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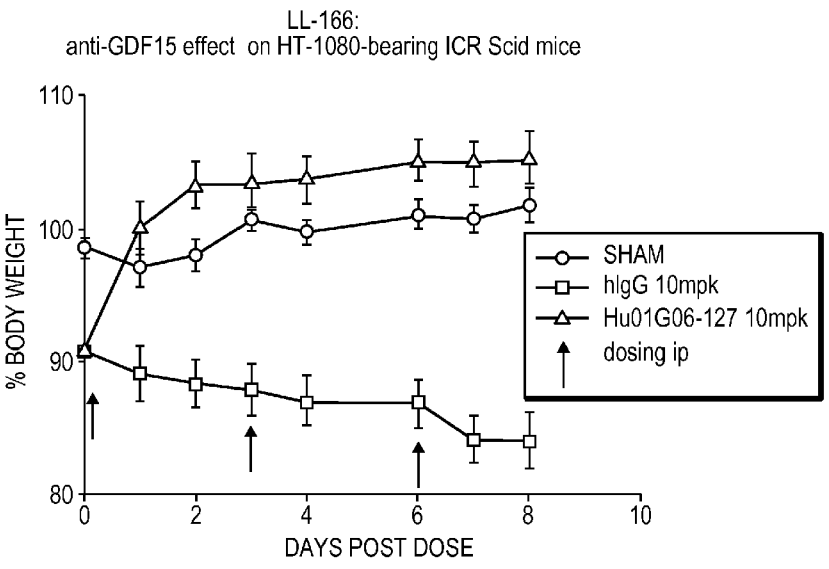

FIG. 8

(57) Abstract: The invention provides methods and compositions of treating a subject having a cardiac- related disorder such as congestive or chronic heart failure (CHF), cardiac hypertrophy, cardiac hypotrophy, and other cardiac myopathies/dystrophies. The methods comprise administering an effective amount of a composition that modulates, for example, reduces or inhibits, GDF 15 activity in the subject.

TREATMENT OF CONGESTIVE HEART FAILURE AND OTHER CARDIAC DYSFUNCTION USING A GDF15 MODULATOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/015,093, filed June 20, 2014, incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to methods of using, and compositions containing, a GDF15 modulator for treating a subject having a cardiac disorder or dysfunction, for example, congestive heart failure, chronic heart failure and acute cardiac conditions such as myocardial infarction.

BACKGROUND OF THE INVENTION

[0003] Heart failure, also called congestive heart failure, is a common and expensive condition that is highly debilitating and potentially lethal. It is a leading cause of hospitalization in people aged over 65 years. Heart failure may be the result of rapid onset, termed "acute heart failure" or may develop over long periods of time, termed "chronic heart failure."

[0004] Heart failure may be associated with a number of other cardiac conditions, disorders and dysfunctions, including: cardiac arrest or heart stoppage; myocardial infarction (also known as a heart attack) which refers to heart muscle damage, usually due to insufficient blood supply, for example, due to a blocked coronary artery; and cardiomyopathy, referring to damage to heart muscle, which may be genetic, or acquired, and which may be dilated, hypertrophic or restrictive. Dilated cardiomyopathy is primarily genetic in origin, and involves stretching and thinning of the muscle, usually in the left ventricle. When this happens, the heart muscle becomes unable to pump blood efficiently around the body, which can lead to fluid accumulating in the lungs ankles, abdomen and other organs, as well as a feeling of breathlessness. Hypertrophic cardiomyopathy involves thickening of the heart muscle, which may result in myocardial disarray of the cell structure, stiffening of the heart muscle and high

blood pressure. Restrictive cardiomyopathy involves a stiffening of the walls of the ventricles, so that they resist normal filling with blood. Restrictive cardiomyopathies can result from a number of causes, such as: hemochromatosis, in which too much iron builds up in the body, which can damage the heart; sarcoidosis, in which abnormal inflammation causes lumps of cells to form in the body's organs, including the heart; and amyloidosis, in which abnormal levels of protein, such as amylin, build up in the organs, including the heart.

[0005] Other cardiac-related conditions that may be associated with heart failure include: cardiac hypertrophy, ischemic/reperfusion injury, dyspnea, idiopathic pulmonary arterial hypertension, ST-segment elevation myocardial infarction (STEMI), and cardiovascular dysfunction.

[0006] Growth Differentiation Factor-15 (GDF15) is a member of the transforming growth factor-beta (TGF-β) superfamily of proteins, which comprise a large group of multifunctional proteins that serve as regulators of cell proliferation and differentiation. Prominent members of this family include the TGF-βs 1-5, activins, bone morphogenetic proteins (BMPs) that serve as regulators of bone, cartilage and other tissue types, and other proteins involved in cellular regulation, such as glial cell-line derived neurotrophic factor (GDNF), and myostatin (also known as GDF-8). GDF15 was isolated initially from such tissues as prostate and placenta, and has been known by the additional names macrophage inhibitory cytokine 1 (or MIC1), NSAID-activated gene 1 protein (or NAG1), NSAID-regulated gene 1 protein (or NRG-1), placental TGF-beta (or PTGFB), placental bone morphogenetic protein (or PLAB), and prostate differentiation factor (or PDF).

[0007] Reports of the activity of GDF15 in subjects with heart injury have been contradictory and inconclusive. Kempf *et al.* reported that endogenous GDF15 protects the heart from ischemic/reperfusion injury (Kempf *et al.*, 2006, CIRCULATION RESEARCH, 98:351-360); and later reported that GDF15 functions as a cardioprotective cytokine during myocardial infarction and heart failure (Kempf *et al.*, 2007, CLINICAL CHEMISTRY, 53:284-291). See also, Tobin and Celeste, 2006, DRUG DISCOVERY TODAY, 11:405-411; Lajer *et al.*, 2010, DIABETES CARE, 33:1567-1572. Breit and Brown, U.S. Patent 7,919,084 postulate treatment of cardiovascular disease by either inhibiting or increasing the activity or expression of GDF15. More recent studies have called for more studies as to whether a causative relationship exists between GDF15 levels and heart failure. See Bonica *et al.*, 2011, ARTERIOSCLEROSIS,

THROMBOSIS AND VASCULAR BIOLOGY, 31:203-210; Wallentin *et al.*, 2013, EUR. HEART J., 34(suppl.):P4048.

[0008] Notwithstanding the progress made to date, there still exists a need for better methods of detecting, preventing, and treating cardiac conditions and disorders.

SUMMARY OF THE INVENTION

[0009] The present inventors have found that subjects suffering from cardiac conditions and disorders, such as congestive heart failure, that are not effectively or optimally treated with presently available methods surprisingly may be effectively treated with a composition that selectively reduces or inhibits the activity of GDF15. This may be effected by reducing the expression, level or amount, or biological activity, of GDF15 in a subject, which can be measured, for example, in the subject's serum or plasma.

[0010] The present invention provides methods and compositions for treating a subject having a cardiovascular disease, congestive or chronic heart failure, myocardial hypertrophy or hypotrophy, acute coronary syndrome, angina, or other cardiac disorder or condition, or who has suffered a cardiac event such as a myocardial infarction, or who has had, or is diagnosed as needing, a cardiac intervention, such as percutaneous coronary intervention, coronary artery bypass grafting, coronary angioplasty or stent placement.

[0011] The invention comprises compositions which reduce or inhibit the activity of GDF15, for example, by reducing the ability of GDF15 to bind to an endogenous binding partner (also referred to as cognate receptor or binding partner), for example, by competitively binding to GDF15 or to an endogenous binding partner, or by otherwise neutralizing the activity of GDF15. In certain embodiments, such a composition may comprise an antibody that binds to GDF15 or an endogenous binding partner, as well as a peptide or fusion molecule that comprises such an antibody. In certain other embodiments, the composition may comprise a peptide or small molecule that binds, for example, competitively binds, to GDF15 or to an endogenous binding partner, such that the activity of GDF15 is reduced or inhibited, for example, by reducing or inhibiting the ability of GDF15 to bind to its endogenous binding partner or otherwise neutralizing the activity of GDF15.

[0012] In certain embodiments, the invention comprises a method of treating a subject exhibiting one or more cardiac related characteristics, which can be symptoms of

cardiovascular disease or dysfunction, congestive or chronic heart failure, cardiac myopathies, cardiac hypertrophy, ischemic/reperfusion injury, dyspnea, idiopathic pulmonary arterial hypertension, ST-segment elevation myocardial infarction (STEMI), or other cardiac disorder or condition.

[0013] Such cardiac-related characteristics include:

(1) the subject exhibits reduced or below-normal peak oxygen consumption (VO_2);

(2) the subject has elevated or above normal levels of brain natriuretic protein (BNP) or an N-terminal fragment thereof (NT-ProBNP);

(3) the subject has elevated or above normal levels of troponin;

(4) the subject has elevated or above normal levels of C-reactive protein (CRP);

(5) the subject has an abnormal electrocardiogram test, or has been diagnosed as having abnormal physiological heart activity, for example, reduced auricular or ventricular ejection volumes;

(6) the subject exhibits signs or symptoms of chest pain or discomfort (angina), shortness of breath, and fatigue with activity or exertion; or subject exhibits reduced capacity in a test of physical capacity, such as the six minute walking test (6MWT) or incremental shuttle walk test (SWT);

(7) the subject has low normal or below normal levels of heart type fatty acid binding protein (hFABP);

(8) the subject exhibits cardiac hypertrophy or cardiac hypotrophy;

(9) the subject has experienced, or is diagnosed to be at risk of experiencing a myocardial infarction, or thromboembolic stroke; or

(10) the subject has had, or is diagnosed as needing, a coronary intervention, such as percutaneous coronary intervention, coronary artery bypass grafting, coronary angioplasty, stent placement, heart transplant, or defibrillator placement.

[0014] The above cardiac-related characteristics can also be used to monitor the subject's progress in response to treatment with a GDF15 modulator in accordance with the present invention, and to modify the dosing regimen if deemed clinically appropriate. In certain embodiments, the subject having a cardiovascular disease or cardiac disorder, such as

congestive or chronic heart failure (CHF), has previously been treated with a known cardiac treatment, but persists in exhibiting at least one of the above characteristics. In such cases, the present invention provides methods and compositions for avoiding or reducing the occurrence and/or severity of at least one of the above cardiac-related characteristics, and may also avoid or reduce the need for one of the cardiac interventions described above.

[0015] In one aspect, the invention provides a method of improving or increasing cardiac function in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a GDF15 modulator thereby to improve or increase cardiac function in the subject. Cardiac function can include any of the biochemical and physiological parameters discussed below.

[0016] In another aspect, the invention provides a method of treating a subject having a cardiac disorder or dysfunction, the method comprising administering an effective amount of a composition comprising a GDF15 modulator thereby to ameliorate a symptom of the cardiac disorder or dysfunction. The symptoms can include any of the biochemical and physiological parameters discussed below.

[0017] In another aspect, the invention provides a method of reducing or reversing cardiac hypotrophy in a subject exhibiting one or more symptoms of congestive heart failure, the method comprising administering an effective amount of a composition comprising a GDF15 modulator, wherein the composition ameliorates at least one symptom of cardiac hypotrophy in the subject. The symptoms can include any of the biochemical and physiological parameters discussed below.

[0018] In another aspect, the invention provides a method of treating or preventing congestive heart failure in a subject in need thereof, the method comprising administering an effective amount of a composition that reduces or inhibits a GDF15 activity in the subject, thereby to treat or prevent CHF in the subject. The symptoms can include any of the biochemical and physiological parameters discussed below.

[0019] In another aspect, the invention provides a method of reducing or reversing cardiac hypotrophy in a subject exhibiting one or more characteristics of congestive heart failure, the method comprising administering an effective amount of a composition that modulates the

activity of GDF15, thereby to reduce cardiac hypotrophy in the subject. The symptoms can include any of the biochemical and physiological parameters discussed below.

[0020] In certain embodiments, the subject has elevated GDF15 activity in a body fluid, for example, serum or plasma. In certain embodiments, elevated GDF15 activity means elevated GDF15 levels. In certain other embodiments, the subject exhibits a peak VO_2 of less than less than 14 mL/kg/min, an LVEF of less than 40%, BNP levels in excess of 100 pg/ml, serum cardiac troponin I (cTnI) levels in excess of 1.5 ng/mL, or any combination of the foregoing. In certain embodiments, the subject has already been diagnosed as having congestive heart failure.

[0021] In certain embodiments, the GDF15 modulator of the invention can reduce or inhibit GDF15 activity in the subject. In some embodiments, the GDF15 modulator inhibits the activity, expression or binding of GDF15 to its cognate receptor. In some embodiments, the GDF15 modulator binds GDF15. The GDF15 modulator can be an anti-GDF15 antibody, which can be humanized or human.

[0022] In certain embodiments, the subject exhibits above normal levels of a biomarker selected from the group consisting of cardiac troponin I, cardiac troponin T, brain natriuretic protein (BNP), N-terminal peptides derived from BNP (NT-proBNP), and cardiac fatty acid binding protein (cFABP).

[0023] Methods according to the invention can include administering an effective amount of a composition that inhibits a GDF15 mediated pathway, thereby to treat a subject having one or more of the following characteristics: cardiac hypertrophy or cardiac hypotrophy; signs or symptoms of chest pain or discomfort (angina), shortness of breath, and fatigue with activity or exertion; peak VO_2; elevated or above normal levels of troponin; elevated or above normal levels of brain natriuretic protein (BNP) or an N-terminal fragment thereof (NT-ProBNP); low normal or below normal levels of heart type fatty acid binding protein (hFABP); an abnormal electrocardiogram test or having abnormal heart physiology or activity, for example, reduced auricular or ventricular ejection volume; having experienced, or diagnosed to be at risk for angina, a myocardial infarction, or thromboembolic stroke; or having had or diagnosed as needing, a coronary intervention, such as percutaneous coronary intervention, coronary artery

bypass grafting, coronary angioplasty, stent placement, heart transplant, or defibrillator placement.

[0024] The use of the GDF15 modulator described herein can be used to improve or ameliorate at least one of the following characteristics in a subject, wherein the subject has been diagnosed as, or considered to be at risk of developing CHF, a cardiac myopathy, or heart failure:

(1) the subject exhibits reduced or below-normal peak oxygen consumption (VO_2);

(2) the subject has elevated or above normal levels of brain natriuretic protein (BNP) or an N-terminal fragment thereof (NT-ProBNP);

(3) the subject has elevated or above normal levels of troponin;

(4) the subject has elevated or above normal levels of C-reactive protein (CRP);

(5) the subject has an abnormal electrocardiogram test, or having abnormal heart physiology or activity, for example, reduced auricular or ventricular ejection volume;

(6) the subject exhibits signs or symptoms of chest pain or discomfort (angina), shortness of breath, and fatigue with activity or exertion, or subject exhibits reduced capacity in a test of physical capacity, such as the six minute walking test (6MWT) or incremental shuttle walk test (SWT);

(7) the subject has low normal or below normal levels of heart type fatty acid binding protein (hFABP);

(8) the subject exhibits cardiac hypertrophy or cardiac hypotrophy;

(9) the subject has experienced, or is diagnosed to be at risk of experiencing a myocardial infarction, or thromboembolic stroke; or

(10) the subject has had, or is diagnosed as needing, a coronary intervention, such as percutaneous coronary intervention, coronary artery bypass grafting, coronary angioplasty, stent placement, heart transplant, or defibrillator placement.

[0025] The above characteristics can be monitored to confirm the subject's response to treatment with GDF15 modulator in accordance with the present invention, and to modify the dosing regimen if deemed clinically appropriate. In certain embodiments, the subject having a cardiovascular disease or cardiac disorder, such as CHF, has previously been treated with a

known treatment, but persists in exhibiting at least one of the above characteristics. In such cases, the present invention provides methods and compositions for avoiding or reducing the occurrence and/or severity of at least one of the above cardiac-related characteristics, and may also avoid or reduce the need for one of the coronary interventions described above. In particular embodiments, the subject exhibits one or more of the following characteristics such that the subject is considered to have or be suffering from CHF, such that the subject may benefit from treatment according to the present invention. As used throughout the application, the term "considered to have CHF" or "considered to be suffering from CHF" means that following the disclosure of this application, one skilled in the art would expect that a subject would benefit from the administration of GDF15 inhibitors in accordance with the present invention. A subject is also "considered to have CHF" or "considered to be suffering from CHF" if a qualified clinical professional, after examination of information related to the subject, has made the professional judgment or diagnosis that the subject presently suffers from CHF. The term "considered to have CHF" or "considered to be suffering from CHF" means that, following the disclosure of this application, one skilled in the art would expect that a subject would benefit from the prophylactic or therapeutic administration of GDF15 inhibitors in accordance with the present invention. A subject is also term "considered to be at risk of developing CHF" if a qualified clinical professional, after examination of information related to the subject, has made the professional judgment or diagnosis that the subject presently a risk of developing CHF, sufficient to justify prophylactic or therapeutic intervention.

BRIEF DESCRIPTION OF THE FIGURES

[0026] **FIG. 1** is a graph illustrating GDF15 levels in human subjects who are not suffering from congestive heart failure ("non-CHF"); subjects who exhibit symptoms of congestive heart failure without cachexia ("CHF"); and subjects who exhibit symptoms of congestive heart failure with cachexia ("CHF Ca").

[0027] **FIG. 2** is a graph illustrating the correlation between GDF15 serum levels and severity of congestive heart failure. NYHA refers to the New York Heart Association classification system (I is least severe, IV is most severe).

[0028] **FIGS. 3A-3C** are graphs illustrating the correlation between GDF15 levels and peak volume of oxygen (VO_2), which is a marker of cardiac function. Peak VO_2 levels decrease

with increased GDF15 levels in 200 subjects with CHF (**FIG. 3A**), comprising 33 subjects with cachexia (**FIG. 3B**), and 167 subjects without cachexia, as a co-morbidity of CHF (**FIG. 3C**).

[0029] **FIG. 4** is a graph illustrating the correlation between GDF15 levels and transferrin saturation (TSAT), an indicator of anemia, which is a frequent co-morbidity of cardiac failure. The accompanying table illustrates transferrin levels; iron levels; hemoglobin levels ("Hb g/dl"), erythrocyte levels and ferritin levels.

[0030] **FIGS. 5A-5C** are graphs illustrating the correlation between GDF15 levels and various markers of decreased kidney function, which is a frequent co-morbidity of CHF. **FIG. 5A** shows that creatinine levels are increased with GDF15 levels in 200 subjects with CHF; **FIG. 5B** shows that urea levels are increased with GDF15 levels in 33 subjects with CHF and cachexia co-morbidity; and **FIG. 5C** shows that creatinine levels are increased with GDF15 levels in 167 subjects with CHF without cachexia co-morbidity.

[0031] **FIGS. 6A-6D** are graphs illustrating the correlation between GDF15 levels and various markers of kidney disease, a frequent co-morbidity of CHF, across subjects with CHF stages I-III (Stage IV was not included due to low number of subjects), including urea (**FIG. 6A**), where urea level increased with GDF15 level; uric acid (**FIG. 6B**), where uric acid level increased with GDF15 level; creatinine (**FIG. 6C**), where creatinine level increased with GDF15 level; and glomerular filtration rate (GFR) (**FIG. 6D**), where GFR decreased with GDF15 level.

[0032] **FIGS. 7A-7B** are graphs summarizing results from an experiment to demonstrate the activity of anti-GDF15 antibody 01G06 (■), dosed at 2 mg/kg, in immune-incompetent mice (ICR-SCID) bearing an HT-1080 fibrosarcoma tumor xenograft model. Treatment with antibody 01G06 reversed body weight loss (**FIG. 7A**), induced a gain of organ mass (liver, heart, spleen and kidney) and induced a gain of tissue mass (gonadal and gastrocnemius) (**FIG. 7B**), compared to the negative control (murine IgG (●)) and baseline (day 1). Vertical arrows indicate days where antibody was administered to test animals via intra-peritoneal injection (**FIG. 7A**).

[0033] **FIG. 8** is a graph illustrating the effects of systemic administration of a monoclonal antibody that binds to and inhibits human GDF15 (Hu01G06-127) on body weight in cachexic

mice bearing human tumor xenografts (▲) compared to similar mice following administration of human IgG (■) and compared to sham mice (no tumor) (●).

DETAILED DESCRIPTION OF THE INVENTION

[0034] The present invention provides methods and compositions for treating a subject having a cardiac related disease or disorder, for example, a subject having congestive or chronic heart failure, acute myocardial infarction, myocardial hypertrophy, and myocardial hypotrophy. The methods and compositions may be useful in treating a subject who exhibits at least one characteristic that is symptomatic of a cardiac myopathy or other heart failure, including one or more of:

(1) the subject exhibits reduced or below-normal peak oxygen consumption (VO_2);

(2) the subject has elevated or above normal levels of brain natriuretic protein (BNP) or an N-terminal fragment thereof (NT-ProBNP);

(3) the subject has elevated or above normal levels of troponin;

(4) the subject has elevated or above normal levels of C-reactive protein (CRP);

(5) the subject has an abnormal electrocardiogram (ECG) test, or having abnormal heart physiology or activity, for example, reduced auricular or ventricular ejection volume;

(6) the subject exhibits signs or symptoms of chest pain or discomfort (angina), shortness of breath, and fatigue with activity or exertion, or subject exhibits reduced capacity in a test of physical capacity, such as the six minute walking test (6MWT) or incremental shuttle walk test (SWT);

(7) the subject has low normal or below normal levels of heart type fatty acid binding protein (hFABP);

(8) the subject exhibits cardiac hypertrophy or cardiac hypotrophy;

(9) the subject has experienced, or is diagnosed to be at risk of experiencing a myocardial infarction, or thromboembolic stroke; or

(10) the subject has had, or is diagnosed as needing, a coronary intervention, such as percutaneous coronary intervention, coronary artery bypass grafting, coronary angioplasty, stent placement, heart transplant, or defibrillator placement.

[0035] Treatment in accordance with the methods and compositions described herein may improve or ameliorate one or more the characteristics or symptoms noted above. As used herein, "treat," "treating" and "treatment" mean the treatment of a disease in a mammal, *e.g.*, in a human. This includes: (a) inhibiting the disease, *i.e.*, arresting its development; and (b) relieving the disease, *i.e.*, causing regression of the disease state.

I. Heart Function Assays

[0036] Heart function can be assessed and monitored using a variety of approaches, including physiological and biochemical parameters, symptoms, functional markers and biomarkers of heart function. Physiological and biochemical parameters of heart function can include glomerular filtration rate (GFR); carotid artery ultrasound evaluation; carotid artery IMT (Intima-media thickness) and carotid plaque burden; left ventricular (LV) geometry and function; LV mass index; end-diastolic diameter and LV ejection fraction (echocardiography); forearm blood flow measurements, including endothelium-dependent and independent vasodilation of forearm; flow mediated dilation; and brachial artery ultrasound examination. Further parameters for assessment include cardiac dysfunction or dysrhythmia measured by echocardiography; pulmonary congestion measured by chest x-ray; reduced exercise capacity; abnormal haemodynamics at rest; cardiac output; systemic vascular resistance; left ventricular stroke volume; aortic pressure; left ventricular pressure; peak rate of change of left ventricular pressure during isovolumic contraction and relaxation; left ventricular end-diastolic pressure; myocardial oxygen consumption; and coronary flow reserve.

[0037] Symptoms of cardiac disorders, such as congestive heart failure, include chest pain, or angina; heart murmur or other abnormal sounds; fast or uneven pulse; an abnormal electrocardiogram or echocardiogram test; and an abnormal stress tests and electrocardiogram. Biomarkers of cardiac disorders, such as congestive heart failure, include: Brain Natriuretic Protein (BNP) and N-terminal fragments of the BNP propeptide (NT-ProBNP); troponins, particularly cardiac troponins (cTn), including troponin I and cardiac troponin I (cTnI); troponin T and cardiac troponin T (cTnT); troponin C (TnC); heart type fatty acid binding protein (hFABP); norepinephrine; atrial natriuretic peptide (ANP); galectin-3; C-reactive protein; tumor necrosis factor-α (TNF-α); interleukin-1; and interleukin-6.

[0038] In addition to each of the foregoing, the subject may also exhibit elevated levels of GDF15 activity relative to a baseline activity level present in subjects without the cardiac disorder or dysfunction.

[0039] Elevated levels of GDF15 activity can determined by measuring the level of GDF15 in a sample from a subject. The amount regarded as an "elevated level" of GDF15 may vary according to the particular tissue or body fluid of interest, as well as the particular assay that is utilized. Generally, an "elevated level" of GDF15 may be determined relative to a control distribution of subjects, for example, subjects without a cardiac disease or dysfunction, for example, CHF, and may be determined at a pre-specified cutoff of, for example, the 75th percentile (*i.e.*, upper quartile or 25%); 90th percentile (*i.e.*, upper 10%); or 95th percentile (*i.e.*, upper 5%). An "elevated level" of GDF15 may also be determined at a pre-specified GDF15 level above the mean, for example one standard deviation above the mean, or two standard deviations above the mean average GDF15 level of a group of control subjects without cardiac disease or dysfunction, for example, CHF. See, for example, Brown *et al.*, 2002, THE LANCET 359:2159-2163; Kempf *et al.*, 2011, NATURE MEDICINE, 17:581-588.

[0040] The preferred body sample is a body fluid, for example, a sample of blood plasma, however a sample of amniotic fluid, placental extract, whole blood, serum, buffy coat, urine, cerebrospinal fluid, seminal fluid, synovial fluid, or a tissue biopsy may also be suitable. A GDF15 concentration of >600 pg/ml, optionally >850 pg/ml, optionally >1000 pg/ml, optionally >1200 pg/ml, optionally >1500 pg/ml, optionally >1700 pg/ml, optionally >1900 pg/ml, optionally >2000 pg/ml, optionally >2500 pg/ml, and optionally >3000 pg/ml in a body fluid (*e.g.*, plasma) can represent an elevated level of GDF15. See, U.S. Patent No. 7,919,084 and Kempf *et al.*, 2007, J. AM. COLL. CARDIOL. 50:1054-1060.

[0041] The amount of GDF15 present in a body sample may be readily determined by, for example, immunoassays (*e.g.*, with a body fluid) or immunohistochemistry (*e.g.*, with sectionalized samples of a tissue biopsy) using an anti-GDF15 antibody. See Tsai *et al.*, 2013, PLOS ONE, 8:e55174.

[0042] A subject is considered to be suffering from congestive heart failure if the subject's peak measurement of oxygen uptake (peak VO_2) is less than a normal value, *e.g.,* 14 mL/kg/min. (See, Wilson *et al.*, 1995, J. AM. COLL. CARDIOL., 26:429-435; Lanier *et al.*, 2012,

J. EXERCISE SCIENCE & FITNESS, 10:23-27). However, it is understood that "normal ranges" of peak VO_2 can vary depending upon the specific laboratory and test.

[0043] A subject is considered to be suffering from congestive heart failure if the subject's left ventricular ejection fraction (LVEF) is below a normal value, *e.g.,* 40%. A subject whose LVEF is between 40 and 55% is considered to have below normal LVEF, and is considered to be at risk of CHF. LVEF can be measured, for example, using transthoracic echocardiography. (See, Cattadori *et al.*, 2011, J. CARDIAC FAILURE, 17:916-922). However, it is understood that "normal ranges" of LVEF can vary depending upon the specific laboratory and test.

[0044] A subject is considered to be suffering from congestive heart failure if the subject's serum BNP levels are in excess 100 pg/ml (mild CHF); or in excess of/below about 500 pg/ml (serious CHF). A subject is considered to be at risk of CHF if the subject's serum BNP levels are high normal or above normal ranges, at a level of 50 pg/ml or greater. The normal BNP range is considered to be at or below 50 pg/ml. "High normal" concentration is considered to be in the upper quarter (25%) of the normal range; preferably in the upper tenth (10%) of the normal range. See, for example, Strunk *et al.*, 2006, AM. J. MED., 119:69e1-11; Clerico *et al.*, 2012, CLIN. CHIM. ACTA, 414:112-119. However, it is understood that "normal ranges" of BNP can vary depending upon the specific laboratory and test.

[0045] A subject is considered to be suffering from congestive heart failure if the subject's serum cardiac troponin I (cTnI) levels are in excess of 1.5 ng/mL (mild CHF), or in excess of 3.1 ng/mL (serious CHF). A subject is considered to be at risk of CHF if his or her serum troponin levels are high normal or above normal ranges, at a level of 1.5 ng/mL or greater. "High normal" concentration is considered to be in the upper quarter (25%) of the normal range; preferably in the upper tenth (10%) of the normal range. See, for example, Galvani *et al.*, 1995, CIRCULATION, 95:2053-2059. However, it is understood that "normal ranges" of troponin can vary depending upon the specific laboratory and test. Additionally, one skilled in the art will recognize that other tests are available for the diagnosis of chronic or congestive heart failure, based upon the quantitation of troponins, including other tests quantitating cTnI, overall TnI, overall cardiac troponins, troponin T (TnT), including high sensitivity TnT (hsTnT), troponin C and/or other troponins. See Heringlake *et al.*, 2013, J. AM. COLL. CARDIOL. 61:672-68.

[0046] In certain embodiments, a subject is considered to be suffering from congestive heart failure if the subject's performance in a test of exercise or physiological capacity is indicative of reduced peak VO_2, for example, in the six mile walking test (6MWT) or a shuttle walking test (SWT). See, Pulz *et al.*, 2008, CANADIAN J. CARDIOLOGY, 24:131-135; Green *et al.*, 2001, J. SCIENCE AND MEDICINE IN SPORTS 4:292-300. For example, a subject who covers a distance less than or equal to approximately 500 m in the 6MWT, or exhibits peak VO_2 of approximately 16.5 ml/kg or less during the 6MWT, is considered to be suffering from CHF. See Faggiano *et al.*, 1997, AMERICAN HEART JOURNAL, 134:203-206. A subject who covers a distance less than or equal to approximately 450 m in the SWT, or exhibits peak VO_2 of less than approximately 14 ml/kg or less in the SWT is considered to be suffering from CHF. See, Morales *et al.*, 1999, AMERICAN HEART JOURNAL, 138:291-298.

[0047] Typically, a subject is diagnosed to be suffering from congestive heart failure if the subject experiences pathological cardiac hypertrophy, or increase in heart mass, which is due to underlying disease. Pathological cardiac hypertrophy is frequently referred to as 'compensated cardiac hypertrophy,' because the heart muscle grows larger in response to a decrease in functionality of myocardial tissue. Pathological or compensated cardiac hypertrophy is different from physiological cardiac hypertrophy, or 'athlete's heart,' wherein a heart muscle grows larger in response to prolonged exercise and exercise regimens. Cardiac hypertrophy may be diagnosed using known techniques and indices. For example, left ventricular hypertrophy (LVH) can be diagnosed using echocardiography. The left ventricular myocardium is normally from about 0.6 to 1.1 cm in thickness at the end of diastole. If the myocardium is more than 1.1 cm thick, the diagnosis of LVH can be made. Cardiac hypertrophy can also result from dilated cardiomyopathy (DCM), wherein a portion of the myocardium may become dilated without apparent reason. DCM may be diagnosed by examination of chest x-rays, electrocardiogram or echocardiogram. (See, myclevelandclinic.org/heart/disorders/hcm/default.aspx.)

[0048] Similarly, a subject is considered to be suffering from congestive heart failure if the subject experiences or is diagnosed with pathological cardiac hypotrophy, or significant decrease in heart mass. Cardiac hypotrophy is often due to reduced left ventricular mass (LVM). Clinically, LVM is often observed in cases of anorexia nervosa, and can be diagnosed by echocardiogram. See Romano *et al.*, 2003, AM. J. CLIN. NUT., 77:308-313; Meczekalski *et al.*, 2013, MATURITAS, 75:215-220. It is understood that the methods and compositions of the

invention can be useful in treating cardiac hypertrophy or cardiac hypotrophy as the methods and conditions ameliorate the symptoms of each condition to help restore normal heart structure, heart physiology, and/or cardiac function.

[0049] The above parameters can be easily measured before, during and after treatment with a GDF15 modulator.

[0050] In certain embodiments, treatment of a subject may improve the left ventricular ejection fraction by at least 1% (compared to the left ventricular ejection fraction prior to treatment). For example, treatment of a subject may improve the left ventricular ejection fraction by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%. The treatment may continue until the subject has attained a left ventricular ejection fraction of at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, or at least 50%. The treatment may provide a residual improvement in the left ventricular ejection fraction for at least 5 minutes, at least 10 minutes, at least 20 minutes, at least 30 minutes, at least 45 minutes, at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 12 hours, at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, or at least 28 days.

[0051] In certain embodiments, treatment of a subject may improve the cardiac output by at least 1% (compared to the cardiac output prior to treatment). For example, treatment of a subject may improve the cardiac output by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%. The treatment may continue until the subject has attained a cardiac output of at least 2.5L/min, at least 3.0 L/min, at least 3.5 L/min, at least 4.0 L/min, at least 4.5 L/min, at least 5.0 L/min, or at least 5.25 L/min. The treatment may provide a residual improvement in the cardiac output for at least 5 minutes, at least 10 minutes, at least 20 minutes, at least 30 minutes, at least 45 minutes, at least 1 hour, at least 2 hours, at least 3

hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 12 hours, at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, or at least 28 days.

[0052] In certain embodiments, treatment of a subject may improve the left ventricular stroke volume by at least 1% (compared to the stroke volume prior to treatment). For example, treatment of a subject may improve the left ventricular stroke volume by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%. The treatment may continue until the subject has attained a left ventricular stroke volume of at least 27 ml, at least 30 ml, at least 35 ml, at least 40 ml, at least 45 ml, at least 50 ml, at least 55 ml, at least 60 ml, at least 65 ml, or at least 70 ml. The treatment may provide a residual improvement in left ventricular stroke volume for at least 5 minutes, at least 10 minutes, at least 20 minutes, at least 30 minutes, at least 45 minutes, at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 12 hours, at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, or at least 28 days.

[0053] In certain embodiments, treatment of a subject may reduce the systemic vascular resistance by at least 1% (compared to the systemic vascular resistance prior to treatment). For example, treatment of a subject may reduce the systemic vascular resistance by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%. The treatment may continue until the subject has attained a systemic vascular resistance of no more than 3500 dyn·s/cm^5, no more than 3000 dyn·s/cm^5, no more than 2500 dyn·s/cm^5, no more than 2000 dyn·s/cm^5, or no more than 1600 dyn·s/cm^5. The treatment may provide a residual improvement in the systemic vascular resistance for at least 5 minutes, at least 10 minutes, at least 20 minutes, at least 30 minutes, at least 45 minutes, at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 12 hours, at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, or at least 28 days.

II. Comorbidities of Chronic or Congestive Heart Failure

[0054] Chronic heart failure is frequently complicated by the occurrence of comorbidities, which may range from minor to serious in degree. It is an advantage of the present invention that inhibition of GDF15 may additionally assist in reducing one or more common comorbidities of CHF. Among the common comorbidities associated with CHF are cachexia, chronic kidney disease, anemia, iron deficiency and hypertension. Accordingly, the present invention includes methods of increasing cardiac function in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a GDF15 inhibitor to increase cardiac function in a subject who exhibits one or more comorbidity of CHF. For example, the subject suffering from cardiac dysfunction or CHF may exhibit a comorbidity of cachexia, chronic kidney disease, anemia, iron deficiency or hypertension.

III. GDF15 Modulators

[0055] As used herein a "GDF15 modulator" is understood to mean an agent that reduces or inhibits GDF15 activity, which can result from reduced expression, amount, or biological activity or function, of GDF15. GDF15 modulators or modulating agents useful in the practice of the invention may comprise an anti-GDF15 antibody, an anti-GDF15 receptor antibody, soluble GDF15 mimetics or analogs that prevent GDF15 from binding to its cognate binding partner, a soluble GDF15 receptor mimetic or analog that prevents GDF15 from binding to its cognate binding partner. Additional exemplary GDF15 modulating agents include small molecule inhibitors of GDF15 or a GDF15 receptor, interfering nucleic acids (for example, interfering RNA or antisense nucleic acids (for example, antisense DNA or RNA) that interfere with expression of endogenous GDF15 or a cognate receptor.

[0056] In a preferred embodiment, the GDF15 modulating agent can comprise an anti-GDF15 antibody, which is humanized or human. As used herein, unless otherwise indicated, the term "antibody" is understood to mean an intact antibody (*e.g.*, an intact monoclonal antibody) or antigen-binding fragment of an antibody, including an intact antibody or antigen-binding fragment of an antibody (*e.g.*, a phage display antibody including a fully human antibody, a semisynthetic antibody or a fully synthetic antibody) that has been optimized, engineered or chemically conjugated. Examples of antibodies that have been optimized are affinity-matured antibodies. Examples of antibodies that have been engineered are Fc optimized antibodies, and multispecific antibodies (*e.g.*, bispecific antibodies). Examples of antigen-binding fragments include Fab, Fab', $F(ab')_2$, Fv, single chain antibodies (*e.g.*, scFv),

minibodies and diabodies. An antibody conjugated to a toxin moiety is an example of a chemically conjugated antibody.

[0057] In certain embodiments, the antibody comprises: (a) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3} and (b) an immunoglobulin light chain variable region, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding GDF15 or a GDF15 receptor. The CDR_{H1}, CDR_{H2}, and CDR_{H3} sequences are interposed between immunoglobulin framework (FR) sequences. In certain other embodiments, the antibody comprises (a) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, and (b) an immunoglobulin heavy chain variable region, wherein the IgG light chain variable region and the IgG heavy chain variable region together define a single binding site for binding GDF15 or a GDF15 receptor. The CDR_{L1}, CDR_{L2}, and CDR_{L3} sequences are interposed between immunoglobulin FR sequences. In certain other embodiments, the antibody comprises: (a) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3} and (b) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding GDF15 or a GDF15 receptor. Exemplary anti-GDF15 antibodies are described, for example, in U.S. Patent Publication No. US 2014-0193427-A1, the disclosure of which is incorporated by reference herein for all purposes.

[0058] Exemplary anti-GDF15 antibodies useful in the methods and compositions of the invention may, for example, include a heavy chain variable region comprising any one of the nine sets of CDR_{H1}, CDR_{H2}, and CDR_{H3} region sequences set forth in Table 1 below.

TABLE 1

	CDR_{H1}	CDR_{H2}	CDR_{H3}
1	DYNMD (SEQ ID NO:1)	QINPNNGGIFFNQKFKG (SEQ ID NO:4)	EAITTVGAMDY (SEQ ID NO:13)
2	DYNMD (SEQ ID NO:1)	QINPNNGGIFFNQKFQG (SEQ ID NO:5)	EAITTVGAMDY (SEQ ID NO:13)
3	DYNMD (SEQ ID NO:1)	QINPYNHLIFFNQKFQG (SEQ ID NO:6)	EAITTVGAMDY (SEQ ID NO:13)
4	DYNMD (SEQ ID NO:1)	QINPNNGLIFFNQKFQG (SEQ ID NO:7)	EAITTVGAMDY (SEQ ID NO:13)
5	DYNMD (SEQ ID NO:1)	QINPNNGLIFFNQKFKG (SEQ ID NO:8)	EAITTVGAMDY (SEQ ID NO:13)
6	DYNMD (SEQ ID NO:1)	QINPYNHLIFFNQKFKG (SEQ ID NO:9)	EAITTVGAMDY (SEQ ID NO:13)
7	TYGMGVS (SEQ ID NO:2)	HIYWDDDKRYNPSLKS (SEQ ID NO:10	RGYDDYWGY (SEQ ID NO:14)
8	TYGMGVS (SEQ ID NO:2)	HIYWDDDKRYNPSLKT (SEQ ID NO:11)	RGYDDYWGY (SEQ ID NO:14)
9	TYGMGVG (SEQ ID NO:3)	DIW-WDDDKYYNPSLKS (SEQ ID NO:12)	RGHYSAMDY (SEQ ID NO:15)

[0059] Exemplary anti-GDF15 antibodies useful in the methods and compositions of the invention may, for example, include a light chain variable region comprising any one of the four sets of CDR_{L1}, CDR_{L2}, and CDR_{L3} region sequences set forth in Table 2 below.

TABLE 2

	$CDRL_1$	$CDRL_2$	$CDRL_3$
1	RTSENLHNYLA (SEQ ID NO:16)	DAKTLAD (SEQ ID NO:18)	QHFWSSPYT (SEQ ID NO:21)
2	RTSENLHNYLA (SEQ ID NO:16)	DAKTLAD (SEQ ID NO:18)	QHFWSDPYT (SEQ ID NO:22)
3	KASQNVGTNVA (SEQ ID NO:17)	SASYRYS (SEQ ID NO:19)	QQYNNYPLT (SEQ ID NO:23)
4	KASQNVGTNVA (SEQ ID NO:17)	SPSYRYS (SEQ ID NO:20)	QQYNSYPHT (SEQ ID NO:24)

[0060] Exemplary anti-GDF-15 antibodies useful in the practice of the invention are described in U.S. Patent Publication No. US 2014-0193427-A1, including 01G06, 03G05, 04F08, 06C11, 08G01, 14F11, 17B11, as well as human or humanized forms thereof. In certain embodiments, the antibodies disclosed herein (*e.g.*, 01G06, 03G05, 04F08, 06C11, 08G01, 14F11, or 17B11, or humanized forms thereof) are used to treat CHF or another cardiac-related disease or disorder who exhibits symptoms of CHF or who is diagnosed as having CHF or at risk of having CHF. In some embodiments, the antibodies reverse a

symptom or characteristic of CHF or another cardiac-related disease or disorder by at least 2%, 5%, 10%, 15%, 20%, 25%, 30% or 35%.

[0061] In a preferred embodiment, an anti-GDF-15 antibody useful in the practice of the invention is referred to as 01G06 in U.S. Patent Publication No. US 2014-0193427-A1. Humanized forms of the 01G06 antibody are listed below together with the amino acid sequences of their respective heavy and light chain variable regions. Exemplary humanized anti-GDF-15 antibodies include: Hu01G06-1; Hu01G06-46; Hu01G06-52; Hu01G06-100; Hu01G06-101; Hu01G06-102; Hu01G06-103; Hu01G06-104; Hu01G06-105; Hu01G06-106; Hu01G06-107; Hu01G06-108; Hu01G06-109; Hu01G06-110; Hu01G06-111; Hu01G06-112; Hu01G06-113; Hu01G06-114; Hu01G06-122; Hu01G06-127; Hu01G06-135; Hu01G06-138; Hu01G06-146; Hu06C11-1; Hu06C11-27; Hu06C11-30; Hu14F11-1; Hu14F11-23; Hu14F11-24; Hu14F11-39; and Hu14F11-47. The amino acid sequences for the heavy chain and light chain for each of the aforementioned antibodies is set forth below in Table 3.

[0062]

TABLE 3

Antibody Name	Light Chain	Heavy Chain
01G06 (murine)	SEQ ID NO:25	SEQ ID NO:37
Hu01G06-1	SEQ ID NO:26	SEQ ID NO:38
Hu01G06-46	SEQ ID NO:27	SEQ ID NO:39
Hu01G06-52	SEQ ID NO:27	SEQ ID NO:40
Hu01G06-100	SEQ ID NO:27	SEQ ID NO:41
Hu01G06-101	SEQ ID NO:27	SEQ ID NO:42
Hu01G06-102	SEQ ID NO:27	SEQ ID NO:43
Hu01G06-103	SEQ ID NO:27	SEQ ID NO:44
Hu01G06-104	SEQ ID NO:27	SEQ ID NO:45
Hu01G06-105	SEQ ID NO:28	SEQ ID NO:41
Hu01G06-106	SEQ ID NO:28	SEQ ID NO:42
Hu01G06-107	SEQ ID NO:28	SEQ ID NO:43
Hu01G06-108	SEQ ID NO:28	SEQ ID NO:44
Hu01G06-109	SEQ ID NO:28	SEQ ID NO:45
Hu01G06-110	SEQ ID NO:29	SEQ ID NO:41
Hu01G06-111	SEQ ID NO:29	SEQ ID NO:42
Hu01G06-112	SEQ ID NO:29	SEQ ID NO:43
Hu01G06-113	SEQ ID NO:29	SEQ ID NO:44
Hu01G06-114	SEQ ID NO:29	SEQ ID NO:45
Hu01G06-122	SEQ ID NO:29	SEQ ID NO:46

Antibody Name	Light Chain	Heavy Chain
Hu01G06-127	SEQ ID NO:30	SEQ ID NO:47
Hu01G06-135	SEQ ID NO:29	SEQ ID NO:48
Hu01G06-138	SEQ ID NO:29	SEQ ID NO:49
Hu01G06-146	SEQ ID NO:30	SEQ ID NO:49
06C11 (murine)	SEQ ID NO:31	SEQ ID NO:50
Hu06C11-1	SEQ ID NO:32	SEQ ID NO:38
Hu06C11-27	SEQ ID NO:33	SEQ ID NO:51
Hu06C11-30	SEQ ID NO:33	SEQ ID NO:52
14F11 (murine)	SEQ ID NO:34	SEQ ID NO:53
Hu14F11-1	SEQ ID NO:35	SEQ ID NO:54
Hu14F11-23	SEQ ID NO:35	SEQ ID NO:55
Hu14F11-24	SEQ ID NO:32	SEQ ID NO:54
Hu14F11-39	SEQ ID NO:36	SEQ ID NO:56
Hu14F11-47	SEQ ID NO:36	SEQ ID NO:57

[0063] It is understood that the antibodies described herein can be designed, tested, and formulated using techniques known in the art.

[0064] SEQ ID NO:25

```
  1 diqmtqspas lsasvgetvt itcrtsenlh nylawyqqkq gkspqllvyd aktladgvps
 61 rfsgsgsgtq yslkinslqp edfgsyycqh fwsspytfgg gtkleikrad aaptvsifpp
121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt
181 ltkdeyerhn sytceathkt stspivksfn rnec
```

[0065] SEQ ID NO:26

```
  1 diqmtqspas lsasvgetvt itcrtsenlh nylawyqqkq gkspqllvyd aktladgvps
 61 rfsgsgsgtq yslkinslqp edfgsyycqh fwsspytfgg gtkleikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0066] SEQ ID NO:27

```
  1 diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkspkllvyd aktladgvps
 61 rfsgsgsgtd ytltisslqp edfatyycqh fwsspytfgq gtkleikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0067] SEQ ID NO:29

```
  1 diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkapklliyd aktladgvps
 61 rfsgsgsgtd ytltisslqp edfatyycqh fwsspytfgq gtkleikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0068] SEQ ID NO:28

```
  1 diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkspklliyd aktladgvps
 61 rfsgsgsgtd ytltisslqp edfatyycqh fwsspytfgq gtkleikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0069] SEQ ID NO:32

```
  1 divmtqsqkf mstsvgdrvs vtckasqnvg tnvawfqqkp gqspkaliys asyrysgvpd
 61 rftgsgsgtd filtisnvqs edlaeyfcqq ynnypltfga gtklelkrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0070] SEQ ID NO:33

```
  1 diqmtqspss lsasvgdrvt itckasqnvg tnvawfqqkp gkapksliys asyrysgvps
 61 rfsgsgsgtd ftltisslqp edfatyycqq ynnypltfgq gtkleikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0071] SEQ ID NO:35

```
  1 divmtqsqkf mstsvgdrvs vtckasqnvg tnvawyqqkp gqspkaliys psyrysgvpd
 61 rftgsgsgtd ftltisnvqs edlaeyfcqq ynsyphtfgg gtklemkrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0072] SEQ ID NO:36

```
  1 diqmtqspss lsasvgdrvt itckasqnvg tnvawfqqkp gkspkaliys psyrysgvps
 61 rfsgsgsgtd ftltisslqp edfatyfcqq ynsyphtfgq gtkleikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0073] SEQ ID NO:37

```
  1 evllqqsgpe lvkpgasvki pckasgytft dynmdwvkqs hgkslewigq inpnnggiff
 61 nqkfkgkatl tvdkssntaf mevrsltsed tavyycarea ittvgamdyw gqgtsvtvss
121 akttppsvyp lapgsaaqtn smvtlgclvk gyfpepvtvt wnsgslssgv htfpavlqsd
181 lytlsssvtv psstwpsetv tcnvahpass tkvdkkivpr dcgckpcict vpevssvfif
241 ppkpkdvlti tltpkvtcvv vdiskddpev qfswfvddve vhtaqtqpre eqfnstfrsv
301 selpimhqdw lngkefkcrv nsaafpapie ktisktkgrp kapqvytipp pkeqmakdkv
361 sltcmitdff peditvewqw ngqpaenykn tqpimdtdgs yfvysklnvq ksnweagntf
421 tcsvlheglh nhhtekslsh spgk
```

[0074] SEQ ID NO:30

```
  1 diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkspklliyd aktladgvps
 61 rfsgsgsgtd ytltisslqp edfatyycqh fwsdpytfgq gtkleikrtv aapsvfifpp
121 sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt
181 lskadyekhk vyacevthqg lsspvtksfn rgec
```

[0075] SEQ ID NO:38

```
  1 evllqqsgpe lvkpgasvki pckasgytft dynmdwvkqs hgkslewigq inpnnggiff
 61 nqkfkgkatl tvdkssntaf mevrsltsed tavyycarea ittvgamdyw gqgtsvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0076] SEQ ID NO:39

```
  1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgkslewigq inpnnggiff
 61 nqkfkgratl tvdtstntay melrslrsdd tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0077] SEQ ID NO:40

```
  1 qvqlvqsgae vkkpgssvkv sckasgytft dynmdwvrqa pgkslewigq inpnnggiff
 61 nqkfkgratl tvdkstntay melsslrsed tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0078] SEQ ID NO:41

```
  1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqglewmgq inpnnggiff
 61 nqkfkgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0079] SEQ ID NO:43

```
  1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqslewmgq inpnnggiff
 61 nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
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[0080] SEQ ID NO:42

```
  1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqglewmgq inpnnggiff
 61 nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0081] SEQ ID NO:44

```
  1 qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpnnggiff
 61 nqkfkgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0082] SEQ ID NO:45

```
  1 qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpnnggiff
 61 nqkfqgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0083] SEQ ID NO:46

```
  1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqslewmgq inpynhliff
 61 nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0084] SEQ ID NO:47

```
  1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqslewmgq inpnngliff
 61 nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0085] SEQ ID NO:48

```
  1 qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpnngliff
 61 nqkfkgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0086] SEQ ID NO:49

```
  1 qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpynhliff
 61 nqkfkgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtlvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0087] SEQ ID NO:38

```
  1 evllqqsgpe lvkpgasvki pckasgytft dynmdwvkqs hgkslewigq inpnnggiff
 61 nqkfkgkatl tvdkssntaf mevrsltsed tavyycarea ittvgamdyw gqgtsvtvss
121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
421 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0088] SEQ ID NO:51

```
  1 qvtlkesgpa lvkptqtltl tctfsgfsln tygmgvswir qppgkalewl ahiywdddkr
 61 ynpslktrlt iskdtsknqv vltitnvdpv dtavyycaqr gyddywgywg qgtlvtissa
121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp
241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns
301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem
361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq
421 qgnvfscsvm healhnhytq kslslspgk
```

[0089] SEQ ID NO:52

```
  1 qvtlkesgpt lvkptqtltl tctfsgfsln tygmgvswir qppgkglewl ahiywdddkr
 61 ynpslksrlt itkdtsknqv vltitnmdpv dtatyycaqr gyddywgywg qgtlvtvssa
121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp
241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns
301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem
361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq
421 qgnvfscsvm healhnhytq kslslspgk
```

[0090] SEQ ID NO:54

```
  1 qvtlkesgpg ilqpsqtlsl tcsfsgfsls tygmgvgwir qpsgkglewl adiwwdddky
 61 ynpslksrlt iskdtssnev flkiaivdta dtatyycarr ghysamdywg qgtsvtvssa
121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp
241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns
301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem
361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq
421 qgnvfscsvm healhnhytq kslslspgk
```

[0091] SEQ ID NO:55

```
  1 qvtlkesgpg ilqpsqtlsl tcsfsgfsln tygmgvswir qpsgkglewl ahiywdddkr
 61 ynpslksrlt iskdasnnrv flkitsvdta dtatyycaqr gyddywgywg qgtlvtisaa
121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp
241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns
301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem
361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq
421 qgnvfscsvm healhnhytq kslslspgk
```

[0092] SEQ ID NO:56

```
  1 qitlkesgpt lvkptqtltl tctfsgfsls tygmgvgwir qppgkalewl adiwwdddky
 61 ynpslksrlt itkdtsknqv vltmtnmdpv dtatyycarr ghysamdywg qgtlvtvssa
121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp
241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns
301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem
361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq
421   nvfscsvm healhnhytq kslslspgk
```

[0093] SEQ ID NO:57

```
  1 qvtlkesgpa lvkptqtltl tctfsgfsls tygmgvgwir qppgkalewl adiwwdddky
 61 ynpslksrlt iskdtsknqv vltmtnmdpv dtavyycarr ghysamdywg qgtlvtvssa
121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp
241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns
301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem
361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq
421 qgnvfscsvm healhnhytq kslslspgk
```

[0094] SEQ ID NO:50

```
  1 qvtlkesgpg ilqpsqtlsl tcsfsgfsln tygmgvswir qpsgkglewl ahiywdddkr
 61 ynpslksrlt iskdasnnrv flkitsvdta dtatyycaqr gyddywgywg qgtlvtisaa
121 kttppsvypl apgsaaqtns mvtlgclvkg yfpepvtvtw nsgslssgvh tfpavlqsdl
181 ytlsssvtvp sstwpsetvt cnvahpasst kvdkkivprd cgckpcictv pevssvfifp
241 pkpkdvltit ltpkvtcvvv diskddpevq fswfvddvev htaqtqpree qfnstfrsvs
301 elpimhqdwl ngkefkcrvn saafpapiek tisktkgrpk apqvytippp keqmakdkvs
361 ltcmitdffp editvewqwn gqpaenyknt qpimdtdgsy fvysklnvqk snweagntft
421 csvlheglhn hhtekslshs pgk
```

[0095] SEQ ID NO:31

```
  1 divmtqsqkf mstsvgdrvs vtckasqnvg tnvawfqqkp gqspkaliys asyrysgvpd
 61 rftgsgsgtd filtisnvqs edlaeyfcqq ynnypltfga gtklelkrad aaptvsifpp
121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt
181 ltkdeyerhn sytceathkt stspivksfn rnec
```

[0096] SEQ ID NO:53

```
  1 qvtlkesgpg ilqpsqtlsl tcsfsgfsls tygmgvgwir qpsgkglewl adiwwdddky
 61 ynpslksrlt iskdtssnev flkiaivdta dtatyycarr ghysamdywg qgtsvtvssa
121 kttppsvypl apgsaaqtns mvtlgclvkg yfpepvtvtw nsgslssgvh tfpavlqsdl
181 ytlsssvtvp sstwpsetvt cnvahpasst kvdkkivprd cgckpcictv pevssvfifp
241 pkpkdvltit ltpkvtcvvv diskddpevq fswfvddvev htaqtqpree qfnstfrsvs
301 elpimhqdwl ngkefkcrvn saafpapiek tisktkgrpk apqvytippp keqmakdkvs
361 ltcmitdffp editvewqwn gqpaenyknt qpimdtdgsy fvysklnvqk snweagntft
421 csvlheglhn hhtekslshs pgk
```

[0097] SEQ ID NO:34

```
  1 divmtqsqkf mstsvgdrvs vtckasqnvg tnvawyqqkp gqspkaliys psyrysgvpd
 61 rftgsgsgtd ftltisnvqs edlaeyfcqq ynsyphtfgg gtklemkrad aaptvsifpp
121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt
181 ltkdeyerhn sytceathkt stspivksfn rnec
```

[0098] The antibody may be a neutralizing antibody, which reduces GDF15 activity. For example, the antibody may reduce GDF15 activity in an *in vivo* assay (see, *e.g.*, Johnen *et al.*, 2007, NATURE MEDICINE 13:1333-1340) by at least 10%, preferably 20%, 30% or 40%, and more preferably at least about 50%, 60%, 80% or 90% of GDF15 compared to GDF15 activity measured in the same assay under the same conditions in the absence of the antibody. The antibody may selectively and/or significantly reduce or inhibit the binding of GDF15 to its endogenous receptor. As used herein, the term "significantly reduces or inhibits binding" of GDF15 to its receptor is understood to mean that the antibody inhibits GDF15 binding with a potency or percent inhibition that measures at least 10%, preferably 20%, 30% or 40%, and more preferably at least about 50%, 60%, 80% or 90% of GDF15 (serum level/activity) in the absence of said antibody. Binding can be measured using a direct or sandwich enzyme-linked immunosorbent assay (ELISA), as described, *e.g.*, in Tsai *et al.*, 2013, PLOS ONE, 8:e55174. As used herein, the term "selectively" in the context of an antibody that binds to GDF15 or GDF15 receptor is understood to mean that the antibody binds GDF15 or a GDF15 receptor with a binding affinity that is at least two, three, four, five or ten times greater than that of a functionally unrelated protein or another member of the TGF-β superfamily or a receptor of a member of the TGF-β superfamily.

[0099] Methods for reducing or eliminating the antigenicity of antibodies and antibody fragments are known in the art. When the antibodies are to be administered to a human, the antibodies preferably are "humanized" to reduce or eliminate antigenicity in humans. Preferably, each humanized antibody has the same or substantially the same affinity for the antigen as the non-humanized mouse antibody from which it was derived.

[00100] In one humanization approach, chimeric proteins are created in which mouse immunoglobulin constant regions are replaced with human immunoglobulin constant regions. See, *e.g.*, Morrison *et al.*,1984, PROC. NAT. ACAD. SCI. 81:6851-6855, Neuberger *et al.*, 1984, NATURE 312:604-608; U.S. Patent Nos. 6,893,625 (Robinson); 5,500,362 (Robinson); and 4,816,567 (Cabilly).

[00101] In an approach known as CDR grafting, the CDRs of the light and heavy chain variable regions are grafted into frameworks from another species. For example, murine CDRs can be grafted into human FRs. In some embodiments, the CDRs of the light and heavy chain variable regions of an anti-GDF15 antibody are grafted into human FRs or consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. CDR grafting is described in U.S. Patent Nos. 7,022,500 (Queen); 6,982,321 (Winter); 6,180,370 (Queen); 6,054,297 (Carter); 5,693,762 (Queen); 5,859,205 (Adair); 5,693,761 (Queen); 5,565,332 (Hoogenboom); 5,585,089 (Queen); 5,530,101 (Queen); Jones *et al.*, 1986, NATURE 321: 522-525; Riechmann *et al.*, 1988, NATURE 332: 323-327; Verhoeyen *et al.*, 1988, SCIENCE 239: 1534-1536; and Winter, 1998, FEBS LETT 430: 92-94.

[00102] In an approach called "SUPERHUMANIZATION™," human CDR sequences are chosen from human germline genes, based on the structural similarity of the human CDRs to those of the mouse antibody to be humanized. See, *e.g.*, U.S. Patent No. 6,881,557 (Foote); and Tan *et al.*, 2002, J. IMMUNOL. 169:1119-1125.

[00103] Other methods to reduce immunogenicity include "reshaping," "hyperchimerization," and "veneering/resurfacing." See, *e.g.*, Vaswami *et al.*, 1998, ANNALS OF ALLERGY, ASTHMA, & IMMUNOL. 81:105; Roguska *et al.*, 1996, PROT. ENGINEER 9:895-904; and U.S. Patent No. 6,072,035 (Hardman). In the veneering/resurfacing approach, the surface accessible amino acid residues in the murine antibody are replaced by amino acid residues

more frequently found at the same positions in a human antibody. This type of antibody resurfacing is described, *e.g.*, in U.S. Patent No. 5,639,641 (Pedersen).

[00104] Another approach for converting a mouse antibody into a form suitable for medical use in humans is known as ACTIVMAB™ technology (Vaccinex, Inc., Rochester, NY), which involves a vaccinia virus-based vector to express antibodies in mammalian cells. High levels of combinatorial diversity of IgG heavy and light chains are said to be produced. See, *e.g.*, U.S. Patent Nos. 6,706,477 (Zauderer); 6,800,442 (Zauderer); and 6,872,518 (Zauderer).

[00105] Another approach for converting a mouse antibody into a form suitable for use in humans is technology practiced commercially by KaloBios Pharmaceuticals, Inc. (Palo Alto, CA). This technology involves the use of a proprietary human "acceptor" library to produce an "epitope focused" library for antibody selection.

[00106] Another approach for modifying a mouse antibody into a form suitable for medical use in humans is HUMAN ENGINEERING™ technology, which is practiced commercially by XOMA (US) LLC. See, *e.g.*, PCT Publication No. WO 93/11794 and U.S. Patent Nos. 5,766,886 (Studnicka); 5,770,196 (Studnicka); 5,821,123 (Studnicka); and 5,869,619 (Studnicka).

[00107] Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of an antibody.

[00108] In addition, it is possible to create fully human antibodies in mice. Fully human mAbs lacking any non-human sequences can be prepared from human immunoglobulin transgenic mice by techniques referenced in, *e.g.*, Lonberg *et al.,* NATURE 368:856-859, 1994; Fishwild *et al.,* NATURE BIOTECHNOLOGY 14:845-851, 1996; and Mendez *et al.,* NATURE GENETICS 15:146-156, 1997. Fully human mAbs can also be prepared and optimized from phage display libraries by techniques referenced in, *e.g.*, Knappik *et al.,* J. MOL. BIOL. 296:57-86, 2000; and Krebs *et al.,* J. IMMUNOL. METH. 254:67-84 2001).

[00109] It is contemplated that variants and derivatives of GDF15 that act as decoys can be useful in the practice of the invention. For example, through deletion analysis, it may be possible to identify smaller biologically active fragments of GDF15 that compete with endogenous GDF15 for its cognate receptor. Similarly, it is possible to create soluble

biologically active fragments of the GDF15 receptor that compete with endogenous GDF15 receptor for available GDF. For example, "biologically active fragments" include, but are not limited to, fragments of a naturally-occurring GDF15 (or homolog) or a GDF15 receptor (or homolog) that compete with endogenous GDF15 or an endogenous GDF15 receptor, respectively, for binding to a cognate binding partner (*e.g.*, GDF15 receptor or GDF15, respectively).

[00110] It is contemplated that antisense nucleic acids (DNA and RNA) and small interfering nucleic acids (*e.g.*, siRNAs) can be designed and used using techniques known in the art. Exemplary siRNA inhibitors of GDF15 include siRNAs from Santa Cruz Biotech (Catalog No. sc-39799, targeting mouse GDF15; and Catalog No. sc-39798, targeting human GDF15), siRNAs from Life Technologies (Cat. Nos. AM16708, 4392420, and 1299001, targeting human GDF15; and Cat. Nos. 1320001 and 4390771, targeting mouse GDF15; and Cat. Nos. 1330001 and 4390771, targeting rat GDF15), siRNAs from Fisher Scientific (Catalog No. NC0683807, targeting human GDF15), siRNAs from Origene (Catalog No. SR306321, targeting human GDF15), siRNAs from amsbio (Catalog No. SR509800, targeting rate GDF15), siRNAs from Dharmacon (including Catalog No. D-019875-02, targeting human GDF15), siRNAs from Sigma-Aldrich (Catalog No. EHU052901, targeting human GDF15), and siRNAs described in Kim *et al.*, 2005, MOLECULAR CANCER THERAPEUTICS, 4:487-493, Chang *et al.*, 2007, MOL. CANCER THERAPEUTICS, 6:2271-2279, and Boyle *et al.*, 2009, J. INVEST. DERMATOL., 129:383-391.

IV. Formulation and Delivery of GDF15 Modulators

[00111] Pharmaceutical compositions containing GDF15 modulators, such as those disclosed herein, can be formulated into dosage forms or dosage units using standard formulation techniques. However, the pharmaceutical composition should be formulated to be compatible with its intended route of administration.

[00112] The compositions described herein can be administered to a subject via any route, including, but not limited to, intravenous (*e.g.*, by infusion pumps), intraperitoneal, intraocular, intra-arterial, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transdermal, transpleural, intraarterial, topical, inhalational (*e.g.*, as mists of sprays), mucosal (such as via nasal mucosa), subcutaneous, transdermal, gastrointestinal, intraarticular, intracistemal, intraventricular, rectal (*i.e.*, via

suppository), vaginal (*i.e.*, via pessary), intracranial, intraurethral, intrahepatic, and intratumoral. In some embodiments, the compositions are administered systemically (for example by intravenous injection). In some embodiments, the compositions are administered locally (for example by intraarterial or intraocular injection). A preferred route of administration for GDF15 modulators, such as an antibody, is via intravenous infusion.

[00113] Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ed. (Mack Publishing Company, 1990). Formulation components suitable for parenteral administration include a sterile diluent such as bacteriostatic water for injection, physiological saline, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. In some embodiments, the composition (*e.g.*, an antibody) is lyophilized, and then reconstituted in buffered saline, at the time of administration.

[00114] For therapeutic use, the composition (*e.g.*, an antibody) preferably is combined with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art.

[00115] The pharmaceutical compositions preferably are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

[00116] Generally, a therapeutically effective amount of active component is in the range of 0.1 mg/kg to 100 mg/kg, *e.g.*, 1 mg/kg to 100 mg/kg, 1 mg/kg to 10 mg/kg. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health of the patient, the *in vivo* potency of the composition (*e.g.*, an antibody), the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue-level. Alternatively, the initial dosage can be smaller than the optimum, and the daily dosage may be progressively increased during the course of treatment. Human dosage can be optimized, *e.g.*, in a conventional Phase I dose escalation study designed to run from 0.5 mg/kg to 20 mg/kg. Dosing frequency can vary, depending on factors such as route of administration, dosage amount, serum half-life of the composition (*e.g.*, an antibody), and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks.

[00117] The optimal effective amount of the compositions can be determined empirically and will depend on the type and severity of the disease, route of administration, disease progression and health, mass and body area of the subject. Such determinations are within the skill of one in the art. Examples of dosages of GDF15 modulator molecules which can be used for methods described herein include, but are not limited to, an effective amount within the dosage range of any of about 0.01 μg/kg to about 300 mg/kg, or within about 0.1 μg/kg to about 40 mg/kg, or with about 1 μg/kg to about 20 mg/kg, or within about 1 μg/kg to about 10 mg/kg. For example, when administered subcutaneously, the composition may be administered at low microgram ranges, including for example about 0.1 μg/kg or less, about 0.05 μg/kg or less, or 0.01 μg/kg or less.

[00118] In certain embodiments, the amount of GDF15 modulators administered to a subject is about 10 μg to about 500 mg per dose, including for example any of about 10 μg to about 50 μg, about 50 μg to about 100 μg, about 100 μg to about 200 μg, about 200 μg to about 300 μg, about 300 μg to about 500 μg, about 500 μg to about 1 mg, about 1 mg to about 10 mg, about 10 mg to about 50 mg, about 50 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, or about 400 mg to about 500 mg per dose. In certain embodiments, a GDF15 modulator is administered at a dose from about 0.025 mg to about 4 mg, from about 0.035 mg to about 2 mg, from about 0.05 mg to about 2 mg, from about 0.1 mg to about 2 mg, from about 0.2 mg to about 1 mg, or from about 0.2 mg to

about 0.8 mg of the GDF15 modulator can be administered. In one embodiment, 0.5 mg of GDF15 modulator is administered locally. In certain other embodiments, from about 0.05 mg to about 2 mg, from about 0.2 mg to about 2 mg, from about 0.05 mg to about 1.5 mg, from about 0.15 mg to about 1.5 mg, from about 0.4 mg to about 1 mg, or from about 0.5 mg to about 0.8 mg of GDF15 modulator is administered locally.

[00119] The GDF15 modulator compositions may be administered in a single daily dose, or the total daily dose may be administered in divided dosages of two, three, or four times daily. The compositions can also be administered less frequently than daily, for example, six times a week, five times a week, four times a week, three times a week, twice a week, once a week, once every two weeks, once every three weeks, once a month, once every two months, once every three months, or once every six months. The compositions may also be administered in a sustained release formulation, such as in an implant which gradually releases the composition for use over a period of time, and which allows for the composition to be administered less frequently, such as once a month, once every 2-6 months, once every year, or even a single administration. The sustained release devices (such as pellets, nanoparticles, microparticles, nanospheres, microspheres, and the like) may be administered by injection or surgical implanted in various locations in the body.

[00120] In certain embodiments of the invention, the dosing of the GDF15 modulator is titrated such that the dose is sufficient to reduce or prevent adverse effects, but yet fully or partially inhibit the activity of the GDF15.

[00121] In some aspects, the activity of GDF15 can be modulated in a target cell using antisense nucleic acids or small interfering nucleic acids. Modulation can be achieved using expression constructs known in the art, *e.g.*, naked DNA constructs, DNA vector based constructs, and/or viral vector and/or viral based constructs to express nucleic acids encoding an anti-GDF15 siRNA or antisense molecule.

[00122] Exemplary DNA constructs and the therapeutic use of such constructs are well known to those of skill in the art (see, *e.g.*, Chiarella *et al.*, 2008, RECENT PATENTS ANTI-INFECT. DRUG DISC., 3:93-101; Gray *et al.*, 2008, EXPERT OPIN. BIOL. THER., 8:911-922; Melman *et al.*, 2008, HUM. GENE THER., 17:1165-1176). Naked DNA constructs typically include one or more therapeutic nucleic acids (*e.g.*, GDF15 modulators) and a promoter

sequence. A naked DNA construct can be a DNA vector, commonly referred to as pDNA. Naked DNA typically do not integrate into chromosomal DNA. Generally, naked DNA constructs do not require, or are not used in conjunction with, the presence of lipids, polymers, or viral proteins. Such constructs may also include one or more of the non-therapeutic components described herein.

[00123] DNA vectors are known in the art and typically are circular double stranded DNA molecules. DNA vectors usually range in size from three to five kilo-base pairs (*e.g.*, including inserted therapeutic nucleic acids). Like naked DNA, DNA vectors can be used to deliver and express one or more therapeutic proteins in target cells. DNA vectors do not integrate into chromosomal DNA.

[00124] Generally, DNA vectors include at least one promoter sequence that allows for replication in a target cell. Uptake of a DNA vector may be facilitated by combining the DNA vector with, for example, a cationic lipid, and forming a DNA complex. Typically, viral vectors are double stranded circular DNA molecules that are derived from a virus. Viral vectors typically are larger in size than naked DNA and DNA vector constructs and have a greater capacity for the introduction of foreign (*i.e.*, not virally encoded) genes. Like naked DNA and DNA vectors, viral vectors can be used to deliver and express one or more therapeutic nucleic acids in target cells. Unlike naked DNA and DNA vectors, certain viral vectors stably incorporate themselves into chromosomal DNA. Typically, viral vectors include at least one promoter sequence that allows for replication of one or more vector encoded nucleic acids, *e.g.*, a therapeutic nucleic acid, in a host cell. Viral vectors may optionally include one or more non-therapeutic components described herein. Advantageously, uptake of a viral vector into a target cell does not require additional components, *e.g.*, cationic lipids. Rather, viral vectors transfect or infect cells directly upon contact with a target cell.

[00125] The approaches described herein include the use of retroviral vectors, adenovirus-derived vectors, and/or adeno-associated viral vectors as recombinant gene delivery systems for the transfer of exogenous genes *in vivo*, particularly into humans. Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Ausubel, F. M. *et al.* (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14, and other standard laboratory manuals.

[00126] Viruses that are used as transduction agents of DNA vectors and viral vectors such as adenoviruses, retroviruses, and lentiviruses may be used in practicing the present invention. Illustrative retroviruses include, but are not limited to: Moloney murine leukemia virus (M-MuLV), Moloney murine sarcoma virus (MoMSV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), gibbon ape leukemia virus (GaLV), feline leukemia virus (FLV), spumavirus, Friend murine leukemia virus, Murine Stem Cell Virus (MSCV) and Rous Sarcoma Virus (RSV)) and lentivirus. As used herein, the term "lentivirus" refers to a group (or genus) of complex retroviruses. Illustrative lentiviruses include, but are not limited to: HIV (human immunodeficiency virus; including HIV type 1, and HIV type 2); visna-maedi virus (VMV) virus; the caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV).

[00127] In certain embodiments, an adenovirus can be used in accordance with the methods described herein. The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 dl324 or other strains of adenovirus (*e.g.*, Ad2, Ad3, Ad7 etc.) are known to those skilled in the art. Recombinant adenoviruses can be advantageous in certain circumstances in that they are not capable of infecting nondividing cells and can be used to infect a wide variety of cell types, including epithelial cells Furthermore, the virus particle is relatively stable and amenable to purification and concentration, and as above, can be modified so as to affect the spectrum of infectivity. Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis *in situ* where introduced DNA becomes integrated into the host genome (*e.g.*, retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors.

[00128] Adeno-associated virus is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration.

[00129] In various embodiments, one or more viral vectors that expresses a therapeutic transgene or transgenes encoding a GDF15 modulator is administered by direct injection to a cell, tissue, or organ of a subject, *in vivo*. In various other embodiments, cells are transduced *in vitro* or *ex vivo* with such a vector encapsulated in a virus, and optionally expanded *ex vivo*. The transduced cells are then administered to the subject. Cells suitable for transduction include, but are not limited to stem cells, progenitor cells, and differentiated cells. In certain embodiments, the transduced cells are embryonic stem cells, bone marrow stem cells, umbilical cord stem cells, placental stem cells, mesenchymal stem cells, neural stem cells, liver stem cells, pancreatic stem cells, cardiac stem cells, kidney stem cells, or hematopoietic stem cells.

[00130] In particular embodiments, host cells transduced with viral vector of the invention that expresses one or more polypeptides, are administered to a subject to treat and/or prevent an auditory disease, disorder, or condition. Other methods relating to the use of viral vectors, which may be utilized according to certain embodiments of the present invention, can be found in, *e.g.*, Kay, 1997, CHEST, 111(6 Supp.):138S-142S; Ferry *et al.*, 1998, HUM. GENE THER., 9:1975-81; Shiratory *et al.*, 1999, LIVER, 19:265-74; Oka *et al.*, 2000, CURR. OPIN. LIPIDOL., 11:179-86; Thule *et al.*, 2000, GENE THER., 7: 1744-52; Yang, 1992, CRIT. REV. BIOTECHNOL., 12:335-56; Alt, 1995, J. HEPATOL., 23:746-58; Brody *et al.*, 1994, ANN. N. Y. ACAD. SCI., 716:90-101; Strayer, 1999, EXPERT OPIN. INVESTIG. DRUGS, 8:2159-2172; Smith-Arica *et al.*, 2001, CURR. CARDIOL. REP., 3:43-49; and Lee *et al.*, 2000, NATURE, 408:483-8.

[00131] Certain embodiments of the invention provide conditional expression of a polynucleotide of interest. For example, expression is controlled by subjecting a cell, tissue, organism, *etc.*, to a treatment or condition that causes the polynucleotide to be expressed or that causes an increase or decrease in expression of the polynucleotide encoded by the polynucleotide of interest. Illustrative examples of inducible promoters/systems include, but are not limited to, steroid-inducible promoters such as promoters for genes encoding glucocorticoid or estrogen receptors (inducible by treatment with the corresponding hormone), metallothionine promoter (inducible by treatment with various heavy metals), MX-1 promoter (inducible by interferon), the "GeneSwitch" mifepristone-regulatable system (Sirin *et al.*, 2003, GENE, 323:67), the cumate inducible gene switch (WO 2002/088346), tetracycline-dependent regulatory systems, etc.

[00132] Conditional expression can also be achieved by using a site specific DNA

recombinase. According to certain embodiments of the invention the vector comprises at least one (typically two) site(s) for recombination mediated by a site specific recombinase. As used herein, the terms "recombinase" or "site specific recombinase" include excisive or integrative proteins, enzymes, co-factors or associated proteins that are involved in recombination reactions involving one or more recombination sites (*e.g.*, two, three, four, five, seven, ten, twelve, fifteen, twenty, thirty, fifty, etc.), which may be wild-type proteins (see Landy, 1993, CURRENT OPINION IN BIOTECHNOLOGY, 3:699-707), or mutants, derivatives (*e.g.*, fusion proteins containing the recombination protein sequences or fragments thereof), fragments, and variants thereof. Illustrative examples of recombinases suitable for use in particular embodiments of the present invention include, but are not limited to: Cre, Int, IHF, Xis, Flp, Fis, Hin, Gin, OC31 , Cin, Tn3 resolvase, TndX, XerC, XerD, TnpX, Hjc, Gin, SpCCEl. and ParA.

[00133] The vectors may comprise one or more recombination sites for any of a wide variety of site specific recombinases. It is to be understood that the target site for a site specific recombinase is in addition to any site(s) required for integration of a vector (*e.g.*, a retroviral vector or lentiviral vector).

[00134] In certain embodiments, vectors comprise a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, neomycin, hygromycin, methotrexate, Zeocin, Blastocidin, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, *e.g.*, the gene encoding D-alanine racemase for Bacilli. Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, 1977, CELL, 11 :223-232) and adenine phosphoribosyltransferase (Lowy *et al.*, 1990, CELL, 22:817-823) genes which can be employed in tk- or aprt- cells, respectively.

[00135] All the molecular biological techniques required to generate an expression construct described herein are standard techniques that will be appreciated by one of skill in the art.

[00136] In certain embodiments, DNA delivery may occur parenterally, intravenously, intramuscularly, or even intraperitoneally as described, for example, in U.S. Patent Nos. 5,543,158; 5,641,515; and 5,399,363 (each specifically incorporated herein by reference in its

entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00137] In certain embodiments, DNA delivery may occur by use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, optionally mixing with cell penetrating polypeptides, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, a nanoparticle or the like. The formulation and use of such delivery vehicles can be carried out using known and conventional techniques.

[00138] Exemplary formulations for *ex vivo* DNA delivery may also include the use of various transfection agents known in the art, such as calcium phosphate, electroporation, heat shock and various liposome formulations (*i.e.*, lipid-mediated transfection). Particular embodiments of the invention may comprise other formulations, such as those that are well known in the pharmaceutical art, and are described, for example, in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 20th Edition. Baltimore, MD: Lippincott Williams & Wilkins, 2000.

[00139] In certain embodiments, GDF15 activity is inhibited by contacting a body fluid with a composition comprising a GDF15 modulator *ex vivo* under conditions that permit the GDF15 modulators to reduce or inhibit GDF15 activity. Suitable body fluids include those that can be returned to the individual, such as blood, plasma, or lymph. Affinity adsorption apheresis is described generally in Nilsson *et al.*, 1988, BLOOD, 58(1):38-44; Christie *et al.*, 1993, TRANSFUSION, 33:234-242; Richter *et al.*, 1997, ASAIO J., 43(1):53-59; Suzuki *et al.*, 1994, AUTOIMMUNITY, 19: 105-112; U.S. Pat. No. 5,733,254; Richter *et al.*, 1993, METABOL. CLIN. EXP., 42:888-894; and Wallukat *et al.*, 1996, INT'L J. CARD., 54:1910195.

[00140] Accordingly, the invention includes methods of treating one or more diseases described herein in a subject comprising treating the subject's blood extracoporeally (*i.e.*, outside the body or *ex vivo*) with a composition comprising a GDF15 modulator under

conditions that permit the modulator to reduce or inhibit GDF15 activity in the blood of the subject.

EXAMPLES

EXAMPLE 1. GDF15 Levels in Subjects With and Without Congestive Heart Failure

[00141] Samples of plasma from 245 subjects were examined, and the results are summarized in **FIGS 1-6**. GDF15 was assessed at a 1:50 plasma dilution with the DuoSet ELISA Development Kit (R&D Systems, #DY957) according to the manufacturer's recommendation. The inter-assay coefficient of variation (CV) was 5.6%, and the intra-assay CV was 2.9%.

[00142] It was discovered that GDF15 levels were significantly higher in subjects who had been diagnosed with CHF (n=200; mean of about 1900 pg/ml GDF15 for CHF without cachexia; mean of about 3000 pg/ml GDF15 for CHF with cachexia) than in those who were not (n=45; mean of about 1000 pg/ml) (**FIG. 1**). GDF15 levels were significantly higher in subjects with CHF regardless of whether they presented with cachexia co-morbidity (n=33; mean of about 3000 pg/ml GDF15) or not (n=167; mean of about 1900 pg/ml GDF15) (**FIG. 1**). Average GDF15 levels increased with increased severity of CHF (**FIG. 2**).

[00143] Analysis of peak VO_2, a functional marker for CHF, demonstrate that the peak VO_2 decreased (increased severity of CHF) with increased GDF15 levels (**FIGS. 3A-3C**).

[00144] Analysis of total saturation of transferrin (TSAT), a functional marker of anemia, a frequent comorbidity of CHF, demonstrate that TSAT decreased (increased severity of anemia) with increased GDF15 levels (**FIG. 4**).

[00145] Analysis of creatinine and urea levels, which are markers of renal function, another frequent comorbidity of CHF, demonstrate that creatinine levels are increased (increased severity of renal impairment) in subjects with CHF (both with and without cachexia) together with increased GDF15 levels (**FIGS. 5A** and **5B**). Urea levels also increased (increased severity of renal impairment) with increased GDF15 levels in subjects with CHF, in the absence of cachexia (**FIG. 5C**).

[00146] Analysis of renal function markers in 200 subjects with CHF demonstrate that levels

of urea, uric acid and creatinine all increased (increased renal impairment) with increased GDF15 levels (**FIGS. 6A, 6B** and **6C**), while glomerular filtration rate (GFR), a measure of kidney function, decreased with increased GDF15 levels (**FIG. 6D**).

EXAMPLE 2. Treatment of Cardiac Hypotrophy in an HT-1080 Xenograft Tumor Model

[00147] This Example demonstrates the treatment of cardiac hypotrophy (as indicated by heart weight loss) with an anti-GDF15 antibody 01G06 in an HT-1080 fibrosarcoma xenograft model.

[00148] HT-1080 cells were grown in culture at 37°C in an atmosphere containing 5% CO_2, using Eagle's Minimum Essential Medium (ATCC, Catalog No. 30-2003) containing 10% FBS. Cells were inoculated subcutaneously into the flank of 8-week old female ICR SCID mice with 5×10^6 cells per mouse in 50% matrigel. Body weight was measured daily. When body weight reached 80%, the mice were randomized into two groups of five mice each. Each group received one of the following treatments: murine IgG control ("mIgG"), or 01G06 dosed at 2 mg/kg on day 1 and day 7, via intra-peritoneal injection. Treatment with antibody 01G06 resulted in body weight increase to initial weight or 100% ($p<0.001$) (**FIG. 7A**).

[00149] The data in **FIGS. 7A-B** indicate that administration of the anti-GDF15 antibody can reverse heart weight loss in an HT-1080 fibrosarcoma xenograft model.

[00150] In this experiment, a group of five mice were sacrificed at the time of dosing (baseline or 80% body weight loss, without treatment) and at the end of study (seven days post dose, either mIgG or 01G06). Liver, heart, spleen, kidney, gonadal fat and the gastrocnemius muscles were removed surgically and weighed. As shown in **FIG. 7B**, a significant loss in liver, heart, spleen, kidney, gonadal fat and gastrocnemius muscle mass was observed seven days post dose with mIgG, but not in the group treated with antibody 01G06.

[00151] These results indicate that administration of the anti-GDF15 antibody reserves the loss of key organ mass, such as heart, loss of muscle mass, loss of fat and involuntary weight loss in an HT-1080 xenograft tumor model.

[00152] In a similar experiment, the effects of systemic administration of a monoclonal antibody that binds to and inhibits human GDF15 (Hu01G06-127) on body weight in cachexic mice bearing human tumor xenografts were compared to similar animals receiving human IgG

or sham mice (*i.e.*, no tumor). Administration of the anti-GDF15 antibody resulted in retention or increase in body weight, compared to the mice without tumors, while mice that were injected with human IgG exhibited significant loss in body weight (**FIG. 8**).

EXAMPLE 3. *In vivo* Model of Pressure-Induced Cardiac Hypertrophy

[00153] A reproducible transverse aortic constriction of 65-70% is made in mice, as described in Rockman *et al.*, 1991, PROC. NATL ACAD. SCI., 88:8277-8291. The animals are extubated and allowed to recover, and blood pressure in the left and right carotids is measured. Animals then are dosed with either an anti-GDF15 antibody or control. After seven days, heart size and weight are assessed for the existence and /or extent of cardiac hypertrophy.

EXAMPLE 4: *In vivo* Model of Heart Failure Due to Chronic Volume Overload

[00154] An aortocaval shunt is implanted in mice, as described in Scheuermann-Freestone *et al.*, 2001, EUR. J. HEART FAILURE, 3:535-543. Animals are dosed with either an anti-GDF15 antibody or control. After thirty days, animals are assessed for mortality, development of myocardial hypertrophy, hemodynamic parameters, and expression levels of BNP-mRNA.

EXAMPLE 5: Treatment of Subjects Previously Treated with Other Cardiac Interventions

[00155] Subjects exhibiting cardiac hypotrophy, who have previously been treated with known cardiac interventions, but who exhibit at least one characteristic of congestive heart failure, are dosed with anti-GDF15 antibody. Treatment with anti-GDF15 antibody lasts for a duration of three months, during which heart size, peak VO_2, troponin levels and BNP levels are monitored at regular intervals.

INCORPORATION BY REFERENCE

[00156] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[00157] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing

description, and all changes that come within the meaning and the range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A method of increasing cardiac function in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a GDF15 modulator thereby to increase cardiac function in said subject.

2. The method of claim 1, wherein the subject has elevated GDF15 activity in a body fluid.

3. A method of treating a subject having a cardiac disorder or dysfunction, the method comprising administering an effective amount of a composition comprising a GDF15 modulator thereby to ameliorate a symptom of the cardiac disorder or dysfunction.

4. The method of claim 3, wherein the subject has elevated GDF15 activity in a body fluid.

5. A method of reducing or reversing cardiac hypotrophy in a subject exhibiting one or more symptoms of congestive heart failure, the method comprising administering an effective amount of a composition comprising a GDF15 modulator, wherein the composition ameliorates at least one symptom of cardiac hypotrophy in the subject.

6. The method of claim 5, wherein the subject has elevated GDF15 activity in a body fluid.

7. A method of treating or preventing congestive heart failure (CHF) in a subject in need thereof, the method comprising administering an effective amount of a composition that reduces or inhibits a GDF15 activity in the subject, thereby to treat or prevent CHF in the subject.

8. The method of claim 7, wherein the subject has elevated GDF15 activity in a body fluid.

9. A method of reducing cardiac hypotrophy in a subject exhibiting one or more characteristics of congestive heart failure, the method comprising administering an effective amount of a composition that modulates the activity of GDF15, thereby to reduce cardiac hypotrophy in the subject.

10. The method of claim 9, wherein the subject has elevated GDF15 activity in a body fluid.

11. The method of any one of claims 1-10, wherein the subject exhibits a peak VO_2 of less than less than 14 mL/kg/min.

12. The method of any one of claims 1-11, wherein the subject exhibits an LVEF of less than 40%.

13. The method of any one of claims 1-12, wherein the subject exhibits BNP levels in excess of 100 pg/ml.

14. The method of any one of claims 1-13, wherein the subject exhibits serum cardiac troponin I (cTnI) levels in excess of 1.5 ng/mL.

15. The method of any one of claims 1-14, wherein the subject has been diagnosed as having congestive heart failure.

16. The method of any one of claims 1-15, wherein the GDF15 modulator reduces or inhibits GDF15 activity in the subject.

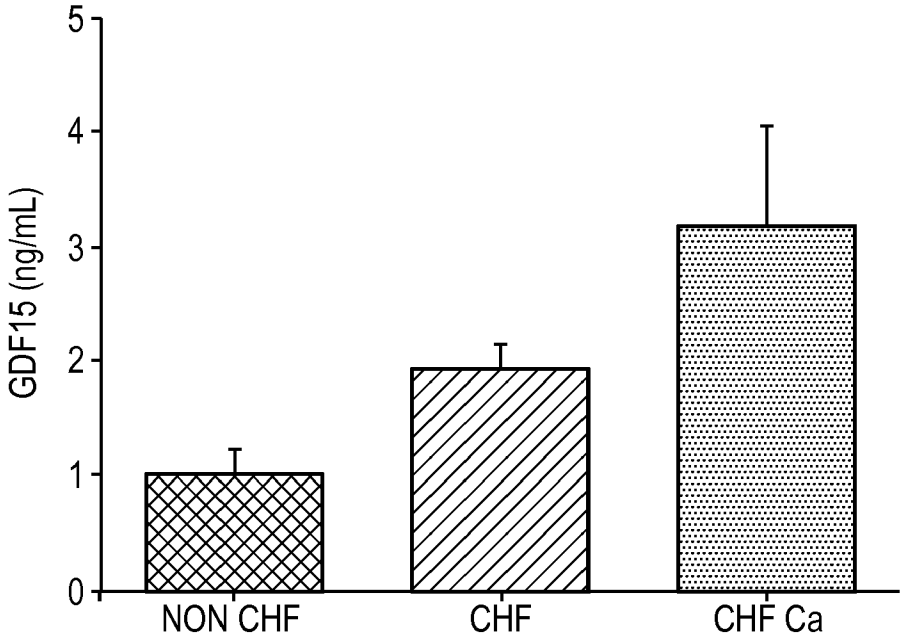
17. The method of claim 16, wherein the GDF15 modulator binds GDF15.

18. The method of claim 17, wherein the GDF15 inhibitor is an anti-GDF15 antibody.

19. The method of claim 18, wherein the antibody is humanized or human.

20. The method of any one of claims 1-19, wherein the subject exhibits above normal levels of a marker selected from the group consisting of cardiac troponin I, cardiac troponin T, brain natriuretic protein (BNP), N-terminal peptides derived from BNP (NT-proBNP), and cardiac fatty acid binding protein (cFABP).

21. The method of any one of claims 2, 4, 6, 8, or 10, wherein the body fluid is plasma or serum.

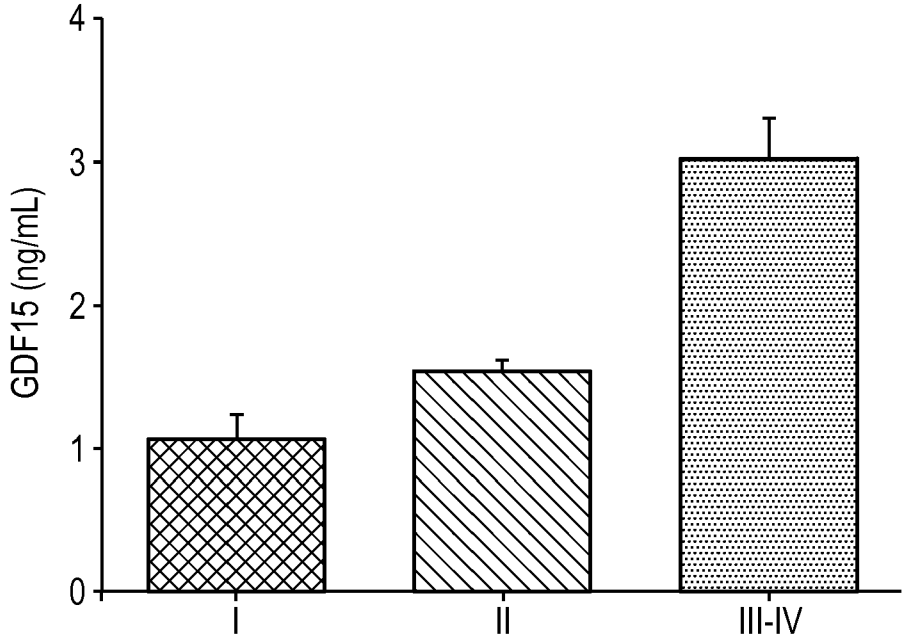


NON CHF: N=45

CHF WITHOUT CACHEXIA (CHF); N=167

CHF WITH CACHEXIA (CHF Ca); N=33

FIG. 1



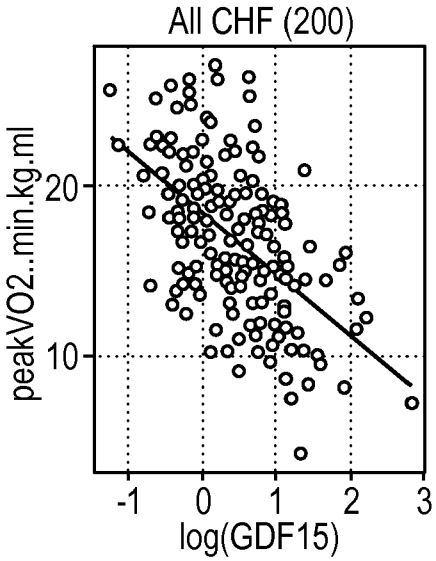
AVERAGE GDF-15 SERUM LEVELS INCREASE WITH SEVERITY OF CHF

NYHA I: 16

NYHA II: 102

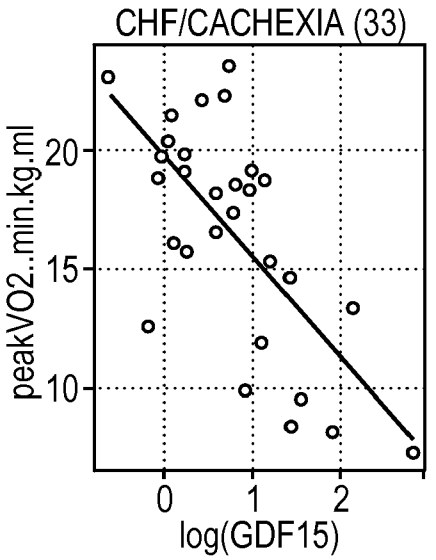
NYHA III-IV: 80

FIG. 2



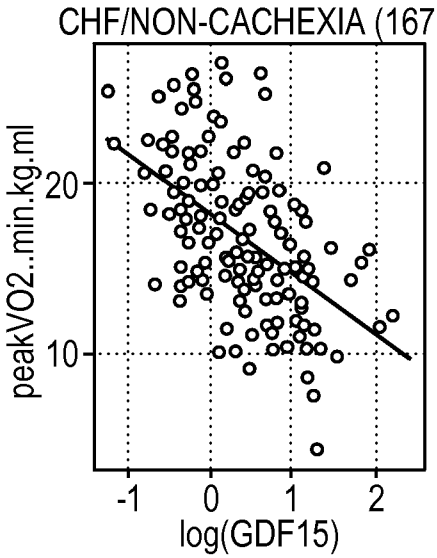
Type	Annotation	R	P-Val
perf	peakVO2..min.kg.ml	-0.62	1E-07
perf	X6.minute.walk..m.	-0.49	0.142
perf	gait.speed..m.s.	-0.49	0.142
perf	hand.grip.strength.right..kg.	0.33	0.436
perf	leg.grip.strength.right..kg.	-0.20	0.546
perf	hand.grip.strength.left..kg.	0.23	0.677
perf	leg.grip.strength.left..kg.	0.31	0.736

FIG. 3A



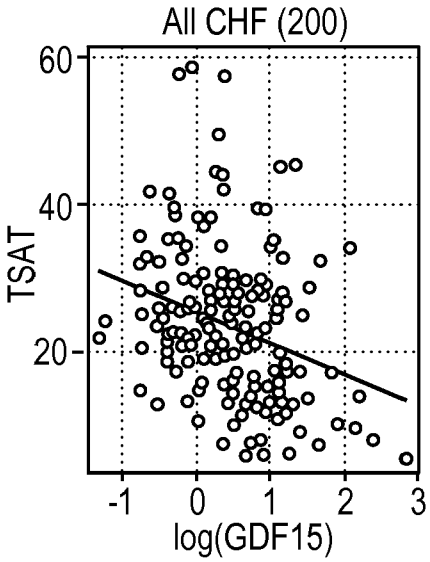
Type	Annotation	R	P-Val
perf	peakVO2..min.kg.ml	-0.69	0.002
perf	hand.grip.strenght.right..kg.	0.52	0.343
perf	leg.grip.strenght.right..kg.	-0.32	0.398
perf	gait.speed..m.s.	-0.70	0.487
perf	X6.minute.walk..m.	-0.70	0.487
perf	hand.grip.strenght.left..kg.	-0.43	0.727
perf	leg.grip.strenght.left..kg.	-0.62	0.887

FIG. 3B



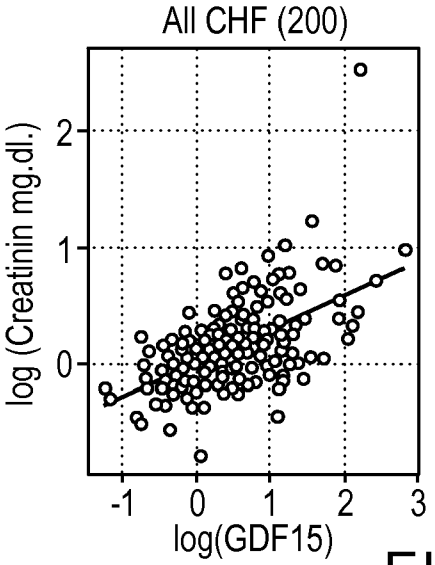
Type	Annotation	R	P-Val
perf	peakVO2..min.kg.ml	-0.62	5E-06
perf	X6.minute.walk..m.	-0.46	0.143
perf	gait.speed..m.s.	-0.46	0.143
perf	hand.grip.strenght.left..kg.	0.20	0.330
perf	leg.grip.strenght.left..kg.	0.27	0.353
perf	hand.grip.strenght.right..kg.	0.30	0.489
perf	leg.grip.strenght.right..kg.	-0.21	0.972

FIG. 3C



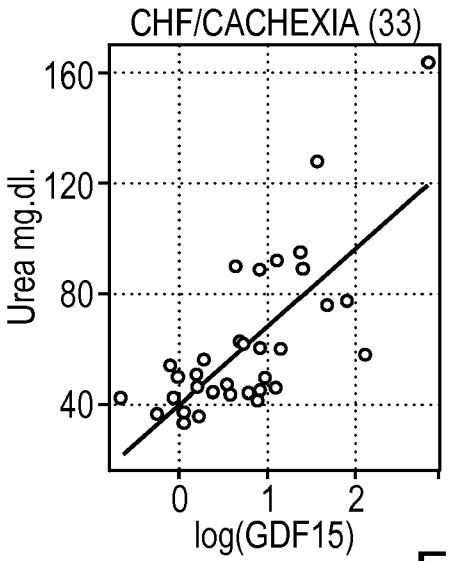
Type	Annotation	R	P-Val
anemia	TSAT....	-0.38	7E-05
anemia	Iron	-0.31	0.001
anemia	Transferrin	0.26	0.017
anemia	Hb..g.dl.	-0.18	0.024
anemia	Erythrocyte	-0.08	0.267
anemia	Ferritin	-0.13	0.363

FIG. 4



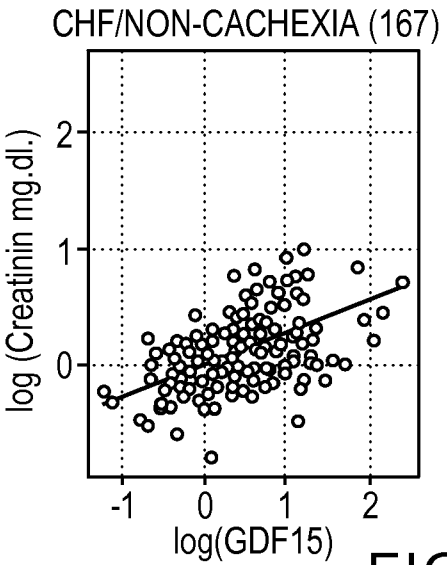
Type	Annotation	R	P-Val
kidney	Creatinin..mg.dl.	0.56	1E-14
kidney	Urea..mg.dl.	0.58	4E-14
kidney	GFR	-0.54	3E-10
kidney	Uric.acid..mg.dl.	0.47	8E-10
kidney	Anorg..Phosphat	0.24	0.112
kidney	Potassium	0.07	0.333
kidney	Calcium	-0.14	0.446
kidney	Chlorid	-0.07	0.543
kidney	Sodium	0.04	0.835

FIG. 5A



Type	Annotation	R	P-Val
kidney	Urea..mg.dl.	0.74	7E-06
kidney	Creatinin..mg.dl.	0.72	3E-05
kidney	GFR	-0.67	0.001
kidney	Uric.acid..mg.dl.	0.53	0.007
kidney	Anorg..Phosphat	0.43	0.017
kidney	Calcium	0.29	0.159
kidney	Sodium	0.14	0.507
kidney	Potassium	0.10	0.605
kidney	Chlorid	0.10	0.964

FIG. 5B



Type	Annotation	R	P-Val
kidney	Creatinin..mg.dl.	0.51	2E-10
kidney	Urea..mg.dl.	0.54	1E-09
kidney	Uric.acid..mg.dl.	0.45	1E-07
kidney	GFR	-0.49	9E-07
kidney	Potassium	0.10	0.250
kidney	Calcium	-0.16	0.288
kidney	Chlorid	-0.07	0.497
kidney	Anorg..Phosphat	0.28	0.587
kidney	Sodium	0.04	0.899

FIG. 5C

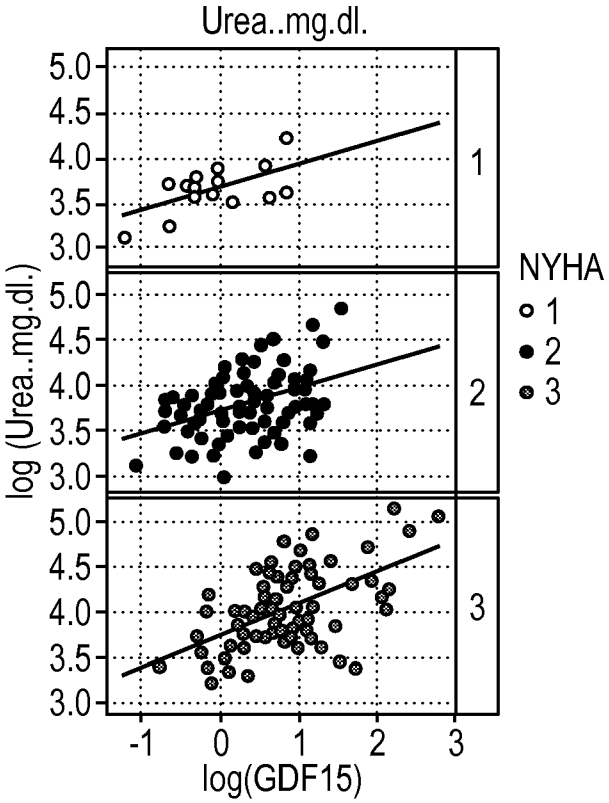


FIG. 6A

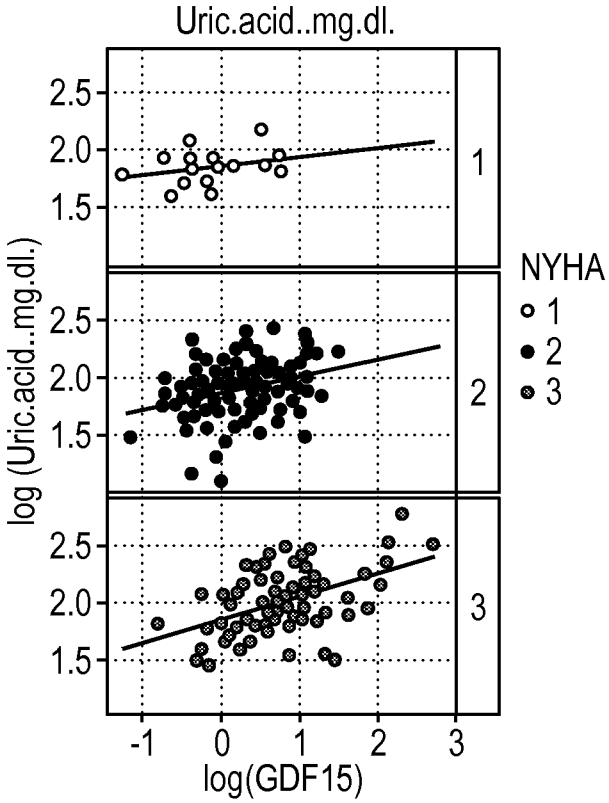


FIG. 6B

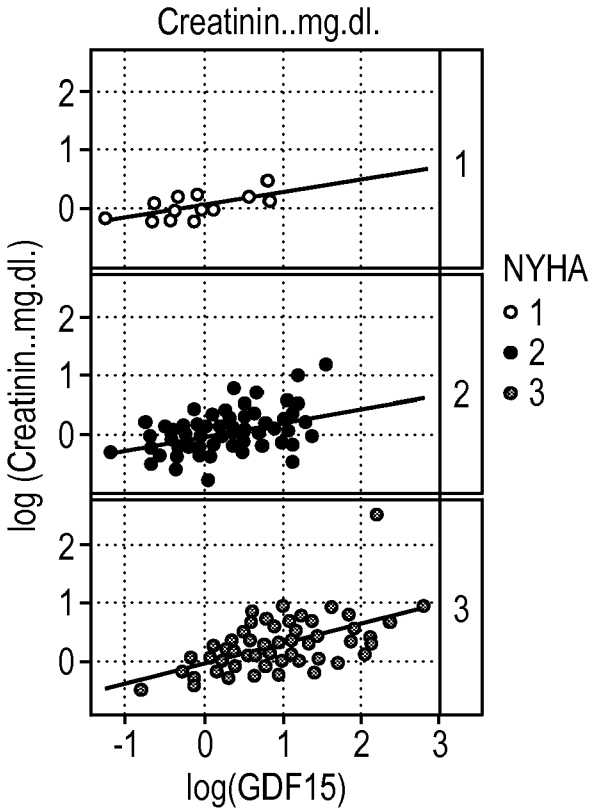


FIG. 6C

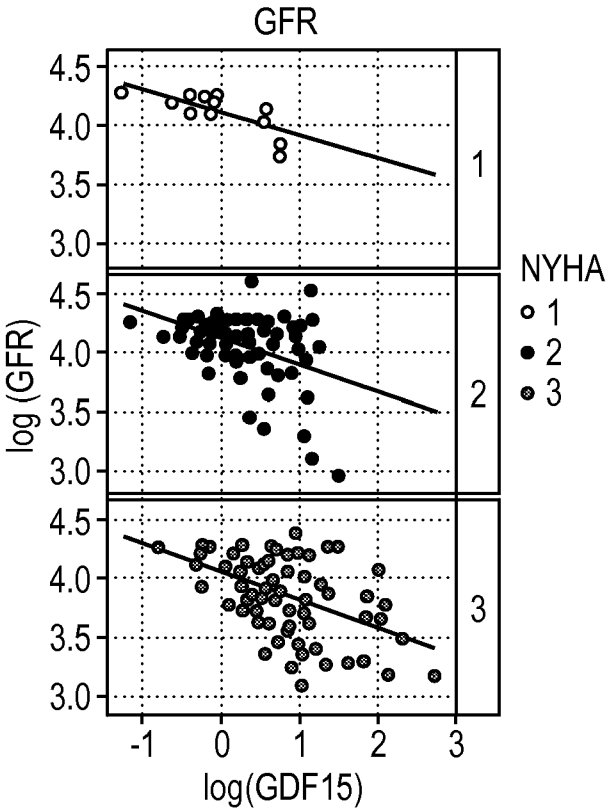


FIG. 6D

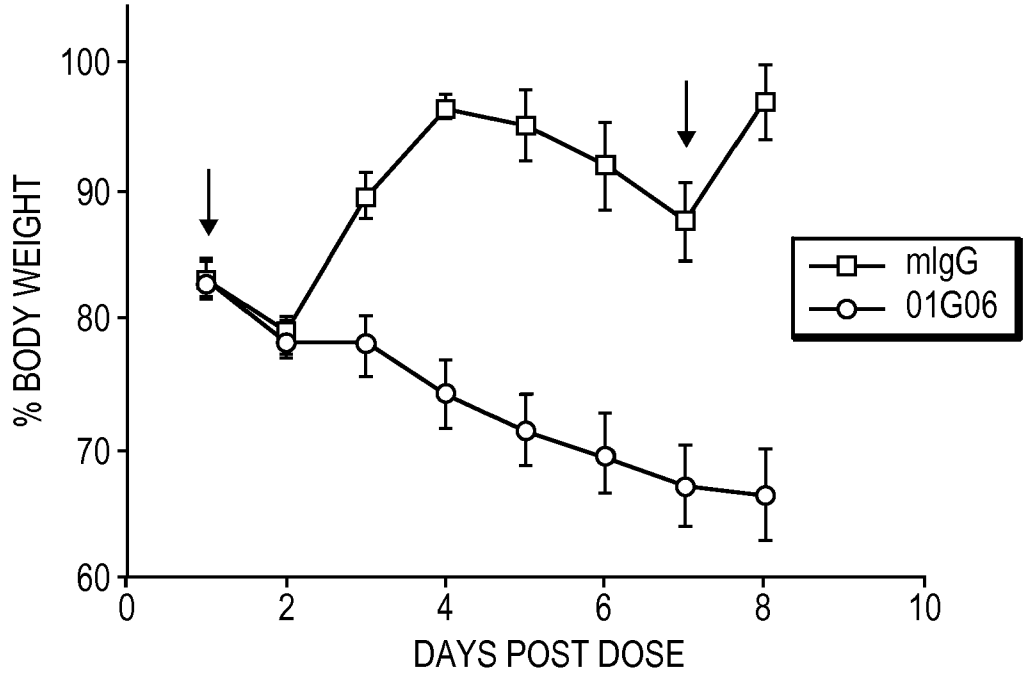

100
90
80
70
60
% BODY WEIGHT
0
2
4
6
8
10
DAYS POST DOSE
mIgG
01G06

FIG. 7A

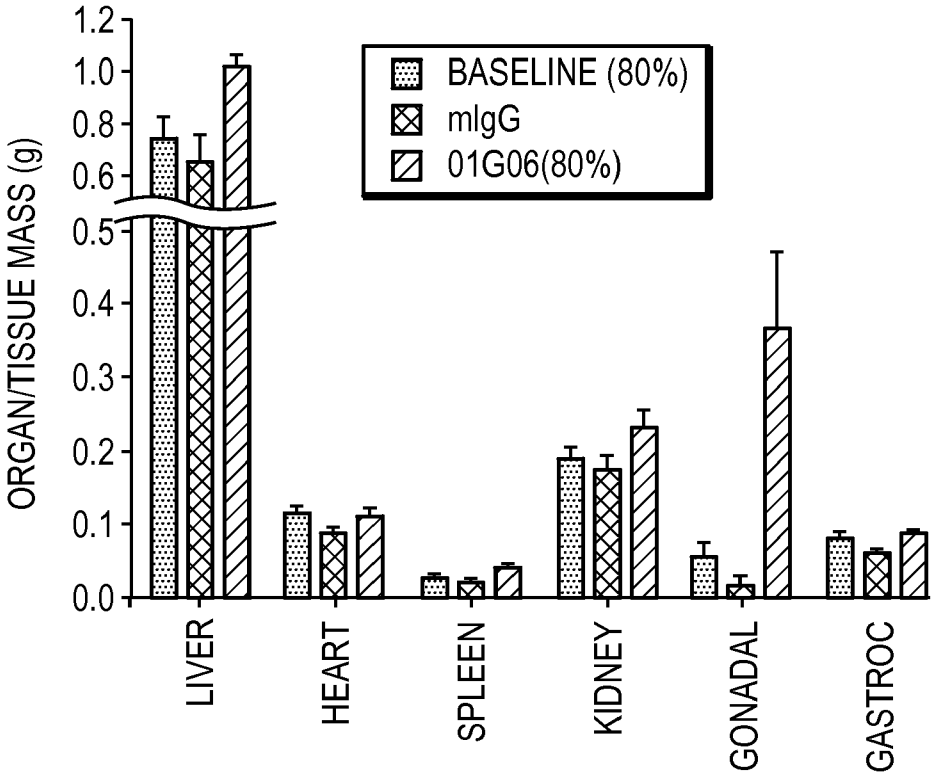

1.2
1.0
0.8
0.6
0.5
0.4
0.3
0.2
0.1
0.0
ORGAN/TISSUE MASS (g)
BASELINE (80%)
mIgG
01G06(80%)
LIVER
HEART
SPLEEN
KIDNEY
GONADAL
GASTROC

FIG. 7B

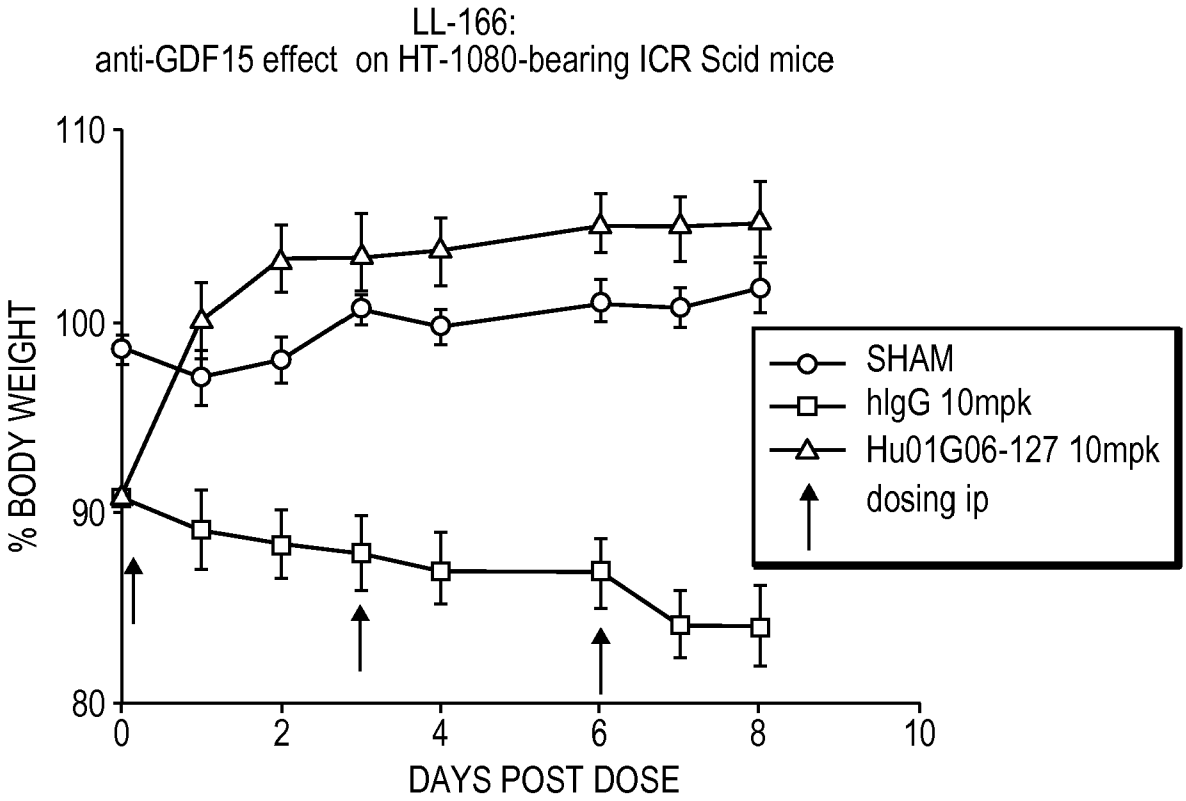

LL-166:
anti-GDF15 effect on HT-1080-bearing ICR Scid mice
% BODY WEIGHT
110
100
90
80
0
2
4
6
8
10
DAYS POST DOSE
SHAM
hIgG 10mpk
Hu01G06-127 10mpk
dosing ip

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/036790

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/22 A61P9/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 919 084 B2 (BREIT SAMUEL N [AU] ET AL) 5 April 2011 (2011-04-05) cited in the application	1-10, 15-18,21
Y	tables 1-4 examples 1-2 claims	11-14, 19,20

X	WO 2009/046495 A1 (ST VINCENTS HOSP SYDNEY [AU]; BREIT SAMUEL NORBERT [AU]) 16 April 2009 (2009-04-16)	3,4, 15-18,21
Y	page 5 example 3 figure 8	11-14, 19,20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2015	30/11/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bernhardt, Wiebke

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LATINI ROBERTO ET AL: "Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure", CIRCULATION, LIPPINCOT WILLIAMS AND WILKINS, BALTIMORE, US, vol. 116, no. 11, 11 September 2007 (2007-09-11), pages 1242-1249, XP002458356, ISSN: 1524-4539, DOI: 10.1161/CIRCULATIONAHA.106.655076 abstract page 1243, left-hand column	11-14,20
Y	LONBERG ET AL: "Fully human antibodies from transgenic mouse and phage display platforms", CURRENT OPINION IN IMMUNOLOGY, ELSEVIER, OXFORD, GB, vol. 20, no. 4, 1 August 2008 (2008-08-01) , pages 450-459, XP025771204, ISSN: 0952-7915, DOI: 10.1016/J.COI.2008.06.004 [retrieved on 2008-07-21] abstract	19
Y	STEPHAN DUEBEL ED - STEFAN DÜBEL: "Handbook of Therapeutic Antibodies Chapter 6", 1 January 2007 (2007-01-01), HANDBOOK OF THERAPEUTIC ANTIBODIES, WILEY-VCH, WEINHEIM, PAGE(S) 119 - 144, XP007913671, ISBN: 978-3-527-31453-9 introduction	19
X,P Y,P	WO 2014/100689 A1 (AVEO PHARMACEUTICALS INC [US]) 26 June 2014 (2014-06-26) pages 3,4, paragraphs [0195], [0198], examples, claims	3,4, 15-18,21 11-14, 19,20

-/--

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M. P. BONACA ET AL: "Growth Differentiation Factor-15 and Risk of Recurrent Events in Patients Stabilized After Acute Coronary Syndrome: Observations From PROVE IT-TIMI 22", ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY., vol. 31, no. 1, 21 October 2010 (2010-10-21), pages 203-210, XP055227446, US ISSN: 1079-5642, DOI: 10.1161/ATVBAHA.110.213512 abstract pages 203, 208-209 -----	1-21
A	LARS WALLENTIN ET AL: "GDF-15 for Prognostication of Cardiovascular and Cancer Morbidity and Mortality in Men", PLOS ONE, vol. 8, no. 12, 2 December 2013 (2013-12-02), page e78797, XP055227449, DOI: 10.1371/journal.pone.0078797 abstract -----	1-21
A	KAI C WOLLERT ET AL: "Growth Differentiation Factor 15 in Heart Failure: An Update", CURRENT HEART FAILURE REPORTS, CURRENT SCIENCE INC, NEW YORK, vol. 9, no. 4, 9 September 2012 (2012-09-09), pages 337-345, XP035134728, ISSN: 1546-9549, DOI: 10.1007/S11897-012-0113-9 abstract pages 337, 342 -----	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/036790

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 2209486 A1	28-07-2010
		JP 2011502106 A	20-01-2011
		US 2010266707 A1	21-10-2010
		WO 2009046495 A1	16-04-2009
WO 2014100689 A1	26-06-2014	AU 2013364133 A1	16-07-2015
		CA 2896076 A1	26-06-2014
		EP 2934584 A1	28-10-2015
		KR 20150100837 A	02-09-2015
		US 2014193427 A1	10-07-2014
		WO 2014100689 A1	26-06-2014