CLAIMS:

1. A polypeptide, comprising at least one mutant SPINK9 domain, wherein said at least one mutant SPINK9 domain comprises, in N-terminus to C-terminus order, a first amino acid sequence that shares at least 70% sequence identity to amino acids 1-20 set forth in SEQ ID NO: 2, a second amino acid sequence that comprises at least one amino acid substitution relative to amino acids 21-34 set forth in SEQ ID NO: 2, and a third amino acid sequence that shares at least 70% sequence identity to amino acids 35-67 set forth in SEQ ID NO: 2.

2. The polypeptide of claim 1, wherein the second amino acid sequence comprises at least one amino acid substitution relative to positions 22, 24, 25, 26, 28, 29, 30 of SEQ ID NO: 2, or any combination thereof, and optionally one or more amino acid changes relative to positions 21, 23, 27, 31, 32, 33, and 34 of SEQ ID NO: 2.

3. The polypeptide of claim 1 or 2, wherein the first amino acid sequence optionally comprises the amino acids at positions 1, 2, and 3 of SEQ ID NO: 2, the second amino acid sequence comprises at least one amino acid substitution relative to positions 22, 24, 25, 26, 28, 29, 30 of SEQ ID NO: 2, or any combination thereof, and optionally one or more amino acid changes relative to positions 21, 31, 32, 33, and 34 of SEQ ID NO: 2.

4. The polypeptide of any one of claims 1 to 3, wherein the first amino acid sequence comprises a deletion of the amino acids at positions 1, 2, and 3 of SEQ ID NO: 2, the second amino acid sequence comprises at least one amino acid substitution relative to positions 22, 24, 25, 26, 28, 29, 30 of SEQ ID NO: 2, or any combination thereof, and optionally one or more amino acid changes relative to positions 21, 31, 32, 33, and 34 of SEQ ID NO: 2.

5. The polypeptide of any one of claims 1 to 3, wherein the at least one mutant SPINK9 domain comprises an amino acid sequence selected from SEQ ID NOS: 4-23 or 115-134.

6. The polypeptide of any one of claims 1 to 5, wherein the polypeptide comprises a first and a second independently selected mutant SPINK9 domain; and each of the first and the second mutant SPINK9 domains comprise an independently selected amino acid sequence of any one of SEQ ID NOS: 4-23 or 115-134.

7. The polypeptide of any one of claims 1 to 5, wherein said at least one mutant SPINK9 domain comprises an amino acid sequence represented by Formula IV;
X_9 X_{10} X_{11} Ala Lys Gln Thr Lys Gln Met Val Asp Cys Ser His Tyr Lys Lys Leu Pro Pro X_1 Gln X_2 X_3 X_4 Cys X_5 X_6 X_7 Tyr Asp Pro Ile Cys Gly Ser Asp Gly Lys Thr Tyr X_8 Asn Asp Cys Phe Phe Cys Ser Lys Val Lys Lys Thr Asp Gly Thr Leu Lys Phe Val His Phe Gly Lys Cys (SEQ ID NO: 136);
provided that the amino acid sequence represented by Formula IV is not SEQ ID NO: 2.

8. The polypeptide of claim 7, wherein the polypeptide binds to and inhibits an active kallikrein-related peptidase.

9. The polypeptide of claim 7 or 8, wherein the polypeptide inhibits the activity of kallikrein-related peptidase 5 (KLK5).

10. The polypeptide of claim 9, wherein the inhibition is selective for or specific to KLK5.

11. The polypeptide of any one of claims 7 to 10, wherein X_1 is selected from: i) Gly, Glu, Met, Gln, Ala, Leu, Val, Asp, Asn, Ser, Lys, or His; ii) Gly, Glu, or Met; iii) Glu, Met, Gln, Ala, Leu, Val, Asp, Asn, Ser, Lys, or His; or iv) Glu or Met;

wherein X_2 is selected from: i) Gln, Glu, Thr, Val, Leu, Ala, Ile, Phe, Ser, or Tyr; ii) Gln, Glu, or Thr; iii) Glu, Thr, Val, Leu, Ala, Ile, Phe, Ser, or Tyr; or iv) Glu or Thr;

wherein X_3 is selected from: i) Arg, Leu, Ile, His, Glu, Trp, Ser, Ala, Val, Tyr, Asp, or Met; ii) Arg, Leu, Ile, His, Glu, or Trp; iii) Leu, Ile, His, Glu, Trp, Ser, Ala, Val, Tyr, Asp, or Met; or iv) Leu, Ile, His, Glu, or Trp;

wherein X_4 is selected from: i) Phe, Tyr, Trp, Met, His, Lys, or Asn; ii) Phe, Tyr, or Trp; iii) Tyr, Trp, Met, His, Lys, or Asn; or iv) Trp or Tyr;

wherein X_5 is selected from: i) His, Thr, Ser, or Gly; ii) His or Thr; iii) Thr, Ser, or Gly; or iv) Thr;

wherein X_6 is selected from: i) His, Arg or Lys; ii) His or Arg; iii) Arg or Lys; or iv) Arg;

wherein X_7 is selected from: i) Met, Glu or Asp; ii) Met or Glu; iii) Glu or Asp; or iv) Glu;

wherein X_8 is selected from: i) Lys or Gly; ii) Lys; or iii) Gly;

wherein X_9 is selected from: i) absent; or ii) Ile;

wherein X_{10} is selected from: i) absent; or ii) Glu; and

wherein X_{11} is selected from: i) absent; or ii) Cys.

12. The polypeptide of any one of claims 7 to 11, wherein the polypeptide comprises from two to twenty independently selected mutant SPINK9 domains; and each mutant SPINK9 domain comprises an independently selected amino acid sequence of Formula IV or an amino acid sequence selected from SEQ ID NOS: 4-23 and SEQ ID NOS: 115-134.

13. The polypeptide of any one of claims 7 to 11, wherein the polypeptide comprises a first and a second independently selected mutant SPINK9 domain; and each of the first and the second mutant SPINK9 domains comprise an independently selected amino acid sequence Formula IV or SEQ ID NOS: 115-134.

14. The polypeptide of claim 13, wherein the polypeptide comprises a first and a second independently selected mutant SPINK9 domain and wherein the first and the second mutant SPINK9 domains are identical or wherein the first and the second mutant SPINK9 domains are not identical.

15. The polypeptide of claim 11, wherein each of said mutant SPINK9 domains are identical, or wherein each of said mutant SPINK9 domains are not identical.

16. The polypeptide of any one of claims 12 to 15, wherein adjacent mutant SPINK9 domains are linked by direct fusion, a linker sequence, or any combination thereof.

17. The polypeptide of claim 16, wherein the linker sequence comprises a cleavage site, such as a cleavage site recognized by a subtilisin-like proprotein convertase.

18. The polypeptide of any one of claims 1 to 17, further comprising a signal sequence, wherein the signal sequence is linked to the amino (N)-terminus or to the carboxy (C)-terminus of the polypeptide by direct fusion, or by a linker sequence.

19. The polypeptide of any one of claims 1 to 18, further comprising an immunoglobulin Fc region or a functional fragment thereof, wherein the immunoglobulin Fc region or functional fragment thereof comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 39-54.

20. The polypeptide of claim 19, wherein the immunoglobulin Fc region or functional fragment thereof comprises an amino acid sequence of Formula II:
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro X_1 Cys Pro Ala Pro X_2 X_3 X_4 Gly X_5 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu X_6 Ile X_7 Arg X_8 Pro Glu Val Thr Cys Val Val X_9 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr X_{10} Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val X_{11} His X_{12} Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys X_{13} Leu Pro X_{14} X_{15} Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val X_{16} His Glu Ala Leu X_{17} X_{18} His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys (SEQ ID NO: 24);

wherein: X_1 is Pro or Ser; X_2 is Glu or Pro; X_3 and X_4 are each independently Lue or Ala; X_5 is Gly or Ala; X_6 is Met or Tyr; X_7 is Ser of Thr; X_8 is Thr or Glu; X_9 is Val or Glu; X_{10} is Asn or Ala; X_{11} is Leu or Asp; X_{12} is Gln or His; X_{13} is Ala or Gly; X_{14} is Ala or Ser; X_{15} is Pro or Ser; X_{16} is Met or Leu; X_{17} is His or Lys; and X_{18} is Asn, Ser, or Phe.

21. The polypeptide of claim 19 or 20, wherein the immunoglobulin Fc region or functional fragment thereof is linked to a mutant SPINK9 domain by direct fusion, by a linker sequence, or any combination thereof.

22. The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 55-114; and SEQ ID NOS: 55-114, wherein amino acids 1-3 of SEQ ID NOS: 55-114 are deleted.

23. The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, or SEQ ID NO: 60.

24. The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, or SEQ ID NO: 80.

25. The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, or SEQ ID NO: 100.

26. The polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO:137, SEQ ID NO: 138, or SEQ ID NO: 139.

27. The polypeptide of claim 6, wherein the first and second mutant SPINK9 domains comprise an independently selected amino acid sequence of any one of SEQ ID NOS 5-9 or 116-120.

28. The polypeptide of claim 27, wherein the polypeptide further comprises an immunoglobulin Fc region or a functional fragment thereof, wherein the immunoglobulin Fc region or a functional fragment thereof comprises an amino acid sequence of any one of SEQ ID NOS: 39-54.

29. A nucleic acid, encoding the polypeptide of any one of claims 1-28.

30. A vector, comprising the nucleic acid of claim 29.

31. A host cell, comprising the nucleic acid of claim 29 or the vector of claim 30.

32. A method of producing a polypeptide comprising at least one mutant SPINK9 domain, said method comprising expressing the polypeptide in the host cell of claim 31, and isolating the polypeptide.

33. A composition, comprising the polypeptide of any one of claims 1 to 28, the nucleic acid according to claim 29, the vector according to claim 30, or the host cell according to claim 31.

34. A pharmaceutical composition, comprising a polypeptide of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

35. Use of a therapeutically effective amount of a polypeptide of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a disease or condition characterized by aberrant kallikrein activity.

36. The use of claim 35, wherein the disease or condition is characterized by aberrant kallikrein-related peptidase 5 (KLK5) activity.

37. The use of claim 35 or 36, wherein the disease or condition is a skin disease, wherein the skin disease is eczema, atopic eczema, atopic dermatitis, autosomal recessive ichthyosis, ichthyosiform erythroderma, psoriasis, UV-induced skin injury, rosacea, or a skin infection.

38. The use of claim 35 or 36, wherein the disease or condition is Netherton Syndrome.

39. The use of claim 35 or 36, wherein the disease or condition is selected from the group consisting of hypersensitivity of the immune system (atopy), hyper IgE syndrome, allergies (including allergies to food and airborne agents), asthma, allergic asthma, chronic inflammation, rhinitis, conjunctivitis, angioedema, eosinophilia, eosinophilic esophagitis, growth delay, failure to thrive, trichorrhexis invaginata (TI), respiratory tract infections, systemic infections, and gastrointestinal disorders.

40. The use of claim 35 or 36, wherein the disease or condition is cancer, wherein the cancer is selected from the group consisting of ovarian cancer, uterine cancer, colorectal cancer, bladder urothelial cancer, oral squamous cell carcinoma, breast cancer, prostate cancer, bladder cancer, cervical cancer, melanoma, head and neck cancer glioma, glioblastoma multiforme, and neuroblastoma.

41. A polypeptide of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, for use in therapy.