185 190

Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn Leu Gln Ser Gly Val Pro
195 200 205

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
210 215 220

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
225 230 235 240

Tyr Ser Phe Pro Leu Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys
245 250 255

<210> 90

<211> 380

<212> PRT

<213> Artificial

<220>

<223> W4-RAD scFv-V2L2 VH sequences in Bs2 vector

<400> 90

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

Thr Leu Ser Leu Thr Cys Asn Val Ala Gly Gly Ser Ile Ser Pro Tyr
20 25 30

Tyr Trp Thr Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Leu Ile
35 40 45

108
AT 10W01 (1)

Gly Tyr Ile His Ser Ser Gly Tyr Thr Asp Tyr Asn Pro Ser Leu Lys
50 55 60

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

His Val Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Ala Asp Trp Asp Leu Leu His Ala Leu Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
130 135 140

Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly Asp Arg Val Thr Ile
145 150 155 160

Thr Cys Arg Ala Ser Gln Ser Ile Arg Ser His Leu Asn Trp Tyr Gln
165 170 175

Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn
180 185 190

Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
195 200 205

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
210 215 220

Tyr Tyr Cys Gln Gln Ser Tyr Ser Phe Pro Leu Thr Phe Gly Cys Gly
225 230 235 240

Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
245 250 255

109
 AT 10W01 (1)
 Glu Met Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 260 265 270
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 275 280 285
 Ala Met Asn Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Val
 290 295 300
 Ser Ala Ile Thr Ile Ser Gly Ile Thr Ala Tyr Tyr Thr Asp Ser Val
 305 310 315 320
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 325 330 335
 Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys
 340 345 350
 Ala Lys Glu Glu Phe Leu Pro Gly Thr His Tyr Tyr Tyr Gly Met Asp
 355 360 365
 Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 370 375 380

<210> 91
 <211> 292
 <212> PRT
 <213> Artificial

<220>
 <223> W4-RAD scFv in Bs4 vector

<400> 91

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Gly Gly Gly Gly Ser
 1 5 10 15
 Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Pro Gly Leu
 20 25 30
 Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Asn Val Ala Gly Gly
 35 40 45

110
AT 10W01 (1)

Ser Ile Ser Pro Tyr Tyr Trp Thr Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Cys Leu Glu Leu Ile Gly Tyr Ile His Ser Ser Gly Tyr Thr Asp Tyr
65 70 75 80

Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Gly Asp Thr Ser Lys
85 90 95

Lys Gln Phe Ser Leu His Val Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Phe Cys Ala Arg Ala Asp Trp Asp Leu Leu His Ala Leu Asp
115 120 125

Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly
165 170 175

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Ser His
180 185 190

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
195 200 205

Tyr Gly Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
210 215 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
225 230 235 240

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Phe Pro Leu
245 250 255

111
AT 10W01 (1)

Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
260 265 270

Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
275 280 285

Pro Glu Leu Leu
290

<210> 92
<211> 214
<212> PRT
<213> Artificial

<220>
<223> Bs4-V2L2-C2 light

<400> 92

Ala 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 Gly Ile Arg Asn Asp
20 25 30

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asn Tyr 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

112
 AT 10W01 (1)
 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> 93
 <211> 720
 <212> PRT
 <213> Artificial

<220>
 <223> Bs4-V2L2-C2 heavy

<400> 93

Glu Met Gln Leu Leu 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 Ser Tyr
 20 25 30

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

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

113
AT 10W01 (1)

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 Gly Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Glu Glu Phe Leu Pro Gly Thr His Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

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

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

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

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

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

Lys Ser Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln
225 230 235 240

Leu Leu Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser
245 250 255

Leu Thr Cys Asn Val Ala Gly Gly Ser Ile Ser Pro Tyr Tyr Trp Thr
260 265 270

114
AT 10W01 (1)

Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Leu Ile Gly Tyr Ile
275 280 285

His Ser Ser Gly Tyr Thr Asp Tyr Asn Pro Ser Leu Lys Ser Arg Val
290 295 300

Thr Ile Ser Gly Asp Thr Ser Lys Lys Gln Phe Ser Leu His Val Ser
305 310 315 320

Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala Arg Ala Asp
325 330 335

Trp Asp Leu Leu His Ala Leu Asp Ile Trp Gly Gln Gly Thr Leu Val
340 345 350

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
355 360 365

Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro
370 375 380

Ser Ser Leu Ser Thr Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
385 390 395 400

Ala Ser Gln Ser Ile Arg Ser His Leu Asn Trp Tyr Gln Gln Lys Pro
405 410 415

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn Leu Gln Ser
420 425 430

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
435 440 445

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
450 455 460

Gln Gln Ser Tyr Ser Phe Pro Leu Thr Phe Gly Cys Gly Thr Lys Leu
465 470 475 480

115
AT 10W01 (1)

Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr
485 490 495

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
500 505 510

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
515 520 525

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
530 535 540

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
545 550 555 560

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
565 570 575

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
580 585 590

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
595 600 605

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
610 615 620

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
625 630 635 640

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
645 650 655

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
660 665 670

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
675 680 685

116
AT 10W01 (1)

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
690 695 700

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
705 710 715 720

<210> 94
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Psl0096-Germline VHCDR3

<400> 94

Ala Asp Trp Asp Arg Leu Arg Ala Leu Asp Ile
1 5 10

<210> 95
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Psl0096-Germline VLCDR3

<400> 95

Gln Gln Ser Thr Gly Ala Trp Asn Trp
1 5

<210> 96
<211> 119
<212> PRT
<213> Artificial

<220>
<223> Psl0096-Germline VH

<220>
<221> misc_feature
<222> (44)..(44)
<223> Xaa is Gly or Cys

<400> 96

117
AT 10W01 (1)

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Pro Tyr
20 25 30

Tyr Trp Thr Trp Ile Arg Gln Pro Pro Gly Lys Xaa Leu Glu Leu Ile
35 40 45

Gly Tyr Ile His Ser Ser Gly Tyr Thr Asp Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ala Asp Trp Asp Arg Leu Arg Ala Leu Asp Ile Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 97
<211> 107
<212> PRT
<213> Artificial

<220>
<223> Psl0096-Germline VL

<220>
<221> misc_feature
<222> (100)..(100)
<223> Xaa can be Gly or Cys

<400> 97

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

118
AT 10W01 (1)

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

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

Tyr Gly Ala Ser Asn 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 Thr Gly Ala Trp Asn
85 90 95

Trp Phe Gly Xaa Gly Thr Lys Val Glu Ile Lys
100 105

<210> 98
<211> 124
<212> PRT
<213> Artificial

<220>
<223> V2L2-MD VH

<400> 98

Glu Met Gln Leu Leu 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 Ser Tyr
20 25 30

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

120
AT 10W01 (1)

<210> 100
<211> 214
<212> PRT
<213> Artificial

<220>
<223> Bs4-GLO LC

<400> 100

Ala 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 Gly Ile Arg Asn Asp
20 25 30

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

Tyr Ser Ala Ser Thr 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 Leu Gln Asp Tyr Asn Tyr 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

121
 AT 10W01 (1)
 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> 101
 <211> 720
 <212> PRT
 <213> Artificial

<220>
 <223> Bs4-GLO HC

<400> 101

Glu Val Gln Leu Leu 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 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 Thr Met Ser Gly Ile Thr Ala Tyr Tyr Thr Asp Asp 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

Ala Lys Glu Glu Phe Leu Pro Gly Thr His Tyr Tyr Tyr Gly Met Asp
 100 105 110

122
AT 10W01 (1)

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

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

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

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

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

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

Lys Ser Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
225 230 235 240

Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser
245 250 255

Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Pro Tyr Tyr Trp Thr
260 265 270

Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Leu Ile Gly Tyr Ile
275 280 285

His Ser Ser Gly Tyr Thr Asp Tyr Asn Pro Ser Leu Lys Ser Arg Val
290 295 300

Thr Ile Ser Gly Asp Thr Ser Lys Lys Gln Phe Ser Leu Lys Leu Ser
305 310 315 320

123
AT 10W01 (1)

Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Asp
325 330 335

Trp Asp Arg Leu Arg Ala Leu Asp Ile Trp Gly Gln Gly Thr Met Val
340 345 350

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
355 360 365

Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro
370 375 380

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
385 390 395 400

Ala Ser Gln Ser Ile Arg Ser His Leu Asn Trp Tyr Gln Gln Lys Pro
405 410 415

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn Leu Gln Ser
420 425 430

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
435 440 445

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
450 455 460

Gln Gln Ser Thr Gly Ala Trp Asn Trp Phe Gly Cys Gly Thr Lys Val
465 470 475 480

Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr
485 490 495

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
500 505 510

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
515 520 525

124
AT 10W01 (1)

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
530 535 540

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
545 550 555 560

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
565 570 575

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
580 585 590

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
595 600 605

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
610 615 620

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
625 630 635 640

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
645 650 655

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
660 665 670

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
675 680 685

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
690 695 700

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
705 710 715 720

WHAT IS CLAIMED IS:

1. Use of an antibody or antigen-binding fragment thereof that specifically binds to a *Staphylococcus aureus* (*S. aureus*) alpha toxin antigen in the manufacture of a medicament for treating or preventing a polybacterial infection in a patient, wherein the antibody or antigen-binding fragment thereof is to be administered to the patient, wherein the polybacterial infection comprises *S. aureus* and at least one gram-negative bacterium, wherein the *S. aureus* alpha toxin potentiates the growth of the at least one gram-negative bacterium; and wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin binds to the same alpha toxin epitope as an antibody comprising the VH and VL sequences of SEQ ID NOs: 45 and 46.
2. The use of claim 1, wherein the at least one gram-negative bacterium is *Pseudomonas*, *Klebsiella* or *Acinetobacter*.
3. The use of claim 2, wherein the *Pseudomonas* is *Pseudomonas aeruginosa* (*P. aeruginosa*), the *Klebsiella* is *Klebsiella pneumoniae* (*K. pneumoniae*) or the *Acinetobacter* is *Acinetobacter baumannii* (*A. baumannii*).
4. The use of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 sequences of SEQ ID NOs: 57, 58, 59, 1, 2 and 56.
5. The use of claim 4, wherein antibody or antigen-binding fragment thereof comprises the VH and VL sequences of SEQ ID NOs: 45 and 46.
6. The use of claim 4, wherein the antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* alpha toxin comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 68 and a light chain comprising the amino acid sequence of SEQ ID NO: 69.

7. The use of any one of claims 1-4, wherein the antibody of antigen-binding fragment thereof is an IgG antibody of antigen-binding fragment thereof.
8. The use of claim 7, wherein the IgG antibody comprises the YTE substitutions of M252Y, S254T, and T256E, wherein the numbering is according to the EU index.
9. The use of any one of claims 1-8, wherein the polybacterial infection is an ocular infection, a lung infection, a burn infection, a wound infection, a surgical wound infection, a skin infection, a soft tissue infection, a blood infection, a bone infection, or a combination of two or more of said infections.
10. The use of any one of claims 1-9, wherein the patient has acute pneumonia, burn injury, corneal infection, cystic fibrosis, ventilator-associated pneumonia, a skin infection, a wound infection, or a combination thereof.
11. The use of any one of claims 1-10, wherein the polybacterial infection is a nosocomial infection.