

## CLAIMS

1. An isolated polypeptide comprising a desmoglein-2 (DSG2) fusion polypeptide, wherein the DSG2 fusion polypeptide comprises:
  - a. a whole or a portion of a DSG2 protein, wherein the DSG2 protein is a *Homo sapiens* DSG2 protein, a *Mus musculus* DSG2 protein, a *Rattus norvegicus* DSG2 protein, a *Macaca mulatta* DSG2 protein, a *Canis lupus familiaris* DSG2 protein, or a *Danio rerio* DSG2 protein; and
  - b. a protein or a fragment of a protein which is capable of improving the expression and/or stability of the DSG2 protein *in vitro* or *in vivo* or used for purification of the DSG2 fusion polypeptide.
2. The isolated polypeptide of claim 1, wherein the DSG2 protein is a *Homo sapiens* DSG2 protein (SEQ ID NO. 1).
3. The isolated polypeptide of claim 1, wherein the DSG2 protein is a *Mus musculus* DSG2 protein (SEQ ID NO. 14).
4. The isolated polypeptide of claim 1, wherein the DSG2 protein is a *Rattus norvegicus* DSG2 protein (SEQ ID NO. 15).
5. The isolated polypeptide of claim 1, wherein the DSG2 protein is a *Macaca mulatta* DSG2 protein (SEQ ID NO. 16).
6. The isolated polypeptide of claim 1, wherein the DSG2 protein is a *Canis lupus familiaris* DSG2 protein (SEQ ID NO. 17).
7. The isolated polypeptide of claim 1, wherein the DSG2 protein is a *Danio rerio* DSG2 protein (SEQ ID NO. 18).
8. The isolated polypeptide of any one of claims 1 to 7, wherein the DSG2 fusion polypeptide comprises a portion of the DSG2 protein.

9. The isolated polypeptide of claim 8, wherein the portion of the DSG2 protein is a whole or a portion of an extracellular region of the DSG2 protein.
10. The isolated polypeptide of claim 8, wherein the portion of DSG2 protein is the whole extracellular region of DSG2 protein.
11. The isolated polypeptide of claim 1, wherein the fragment of the protein comprises a portion of an immunoglobulin protein.
12. The isolated polypeptide of claim 11, wherein the immunoglobulin protein is an IgG, an IgM, an IgA, an IgD or, an IgE.
13. The isolated polypeptide of claim 12, wherein the immunoglobulin protein is an IgE.
14. The isolated polypeptide of claim 12, wherein the immunoglobulin is an IgG.
15. The isolated polypeptide of claim 14, wherein the IgG is an IgG1, an IgG2, an IgG3, or an IgG4.
16. The isolated polypeptide of any one of claims 11 to 15, wherein the portion of the immunoglobulin protein is an Fc region, an Fab region, a heavy chain variable (VH) domain, a heavy chain constant domain, a light chain variable (VL) domain, or a light chain constant domain.
17. The isolated polypeptide of any one of claims 14 to 16, wherein the portion of the immunoglobulin protein is an Fc region.
18. The isolated polypeptide of any one of claims 14 to 17, wherein the Fc region is a human Fc region and where in the human Fc region is a human IgG1 Fc region (SEQ ID NO: 5), a

human IgG2 Fc region (SEQ ID NO: 7), a human IgG3 Fc region (SEQ ID NO: 9), or a human IgG4 Fc region (SEQ ID NO: 11).

19. The isolated polypeptide of any one of claims 14 to 18, wherein the Fc region is a canine Fc region and wherein the canine Fc region is a canine IgG heavy chain D Fc region (SEQ ID NO: 20), a canine IgG heavy chain A Fc region (SEQ ID NO: 22), a canine IgG heavy chain B Fc region (SEQ ID NO: 24), or a canine IgG heavy chain C Fc region (SEQ ID NO: 26).

20. The isolated polypeptide of claim 16, wherein the portion of the immunoglobulin protein is a heavy chain constant domain.

21. The isolated polypeptide of claim 20, wherein the heavy chain constant is a human heavy chain constant region and wherein the human heavy chain constant region is a human IgG1 heavy chain constant domain (SEQ ID NO: 4), a human IgG2 heavy chain constant domain (SEQ ID NO: 6), a human IgG3 heavy chain constant domain (SEQ ID NO: 8), or a human IgG4 heavy chain constant domain (SEQ ID NO: 10).

22. The isolated polypeptide of claim 20, wherein the heavy chain constant is a canine heavy chain constant region and wherein the canine heavy chain constant region is a canine IgG heavy chain constant domain chain D (SEQ ID NO: 19), a canine IgG heavy chain constant domain chain A (SEQ ID NO: 21), a canine IgG heavy chain constant domain chain B (SEQ ID NO: 23), or a canine IgG heavy chain constant domain chain C (SEQ ID NO: 25).

23. The isolated polypeptide of any one of claims 1 to 22, wherein the DSG2 fusion polypeptide further comprises a linker.

24. The isolated polypeptide of claim 23, wherein the linker is from about 5 amino acids to about 50 amino acids in length.

25. The isolated polypeptide of claim 24, wherein the linker is GGGGGS (SEQ ID NO: 12), EAAAK (SEQ ID NO: 13), GGGGS (SEQ ID NO: 27) or IEGRMD (SEQ ID NO: 28).

26. The isolated polypeptide of any one of claims 1 to 25, wherein the protein or the fragment of the protein comprises an affinity tag.
27. The isolated polypeptide of claim 10, wherein the whole extracellular region of DSG2 protein comprises the amino acid sequence of SEQ ID NO: 3.
28. The isolated polypeptide of claim 9, wherein the portion of the DSG2 protein is a portion of an extracellular region of the DSG2 protein.
29. The isolated polypeptide of claim 6, wherein the portion of an extracellular region of the DSG2 protein comprises at least one domain selected from the group consisting of extracellular cadherin domain 1 (EC1), extracellular cadherin domain 2 (EC2), extracellular cadherin domain 3 (EC3), extracellular cadherin domain 4 (EC4), and extracellular anchor domain (EA).
30. A cell expressing the isolated polypeptide of any one of claims 1 to 29.
31. A composition comprising the isolated polypeptide of any one of claims 1 to 29 and at least one therapeutic agent.
32. The composition of claim 31, wherein the at least one therapeutic agent is an anti-CD20 antibody.
33. The composition of claim 31, wherein the at least one therapeutic agent is an FcRn-blocking antibody.
34. The composition of claim 31, wherein the at least one therapeutic agent is intravenous immunoglobulins (IVIG).
35. The composition of claim 31, wherein the at least one therapeutic agent is eculizumab.

36. Use of a desmoglein 2 (DSG2) fusion polypeptide in the manufacture of a pharmaceutical composition for the treatment of a disease or disorder caused by anti-desmoglein-2 (DSG2) autoantibodies, the fusion polypeptide comprising:

an extracellular region of a human DSG2 protein having at least about 85% sequence identity with amino acid residues 50 to 609 of SEQ ID NO: 1, or a portion thereof, and a protein or a fragment of a protein which is capable of improving the expression and/or stability of the DSG2 protein *in vitro* or *in vivo* or used for purification of the DSG2 fusion polypeptide.

37. The use of claim 36, wherein the portion of the extracellular region of the human DSG2 protein includes any one of or a combination of DSG2 domains selected from the group consisting of: extracellular cadherin domain 1 (EC1), extracellular cadherin domain 2 (EC2), extracellular cadherin domain 3 (EC3), extracellular cadherin domain 4 (EC4), and extracellular anchor domain (EA).

38. The use of claim 36 or 37, wherein the fragment of the protein is an Fc region of an immunoglobulin.

39. The use of claim 38, wherein the immunoglobulin is IgG1 or IgG4.

40. The use of claim 38, wherein the immunoglobulin is a variant of IgG1 having the sequence of SEQ ID NO: 31.

41. The use of claim 38, wherein the immunoglobulin is a variant of IgG4 having the sequence of SEQ ID NO: 32.

42. The use of claim 36 or 37, wherein the fragment of the protein is a polyhistidine tag.

43. The use of any one of claims 36 to 42 further comprising a linker sequence located between the extracellular region of a human DSG2 protein or portion thereof, and the affinity tag.
44. The use of claim 43, wherein the linker sequence is SEQ ID NO: 12, 13, 27 or 28.
45. The use of any one of claims 36 to 44, wherein the disease or disorder is arrhythmia.
46. The use of claim 45, wherein the arrhythmia is caused proximally or distally by a virus.
47. The use of claim 46, wherein the virus is SARS-CoV2, adenovirus, hepatitis virus, hepatitis C virus, parvovirus, herpes simplex virus, echovirus, Epstein-Barr virus, rubella, cytomegalovirus, or HIV.
48. The use of any one of claims 36 to 44, wherein the disease or disorder is cardiomyopathy.
49. The use of claim 48, wherein the cardiomyopathy is arrhythmogenic right ventricular cardiomyopathy (ARVC), or dilated cardiomyopathy.
50. The use of claim 48 or 49, wherein the cardiomyopathy is caused proximally or distally by a virus.
51. The use of claim 50, wherein the virus is SARS-CoV2, adenovirus, hepatitis virus, hepatitis C virus, parvovirus, herpes simplex virus, echovirus, Epstein-Barr virus, rubella, cytomegalovirus, or HIV.
52. The use of any one of claims 36 to 44, wherein the disease or disorder is associated with sarcoidosis.
53. The use of any one of claims 36 to 44, wherein the disease or disorder is post-acute sequelae of COVID-19.

54. The use of any one of claims 36 to 44, wherein the disease or disorder is impaired cardiomyocyte electrical function.
55. The use of claim 54, wherein the use further comprises measuring cardiomyocyte sodium spike ( $\mu\text{V}/\text{m}$ ), wherein increase in the sodium spike after the treatment is indicative of improved cardiomyocyte electrical function.
56. A desmoglein 2 (DSG2) fusion polypeptide for use in therapy, the fusion polypeptide comprising an extracellular region of a human DSG2 protein having at least about 85% sequence identity with amino acid residues 50 to 609 of SEQ ID NO: 1, or a portion thereof, and a protein or a fragment of a protein which is capable of improving the expression and/or stability of the DSG2 protein *in vitro* or *in vivo* or used for purification of the DSG2 fusion polypeptide.