

DSG2 COMPOSITIONS AND METHODS FOR THE TREATMENT OF COVID-19**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to 63/125,583 filed on December 15, 2020, entitled DSG2 COMPOSITIONS AND METHODS FOR THE TREATMENT OF COVID-19 and 63/274,715 filed on November 2, 2021, entitled, DSG2 COMPOSITIONS AND METHODS FOR THE TREATMENT OF COVID-19, the contents of each of which are herein incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing file, entitled 2198_1001PCT_SL.txt, was created on December 10, 2021, and is 44,002 bytes in size. The information in electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The disclosure generally relates to DSG2 based methods for treating COVID-19 by administering the compositions disclosed herein. The methods also include the treatment of therapeutic indications associated with the long-term effects of COVID-19 (such as, but not limited to post COVID-19 syndrome or post-COVID-19 cardiac syndrome), including, inflammation in the myocardium and/or reduced ejection fraction/heart failure/cardiomyopathy, as well as the treatment of diseases associated DSG2 autoantibodies e.g., arrhythmogenic right ventricular cardiomyopathy (ARVC), sarcoidosis.

BACKGROUND

[0004] Beginning in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a pandemic infecting millions of people with coronavirus disease (referred to as COVID-19) (Wu et al., 2020 Nature 579, 265–269) which has led to over a million deaths worldwide. Patients infected with SARS-CoV-2 can experience a range of clinical manifestations, ranging from no symptoms to critical illness. Emerging studies suggest that in some cases, individuals, even those who had mild versions of the disease, may sometimes continue to experience symptoms after their initial recovery. This condition has been called post-COVID-19 syndrome or "long COVID-19." In addition, patients may also develop a reduced ejection fraction or cardiomyopathy, even after the acute infection of COVID-19 has resolved. Post-COVID-19 cardiac signs and symptoms may coexist with effects on other

organ systems, but may also present alone. Patients with post-COVID cardiomyopathy range from those who are asymptomatic to those with fulminant heart failure, arrhythmia and/or sudden cardiac death.

[0005] The COVID-19 virus, SARS-CoV-2 affects multiple organ systems, especially lungs and heart. Elevation of cardiac biomarkers, particularly high-sensitivity troponin and/or creatine kinase MB have been commonly observed in patients in COVID-19 infection. A review of clinical analyses conducted by Bavishi et al. found that myocardial injury occurred in 20% of patients with COVID-19 infection (Prog Cardiovasc Dis. 2020 September-October; 63(5): 682-689). The plausible mechanisms of myocardial injury associated with COVID-19 include but are not limited to, 1) hyperinflammation and cytokine storm mediated through pathologic T-cells and monocytes leading to myocarditis, 2) respiratory failure and hypoxemia resulting in damage to cardiac myocytes, 3) down regulation of ACE2 expression and subsequent protective signaling pathways in cardiac myocytes, 4) hypercoagulability and development of coronary microvascular thrombosis, 5) diffuse endothelial injury, and/or, 6) inflammation and/or stress causing coronary plaque rupture or supply-demand mismatch leading to myocardial ischemia/infarction.

[0006] The post-COVID-19 syndrome has also been associated with multiple organ damage, including cardiovascular damage. Imaging tests taken months after recovery from COVID-19 have shown lasting damage to the heart muscle, even in people who experienced only mild COVID-19 symptoms. Post-COVID-19 syndrome also appears to be associated with myocarditis and/or cardiomyopathy with increased risk of arrhythmia.

[0007] Currently, therapeutic strategies for treating and/or managing COVID-19 and post-COVID-19 syndrome are lacking. The cardiac manifestations of COVID-19 place an already overwhelmed health care system under considerable stress due to the substantial resources and potential intensive care support required for these patients. In particular, there is an urgent need for the development of treatment modalities for inhibiting inflammatory responses to reduce the incidence and mortality associated with COVID-19 and post-COVID-19 syndrome related myocardial injury. The present disclosure provides DSG2 fusion polypeptides based compositions and methods for treating diseases such as, but not limited to COVID-19, post-COVID-19 syndrome and/or post-COVID-19 cardiac syndrome.

SUMMARY

[0008] The present disclosure provides compositions comprising isolated polypeptides. The polypeptides of the disclosure may include a whole or a portion of the DSG2 protein. In

some embodiments, the isolated polypeptide is a Desmoglein 2 (DSG2) fusion polypeptide. The DSG2 fusion polypeptide may include (a) a whole or a portion of a DSG2 protein (SEQ ID NO: 1); and/or (b) a whole or a portion of an immunoglobulin protein. In one embodiment, the DSG2 polypeptide may include a portion of DSG2 protein. The portion of the DSG2 protein may include the extracellular region of DSG2 protein. In some aspects, the entire extracellular region of DSG2 may be included in the fusion polypeptide. In one embodiment, the entire extracellular region of DSG2 includes the amino acid sequence of SEQ ID NO: 3. Embodiments of the disclosure may also include a portion of the extracellular region of DSG2. For example, a portion of the extracellular region may be extracellular cadherin domain 1 (EC1), extracellular cadherin domain 2 (EC2), extracellular cadherin domain 3 (EC3), extracellular cadherin domain 4 (EC4), and/or extracellular anchor domain (EA). In some aspects, the DSG2 fusion polypeptides include 2 domains of the extracellular region. For example, the two domains may be EC4EA, EC1EC2, EC2EC3, EC3EC4, EC1EA, EC1EC3, EC2EC4, and/or EC3EA. In some aspects, the DSG2 fusion polypeptides include three domains of the extracellular region. For example, the three domains may be EC1EC3EA, EC1EC4EA, EC1EC3EA, EC3EC4EA, EC1EC2EC3, EC2EC3EC4, and/or EC2EC4EA. In some aspects, the DSG2 fusion polypeptides may include four domains of the extracellular region. For example, the three domains may be EC1EC2EC4EA, EC2EC3EC4EA, EC1EC2EC3EC4EA, EC1EC2EC3EC4, and/or EC1EC2EC3EA.

[0009] DSG2 fusion polypeptides may include a portion of an immunoglobulin. The portion may be Fc region, an Fab region, a heavy chain variable (VH) domain, a heavy chain constant domain, a light chain variable (VL) domain, and/or a light chain constant domain. In one aspect, the portion of the immunoglobulin may be an Fc region. The immunoglobulin may be an IgG, an IgM, an IgA, an IgD and/or an IgE. As a non-limiting example, the immunoglobulin may be IgG. The compositions may include an IgG such as IgG1, IgG2, IgG3, and/or IgG4. Non-limiting examples of portions of immunoglobulin useful in the present disclosure include IgG1 Fc region (SEQ ID NO: 5), IgG2 Fc region (SEQ ID NO: 7), IgG3 Fc region (SEQ ID NO: 9), IgG4 Fc region (SEQ ID NO: 11), IgG1 heavy chain constant domain (SEQ ID NO: 4), IgG2 heavy chain constant domain (SEQ ID NO: 6), IgG3 heavy chain constant domain (SEQ ID NO: 8), IgG4 or heavy chain constant domain (SEQ ID NO: 10).

[0010] Polypeptides of the disclosure may further include a linker and/or a signal sequence. The linker may be from about 5 amino acids to about 50 amino acids in length. In

one embodiment, the linker may be GGGGS (SEQ ID NO: 12). In another aspect, the linker may be EAAAK (SEQ ID NO: 13).

[0011] The present disclosure also provides methods of treatment using the compositions described herein. In some embodiment, the disclosure provides methods of treating post-COVID-19 syndrome. Such methods may include, i) contacting the subject with the isolated polypeptide of the disclosure and (ii) measuring one or more symptoms associated with post-COVID-19 syndrome selected from the group consisting of arrhythmia, myocarditis, heart failure, shortness of breath, fatigue, edema, orthopnea, limitations to exertion, impaired cognitive abilities, palpitations, dizziness, syncope, and/or lightheadedness. Treatment with the polypeptides of the disclosure may be effective in ameliorating one or more symptoms associated with post-COVID-19 cardiac syndrome. In some aspects, the subjects with post-COVID-19 have been previously diagnosed with COVID-19 using methods known in the art. In one aspect, the serum of the subject has detectable levels of anti-SARS-CoV-2 antibodies. In some embodiments, the serum of the subject has no detectable levels of anti-SARS-CoV-2 antibodies. Also provided herein are methods of treating a subject with COVID-19 by administering the compositions described herein. In some embodiments, the serum of the subject with COVID-19 or post-COVID-19 may have anti-DSG2 antibodies.

[0012] The present disclosure also provides a method of treating a condition associated with serum DSG2 autoantibodies. Such methods may include administering the compositions described herein or cells expressing the compositions described herein to a subject. In some embodiments, the condition may be a cardiomyopathy. In some aspects, the condition may be an autoimmune disorder.

[0013] The present disclosure provides methods of treating cardiomyopathy in a subject. Such methods may include contacting the subject with the isolated polypeptides or the cells of the disclosure followed by measuring one or more symptoms associated with cardiomyopathy such as arrhythmia, palpitations, myocarditis, heart failure, poor cardiac output, and/or reduced ejection fraction. As a non-limiting example, the cardiomyopathy may be arrhythmogenic right ventricular cardiomyopathy (ARVC). The cardiomyopathy may also be caused by a virus (e.g., SARS-CoV2, adenovirus, hepatitis virus, hepatitis C virus, parvovirus, herpes simplex virus, echovirus, Epstein-Barr virus, rubella, cytomegalovirus, or HIV), a bacterium (Staphylococcus, Streptococcus, or Borrelia), a parasite (Trypanosoma or Toxoplasma) or a fungus (Candida, Aspergillus, or Histoplasma). In some embodiments, the subject may have detectable levels of anti-DSG2 antibodies in their serum.

DESCRIPTION OF THE FIGURES

[0014] The foregoing and other objects, features and advantages of particular embodiments of the disclosure will be apparent from the following description and illustrations in the accompanying figures. The drawings are not necessarily to scale; emphasis instead being placed upon illustrating the principles of various embodiments of the disclosure.

[0015] Fig. 1 is a graph showing comparative levels of anti-DSG2 antibody signal in healthy controls (N=152), post-COVID-19 (N=300) and arrhythmogenic right ventricular cardiomyopathy samples (N=5). HC, healthy controls; PC, post-COVID-19; ARVC, arrhythmogenic right ventricular cardiomyopathy; S/NC, signal/negative control; individual diamonds represent a single serum sample each; box and whisker limits represent 25th-75th and 10th-90th percentiles respectively. P-values are based on non-parametric rank-based Wilcoxon-Mann-Whitney 2-sided test.

[0016] Fig. 2A is a bar graph showing anti-DSG2 antibody signal at 6 months and 9 months in all samples analyzed by month of collection post-COVID-19 infection (N = 300).

[0017] Fig. 2B is a bar graph showing anti-DSG2 antibody signal at 6 months and 9 months in paired samples analyzed by month of collection post-COVID-19 infection (N = 17).

DETAILED DESCRIPTION

I. INTRODUCTION

[0018] The most recent outbreak of COVID-19 has caused a severe respiratory disease in humans and has threatened human health worldwide. The novel virus causing COVID-19 has been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee of Taxonomy of Viruses (ICTV) as SARS-CoV-2 is closely linked to the SARS virus.

[0019] The SARS-CoV-2 particles use a special surface glycoprotein (spike protein) to bind to angiotensin converting enzyme 2 (ACE2) which is most abundant in the type II alveolar cells of the lungs, and thus enters the host cell. The genome of coronavirus is then replicated in the host cell. The density of ACE2 receptors in each tissue correlates with the severity of the COVID-19 disease in that tissue. ACE2 receptors are also expressed on the outer surface of cells in the arteries, heart, kidney, and intestines. As a result, COVID-19 may cause multi-organ failure in extremely severe cases.

[0020] The symptoms of COVID-19 range from mild (e.g., fever, cough, shortness of breath), to severe, such as pneumonia and acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi organ failure, including acute kidney injury, and cardiac injury. Although respiratory illness is the dominant clinical manifestation of COVID-19 infection, multi organ failure may also occur. In one multi-center study analyzing fatal cases of COVID-19, myocardial injury was observed to be the cause of death in 40% of the cases (Ruan Q. et al. *Intensive Care Med.* 2020;46(5):846–848). Various cardiac complications have been associated with active COVID-19 infection, including arrhythmia, myocarditis, and acute myocardial injury. Systemic inflammation, direct injury of cardiomyocytes, cytokine storm, and hypoxia are some of the proposed mechanisms of the multifactorial pathophysiology. Arrhythmias associated with COVID-19 can also be attributed to the treatment with azithromycin, hydroxychloroquine, and some antivirals that can cause QT prolongation. Acute myocardial injury in COVID-19 can range from asymptomatic elevation of cardiac troponins to fulminant myocarditis and circulatory shock. Myocardial injury can manifest either alone or can occur in combination with arrhythmia based on the clinical course of the infection.

[0021] The proinflammatory milieu and increased sympathetic stimulation in COVID-19 may further increase the risk for cardiovascular complications, such as cardiac arrhythmias, worsening of existing heart failure (HF), or development of new-onset HF. In patients with severe disease, hypoxia and electrolyte disturbances can further potentiate the risk for arrhythmias.

[0022] In some instances, patients may experience symptoms weeks, months or years after virus particles can be detected in patient samples (herein referred to as post-COVID-19 syndrome or "long COVID-19" or post viral syndrome). Post-COVID-19 syndrome may also be associated with cardiac symptoms and is herein referred to as Post-COVID-19 cardiac syndrome. Many patients who have recovered from COVID-19 show persistent inflammation in the myocardium as measured by MRI. In one study, up to 60% of both symptomatic and asymptomatic COVID-19 patients had MRI evidence of ongoing myocardial inflammation, an average of 71 days after recovery from the acute phase of COVID-19 (Puntmann et al. *JAMA Cardiol.* 2020;5(11):1265-1273; the contents of which are herein incorporated by reference in their entirety). In a smaller study, 15% of athletes had evidence of myocarditis after recovery from COVID-19 (Metzel et al. 2020, *HSS Journal*, Volume 16, pages 102–107). A significant proportion of post-COVID-19 syndrome patients subsequently develop compromised cardiac function, most notably a reduced ejection fraction, with or without

overt symptoms of heart failure. For clarity, patients with post-COVID-19 cardiac manifestations may herein be referred to as post-COVID-19 cardiac syndrome. Patients with post-COVID-19 syndrome also experience chronic fatigue syndrome which may be driven by undiagnosed cardiac output reductions. Symptoms may include shortness of breath, fatigue, edema, orthopnea, limitations to exertion and impaired cognitive abilities due to poor cardiac output ("brain fog"), arrhythmia, palpitations, dizziness, syncope, lightheadedness, heart failure, hospitalizations due to heart failure and/or arrhythmia. In some cases, death may occur as a result of heart failure and/or arrhythmia. In some embodiments, the post-COVID-19 syndrome may not be associated with cardiac manifestations.

[0023] The cardiac symptoms, including arrhythmia have been associated with other diseases such as, but not limited to, arrhythmogenic right ventricular cardiomyopathy (ARVC). Similar to ARVC, patients with COVID-19 and/or post-COVID-19 syndrome also display worsened cardiac function upon physical exertion. In the case of ARVC, Chatterjee et al. identified autoantibodies to the cardiac Desmoglein 2 (DSG2) protein as a common feature in the sera of patients with ARVC (Chatterjee D, et al., Eur Heart J. 2018;39(44):3932-3944; the contents of which are herein incorporated by reference in its entirety). These autoantibodies were specific to ARVC, as they were essentially absent in two independent sets of control sera, as well as sera from subjects with other forms of heritable cardiomyopathy. DSG2 antibodies can also be found in some cases of sarcoidosis, a systemic inflammatory disease which results in granulomas in organs, such as, but not limited to the heart. Anti-DSG2 antibodies are also found in sarcoid patients with cardiac involvement (Suna et al. 2020, Eur. Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.2127; the contents of which are herein incorporated by reference in its entirety). Patients with a diagnosis of dilated cardiomyopathy may have mutations in the same desmosome proteins that are associated with ARVC. These observations suggest that some dilated cardiomyopathy patients may actually have ARVC-like disease, mediated by DSG2 antibodies, but have been diagnosed as dilated cardiomyopathy because they do not fit the typical age and/or presentation associated with ARVC. Anti-DSG2 autoantibodies are considered to arise when there is a combination of cardiac cellular damage and an activated immune system -- typically in the setting of an infection known to affect the myocardium directly. From a pathogenesis standpoint, viral infections such as COVID-19, generally trigger a vigorous immune response that is crucial for viral clearance, with a cascade of events involving both the innate and adaptive immune arms. Direct and indirect myocardial damage is also caused by COVID-19 infection, allowing for cardiac proteins to be exposed to

the activated immune system. Immunological alterations are also observed in patients with COVID-19 condition. These range from a maladaptive immune response and abnormal cytokine/chemokine production, to hyperactivation of T cells and increased number of activated monocytes, macrophages and neutrophils (Chang, S.E., et al. *Nature Communications* 2021; 12:5417; Liu, Y., et al. *Curr. Opin. Rheumatol.* 2021; 33:155-162; Lee, C. C. E., et al. *Diseases* 2021; 9:47; the contents of each of which are herein incorporated by reference in their entirety).

[0024] COVID-19 has infected at least 200 million people worldwide with approximately 4.5 million deaths attributable to COVID 19 disease to date. There is growing recognition that COVID-19 infections can cause a variety of long-term sequelae, of which, cardiac involvement may be the most under-recognized as its symptoms may be attributed to other organ systems.

[0025] COVID 19 infections have been associated with MRI evidence of myocardial involvement and arrhythmias well into recovery, independent of preexisting conditions, severity and overall course of the acute illness, and the time from the original diagnosis. The percentage of patients who will develop a depressed ejection fraction subsequently is currently not well-understood, although frank cardiomyopathy has been described in post-COVID-19 patients.

[0026] The findings of cardiomyopathy and increased predilection for arrhythmias are also observed in arrhythmogenic right ventricular cardiomyopathy (ARVC). Antibodies to the desmosome protein desmoglein-2 (DSG2), have been shown to be present in patients with ARVC (Diptendu Chatterjee D., et al. *EHJ* 2018 (39) 3932-3944; the contents of which are herein incorporated by reference in its entirety). Concentrations of anti-DSG2 antibodies correlate positively to arrhythmia burden, and presence of these antibodies in borderline ARVC cases predicts the development of fulminant ARVC. Exposure of iPSC-derived cardiomyocytes to anti-DSG2 antibodies results in a reduction in gap junction function that may reflect direct cardiotoxicity. Together, these data suggest that anti-DSG2 antibodies may play a role in cardiac pathology. The present disclosure also provides evidence showing the anti-DSG2 antibody levels are elevated in COVID-19 patients even 6-9 months after diagnosis.

[0027] Viral infections, including COVID-19, have been hypothesized to contribute to autoimmune responses, e.g., by exposing previously hidden cryptic epitopes on damaged cells to an activated immune system (Ehrenfeld M., et al. *Autoimmunity Reviews* 2020 102597; the contents of which are herein incorporated by reference in its entirety). The high

incidence of cardiac involvement seen in COVID-19 infections, indicates that anti-DSG2 autoantibodies may be generated as a result.

[0028] The presence of arrhythmia as well as the role of the immune system in the progression of COVID-19, post-COVID-19 syndrome and ARVC together suggest the involvement of DSG2 autoantibodies in the pathogenesis of these diseases. Strategies targeting anti-DSG2 antibodies (e.g., DSG2 autoantibodies) may therefore be beneficial in the treatment of COVID-19, post-COVID-19 syndrome and/or ARVC.

[0029] The present disclosure provides compositions and methods related to DSG2 fusion polypeptides for targeting anti-DSG2 antibodies. The DSG2 fusion polypeptides of the disclosure may therefore be a viable therapeutic strategy in the treatment of COVID-19, post-COVID-19 cardiac syndrome, and/or ARVC. DSG2 fusion polypeptides may also be used in the treatment of other diseases associated with cardiac cellular damage, such as, but not limited to, arrhythmogenic cardiomyopathy (AC), sarcoidosis, dilated cardiomyopathy with anti-DSG2 autoantibodies and viral infections, including but not limited to those caused by coxsackie virus, adenovirus, echoviruses, parvovirus, rubella and/or cytomegalovirus.

II. COMPOSITIONS

[0030] In some embodiments, the present disclosure provides compositions that include DSG2 fusion polypeptides. Compositions described herein, may be capable of binding to or interacting with anti-DSG2 antibodies. In one embodiment, the compositions of the disclosure may modulate the activity of anti-DSG2 antibodies. In one embodiment, the compositions of the disclosure may inhibit the activity of the anti-DSG2 antibodies.

[0031] In some embodiments, the present disclosure includes a DSG2 protein. In some aspects the DSG2 protein may be the whole DSG2 protein or a portion of the DSG2 protein. In some embodiments, the DSG2 protein may be fused to any other protein or fragment of a protein.

[0032] DSG2 fusion polypeptides of the present disclosure may include the whole or a portion of a DSG2 protein and a whole or a portion of an immunoglobulin protein. In some embodiments, the DSG2 fusion polypeptides may further include a linker and/or a signal peptide. In some embodiments, the whole or a portion of DSG2 protein may be fused to a protein that is not an immunoglobulin. The DSG2 protein may be fused to a protein or a fragment of a protein that is capable of improving the expression of DSG2 protein *in vitro* or *in vivo*.

[0033] DSG2 mutations within intercalated discs in heart cells have been implicated in cardiac diseases including arrhythmia, dilated cardiomyopathy, and particularly ARVC (Arrhythmogenic right ventricular cardiomyopathy). Chatterjee et al. identified autoantibodies to the cardiac DSG2 protein as a common feature in the sera of patients with ARVC (Chatterjee D, et al., Eur Heart J. 2018;39(44):3932-3944; the contents of which are herein incorporated by reference in its entirety). These autoantibodies were specific to ARVC, as they were essentially absent in two independent sets of control sera, as well as sera from subjects with other forms of heritable cardiomyopathy. The presence of DSG2 autoantibodies identified by Chatterjee et al. suggests that targeting DSG2 antibodies may represent a therapeutic strategy in the treatment of cardiomyopathies associated with diseases such as, but not limited to ARVC and/or COVID-19. The present disclosure provides DSG2 fusion polypeptides as a therapeutic strategy for targeting DSG2 autoantibodies. In some embodiments, DSG2 fusion polypeptides of the present disclosure may bind to DSG2 autoantibodies. In some embodiments, binding of the DSG2 fusion polypeptides of the disclosure to the DSG2 autoantibodies precludes the binding of the autoantibodies to the endogenous DSG2 in a subject. In this aspect of the disclosure, the DSG2 fusion polypeptides function as a decoy protein or a ligand trap.

[0034] Chatterjee et al. propose that the DSG2 protein may include epitopes, which are exposed or released into the intercellular space and/or circulation and as a result of DSG2 mutations. Unmasking of these epitopes may also occur from any cardiac damage (such as, but not limited to, infective myocarditis, and/or cardiac trauma). In some embodiments, the compositions of the disclosure may not include any mutations. Such released DSG2 proteins may link with an antigen-presenting cell to stimulate a T-cell response, generating the observed autoantibodies. Unmasking of cryptic epitopes by gene mutations could contribute to other forms of autoimmunity. In some embodiments, DSG2 fusion polypeptides of the disclosure may include epitopes containing one or more mutations in DSG2.

[0035] DSG2 fusion polypeptide may be a soluble and/or recombinant polypeptides. The arrangement of components in the DSG2 fusion polypeptide may be optimized to achieve the suitable protein expression and/or the intended therapeutic effect. In some embodiments, the DSG2 fusion polypeptide may include formats described herein. The formats provided herein include components from N terminus to C terminus delineated by a “;” between the components. Non-limiting examples of the formats of the DSG2 fusion polypeptides include, (i) the whole or a portion of DSG2 protein; Fc region (ii) Fc region; the whole or a portion of the DSG2 protein (iii) signal sequence; the whole or a portion of the DSG2 protein; Fc region

(iv) the signal sequence; Fc region; the whole or a portion of the DSG2 protein (v) the whole or a portion of DSG2 protein; linker; Fc region (vi) Fc region; linker; the whole or a portion of the DSG2 protein (vii) signal sequence; the whole or a portion of the DSG2 protein; linker; Fc region (viii) signal sequence; Fc region; linker; whole or a portion of the DSG2 protein.

DSG2 protein

[0036] In some embodiments, the DSG2 fusion polypeptides of the present disclosure may include the entire DSG2 protein. The desmosomal cadherin desmoglein-2 (DSG2) is a transmembrane cell adhesion protein that is widely expressed in epithelial and non-epithelial tissues, such as the heart, intestine, and epidermis. DSG2 has been shown to regulate numerous cellular processes, including proliferation and apoptosis. In epithelial and myocyte cells, DSG2 is a component of the cell-cell adhesion structure and its cytoplasmic tail interacts with a series of proteins in direct contact with cell adhesion and intercellular junction/cell type regulators. In some embodiments, the DSG2 protein is a human DSG2 protein (UniProt ID: Q14126; ENSEMBL Protein ID: ENSP00000261590.8) which consists of 1,118 amino acids, and includes the amino acid sequence of SEQ ID NO: 1. In one embodiment, the DSG2 protein may be encoded by nucleic acid sequence of SEQ ID NO: 2 (NCBI Reference Sequence: NM_001943.5; ENSEMBL ID: ENST00000261590.13).

[0037] In some embodiments, the DSG2 fusion polypeptide of the present disclosure may be a fully processed DSG2 protein comprising amino acids 50-1118 of SEQ ID NO: 1.

[0038] The DSG2 protein may also include one or more mutations with respect to the sequence of SEQ ID NO: 1. In some embodiments, DSG2 protein mutation may be a mutation associated with a disease state. In one embodiment, the disease state may be Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. In some embodiments, DSG2 fusion polypeptides of the disclosure may include epitopes containing one or more mutations in DSG2. As a non-limiting example, DSG2 fusion polypeptides may include one or more mutations in the region of amino acids 485–531 and/or amino acids 586–610 of SEQ ID NO: 1.

[0039] DSG2 belongs to the cadherin superfamily of cell adhesion proteins, which commonly feature the three distinct regions: an extracellular region, a transmembrane domain and an intracellular signaling region. In some embodiments, the extracellular region of DSG2 may include the amino acid sequence of SEQ ID NO: 3, which is amino acids 50- 609 of SEQ ID NO: 1. The extracellular region of cadherin family of proteins contain a varying number of repeats of calcium-binding motifs, known as cadherin motifs or EC domains.

DSG2 contains four EC domains herein referred to as EC1, EC2, EC3 and EC4. DSG2 also includes an extracellular anchor (EA) domain that is proximal to the membrane. In some embodiments, the DSG2 fusion polypeptides of the disclosure may include the entire extracellular region of DSG2. In some aspects, the DSG2 fusion polypeptide may include at least one domain, such as, but not limited to, EC1, EC2, EC3, EC4, and/or EA. In some embodiments the EC1 domain may be amino acids 50-155 of SEQ ID NO: 1. In some embodiments the EC2 domain may be amino acids 151-268 of SEQ ID NO: 1. In some embodiments the EC3 domain may be amino acids 264-384 of SEQ ID NO: 1. In some embodiments the EC4 domain may be amino acids 382-495 of SEQ ID NO: 1. In some embodiments the EA domain may be amino acids 491-608 of SEQ ID NO: 1. Table 1 provides the amino acid sequence of the DSG2 protein as well as the amino acid sequence of the extracellular region of DSG2. In some embodiments, the DSG2 proteins of the present disclosure may have at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or 100% identity to any of the sequences in Table 1 or fragments of the sequences in Table 1.

Table 1. Sequences of the DSG2 protein and DSG2 extracellular domain

(SEQ ID NO:)	Sequence	Description
1	MARSPGRAYALLLLICFNVGSGHLQVLSTRNENKLLP KPHPLVRQKRAWITAPVALREGEDLSKKNPIAKIHSDLA EERGLKITYKYTGKGITEPPFGIFVFNKDTGELNVTSLDR EETPFFLLTGYALDARGNNVEKPLELRIKVLINDNEPVF TQDVVFGSVEELSAHTLVMKINATDAEPNTLNSKISY RIVSLEPAYPPVFYLNKDTGEIYTTSTVLDREEHSSYTLT VEARDGNGEVTDKPVKQAQVQIRILDVNDNIPVVENKV LEGMVEENQVNVEVTRIKVFDADAEIGSDNWLANFTFAS GNEGYYFHIEDTAQTNEGIVTLIKEVDYEEEMKNLDFSVI VANKAAAFHKSRISKYKPTPIPIKVKNVKEGIHFKSSVIS IYVESMDRSSKGQIIGNFQAFDEDTGLPAHARYVKLED RDNWISVDSVTSEIKLAKLPDFESRYVQNGTYTVKIVAIS EDYPRKTITGTVLINVEDINDNCPTLIEPVQTICHDAEYV NVTAEGLDGHPSGPFSSVIDKPPGMAEKWKIARQEST SVLLQOSEKKLGRSEIQFLISDNQGFSCPEKQVLTTLTVCE CLHGSGCREAQHDSYVGLGPAALMLAFLLLLPLLL LLMCHCGKGAKGFTPIPGTIEMLHPWNNEGAPPEDKV PSFLPVDQGGSLVGRNGVGGMAKEATMKGSSASIVKG QHEMSEMDGRWEEHRSLLSGRATQFTGATGAIMTTETT KTARATGASRDMAGAQAVALNEEFLRNYFTDKAAS YTEEDENHTAKDCLLVYSQEETESLNASIGCCSFIEGELD DRFLDDLGLKFKTLAEVCLGOKIDINKEIEQROKPATETS MNTASHSLCEQTMVNSENTYSSGSSFPVPKSLQEANA VTQEIIVTERS SVSSRQAQKVATPLPDPMASRNVIAETSY VTGSTMPPTTVILGPSQPQSLIVTERVYAPASTLVDQPYA NEGTVVVTERVIQPHGGGSPLEGTQHLQDVVYVMVRE RESFLAPSSGVQPTLAMPNIAVGQNVTVTERVLAPASTL QSSYQIPTENSMTARNTTVSGAGVPGPLPDFGLEESGHS NSTITTSSTRVTKHSTVQHSYS	Human DSG2 preprotein

3	AWITAPVALREGEDLSKKNPIAKIHSDLAERGLKITYKY TGKGITEPPFGIFVFNKDTGELNVTSLDREETPFLLTGY ALDARGNNVEKPLELRIKVLNDNEPVFTQDVFVGSVE ELSAHTLVMKINATDAEPNTLNSKISYRIVSLEPAYPP VFYLNKDTGEIYTTSTVLDREEHSSYTLTVEARDGNGEV TDKPVKQAQVQIRILDVNDNIPVVENKVLEGMVEENQV NVEVTRIKVFDAGEIGSDNWLANFTFASGNEGGYFHET DAQTNEGIVTLIKEVDYEEMKNLDFSVIVANKAAFHKSI RSKYKPTPIPIKVKVKNVKEGIHFKSSVISIYVSESMDRSS KGQIIGNFQAFDEDTGLPAHARYVKLEDRDNWISVDSVT SEIKLAKLPDFESRYVQNGTYTVKIVAISEDYPRKTTTGT VLINVEDINDNCPTLIEPVQTICHAIEYVNVTAEDLDGHP NSGPFSSVIDKPPGMAEKWKIARQESTSVLLQQSEKKL GRSEIQFLISDNQGFSCPEKQVLTTLTVCECLHGSGCREAQ HDSYVG	Human DSG2 extracellular domain
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[0040] The DSG2 fusion polypeptides of the present disclosure may include one or more domains of the extracellular region of DSG2. The domains from the extracellular region of DSG2 may include repeats of one or more of the EC domains or EA domains, in tandem or in a mixed order. For example, DSG2 fusion polypeptide may include 2, 3, or more repeats of EC1, EC2, EC3, EC4 or EA domains. When more than one domain and/or more than one repeat of a domain of the extracellular region of DSG2 is present, the domains may be operably linked via a linker described herein.

[0041] In some embodiments, the DSG2 fusion polypeptide may include two domains of the extracellular region of DSG2. Non limiting examples domains of extracellular region of DSG2 present in the fusion polypeptides of the present disclosure include, EC1EC2, EC1EC3, EC1EC4, EC1EA, EC2EC1, EC2EC3, EC2EC4, EC2EA, EC3EC1, EC3EC2, EC3EC4, EC3EA, EC4EC1, EC4EC2, EC4EC3, EC4EA, EAEC1, EAEC2, EAEC3, and/or EAEC4.

[0042] In some embodiments, the DSG2 fusion polypeptide may include three domains of the extracellular region of DSG2. Non limiting examples domains of extracellular region of DSG2 present in the fusion polypeptides of the present disclosure include, EC1EC2EC3, EC1EC2EC4, EC1EC2EA, EC1EC3EC2, EC1EC3EC4, EC1EC3EA, EC1EC4EC2, EC1EC4EC3, EC1EC4EA, EC1EAEC2, EC1EAEC3, EC1EAEC4, EC2EC1EC3, EC2EC1EC4, EC2EC1EA, EC2EC3EC1, EC2EC3EC4, EC2EC3EA, EC2EC4EC1, EC2EC4EC3, EC2EC4EA, EC2EAEC1, EC2EAEC3, EC2EAEC4, EC3EC1EC2, EC3EC1EC4, EC3EC1EA, EC3EC2EC1, EC3EC2EC4, EC3EC2EA, EC3EC4EC1, EC3EC4EC2, EC3EC4EA, EC3EAEC1, EC3EAEC2, EC3EAEC4, EC4EC1EC2, EC4EC1EC3, EC4EC1EA, EC4EC2EC1, EC4EC2EC3, EC4EC2EA, EC4EC3EC1, EC4EC3EC2, EC4EC3EA, EC4EAEC1, EC4EAEC2, EC4EAEC3, EAEC1EC2,

EAEC1EC3, EAEC1EC4, EAEC2EC1, EAEC2EC3, EAEC2EC4, EAEC3EC1, EAEC3EC2, EAEC3EC4, EAEC4EC1, EAEC4EC2, and/or EAEC4EC3.

[0043] In some embodiments, the DSG2 fusion polypeptide may include four domains of the extracellular region of DSG2. Non limiting examples domains of extracellular region of DSG2 present in the fusion polypeptides of the present disclosure include, EC1EC2EC3EC4, EC1EC2EC3EA, EC1EC2EC4EC3, EC1EC2EC4EA, EC1EC2EAEC3, EC1EC2EAEC4, EC1EC3EC2EC4, EC1EC3EC2EA, EC1EC3EC4EC2, EC1EC3EC4EA, EC1EC3EAEC2, EC1EC3EAEC4, EC1EC4EC2EC3, EC1EC4EC2EA, EC1EC4EC3EC2, EC1EC4EC3EA, EC1EC4EAEC2, EC1EC4EAEC3, EC1EAEC2EC3, EC1EAEC2EC4, EC1EAEC3EC2, EC1EAEC3EC4, EC1EAEC4EC2, EC1EAEC4EC3, EC2EC1EC3EC4, EC2EC1EC3EA, EC2EC1EC4EC3, EC2EC1EC4EA, EC2EC1EAEC3, EC2EC1EAEC4, EC2EC3EC1EC4, EC2EC3EC1EA, EC2EC3EC4EC1, EC2EC3EC4EA, EC2EC3EAEC1, EC2EC3EAEC4, EC2EC4EC1EC3, EC2EC4EC1EA, EC2EC4EC3EC1, EC2EC4EC3EA, EC2EC4EAEC1, EC2EC4EAEC3, EC2EAEC1EC3, EC2EAEC1EC4, EC2EAEC3EC1, EC2EAEC3EC4, EC2EAEC4EC1, EC2EAEC4EC3, EC3EC1EC2EC4, EC3EC1EC2EA, EC3EC1EC4EC2, EC3EC1EC4EA, EC3EC1EAEC2, EC3EC1EAEC4, EC3EC2EC1EC4, EC3EC2EC1EA, EC3EC2EC4EC1, EC3EC2EC4EA, EC3EC2EAEC1, EC3EC2EAEC4, EC3EC4EC1EC2, EC3EC4EC1EA, EC3EC4EC2EC1, EC3EC4EC2EA, EC3EC4EAEC1, EC3EC4EAEC2, EC3EAEC1EC2, EC3EAEC1EC4, EC3EAEC2EC1, EC3EAEC2EC4, EC3EAEC4EC1, EC3EAEC4EC2, EC4EC1EC2EC3, EC4EC1EC2EA, EC4EC1EC3EC2, EC4EC1EC3EA, EC4EC1EAEC2, EC4EC1EAEC3, EC4EC2EC1EC3, EC4EC2EC1EA, EC4EC2EC3EC1, EC4EC2EC3EA, EC4EC2EAEC1, EC4EC2EAEC3, EC4EC3EC1EC2, EC4EC3EC1EA, EC4EC3EC2EC1, EC4EC3EC2EA, EC4EC3EAEC1, EC4EC3EAEC2, EC4EAEC1EC2, EC4EAEC1EC3, EC4EAEC2EC1, EC4EAEC2EC3, EC4EAEC3EC1, EC4EAEC3EC2, EAEC1EC2EC3, EAEC1EC2EC4, EAEC1EC3EC2, EAEC1EC3EC4, EAEC1EC4EC2, EAEC1EC4EC3, EAEC2EC1EC3, EAEC2EC1EC4, EAEC2EC3EC1, EAEC2EC3EC4, EAEC2EC4EC1, EAEC2EC4EC3, EAEC3EC1EC2, EAEC3EC1EC4, EAEC3EC2EC1, EAEC3EC2EC4, EAEC3EC4EC1, EAEC3EC4EC2, EAEC4EC1EC2, EAEC4EC1EC3, EAEC4EC2EC1, EAEC4EC2EC3, EAEC4EC3EC1, and/or EAEC4EC3EC2 .

[0044] In some embodiments, the DSG2 fusion polypeptide may include five domains of the extracellular region of DSG2. Non limiting examples domains of extracellular region of DSG2 present in the fusion polypeptides of the present disclosure include EC1EC2EC3EC4EA, EC1EC2EC3EAEC4, EC1EC2EC4EC3EA, EC1EC2EC4EAEC3, EC1EC2EAEC3EC4, EC1EC2EAEC4EC3, EC1EC3EC2EC4EA, EC1EC3EC2EAEC4,

EC1EC3EC4EC2EA, EC1EC3EC4EAEC2, EC1EC3EAEC2EC4, EC1EC3EAEC4EC2,
 EC1EC4EC2EC3EA, EC1EC4EC2EAEC3, EC1EC4EC3EC2EA, EC1EC4EC3EAEC2,
 EC1EC4EAEC2EC3, EC1EC4EAEC3EC2, EC1EAEC2EC3EC4, EC1EAEC2EC4EC3,
 EC1EAEC3EC2EC4, EC1EAEC3EC4EC2, EC1EAEC4EC2EC3, EC1EAEC4EC3EC2,
 EC2EC1EC3EC4EA, EC2EC1EC3EAEC4, EC2EC1EC4EC3EA, EC2EC1EC4EAEC3,
 EC2EC1EAEC3EC4, EC2EC1EAEC4EC3, EC2EC3EC1EC4EA, EC2EC3EC1EAEC4,
 EC2EC3EC4EC1EA, EC2EC3EC4EAEC1, EC2EC3EAEC1EC4, EC2EC3EAEC4EC1,
 EC2EC4EC1EC3EA, EC2EC4EC1EAEC3, EC2EC4EC3EC1EA, EC2EC4EC3EAEC1,
 EC2EC4EAEC1EC3, EC2EC4EAEC3EC1, EC2EAEC1EC3EC4, EC2EAEC1EC4EC3,
 EC2EAEC3EC1EC4, EC2EAEC3EC4EC1, EC2EAEC4EC1EC3, EC2EAEC4EC3EC1,
 EC3EC1EC2EC4EA, EC3EC1EC2EAEC4, EC3EC1EC4EC2EA, EC3EC1EC4EAEC2,
 EC3EC1EAEC2EC4, EC3EC1EAEC4EC2, EC3EC2EC1EC4EA, EC3EC2EC1EAEC4,
 EC3EC2EC4EC1EA, EC3EC2EC4EAEC1, EC3EC2EAEC1EC4, EC3EC2EAEC4EC1,
 EC3EC4EC1EC2EA, EC3EC4EC1EAEC2, EC3EC4EC2EC1EA, EC3EC4EC2EAEC1,
 EC3EC4EAEC1EC2, EC3EC4EAEC2EC1, EC3EAEC1EC2EC4, EC3EAEC1EC4EC2,
 EC3EAEC2EC1EC4, EC3EAEC2EC4EC1, EC3EAEC4EC1EC2, EC3EAEC4EC2EC1,
 EC4EC1EC2EC3EA, EC4EC1EC2EAEC3, EC4EC1EC3EC2EA, EC4EC1EC3EAEC2,
 EC4EC1EAEC2EC3, EC4EC1EAEC3EC2, EC4EC2EC1EC3EA, EC4EC2EC1EAEC3,
 EC4EC2EC3EC1EA, EC4EC2EC3EAEC1, EC4EC2EAEC1EC3, EC4EC2EAEC3EC1,
 EC4EC3EC1EC2EA, EC4EC3EC1EAEC2, EC4EC3EC2EC1EA, EC4EC3EC2EAEC1,
 EC4EC3EAEC1EC2, EC4EC3EAEC2EC1, EC4EAEC1EC2EC3, EC4EAEC1EC3EC2,
 EC4EAEC2EC1EC3, EC4EAEC2EC3EC1, EC4EAEC3EC1EC2, EC4EAEC3EC2EC1,
 EAEC1EC2EC3EC4, EAEC1EC2EC4EC3, EAEC1EC3EC2EC4, EAEC1EC3EC4EC2,
 EAEC1EC4EC2EC3, EAEC1EC4EC3EC2, EAEC2EC1EC3EC4, EAEC2EC1EC4EC3,
 EAEC2EC3EC1EC4, EAEC2EC3EC4EC1, EAEC2EC4EC1EC3, EAEC2EC4EC3EC1,
 EAEC3EC1EC2EC4, EAEC3EC1EC4EC2, EAEC3EC2EC1EC4, EAEC3EC2EC4EC1,
 EAEC3EC4EC1EC2, EAEC3EC4EC2EC1, EAEC4EC1EC2EC3, EAEC4EC1EC3EC2,
 EAEC4EC2EC1EC3, EAEC4EC2EC3EC1, EAEC4EC3EC1EC2, and/or
 EAEC4EC3EC2EC1.

[0045] Non-limiting examples of a portion of the DSG2 protein as well as possible configurations present in the DSG2 fusion polypeptide are provided in Table 2. Any of the DSG2 domains described in Table 2 may be operably linked to another domain within the fusion polypeptide or to another DSG2 domain using any of the linker provided herein or any linker known in the art. The compositions of the disclosure may include a portion or a

fragment of any of the domains described in Table 2. The domains or combination of domains of SEQ ID NO: 1 or SEQ ID NO: 3 included in the polypeptides of the disclosure may be extended by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40 or 50 amino acids upstream or downstream of the domains defined in Table 2. In some embodiments, the domains or combination of domains of SEQ ID NO: 1 or SEQ ID NO: 3 included in the polypeptides of the disclosure may be truncated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40 or 50 amino acids at the N terminus or the C terminus of the domains defined in Table 2. As a non-limiting example, the extracellular region of DSG2 protein may extend from the amino acids spanning from 50-610 of SEQ ID NO: 1.

Table 2. DSG2 domain combination for the DSG2 extracellular region

DSG2 domain or combination	Amino acids of SEQ ID NO: 1
EC1	50-155
EC2	151-268
EC3	264-384
EC4	382-495
EA	491-608
EC4EA	382-608
EC3EC4EA	264-608
EC2EC3EC4EA	151-608
EC1EC2EC3EC4EA	50-608
EC1EC2	50-268
EC1EC2EC3	50-384
EC1EC2EC3EC4	50-495
EC2EC3	151-384
EC2EC3EC4	151-495
EC3EC4	264-495
EC1EC3EC4EA	50-155, 264-608
EC1EC4EA	50-155, 382-608
EC1EA	50-155, 491-608
EC1EC2EC4EA	50-268, 382-608
EC1EC2EC3EA	50-384, 491-608
EC1EC3	50-155, 264-384
EC1EC3EC4EA	50-155, 264-384, 491-608

EC2EC4EA	151-268, 491-608
EC2EC4	151-268, 382-495
EC3EA	264-384, 491-608

Immunoglobulin protein

[0046] In some embodiments, DSG2 fusion polypeptides of the present disclosure may include a whole or a portion of an immunoglobulin protein. The immunoglobulin protein may be an IgG, an IgM, an IgA, an IgD and an IgE. In one embodiment, the immunoglobulin protein may be an IgG. Non-limiting examples of IgG may be IgG1, IgG2, IgG3 and/or IgG4. DSG2 fusion polypeptides may include a region or a portion of an immunoglobulin. Non-limiting examples of a region of an immunoglobulin such as, Fc region, an Fab region, a heavy chain variable (VH) domain, a heavy chain constant domain, a light chain variable (VL) domain, and/or a light chain constant domain.

[0047] DSG2 fusion polypeptides may include one or more Fc regions of an immunoglobulin. In some embodiments, the Fc region may include the first constant region immunoglobulin domain (e.g., CH1) or a portion thereof, and in some cases, part of the hinge. In other aspects, the Fc region excludes the first constant region immunoglobulin domain. Thus, an Fc may refer to the last two constant region immunoglobulin domains (e.g., CH2 and CH3) of IgA, IgD, and IgG, the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM, Fc may include the J chain. For IgG, the Fc domain comprises immunoglobulin domains C γ 2 and C γ 3 (C γ 2 and C γ 3) and the lower hinge region between C γ 1 (C γ 1) and C γ 2 (C γ 2). In some embodiments, an Fc refers to a truncated CH1 domain, and CH2 and CH3 of an immunoglobulin. Although the boundaries of the Fc region may vary, the human IgG heavy chain Fc region are typically usually defined to include residues E216 or C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat Antibody Numbering sequence.

[0048] In some embodiments, the immunoglobulin protein may include additional cell targeting modules (and may herein be referred to as cell targeting antibody CTAB).

[0049] Non-limiting examples of the sequences of portions of immunoglobulin are provided in Table 3. In some embodiments, the DSG2 fusion polypeptides may include an immunoglobulin protein or a portion thereof having at least 50%, 55%, 60%, 65%, 70%,

75%, 80%, 85%, 90%, 95%, 99% or 100% identity to any of the sequences in Table 3 or fragments of the sequences in Table 3.

Table 3. Sequences of the Immunoglobulin regions

SEQ ID NO:	Description	Sequence
4	Human IgG1 Immunoglobulin heavy chain constant region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK
5	Human IgG1 Immunoglobulin heavy chain constant Fc Domain	DKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK
6	Human IgG2 Immunoglobulin heavy chain constant region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK
7	Human IgG2 Immunoglobulin heavy chain constant Fc domain	ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK
8	Human IgG3 Immunoglobulin heavy chain constant region	ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPGLDITHTCPRCPPEPKSCDTPPPCPRCPPEPKSCDTPPPCPRCPPEPKSCDTPPPCPRCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMEALHNRTQKSLSLSPGK
9	Human IgG3 Immunoglobulin heavy chain Fc domain	ELKTPGLDITHTCPRCPPEPKSCDTPPPCPRCPPEPKSCDTPPPCPRCPPEPKSCDTPPPCPRCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVS VLT VVHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMEALHNRTQKSLSLSPGK
10	Human IgG4 Immunoglobulin heavy chain constant region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVVFSCSVMEALHNHYTQKSLSLSLGK
11	Human IgG4 Immunoglobulin heavy	ESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT

chain Fc domain	CLVKGFYPSDIAVEWESNGOPENNYKTPPVLDSDGSFFLYSRLTVDKSR WQEGNVFSCSVMEALHNHYTQKSLSLSLGK
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Signal Sequence

[0050] Signal sequences (sometimes referred to as signal peptides, targeting signals, target peptides, localization sequences, transit peptides, leader sequences or leader peptides) direct proteins (e.g., the polypeptides of the present disclosure) to their designated cellular and/or extracellular locations. A signal sequence may be a short (about 5-50 amino acids long) peptide present at the N-terminus of the majority of newly synthesized proteins that are destined towards a particular location. Signal sequences can be recognized by signal recognition particles (SRPs) and cleaved using type I and type II signal peptide peptidases. Signal sequences derived from human proteins can be incorporated as a DSG2 fusion polypeptides of the present disclosure to direct the polypeptides of the disclosure to a particular cellular and/or extracellular location. These signal sequences are experimentally verified and can be cleaved (Zhang et al., *Protein Sci.* 2004, 13:2819-2824).

[0051] In some embodiments, a signal sequence may be located at the N-terminus or C-terminus of the polypeptides of the present disclosure, and may be, although not necessarily, cleaved off the polypeptide to yield a "mature" polypeptide, as discussed herein.

[0052] In some examples, a signal sequence may be a secreted signal sequence derived from a naturally secreted protein, and its variant thereof.

[0053] In some instances, signal sequences directing the polypeptides of the disclosure to the surface membrane of a target cell may be used. Expression of the polypeptides of the disclosure on the surface of the target cell may be useful to limit the diffusion of the polypeptides of the disclosure to non-target *in vivo* environments, thereby potentially improving the safety profile of the polypeptides of the disclosure. Additionally, the membrane presentation of the polypeptides of the disclosure may allow for physiological and qualitative signaling as well as stabilization and recycling of the polypeptide for a longer half-life.

[0054] A signal sequence may be a heterogeneous signal sequence from other organisms such as virus, yeast and bacteria, which can direct the polypeptides of the disclosure to a particular cellular site, such as a nucleus (e.g., EP 1209450). Other examples may include Aspartic Protease (NSP24) signal sequences from *Trichoderma* that can increase secretion of fused protein such as enzymes (e.g., U. S. Pat. NO. 8,093,016 to Cervin and Kim), bacterial lipoprotein signal sequences (e.g., PCT publication NO. 1991/09952 to Lau and Rioux),

E. coli enterotoxin II signal peptides (e.g., U.S. Pat. NO. 6,605,697 to Kwon et al.), *E. coli* secretion signal sequence (e.g., U.S. patent publication NO. 2016/090404 to Malley et al.), a lipase signal sequence from a methylotrophic yeast (e.g., U.S. Pat. NO. 8,975,041), and signal peptides for DNases derived from *Corynebacterium* bacteria (e.g., U.S. Pat. NO. 4,965,197); the contents of each of which are incorporated herein by reference in their entirety.

Linkers

[0055] In some embodiments, the DSG2 fusion polypeptides of the present disclosure may include at least one linker. The linker may be positioned between one or more regions of the polypeptides of the disclosure. In one embodiment, the linker may be positioned between the whole or a portion of a DSG2 protein and the whole or a portion of an immunoglobulin protein. In one aspect, the linker may be positioned between one or more domains of the DSG2 protein.

[0056] In some embodiments, the linker may be a polypeptide. In some embodiments, the linker may comprise a combination of amino acid residues. In some embodiments, the linker may comprise about 1-50 amino acid residues. In some embodiments, the linker may comprise about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45 or 50 amino acid residues.

[0057] The linkers of the present disclosure may be from about 1 to 100 amino acids in length, which links together any of the domains/regions of the effector module (also called peptide linker). The linker may be 1-40 amino acids in length, or 2-30 amino acids in length, or 20-80 amino acids in length, or 50-100 amino acids in length. Linker length may also be optimized depending on the type of configuration of the polypeptide and based on the crystal structure of the polypeptide. In some instances, a shorter linker length may be preferably selected. In some aspects, the peptide linker may be made up of amino acids linked together by peptide bonds, preferably from 1 to 20 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids: Glycine (G), Alanine (A), Valine (V), Leucine (L), Isoleucine (I), Serine (S), Cysteine (C), Threonine (T), Methionine (M), Proline (P), Phenylalanine (F), Tyrosine (Y), Tryptophan (W), Histidine (H), Lysine (K), Arginine (R), Aspartate (D), Glutamic acid (E), Asparagine (N), and Glutamine (Q). One or more of these amino acids may be glycosylated, as is understood by those in the art. In some aspects, amino acids of a peptide linker may be selected from

Alanine (A), Glycine (G), Proline (P), Asparagine (R), Serine (S), Glutamine (Q) and Lysine (K).

[0058] In some embodiments, the linker may be a flexible linker or a rigid linker. Flexible linkers may be composed of small, non-polar (e.g., Gly) or polar (e.g., Ser or Thr) amino acids. The small size of these amino acids provides flexibility, and allows for mobility of the connecting functional domains. The most commonly used flexible linkers have sequences consisting primarily of stretches of Gly and Ser residues ("GS" linker). An example of the most widely used flexible linker has the sequence of (Gly-Gly-Gly-Gly-Ser)_n. By adjusting the copy number "n", the length of this GS linker may be optimized to achieve appropriate separation of the functional domains, or to maintain necessary inter-domain interactions. In some embodiments, linkers may include additional amino acids such as Thr and Ala to maintain flexibility, as well as polar amino acids such as Lys and Glu to improve solubility. In some embodiments, the DSG2 fusion polypeptide may include a flexible linker, such as (Gly)₈ (SEQ ID NO: 14), consisting of purely of glycine residues. The linker sequence avoided large hydrophobic residues to maintain good solubility in aqueous solutions.

[0059] In some embodiments, the linker may be a rigid linker. Non limiting examples of an rigid linker includes a linker with the sequence of (EAAAK)_n (n = 2-5) (SEQ ID NO: 15). In some embodiments, the rigid linker may have a Proline-rich sequence, (XP)_n, with X designating any amino acid, preferably Ala, Lys, or Glu.

[0060] In some embodiments, the linker may be GGGGS (SEQ ID NO: 12). In some embodiments, the linker may be GGGGGS (SEQ ID NO: 16) and EAAAK (SEQ ID NO: 13).

Polynucleotides

[0061] In some embodiments, the polypeptides of the present disclosure are encoded by polynucleotides or variants thereof described herein. Exemplary nucleic acids or polynucleotides include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β-D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2'-amino-LNA having a 2'-amino functionalization, and 2'-amino-α-LNA having a 2'-amino functionalization), ethylene nucleic acids (ENA), cyclohexenyl nucleic acids (CeNA) or hybrids or combinations thereof.

[0062] As such, polynucleotides encoding peptides or polypeptides containing substitutions, insertions and/or additions, deletions, and covalent modifications with respect to reference sequences, in particular the polypeptide sequences are disclosed herein. For example, sequence tags or amino acids, such as one or more lysines, can be added to the peptide sequences described herein (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

[0063] Once any of the features have been identified or defined as a desired component of a polypeptide to be encoded by a polynucleotide described herein, any of several manipulations and/or modifications of these features may be performed by moving, swapping, inverting, deleting, randomizing or duplicating. Furthermore, it is understood that manipulation of features may result in the same outcome as a modification to the molecules described herein. For example, a manipulation which involved deleting a domain would result in the alteration of the length of a molecule just as modification of a nucleic acid to encode less than a full length molecule would.

III. PHARMACEUTICAL COMPOSITIONS AND DELIVERY

[0064] The fusion polypeptides described herein may be used as therapeutic agents. In some embodiments, the present disclosure provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier and a fusion polypeptide.

[0065] In some embodiments, compositions are administered to humans, human patients, or subjects. Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, e.g., to non-human animals, e.g., non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which

administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as dogs, cattle, pigs, horses, sheep, cats, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys. As a non-limiting example, compositions of the disclosure may be administered to dogs to treat ARVC.

[0066] Provided herein are the fusion polypeptides and pharmaceutical composition thereof which may be used in combination with one or more pharmaceutically acceptable excipients.

[0067] In some embodiments, the pharmaceutically acceptable excipients include, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, flavoring agents, stabilizers, antioxidants, osmolality adjusting agents, pH adjusting agents and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, Md., 2006; incorporated herein by reference in its entirety). The use of a conventional excipient medium may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this disclosure.

[0068] In some embodiments, a pharmaceutically acceptable excipient may be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient may be approved by United States Food and Drug Administration. In some embodiments, an excipient may be of pharmaceutical grade. In some embodiments, an excipient may meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[0069] Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents,

preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in pharmaceutical compositions. The composition may also include excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents.

[0070] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, etc., and/or combinations thereof.

[0071] Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked polyvinylpyrrolidone (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, crosslinked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM®), sodium lauryl sulfate, quaternary ammonium compounds, etc., and/or combinations thereof.

[0072] Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondron, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite (aluminum silicate) and VEEGUM® (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate (TWEEN®20), polyoxyethylene sorbitan (TWEEN®60), polyoxyethylene sorbitan monooleate (TWEEN®80), sorbitan monopalmitate (SPAN®40), sorbitan monostearate (SPAN®60), sorbitan tristearate (SPAN®65), glyceryl monooleate, sorbitan monooleate (SPAN®80), polyoxyethylene esters (e.g. polyoxyethylene monostearate (MYRJ®45),

polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and SOLUTOL®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. CREMOPHOR®), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether (BRIJ®30), poly (vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLUORINC®F 68, POLOXAMER® 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof.

[0073] Exemplary binding agents include, but are not limited to, starch (e.g. cornstarch and starch paste); gelatin; sugars (e.g. sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol); amino acids (e.g. , glycine); natural and synthetic gums (e.g. acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (VEEGUM®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; etc.; and combinations thereof.

[0074] Exemplary preservatives may include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Oxidation is a potential degradation pathway for mRNA, especially for liquid mRNA formulations. In order to prevent oxidation, antioxidants can be added to the formulation. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, benzyl alcohol, butylated hydroxyanisole, EDTA, m-cresol, methionine, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, thioglycerol and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and/or trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylonol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and/or thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium

sorbate, sodium benzoate, sodium propionate, and/or sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and/or phenyl ethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and/or phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, GLYDANT PLUS®, PHENONIP®, methylparaben, GERMALL®115, GERMABEN®, NEOLONE™, KATHON™, and/or EUXYL®.

[0075] In some embodiments, the pH of the pharmaceutical solutions is maintained between pH 5 and pH 8 to improve stability. Exemplary buffers to control pH may include, but are not limited to sodium phosphate, sodium citrate, sodium succinate, histidine (or histidine-HCl), sodium carbonate, and/or sodium malate. In another embodiment, the exemplary buffers listed above may be used with additional monovalent counterions (including, but not limited to potassium). Divalent cations may also be used as buffer counterions; however, these are not preferred due to complex formation and/or mRNA degradation.

[0076] Exemplary buffering agents may also include, but are not limited to, citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, etc., and/or combinations thereof.

[0077] Exemplary lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable

oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, etc., and combinations thereof.

[0078] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mint, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and/or combinations thereof.

[0079] Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be present in the composition, according to the judgment of the formulator.

[0080] Exemplary additives include physiologically biocompatible buffers (e.g., trimethylamine hydrochloride), addition of chelants (such as, for example, DTPA or DTPA-bisamide) or calcium chelate complexes (as for example calcium DTPA, CaNaDTPA-bisamide), or, optionally, additions of calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate). In addition, antioxidants and suspending agents can be used.

[0081] In some embodiments, the compositions of the present disclosure may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited to enteral (into the intestine), gastroenteral, epidural (into the dura matter), oral (by way of the mouth), transdermal, peridural, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intraarterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal, (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis),

intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), in ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electroosmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intraabdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracornal, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corpus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aurus media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique, ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), intramyocardial (entering the myocardium), soft tissue, subarachnoid, subconjunctival, submucosal, transplacental (through or across the placenta), transtracheal

(through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photopheresis or spinal. In specific embodiments, compositions may be administered in a way which allows them to cross the blood-brain barrier, vascular barrier, or other epithelial barrier.

[0082] Therapeutically effective doses will be easily determined by one of skill in the art and will depend on the severity and course of the disease, the patient's health and response to treatment, and the judgment of the treating physician.

IV. METHODS OF USE

[0083] Provided herein are methods of use of the DSG2 fusion polypeptide compositions of the present disclosure. In some embodiments, the DSG2 fusion polypeptides of the disclosure may be used to treat one or more diseases or conditions described herein, in a subject. Such methods may include contacting the subject with the DSG2 fusion polypeptides. In some embodiments, the contacting the subject may include administering DSG2 fusion polypeptides to the subject. In some embodiments, the contacting the subject may include treating the subject with the DSG2 fusion polypeptides of the disclosure. In one embodiment, compositions of the disclosure may be used to treat diseases associated with DSG2 autoantibodies. In one embodiment, the compositions of the disclosure mitigate cardiotoxicity associated with DSG2 antibodies.

[0084] In some embodiments, any therapeutic disease associated with the inflammation in myocardium may be treated with the DSG2 fusion polypeptides as described herein. Non-limiting examples of such indications include arrhythmogenic right ventricular cardiomyopathy (ARVC), sarcoidosis, dilated cardiomyopathy, post-infectious cardiomyopathy, compromised cardiac function, reduced ejection fraction, heart failure, arrhythmia and myocarditis.

[0085] Efficacy of treatment or amelioration of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of a fusion polypeptides or pharmaceutical composition thereof, "effective against" a disease or disorder indicates that

administration in a clinically appropriate manner results in a beneficial effect for at least a fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease load, extension of life, improvement in quality of life, a reduction in the need for blood transfusions or other effect generally recognized as positive by medical doctors familiar with treating the particular type of disease or disorder.

[0086] A treatment or preventive effect is evident when there is a significant improvement, often statistically significant, in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more may be indicative of effective treatment. Efficacy for a given compound or composition may also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant modulation in a marker or symptom is observed.

COVID-19

[0087] The DSG2 fusion polypeptides or compositions containing the fusion polypeptides as described herein can be administered to treat COVID-19 or long-term effects of COVID-19.

[0088] In some embodiments, the compositions of the disclosure may be useful in treating COVID-19 and/or individuals infected with SARS-CoV-2. An infected person may be symptomatic, pre-symptomatic, and asymptomatic. According to the World Health Organization (WHO), COVID-19 transmission may occur from symptomatic, pre-symptomatic, and asymptomatic people infected with SARS-CoV-2. Symptomatic transmission may refer to transmission occurring before a person experiencing symptoms. Pre-symptomatic transmission may refer to transmission occurring prior to onset of symptoms of COVID-19.

[0089] COVID-19 may be associated with one or more symptoms such as, but not limited to, fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, trouble breathing, persistent pain or pressure in the chest.

[0090] DSG2 fusion polypeptides may be used to treat one or more stages of COVID-19 disease. In general, adults with SARS-CoV-2 infection may be grouped into the following severity of illness categories. However, the criteria for each category may overlap or vary

across clinical guidelines and clinical trials, and a patient's clinical status may change over time (COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at www.covid19treatmentguidelines.nih.gov/. Accessed 12/11/2020). In some embodiments, the compositions of the disclosure may be used to treat asymptomatic or presymptomatic infection which may include individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19. In some embodiments, the compositions of the disclosure may be used to treat mild illness which includes individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. In some embodiments, the compositions of the disclosure may be used to treat moderate illness which may include individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) $\geq 94\%$ on room air at sea level. In some embodiments, the compositions of the disclosure may be used to treat severe illness which includes individuals who have $\text{SpO}_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mmHg, respiratory frequency > 30 breaths per minute, or lung infiltrates $> 50\%$. In some embodiments, the compositions of the disclosure may be used to treat critical illness which includes individuals who have respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), sepsis, septic shock, multiple organ dysfunction, and/or multi organ failure, including acute kidney injury, and cardiac injury.

[0091] Methods of preventing one or more conditions associated with COVID-19 are also provided herein. In one embodiment, the compositions of the disclosure may be provided to the subject prior to the onset of symptoms but after exposure to the virus since there is an incubation period between exposure and symptom onset to the virus. The incubation period of novel coronavirus SARS-CoV-2 is generally between two and fourteen days, with an average of five days (Lombardi et al., *J. Hosp. Infect.* 2020 doi: 10.1016/j.jhin.2020.03.003; the contents of which are herein incorporated by reference in its entirety).

[0092] Compositions of the disclosure may also be administered in combination with one or more therapeutic agents recommended for use in the treatment of COVID-19. In some embodiments, DSG2 fusion polypeptides described herein may be used in combination with one or more therapeutic agents such as, but not limited to, Remdesivir, chloroquine, hydroxychloroquine, loop diuretics, azithromycin, Lopinavir, Ritonavir, ivermectin,

interleukin inhibitors, interferons, kinase inhibitors, glucocorticosteroids, and/or SARS CoV-2 monoclonal antibodies (e.g., Bamlanivimab, Casirivimab, Imdevimab).

Post-COVID-19 syndrome

[0093] In some embodiments, compositions of the present disclosure may be used to treat post-COVID-19 syndrome. There have been an increasing number of reports of patients who experience persistent symptoms after recovering from acute COVID-19 and is herein referred to as “post-COVID-19 syndrome” and individuals suffering from these symptoms are commonly referred to as “long haulers.” In some embodiments, a patient may be considered to have post-COVID-19 syndrome if they suffer from one or more symptoms for up to a month, up to two months, up to three months, up to four months, up to five months, up to six months, up to seven months, up to eight months, up to nine months, up to ten months, up to eleven months, up to a year or more after SARS CoV-2 infection. In some embodiments, the subject may have no symptoms after SARS CoV-2 infection. In some embodiments, the subject may have no known COVID-19 or SARS CoV2 infection but may have serum anti-DSG2 antibodies.

[0094] Compositions of the present disclosure may be used to treat one or more symptoms associated with the cardiovascular system in post-COVID-19 syndrome (i.e., post COVID-19 cardiac syndrome). One study including 100 patients recently recovered from COVID-19, cardiac magnetic resonance imaging revealed cardiac involvement in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%), which was independent of preexisting conditions, severity and overall course of the acute illness, and the time from the original diagnosis (Puntmann et al. JAMA Cardiol. 2020;5(11):1265-1273). In a smaller study, 15% of athletes had evidence for myocarditis after recovery from acute COVID-19. In one embodiment, the DSG2 fusion polypeptides may be used to treat myocarditis in a subject with post-COVID-19 syndrome.

[0095] In some embodiments, the compositions described herein may be used to treat post-COVID-19 syndrome that is not associated with any cardiac indications.

[0096] In some embodiments, the compositions of the present disclosure may be used to treat subjects who show symptoms of COVID-19, for up to weeks, months, and/or years after initial diagnosis of COVID-19. In some embodiments, post-COVID-19 syndrome patients may demonstrate symptoms for and/or after 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months,

12 months, 1 year, 2 years, 3 years, 4 years, 5 years or more after initial diagnosis of COVID-19. Diagnosis of COVID-19 may be established using methods known in the art (for e.g., reverse transcription polymerase chain reaction and/or antibody tests). In some embodiments, subjects affected by post-COVID-19 syndrome may be treated with the compositions of the disclosure for up to 1 week, up to 1 month, and/or up to one year.

[0097] In some embodiments, compositions of the disclosure may be used to treat COVID-19 patients who have or develop compromised cardiac function, most notably a reduced ejection fraction, with or without overt symptoms of heart failure. In some embodiments, the compositions of the disclosure may be used to treat arrhythmia.

[0098] Compositions of the present disclosure may ameliorate one or more symptoms associated with post-COVID-19 syndrome. In some embodiments, the symptoms of post-COVID-19 syndrome may be the same as acute COVID-19. In some aspects, the symptoms associated with post-COVID-19 syndrome may be shortness of breath, fatigue, edema, orthopnea, limitations to exertion, impaired cognitive abilities, palpitations, dizziness, syncope, lightheadedness, heart failure, and/or arrhythmia.

[0099] In some embodiments, compositions of the disclosure may be used to treat post COVID-19 syndrome with symptoms that overlap with the post-intensive care syndrome that has also been described in patients without COVID-19.

[0100] In some embodiments, the compositions of the disclosure may be used to treat subjects with post-COVID-19 syndrome who may have one or more long-term complications associated with the cardiovascular system (e.g., inflammation of the heart muscle), respiratory system (lung function abnormalities), renal systems (acute kidney injury), dermatologic (rash, hair loss), neurological complications (smell and taste problems, sleep issues, difficulty with concentration, memory problems), and/or psychiatric problems (depression, anxiety, changes in mood).

[0101] In some embodiments, compositions of the disclosure may be used to treat post-COVID-19 syndrome subjects who may have one, two or more associated co-morbidities. Non-limiting examples of co-morbidities include, but are not limited to, hypertension, thyroid disease, immune disorders, COPD (chronic obstructive pulmonary disease), high blood pressure, obesity, mental health conditions, and diabetes.

Autoimmunity associated with COVID-19

[0102] From a pathogenesis standpoint, viral infections such as COVID-19, generally trigger a vigorous immune response that is crucial for viral clearance, with a cascade of

events involving both the innate and adaptive immune arms. Direct and indirect myocardial damage is also caused by COVID-19 infection, allowing for cardiac proteins to be exposed to the activated immune system. Immunological alterations are also observed in patients with COVID-19 condition. These range from a maladaptive immune response and abnormal cytokine/chemokine production, to hyperactivation of T cells and increased number of activated monocytes, macrophages and neutrophils.

[0103] Autoantibodies known to occur in a number of autoimmune diseases have been detected in patients with COVID-19. Because COVID-19 infection can break immune tolerance and trigger autoimmune responses, it is also likely to induce clinical autoimmunity. Autoantibodies detected in patients with COVID-19 included antinuclear antibodies (ANA), antiphospholipid (APL), lupus anticoagulant, cold agglutinins, anti-Ro/Sjögren's syndrome A (SSA) antibodies, anti-Caspr2 antibody, anti-GD1b antibody, anti-myelin oligodendrocyte glycoprotein (MOG) antibody and red cell bound antibodies (Liu, Y., et al. *Curr. Opin. Rheumatol.* 2021; 33:155-162; the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, compositions of the disclosure may be used to block autoantibodies generated during COVID-19 or SARS CoV2 infection.

[0104] In a study, three protein arrays were assembled to measure IgG autoantibodies associated with connective tissue diseases, anti-cytokine antibodies, and antiviral antibody responses in serum from 147 hospitalized COVID-19 patients. Autoantibodies were identified in approximately 50% of patients but in less than 15% of healthy controls. It was found that autoantibodies largely targeted autoantigens associated with rare disorders such as myositis, systemic sclerosis and overlap syndromes. However, a subset of autoantibodies targeting traditional autoantigens or cytokines were developed de novo following COVID-19 infection (Chang, S.E., et al. *Nature Communications* 2021; 12:5417; the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, compositions of the disclosure may be used to block autoantibodies developed following COVID-19 infection.

[0105] In severe and critical cases, immunomodulatory drugs and biological agents targeting pro inflammatory cytokines have been applied to contain the robust immune response in COVID-19. Corticosteroids, JAK inhibitors, IL-1 blockade and IL-6 receptor antagonists have been used to treat COVID-19 patients. In some embodiments, compositions of the disclosure may be used in combination with immunomodulatory drugs and biological agents targeting pro inflammatory cytokines. In some embodiments, compositions of the

disclosure may be used in combination with corticosteroids, JAK inhibitors, IL-1 blockade and IL-6 receptor antagonists.

[0106] There have been reports of thromboembolic events following ChAdOx1 nCov-19 (AstraZeneca) vaccination and potentially the Ad26.COV2.S (Johnson & Johnson) vaccination. While rare, thrombosis was observed to occur at unusual sites, such as cerebral and splanchnic veins. Based on the observation of thrombocytopenia and raised antibodies to platelet factor 4-polyanion complexes, it has been suggested to be an immune-mediated reaction (Lee, C. C. E., et al. *Diseases* 2021; 9:47; the contents of each of which are herein incorporated by reference in their entirety).

[0107] In one study, a high-throughput autoantibody discovery method known as rapid extracellular antigen profiling (REAP) was implemented to screen a cohort of 194 individuals infected with COVID-19, comprising 172 patients with COVID-19 and 22 healthcare workers with mild disease or asymptomatic infection, for autoantibodies against 2,770 extracellular and secreted proteins (members of the exoproteome). After screening patient samples identification and validation of numerous protein targets across a wide range of tissues and immunological and physiological functions was performed. These autoantibodies had potent functional activities and could be directly correlated with various virological, immunological and clinical parameters in vivo within samples from patients with COVID-19. The analysis suggested that some of these autoantibodies probably predated infection, whereas others were induced after infection. Furthermore, mouse surrogates of these autoantibodies led to increased disease severity in a mouse model of COVID-19 infection. These results provide evidence that autoantibodies are capable of altering the course of COVID-19 by perturbing the immune response to SARS-CoV2 and tissue homeostasis (Wang, E. Y., et al. *Nature* 2021; 595:283; the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, compositions of the disclosure may be used to block autoantibodies that predated COVID-19 infection. In some embodiments, compositions of the disclosure may be used to block autoantibodies that may be induced after COVID-19 infection.

Cardiomyopathies

[0108] In some embodiments, compositions of the disclosure may be used to treat cardiomyopathies. Cardiomyopathy refers to progressive impairment of the structure and function of the muscular walls of the heart chambers. Compositions of the disclosure may be used to treat one or more types of cardiomyopathies, such as, but not limited to, dilated

cardiomyopathy, hypertrophic cardiomyopathy and/or restrictive cardiomyopathy. In one embodiment, patients with cardiomyopathies may demonstrate serum DSG2 autoantibodies in their serum.

[0109] In one embodiment, the compositions of the disclosure may be used to treat Arrhythmogenic right ventricular cardiomyopathy (ARVC). Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/ARVD) is a heart muscle disorder associated with ventricular arrhythmia, heart failure, and sudden death. ARVC is a degenerative cardiac disease characterized by the progressive loss of ventricular function and arrhythmias. In addition to genetic mutations to the structural and signaling proteins of cardiomyocyte desmosomes, patient immune systems also have been known to play a role in ARVC disease pathology. Mutations in DSG2 protein have been associated with ARVC and autoantibodies targeting DSG2 have been identified in patients with the disease. Approximately 50% of ARVC patients do not have known desmosome mutations; nevertheless these patients express DSG2 antibodies. In some embodiments, DSG2 fusion proteins may be used to treat ARVC patients who have one or more mutations in the DSG2 protein. In some aspects, the DSG2 fusion proteins may be used to treat ARVC patients with no known mutations in the DSG2 protein. In some embodiments, DSG2 fusion polypeptides of the disclosure may target DSG2 autoantibodies associated with ARVC.

[0110] Cardiomyopathy may be associated with inflammation and is herein referred to as myocarditis. In some embodiments, myocarditis may be caused by viruses, bacteria, parasites, and/or fungi. In some embodiments, compositions of the disclosure may be used to treat and/or prevent myocarditis associated with viruses. Non-limiting examples of viruses associated with myocarditis include, common cold causing adenovirus, COVID-19; hepatitis B and C; parvovirus, which causes a mild rash, usually in children (fifth disease); and/or herpes simplex virus, gastrointestinal infections causing echoviruses, mononucleosis causing Epstein-Barr virus, rubella, cytomegalovirus, and HIV.

[0111] Cardiovascular complications have occurred frequently in association with COVID-19 and even months after the infection. These cardiovascular complications include myocardial injury and myocarditis, acute coronary syndromes, heart failure, arrhythmias, and thromboembolic events. In addition, cardiac symptoms, palpitations, chest pain, and dyspnea have been observed in patients, weeks to months after the initial infection. (Lee, C. C. E., et al. Diseases 2021; 9:47; the contents of each of which are herein incorporated by reference in their entirety). In some embodiments, compositions of the disclosure may be used to treat

cardiovascular complications such as myocardial injury and myocarditis, acute coronary syndromes, heart failure, arrhythmias, and thromboembolic events.

[0112] In some embodiments, compositions of the disclosure may be used to treat and/or prevent myocarditis caused by bacteria. Non-limiting examples of bacteria associated with myocarditis include, *Staphylococcus*, *Streptococcus*, and/or *Borrelia*. In some embodiments, compositions of the disclosure may be used to treat and/or prevent myocarditis caused by parasites. Non-limiting examples of parasites associated with myocarditis include, *Trypanosoma cruzi* and *Toxoplasma*, including some that are transmitted by insects and can cause a condition called Chagas disease. In some embodiments, compositions of the disclosure may be used to treat and/or prevent myocarditis caused by fungi. Non-limiting examples of fungi associated with myocarditis include, *Candida*, *Aspergillus*; and other fungi, such as *Histoplasma*.

V. DEFINITIONS

[0113] *Domain*: As used herein when referring to polypeptides the term “domain” refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

[0114] *Expression vector*: The term “expression vector” as used herein refers to a vector containing a nucleic acid sequence coding for at least part of a gene product capable of being transcribed. Expression vectors can contain a variety of control sequences, which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operatively linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well. The term also includes a recombinant plasmid or virus that comprises a polynucleotide to be delivered into a host cell, either in vitro or in vivo. In some embodiments, the host cell is a transient cell line or a stable cell line. In some embodiments, it is selected from the group consisting of CHO, HEK293 and NSO.

[0115] *Features*: “Features” when referring to polypeptides are defined as distinct amino acid sequence-based components of a molecule. Features of the polypeptides encoded by the polynucleotides described herein include local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini, or any combination thereof.

[0116] *Fusion protein*: As used herein, the term “fusion protein” or chimeric protein refers to protein or polypeptide comprising two or more sequences of amino acids or active fragments thereof that are not naturally present in the same polypeptide. In some embodiments, two or more separate polypeptides are operably covalently linked, e.g., chemically linked, or fused together by peptide bonds. Recombinant fusion polypeptides are created artificially by recombinant DNA technology.

[0117] *Half-domain*: As used herein when referring to polypeptides the term “half-domain” means a portion of an identified domain having at least half the number of amino acid residues as the domain from which it is derived. It is understood that domains may not always contain an even number of amino acid residues. Therefore, in those cases where a domain contains or is identified to comprise an odd number of amino acids, a half-domain of the odd-numbered domain will comprise the whole number portion or next whole number portion of the domain (number of amino acids of the domain/2+/-0.5 amino acids). For example, a domain identified as a 7 amino acid domain could produce half-domains of 3 amino acids or 4 amino acids ($7/2=3.5+1-0.5$ being 3 or 4). It is also understood that subdomains may be identified within domains or half-domains, these subdomains possessing less than all of the structural or functional properties identified in the domains or half domains from which they were derived. It is also understood that the amino acids that comprise any of the domain types herein need not be contiguous along the backbone of the polypeptide (i.e., nonadjacent amino acids may fold structurally to produce a domain, half-domain or subdomain).

[0118] *Immune response*: As used herein, the term “immune response” refers to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

[0119] *Linker*: As used herein, “linker” refers to a functional group (e.g., a chemical or polypeptide) in which a covalent bond joins two or more polypeptides. As used herein, a “peptide linker” is two or more amino acids used to bind two proteins to each other.

[0120] *Modulation*: As used herein, the term “modulation” is recognized in the art and refers to up regulation (i.e., activation or stimulation), down regulation (i.e., inhibition or suppression) of a response, or the two in combination or apart.

[0121] *Polynucleotide*: The term “polynucleotide” as used herein refers to a sequence of nucleotides connected by phosphodiester linkages. Polynucleotides are presented herein in

the direction from the 5' to the 3' direction. A polynucleotide can be a deoxyribonucleic acid (DNA) molecule or ribonucleic acid (RNA) molecule. Where a polynucleotide is a DNA molecule, that molecule can be a gene or a cDNA molecule. Nucleotide bases are indicated herein by a single letter code: adenine (A), guanine (G), thymine (T), cytosine (C), inosine (I) and uracil (U). A polynucleotide can be prepared using standard techniques well known to one of skill in the art.

[0122] *Polypeptides*: In some embodiments, the compositions of the present disclosure are polypeptides or proteins or variants thereof. According to the present disclosure, any amino acid-based molecule (natural or non-natural) may be termed a "polypeptide" and this term embraces "peptides," "peptidomimetics," and "proteins." As used herein, "polypeptide" means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. A "peptidomimetic" or "polypeptide mimetic" is a polypeptide in which the molecule contains structural elements that are not found in natural polypeptides (*i.e.*, polypeptides comprised of only the 20 proteinogenic amino acids). In some embodiments, peptidomimetics are capable of recapitulating or mimicking the biological action(s) of a natural peptide.

[0123] *Polypeptide variant*: The term "polypeptide variant" refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology) to a native or reference sequence, and preferably, they will be at least about 80%, more preferably at least about 90% identical (homologous) to a native or reference sequence.

[0124] *Recombinant*: The term "recombinant" as used herein refers to a genetic entity distinct from that generally found in nature. As applied to a polynucleotide or gene, this means that the polynucleotide is the product of various combinations of cloning, restriction and/or ligation steps, and other procedures that result in the production of a construct that is distinct from a polynucleotide found in nature.

[0125] *Sample*: As used herein, the term "sample" refers to an aliquot or portion taken from a source and/or provided for analysis or processing. In some embodiments, a sample is from a biological source such as a tissue, cell or component part (e.g., a body fluid, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). In some embodiments, a

sample may be or include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, or organs. In some embodiments, a sample is or includes a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins. In some embodiments, a “primary” sample is an aliquot of the source. In some embodiments, a primary sample is subjected to one or more processing (e.g., separation, purification, etc.) steps to prepare a sample for analysis or other use.

[0126] *Substantially*: As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0127] *Terminus*: As used herein the terms “termini” or “terminus” when referring to polypeptides refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids in the terminal regions. The poly peptide-based molecules described herein may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH₂)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins described herein are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

[0128] *Therapeutically effective amount*: As used herein, the term “therapeutically effective amount” means an amount of an agent to be delivered that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition.

[0129] *Treating*: As used herein, the term “treating” refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of,

reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0130] *Treatment*: As used herein the terms “treat,” “treatment,” and the like, refer to relief from or alleviation of pathological processes. In the context of the present disclosure, it relates to any of the other conditions recited herein below, the terms “treat,” “treatment,” and the like mean to relieve or alleviate at least one symptom associated with such condition, or to slow or reverse the progression or anticipated progression of such condition.

[0131] *Treatment dose*: As used herein, “treatment dose” refers to one or more doses of a therapeutic agent administered in the course of addressing or alleviating a therapeutic indication. Treatment doses may be adjusted to maintain a desired concentration or level of activity of a therapeutic agent in a body fluid or biological system.

VI. EQUIVALENTS AND SCOPE

[0132] While various embodiments of the disclosure have been particularly shown and described in the present disclosure, it will be understood by those skilled in the art that various changes in form and details may be made without departing from the spirit and scope of the embodiments disclosed herein and set forth in the appended claims.

[0133] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. The scope of the present disclosure is not intended to be limited to the above description, but rather is as set forth in the appended claims.

[0134] In the claims, articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of a group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all group members are present in, employed in, or otherwise relevant to a given product or process.

[0135] It is also noted that the term “comprising” is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term “comprising” is used herein, the terms “consisting of” and “or including” are thus also encompassed and disclosed.

[0136] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0137] In addition, it is to be understood that any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to those of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiments of compositions disclosed herein can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[0138] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

[0139] Section and table headings are not intended to be limiting.

EXAMPLES

Example 1. DSG2 fusion polypeptide synthesis methods

[0140] DSG2 fusion polypeptides described herein are produced by recombinant DNA techniques by synthesizing DNA encoding the desired polypeptide. Once coding sequences for the desired polypeptides are synthesized or isolated, they are cloned into any suitable vector for expression.

[0141] The expression vector is inserted into a suitable host cell by transformation, transduction, and/or transfection. The sequences of the DSG2 fusion polypeptides may be optimized to yield maximal expression in a host cell. The host cell is any host cell known in the art for expression of recombinant proteins. A number of mammalian cell lines are known in the art and include immortalized cell lines available from the American Type Culture Collection (ATCC), such as, but not limited to, Chinese hamster ovary (CHO) cells, HeLa cells, HEK293, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human

hepatocellular carcinoma cells (e.g., Hep G2), Madin-Darby bovine kidney ("MDBK") cells, NOS cells derived from carcinoma cells, such as sarcoma, as well as others. Bacterial species may also be used as host cells. Non-limiting examples include *Escherichia coli*, *Bacillus subtilis*, and *Streptococcus*. Non-limiting examples of yeast host cells useful in the present disclosure include inter alia, *Saccharomyces cerevisiae*, *Candida albicans*, *Candida maltosa*, *Hansenula polymorpha*, *Kluyveromyces fragilis*, *Kluyveromyces lactis*, *Pichia guilliermondii*, *Pichia pastoris*, *Schizosaccharomyces pombe* and *Yarrowia lipolytica*.

[0142] Depending on the expression system and host selected, the fusion polypeptides of the present disclosure are produced by growing host cells expressing the expression vector under conditions whereby the protein of interest is expressed. The protein is then isolated from the host cells and purified.

[0143] Alternatively, the fusion polypeptides of the present disclosure may be synthesized by conventional techniques known in the art, for example, by chemical synthesis such as solid phase peptide synthesis.

Example 2. Anti-DSG2 antibodies in post COVID-19 serum samples

[0144] Viral infections, including COVID-19, have been hypothesized to contribute to autoimmune responses, e.g., by exposing previously hidden cryptic epitopes on damaged cells to an activated immune system (Ehrenfeld M, et al., *Autoimmunity Reviews* 2020;102597; the contents of which are herein incorporated by reference in its entirety). Given the high incidence of cardiac involvement seen in COVID-19 infections, it was hypothesized that anti-DSG2 autoantibodies might be generated as a result.

[0145] 300 convalescent serum samples were obtained from a group of post COVID-19 infected patients from October 2020 to February 2021 from East Asian population. The mean age of the study population was 37 years old (range 21-65 years). 154 samples were drawn 6 months post-COVID-19 infection and 146 samples were drawn 9 months post COVID infection. 17 samples were obtained from the same patient at the 6- and 9-month mark (symptom status unknown). The negative control group sera were obtained from a commercial source of self-declared healthy individuals. Positive control ARVC sera were obtained under International Council of Harmonization (ICH) guidelines. An anti-drug antibody (ADA) format assay was used for the detection of the anti-DSG2 antibodies. The mean signal intensity of anti-DSG2 antibodies in the post COVID-19 samples was significantly higher than that of a healthy control population as shown in Fig. 1 (19 ± 83.2 in the post COVID-19 sample vs. 2.1 ± 6.8 in the healthy control population, p value < 0.001). Of

note, 29.3% of the post COVID-19 infection samples demonstrated a signal higher than the 90th percentile of the control population and 8.7% have signals higher than the median found in ARVC patients. The presence of anti-DSG2 antibodies in samples obtained 6-9 months after COVID-19 infection suggests that the antibodies are not an acute phase reactant. The results are also shown in Table 4 and Table 5.

Table 4. Analysis of anti-DSG2 antibody levels

Type	N	Mean	Std Dev	Minimum	Median	Maximum	p-value 1	p-value2
ARVC Samples	5	33.58	30.36	6.20	29.90	84.80		
Convalescent Covid Sample	300	18.99	83.18	0.90	1.20	1070.00	0.0030	
Pre-Covid Samples	152	2.13	6.82	0.71	0.88	80.44	0.0003	<.0001
Note: p-values are based on the non-parametric rank-based Wilcoxon-Mann-Whitney 2-sided test, 3 pairwise comparison of the groups. P-value 1 is the comparison versus the ARVC Samples; p-value 2 is the comparison versus the Convalescent Covid Sample								

Table 5. Analysis of anti-DSG2 antibody levels

	Pre-Covid Samples	Convalescent Covid Samples	ARVC Samples
Number of values	152	300	5
Minimum	0.71	0.9	6.2
25% Percentile	0.8	1	11.35
Median	0.88	1.2	29.9
75% Percentile	1.375	4.375	57.65
Maximum	80.44	1070	84.8
Range	79.73	1069	78.6
10% Percentile	0.753	0.9	6.2
90% Percentile	3.044	28.27	84.8
Mean	2.134	18.99	33.58
Std. Deviation	6.82	83.18	30.36
Std. Error of Mean	0.5532	4.803	13.58

[0146] The signal intensity between the 6-month and 9-month samples did not differ significantly between each other ($p=0.529$). This was observed when all non-contemporaneously assessed 6 and 9 month samples ($N=300$; Fig. 2A) as well as in paired 6 month and 9 month samples analyzed by month of collection after COVID-19 infection ($N=17$; Fig. 2B)

[0147] In conclusion, recovered COVID-19 patients demonstrated significantly higher and sustained levels of anti-DSG2 autoantibodies as compared to a healthy control population, and comparable to that of a diagnosed ARVC group. Of note, these sera were obtained well after acute COVID-19 infection, suggesting that these antibodies may persist long-term.

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 (SEQ ID NO: 1); and
 - b. a whole or a portion of an immunoglobulin protein.
2. The isolated polypeptide of claim 1, wherein the DSG2 fusion polypeptide comprises a portion of the DSG2 protein.
3. The isolated polypeptide of claim 2, wherein the portion of the DSG2 protein is a whole or a portion of an extracellular region of the DSG2 protein.
4. The isolated polypeptide of claim 3, wherein the portion of DSG2 protein is the whole extracellular region of DSG2 protein.
5. The isolated polypeptide of claim 4, wherein the whole extracellular region of DSG2 protein comprises the amino acid sequence of SEQ ID NO: 3.
6. The isolated polypeptide of claim 3, wherein the portion of the DSG2 protein is a portion of an extracellular region of the DSG2 protein.
7. The isolated polypeptide of claim 6, wherein the portion of an extracellular region of the DSG2 protein comprises at least one domain, wherein the at least one domain is an extracellular cadherin domain 1 (EC1), an extracellular cadherin domain 2 (EC2), an extracellular cadherin domain 3 (EC3), an extracellular cadherin domain 4 (EC4), or an extracellular anchor domain (EA).
8. The isolated polypeptide of claim 7, wherein the portion of an extracellular region of the DSG2 protein comprises two domains.
9. The isolated polypeptide of claim 8, wherein the portion of the extracellular region of the DSG2 protein is EC4EA, EC1EC2, EC2EC3, EC3EC4, EC1EA, EC1EC3, EC2EC4, or EC3EA.

10. The isolated polypeptide of claim 7, wherein the portion of an extracellular region of the DSG2 protein comprises three domains.

11. The isolated polypeptide of claim 10, wherein the portion of the extracellular region of the DSG2 protein is EC1EC3EA, EC1EC4EA, EC1EC3EA, EC3EC4EA, EC1EC2EC3, EC2EC3EC4, or EC2EC4EA.

12. The isolated polypeptide of claim 7, wherein the portion of an extracellular region of the DSG2 protein comprises four domains.

13. The isolated polypeptide of claim 12, wherein the portion of the extracellular region of the DSG2 protein is EC1EC2EC4EA, EC2EC3EC4EA, EC1EC2EC3EC4EA, EC1EC2EC3EC4, or EC1EC2EC3EA.

14. The isolated polypeptide of claim 1, wherein the DSG2 fusion polypeptide comprises a portion of an immunoglobulin protein.

15. The isolated polypeptide of claim 1 or claim 14, wherein the immunoglobulin protein is an IgG, an IgM, an IgA, an IgD or, an IgE.

16. The isolated polypeptide of claim 15, wherein the immunoglobulin is an IgG.

17. The isolated polypeptide of claim 16, wherein the IgG is an IgG1, an IgG2, an IgG3, and an IgG4.

18. The isolated polypeptide of claim 14, 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.

19. The isolated polypeptide of claim 18, wherein the portion of the immunoglobulin protein is an Fc region.

20. The isolated polypeptide of claim 19, wherein the Fc region is an IgG1 Fc region (SEQ ID NO: 5), an IgG2 Fc region (SEQ ID NO: 7), an IgG3 Fc region (SEQ ID NO: 9), or an IgG4 Fc region (SEQ ID NO: 11).
21. The isolated polypeptide of claim 18, wherein the portion of the immunoglobulin protein is a heavy chain constant domain.
22. The isolated polypeptide of claim 21, wherein the heavy chain constant is an IgG1 heavy chain constant domain (SEQ ID NO: 4), an IgG2 heavy chain constant domain (SEQ ID NO: 6), an IgG3 heavy chain constant domain (SEQ ID NO: 8), or an IgG4 heavy chain constant domain (SEQ ID NO: 10).
23. The isolated polypeptide of any one of claims 1-22, 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 GGGGS (SEQ ID NO: 12).
26. The isolated polypeptide of claim 24, wherein the linker is EAAAK (SEQ ID NO: 13).
27. The isolated polypeptide of any one of claims 1-26, wherein the DSG2 fusion polypeptide further comprises a signal sequence.
28. A cell expressing the isolated polypeptide of any one of claims 1-27.
29. A method of treating a condition associated with serum anti DSG2 autoantibodies, the method comprising contacting the subject with the isolated polypeptide of any one of claims 1-27, or a cell of claim 28.
30. The method of claim 29, wherein the condition is a cardiomyopathy.

31. The method of any one of claims 29 or 30, wherein the condition is an autoimmune disorder.
32. A method of treating post-COVID-19 syndrome in a subject, the method comprising:
(i) contacting the subject with the isolated polypeptide of any one of claims 1-27, or a cell of claim 28; and
(ii) evaluating one or more symptoms associated with post-COVID-19 syndrome selected from the group consisting of arrhythmia, myocarditis, heart failure, shortness of breath, fatigue, edema, orthopnea, limitations to exertion, impaired cognitive abilities, palpitations, dizziness, syncope, and lightheadedness,
wherein the treatment is effective in ameliorating the one or more symptoms associated with post-COVID-19 syndrome.
33. The method of claim 32, wherein serum of the subject comprises anti-DSG2 antibodies.
34. The method of claim 32, wherein the subject was previously diagnosed with COVID-19.
35. The method of claim 34, wherein serum of the subject comprises anti-SARS-CoV-2 antibodies.
36. The method of claim 34, wherein the serum of the subject does not comprise anti-SARS-CoV-2 antibodies.
37. A method of treating COVID-19 in a subject, the method comprising:
(i) contacting the subject with the isolated polypeptide of any one of claims 1-27, or a cell of claim 28; and
(ii) evaluating one or more symptoms associated with COVID-19 selected from the group consisting of fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, trouble breathing, persistent pain or pressure in the chest,
wherein the treatment is effective in ameliorating the one or more symptoms associated with COVID-19.

38. A method of treating cardiomyopathy in a subject, the method comprising:
- (i) contacting the subject with the isolated polypeptide of any one of claims 1-27, or a cell of claim 28, and
 - (ii) measuring one or more symptoms associated with cardiomyopathy selected from the group consisting of arrhythmia, palpitations, myocarditis, heart failure, poor cardiac output, and reduced ejection fraction.
39. The method of claim 38, wherein the cardiomyopathy is arrhythmogenic right ventricular cardiomyopathy.
40. The method of claim 38, wherein the cardiomyopathy is caused by a virus, a bacterium, a parasite or a fungus.
41. The method of claim 40, wherein the cardiomyopathy is caused by a virus and wherein the virus is a SARS- CoV2, an adenovirus, a hepatitis virus, a parvovirus, a herpes simplex virus, an echovirus, an Epstein-Barr virus, a rubella virus , a cytomegalovirus, or an HIV.
42. The method of claim 40, wherein the cardiomyopathy is caused by a bacterium and wherein the bacterium is a Staphylococcus, a Streptococcus, or a Borrelia.
43. The method of claim 40, wherein the cardiomyopathy is caused by a parasite and wherein the parasite is a Trypanosoma or a Toxoplasma.
44. The method of claim 40, wherein the cardiomyopathy is caused by a fungus and wherein the fungus a Candida, an Aspergillus, or a Histoplasma.
45. The method of claim 38, wherein the serum of the subject comprises anti-DSG2 antibodies.