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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 April 2020 (16.04.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/076789 A2

(51) International Patent Classification:
Not classified

(21) International Application Number:
PCT/US2019/055143

(22) International Filing Date:
08 October 2019 (08.10.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/743,490	09 October 2018 (09.10.2018)	US
62/833,297	12 April 2019 (12.04.2019)	US

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

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

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: COMBINATIONS OF ANTI-STAPHYLOCOCCUS AUREUS ANTIBODIES

(57) Abstract: The present disclosure is directed to anti- Staphylococcus aureus antibody combinations including combinations of antibodies that bind to *S. aureus* alpha toxin (AT) protein, clumping factor A protein (ClfA), and/or at least one leukotoxin protein. Methods of treating and preventing infections comprising administering the antibody combinations are also provided herein.

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COMBINATIONS OF ANTI-*STAPHYLOCOCCUS AUREUS* ANTIBODIES

BACKGROUND

[0001] Infections caused by antimicrobial resistant (AMR) bacterial pathogens are an increasing threat to public health. The ongoing AMR epidemic has been fueled, in part, by empiric broad spectrum antibiotic therapy. This has led to the exploration of pathogen specific methods, including monoclonal antibodies (mAbs), to prevent or treat serious bacterial infections. Numerous monoclonal antibodies are currently in development for the prevention or treatment of antibiotic resistant bacterial infections (see, e.g., DiGiandomenico, A., and B.R. Sellman, *Curr. Opin. Microbiol.*, *27*: 78-85 (2015)). Such passive immunization strategies provide an immediate and potent immunoglobulin response against the target pathogen. Ideally, the monoclonal antibody or monoclonal antibody cocktail provides multiple mechanisms of action to neutralize key bacterial virulence mechanisms and augment the host innate immune response, thus providing the greatest opportunity for clinical success.

[0002] *Staphylococcus aureus* is a bacterial pathogen that causes a wide array of diseases including skin and soft tissue infections, endocarditis, osteomyelitis, pneumonia, and bacteremia (Lowy, F.D., *N. Engl. J. Med.*, *339*(8): 520-32 (1998)). Preclinical studies indicate monoclonal antibody-based approaches hold promise for prophylaxis and adjunctive therapy against *S. aureus* infections (see, e.g., Hazenbos et al., *PLoS Pathog.*, *9*(10):e1003653. doi: 10.1371/journal.ppat.10036532013 (2013); Rouha, H., *MAbs*, *7*(1): 243-254 (2015); Foletti et al., *J. Mol. Biol.*, *425*(10): 1641-1654 (2013); Karauzum et al., *J Biol Chem.*, *287*(30): 25203-15 (2012); and Hua et al., *Antimicrob Agents Chemother.*, *58*(2): 1108-17 (2014)). However, treatment with individual antibodies may not be sufficient to address all *Staphylococcus aureus* infections. Thus, there remains a need for compositions and methods for treating *Staphylococcus aureus* infections, particularly infections that are resistant to currently-available antibiotics and that provide broad disease and strain coverage. The present disclosure provides such compositions and methods.

BRIEF SUMMARY OF THE INVENTION

[0003] As demonstrated herein, combinations of antibodies that target several different bacterial virulence factors via complementary mechanism of action can provide broad strain coverage and broad disease coverage. Exemplary animal models supporting the breadth of strain and disease coverage encompassed by the combinations of antibodies provided herein is provided in Figure 1.

[0004] Provided herein are methods of treating or preventing a *Staphylococcus aureus* (*S. aureus*) infection in a subject comprising administering to the subject (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin (AT), (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* clumping factor A (ClfA), and (c) an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

[0005] Provided herein are also methods of treating or preventing a *S. aureus* infection in a subject comprising administering to the subject an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin and (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin (AT) or (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* clumping factor A (ClfA).

[0006] Provided herein are also compositions comprising (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT, (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA, and (c) an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

[0007] Provided herein are also compositions comprising an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin and (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT or (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA.

[0008] In certain instances, the composition is for use in treating or preventing a *S. aureus* infection in a subject.

[0009] Provided herein are also antibodies and antigen-binding fragments thereof that bind to *S. aureus* AT for use in treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

[0010] Provided herein are also antibodies and antigen-binding fragments thereof that bind to *S. aureus* ClfA for use in treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

[0011] Provided herein are also antibodies and antigen-binding fragments thereof that bind to at least one *S. aureus* leukotoxin for use in treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and/or an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA.

[0012] In certain instances, the composition is used in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject.

[0013] Provided herein are also uses of an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

[0014] Provided herein are also uses of an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

[0015] Provided herein are also uses of an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and/or an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA.

[0016] In certain instances of the method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT binds to the same *S. aureus* AT epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33. In certain instances, the antibody or antigen-binding fragment thereof that binds

to *S. aureus* AT competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33 to *S. aureus* AT. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a variable heavy chain (VH) complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3, a variable light chain (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:12. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VH comprising the amino acid sequence of SEQ ID NO:19. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VL comprising the amino acid sequence of SEQ ID NO:33. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:47. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a light chain comprising the amino acid sequence of SEQ ID NO:52. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of MEDI4893. In certain instances, the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a heavy chain constant region. In certain instances, the heavy chain constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions. In certain instances, the heavy chain constant region is a human IgG_1 constant region. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a light chain constant region. In certain instances, the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions. In certain instances, the light chain constant region is a human IgGκ light chain constant region. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT is an IgG antibody or antigen-binding fragment thereof. In certain instances, the antibody or

antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region that has been engineered to improve half-life. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region with a YTE mutation. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* AT is a monoclonal antibody or antigen-binding fragment. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* AT is a full–length antibody. In certain instances, the antibody or antigen-binding the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT has an affinity of 80-100 pM for *S. aureus* AT.

[0017] In certain instances of the method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA binds to the same *S. aureus* ClfA epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:20 and a VL comprising the amino acid sequence of SEQ ID NO:34. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:20 and a VL comprising the amino acid sequence of SEQ ID NO:34 to *S. aureus* ClfA. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:5, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR1 comprising the amino acid sequence of SEQ ID NO:13, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:14, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:15. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH comprising the amino acid sequence of SEQ ID NO:20. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VL comprising the amino acid sequence of SEQ ID NO:34. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a heavy chain constant domain comprising the amino acid sequence of CSYHLC (SEQ ID NO:55). In

certain instances, the heavy chain constant domain comprises the amino acid sequence of MHEACSYHLCQKSLSLS (SEQ ID NO:56). In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:49. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a light chain comprising the amino acid sequence of SEQ ID NO:53. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of SAR114-N3Y. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of 11H10, SAR72, SAR80, SAR113, SAR132, SAR352, SAR372, SAR510, SAR547, SAS1, SAS19, or SAS203. In certain instances, the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH and a VL, wherein the VH comprises the amino acid sequence set forth in any one of SEQ ID NOs:21-31 and 68. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH and a VL, wherein the VL comprises the amino acid sequence set forth in any one of SEQ ID NOs: 35-45 and 69. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises VH and VL sequences comprising the amino acid sequences set forth in (a) SEQ ID NOs:21 and 35, respectively (b) SEQ ID NOs:22 and 36, respectively, (c) SEQ ID NOs:23 and 37, respectively, (d) SEQ ID NOs:24 and 38, respectively, (e) SEQ ID NOs:25 and 39, respectively, (f) SEQ ID NOs:26 and 40, respectively, (g) SEQ ID NOs:27 and 41, respectively, (h) SEQ ID NOs:28 and 42, respectively (i) SEQ ID NOs:29 and 43, respectively, (j) SEQ ID NOs:30 and 44, respectively, (k) SEQ ID NOs:31 and 45, respectively, or (l) SEQ ID NOs: 68 and 69, respectively. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA further comprises a heavy chain constant region. In certain instances, the heavy chain constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions. In certain instances, the heavy chain constant region is a human IgG_1 constant region. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA further comprises a light chain constant

region. In certain instances, the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions. In certain instances, the light chain constant region is a human IgGκ light chain constant region. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA comprises a mutation that extends half-life relative to the same antibody without the mutation in human FcRn mice. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA comprises a mutation that extends half-life relative to the same antibody without the mutation, and wherein the mutation does not inhibit OPK activity relative to the same antibody or antigen-binding fragment the mutation. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA is a monoclonal antibody or antigen-binding fragment. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA is a full–length antibody. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA is an antigen-binding fragment. In certain instances, the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has IC50s for ClfA001, ClfA002, and ClfA004 in a fibrinogen binding inhibition assay that are within 2 μg/ml of each other. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has IC50s for ClfA001, ClfA002, and ClfA004 in a fibrinogen binding inhibition assay that are all between 1 μg/ml and 5 μg/ml. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has binding affinities (K_D) for ClfA001, ClfA002, and ClfA004 that are all between 200 and 350 pM. In certain instances, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has binding affinities (K_D) of less than 1 nM for all ClfA genotypes. In certain instances, the antibody or antigen-binding fragment that binds to *S. aureus* ClfA has a monomer purity that decreases by no more than 5% after exposure of the antibody or antigen-binding fragment to conventional white light at 2kLux/hr at 23^0C for 14 days.

[0018] In certain instances of the method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin binds to LukF, LukD, and/or HlgB, and/or wherein the antibody

or antigen-binding fragment thereof neutralizes LukF, LukD, and/or HlgB. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin binds to LukF, LukD, and HlgB, and/or wherein the antibody or antigen-binding fragment thereof neutralizes LukF, LukD, and HlgB. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin binds to the same *S. aureus* leukotoxin epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:32 and a VL comprising the amino acid sequence of SEQ ID NO:46. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:32 and a VL comprising the amino acid sequence of SEQ ID NO:46 to the *S. aureus* leukotoxin. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a VHCDR1 comprising the amino acid sequence of SEQ ID NO:7, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:8, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:9, a VL CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:17, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:18. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a VH comprising the amino acid sequence of SEQ ID NO:32. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a VL comprising the amino acid sequence of SEQ ID NO:46. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:50. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a light chain comprising the amino acid sequence of SEQ ID NO:54. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of SAN481-SYT. In certain instances, the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs. In certain instances, the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin further comprises a heavy chain constant region. In certain instances, the heavy chain

constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions. In certain instances, the heavy chain constant region is a human IgG_1 constant region. In certain instances, the antibody or antigen-binding fragment that binds at least one *S. aureus* leukotoxin further comprises a light chain constant region. In certain instances, the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions. In certain instances, the light chain constant region is a human IgGκ light chain constant region. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin is an IgG antibody or antigen-binding fragment thereof. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises an Fc region that has been engineered to improve half-life. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises an Fc region with a YTE mutation. In certain instances, the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin is a monoclonal antibody or antigen-binding fragment. In certain instances, the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin is a full–length antibody. In certain instances, the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin is an antigen-binding fragment. In certain instances, the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin has an affinity of less than 75 pM for *S. aureus* LukF, LukD, and HlgAB. In certain instances, the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin has similar binding affinities for LukF, LukD, and HIgB. .

[0019] In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is sepsis. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is bacteremia. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is pneumonia. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or

use provided herein, the *S. aureus* infection is pneumonia the *S. aureus* infection is ICU pneumonia. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a skin or soft tissue infection (SSTI). In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a diabetic infection of the lower limbs. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a diabetic foot ulcer (DFU). In certain instances, the DFU is uninfected. In certain instances, the DFU is infected. In certain instances, the DFU is a grade 1, 2 or 3 DFU. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a bone or joint infection. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a joint infection, a device infection, a wound infection, a surgical site infection, or osteomyelitis.

[0020] In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the subject is a surgical subject.

[0021] In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection comprises antibiotic-resistant *S. aureus*.

[0022] In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the subject has diabetes. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the subject is human.

[0023] In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the treating or preventing an *S. aureus* infection comprises inhibiting *S. aureus* agglutination, toxin neutralization, inducing opsonophagocytosis, inhibiting *S. aureus* fibrinogen binding, inhibiting *S. aureus* agglutination, inhibiting thromboembolic lesion formation, inhibiting *S. aureus*-associated sepsis, or any combination of the foregoing.

[0024] In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA are administered in the same pharmaceutical composition. In certain instances of a method,

composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA are administered in the separate pharmaceutical compositions. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the same pharmaceutical composition. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the separate pharmaceutical compositions. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the same pharmaceutical composition. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the separate pharmaceutical compositions. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the separate pharmaceutical compositions are administered simultaneously. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the separate pharmaceutical compositions are administered sequentially. In certain instances of a method, composition, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA, and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the same pharmaceutical composition.

[0025] Provided herein are also methods of treating or preventing a *S. aureus* infection in a subject with diabetes comprising administering to the subject an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT.

[0026] Provided herein are also antibodies or antigen-binding fragments thereof that bind to *S. aureus* AT for use in treating or preventing a *S. aureus* infection in a subject with diabetes.

[0027] Provided herein are also uses of an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject with diabetes.

[0028] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT binds to the same *S. aureus* AT epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33.

[0029] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33 to *S. aureus* AT.

[0030] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3, a VL CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:12.

[0031] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VH comprising the amino acid sequence of SEQ ID NO:19.

[0032] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VL comprising the amino acid sequence of SEQ ID NO:33.

[0033] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:47.

[0034] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a light chain comprising the amino acid sequence of SEQ ID NO:52.

[0035] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of MEDI4893. In certain instances, the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

[0036] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a heavy chain constant region. In certain instances, the heavy chain constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions. In certain instances, the heavy chain constant region is a human IgG_1 constant region.

[0037] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a light chain constant region. In certain instances, the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions. In certain instances, the light chain constant region is a human IgGκ light chain constant region.

[0038] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT is an IgG antibody or antigen-binding fragment thereof.

[0039] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region that has been engineered to improve half-life.

[0040] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region with a YTE mutation.

[0041] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment that binds to *S. aureus* AT is a monoclonal antibody or antigen-binding fragment.

[0042] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment that binds to *S. aureus* AT is a full–length antibody.

[0043] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment that binds to *S. aureus* AT is an antigen-binding fragment. In certain instances, the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc.

[0044] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT has an affinity of 80-100 pM for *S. aureus* AT.

[0045] In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is sepsis. In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is bacteremia. In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is pneumonia. In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is ICU pneumonia. In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a SSTI. In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a diabetic infection of the lower limbs. In certain instances of a method, antibody or antigen-binding

fragment thereof, or use provided herein, the *S. aureus* infection is a DFU. In certain instances, the DFU is uninfected. In certain instances, the DFU is infected. In certain instances, the DFU is a grade 1, 2 or 3 DFU. In certain instances of a method, antibody or antigen-binding fragment thereof, or use provided herein, the *S. aureus* infection is a bone or joint infection.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

[0046] Figure 1 is a schematic showing that a range of animal models supports the use of the combination of antibodies directed against alpha toxin (AT), clumping factor A (ClfA), and leukotoxins to achieve broad strain and disease coverage.

[0047] Figure 2 is a graph showing the efficacy of the combination of antibodies directed against AT, ClfA, and leukotoxins (MEDI6389) in inhibiting red blood cell (RBC) hemolysis as compared to the efficacy of an antibody directed against AT (MEDI4893*) alone and the efficacy of a combination of antibodies directed against ClfA (SAR114) and leukotoxins (SAN481-SYT*). (See Example 1.)

[0048] Figure 3 is a graph showing the efficacy of the combination of antibodies directed against AT, ClfA, and leukotoxins (MEDI6389) in maintaining monocyte viability as compared to the efficacy an antibody directed against leukotoxins (SAN481-SYT*) alone and the efficacy of a combination of antibodies directed against AT (MEDI4893*) and ClfA (SAR114). (See Example 1.)

[0049] Figure 4 is a graph showing the efficacy of the combination of antibodies directed against AT, ClfA, and leukotoxins (MEDI6389) in inhibiting fibrinogen (Fg) binding as compared to the efficacy of an antibody directed against ClfA (SAR114) alone and the efficacy of a combination of antibodies directed against AT (MEDI4893*) and leukotoxins (SAN481-SYT*). (See Example 1.)

[0050] Figure 5 provides a graph and images showing that the combination of SAN481-SYT* and MEDI4893* is superior to the activity of either SAN481-SYT* or MEDI4893* alone in a dermonecrosis model with a *S. aureus* wound isolate. (See Example 2.)

[0051] Figure 6 provides graphs showing that neutralization of AT, ClfA, and leukotoxins are necessary for protection in the rabbit bacteremia model. (See Example 3.)

[0052] Figure 7 provides graphs comparing the efficacy of the combination of antibodies directed against AT, ClfA, and leukotoxins (MEDI6389) against two different bacterial bloodstream infections: HA-MRSA NRS382 (top panel) and CA-MRSA SF8300 (bottom panel). (See Example 4).

[0053] Figure 8 provides a graph and images showing that a mixed infection of *S. aureus* (SA), *Pseudomonas aeruginosa* (PA), and *Streptococcus pyogenese* (SP) resulted in delayed closure of skin lesions in a diabetic mouse dermonecrosis model compared to an infection by SA alone. The images show lesions at Day 43 post intra-dermal challenge. (See Example 5.)

[0054] Figure 9 provides graphs and images showing that the combination of antibodies directed against AT, ClfA, and leukotoxins (MEDI6389) improves the healing of wounds resulting from mixed-bacteria infections. (See Example 5).

[0055] Figure 10 provides a sequence alignment of HIgB (SEQ ID NO:59), LukF (SEQ ID NO:60), and LukD (SEQ ID NO:61).

[0056] Figures 11A-G show that elevated glucose levels correlate with more severe *S. aureus* infections. (A and B) After infection with *S. aureus*, diabetic *db/db* (A) and STZ (B) mice had increased mortality as compared to non-diabetic controls. (C) After infection with *S. aureus*, diabetic *db/db* mice had similar levels of *S. aureus* in their kidneys as non-diabetic controls. (D) After infection with *S. aureus*, diabetic STZ mice had similar levels of *S. aureus* in their kidneys as non-diabetic controls. (E, F, and G) Treatment with Rosiglitazone for 1 week prior to infection with *S. aureus* reduced circulating glucose (E) and increased survival (F), but did not affect the bacterial burden in the kidney (G). (See Example 7.)

[0057] Figures 12A-D show that systemic infection of the diabetic host lead to an AT-dependent increase in circulating NETs. (A) After infection with *S. aureus*, ELISA detected increased serum NETs in diabetic mice as compared to non-diabetic controls. (B) Neutralization of *S. aureus* alpha toxin (AT) with the anti-alpha toxin monoclonal antibody MEDI4893* significantly reduced the number of NE-DNA complexes in the serum 48 hours post-infection in diabetic mice. (C) After infection with *S. aureus*, Western blot showed increased citrinulated Histone H3 (H3cit) in diabetic mice as compared to non-diabetic controls. (D) Neutralization of *S. aureus* AT increased survival of diabetic mice infected with *S. aureus*. (See Example 8.)

[0058] Figures 13A-D show that diabetic *db/db* mice have increased low density neutrophils (LDNs). (A) After infection with *S. aureus*, the amount of LDNs in the blood of infected diabetic *db/db* mice was significantly increased as compared to uninfected *db/db* mice or non-diabetic controls. (B) Treatment with Rosiglitazone for 1 week prior to infection with *S. aureus* reduced LDNs 48 hours post-infection. (C and D) Neutralization of *S. aureus* AT prior to infection reduced LDNs (C) but did not affect overall numbers of neutrophils (D) in diabetic *db/db* mice. (See Example 9.)

[0059] Figure 14 shows that, after infection with *S. aureus*, diabetic STZ mice had increased low density neutrophils LDNs. (See Example 9.)

[0060] Figure 15A-D shows that delivery of a TGFβ neutralizing antibody prior to infection is protective in diabetic mice (A) TGFβ significantly increased the number of LDNs in diabetic *db/db* blood, but not in non-diabetic control blood. (B and C) Delivery of a TGFβ neutralizing antibody provided prior to *S. aureus* infection reduced LDNs in blood (B), but did not affect the amount of bacteria in the kidney (C). (D) Delivery of a TGFβ neutralizing antibody provided prior to infection increased survival of diabetic *db/db* mice. (See Example 10.)

[0061] FIGURES 16A-E show that blocking the αVβ6/8 pathway prior to infection is protective in diabetic mice. (A) β8 positive inflammatory monocytes and dendritic cells (DCs) increased in the livers of diabetic *db/db* mice, not C57BKS mice, following infection. (B) Integrin expression increased on the surface of monocytes, and the overall number of DCs (not the density of β8 on DCs) increased. (C) Neutralizing αVβ6/8 prior to infection decreased LDNs in the blood stream as compared to administration of an anti-αVβ6 antibody or a control antibody (c-IgG). (D) Neutralizing αVβ6/8 prior to infection did not affect the amount of bacteria in the kidney. (E) Neutralizing αVβ6/8 prior to infection increased survival as compared to administration of a control antibody (c-IgG). (See Example 10.)

[0062] FIGURES 17A-C show that AT influences activation of TGFß independently of αVβ8 expression on innate immune cells. (A) pSMAD levels were higher in the livers of infected diabetic mice as compared with naïve diabetic mice and infected non-diabetic mice. (B) Neutralizing AT significantly reduced pSMAD levels in the liver. (C) Neutralizing AT did not alter the numbers of αVβ8 expressing innate immune cells. (See Example 11.)

DETAILED DESCRIPTION OF THE INVENTION

[0063] The present disclosure provides combinations of antibodies and antigen-binding fragments thereof (e.g., monoclonal antibodies and antigen-binding fragments thereof) that bind to *Staphylococcus aureus* (*S. aureus*) alpha toxin (AT), clumping factor A (ClfA), and at least one leukotoxin. The present disclosure also provides methods of using such combinations, for example, in the treatment or prevention of *S. aureus* infections.

I. Definitions

[0064] As used herein, the term "alpha toxin" or "AT" refers to bacterial alpha toxin polypeptides including, but not limited to, native alpha toxin polypeptides and isoforms of alpha toxin polypeptides. "Alpha toxin" encompasses full-length, unprocessed alpha toxin polypeptides as well as forms of alpha toxin polypeptides that result from processing within the cell. As used herein, the term "*S. aureus* alpha toxin" refers to a polypeptide comprising the amino acid sequence of adsdiniktgttdigsnttvktgdlvtydkengmhkkvfysfiddknhnkkllvirtkgtiagqyrvyseeganksglawpsafkvqlql pdnevaqisdyyprnsidtkeymstltygfngnvtgddtgkiggliganvsightlkyvqpdfktilesptdkkvgwkvifnnmvnq nwgpydrdswnpvygnqlfmktrngsmkaadnfldpnkassllssgfspdfatvitmdrkaskqqtnidviyervrddyqlhwtst nwkgtntkdkwtdrsserykidwekeemtn (SEQ ID NO:57). The *S. aureus* alpha toxin H35L mutant has the sequence adsdiniktgttdigsnttvktgdlvtydkengmlkkvfysfiddknhnkkllvirtkgtiagqyrvyseeganksglawpsafkvqlql pdnevaqisdyyprnsidtkeymstltygfngnvtgddtgkiggliganvsightlkyvqpdfktilesptdkkvgwkvifnnmvnq nwgpydrdswnpvygnqlfmktrngsmkaadnfldpnkassllssgfspdfatvitmdrkaskqqtnidviyervrddyqlhwtst nwkgtntkdkwtdrsserykidwekeemtn (SEQ ID NO:58).

[0065] A "alpha toxin polynucleotide," "alpha toxin nucleotide," or "alpha toxin nucleic acid" refer to a polynucleotide encoding alpha toxin.

[0066] As used herein, the term "clumping factor A" or "ClfA" refers to bacterial clumping factor A polypeptides including, but not limited to, native clumping factor A polypeptides and isoforms of clumping factor A polypeptides. "Clumping factor A" encompasses full-length, unprocessed clumping factor A polypeptides as well as forms of clumping factor A polypeptides that result from processing within the cell. A "clumping factor A polynucleotide," "clumping

factor A nucleotide," or "clumping factor A nucleic acid" refer to a polynucleotide encoding alpha toxin.

[0067] As used herein, the term "leukotoxin" refers to bacterial leukotoxin polypeptides including, but not limited to, native leukotoxin polypeptides and isoforms of leukotoxin polypeptides. "Leukotoxin" encompasses a full-length, unprocessed leukotoxin polypeptides as well as forms of leukotoxin polypeptides that result from processing within the cell. Leukotoxins include LukSF, leukotoxin ED (LukED), HlgAB, HlgCB), and leukotoxin AB (LukAB, also known as LukGH). As used herein, the term "*S. aureus* HIgB" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO:59. As used herein, the term "*S. aureus* LukF" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO:60. As used herein, the term "*S. aureus* LukD" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO:61. As used herein, the term "*S. aureus* HIgB" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO:59. (See Figure 10.) A "leukotoxin polynucleotide," "leukotoxin nucleotide," or "leukotoxin nucleic acid" refer to a polynucleotide encoding a leukotoxin.

[0068] 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, chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antibody, and any other modified immunoglobulin molecule 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.

[0069] The term "monoclonal antibodies," as used herein, refers to antibodies that are produced by a single clone of B-cells and bind to the same epitope. In contrast, the term

"polyclonal antibodies" refers to a population of antibodies that are produced by different B-cells and bind to different epitopes of the same antigen.

[0070] The term "antibody fragment" refers to a portion of an intact antibody. An "antigen-binding fragment," "antigen-binding domain," or "antigen-binding region," refers to a portion of an intact antibody that binds to an antigen. An antigen-binding fragment can contain the antigenic determining regions of an intact antibody (e.g., the complementarity determining regions (CDR)). Examples of antigen-binding fragments of antibodies include, but are not limited to Fab, Fab', F(ab')2, and Fv fragments, linear antibodies, and single chain antibodies. An antigen-binding fragment of an antibody can be derived from any animal species, such as rodents (*e.g.*, mouse, rat, or hamster) and humans or can be artificially produced.

[0071] A whole antibody typically consists of four polypeptides: two identical copies of a heavy (H) chain polypeptide and two identical copies of a light (L) chain polypeptide. Each of the heavy chains contains one N-terminal variable (VH) region and three C-terminal constant (CHI , CH2 and CH3) regions, and each light chain contains one N-terminal variable (VL) region and one C-terminal constant (CL) region. The variable regions of each pair of light and heavy chains form the antigen binding site of an antibody. The VH and VL regions have the same general structure, with each region comprising four framework regions, whose sequences are relatively conserved. The term "framework region," as used herein, refers to the relatively conserved amino acid sequences within the variable region which are located between the hypervariable or complementary determining regions (CDRs). There are four framework regions in each variable domain, which are designated FR1, FR2, FR3, and FR4. The framework regions form the β sheets that provide the structural framework of the variable region (see, e.g., C.A. Janeway et al. (eds.), *Immunobiology*, 5th Ed., Garland Publishing, New York, NY (2001)). The three CDRs, known as CDR1, CDR2, and CDR3, form the "hypervariable region" of an antibody, which is responsible for antigen binding.

[0072] The terms "VL" and "VL domain" are used interchangeably to refer to the light chain variable region of an antibody.

[0073] The terms "VH" and "VH domain" are used interchangeably to refer to the heavy chain variable region of an antibody.

[0074] The term "Kabat numbering" and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody or an antigen-binding fragment thereof. In certain aspects, CDRs can be determined according to the Kabat numbering system (see, *e.g.*, Kabat EA & Wu TT (1971) Ann NY Acad Sci 190: 382-391 and Kabat EA *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

[0075] 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.

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

[0076] As used herein, the term "constant region" or "constant domain" are interchangeable and have its meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain.

[0077] As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG_1, IgG_2, IgG_3, and IgG_4. Heavy chain amino acid sequences are well known in the art. In specific embodiments, the heavy chain is a human heavy chain.

[0078] As used herein, the term "light chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[0079] A "chimeric" antibody refers to an antibody or fragment thereof comprising both human and non-human regions. A "humanized" antibody is a antibody comprising a human antibody scaffold and at least one CDR obtained or derived from a non-human antibody. Non-human antibodies include antibodies isolated from any non-human animal, such as, for example,

a rodent (e.g., a mouse or rat). A humanized antibody can comprise, one, two, or three CDRs obtained or derived from a non-human antibody. A fully human antibody does not contain any amino acid residues obtained or derived from a non-human animal. It will be appreciated that fully human and humanized antibodies carry a lower risk for inducing immune responses in humans than mouse or chimeric antibodies (see, e.g., Harding et al., *mAbs*, *2*(3): 256-26 (2010)).

[0080] As used herein, an "epitope" is a term in the art and refers to a localized region of an antigen to which an antibody or antigen-binding fragment thereof can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope to which an antibody or antigen-binding fragment thereof binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (e.g., liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization can be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.,* (1994) Acta Crystallogr D Biol Crystallogr 50(Pt 4): 339-350; McPherson A (1990) Eur J Biochem 189: 1-23; Chayen NE (1997) Structure 5: 1269-1274; McPherson A (1976) J Biol Chem 251: 6300-6303). Antibody/antigen-binding fragment thereof:antigen crystals can be studied using well known X-ray diffraction techniques and can be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; *see*, e.g., Meth Enzymol (1985) volumes 114 & 115, eds Wyckoff HW *et al.,*; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) Acta Crystallogr D Biol Crystallogr 49(Pt 1): 37-60; Bricogne G (1997) Meth Enzymol 276A: 361-423, ed Carter CW; Roversi P *et al.,* (2000) Acta Crystallogr D Biol Crystallogr 56(Pt 10): 1316-1323). Mutagenesis mapping studies can be accomplished using any method known to one of skill in the art. *See*, *e.g.*, Champe M *et al.,* (1995) J Biol Chem 270: 1388-1394 and Cunningham BC & Wells JA (1989) Science 244: 1081-1085 for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques.

[0081] An antibody that "binds to the same epitope" as a reference antibody refers to an antibody that binds to the same amino acid residues as the reference antibody. The ability of an antibody to bind to the same epitope as a reference antibody can determined by a hydrogen/deuterium exchange assay (see Coales et al. Rapid Commun. Mass Spectrom. 2009; 23: 639–647) or x-ray crystallography.

[0082] As used herein, the terms "immunospecifically binds," "immunospecifically recognizes," "specifically binds," and "specifically recognizes" are analogous terms in the context of antibodies or antigen-binding fragments thereof. These terms indicate that the antibody or antigen-binding fragment thereof binds to an epitope via its antigen-binding domain and that the binding entails some complementarity between the antigen binding domain and the epitope. Accordingly, for example, an antibody that "specifically binds" to a first *S. aureus* leukotoxin may also bind to other *S. aureus* leukotoxins, but the extent of binding to an un-related, non-leukotoxin protein is less than about 10% of the binding of the antibody to the first *S. aureus* leukotoxin as measured, e.g., by a radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), BiaCore or an octet binding assay.

[0083] An antibody is said to "competitively inhibit" binding of a reference antibody to a given epitope if it preferentially binds to that epitope or an overlapping 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%.

[0084] The term "nucleic acid sequence" is intended to encompass a polymer of DNA or RNA, i.e., a polynucleotide, which can be single-stranded or double-stranded and which can contain non-natural or altered nucleotides. The terms "nucleic acid" and "polynucleotide" as used herein refer to a polymeric form of nucleotides of any length, either ribonucleotides (RNA) or deoxyribonucleotides (DNA). These terms refer to the primary structure of the molecule, and thus include double- and single-stranded DNA, and double- and single-stranded RNA. The terms include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs and modified polynucleotides such as, though not limited to, methylated and/or capped polynucleotides. Nucleic acids are typically linked via phosphate bonds to form nucleic acid

sequences or polynucleotides, though many other linkages are known in the art (e.g., phosphorothioates, boranophosphates, and the like).

[0085] An *S. aureus* infection can occur, for example, as a skin or soft tissue infection (SSTI) or bacteremia. *S. aureus* bacteria can travel through the bloodstream and infect a site in the body, resulting in pneumonia, ICU pneumonia, a diabetic infection of the lower limbs, diabetic foot ulcer (DFU), a bone or joint infection, a device infection, a wound infection, a surgical site infection, or osteomyelitis.

[0086] "Transfection," "transformation," or "transduction," as used herein, refer to the introduction of one or more exogenous polynucleotides into a host cell by using physical or chemical methods. Many transfection techniques are known in the art and include, for example, calcium phosphate DNA co-precipitation (see, e.g., Murray E.J. (ed.), *Methods in Molecular Biology, Vol. 7, Gene Transfer and Expression Protocols*, Humana Press (1991)); DEAE-dextran; electroporation; cationic liposome-mediated transfection; tungsten particle-facilitated microparticle bombardment (Johnston, *Nature*, *346*: 776-777 (1990)); and strontium phosphate DNA co-precipitation (Brash et al, *Mol. Cell Biol.*, *7*: 2031-2034 (1987)). Phage or viral vectors can be introduced into host cells, after growth of infectious particles in suitable packaging cells, many of which are commercially available.

[0087] As used herein, the terms "treatment," "treating," and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. In one embodiment, the effect is therapeutic, i.e., the effect partially or completely cures a disease and/or adverse symptom attributable to the disease.

[0088] A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result (e.g., treatment of *S. aureus* infection). The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antigen-binding fragment to elicit a desired response in the individual.

[0089] A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired prophylactic result (e.g., prevention of *S. aureus* infection or disease onset).

[0090] The terms “administer”, “administering”, “administration”, and the like, as used herein, refer to methods that may be used to enable delivery of a drug, e.g., a combination of anti-*S. aureous* antibodies or antigen-binding fragments thereof to the desired site of biological action (e.g., intravenous administration). Administration techniques that can be employed with the agents and methods described herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current edition, Pergamon; and Remington’s, *Pharmaceutical Sciences*, current edition, Mack Publishing Co., Easton, Pa.

[0091] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) or consecutive administration in any order.

[0092] As used in the present disclosure and claims, the singular forms "a," "an," and "the" include plural forms unless the context clearly dictates otherwise.

[0093] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both "A and B," "A or B," "A," and "B." Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

II. Anti-Staphylococcus aureus antibodies and combinations thereof

[0094] As provided herein, antibodies and antigen-binding fragments thereof (e.g., monoclonal antibodies and fragments) that bind to *S. aureus* proteins can be used in combination. In particular, antibodies and antigen-binding fragments thereof that bind to *S. aureus* alpha toxin (AT) protein, antibodies and antigen-binding fragments thereof that bind to *S. aureus* clumping factor A (ClfA) protein, and antibodies an antigen-binding fragments thereof that bind to at least one *S. aureus* leukotoxin protein can advantageously be used in combination.

[0095] Alpha toxin (AT) is a key virulence factor in several *S. aureus* diseases, including pneumonia, skin and soft tissue infections (SSTI), and bacteremia (Bubeck Wardenburg, J. and O. Schneewind, *J. Exp. Med.*, *205*: 287-294 (2008); Inoshima et al., *J. Invest. Dermatol.*, *132*: 1513-1516 (2012); and Foletti et al., *supra*). Passive immunization with anti-AT monoclonal antibodies reduced disease severity in pneumonia and dermonecrosis models (Hua et al.,

Antimicrob. Agents Chemother., *58*: 1108-1117 (2014); Tkaczyk et al., *Clin. Vaccine Immunol.*, *19*: 377-385 (2012); and Ragle, B.E. and J. Wardenburg Bubeck, *Infect. Immun.*, *77*: 2712-2718 (2009)), and vaccination with an AT toxoid containing an H35L mutation (ATH35L) protected against death in mouse lethal bacteremia and pneumonia models (Bubeck Wardenburg, *supra*, Foletti et al., *supra*, Hua et al., *supra*, Ragle, *supra*, Menzies, B.E. and D.S Kernodle, *Infect. Immun.*, *77*: 2712-2718 (2009); and Adhikari et al., *PLoS One*, *7*: e38567 (2012)). AT contributes to multiple aspects of *S. aureus* pathogenesis during bacteremia and sepsis, including stimulating a hyperinflammatory response characteristic of sepsis and activating ADAM10-mediated cleavage of endothelial tight junctions, leading to a loss in vascular integrity (Powers et al., *J Infect. Dis.*, *206*: 352-356 (2012); Wilke, G.A. and J. Bubeck Wardenburg, *Proc. Natl. Acad. Sci. USA*, *107*: 13473-13478 (2010); and Becker et al., *J Innate Immun.*, *6*: 619-631 (2014)). AT also has been demonstrated to target platelets, which prevents repair of the injured endothelial barrier and promotes organ dysfunction through platelet-neutrophil aggregate formation (Powers et al., *Cell Host Microbe*, *17*: 775-787 (2015)). Alpha toxin structure and function is described in detail in, for example, Bhakdi, S. and J. Tranum-Jensen, *Microbiol. Mol. Biol. Rev.*, *55*(4): 733-751 (1991).

[0096] Monoclonal and polyclonal antibodies that bind AT are known in the art (see, e.g., Hua et al., *Antimicrob. Agents Chemother.*, *58*(2): 1108-1117 (2014); and Oganesyan et al., *J. Biol. Chem.*, *289*: 29874-29880 (2014)) and are commercially available from sources such as, for example, Sigma Aldrich (St. Louis, MO) and AbCam (Cambridge, MA). Exemplary antibodies that bind to AT are disclosed, for example, in WO 2012/109285 and WO 2014/074540 (both of which are herein incorporated by reference in their entireties).

[0097] In one instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* alpha toxin (AT) comprises, consists essentially of, or consists of (i) a heavy chain polypeptide comprising a CDR1 amino acid sequence of SEQ ID NO:1, a CDR2 amino acid sequence of SEQ ID NO:2, and a CDR3 amino acid sequence of SEQ ID NO:3, and (ii) a light chain polypeptide comprising a CDR1 amino acid sequence of SEQ ID NO:10, a CDR2 amino acid sequence of SEQ ID NO:11, and a CDR3 amino acid sequence of SEQ ID NO:12. In another instance, the heavy chain polypeptide of an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S.*

aureus AT comprises, consists essentially of, or consists of a variable region amino acid sequence of SEQ ID NO:19. In another instance, the light chain polypeptide of an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* AT comprises, consists essentially of, or consists of a variable region amino acid sequence of SEQ ID NO:33. In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* AT comprises, consists essentially of, or consists of a variable heavy chain comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:19 and a light chain variable region comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:33. In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* AT comprises, consists essentially of, or consists of a heavy chain comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:47 and/or a light chain variable region comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:52.

[0098] Among the many *S. aureus* surface adhesins, clumping factor A (ClfA) has been demonstrated to play an important role in serious bloodstream infections (Foster et al., *Nat. Rev. Microbiol.*, *12*: 49-62 (2014); and Murphy et al., *Hum. Vaccin.*, *7*(Suppl): 51-59 (2011)). ClfA binds fibrinogen and facilitates both bacterial adherence to fibrinogen and bacterial clumping, both of which are key attributes in the development of an *S. aureus* bloodstream infection (Vaudaux et al., *Infect. Immun.*, *63*: 585-590 (1995); McDevitt et al., *Mol. Microbiol.*, *11*: 237-248 (1994); and McDevitt et al., *Eur. J. Biochem.*, *247*: 416-424 (1997)). ClfA bound to fibrin or fibrinogen at a site of injury or coated on an indwelling device can facilitate bacterial colonization (Foster et al., *supra*) and bacterial clumping, which is thought to enhance bacterial invasiveness (McDevitt et al., *Eur. J. Biochem.*, *247*: 416-424 (1997); McAdow et al., *PLoS Pathog.*, *7*:e1002307 (2011); Flick et al., *Blood*, *121*: 1783-1794 (2013); and Rothfork et al., *J. Immunol.*, *171*: 5389-5395 (2003)). ClfA also has been reported to impair complement deposition required for opsonophagocytic bacterial killing (OPK) (Hair et al., *Infect. Immun.*, *78*: 1717-1727 (2010)). Consistent with these observations, isogenic ΔclfA mutants exhibited reduced virulence in infection models (McAdow et al., *supra*; Josefsson et al., *PLoS One*, *3*: e2206 (2008); and Josefsson et al., *J Infect. Dis.*, *184*: 1572-1580 (2001)). In addition, passive

immunization with human anti-ClfA-enriched intravenous (i.v.) immunoglobulin (Ig) (INH-A21 or Veronate) or a monoclonal antibody (tefibazumab or Aurexis) improved disease outcomes for patients with *S. aureus* bloodstream infections (Vernachio et al., *Antimcirob. Agents Chemother.*, *47*: 3400-3406 (2003); and Vernachio et al., *Antimicrob. Agents Chemother.*, *50*: 511-518 (2006)). However, these antibody preparations failed to improve outcomes in clinical studies of prophylaxis or adjunctive therapy with vancomycin to prevent or treat *S. aureus* bacteremia in very-low-birth-weight infants (DeJonge et al., *J. Pediatr.*, *151*: 260-265 (2007); Capparelli et al., Antimicrob. Agents Chemother., 49: 4121-4127 (2005); and Bloom et al., *Pediatr. Infect. Dis.*, *24*: 858-866 (2005)). ClfA structure and function is described in detail in, for example, McDevitt et al., *Mol. Microbiol.*, *11*: 237-248 (1994)).

[0099] Monoclonal and polyclonal antibodies which bind ClfA are known in the art (see, e.g., U.S. Patent 7,364,738; Hall et al., *Infect. Immun.*, *71*(12): 6864-6870 (2003); and Vernachio et al., *Antimicrob. Agents Chemother.*, *47*(11): 3400-3406 (2003)) and are commercially available from sources such as, for example, Creative Biolabs (Shirley, NY). Exemplary antibodies that bind to ClfA are disclosed, for example, in WO 2014/074540 and US 62/702,762 (both of which are herein incorporated by reference in their entireties).

[00100] In one instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* clumping factor A (ClfA) comprises, consists essentially of, or consists of (i) a heavy chain polypeptide comprising a CDR1 amino acid sequence of SEQ ID NO:4, a CDR2 amino acid sequence of SEQ ID NO:5, and a CDR3 amino acid sequence of SEQ ID NO:6, and (ii) a light chain polypeptide comprising a CDR1 amino acid sequence of SEQ ID NO:13, a CDR2 amino acid sequence of SEQ ID NO:14, and a CDR3 amino acid sequence of SEQ ID NO:15. In another instance, the heavy chain polypeptide of an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* ClfA comprises, consists essentially of, or consists of a variable region amino acid sequence of SEQ ID NO:20. In another instance, the light chain polypeptide of an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* ClfA comprises, consists essentially of, or consists of a variable region amino acid sequence of SEQ ID NO:34. In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* ClfA comprises, consists

essentially of, or consists of a variable heavy chain comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:20 and a light chain variable region comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:34. In certain instances, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* ClfA comprises a heavy chain constant domain comprising the amino acid sequence of CSYHLC (SEQ ID NO:55), MHEACSYHLCQKSLSLS (SEQ ID NO:56), or amino acids 233-454 of SEQ ID NO:49. In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* ClfA comprises, consists essentially of, or consists of a heavy chain comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:49 and/or a light chain variable region comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:53.

[00101] In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* ClfA (e.g., an antibody with the CDR, VH and/or VL, or heavy and or light chains of SAR114-N3Y) has IC50's for ClfA001, ClfA002, and ClfA004 in a fibrinogen binding inhibition assay that are within 2 μg/ml of each other. For example, the IC_{50}'s of the antibody or antigen-binding fragment thereof for ClfA001, ClfA002, and ClfA004 can all be between 1 μg/ml and 5 μg/ml. The binding affinities (K_D) of the antibody or antigen-binding fragment thereof for ClfA001, ClfA002, and ClfA004 can all be all between 200 and 350 pM.

[00102] In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to *S. aureus* ClfA (e.g., an antibody with the CDR, VH and/or VL, or heavy and or light chains of SAR114-N3Y) has a monomeric purity that decreases by no more than 5% after exposure to conventional white light at 2kLux/hr at 23°C for 14 days.

[00103] Leukotoxins are another type of *S. aureus* virulence factor. Leukotoxins target a broad range of immune cells for destruction. Leukotoxins include Panton–Valentine leukocidin (LukSF-PV also known as LukSF), leukotoxin ED (LukED), gamma hemolysin (which exists as two toxins: HlgAB and HlgCB), and leukotoxin AB (LukAB, also known as LukGH). In certain instances, an antibody or antigen-binding fragment thereof that binds to at least one leukotoxin

binds to LukF, LukD, and/or HIgAB. In certain instances, an antibody or antigen-binding fragment thereof that binds to at least one leukotoxin binds to LukF, LukD, and HIgB.

[00104] In one instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to at least one *S. aureus* leukotoxin comprises, consists essentially of, or consists of (i) a heavy chain polypeptide comprising a CDR1 amino acid sequence of SEQ ID NO:7, a CDR2 amino acid sequence of SEQ ID NO:8, and a CDR3 amino acid sequence of SEQ lD NO:9, and (ii) a light chain polypeptide comprising a CDR1 amino acid sequence of SEQ ID NO:16, a CDR2 amino acid sequence of SEQ ID NO:17, and a CDR3 amino acid sequence of SEQ ID NO:18. In another instance, the heavy chain polypeptide of an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to at least one *S. aureus* leukotoxin comprises, consists essentially of, or consists of a variable region amino acid sequence of SEQ ID NO:32. In another instance, the light chain polypeptide of an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to at least one *S. aureus* leukotoxin comprises, consists essentially of, or consists of a variable region amino acid sequence of SEQ ID NO:46. In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to at least one *S. aureus* leukotoxin comprises, consists essentially of, or consists of a variable heavy chain comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:32 and a light chain variable region comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:46. In another instance, an antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) that specifically binds to at least one *S. aureus* leukotoxin comprises, consists essentially of, or consists of a heavy chain comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:50 and/or a light chain variable region comprising, consisting essentially of, or consisting of the amino acid sequence of SEQ ID NO:54.

[00105] Sequences of exemplary anti-AT, anti-ClFA, and anti-leukotoxin antibodies are provided below. Additional anti-AT antibodies are provided, for example, in U.S. Patent No. 9,527,905, which is herein incorporated by reference in its entirety.) In certain instances, an antibody or antigen-binding fragment thereof described herein binds to AT, ClfA, or at lease one leukotoxin and comprises the six CDRs of an antibody listed in the two tables below (i.e., the

three VH CDRs of the antibody listed in the first table and the three VL CDRs of the same antibody listed in the second table).

[00106] The anti-AT antibody MEDI4893 is the half-life extended (YTE) version of MEDI4893* or "LC10" described previously in International Patent Application Publications WO 2012/109285 and WO 2014/074540 (both of which are herein incorporated by reference in their entireties). The anti-ClfA antibody SAR114-N3Y is described in U.S. Provisional Application No. 62/702,762. The anti-leukotoxin antibody SAN481-SYT is the half-life extended (YTE) version of SAN481-SYT*. SAN481-SYT* does not contain the YTE mutation.

VH CDR Amino Acid Sequences

Antibody Name	**Antibody Target**	**VH CDR1 (SEQ ID NO:)**	**VH CDR2 (SEQ ID NO:)**	**VH CDR3 (SEQ ID NO:)**
MEDI4893 and MEDI4893*	AT	SHDMH (SEQ ID NO:1)	GIGTAGDTYYPD SVKG (SEQ ID NO:2)	DRYSPTGHYYGMDV (SEQ ID NO:3)
SAR114 and SAR114-N3Y	ClfA	NSYWS (SEQ ID NO:4)	YLYSSGRTNYTPS LKS (SEQ ID NO:5)	THLGGFHYGGGFWF DP (SEQ ID NO:6)
11H10	ClfA	SFAMS (SEQ ID NO:62)	AISGSGGNTYYA DSVKG (SEQ ID NO:63)	IAFDI (SEQ ID NO:64)
SAN481-SYT and SAN481-SYT*	Leuko-toxin	TYAMH (SEQ ID NO:7)	VTSFDGSNEYYID SVKG (SEQ ID NO:8)	DEYTGGWYSVGY (SEQ ID NO:9)

VL CDR Amino Acid Sequences

Antibody	**Antibody Target**	**VL CDR1 (SEQ ID NO:)**	**VL CDR2 (SEQ ID NO:)**	**VL CDR3 (SEQ ID NO:)**
MEDI4893 and MEDI4893*	AT	RASQSISSWLA (SEQ ID NO:10)	KASSLES (SEQ ID NO:11)	KQYADYWT (SEQ ID NO:12)

SAR114 and SAR114-N3Y	ClfA	RASQSITSYLN (SEQ ID NO:13)	ASSSLQS (SEQ ID NO:14)	QESYSTPPT (SEQ ID NO15)
11H10	ClfA	RASQGIRNDL G (SEQ ID NO:65)	VASSLQS (SEQ ID NO:66)	LQHNSYPFT (SEQ ID NO:67)
SAN481-SYT and SAN481-SYT *	Leuko-toxin	SGSSYNIGSNY VY (SEQ ID NO:16)	RSIQRPS (SEQ ID NO:17)	AAWDDSLRAWV (SEQ ID NO:18)

[00107] In certain instances, an antibody or antigen-binding fragment thereof described herein binds to AT, ClfA, or at least one leukotoxin and comprises the VH of an antibody listed in the following table, e.g., in combination with a VL.

Variable Heavy Chain (VH) Amino Acid Sequence

Antibody	**Antibody Target**	**VH Amino Acid Sequence (SEQ ID NO)**
MEDI4893 and MEDI4893*	AT	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHDMHWVRQA TGKGLEWVSGIGTAGDTYYPDSVKGRFTISRENAKNSLYLQ MNSLRAGDTAVYYCARDRYSPTGHYYGMDVWGQGTTVT VSS (SEQ ID NO:19)
SAR114 and SAR114-N3Y	ClfA	QVQLQESGPGLVKPSETLSLTCTVSGGSIQNSYWSWIRQPPG KGLEWIGYLYSSGRTNYTPSLKSRVTISVDTSKNQFSLKLSS VTAADTAVYYCARTHLGGFHYGGGFWFDPWGQGTLVTVS S (SEQ ID NO:20)
11H10	ClfA	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFAMSWVR QAPGKGLEWVSAISGSGGNTYYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCAKIAFDIWGQGTMVT VSS (SEQ ID NO:68)
SAR72	ClfA	EVQLVESGGGLVKPGGSLRVSCAASGFSFRNALMSWVRQA PGKGLEWVGRSKTDGGTTDYAAPVKGRFTISRDDSKNTLY LQMNSLKTEDTAVYYCTTGPGGGPPGDYYYDGMDVWGQG TTVTVSS (SEQ ID NO:21)
SAR80	ClfA	EVQLVESGGDLVKPGGSLRLSCAASGFTFSDAWMTWVRQA PGKGLEWVGRIRSKTAGGTTDYAAPVKGRFTISRDDSKNTL YLQMTSLKIEDTALYYCMTDGLGLLNFGDSDPHHYWGQGT RVTVSS (SEQ ID NO:22)
SAR113	ClfA	EVQLVQSGAEVKKPGESLKISCKAXGYXFTSYWIGWVRQV PGKGLEWMGIIYPGDSDTRHSPSFQGQVTISVDKSISTAYLQ

		WSSLKASDSAMYYCARHQSGSHGFDAFEIWGQGTMVTVSS (SEQ ID NO:23)
SAR132	ClfA	EVQLVQSGAEVKKPGESLKISCKGSGYNFTNYWIAWVRQM PGKGLEWMGIIYSGDSDTRYSPSFLGQVSISVDKSFTTAYLQ WRSLKASDTAMYYCARRPGGQKPYDYWGQGTLVTVSS (SEQ ID NO:24)
SAR352	ClfA	EVQLVESGGGLVKPGGSLRLSCAASGFTFNNAWMSWVRQA PGKGLEWVGRIKSETAGGTTDYAAPVKGRFSISRDDSRNTL YLEMNSLKTEDTAVYYCTTDSYTPLEEPCPNGVCYTYYYY GMDVWGQGTTVTVSS (SEQ ID NO:25)
SAR372	ClfA	EVQLVESGGGLVQPGGSLRLSCAASGFIFNRYSMNWVRQA PGKGLEWVSYISSSSSPIYYADSVKGRFTISRDNAKNSLYLQ MNSLRDEDTAVYYCASRVTLGLEFDFWGQGTLVTVSS (SEQ ID NO:26)
SAR510	ClfA	QVTLRESGPALVKPTQTLTLTCTFSGFSLSTSGMCVGWIRQP PGKALEWLALIEWDDDKYYNTSLKTRLSISKDTSKNQVVLT MTNMDPVDTGTYYCARHSSSSRGFDYWGQGALVTVSS (SEQ ID NO:27)
SAR547	ClfA	EVQLVQSGAEVKKPGESLKISCKGSGYSFTTYWIAWVRQMP GKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSTATAYLQ WSSLNASDSAMYYCARQGGSHGYDAFHMWGQGTMVTVS S (SEQ ID NO:28)
SAS1	ClfA	EVQLLESGGGLVQPGGSLRLSCTASGFTFSTYALNWVRQAP GKGLEWVAGINGTGYNTYYADSVRGRFTISRDNSKNTVTLE MNSLRVEDTATYYCHKVPWWGQGTLVSVSS (SEQ ID NO: 29)
SAS19	ClfA	QVQLQESGPRLVKPSETLSLTCFVSGGSINNSYWTWIRQPPG QGLEWIGFVFSSGRTNYSPSLKSRVTISVDTSKNLFSLRLTSV TAADTAVYFCARQVHYDFWSGYSLTKTNWFDPWGQGTLV TVSS (SEQ ID NO:30)
SAS203	ClfA	QVQLQESGPGLVKPSETLSLTCVVSGGSINNSYWTWIRQPPG QGLEWIGFVYSSGRTYYSPSLKSRVTISVDTSKNFFSLRLNS VTAADTAVYFCARQVHYDLWSGYSLTKTNWFDPWGQGTL VTVSS (SEQ ID NO:31)
SAN481-SYT and SAN481-SYT*	Leuko-toxin	QLQLVESGGGAVQPGRSLKLSCAASGFTFSTYAMHWVRQA PGRGLEWVAVTSFDGSNEYYIDSVKGRFTISRDNTKNTLYL QMTGLRVEDTALYFCARDEYTGGWYSVGYWGQGTLVTVS S (SEQ ID NO:32)

[00108] In certain instances, an antibody or antigen-binding fragment thereof described herein binds to AT, ClfA, or at least one leukotoxin and comprises the VL of an antibody listed in the

following table, e.g., in combination with a VH, optionally the VH of the same antibody listed in the preceding table.

Variable Light Chain (VL) Amino Acid Sequence

Antibody	**Antibody Target**	**VL Amino Acid Sequence (SEQ ID NO)**
MEDI4893 and MEDI4893*	AT	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPG KAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFAT YYCKQYADYWTFGQGTKVEIK (SEQ ID NO:33)
SAR114 and SAR114-N3Y	ClfA	DIQMTQSPSSLSASVGDRVTITCRASQSITSYLNWYQQKPGK APKLLIYASSSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQESYSTPPTFGQGTKVEIK (SEQ ID NO:34)
11H10	ClfA	DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQ KPGKAPKRLIYVASSLQSGVPSRFSGSGSGTEFTLTISSL QPEDFATYYCLQHNSYPFTFGPGTKVDIK (SEQ ID NO:69)
SAR72	ClfA	SYELTQPPSVSVSPGQTARITCSGDAVPKKYAYWYQQKSGQ APVLVIYEDKKRPSGIPERFSGSSSGTMATLTISGAQVEDEA DYYCYSTDSSEGVFGGGTKLTVL (SEQ ID NO:35)
SAR80	ClfA	SYELTQPPSVSVSPGQTARITCSGDALPKKYAYWYQQKSGQ APVLVIHEDTKRPSGIPERFSGSSSGTMATLTISGAQVEDEAD YHCYSTDSSGVVFGGGTKLTVL (SEQ ID NO:36)
SAR113	ClfA	DIVLTQSPDSLAVSLGERATINCKSSQGVLSRSNNKNYLAW YQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQQYYNNLRTFGQGTKVEIR (SEQ ID NO:37)
SAR132	ClfA	DIQMTQSPSTLSASVGDRVTITCRASQRISNWLAWYQKKPG KAPKLLIYKASTLESEVPSRFSGSGSGTEFTLTISSLQPDDLAT YYCHQYISYYTFGQGTKLEIK (SEQ ID NO:38)
SAR352	ClfA	QSVLTQPPSVSAAPGEKVTISCSGSSSNIGANSVSWYQQFPG TAPKLLIYDNDKRPSGVPDRFSGSKSGTSATLGITGLQTGDE ADYYCGTWVGILSAGWVFGGGTKLTVL (SEQ ID NO:39)
SAR372	ClfA	EIVLTQSPATLSLSPGERATLSCRASQSVSSNLAWYQQKPGQ APRLLIYDASNRATGIPDRFSGSGSGTDFTLTISSLKPEDFAV YYCQLRSNWAYTFGQGTKLEIK (SEQ ID NO:40)
SAR510	ClfA	SYGLTQPPSVSVSPGQTARITCSGDALAKQYVYWYQQKPG QAPVLVIDKDRERPSGIPERFSGSSSGTTVTLTISGVQAEDEA DYYCQSADSSRTYVFGTGTKVTVL (SEQ ID NO: 41)
SAR547	ClfA	DVVMTQSPLSLPVTLGQPASISCRSSQSLVHSDGNTYLNWF QQRPGQSPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRV

		EAEDVGVYYCMQGTHLTWTFGQGTKVEIK (SEQ ID NO:42)
SAS1	ClfA	DIVLTQSPESLAVSLGERATISCKSSQSLFFKSNNKNYLAWY QQKPGQPPKVIIYWASTRESGVPARFSGSGSGTDFTLTISSLQ AEDVAVYFCHQYYSTQYSFGQGTKLEIK (SEQ ID NO:43)
SAS19	ClfA	DIQMTQSPSSLSASVGDTVTITCRTSQSISNFLNWYQQKPGK APKLLIYAASSLQSGVPSRVNGSTSGTEFTLTLSSLQPEDFAT YYCQQSYSTPWTFGQGTKVEIK (SEQ ID NO:44)
SAS203	ClfA	DIQMTQSPSSLSASVGDTVTITCRTSQSISNFLNWYQQKPGK APKLLIYAASSLQSGVPSRFNGSTSGTDFTLTLSSLQPEDFAT YYCQQSYSTPWTFGQGTKVEIK (SEQ ID NO:45)
SAN481-SYT and SAN481-SYT*	Leuko-toxin	QSVLTQPPSASGTPGQRVTISCSGSSYNIGSNYVYWYQQFPG TAPKLLISRSIQRPSGVPDRFSGSKSVTSASLAISGLRSEDEAD YYCAAWDDSLRAWVFGGGTKLTVL (SEQ ID NO:46)

[00109] In certain instances, an antibody or antigen-binding fragment thereof described herein binds to AT, ClfA, or at least one leukotoxin and comprises the heavy chain of an antibody listed in the following table, e.g., in combination with a light chain.

Full-length heavy chain amino acid sequences

Antibody	**Antibody Target**	**Full-Length Heavy Chain Amino Acid Sequence (SEQ ID NO)**
MEDI4893	AT	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHDMHWVRQA TGKGLEWVSGIGTAGDTYYPDSVKGRFTISRENAKNSLYL QMNSLRAGDTAVYYCARDRYSPTGHYYGMDVWGQGTTV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK (SEQ ID NO:47)
MEDI4893*	AT	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHDMHWVRQA TGKGLEWVSGIGTAGDTYYPDSVKGRFTISRENAKNSLYLQ MNSLRAGDTAVYYCARDRYSPTGHYYGMDVWGQGTTVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY

		KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO:48)
SAR114-N3Y	ClfA	QVQLQESGPGLVKPSETLSLTCTVSGGSIQNSYWSWIRQPPG KGLEWIGYLYSSGRTNYTPSLKSRVTISVDTSKNQFSLKLSS VTAADTAVYYCARTHLGGFHYGGGFWFDPWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEACSYHLCQKSLSLSP GK (SEQ ID NO:49)
SAR114	ClfA	QVQLQESGPGLVKPSETLSLTCTVSGGSIQNSYWSWIRQPPG KGLEWIGYLYSSGRTNYTPSLKSRVTISVDTSKNQFSLKLSS VTAADTAVYYCARTHLGGFHYGGGFWFDPWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO:70)
SAN481-SYT	Leuko-toxin	QLQLVESGGGAVQPGRSLKLSCAASGFTFSTYAMHWVRQA PGRGLEWVAVTSFDGSNEYYIDSVKGRFTISRDNTKNTLYL QMTGLRVEDTALYFCARDEYTGGWYSVGYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO:50)
SAN481-SYT*	Leuko-toxin	QLQLVESGGGAVQPGRSLKLSCAASGFTFSTYAMHWVRQA PGRGLEWVAVTSFDGSNEYYIDSVKGRFTISRDNTKNTLYL QMTGLRVEDTALYFCARDEYTGGWYSVGYWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC

		NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO:51)

[00110] In certain instances, an antibody or antigen-binding fragment thereof described herein binds to AT, ClfA, or at least one leukotoxin and comprises the light chain of an antibody listed in the following table, e.g., in combination with a heavy chain, optionally the heavy chain of the same antibody listed in the preceding table.

Full-length light chain amino acid sequences

Antibody	**Antibody Target**	**Full-Length Light Chain Amino Acid Sequence (SEQ ID NO)**
MEDI4893 and MEDI4893*	AT	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQK PGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISSLQP DDFATYYCKQYADYWTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGE (SEQ ID NO:52)
SAR114-N3Y	ClfA	DIQMTQSPSSLSASVGDRVTITCRASQSITSYLNWYQQK PGKAPKLLIYASSSLQSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQESYSTPPTFGQGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC (SEQ ID NO:53)
SAN481-SYT and SAN481-SYT*	Leuko-toxin	QSVLTQPPSASGTPGQRVTISCSGSSYNIGSNYVYWYQQ FPGTAPKLLISRSIQRPSGVPDRFSGSKSVTSASLAISGLR SEDEADYYCAAWDDSLRAWVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO:54)

[00111] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (*see*, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B *et al.*, (1997) J Mol Biol 273: 927-948; Chothia C *et al.*, (1992) J Mol Biol

227: 799-817; Tramontano A *et al.*, (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226). Typically, when using the Kabat numbering convention, the Chothia CDR-H1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDR-H2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDR-H3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDR-L1 loop is present at light chain amino acids 24 to 34, the Chothia CDR-L2 loop is present at light chain amino acids 50 to 56, and the Chothia CDR-L3 loop is present at light chain amino acids 89 to 97. 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).

[00112] In certain aspects, provided herein are combinations of antibodies and antigen-binding fragments thereof that comprise the Chothia VH and VL CDRs of the MEDI4893, SAR114-N3Y, and/or SAN481-SYT antibodies. In certain embodiments, antibodies or antigen-binding fragments thereof comprise one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, provided herein are antibodies and antigen-binding fragments thereof comprise combinations of Kabat CDRs and Chothia CDRs.

[00113] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to the IMGT numbering system as described in Lefranc M-P, (1999) The Immunologist 7: 132-136 and Lefranc M-P *et al.*, (1999) Nucleic Acids Res 27: 209-212. According to the IMGT numbering scheme, VH-CDR1 is at positions 26 to 35, VH-CDR2 is at positions 51 to 57, VH-CDR3 is at positions 93 to 102, VL-CDR1 is at positions 27 to 32, VL-CDR2 is at positions 50 to 52, and VL-CDR3 is at positions 89 to 97. In a particular embodiment, provided herein are combinations of antibodies and antigen-binding fragments thereof that comprise the IMGT VH and VL CDRs of MEDI4893, SAR114-N3Y, and/or SAN481-SYT antibodies, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*).

[00114] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to MacCallum RM *et al.*, (1996) J Mol Biol 262: 732-745. *See also, e.g.*, Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in

Antibody Engineering, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001). In a particular embodiment, provided herein are combinations of antibodies or antigen-binding fragments thereof comprise the VH and VL CDRs of the MEDI4893, SAR114-N3Y, and/or SAN481-SYT antibodies determined by the method in MacCallum RM *et al.*

[00115] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to the AbM numbering scheme, which refers AbM hypervariable regions which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.). In a particular embodiment, provided herein are combinations of antibodies or antigen-binding fragments that and comprise VH and VL CDRs of the MEDI4893, SAR114-N3Y, and/or SAN481-SYT antibodies as determined by the AbM numbering scheme.

[00116] In another aspect, the antibody or antigen-binding fragment thereof (e.g., monoclonal antibody or fragment) described herein can comprise a constant region (Fc) of any suitable class (e.g., IgG, IgA, IgD, IgM, and IgE) that has been modified in order to improve the half-life of the antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment). For example, the antibody or antigen-binding fragment thereof (e.g., monoclonal antibody or fragment) described herein can comprise an Fc that comprises a mutation that extends half-life relative to the same antibody without the mutation.

[00117] Fc region engineering is widely used in the art to extend the half-life of therapeutic antibodies and protect from degradation *in vivo*. In some embodiments, the Fc region of an IgG antibody or antigen-binding fragment can be modified in order to increase the affinity of the IgG molecule for the Fc Receptor-neonate (FcRn), which mediates IgG catabolism and protects IgG molecules from degradation. Suitable Fc region amino acid substitutions or modifications are known in the art and include, for example, the triple substitution M252Y/S254T/T256E (referred to as "YTE") (see, e.g., U.S. Patent 7,658,921; U.S. Patent Application Publication 2014/0302058; and Yu et al., *Antimicrob. Agents Chemother.*, *61*(1): e01020-16 (2017)). In certain aspects, an antibody or antigen-binding binding fragment (e.g., monoclonal antibody or fragment) that binds to *S. aureus* AT comprises an Fc region comprising the YTE mutation. In certain aspects, an antibody or antigen-binding binding fragment (e.g., monoclonal antibody or fragment) that binds to at least one *S. aureus* leukotoxin comprises an Fc region comprising the

YTE mutation. In certain aspects, an antibody or antigen-binding binding fragment (e.g., monoclonal antibody or fragment) that binds to *S. aureus* AT comprises an Fc region comprising the YTE mutation and an antibody or antigen-binding binding fragment (e.g., monoclonal antibody or fragment) that binds to at least one *S. aureus* leukotoxin comprises an Fc region comprising the YTE mutation.

[00118] In another aspect, the Fc region can comprise the sequence CSYHLC (referred to as "N3Y"; SEQ lD NO:55). In certain aspects, an antibody or antigen-binding binding fragment (e.g., monoclonal antibody or fragment) that binds to *S. aureus* ClfA comprises an Fc region comprising the N3Y Fc variant.

[00119] In another aspect, the antibody or antigen-binding fragment thereof (e.g., monoclonal antibody or fragment) described herein can comprise a constant region (Fc) of any suitable class (IgG, IgA, IgD, IgM, and IgE) that has been modified in order to improve effector functions (e.g., opsonophagocytic bacterial killing (OPK)), optionally wherein the half-life of the antibody or antigen-binding fragment (e.g., monoclonal antibody or fragment) is also improved. For example, the antibody or antigen-binding fragment thereof (e.g., monoclonal antibody or fragment) described herein may comprise an Fc that comprises a mutation that extends half-life relative to the same antibody without the mutation, and wherein the mutation does not inhibit OPK activity relative to the same antibody or antigen-binding fragment the mutation. The N3Y Fc variant, in particular, exhibits enhanced pharmacokinetic (PK) properties (e.g., serum persistence) and effector functions (e.g., opsonophagocytic bacterial killing (OPK)) in certain antibodies as compared to the YTE variants.

[00120] An antibody or antigen-binding fragment (e.g. monoclonal antibody or fragment) described herein can be, or can be obtained from, a human antibody, a humanized antibody, a non-human antibody, or a chimeric antibody. In one aspect, an antibody described herein, or antigen-binding fragment thereof, is a fully human antibody.

[00121] A human antibody, a non-human antibody, a chimeric antibody, or a humanized antibody can be obtained by any means, including via *in vitro* sources (e.g., a hybridoma or a cell line producing an antibody recombinantly) and *in vivo* sources (e.g., rodents, human tonsils). Methods for generating antibodies are known in the art and are described in, for example, Köhler and Milstein, *Eur. J. Immunol.*, *5*: 511-519 (1976); Harlow and Lane (eds.), *Antibodies: A*

Laboratory Manual, CSH Press (1988); and Janeway et al. (eds.), *Immunobiology, 5th Ed.*, Garland Publishing, New York, N.Y. (2001)). In certain embodiments, a human antibody or a chimeric antibody can be generated using a transgenic animal (e.g., a mouse) wherein one or more endogenous immunoglobulin genes are replaced with one or more human immunoglobulin genes. Examples of transgenic mice wherein endogenous antibody genes are effectively replaced with human antibody genes include, but are not limited to, the Medarex HUMAB-MOUSE™, the Kirin TC MOUSE™, and the Kyowa Kirin KM-MOUSE™ (see, e.g., Lonberg, *Nat. Biotechnol.*, *23*(9): 1117-25 (2005), and Lonberg, *Handb. Exp. Pharmacol.*, *181*: 69-97 (2008)). A humanized antibody can be generated using any suitable method known in the art (see, e.g., An, Z. (ed.), *Therapeutic Monoclonal Antibodies: From Bench to Clinic*, John Wiley & Sons, Inc., Hoboken, N.J. (2009)), including, e.g., grafting of non-human CDRs onto a human antibody scaffold (see, e.g., Kashmiri et al., *Methods*, *36*(1): 25-34 (2005); and Hou et al., *J. Biochem.*, *144*(1): 115-120 (2008)). In one embodiment, a humanized antibody can be produced using the methods described in, e.g., U.S. Patent Application Publication 2011/0287485 A1.

III. Nucleic acids, vectors, and host cells

[00122] Also provided herein are one or more isolated nucleic acid sequences that encode the antibody or antigen-binding fragment thereof that binds to AT, the antibody or antigen-binding fragment thereof that binds to ClfA, or the antibody or antigen-binding fragment thereof that binds to at least one leukotoxin (optionally wherein one or more of the antibodies or antigen-binding fragments thereof is a monoclonal antibody or fragment).

[00123] The disclosure further provides one or more vectors comprising one or more nucleic acid sequences encoding antibody or antigen-binding fragment thereof that binds to AT, the antibody or antigen-binding fragment thereof that binds to ClfA, and/or the antibody or antigen-binding fragment thereof that binds to at least one leukotoxin (optionally wherein one or more of the antibodies or antigen-binding fragments thereof is a monoclonal antibody or fragment). The vector can be, for example, a plasmid, episome, cosmid, viral vector (e.g., retroviral or adenoviral), or phage. Suitable vectors and methods of vector preparation are well known in the art (see, e.g., Sambrook et al., *Molecular Cloning, a Laboratory Manual, 3rd edition*, Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (2001), and Ausubel et al., *Current Protocols in*

Molecular Biology, Greene Publishing Associates and John Wiley & Sons, New York, N.Y. (1994)).

[00124] In addition to the nucleic acid sequence encoding the antibody or antigen-binding fragment thereof that binds to AT, the antibody or antigen-binding fragment thereof that binds to ClfA, and/or the antibody or antigen-binding fragment thereof that binds to at least one leukotoxin (optionally wherein one or more of the antibodies or antigen-binding fragments thereof is a monoclonal antibody or fragment), the vector desirably comprises expression control sequences, such as promoters, enhancers, polyadenylation signals, transcription terminators, internal ribosome entry sites (IRES), and the like, that provide for the expression of the coding sequence in a host cell. Exemplary expression control sequences are known in the art and described in, for example, Goeddel, *Gene Expression Technology: Methods in Enzymology*, Vol. 185, Academic Press, San Diego, Calif. (1990).

[00125] The vector(s) comprising the nucleic acid(s) encoding the antibody or antigen-binding fragment thereof that binds to AT, the antibody or antigen-binding fragment thereof that binds to ClfA, or the antibody or antigen-binding fragment thereof that binds to at least one leukotoxin (optionally wherein one or more of the antibodies or antigen-binding fragments thereof is a monoclonal antibody or fragment) can be introduced into a host cell that is capable of expressing the polypeptides encoded thereby, including any suitable prokaryotic or eukaryotic cell. As such, the present disclosure provides an isolated cell comprising the vector. Host cells that may be used include those that can be easily and reliably grown, have reasonably fast growth rates, have well characterized expression systems, and can be transformed or transfected easily and efficiently. Examples of suitable prokaryotic cells include, but are not limited to, cells from the genera *Bacillus* (such as *Bacillus subtilis* and *Bacillus brevis*), *Escherichia* (such as *E. coli*), *Pseudomonas*, *Streptomyces*, *Salmonella*, and *Erwinia*. Particularly useful prokaryotic cells include the various strains of *Escherichia coli* (e.g., K12, HB101 (ATCC No. 33694), DH5a, DH10, MC1061 (ATCC No. 53338), and CC102). Suitable eukaryotic cells are known in the art and include, for example, yeast cells, insect cells, and mammalian cells. In one embodiment, the vector is expressed in mammalian cells. A number of suitable mammalian host cells are known in the art, and many are available from the American Type Culture Collection (ATCC, Manassas, VA). Examples of suitable mammalian cells include, but are not limited to, Chinese

hamster ovary cells (CHO) (ATCC No. CCL61), CHO DHFR- cells (Urlaub et al, *Proc. Natl. Acad. Sci. USA*, *97*: 4216-4220 (1980)), human embryonic kidney (HEK) 293 or 293T cells (ATCC No. CRL1573), and 3T3 cells (ATCC No. CCL92). Other suitable mammalian cell lines are the monkey COS-1 (ATCC No. CRL1650) and COS-7 cell lines (ATCC No. CRL1651), as well as the CV-1 cell line (ATCC No. CCL70). The mammalian cell desirably is a human cell. For example, the mammalian cell can be a human lymphoid or lymphoid derived cell line, such as a cell line of pre-B lymphocyte origin, a PER.C6® cell line (Crucell Holland B.V., The Netherlands), or human embryonic kidney (HEK) 293 or 293T cells (ATCC No. CRL1573).

[00126] A nucleic acid sequence encoding amino acids of any of the antibodies or antigen-binding fragments (optionally monoclonal antibodies or fragments) described herein can be introduced into a cell by transfection, transformation, or transduction.

IV. Pharmaceutical compositions and methods of using combinations of anti-Staphylococcus aureus antibodies

[00127] The present disclosure provides a composition comprising an effective amount of any one or combination of the antibodies or antigen-binding fragments thereof described herein and a pharmaceutically acceptable carrier. In one embodiment, for example, the composition may comprise a first antibody or antigen-binding fragment thereof (optionally monoclonal) that specifically binds to *S. aureus* alpha toxin protein, as described above, a second antibody or antigen-binding fragment thereof (optionally monoclonal) that specifically binds to *S. aureus* ClfA protein, and a third antibody or antigen-binding fragment thereof (optionally monoclonal) that specifically binds to at least one *S. aureus* leukotoxin, as described above, and a pharmaceutically acceptable carrier. Alternatively, the composition can comprise a pharmaceutically acceptable carrier and any one or any two of (i) an antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* AT, (ii) an antibody or antigen-binding fragment thereof that specifically binds to *S. aureus* ClfA, (iii) an antibody or antigen-binding fragment thereof that specifically binds to at least one *S. aureus* leukotoxin.

[00128] In another aspect, the composition may comprise the nucleic acid sequences encoding the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-

binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment, or one or more vectors comprising such nucleic acid sequences. In one asepct, the composition is a pharmaceutically acceptable (e.g., physiologically acceptable) composition, which comprises a carrier, such as a pharmaceutically acceptable (e.g., physiologically acceptable) carrier and the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and/or the anti-leukotoxin antibody or antigen-binding fragment nucleic acid sequence(s), or vector(s).

[00129] Any suitable carrier can be used within the context of the disclosure, and such carriers are well known in the art. The choice of carrier will be determined, in part, by the particular site to which the composition may be administered and the particular method used to administer the composition. The composition optionally can be sterile. The composition can be frozen or lyophilized for storage and reconstituted in a suitable sterile carrier prior to use. The compositions can be generated in accordance with conventional techniques described in, e.g., *Remington: The Science and Practice of Pharmacy*, 21st Edition, Lippincott Williams & Wilkins, Philadelphia, PA (2001).

[00130] The composition desirably comprises the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and the leukotoxin-binding antibody or antigen-binding fragment in an amount that is effective to treat or prevent a *S. aureus* infection. In another aspect, the composition comprises the AT-binding antibody or antigen-binding fragment in an amount that is effective to treat or prevent a *S. aureus* infection in combination with the ClfA-binding antibody or antigen-binding fragment, and the leukotoxin-binding antibody or antigen-binding fragment. In another aspect, the composition comprises the ClfA-binding antibody or antigen-binding fragment in an amount that is effective to treat or prevent a *S. aureus* infection in combination with the AT-binding antibody or antigen-binding fragment, and the leukotoxin-binding antibody or antigen-binding fragment. In another aspect, the composition comprises the leukotoxin-binding antibody or antigen-binding fragment in an amount that is effective to treat or prevent a *S. aureus* infection in combination with the AT-binding antibody or antigen-binding fragment, and the ClfA-binding antibody or antigen-binding fragment. In another aspect, the composition comprises the AT-binding antibody or antigen-binding fragment and the ClfA-binding antibody or antigen-binding fragment in an amount that

is effective to treat or prevent a *S. aureus* infection in combination with the leukotoxin-binding antibody or antigen-binding fragment. In another aspect, the composition comprises the AT-binding antibody or antigen-binding fragment and the leukotoxin-binding antibody or antigen-binding fragment in an amount that is effective to treat or prevent a *S. aureus* infection in combination with the ClfA-binding antibody or antigen-binding fragment. In another aspect, the composition comprises the ClfA-binding antibody or antigen-binding fragment and the leukotoxin-binding antibody or antigen-binding fragment in an amount that is effective to treat or prevent a *S. aureus* infection in combination with the AT-binding antibody or antigen-binding fragment.

[00131] To this end, the disclosed method comprises administering a therapeutically effective amount or prophylactically effective amount of an AT-binding antibody or antigen-binding fragment thereof, a ClfA-binding antibody or antigen-binding fragment thereof, and a leukotoxin-binding antibody or antigen-binding fragment thereof or a composition comprising any one or any combination of the aforementioned antibodies or fragments (including monoclonal antibodies or fragments).

[00132] The disclosure provides a method of treating or preventing a *Staphylococcus aureus* (*S. aureus*) infection in a subject (e.g., a human), which comprises administering the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment described herein to a subject in need thereof, whereupon the *S. aureus* infection is treated or prevented in the subject. The disclosure also provides use of the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment, described herein, or the composition comprising any one or combination of the antibodies or fragments thereof described herein, in the manufacture of a medicament for treating or preventing a *S. aureus* infection.

[00133] As discussed herein, *Staphylococcus aureus* is a major human pathogen that causes a wide range of clinical infections. *S. aureus* is a leading cause of bacteremia and infective endocarditis as well as osteoarticular, skin and soft tissue, pleuropulmonary, and device-related infections. Approximately 30% of the human population is colonized with *S. aureus* (Wertheim et al., *Lancet Infect. Dis.*, *5*: 751-762 (2005)). The symptoms of *S. aureus* skin infections

include, for example, boils, cellulits, and impetigo. *S. aureus* also may cause food poisoning, blood poisoning (also known as bacteremia), toxic shock syndrome, and septic arthritis. The epidemiology, pathophysiology, and clinical manifestations of *S. aureus* infections are described in detail in, e.g., Tong et al., *Clin. Microbiol. Rev.*, *28*(3): 603-661 (2015), and the genomes of several different *S. aureus* strains have been sequenced (see, e.g., GenBank/EMBL Accession Nos. BX571856, BX571857, BX571858, FN433596, FN433597, FN433598, HE681097, FR821777, FR821778, FR821779, and FR821780). As discussed herein, the subject (e.g., human subject) can have diabetes.

[00134] In certain instances, a therapeutically effective amount of the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment, is an amount which inhibits *S. aureus*-associated sepsis, inhibits *S. aureus* agglutination, inhibits thromboembolic lesion formation, neutralizes alpha toxin, neutralizes LukSF, HlgAB, HlgCB and LukED, induces opsonophagocytosis, inhibits *S. aureus* fibrinogen binding, inhibits *S. aureus* agglutination, or any combination of the foregoing, in a human.

[00135] Alternatively, the pharmacologic and/or physiologic effect may be prophylactic, i.e., the effect completely or partially prevents a disease or symptom thereof. In this respect, the disclosed method comprises administering a "prophylactically effective amount" of the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment, (including monoclonal antibodies or fragments).

[00136] Therapeutic or prophylactic efficacy can be monitored by periodic assessment of treated patients. For repeated administrations over several days or longer, depending on the condition, the treatment can be repeated until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful and are within the scope of the present disclosure. The desired dosage can be delivered by a single bolus administration of the composition, by multiple bolus administrations of the composition, or by continuous infusion administration of the composition.

[00137] The method of treating or preventing a *S. aureus* infection can comprise administering the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody

or antigen-binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment in the same composition or in separate compositions. When separate compositions are administered to the subject, each of the compositions can be administered simultaneously or sequentially in any order.

[00138] The composition(s) comprising an effective amount of any one or combination of the antibodies described herein, or antigen-binding fragments thereof, the nucleic acid sequence(s) encoding any of the foregoing, or the vector comprising the nucleic acid sequence can be administered to a subject, such as a human, using standard administration techniques, including intravenous, intraperitoneal, subcutaneous, and intramuscular administration routes. The composition may be suitable for parenteral administration. The term "parenteral," as used herein, includes intravenous, intramuscular, subcutaneous, and intraperitoneal administration. In some embodiments, the composition is administered to a subject using peripheral systemic delivery by intravenous, intraperitoneal, or subcutaneous injection.

[00139] The AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment or composition(s) comprising same, can be administered alone or in combination with other drugs (e.g., as an adjuvant) conventionally used for treating *S. aureus* infections. The composition(s) comprising the AT-binding antibody or antigen-binding fragment, the ClfA-binding antibody or antigen-binding fragment, and/or the leukotoxin-binding antibody or antigen-binding fragment can be used in combination with, for example, one or more antibiotics, such as a penicillinase-resistant β-lactam antibiotic (e.g., oxacillin or flucloxacillin). Gentamicin can be used to treat serious infections, such as endocarditis. Most strains of *S. aureus*, however, are now resistant to penicillin, and two in 100 people carry methicillin-resistant strains of *S. aureus* (MRSA). MRSA infections typically are treated with vancomycin, and minor skin infections can be treated with triple antibiotic ointment.

[00140] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[00141] This example demonstrates that antibodies that bind to alpha toxin (AT), clumping factor A (ClfA), and leukotoxins do not interfere with each other's *in vitro* activities when used in combination.

[00142] Several experiments were conducted to determine if using antibodies that bind to AT, ClfA, and leukotoxins in combination would interfere with the activity of any of these individual assays. In these experiments, the MEDI4893*, SAR114, and SAN481-SYT* antibodies were used in combination and are collectively referred to as "MEDI6389."

[00143] A red blood cell (RBC) hemolysis inhibition assay was performed to determine if the anti-ClfA SAR114 or the anti-leukotoxin SAN481-SYT* antibodies interfered with the activity of MEDI4893*. Washed rabbit red blood cells (50µl) were incubated with native alpha toxin (0.1µg/ml in 25µl) and serial dilution of 25µl of MEDI4893*, SAN481_SYT*+SAR114 or mAb trio combination (MEDI6389) as indicated on Figure 2. Irrelevant mAb c-IgG was used as negative control. After 2hrs incubation at 37°C, hemoglobin release was measured in 50ml supernatants at OD450nm. % hemolysis inhibition was measured as: $100*[(OD_{AT+mAb})/(OD_{AT\ alone})]$. The results, shown in Figure 2 and in Table 1, below, demonstrate that the use of the three antibodies in combination (MED6389) was about equally effective in inhibiting RBC hemolysis as MEDI4893* alone.

[00144] A monocyte viability assay was performed to determine if the anti-AT MEDI4893* or the anti-ClfA SAR114 antibodies interfered with the activity of SAN481-SYT*. Human monocytic cell line HL-60 (5e4/well/25µl) were incubated for 2 hrs at 37°C with a mix of LukS+LukF (100ng/ml each) and serial dilution as indicated on Figure 3 of SAN481_SYT*, MEDI4893*+SAR114, or mAb trio combination (MEDI6389). Irrelevant mAb c-IgG was used as negative control. Cell viability was quantified by measuring luminescent signal in a Cell Glo assay (Promega) following company instructions. % viability was calculated as followed: $100*[(OD_{cells+LukSF+mAb})/(OD_{cells\ alone})]$. The results, shown in Figure 3 and in Table 1, below, demonstrate that the use of the three antibodies in combination (MED6389) was about equally effective in maintaining monocyte viability as SAN481-SYT* alone.

[00145] A fibrinogen-binding inhibition assay was performed to determine if the anti-AT MEDI4893* or the anti-leukotoxin SAN481-SYT* antibodies interfered with the activity of

SAR114. Fibrinogen coated 96 well plate (4µg/ml) was blocked with PBS 2%BSA, and after washes incubated for 1hr at room temperature with a biotinylated ClfA001 (2µg/ml) and serial dilution of SAR114, MEDI4893*+SAN481_SYT*, or mAb trio combination (MEDI6389) as indicated on Figure 4. After 3 washes, plates were incubated with streptavidin-phycoerythrin at 1:10 000 for 1hr, and OD_{450nm} read following addition of 100µl TMB, and then 100µl of H_2S0_4 0.2M. Irrelevant mAb c-IgG was used as negative control. The percentage (%) of fibrinogen binding inhibition was calculated as: $100*[(OD_{ClfA+mAb})/(OD_{ClfA\ alone})]$. The results, shown in Figure 4 and in Table 1, below, demonstrate that the use of the three antibodies in combination (MED6389) was about equally effective in inhibiting fibrinogen binding as SAR114 alone.

Table 1.

IC50 (µg/ml)	MEDI4893*	SAN481-SYT*	SAR114	MEDI6389
RBC assay	0.1731			0.1635
Monocyte viability		0.225		0.2246
Fg binding			3.02	2.63

[00146] The use of the combination of the three antibodies (MEDI6389) did not inhibit the activity of MEDI4893 in the RBC assay, the activity of SAN481* in the monocyte viability assay, or the Fg binding of SAR114.

EXAMPLE 2

[00147] This example demonstrates that the combination of antibodies that bind to alpha toxin (AT) and leukotoxins is superior to either antibody alone in a wound healing model.

[00148] In these experiments, 6-7 week old female Balb/c mice (n=5) were immunized intra-peritoneally with (i) 0.5 mg/kg a control antibody (c-IgG), (ii) 0.1 mg/kg of the anti-AT antibody MEDI4893*, (iii) 0.5 mg/kg of the anti-leukotoxin antibody SAN481-SYT*, or (iv) both MEDI4893* (0.1mg/kg) and SAN481-SYT* (0.5mg/kg). The mice were then intradermally infected 24hrs later with a wound isolate 1447526 (5e7cfu in 50µl PBS).

[00149] Lesions were monitored over 17 days, and the results are shown in Figure 5. Lesion sizes were significantly smaller in mice treated with the combination of anti-AT and anti-leukotoxin antibodies than in mice treated with either antibody alone ($p<0.05$ and indicated with a (*). Pictures on Figure 5 shows lesions at day 7 post-infection.

EXAMPLE 3

[00150] This example demonstrates that neutralization of alpha toxin (AT), clumping factor A (ClfA), and leukotoxins are all necessary for *in vivo* protection in the rabbit bacteremia model.

[00151] In these experiments, 3-month old female rabbits (n=7) received intravenous administration of (i) a control IgG antibody, (ii) the anti-leukotoxin antibody SAN481-SYT*, (iii) SAN481-SYT* and the anti-ClfA antibody SAR114, (iv) SAR114 and the anti-AT antibody MEDI4893*, (v) SAN481-SYT* and MEDI4893*, or (vi) SAN481-SYT*, SAR114 and MEDI4893*, i.e., MEDI6389. All antibodies were administered at 5 mg/kg, other than the control antibody, which was administered at 15 mg/kg. The rabbits were then infected 12 hours later with intravenous CA-MRSA SF8300.

[00152] Survival was monitored over four days after challenge, and the combination of SAN481-SYT*, SAR114 and MEDI4893* (MEDI6389) or MEDI4893*+SAN481_SYT* significantly improved survival over c-IgG as showed by a Log Rank Mantel-Cox statistical test (p=0.0001). The results are shown in Figure 6. Notably, neither targeting AT and ClfA nor targeting leukotoxins is sufficient for protection in this rabbit lethal bacteremia model.

EXAMPLE 4

[00153] This example demonstrates that neutralization of alpha toxin (AT), clumping factor A (ClfA), and leukotoxins are all necessary for *in vivo* protection in the rabbit bloodstream infection model.

[00154] In these experiments, 3-month old female rabbits (n=12) received intravenous administration of 15 mg/kg of (i) a control IgG antibody, (ii) the anti-leukotoxin antibody SAN481-SYT*, (iii) the anti-ClfA antibody SAR114 and the anti-AT antibody MEDI4893*, (iv) SAN481-SYT* and MEDI4893*, or (vi) SAN481-SYT*, SAR114 and MEDI4893*, i.e., MEDI6389. The rabbits were then infected 12 hours later with intravenous HA-MRSA NRS382 or CA-MRSA SF8300.

[00155] Survival was monitored over four days after challenge, and the results are shown in Figure 7. The combination of SAN481-SYT*, SAR114 and MEDI4893*(MEDI6389) or MEDI4893*+SAN481_SYT* significantly improved survival over c-IgG as showed by a Log Rank Mantel-Cox statistical test (p=0.0015 for NRS382 and p=0.0001 for SF8300) was most

effective in increasing survival as a result with either HA-MRSA NRS382 or CA-MRSA SF8300 bacteria.

EXAMPLE 5

[00156] This example demonstrates that a combination of antibodies that bind to alpha toxin (AT), clumping factor A (ClfA), and leukotoxins (MEDI6389) improves wound healing resulting from mixed-bacterial infections in a diabetic mouse dermonecrosis model.

[00157] Mixed-bacterial infections were compared to infections caused by a single bacteria in seven week male (n=10) type 2 diabetic mice (BKS.Cg-*m* +/+ *Lepr*^{db}) mice. The mice were infected intra-dermally with a mixture of *S. aureus* (SA;5e6cfu), *Pseudomonas aeruginosa* (A; 5cfu) and *Streptococcus pyogenese* (SP; 1e1 cfu) under 50µl in PBS, or with SA (5e6cfu). The lesion sizes were monitored over 43 days. The results, shown in Figure 8, demonstrate that the mixed infections result in delay in the time of wound closure in this diabetic mouse dermonecrosis model as compared to infections that result from SA alone.

[00158] The effect of the MEDI6389 combination (comprising anti-AT mAb MEDI4893*, anti-ClfA mAb SAR114, and anti-leukotoxin mAb SAN481_SYT*) on the time of wound closure and bacteria load was examined. Mice were passively immunized intra-peritoneally with MEDI6389 (each mAb at 15mg/kg) or control IgG c-IgG (15mg/kg) and infected intra-dermally 24 hrs later with SA/SP/PA. Lesions were followed over 43 days, and bacteria counts were enumerated at days 7, 14, and 21 in skin lesions. The results, shown in Figure 9, demonstrate that MED6389 increases wound healing and decreases bacteria counts in mixed-bacterial skin lesions in this diabetic mouse dermonecrosis model.

EXAMPLE 6

[00159] This example provides the materials and methods used in Examples 7-11.

In vivo Model of Systemic Infection

[00160] Frozen stock cultures of *S. aureus* USA300 strain SF8300 were thawed and diluted to the appropriate inoculum in sterile PBS, pH 7.2 (Invitrogen) (Hua et al., *Antimicrob Agents Chemother. 58:*1108-17 (2014)). Specific-pathogen-free 7- to 8-week-old female BKS.Cg-Dok7<m>+/+Lepr,db>/J (*db/db*), C57BKS, C57BL/6J – STZ, and C57BL/6J mice (The Jackson Laboratory) were briefly anesthetized and maintained in 3% isoflurane (Butler Schein™ Animal

Health) with oxygen at 3 L/min and infected intravenously. All bacterial suspensions were administered in 100 μL of PBS. In select experiments, neutralizing antibodies MEDI4893*, anti-αVβ6/8, anti-αVβ6, c-IgG (MedImmune antibodies), anti-TGFβ (clone 1D11.16.8, BioXcell), or control mouse IgG1 were administered (15 mg/kg) in 0.5 mL intraperitoneally (IP) 24 hours prior to infection. Rosiglitazone (Sigma-Aldrich) was administered (10 mg/kg) orally for 7 days. Mice were infected 24 hours following the final dose of rosiglitazone. Animals were euthanized with CO_2 at the indicated time points, and blood, liver, or kidneys were collected for analysis. The bacterial load in kidneys was determined by plating serial dilutions on TSA.

NET ELISA

[00161] To measure NETs, a hybrid of 2 different ELISA kits were used. Plates were initially coated with anti-elastase capture antibody (R&D Systems). Fresh serum samples were added to the coated wells, then incubated, and washed. Next, anti-DNA-POD antibody (Roche) was used to detect DNA in the captured proteins in the wells. Plates were developed with ABTS solution and ABTS stop solution. Absorbances were measured at 405 nm on a plate reader using SoftMax Pro software.

HDN and LDN Purification

[00162] High and low density neutrophils (HDN and LDN) were isolated from whole blood. Following sacrifice, blood was collected and layered over with histopaque 1077 (Sigma-Aldrich). Cells were separated by centrifugation (500g, 30 minutes). The lower fraction was treated with ACK lysis buffer (Thermo Fisher Scientific) to remove red blood cells from the high density neutrophils. The upper (PBMC) fraction was washed 2x with PBS, and low density neutrophils were isolated with the EasySep Mouse Neutrophil Enrichment Kit (Stemcell Technologies). Purified cell populations were lysed for protein or RNA analysis.

Flow Cytometry

[00163] Either whole blood or purified low density cells, were washed twice in ice-cold FACs buffer (PBS with 5% fetal bovine serum, and 0.1% sodium azide). Fc receptors were blocked with anti-mouse CD16/CD32 (eBioscience), and cells were stained with antibodies against mouse CD45 (PE conjugated, clone FA-11), CD11c (APC-Cy5.5 or FITC conjugated, clone

N418), CD11b (BV605 conjugated, clone M1/70), Ly6-G (BV421 or PE-Cy7 conjugated, clone 1A8), and Ly6-C. Cells were imaged using the LSR II Flow Cytometer (BD Biosciences) and analyzed with FlowJo. A known concentration of counting beads (Bangs Laboratories) was added to each sample to calculate the number of cells.

Western Blotting

[00164] Cells were lysed with Ripa buffer (ThermoFisher Scientific) containing complete protease inhibitor (Sigma) and frozen. In select experiments, IP3R was immunoprecipitated using anti-IP3R (Abcam cat#ab5804) and the Dynabeads protein G immunoprecipitation kit (ThermoFisher Scientific). Equal amounts of protein were separated on 4-12% bis-Tris NuPage gels and transferred to PVDF membranes (ThermoFisher Scientific). Immunodetection was performed using anti-H3Cit (Abcam cat# ab5103), anti-lactoferrin (Abcam cat# ab77705), anti-MMP9 (Abcam cat#ab38898), anti-IP3R (Abcam cat#ab5804), anti-P-Ser/Thr (Abcam cat#ab17464), and anti-actin (Sigma cat# A3854). Proteins were visualized with the Odyssey imaging system (Li-COR).

EXAMPLE 7

[00165] This example demonstrates that elevated glucose levels correlate with more severe *S. aureus* infections.

[00166] Two models of murine diabetes, STZ induced and *db/db*, were used to study the effect of diabetes on the systemic response to systemic infection with *S. aureus*. In each model, the diabetic mice had a non-fasting glucose level greater than 450 dg/mL, while non-diabetic control levels were less than 200 dg/mL. Mice were infected with 5e7 CFU *S. aureus* (USA300, SF8300). CFU were collected from the kidney 48 hours post infection, and mortality was monitored for 14 days. Increased mortality was observed in both STZ ($P = 0.0011$) and *db/db* ($P = 0.0241$) models as compared with non-diabetic control (FIGs. 11A and 11B). Of note, this did not correlate with a difference in bacterial CFU recovered from the kidneys 48 hours post-infection (FIGs. 11C and 11D). To confirm that increased mortality was a consequence of elevated glucose in the diabetic host, mice were treated with Rosiglitazone for 1 week prior to infection to reduce circulating glucose levels (FIG. 11E). Rosiglitazone significantly reduced

mortality (P = 0.0041) following infection with *S. aureus*, however the bacterial burden in the kidney was unaffected (FIGs. 11F and 11G).

[00167] It is notable that no clearance defect was observed in the diabetic mice as compared with non-diabetic controls. This highlights the contribution of excessive inflammation or exaggerated host response to the increase in mortality.

EXAMPLE 8

[00168] This example demonstrates that enhanced NETosis occurs in diabetic mice.

[00169] Neutrophils in a diabetic host, or in the presence of elevated glucose levels, are increasingly prone to NETosis. In the diabetic population, NET release has been shown to impair wound healing in mice, and the presence of NETs in the serum correlates with non-healing wounds in patients (Fadini, G. P. *et al.*, *Diabetes 65*: 1061-1071 (2016) and Wong, S. L. *et al.*, *Nat Med 21*: 815-819 (2015)). Neutrophils also release NETs in response to bacterial infection, therefore it was hypothesized that *S. aureus* infection would result in increased systemic NET release in diabetic mice. Complexes of neutrophil elastase and double stranded DNA are used as a measurement of NET formation and quantified by ELISA (Fadini, G. P. *et al.*, *Diabetes 65*: 1061-1071 (2016)). Significant increases (P = 0.0003) in serum NETs were observed in diabetic mice intravenously infected with *S. aureus* for 24 hours, while significant increases were not observed in non-diabetic control mice (FIG. 12A). Levels of circulating NETs were not different in uninfected diabetic and non-diabetic mice.

[00170] Alpha toxin (AT), once released by *S. aureus*, binds to the receptor ADAM10 on the surface of platelets. (Neutrophils do not express ADAM10.) In response to AT, platelets aggregate and bind to circulating neutrophils, resulting in activation of caspase-1 mediated signaling and NET production (Powers, M. E. *et al.*, *Cell Host Microbe 17*: 775-787 (2015) and Surewaard, B. G. J. *et al. Cell Host Microbe 24*: 271-284 (2018)). Consistent with these findings, neutralization of AT with monoclonal antibody MEDI4893* significantly reduced the number of NE-DNA complexes in the serum 48 hours post-infection in diabetic animals (FIG. 12B). Increased AT-dependent NET production was confirmed 48 hours post-infection by increased citrinulated Histone H3 (H3cit) in the liver as detected by western blot (FIG. 12C) Visualization of liver sections immunohistochemically stained with anti-Ly6G to mark neutrophils and anti-H3cit also showed increased AT-dependent NET (i.e., less anti-H3 cit

staining in the livers of mice that received MEDI4893*) (Cohen TS, *et al. Staphylococcus aureus drives expansion of low density neutrophils in diabetic mice.* JCI 2019 IN PRESS). Neutralization of AT significantly increased survival (P = 0.0255) of diabetic mice infected with *S. aureus* (FIG 12D). These data indicate that systemic infection of the diabetic host lead to an AT-dependent increase in circulating NETs that can be inhibited by MEDI4893*.

EXAMPLE 9

[00171] This example demonstrates that low density neutrophils correlate with increased NETosis.

[00172] Similar to macrophages, neutrophils can be separated into different classes based on functional characteristics. Severe burns have been shown to alter the phenotype of circulating neutrophils and to alter TLR expression, cytokine production, and their ability to drive macrophage polarization (Tsuda, Y. *et al. Immunity 21*: 215-226 (2004)). Neutrophils are unique in that they can also be separated by cell density. High density neutrophils are anti-tumor, phagocytic cells, while low density neutrophils are considered pro-tumor phagocytic defective cells (Sagiv, J. Y. *et al. Cell Rep 10*: 562-573 (2015)). While Tsuda et. al. did not measure the density of neutrophils isolated from mice susceptible to *S. aureus* infection, the shape of the nuclei in these neutrophils was similar to the shape of nuclei in low density cells (Sagiv, J. Y. *et al. Cell Rep 10*: 562-573 (2015) and Fridlender, Z. G. *et al. Cancer Cell 16*: 183-194 (2009)). The shapes of the nuclei in neutrophils taken from non-diabetic mice and diabetic mice also had striking differences. The nucleus in cells isolated from non-diabetic mice were multilobular or round, while large numbers of cells with ringed nuclei were observed in the blood of diabetic mice (Cohen TS, *et al. Staphylococcus aureus drives expansion of low density neutrophils in diabetic mice.* JCI 2019 IN PRESS). These structures were similar to those reported by Tsuda et. al to be found in the cells isolated from *S. aureus* susceptible mice, indicating that diabetic mice could have an increased number of low density, or immune impaired neutrophils.

[00173] Hyper NET production is a characteristic of low density neutrophils (LDN), and it was hypothesized that higher numbers of LDNs in infected diabetic mice were responsible for the increases in NETs (Villanueva, E. *et al. J Immunol 187*: 538-552 (2011)). Blood was collected from C57BKS and *db/db* mice 48 hours post-IV infection and was analyzed for presence of LDNs. The amount of LDNs in the blood of infected *db/db* mice was significantly

increased compared to uninfected *db/db* mice ($P < 0.0001$) as well as infected C57BKS control mice ($P = 0.0003$) (FIG. 13A). Increases in LDNs were not observed in C57BKS mice (FIG. 13A). Similar increases were observed in STZ induced diabetic mice and not in C57BL/6 controls (FIG. 14). Lowering glucose levels with Rosiglitazone prior to infection significantly ($P = 0.0116$) reduced LDNs 48 hours post-infection (FIG. 13B).

[00174] To ensure that the observations were not based on degranulated neutrophils, LDNs and high density neutrophils (HDNs) were isolated from the blood of infected *db/db* mice, and the amounts of lactoferrin (secondary granules) and MMP9 (tertiary granules) were measured by western blot. Equivalent amounts of both were observed, indicating that LDNs have similar granular content as compared to HDNs (Cohen TS, *et al. Staphylococcus aureus drives expansion of low density neutrophils in diabetic mice.* JCI 2019 IN PRESS). Neutralizing AT prevented systemic NET release, therefore the influence of AT on the number of LDNs was assessed. LDNs in the blood of *db/db* mice treated 24 hours prior to infection with c-IgG or MEDI4893* and infected with *S. aureus* for 48 hours were measured. A significant reduction in LDNs in mice prophylactically treated with MEDI4893* (FIG. 13C) was observed, while overall numbers of neutrophils were not affected (FIG. 13D), indicating that AT contributes to the increase in LDNs.

[00175] These data indicate that LDNs contribute to the pathology associated with diabetic *S. aureus* infection and that these LDNs are associated with excessive NET release in both the liver, a key target organ of systemic infections, and systemically in the blood. Moreover, MEDI4893* reduces LDNs in diabetic mice.

EXAMPLE 10

[00176] This example demonstrates that TGFß drives expansion of LDNs.

[00177] TGFβ has been implicated as a central regulator of neutrophil phenotype, and in tumor models it can drive a phenotypic switch from high to low density neutrophil (Sagiv, J. Y. *et al. Cell Rep 10*: 562-573 (2015) and Fridlender, Z. G. *et al. Cancer Cell 16*: 183-194 (2009). Sagiv et. al. demonstrated that the addition of TGFβ to blood taken from tumor bearing mice, not naïve mice, will increase numbers of LDNs *in vitro* (*id.*). This study was repeated with blood from non-diabetic and diabetic mice. The addition of TGFβ to diabetic blood significantly increased ($P = 0.0021$) the number of LDNs (FIG. 15A). The same was not observed in non-

diabetic blood. Based on this *in vitro* evidence demonstrating that TGFβ can increase numbers of LDNs, its necessity for their induction by blocking *in vivo* was tested. Diabetic mice were prophylactically treated with neutralizing TGFβ antibody 24 hours prior to infection with *S. aureus*. The numbers of LDNs in the bloodstream was significantly reduced (P = 0.0003) by inhibition of TGFβ, while numbers of bacteria in the kidneys were similar between groups (FIGs. 15B and 15C). Survival was significantly improved (P = 0.0072) by neutralizing TGFβ (FIG. 15D). Visualization of NETs in the liver demonstrated a loss of NETs when TGFβ was neutralized (Cohen TS, *et al. Staphylococcus aureus drives expansion of low density neutrophils in diabetic mice.* JCI 2019 IN PRESS). These data suggest that reducing LDNs by blocking TGFβ could promote survival.

[00178] TGFβ is secreted as a pro-form protein (pro-TGFß) and requires cleavage to be activated. Binding of pro-TGFβ by αVβ8 integrin has been linked to its activation and prevention of colitis, and its expression on dendritic cell and monocyte subsets is increased in response to inflammation (Travis, M. A. *et al. Nature 449*: 361-365 (2007) and Kelly, A. *et al. J Exp Med*, doi:10.1084/jem.20171491 (2018)). To determine if *S. aureus* infection influences expression of αVβ8 integrin, innate immune cells were isolated from the liver and spleen of C57BKS and *db/db* mice 24 hours post-infection, and the expression of αVβ8 was analyzed by flow cytometry. Numbers of β8 positive inflammatory monocytes and dendritic cells increased in the livers of *db/db* mice, not C57BKS mice, following infection (FIG. 16A). Interestingly, while integrin expression increased on the surface of monocytes, it was the overall number of DCs that increased, not the density of β8 (FIG. 16B). To demonstrate the functional relevance of αVβ8 in this model, mice were prophylactically treated with antibodies neutralizing αVβ6/8, αVβ6 or c-IgG and infected with *S. aureus*. Forty-eight hours post infection LDNs were significantly decreased (P = 0.0090) in the bloodstream in the mice treated with αVβ6/8 neutralizing antibody compared with c-IgG (FIG. 16C). Neutralization of αVβ6 alone did not reduce the numbers of these cells. Integrin inhibition did not affect the numbers of bacteria in the kidneys 48 hours post-infection (FIG. 16D). Survival was significantly improved in mice treated with anti-αVß6/8 antibody as compared with c-IgG treated mice (FIG. 16E). Therefore, consistent with directly neutralizing TGFβ, blocking the integrin responsible for activating this pathway was protective in diabetic mice.

[00179] These data show that neutralization of either αVß6/8 or TGFβ prevents LDN increases and reduces mortality. These data also show that dendritic cells play a central role in the pathogenesis of diabetic infection due to their ability to activate TGFβ and promote expansion of LDNs.

EXAMPLE 11

[00180] This example demonstrates that AT drives TGFß activation.

[00181] It was hypothesized that AT was influencing LDN numbers by affecting the TGFβ pathway. Following its activation, TGFß binds to its receptor complex, activates SMAD transcription factors, and drives expression of downstream genes. Therefore, activation of SMAD signaling is commonly used as a surrogate measurement of TGFβ activation. pSMAD levels were analyzed in the livers of diabetic and non-diabetic mice that were infected (24 hours) with *S. aureus*. Significantly increased pSMAD was observed in the livers of infected diabetic mice as compared to naïve diabetic mice ($P < 0.0001$) and infected non-diabetic mice ($P = 0.0338$) (FIG. 17A). In diabetic mice, MEDI4893* significantly reduced ($P < 0.0001$) pSMAD levels in the liver, indicating that AT was contributing to activation of TGFβ signaling (FIG. 17B). Neutralizing AT did not alter the numbers of αVβ8 expressing innate immune cells (FIG. 17C). These data indicate that AT influences activation of TGFβ through a mechanism that is independent of αVβ8 expression on innate immune cells. Accordingly, neutralization of AT, which is a key *S. aureus* virulence factor, limits activation of TGFβ signaling, and subsequently reduces LDN numbers and NET release.

[00182] These data indicate that, in addition to binding to ADAM10 on platelets, AT can act through a second pathway that alters the neutrophil phenotype and subsequent response to *S. aureus* infection. In the diabetic host, AT-dependent activation of TGFß signaling drives expansion of LDNs. Thus, AT is both promoting the expansion of the LDN population which spontaneously release NETs and activating platelets, which can bind and further activate neutrophils.

[00183] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[00184] The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term "at least one" followed by a list of one or more items (for example, "at least one of A and B") is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[00185] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIM(S):

1. A method of treating or preventing a *Staphylococcus aureus* (*S. aureus*) infection in a subject comprising administering to the subject (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin (AT), (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* clumping factor A (ClfA), and (c) an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

2. A method of treating or preventing a *Staphylococcus aureus* (*S. aureus*) infection in a subject comprising administering to the subject an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin and (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin (AT) or (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* clumping factor A (ClfA).

3. A composition comprising (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT, (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA, and (c) an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

4. A composition comprising an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin and (a) an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT or (b) an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA.

5. The composition of claim 3 or 4 for use in treating or preventing a *S. aureus* infection in a subject.

6. An antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin (AT) for use in treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

7. An antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA for use in treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

8. An antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin for use in treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and/or an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA.

9. Use of the composition of claim 3 or 4 in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject.

10. Use of an antibody or antigen-binding fragment thereof that binds to *S. aureus* alpha toxin (AT) in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

11. Use of an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin.

12. Use of an antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject in combination with an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and/or an antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA.

13. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT binds to the same *S. aureus* AT epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33.

14. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-13, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33 to *S. aureus* AT.

15. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-14, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a variable heavy chain (VH) complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3, a variable light chain (VL) CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:12.

16. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-15, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VH comprising the amino acid sequence of SEQ ID NO:19.

17. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-16, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VL comprising the amino acid sequence of SEQ ID NO:33.

18. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-17, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:47.

19. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-18, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a light chain comprising the amino acid sequence of SEQ ID NO:52.

20. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-14, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of MEDI4893.

21. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 20, wherein the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

22. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-17 and 19-21, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a heavy chain constant region.

23. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 22, wherein the heavy chain constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions.

24. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 22, wherein the heavy chain constant region is a human IgG_1 constant region.

25. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-18, 20, and 21, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a light chain constant region.

26. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 25, wherein the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions.

27. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 25, wherein the light chain constant region is a human IgGκ light chain constant region.

28. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-27, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT is an IgG antibody or antigen-binding fragment thereof.

29. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-28, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region that has been engineered to improve half-life.

30. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-29, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region with a YTE mutation.

31. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-30, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT is a monoclonal antibody or antigen-binding fragment.

32. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-31, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT is a full–length antibody.

33. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-31, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT is an antigen-binding fragment.

34. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 33, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT wherein the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc.

35. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-34, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT has an affinity of 80-100 pM for *S. aureus* AT.

36. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA binds to the same *S. aureus* ClfA epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:20 and a VL comprising the amino acid sequence of SEQ ID NO:34.

37. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-36, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:20 and a VL comprising the amino acid sequence of SEQ ID NO:34 to *S. aureus* ClfA.

38. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-37, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:4, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:5, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR1 comprising the amino acid sequence of SEQ ID NO:13, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:14, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:15.

39. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-38, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH comprising the amino acid sequence of SEQ ID NO:20.

40. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-39, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VL comprising the amino acid sequence of SEQ ID NO:34.

41. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-40, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a heavy chain constant domain comprising the amino acid sequence of CSYHLC (SEQ ID NO:55).

42. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 41, wherein said heavy chain constant domain comprises the amino acid sequence of MHEACSYHLCQKSLSLS (SEQ ID NO:56).

43. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-42, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:49.

44. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-43, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a light chain comprising the amino acid sequence of SEQ ID NO:53.

45. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-44, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of SAR114-N3Y.

46. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of 11H10, SAR72, SAR80, SAR113, SAR132, SAR352, SAR372, SAR510, SAR547, SAS1, SAS19, or SAS203.

47. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 45 or 46, wherein the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

48. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-35 or 46, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH and a VL, wherein the VH comprises the amino acid sequence set forth in any one of SEQ ID NOs:21-31 and 68.

49. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-35 or 46, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises a VH and a VL, wherein the VL comprises the amino acid sequence set forth in any one of SEQ ID NOs: 35-45 and 69.

50. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA comprises VH and VL sequences comprising the amino acid sequences set forth in (a) SEQ ID NOs:21 and 35, respectively (b) SEQ ID NOs:22 and 36, respectively, (c) SEQ ID NOs:23 and 37, respectively, (d) SEQ ID NOs:24 and 38, respectively, (e) SEQ ID NOs:25 and 39, respectively, (f) SEQ ID NOs:26 and 40, respectively, (g) SEQ ID NOs:27 and 41, respectively, (h) SEQ ID NOs:28 and 42, respectively (i) SEQ ID NOs:29 and 43, respectively, (j) SEQ ID NOs:30 and 44, respectively, (k) SEQ ID NOs:31 and 45, respectively, or (l) SEQ ID NOs:68 and 69.

51. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-40 and 44-50, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA further comprises a heavy chain constant region.

52. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 51, wherein the heavy chain constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions.

53. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 51, wherein the heavy chain constant region is a human IgG_1 constant region.

54. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-43 and 45-53, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA further comprises a light chain constant region.

55. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 54, wherein the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions.

56. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 54, wherein the light chain constant region is a human IgGκ light chain constant region.

57. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-56, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA comprises a mutation that extends half-life relative to the same antibody without the mutation in human FcRn mice.

58. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-57, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA comprises a mutation that extends half-life relative to the same antibody without the mutation, and wherein the mutation does not inhibit OPK activity relative to the same antibody or antigen-binding fragment the mutation.

59. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-58, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA is a monoclonal antibody or antigen-binding fragment.

60. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-59, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA is a full–length antibody.

61. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-59, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA is an antigen-binding fragment.

62. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 61, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA wherein the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc.

63. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-62, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has IC50s for ClfA001, ClfA002, and ClfA004 in a fibrinogen binding inhibition assay that are within 2 μg/ml of each other.

64. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-63, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has IC50s for ClfA001, ClfA002, and ClfA004 in a fibrinogen binding inhibition assay that are all between 1 μg/ml and 5 μg/ml.

65. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-64, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has binding affinities (K_D) for ClfA001, ClfA002, and ClfA004 that are all between 200 and 350 pM.

66. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-65, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA has binding affinities (K_D) of less than 1 nM for all ClfA genotypes.

67. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-66, wherein the antibody or antigen-binding fragment that binds to *S. aureus* ClfA has a monomer purity that decreases by no more than 5% after exposure of the antibody or antigen-binding fragment to conventional white light at 2kLux/hr at 23^0C for 14 days.

68. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-67, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin binds to LukF, LukD, and/or HlgB, and/or wherein the antibody or antigen-binding fragment thereof neutralizes LukF, LukD, and/or HlgB.

69. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 68, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin binds to LukF, LukD, and HlgB, and/or wherein the antibody or antigen-binding fragment thereof neutralizes LukF, LukD, and HlgB.

70. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-69, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin binds to the same *S. aureus* leukotoxin epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:32 and a VL comprising the amino acid sequence of SEQ ID NO:46.

71. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-70, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:32 and a VL comprising the amino acid sequence of SEQ ID NO:46 to the *S. aureus* leukotoxin.

72. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-71, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a VHCDR1 comprising the amino acid sequence of SEQ ID NO:7, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:8, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:9, a VL CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:17, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:18.

73. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-72, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a VH comprising the amino acid sequence of SEQ ID NO:32.

74. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-73, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a VL comprising the amino acid sequence of SEQ ID NO:46.

75. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-74, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:50.

76. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-75, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises a light chain comprising the amino acid sequence of SEQ ID NO:54.

77. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-71, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of SAN481-SYT.

78. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 77, wherein the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

79. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-74 and 76-78, wherein the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin further comprises a heavy chain constant region.

80. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 79, wherein the heavy chain constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions.

81. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 79, wherein the heavy chain constant region is a human IgG_1 constant region.

82. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-75 and 77-81, wherein the antibody or antigen-binding fragment that binds at least one *S. aureus* leukotoxin further comprises a light chain constant region.

83. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 82, wherein the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions.

84. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 82, wherein the light chain constant region is a human IgGκ light chain constant region.

85. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-84, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin is an IgG antibody or antigen-binding fragment thereof.

86. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-85, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises an Fc region that has been engineered to improve half-life.

87. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-86, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin comprises an Fc region with a YTE mutation.

88. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-87, wherein the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin is a monoclonal antibody or antigen-binding fragment.

89. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-88, wherein the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin is a full–length antibody.

90. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-88, wherein the antibody or antigen-binding fragment that binds to at least one *S. aureus* leukotoxin is an antigen-binding fragment.

91. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 90, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT wherein the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc.

92. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-91, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin has an affinity of less than 75 pM for *S. aureus* LukF, LukD, and HlgB.

93. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1-92, wherein the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin has similar binding affinities for LukF, LukD, and HIgB.

94. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is sepsis.

95. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is bacteremia

96. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is pneumonia.

97. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is ICU pneumonia.

98. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is a skin or soft tissue infection (SSTI).

99. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is a diabetic infection of the lower limbs.

100. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is a diabetic foot ulcer (DFU).

101. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 100, wherein the DFU is uninfected.

102. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 100, wherein the DFU is infected.

103. The method, composition, antibody or antigen-binding fragment thereof, or use of claim 100, wherein the DFU is a grade 1, 2 or 3 DFU.

104. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is a bone or joint infection.

105. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-93, wherein the *S. aureus* infection is a joint infection, a device infection, a wound infection, a surgical site infection, or osteomyelitis.

106. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-105, wherein the subject is a surgical subject.

107. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-106, wherein the *S. aureus* infection comprises antibiotic-resistant *S. aureus*.

108. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-107, wherein the subject has diabetes.

109. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-108, wherein the subject is human.

110. The method, composition, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2 and 5-109, wherein the treating or preventing an *S. aureus* infection comprises inhibiting *S. aureus* agglutination, toxin neutralization, inducing opsonophagocytosis, inhibiting *S. aureus* fibrinogen binding, inhibiting *S. aureus* agglutination, inhibiting thromboembolic lesion formation, inhibiting *S. aureus*-associated sepsis, or any combination of the foregoing.

111. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2, 6-8, and 10-110, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA are administered in the same pharmaceutical composition.

112. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2, 6-8, and 10-110, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA are administered in the separate pharmaceutical compositions.

113. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2, 6-8, and 10-110, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the same pharmaceutical composition.

114. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2, 6-8, and 10-110, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the separate pharmaceutical compositions.

115. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2, 6-8, and 10-110, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the same pharmaceutical composition.

116. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2, 6-8, and 10-110, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the separate pharmaceutical compositions.

117. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 112, 114, and 116, wherein the separate pharmaceutical compositions are administered simultaneously.

118. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 112, 114, and 116, wherein the separate pharmaceutical compositions are administered sequentially.

119. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 1, 2, 6-8, and 10-110, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT, the antibody or antigen-binding fragment thereof that binds to *S. aureus* ClfA, and the antibody or antigen-binding fragment thereof that binds to at least one *S. aureus* leukotoxin are administered in the same pharmaceutical composition.

120. A method of treating or preventing a *S. aureus* infection in a subject with diabetes comprising administering to the subject an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT.

121. An antibody or antigen-binding fragment thereof that binds to *S. aureus* AT for use in treating or preventing a *S. aureus* infection in a subject with diabetes.

122. Use of an antibody or antigen-binding fragment thereof that binds to *S. aureus* AT in the preparation of a medicament for treating or preventing a *S. aureus* infection in a subject with diabetes.

123. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-122, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT binds to the same *S. aureus* AT epitope as an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33.

124. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-123, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT competitively inhibits binding of an antibody comprising a VH comprising the amino acid sequence of SEQ ID NO:19 and a VL comprising the amino acid sequence of SEQ ID NO:33 to *S. aureus* AT.

125. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-124, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:1, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:2, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:3, a VL CDR1 comprising the amino acid sequence of SEQ ID NO:10, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:11, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:12.

126. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-125, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VH comprising the amino acid sequence of SEQ ID NO:19.

127. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-126, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a VL comprising the amino acid sequence of SEQ ID NO:33.

128. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-127, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:47.

129. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-128, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises a light chain comprising the amino acid sequence of SEQ ID NO:52.

130. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-124, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of MEDI4893.

131. The method, antibody or antigen-binding fragment thereof, or use of claim 130, wherein the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

132. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-127 and 129-131, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a heavy chain constant region.

133. The method, antibody or antigen-binding fragment thereof, or use of claim 132, wherein the heavy chain constant region is selected from the group consisting of human immunoglobulin IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions.

134. The method, antibody or antigen-binding fragment thereof, or use of claim 132, wherein the heavy chain constant region is a human IgG_1 constant region.

135. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-128, and 130- 134, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT further comprises a light chain constant region.

136. The method, antibody or antigen-binding fragment thereof, or use of claim 135, wherein the light chain constant region is selected from the group consisting of human immunoglobulin IgGκ and IgGλ light chain constant regions.

137. The method, antibody or antigen-binding fragment thereof, or use of claim 135, wherein the light chain constant region is a human IgGκ light chain constant region.

138. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-137, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT is an IgG antibody or antigen-binding fragment thereof.

139. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-138, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region that has been engineered to improve half-life.

140. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-139, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT comprises an Fc region with a YTE mutation.

141. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-140, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT is a monoclonal antibody or antigen-binding fragment.

142. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-141, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT is a full–length antibody.

143. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-141, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT is an antigen-binding fragment.

144. The method, antibody or antigen-binding fragment thereof, or use of claim 143, wherein the antibody or antigen-binding fragment that binds to *S. aureus* AT wherein the antigen-binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc.

145. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-144, wherein the antibody or antigen-binding fragment thereof that binds to *S. aureus* AT has an affinity of 80-100 pM for *S. aureus* AT.

146. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is sepsis.

147. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is bacteremia.

148. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is pneumonia.

149. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is ICU pneumonia.

150. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is a SSTI.

151. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is a diabetic infection of the lower limbs.

152. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is a DFU.

153. The method, antibody or antigen-binding fragment thereof, or use of claim 152, wherein the DFU is uninfected.

154. The method, antibody or antigen-binding fragment thereof, or use of claim 152, wherein the DFU is infected.

155. The method, antibody or antigen-binding fragment thereof, or use of claim 154, wherein the DFU is a grade 1, 2 or 3 DFU.

156. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is a bone or joint infection.

157. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-145, wherein the *S. aureus* infection is a joint infection, a device infection, a wound infection, a surgical site infection, or osteomyelitis.

158. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-157, wherein the subject is a surgical subject.

159. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-158, wherein the *S. aureus* infection comprises antibiotic-resistant *S. aureus*.

160. The method, antibody or antigen-binding fragment thereof, or use of any one of claims 120-159, wherein the subject is human.

Figure 1

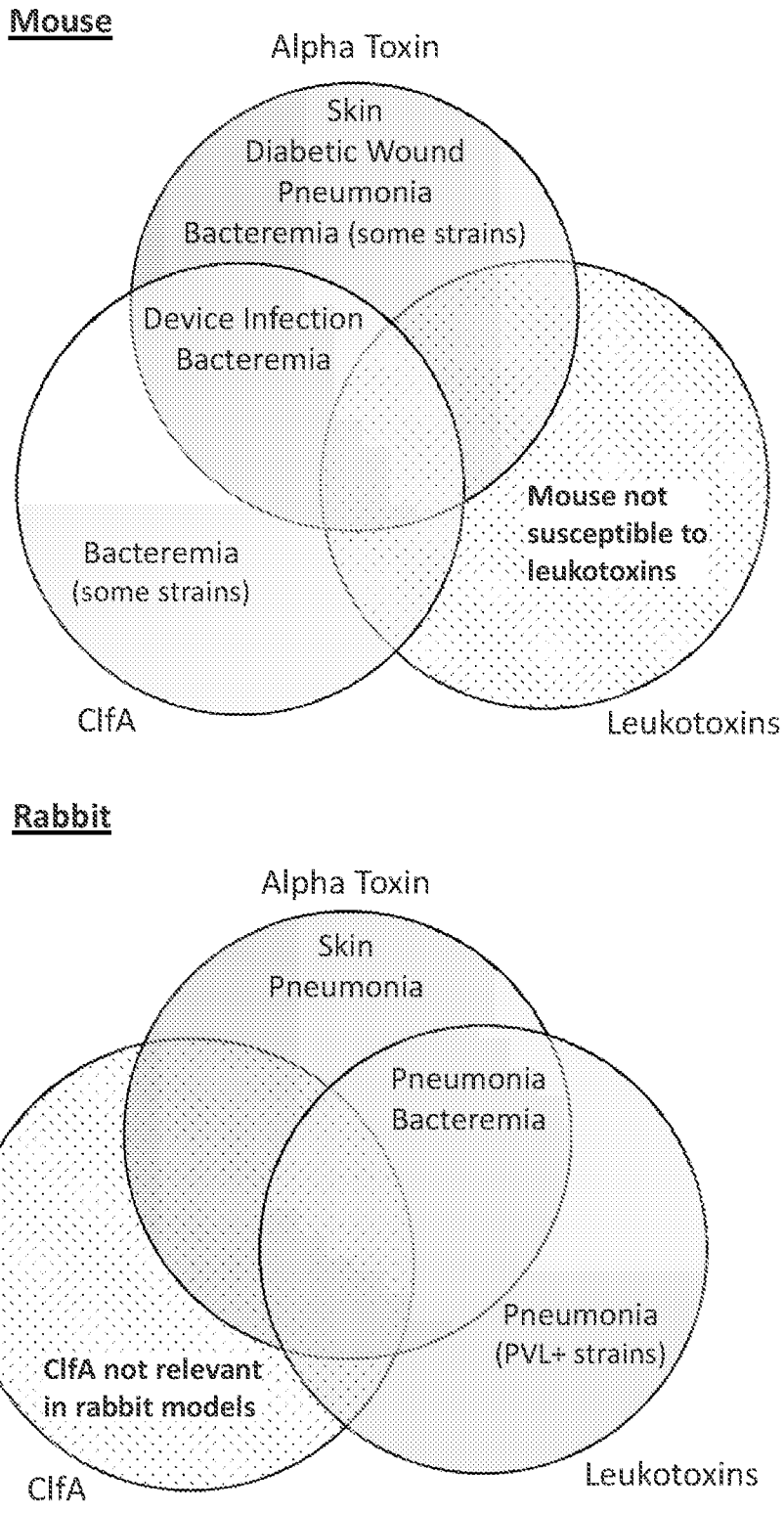

Mouse
Alpha Toxin
Skin
Diabetic Wound
Pneumonia
Bacteremia (some strains)
Device Infection
Bacteremia
Mouse not susceptible to leukotoxins
Bacteremia (some strains)
ClfA
Leukotoxins
Rabbit
Alpha Toxin
Skin
Pneumonia
Pneumonia
Bacteremia
Pneumonia (PVL+ strains)
ClfA not relevant in rabbit models
ClfA
Leukotoxins

Figure 2

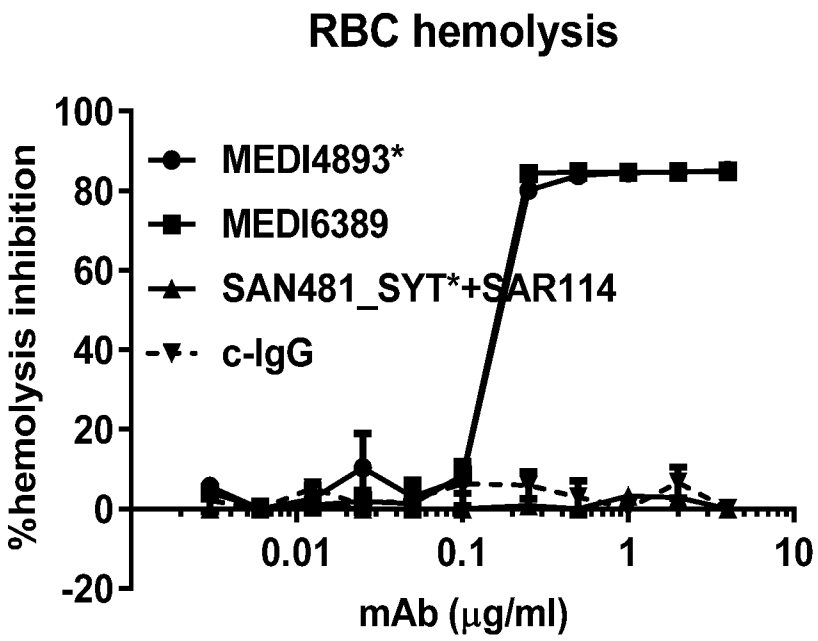


Figure 3

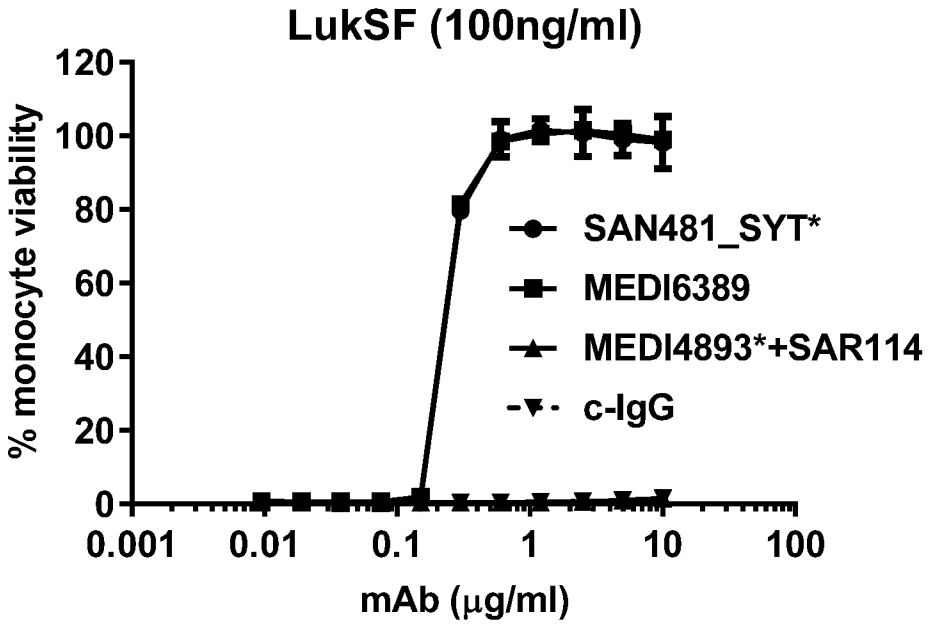


Figure 4

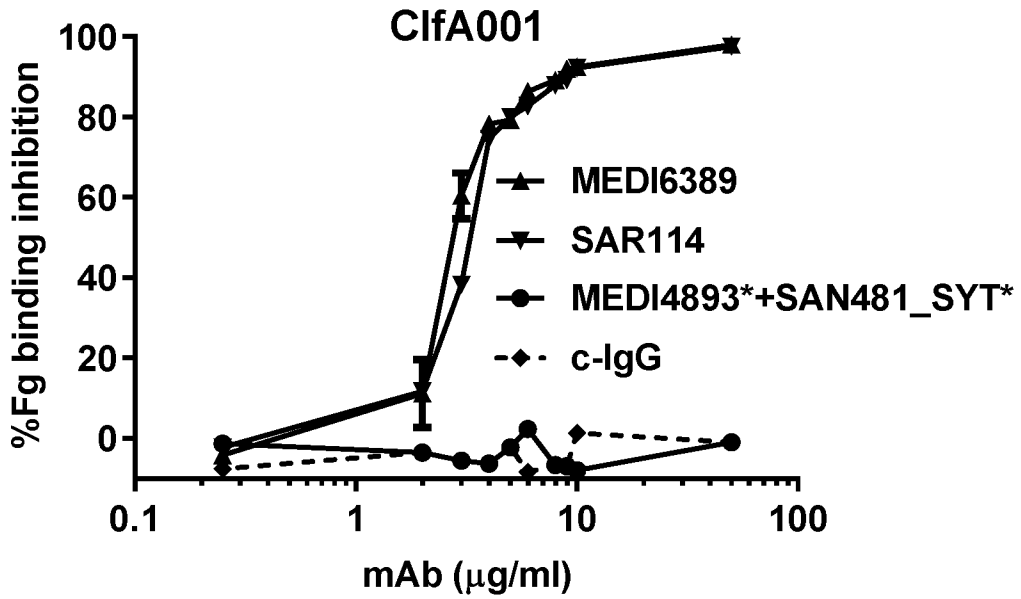
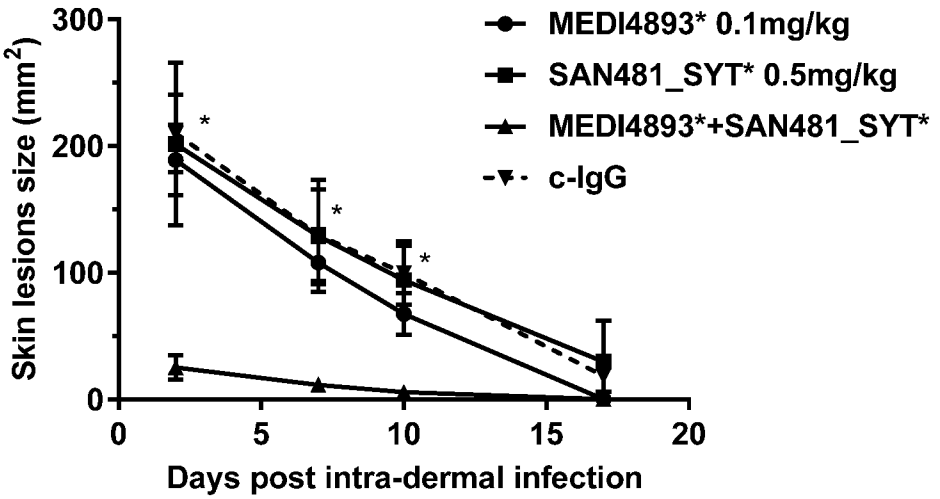

ClfA001
%Fg binding inhibition
100
80
60
40
20
0
0.1
1
10
100
mAb (μg/ml)
MEDI6389
SAR114
MEDI4893*+SAN481_SYT*
c-IgG

Figure 5


MEDI4893* 0.1mg/kg
SAN481_SYT* 0.5mg/kg
MEDI4893*+SAN481_SYT*
c-IgG
Skin lesions size (mm2)
300
200
100
0
0
5
10
15
20
Days post intra-dermal infection
*
*
*

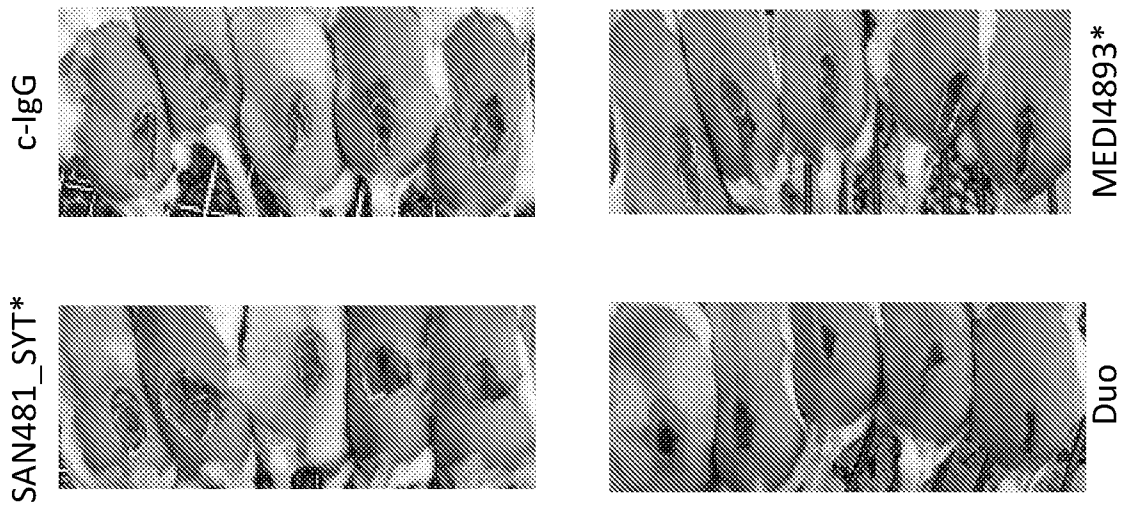
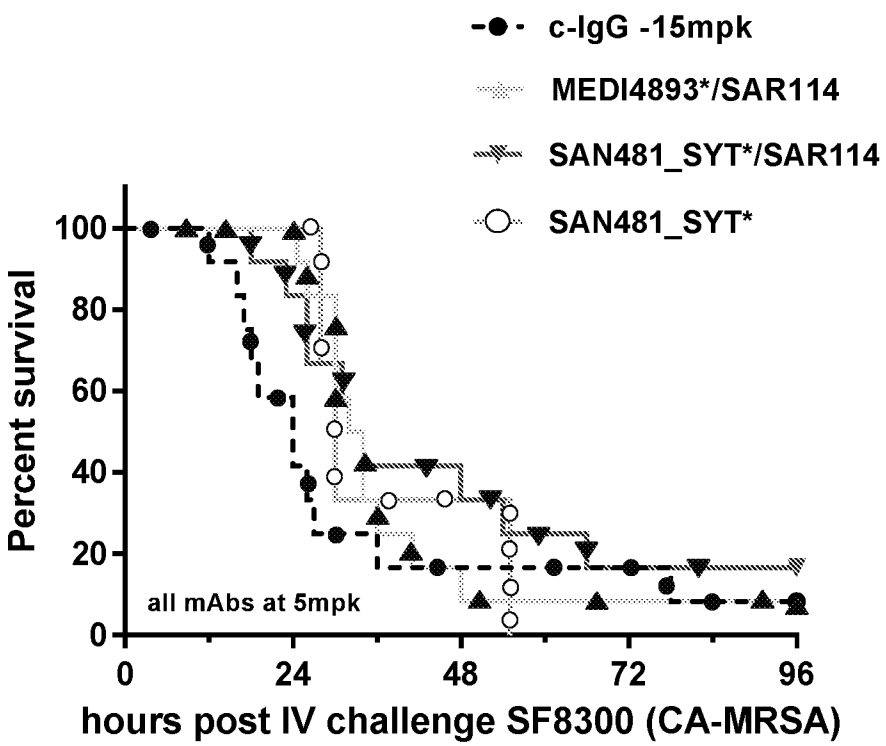

c-IgG
MEDI4893*
SAN481_SYT*
Duo

Figure 6


c-IgG -15mpk
MEDI4893*/SAR114
SAN481_SYT*/SAR114
SAN481_SYT*
Percent survival
100
80
60
40
20
0
all mAbs at 5mpk
0
24
48
72
96
hours post IV challenge SF8300 (CA-MRSA)

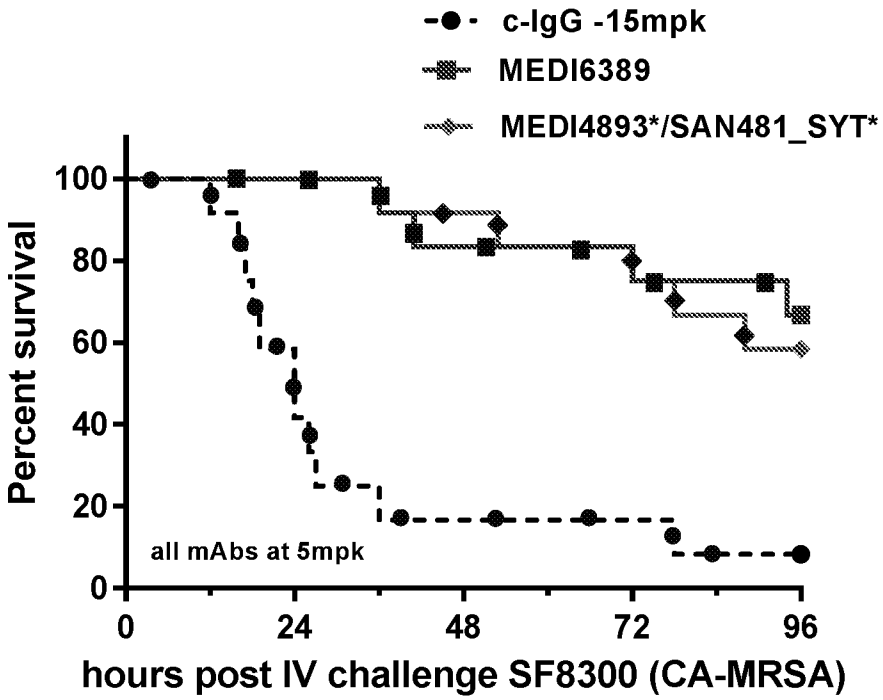
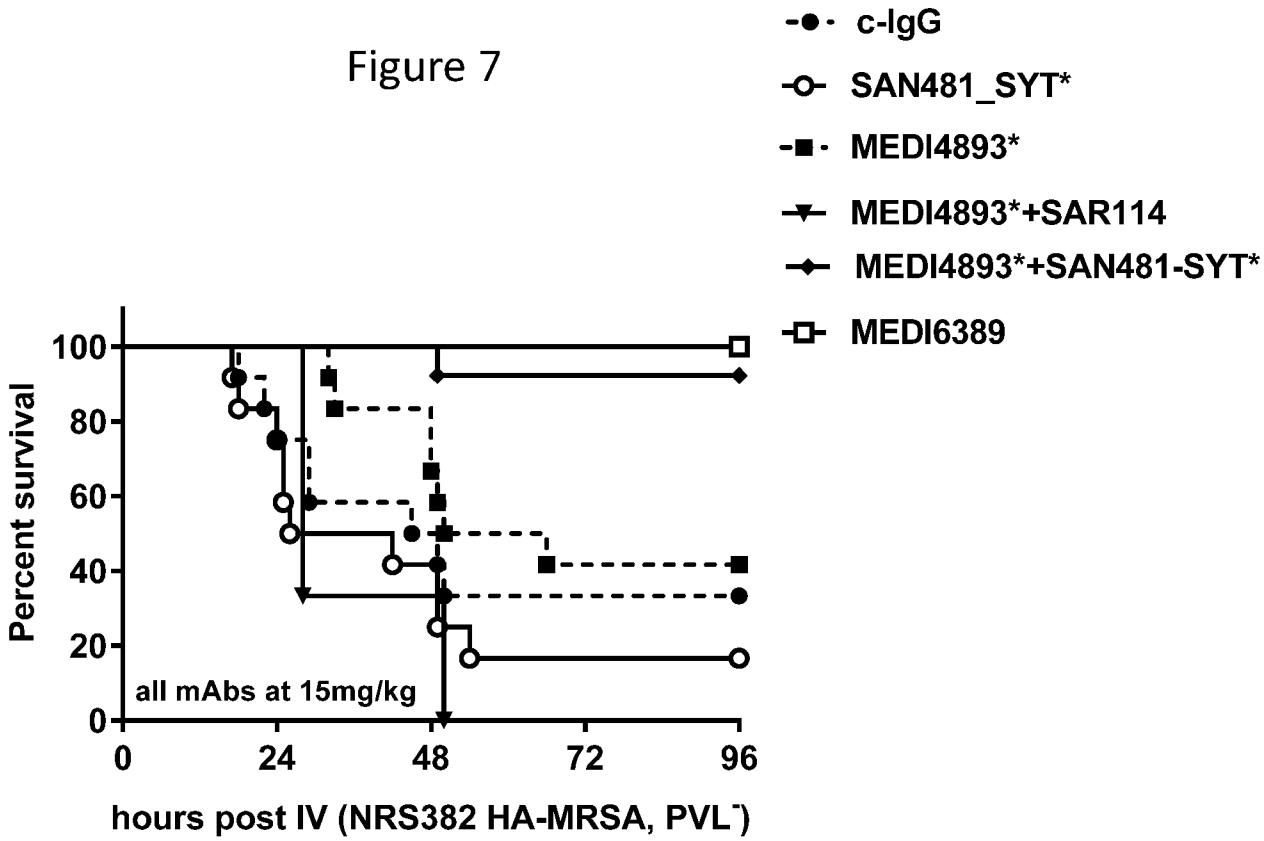

c-IgG -15mpk
MEDI6389
MEDI4893*/SAN481_SYT*
Percent survival
100
80
60
40
20
0
all mAbs at 5mpk
0
24
48
72
96
hours post IV challenge SF8300 (CA-MRSA)

Figure 7


c-IgG
SAN481_SYT*
MEDI4893*
MEDI4893*+SAR114
MEDI4893*+SAN481-SYT*
MEDI6389
Percent survival
100
80
60
40
20
0
all mAbs at 15mg/kg
0
24
48
72
96
hours post IV (NRS382 HA-MRSA, PVL-)

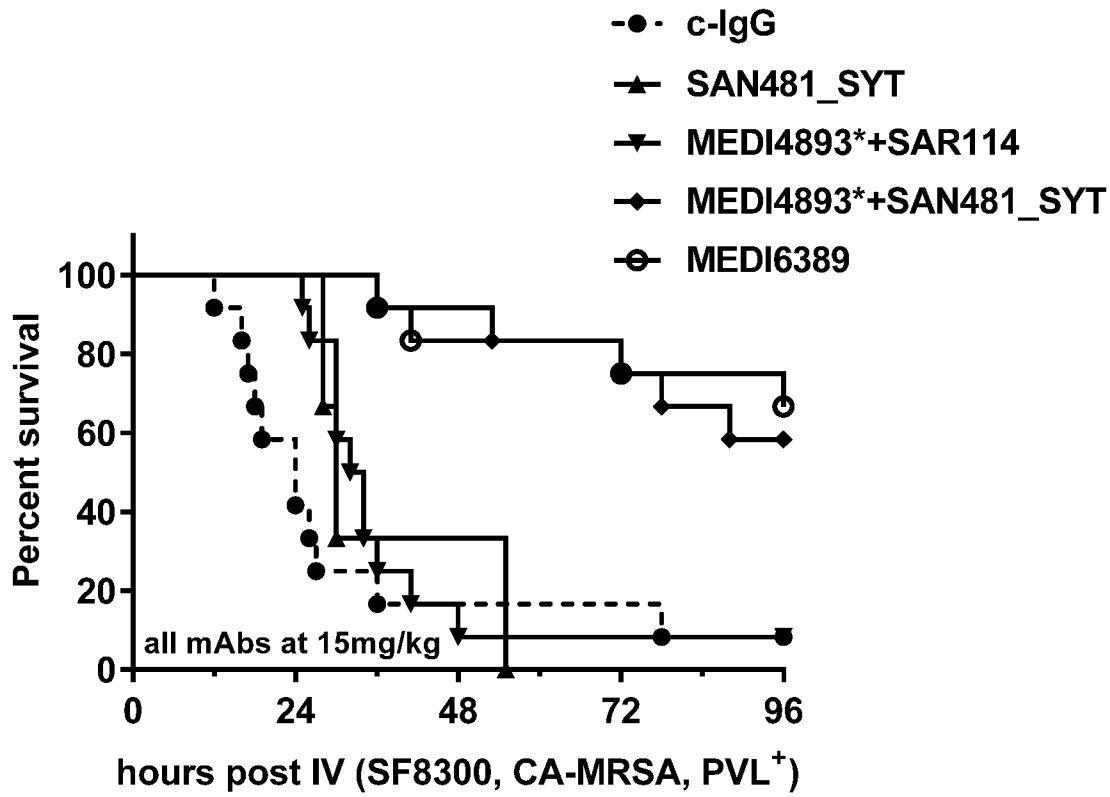
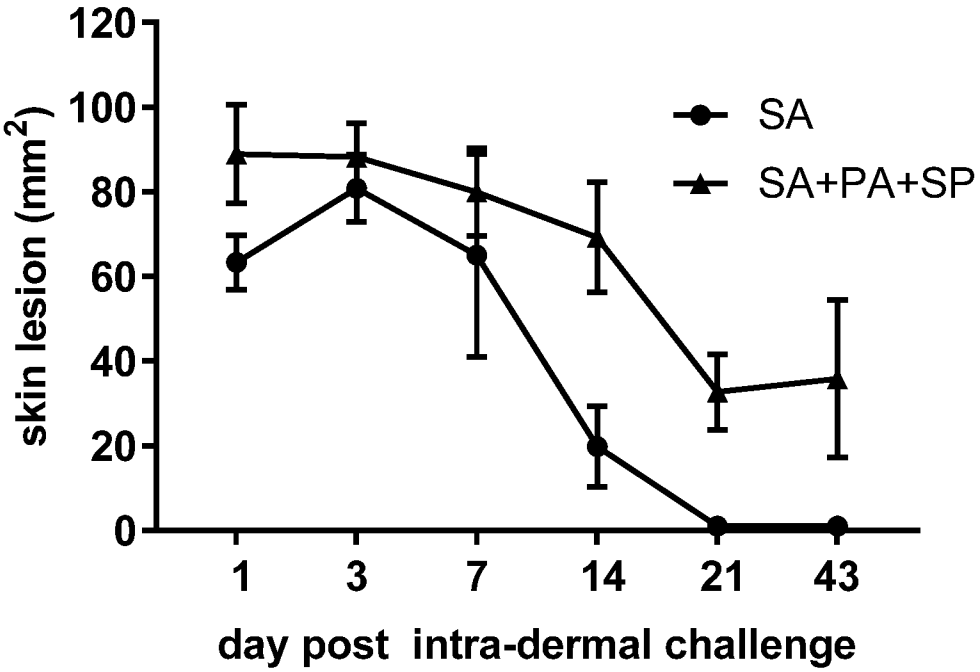

c-IgG
SAN481_SYT
MEDI4893*+SAR114
MEDI4893*+SAN481_SYT
MEDI6389
Percent survival
100
80
60
40
20
0
all mAbs at 15mg/kg
0
24
48
72
96
hours post IV (SF8300, CA-MRSA, PVL+)

Figure 8


120
100
80
60
40
20
0
skin lesion (mm2)
SA
SA+PA+SP
1
3
7
14
21
43
day post intra-dermal challenge

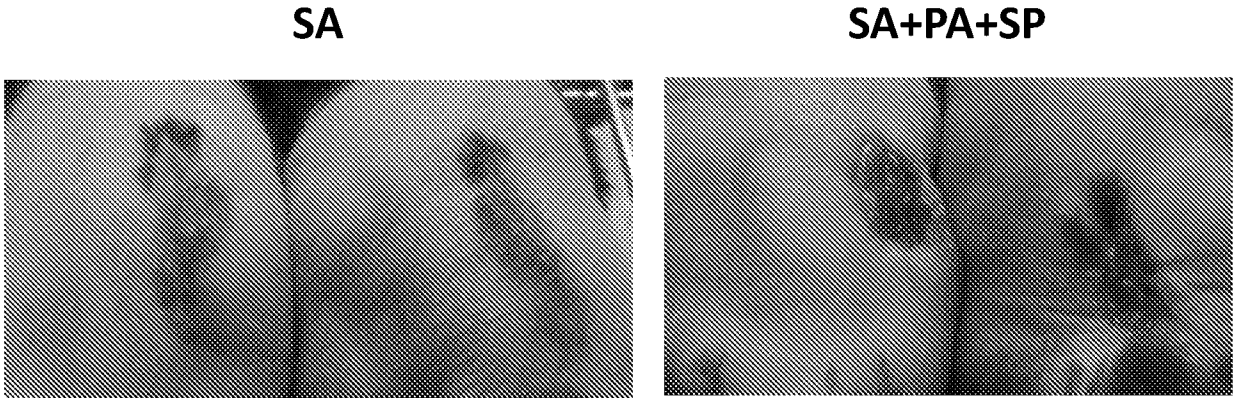

SA
SA+PA+SP

Figure 9

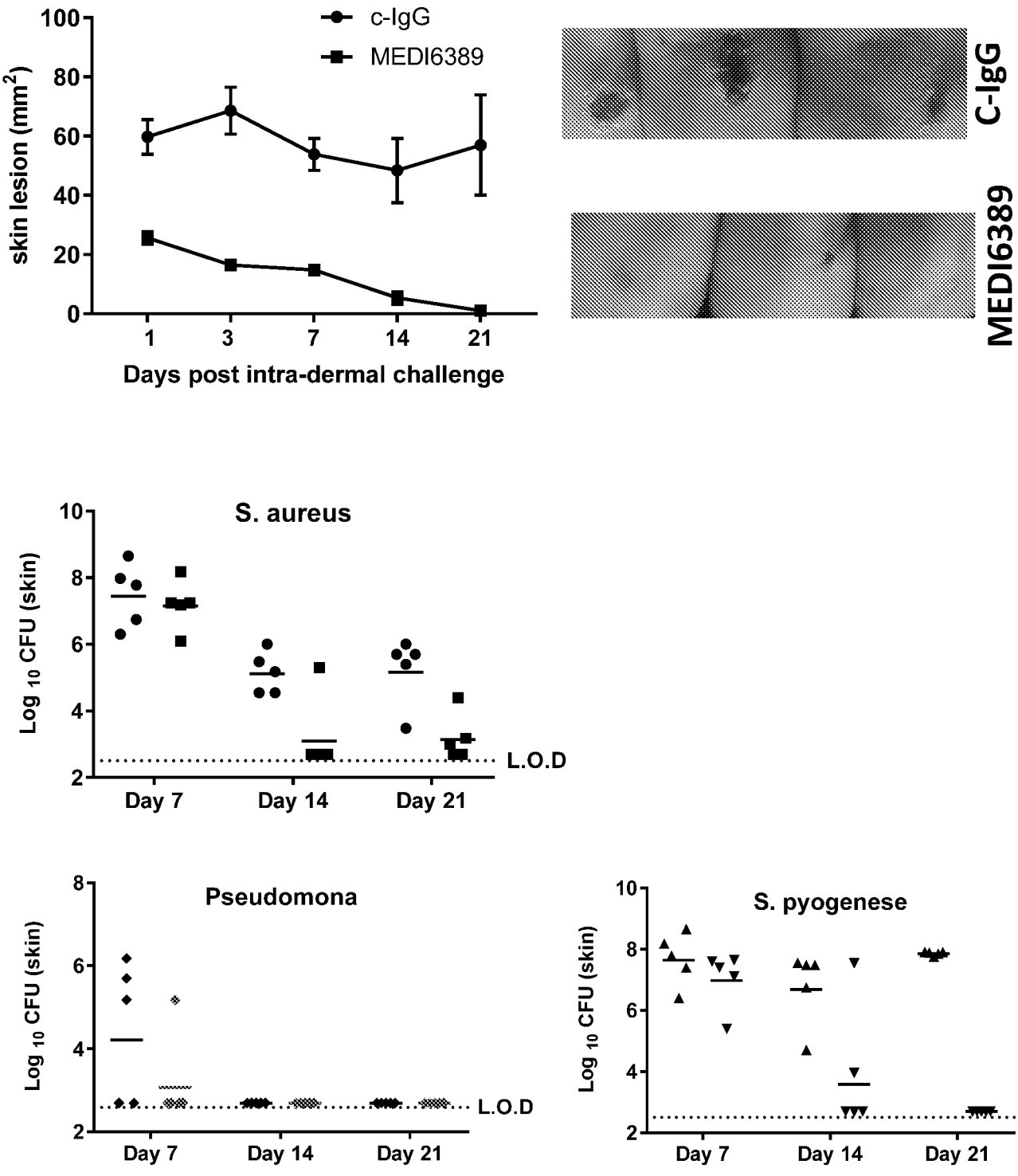

c-IgG
MEDI6389
skin lesion (mm2)
100
80
60
40
20
0
1
3
7
14
21
Days post intra-dermal challenge
C-IgG
MEDI6389
S. aureus
Log 10 CFU (skin)
10
8
6
4
2
L.O.D
Day 7
Day 14
Day 21
Pseudomona
Log 10 CFU (skin)
8
6
4
2
L.O.D
Day 7
Day 14
Day 21
S. pyogenese
Log 10 CFU (skin)
10
8
6
4
2
Day 7
Day 14
Day 21

Figure 10

```
HlgB      GEGKITPVSVKKVDDKVTLYKTTATADSDKFKISQILTFNFIKDKSYDKDTLVLKATGNI      60
LukF      GAQHITPVSEKKVDDKITLYKTTATSDSDKLKISQILTFNFIKDKSYDKDTLILKAAGNI      60
LukD      GAQHITPVSEKKVDDKITLYKTTATSDNDKLNISQILTFNFIKDKSYDKDTLVLKAAGNI      60
          *  :***** ******:*********:*.**::**********************:***:***

HlgB      NSGFVKPNPNDYDFSKLYWGAKYNVSISSQSNDSVNVVDYAPKNQNEEFQVQNTLGYTFG      120
LukF      YSGYTKPNPKDTISSQFYWGSKYNISINSDSNDSVNVVDYAPKNQNEEFQVQQTVGYSYG      120
LukD      NSGYKKPNPKDYNYSQFYWGGKYNVSVSSESNDAVNVVDYAPKNQNEEFQVQQTLGYSYG      120
          **: ****:*   *::***.***:*:.*:***:*********************:*:**::*

HlgB      GDISISNGLSGGLNGNTAFSETINYKQESYRTTLSRNTNYKNVGWGVEAHKIMNNGWGPY      180
LukF      GDINISNGLSGGGNGSKSFSETINYKQESYRTSLDKRTNFKKIGWDVEAHKIMNNGWGPY      180
LukD      GDINISNGLSGGLNGSKSFSETINYKQESYRTTIDRKTNHKSIGWGVEAHKIMNNGWGPY      180
          ***.******** **..:***************::.:.**.*.:**.**************

HlgB      GRDSFHPTYGNELFLAGRQSSAYAGQNFIAQHQMPLLSRSNFNPEFLSVLSHRQDGAKKS      240
LukF      GRDSYHSTYGNEMFLGSRQSNLNAGQNFLEYHKMPVLSRGNFNPEFIGVLSRKQNAAKKS      240
LukD      GRDSYDPTYGNELFLGGRQSSSNAGQNFLPTHQMPLLARGNFNPEFISVLSHKQNDTKKS      240
          ****:. *****:**..***.  *****:  *:**:*:*.******:.***::*: :***

HlgB      KITVTYQREMDLYQIRWNGFYWAGANYKNFKTRTFKSTYEIDWENHKVKLLDTKETENNK      300
LukF      KITVTYQREMDRYTNFWNQLHWIGNNYKDENRATHTSIYEVDWENHTVKLIDTQSKEKNP      300
LukD      KIKVTYQREMDRYTNQWNRLHWVGNNYKNQNTVTFTSTYEVDWQNHTVKLIGTDSKETNP      300
          **.******** *   ** ::* * ***: :  *..* **:**:**.***:.*...*.*
HlgB      -- 300
LukF      MS 302
LukD      GV 302
```

Figure 11A

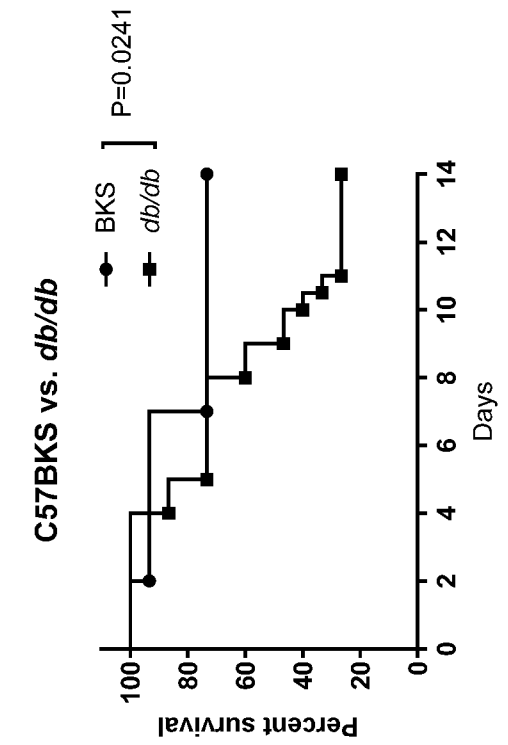


Figure 11B

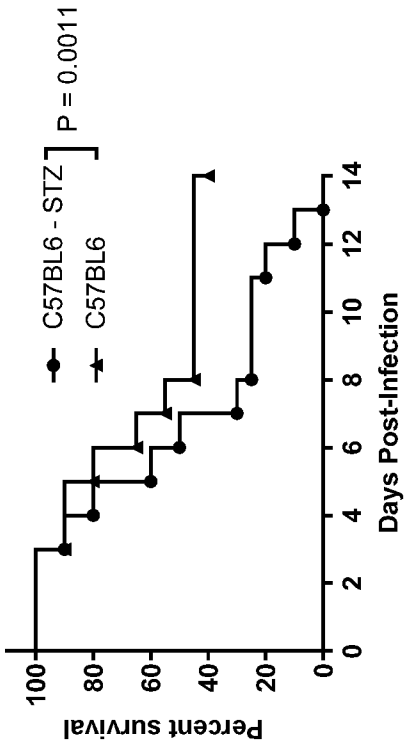


Figure 11C

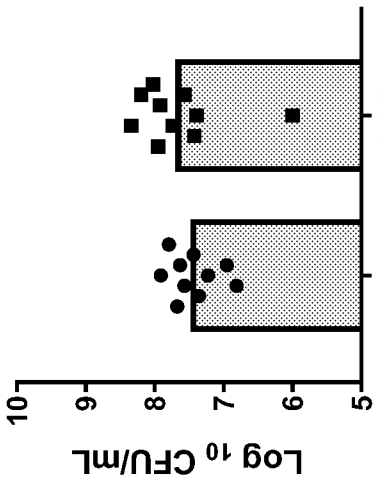


Figure 11D

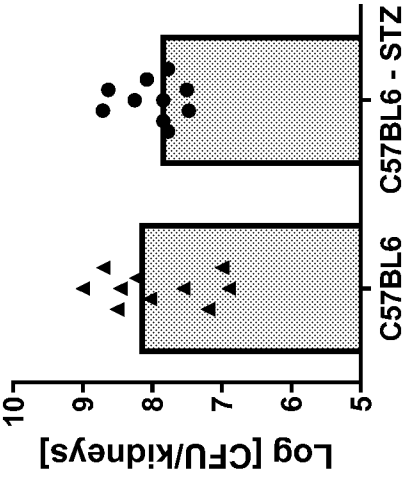


Figure 11E

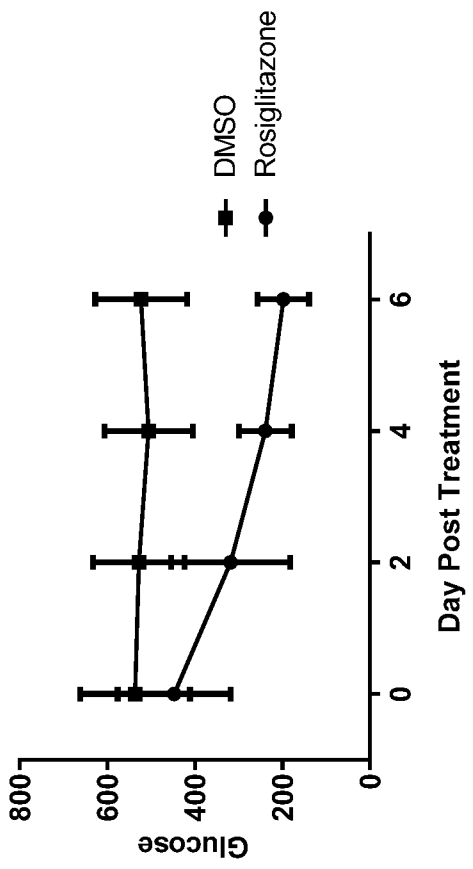


Figure 11F

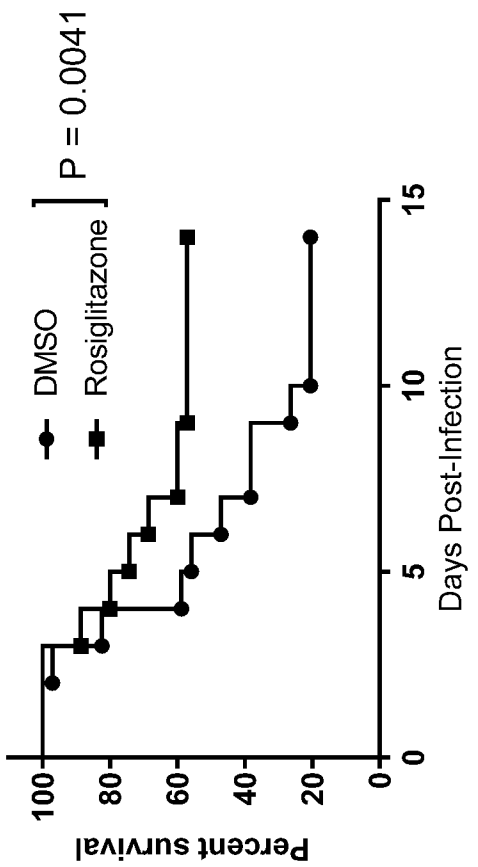


Figure 11G

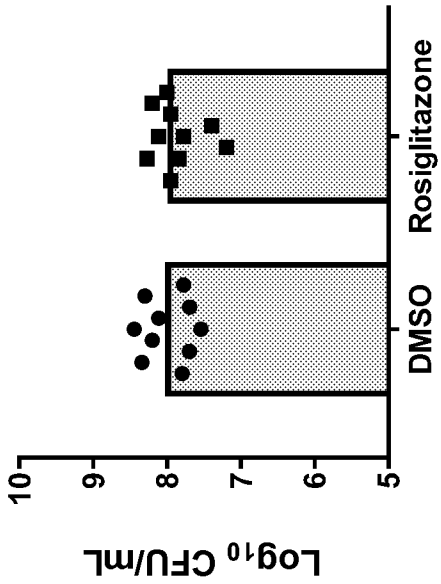


Figure 12A

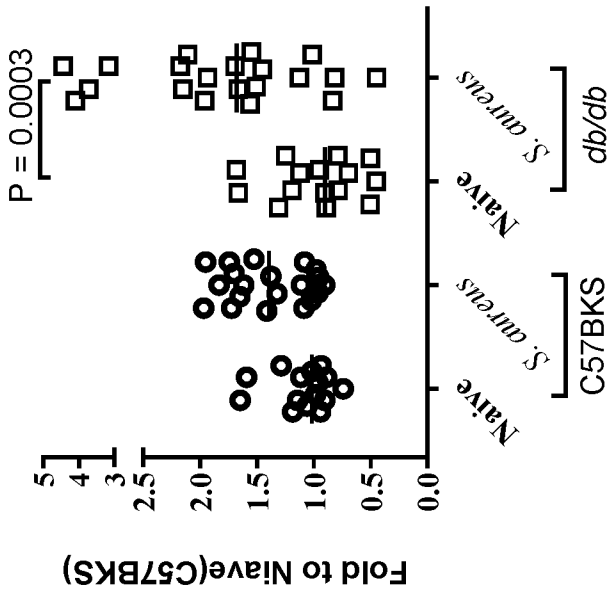


Figure 12B

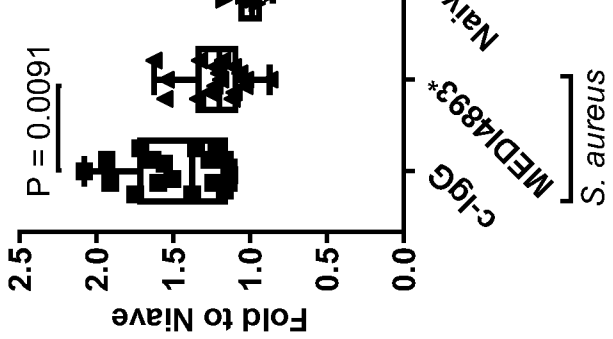


Figure 12C

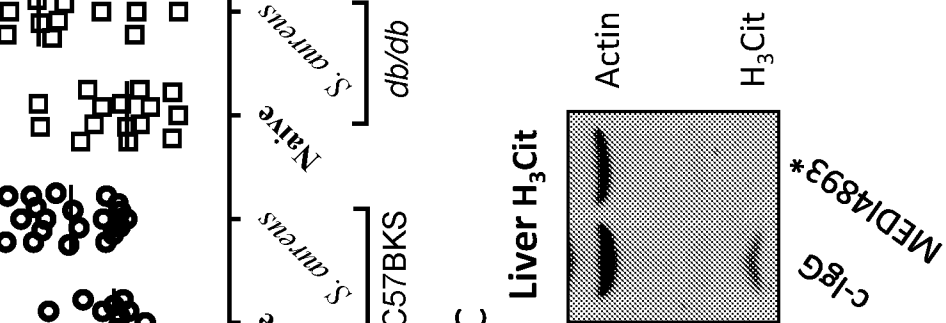
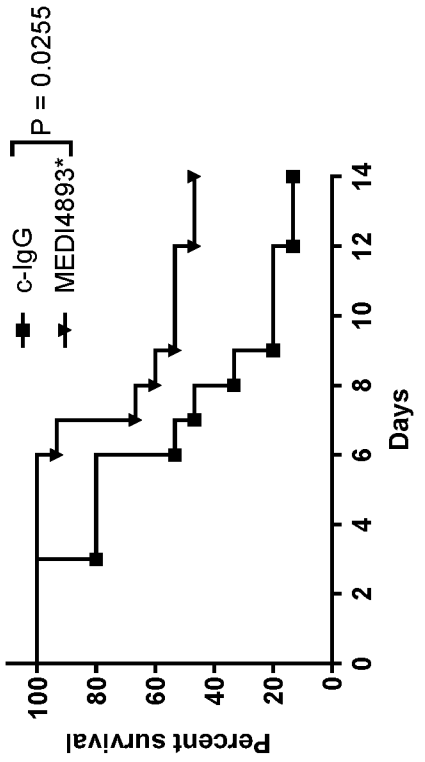


Figure 12D



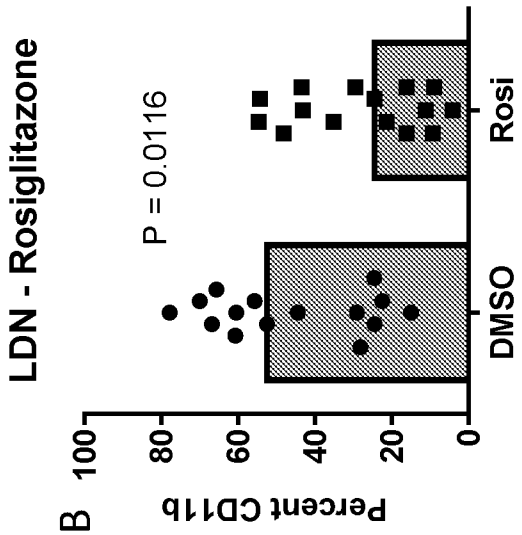


Figure 13B

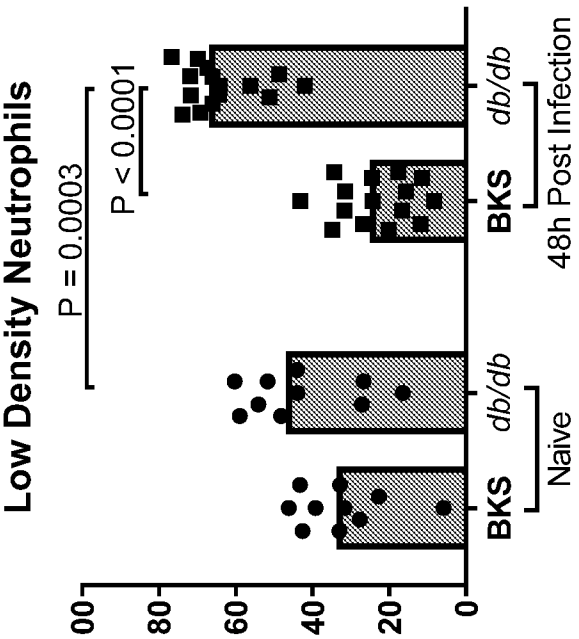


Figure 13A

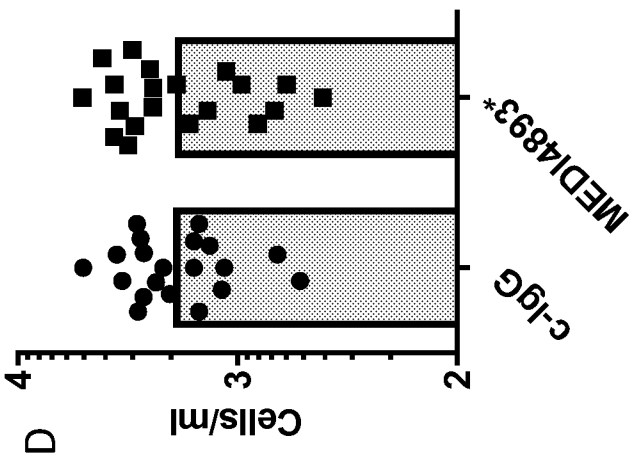


Figure 13D

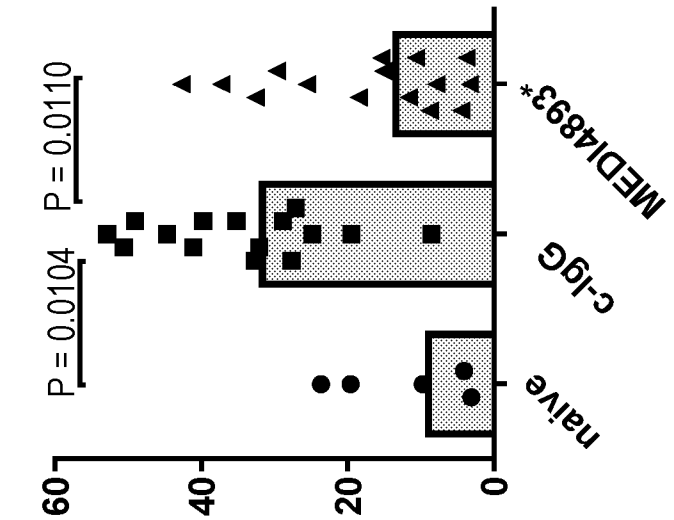


Figure 13C

Figure 14

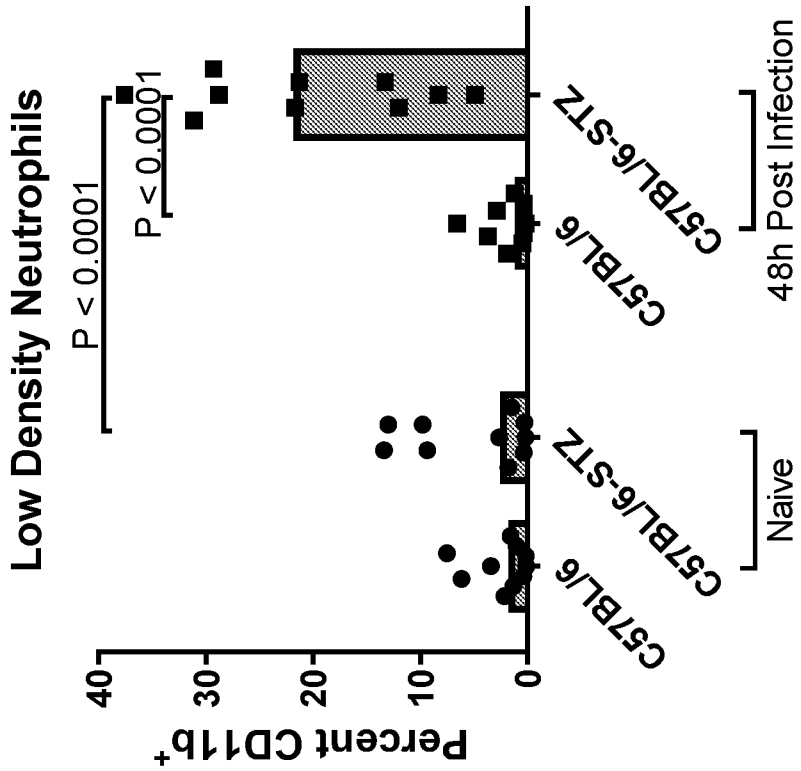
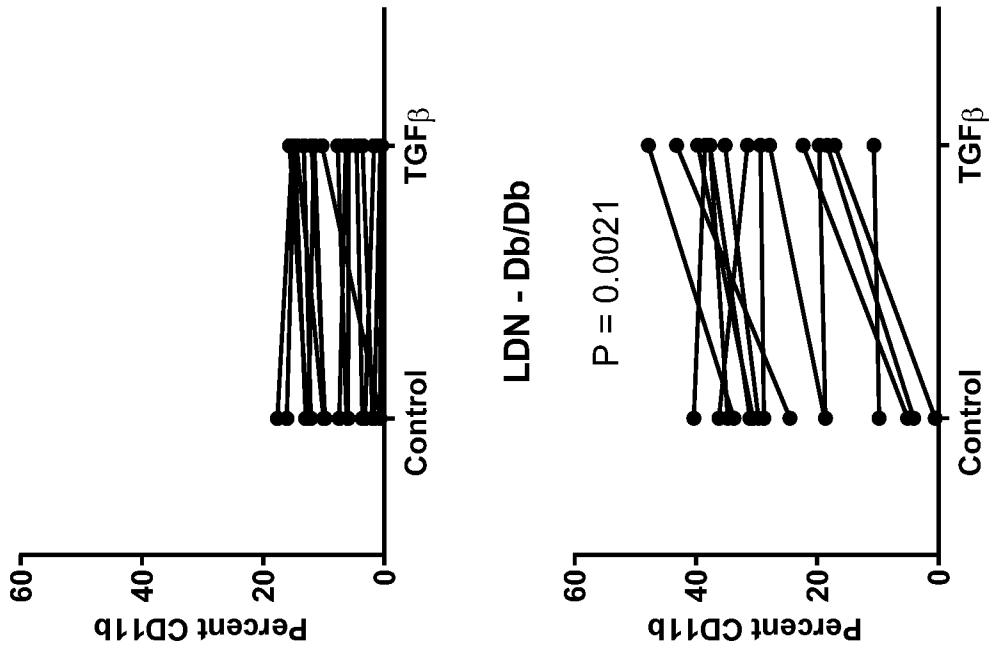

Low Density Neutrophils
P < 0.0001
P < 0.0001
Percent CD11b+
40
30
20
10
0
C57BL/6-STZ
C57BL/6
C57BL/6-STZ
C57BL/6
48h Post Infection
Naive

Figure 15A


LDN - C57BL/6
Percent CD11b
0
20
40
60
Control
TGFβ
LDN - Db/Db
P = 0.0021
Percent CD11b
0
20
40
60
Control
TGFβ

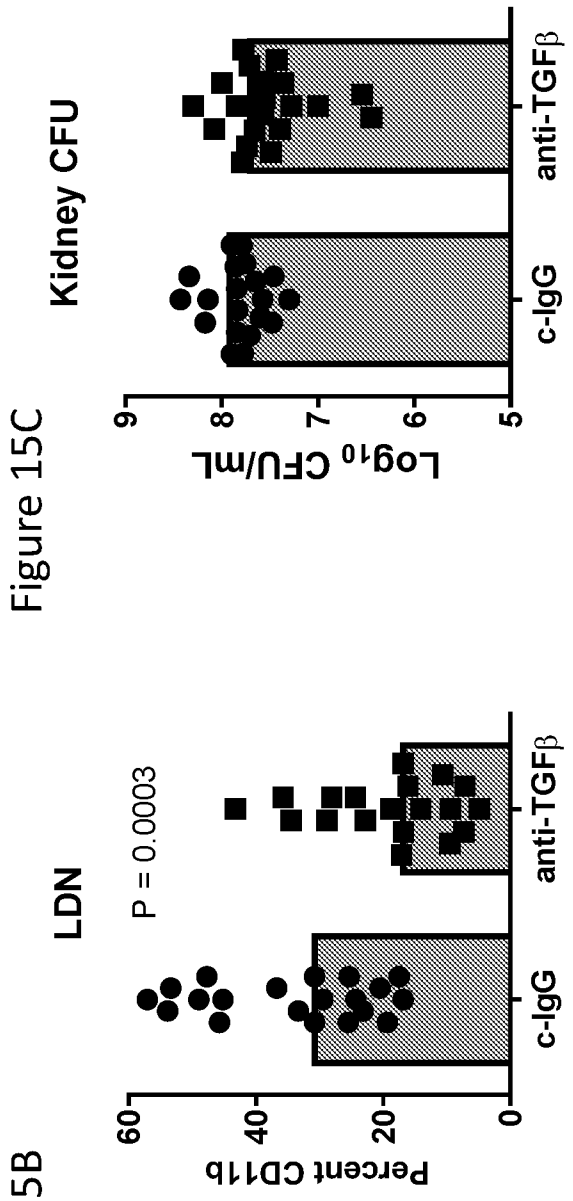


Figure 15B

Figure 15C

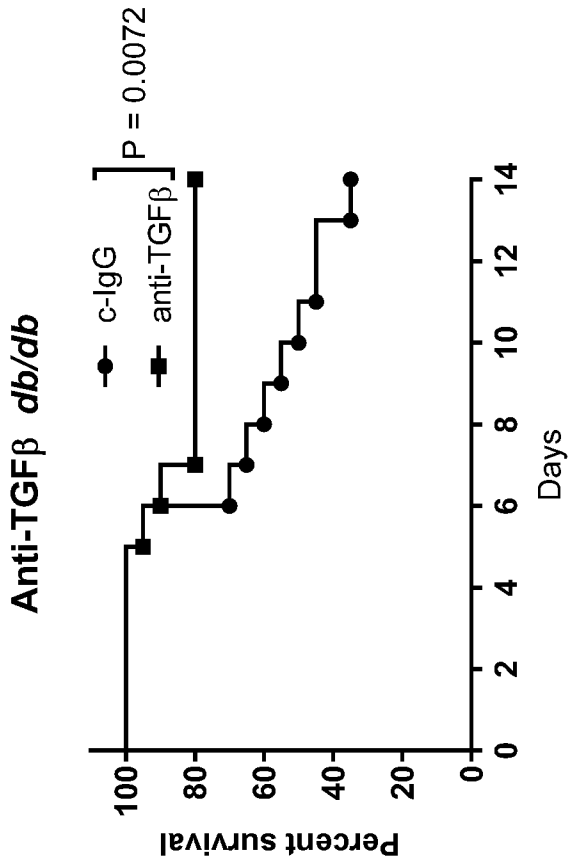
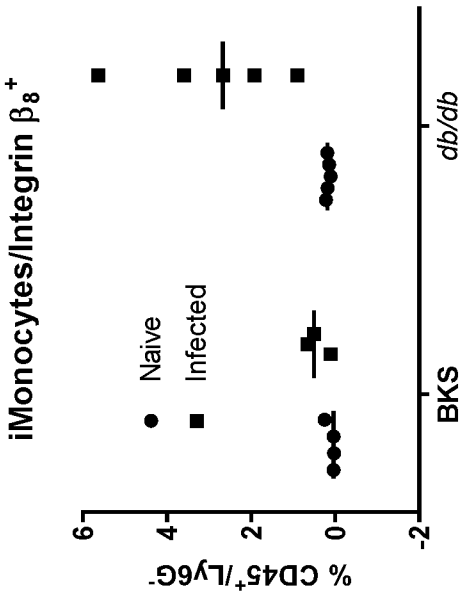


Figure 15D

Figure 16A



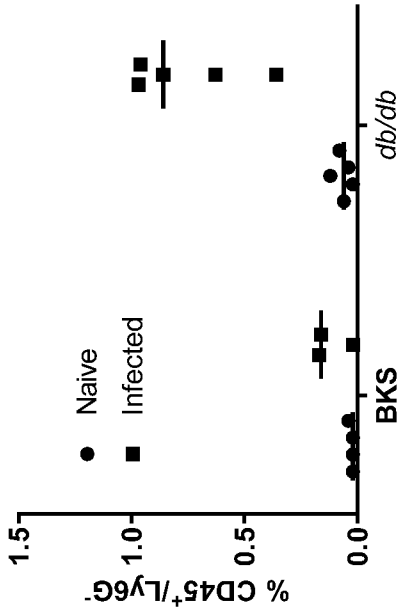
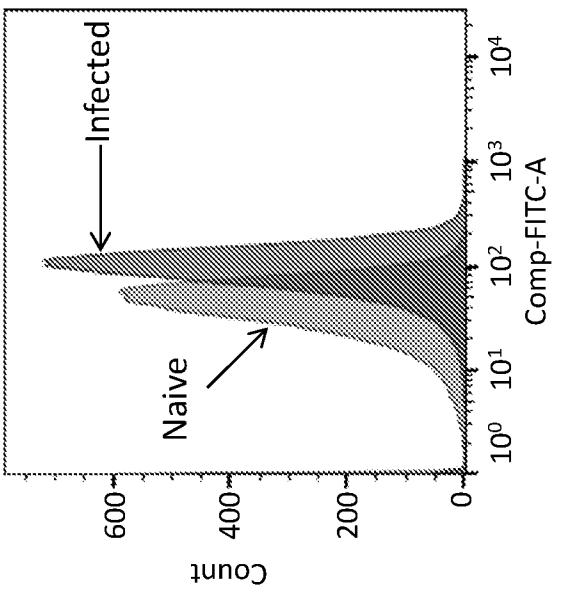


Figure 16B



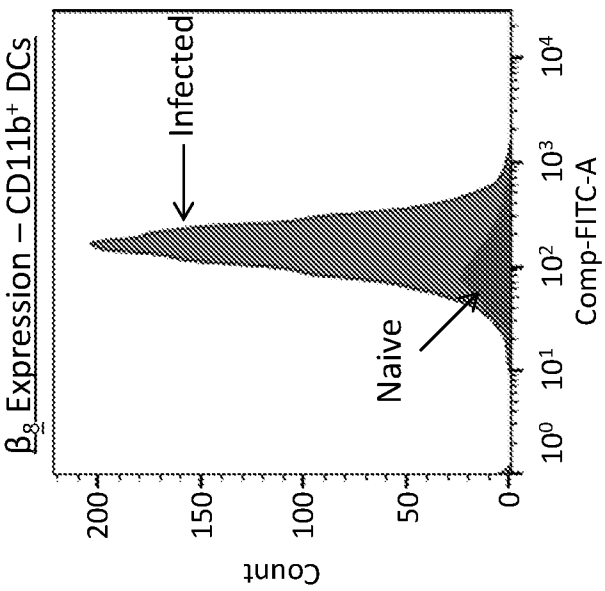


Figure 16C

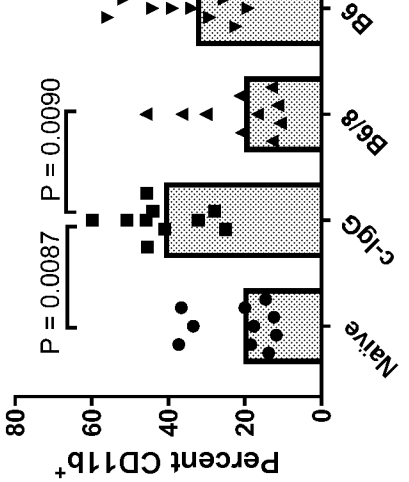


Figure 16D

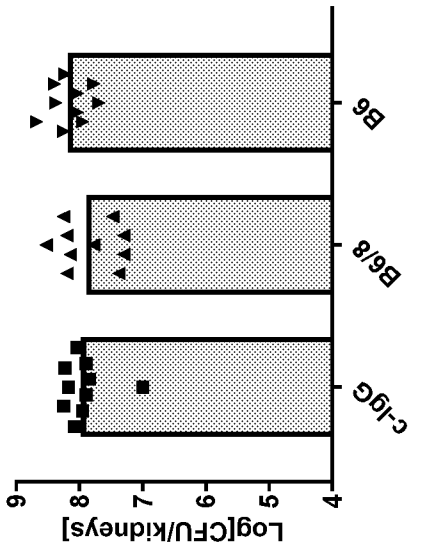


Figure 16E

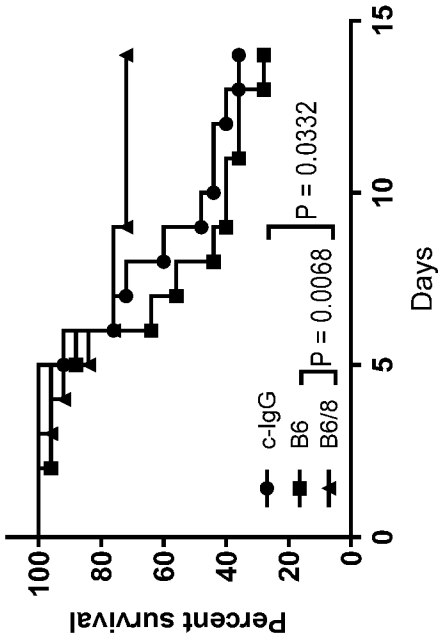


Figure 17A

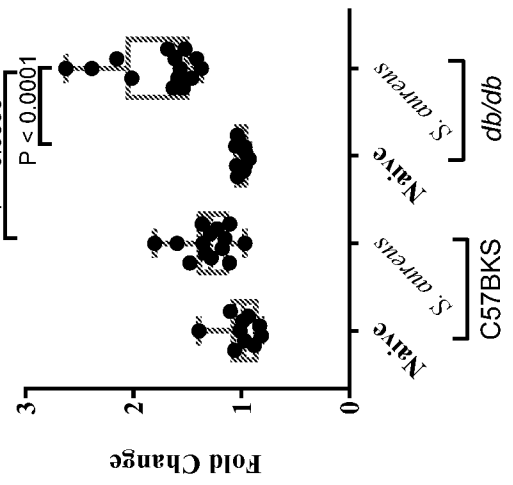


Figure 17B

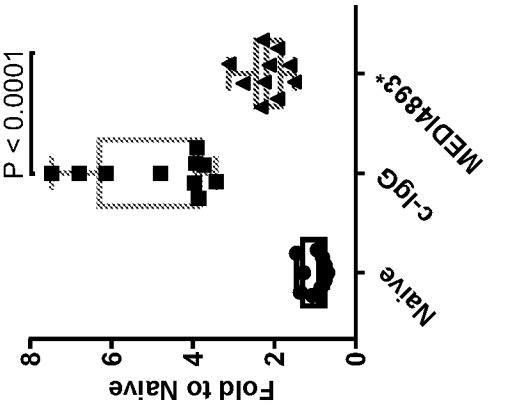


Figure 17C