CLAIMS

It is claimed:

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

(b) a mutant staphylococcal leukocidin subunit polypeptide comprising:

(i) a mutant LukA polypeptide,

(ii) a mutant LukB polypeptide, and/or

(iii) a mutant LukAB dimer polypeptide,

wherein (i), (ii), and/or (iii) have one or more amino acid substitutions, deletions, or a combination thereof,

such that the ability of the mutant LukA, LukB, and/or LukAB polypeptides to form pores in the surface of eukaryotic cells is disrupted, thereby reducing the toxicity of the mutant LukA and/or LukB polypeptide or the mutant LukAB dimer polypeptide relative to the corresponding wild-type LukA and/or LukB polypeptide or LukAB dimer polypeptide.

2. The immunogenic composition of claim 1, wherein the SpA variant polypeptide has at least one amino acid substitution that disrupts Fc binding and at least a second amino acid substitution that disrupts V_H3 binding.

3. The immunogenic composition of claim 1 or 2, wherein the SpA variant polypeptide comprises a SpA D domain and has an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO:58.

4. The immunogenic composition of claim 3, wherein the SpA variant polypeptide has one or more amino acid substitutions at amino acid position 9 or 10 of SEQ ID NO:58.

5. The immunogenic composition of claim 3 or 4, wherein the SpA variant polypeptide further comprises a SpA E, A, B, or C domain.

6. The immunogenic composition of claim 5, wherein the SpA variant polypeptide comprises a SpA E, A, B, and C domain and has an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO:54.

7. The immunogenic composition of claim 5 or 6, wherein each SpA E, A, B, and C domain has one or more amino acid substitutions at positions corresponding to amino acid positions 9 and 10 of SEQ ID NO:58.

8. The immunogenic composition of any one of claims 4 to 7, wherein the amino acid substitution is a lysine residue for a glutamine residue.

9. The immunogenic composition of any one of claims 1 to 4, 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 in the SpA D domain and (ii) a glutamate substitution corresponding to position 33 in the SpA D domain, wherein the polypeptide does not, relative to a negative control, detectably crosslink IgG and IgE in blood or activate basophils.

10. The immunogenic composition of claim 9, wherein the SpA variant polypeptide has a reduced K_A binding affinity for V_H3 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 in the SpA D domain and alanine substitutions for aspartic acid residues in each SpA A-E domain corresponding to positions 36 and 37 of SpA D domain.

11. The immunogenic composition of claim 10, 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}.

12. The immunogenic composition of claim 10 or 11, wherein the SpA variant polypeptide has a K_A binding affinity for V_H3 from human IgG of less than 1×10^5 M^{-1}.

13. The immunogenic composition of any one of claims 1 to 12, wherein the SpA variant polypeptide does not have substitutions in any of the SpA A, B, C, D, or E domains corresponding to amino acid positions 36 and 37 in the SpA D domain.

14. The immunogenic composition of any one of claims 9 to 13, wherein the only substitutions in the SpA variant polypeptide are (i) and (ii).

15. The immunogenic composition of any one of claims 1 to 14, wherein the mutant LukA polypeptide comprises an amino acid sequence having at least 90% sequence identity to any one of SEQ ID NOs:1-28.

16. The immunogenic composition of claim 15, wherein the mutant LukA polypeptide comprises a deletion of the amino acid residues corresponding to amino acid positions 342-351 of any one of SEQ ID NOs:1-14 and at amino acid positions 315-324 of any one of SEQ ID NOs:15-28.

17. The immunogenic composition of any one of claims 1 to 16, wherein the mutant LukB polypeptide comprises an amino acid sequence having at least 80% sequence identity to any of SEQ ID NO:29-53.

18. The immunogenic composition of any one of claims 1 to 17, 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 LukB polypeptide comprising the amino acid sequence of SEQ ID NO:53.

19. The immunogenic composition of any one of claims 1 to 18, further comprising an adjuvant.

20. The immunogenic composition of claim 19, wherein the adjuvant comprises saponins.

21. The immunogenic composition of claim 20, wherein the saponin is QS21.

22. The immunogenic composition of claim 19, wherein the adjuvant comprises a TLR4 agonist.

23. The immunogenic composition of claim 22, wherein the TLR4 agonist is lipid A or an analog or derivative thereof.

24. The immunogenic composition of claim 22 or 23, 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.

25. The immunogenic composition of claim 24, wherein the TLR4 agonist is GLA.

26. The immunogenic composition of any one of claims 1 to 25, 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.

27. One or more isolated nucleic acids encoding a *Staphylococcus aureus* protein A (SpA) variant polypeptide and a mutant Luk A polypeptide, a mutant Luk B polypeptide, or a mutant LukAB dimer polypeptide according to any one of claims 1 to 26.

28. A vector comprising the isolated nucleic acid of claim 27.

29. An isolated host cell comprising the vector of claim 28.

30. The immunogenic composition of any one of claims 1 to 26, the one or more isolated nucleic acids of claim 27, the vector of claim 28, or the host cell of claim 29 for use in therapy.

31. Use of the immunogenic composition of any one of claims 1 to 26, the one or more isolated nucleic acids of claim 27, the vector of claim 28, or the host cell of claim 29 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.

32. The use of claim 31, wherein the medicament is for eliciting an immune response to a *Staphylococcus* bacterium.

33. The use of claim 31, wherein the medicament is for decolonization or preventing colonization or recolonization of a *Staphylococcus* bacterium.