Claims

1. An immunogenic composition comprising:

(a) a *Staphylococcus aureus* protein A (SpA) variant polypeptide, wherein the SpA variant polypeptide comprises at least one SpA A, B, C, D, or E domain, and wherein the at least one domain has (i) lysine substitutions for glutamine residues corresponding to positions 9 and 10 of SEQ ID NO:58 and (ii) a glutamate substitution for a serine residue corresponding to position 33 of SEQ ID NO:58; and

(b) a mutant staphylococcal leukocidin subunit polypeptide comprising:

a mutant LukAB dimer polypeptide,

wherein the mutant LukAB dimer polypeptide has one or more amino acid substitutions, deletions, or a combination thereof,

such that the ability of the mutant LukAB polypeptide to form pores in the surface of eukaryotic cells is disrupted, thereby reducing the toxicity of the mutant LukAB dimer polypeptide relative to the corresponding wildtype LukAB dimer polypeptide.

2. The immunogenic composition of claim 1, wherein the SpA variant polypeptide comprises a SpA D domain.

3. The immunogenic composition of claim 2, wherein the SpA variant polypeptide further comprises a SpA E, A, B, or C domain.

4. The immunogenic composition of claim 3, wherein each SpA E, A, B, and C domain comprises (i) lysine substitutions for glutamine residues corresponding to positions 9 and 10 of SEQ ID NO:58 and (ii) a glutamate substitution for a serine residue corresponding to position 33 of SEQ ID NO:58.

5. The immunogenic composition of claim 1 or 2, wherein the SpA variant polypeptide does not, relative to a negative control, detectably crosslink IgG and IgE in blood or activate basophils.

6. The immunogenic composition of claim 5, wherein the SpA variant polypeptide has a reduced KA binding affinity for VH3 from human IgG as compared to a SpA variant polypeptide (SpA_{KKAA}) comprising lysine substitutions for glutamine residues in each SpA A-E domain corresponding to positions 9 and 10 of SEQ ID NO:58 and alanine substitutions for aspartic acid residues in each SpA A-E domain corresponding to positions 36 and 37 of SEQID NO:58, wherein the K_A binding affinity for V_H3 from human IgG is less than 1×10^{-5} M^{-1}.

7. The immunogenic composition of claim 6, wherein the SpA variant polypeptide has a K_A binding affinity for V_H3 from human IgG that is reduced by at least 2-fold as compared to SpA_{KKAA}.

8. The immunogenic composition of any one of claims 5 to 7, wherein the only substitutions in the SpA variant polypeptide are (i) and (ii).

9. The immunogenic composition of any one of claims 1, 2, 3, 4, 5 to 7, or 8, wherein the mutant LukAB dimer polypeptide comprises a mutant LukA polypeptide having a deletion of the amino acid residues corresponding to positions 315-324 of SEQ ID NO:16; and a mutant LukB polypeptide comprising the amino acid sequence of SEQ ID NO:53.

10. The immunogenic composition of any one of claims 1, 2, 3, 4, 5 to 7, 8, or 9, further comprising an adjuvant.

11. The immunogenic composition of claim 10, wherein the adjuvant comprises saponins.

12. The immunogenic composition of claim 11, wherein the saponin is QS21.

13. The immunogenic composition of claim 10, wherein the adjuvant comprises a TLR4 agonist.

14. The immunogenic composition of claim 13, wherein the TLR4 agonist is lipid A.

15. The immunogenic composition of claim 13 or 14, wherein the TLR4 agonist comprises MPL, 3D-MPL, RC529, GLA, SLA, E6020, PET-lipid A, PHAD, 3D-PHAD, 3D-(6-acyl)-PHAD, ONO4007, or OM-174.

16. The immunogenic composition of claim 15, wherein the TLR4 agonist is GLA.

17. The immunogenic composition of any one of claims 1, 2, 3, 4, 5 to 7, 8, or 9 to 16, further comprising at least one staphylococcal antigen or immunogenic fragment thereof selected form the group consisting of CP5, CP8, Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, EsxAB(fusion), SdrC, SdrD, SdrE, IsdA, IsdB, IsdC, ClfA, ClfB, Coa, Hla, mHla, MntC, rTSST-1, rTSST-1v, TSST-1, SasF, vWbp, vWh vitronectin binding protein, Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Can, collagen binding protein, Csa1A, EFB, Elastin binding protein, EPB, FbpA, fibrinogen binding protein, Fibronectin binding protein, FhuD, FhuD2, FnbA, FnbB, GehD, HarA, HBP, Immunodominant ABC transporter, IsaA/PisA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analog, MRPII, NPase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK, SBI, SdrF, SdrG, SdrH, SEA exotoxins, SEB exotoxins, mSEB, SitC, Ni ABC transporter, SitC/MntC/saliva binding protein, SsaA, SSP-1, SSP-2, Spa5, SpAKKAA, SpAkR, Sta006, Sta011, PVL, LukED and Hlg.

18. An isolated nucleic acid encoding a *Staphylococcus aureus* protein A (SpA) variant polypeptide and/or a mutant LukAB dimer polypeptide according to any one of claims 1, 2, 3, 4, 5 to 7, 8, or 9 to 17.

19. A vector comprising the isolated nucleic acid of claim 18.

20. An isolated host cell comprising the vector of claim 19.

21. The immunogenic composition of any one of claims 1 to 17 for use in therapy.

22. Use of the immunogenic composition of any one of claims 1 to 17 in the manufacture of a medicament for the treatment or prevention of a *Staphylococcus* infection,

wherein an effective amount of the immunogenic composition is to be administered to a subject in need thereof.

23. The use of claim 22, wherein the medicament is for eliciting an immune response to a *Staphylococcus* bacterium.

24. The use of claim 22, wherein the medicament is for decolonization or preventing colonization or recolonization of a *Staphylococcus* bacterium.