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(54) Title: TREATMENT OF CHRONIC KIDNEY DISEASE AND OTHER RENAL DYSFUNCTION USING A GDF15 MODULATOR

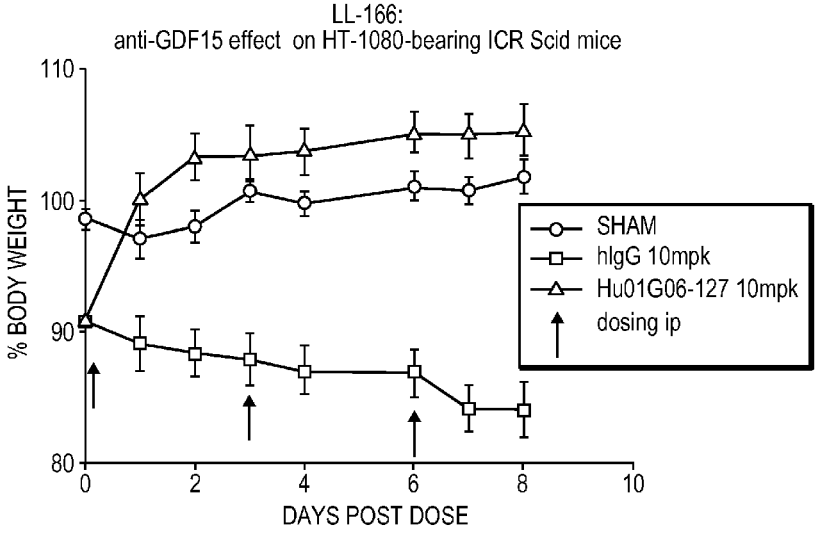

FIG. 5A

(57) Abstract: The invention provides methods and compositions for treating a subject having a renal- related disorder, such as chronic kidney disease (CKD), end stage renal failure, diabetes, insulin resistance, kidney hypertrophy, kidney hypotrophy, polycystic kidney disease, proteinuria, hyperglycemia, hyperuricemia, gout, kidney stones, hypertension or hypertensive nephropathy, dyslipidemia, anemia and/or reduced erythropoietin production, iron deficiency or hyperfiltration. The methods and compositions use or contain a composition that reduces or inhibits GDF15 activity.

TREATMENT OF CHRONIC KIDNEY DISEASE AND OTHER RENAL DYSFUNCTION USING A GDF15 MODULATOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/015,242, 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 renal disorder or renal dysfunction, particularly chronic kidney disease, acute, chronic or end stage renal failure, glomerulonephritis, anemia, diabetic nephropathy and insulin resistance.

BACKGROUND OF THE INVENTION

[0003] Kidney disease is a common and expensive condition that is a major source of morbidity and mortality in humans. From a clinical perspective, kidney diseases can be classified as acute kidney injury (AKI) and chronic kidney disease (CKD). AKI, also termed acute kidney failure or acute renal failure, is a rapid loss of renal function, and may end up with full, partial or no recovery of normal renal function. AKI is an abrupt (within 48 hours) reduction in kidney function, which may include an absolute increase in serum creatinine of at least 0.3 mg/dl, a percentage increase in serum creatinine of at least 50%, or a reduction in urine output of less than 0.5 ml/kg per hour for more than six hours. See Metha *et al.*, 2007, CRITICAL CARE, 11:R31. Epidemiologically, AKI may be brought about post-renally, through obstruction of the urinary collection system by either intrinsic or extrinsic masses. Alternatively, AKI may originate within the renal system itself, by disorders of or injury affecting the structures of the nephron, such as the glomeruli, tubules, vessels, or interstitium.

[0004] CKD is a progressive loss of function over a prolonged period of time. An AKI patient who does not recover renal function may progress to CKD. Moreover, CKD-affected patients are prone to suffer AKI-like events.

[0005] 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 initially isolated from tissues such 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).

[0006] Notwithstanding the progress made to date, there still exists a need for new methods and compositions for detecting, preventing and/or treating renal conditions and disorders, such as acute kidney injury and chronic kidney disease.

SUMMARY OF THE INVENTION

[0007] The present invention provides methods and compositions useful for detecting, preventing, and treating conditions and disorders that involve disease, dysfunction, hypertrophy or hypotrophy of kidneys or renal tissue. Such conditions include, for example, chronic kidney or end stage renal failure, uremic syndrome, anemia and/or reduced erythropoietin production from the kidneys, diabetes, insulin resistance and reduced kidney function or kidney size.

[0008] The present inventors have discovered that, among other things, subjects suffering from renal conditions and disorders, such as chronic kidney disease, that are not effectively or optimally treated with presently available methods may be effectively treated with a composition that selectively reduces or inhibits GDF15 activity. 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.

[0009] In one aspect, the invention provides a method of increasing renal function in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a GDF15 modulator thereby to increase renal function in the subject. Renal function can include any of the biochemical and physiological parameters discussed below.

[0010] In another aspect, the invention provides a method of treating a subject having a renal disorder or renal dysfunction, the method comprising administering an effective amount of a composition comprising a GDF15 modulator thereby to ameliorate a symptom of the renal disorder or renal dysfunction. The symptoms can include any of the biochemical and physiological parameters discussed below.

[0011] In another aspect, the invention provides a method of reducing or reversing renal hypotrophy in a subject in need thereof wherein the subject has one or more symptoms of chronic kidney disease, the method comprising administering an effective amount of a composition comprising a GDF15 modulator thereby to reduce or reverse renal hypotrophy in the subject. The symptoms can include any of the biochemical and physiological parameters discussed below.

[0012] In another aspect, the invention provides a method of treating or preventing chronic kidney disease (CKD) in a subject in need thereof, the method comprising administering to the subject an effective amount of a composition comprising a GDF15 modulator thereby to treat or prevent CKD in the subject.

[0013] In certain embodiments, the subject exhibits a glomerular filtration rate (GFR) below 90 ml creatinine/minute/1.73m^2 body-surface area. In certain embodiments, the subject exhibits albuminuria (*e.g.*, urinary excretion of albumin in excess of 30 mg per day, 30 mg per liter of urine, or 30 µg/mg of creatinine in urine). In certain embodiments, the subject exhibits hyperuricemia, exhibits a serum uric acid level of at least 6.3 mg/dL, exhibits iron deficiency, or exhibits transferrin saturation of below 25% and a low ferritin level. In certain embodiments, the subject has been diagnosed as having chronic kidney disease.

[0014] In certain embodiments, the GDF15 modulator of the invention can decrease or inhibit GDF15 activity in the subject. In certain embodiments, the GDF15 modulator inhibits the activity, expression or binding of GDF15 to its cognate receptor. The GDF15 modulator can be an anti-GDF15 antibody, which can be humanized or human.

[0015] In other embodiments, the invention comprises a method of treating a subject exhibiting one or more of the following characteristics, which can be indicative of renal dysfunction or disease, such as chronic kidney disease. Such renal-related characteristics include:

(1) the subject exhibits reduced or below normal glomerular filtration rate (GFR);

(2) the subject exhibits albuminuria (microalbuminuria or macroalbuminuria);

(3) the subject exhibits elevated or above normal levels of serum creatinine (SCr);

(4) the subject exhibits reduced or below normal levels of urine output;

(5) the subject exhibits increased or above normal urinary excretion of neutrophil gelatinase-associated lipocalin (NGAL);

(6) the subject exhibits signs of proteinuria (protein in the urine), such as albumin, 2 macroglobulin or IgG, in amounts greater than 3.5 g/day;

(7) the subject exhibits hyperglycemia, hyperuricemia or dyslipidemia;

(8) the subject exhibits anemia or reduced erythropoietin production;

(9) the subject exhibits iron deficiency;

(10) the subject exhibits hyperfiltration;

(11) the subject has experienced, or is diagnosed to be at risk of experiencing a kidney failure;

(12) the subject has had, or has been diagnosed as being in need of, renal intervention, such as a kidney transplant or dialysis;

(13) the subject exhibits renal hypertrophy or renal hypotrophy;

(14) the subject exhibits levels of one or more biomarkers that are indicative of renal dysfunction.

[0016] In certain embodiments, useful biomarkers indicative of renal dysfunction include one or more of the following: cystatin C in the urine or plasma; urinary C-reactive protein (uCRP); urinary retinol-binding protein (uRBP); neutrophil gelatinase-associated lipocalin (NGAL); hepcidin; creatinine; hemojuvelin; uric acid and/or urea; beta trace protein; kidney injury molecule-1 (KIM-1); urinary N-acetyl-beta-(D)-glucosaminidase (NAG); urinary interleukin-18 (uIL-18); liver fatty acid binding protein-1 (L-FABP-1); blood urea nitrogen (BUN); micro-RNA 21 (miRNA-21); and electrolytes.

[0017] Subjects with abnormal levels of these biomarkers may be candidates for treatment with GDF15 modulators. In some embodiments, the clinician will use one or more of the above characteristics in combination with other observations, such as family history of kidney disease, or whether the subject has had, or has been diagnosed as requiring renal intervention, such as kidney transplant or dialysis.

[0018] The above renal-related characteristics and biomarkers 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 renal disorder, such as chronic kidney disease (CKD), has previously been treated with a known renal treatment, such as dialysis, 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 renal-related characteristics, and may also avoid or reduce the need for further renal treatments, by administering to the subject a GDF15 inhibitor.

[0019] In yet another aspect, the present invention comprises methods of improving 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 chronic kidney disease:

(1) reduced or below normal glomerular filtration rate (GFR);

(2) elevated or above normal levels of serum creatinine (SCr);

(3) reduced or below normal levels of urine output;

(4) increased or above normal urinary excretion of neutrophil gelatinase-associated lipocalin (NGAL);

(5) signs of proteinuria (protein in the urine), such as albumin, 2-macroglobulin or IgG, in amounts greater than 3.5 g/day;

(6) hyperglycemia, hyperuricemia or dyslipidemia;

(7) anemia or reduced erythropoietin production;

(8) iron deficiency;

(9) hyperfiltration; or

(10) has experienced, or is diagnosed to be at risk of experiencing a kidney failure;

(11) has had, or has been diagnosed as being in need of, renal intervention, such as a kidney transplant or dialysis.

(12) renal hypertrophy or renal hypotrophy;

(13) levels of one or more biomarkers that are indicative of renal dysfunction.

[0020] In certain embodiments, the GDF15 modulator of the invention can decrease or inhibit GDF15 activity in the subject. In certain embodiments, the GDF15 modulator inhibits the activity, expression or binding of GDF15 to its cognate receptor. The GDF15 modulator can be an anti-GDF15 antibody, which can be humanized or human.

[0021] The above renal-related characteristics can be monitored to confirm the subject's progress in response to treatment with GDF15 binding inhibitors in accordance with the present invention, and to modify the dosage regime if deemed clinically appropriate. In certain embodiments, the subject having a renal disorder, such as chronic kidney disease (CKD), has

previously been treated with a known renal 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 characteristics, and may also avoid or reduce the need for one of the renal interventions described above.

BRIEF DESCRIPTION OF THE FIGURES

[0022] **FIG. 1** is a graph showing the effect on mice of intra-peritoneal administration of 40 μg recombinant murine Fc-GDF15 protein or phosphate buffered saline (PBS), where body weight decreased significantly in animals treated with mFC-GDF15 (■) but not with PBS (●).

[0023] **FIGS. 2A-2B** are bar charts showing the effect of a single dose of 40 μg murine Fc-GDF15 recombinant protein injected intraperitoneally into mice, where both gonadal (**FIG. 2A**) and gastroc muscle (**FIG. 2B**) mass decreased significantly. For each time point, left hand bar is PBS, right-hand bar is mFc-GDF15.

[0024] **FIG. 3** is a bar chart showing the effect on mice following injection of recombinant murine Fc-GDF15. For each marker (*e.g.*, ALT), left-hand bar is naïve, right hand bar is GDF15. Mice treated with GDF15 exhibited lower levels of liver enzymes alanine aminotransferase (ALT); alkaline phosphatase (ALK), as well an increase in urea levels (urea nitr.) in blood, a marker of kidney impairment.

[0025] **FIG. 4A** is a graph showing that body weight loss is reversed in immune-incompetent mice (ICR-SCID) bearing an HT-1080 fibrosarcoma tumor xenograft model following administration of 2 mg/kg of an anti-GDF15 antibody (01G06). Arrows indicate intra-peritoneal injection of antibody. **FIG. 4B** is a bar chart showing that administration of the anti-GDF15 antibody increased organ mass (liver, heart, spleen, kidney) and increased tissue mass (gonadal and gastrocnemius) compared to negative control (murine IgG (●) and baseline (day 1).

[0026] **FIG. 5A** is a graph showing the effect of systemic administration of anti-GDF15 antibody (Hu01G06-127) on ICR Scid mice bearing HT-1080 human tumor xenografts. Such mice exhibit significant body weight loss. Administration of anti-GDF15 antibody (▲) but not

human IgG (■) reversed the loss of body weight. **FIG. 5B** is a bar chart showing that administration of an anti-GDF antibody, but not human IgG, restored gonadal mass.

[0027] **FIG. 6** is a bar chart showing the effect on serum levels of urea nitrogen following administration of antibody to GDF15. Mice bearing HT-1080 human tumor xenografts exhibited increased levels of serum urea nitrogen, a marker of kidney impairment. This increase is reversed by the administration of an anti-GDF15 antibody. Bars from left to right are SHAM, Baseline (93%), hIgG 10 mpk, and Hu01G06-127 10 mpk.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The present invention provides methods and compositions for treating a subject having any of a number of kidney-related or renal disease states, for example, a subject having chronic kidney disease, end stage renal failure, diabetes, insulin resistance, kidney hypertrophy, kidney hypotrophy, polycystic kidney disease, proteinuria, hyperglycemia, hyperuricemia, uremic syndrome, gout, kidney stones, hypertension or hypertensive nephropathy, dyslipidemia, anemia and/or reduced erythropoietin production; iron deficiency or hyperfiltration, where such disease state is associated with a renal disorder. The methods and compositions may be useful in treating a subject with chronic kidney disease, which may be caused by the above disease states, or who exhibits at least one characteristic that is symptomatic of chronic kidney disease, renal failure, uremic syndrome, renal dystrophies, other renal conditions or disorders, acute kidney injury, acute kidney disease or adverse clinical outcomes resulting in acute renal failure, for example, obstructive nephropathy, including one or more of the following:

(1) reduced or below normal glomerular filtration rate (GFR);

(2) elevated or above normal levels of serum creatinine (SCr);

(3) reduced or below normal levels of urine output;

(4) increased or above normal urinary excretion of neutrophil gelatinase-associated lipocalin (NGAL);

(5) signs of proteinuria (protein in the urine), such as albumin, 2 macroglobulin or IgG, in amounts greater than 3.5 g/day;

(6) hyperglycemia, hyperuricemia or dyslipidemia;

(7) anemia or reduced erythropoietin production;

(8) iron deficiency;

(9) hyperfiltration; or

(10) is experiencing, or is diagnosed to be at risk of experiencing a kidney failure;

(11) has had, or has been diagnosed as needing renal intervention, such as a kidney transplant or dialysis.

(12) renal hypertrophy or renal hypotrophy;

(13) levels of one or more biomarkers that are indicative of renal dysfunction.

[0029] In a particular embodiment of the present invention, the subject exhibits chronic kidney disease (CKD). Accordingly, a subject having CKD or another kidney-related disease or disorder who exhibits symptoms of CKD or who is diagnosed as having CKD or at risk of having CKD may not be optimally treated by existing treatments. In such cases, treatment in accordance with the methods and compositions of the present invention may be especially beneficial in improving one or more of the characteristics above. In particular embodiments, the subject exhibits one or more of the following characteristics such that the subject is considered to have CKD or considered to be suffering from CKD, such that the subject may benefit from treatment according to the present invention. As used throughout the application, the term "considered to have CKD" or "considered to be suffering from CKD" 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 CKD" or "considered to be suffering from CKD" 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 CKD. The term "considered to be at risk of developing CKD" 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 CKD" 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 CKD, sufficient to justify prophylactic or therapeutic intervention.

[0030] 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. Symptoms of Chronic Kidney Disease, Renal Failure or Kidney Dysfunction

[0031] A major criteria useful for the classification, diagnosis and monitoring of subjects for chronic kidney disease is glomerular filtration rate (GFR). The National Kidney Foundation has established criteria for the definition of CKD in which a subject with one or more CKD risk factors. Generally, GFR is measured in terms of clearance or filtration of ml of creatinine per minute per 1.73m^2 body-surface area. However, cystatin C, another marker for CKD prognosis, is a potential alternative to serum creatinine for estimating GFR. See, Inker *et al.*, 2012, N. E. J. MEDICINE, 367:20-29.

[0032] A subject exhibiting GFR less than 90 is considered to have CKD. A subject exhibiting GFR greater than or equal to 90 (ml/minute/1.73m^2 body-surface area) may be considered to be at CKD stage 1, or at an increased risk of CKD, after taking into consideration other indicators of CKD. For example, indicators of CKD risk factors include higher than normal levels of creatinine or urea in the blood, blood or protein in the urine, and a family history of polycystic kidney disease. A subject exhibiting kidney damage with a GFR between 60 and 89 ml/minute/1.73m^2 body-surface area is considered to be at CKD stage 2. A subject exhibiting a GFR between 30 and 59 ml/minute/1.73m^2 body-surface area is considered to be at CKD stage 3, at which many clinicians consider the possibilities of renal intervention. Among the interventions are strict dietary modification plans, in which daily intake of phosphorus, calcium, carbohydrates and sodium may be recommended. Supplementation of the diet with protein, water-soluble vitamin B complex, and vitamin C also may be recommended. A subject exhibiting GFR between 15 and 29 ml/minute/1.73m^2 body-surface area is considered to be at CKD stage 4, at which many clinicians consider dialysis and/or preparation for kidney replacement. A subject exhibiting GFR of less than 15 ml/minute/1.73m^2 body-surface area is considered to be at CKD stage 5, or kidney failure, an urgent stage at which intervention such as kidney replacement may be urgently needed, particularly if uremia is present. A subject presenting with CKD stages 1-5 may benefit from therapy according to the present invention,

in order to fully or partially restore the loss of kidney function, or to slow or prevent further deterioration of kidney function.

[0033] A subject is considered to be suffering from chronic kidney disease if their urinary NGAL levels are in excess 50 μg/L; and more serious CKD if the urinary or plasmatic NGAL levels are in excess of 100 μg/L. Lippi *et al.*, 2011, CLIN CHEM LAB MED, 50(9):1581-1584; Bolignano *et al.*, 2008, AMERICAN J. OF KIDNEY DISEASES, 52:595-605.

[0034] A subject can be considered to be suffering from chronic kidney disease if they exhibit microalbuminuria: urinary excretion of albumin in excess of 30 mg per day, 30 mg per liter of urine, or 30 μg/mg of creatinine in urine. A subject is considered to be suffering from serious CKD if they exhibit macroalbuminuria: their urinary excretion of albumin is 300 mg or more per day, 300 mg or more per liter of urine, or 300 μg or more/mg of creatinine in urine. See Levey and Coresh, 2012, THE LANCET, 379:165-180.

[0035] For purposes of the present invention, a subject is considered to be suffering from chronic kidney disease if they exhibit uric acid in the blood in excess of 530 micromol/L (6 mg/dL) for women and 619 micromol/L (7 mg/dL) for men or if they suffer from kidney stones. See also, peak VO_2, Jalal *et al.*, 2012, AM. J. OF KIDNEY DISEASE, 62:134-146.

[0036] For purposes of the present invention, a subject is considered to be suffering from chronic kidney disease if they exhibit iron deficiency, particularly a low transferrin saturation (<25%) coupled with low ferritin (< 200 ng/mL in dialysis patients; < 100 ng/mL in non-dialysis patients). See Larson and Coyne, 2013, KIDNEY RESEARCH AND CLINICAL PRACTICE, 32:11-15.

[0037] For purposes of the present invention, a subject is considered to be suffering from chronic kidney disease if they experience renal or kidney hypertrophy, hyperplasia, or increase in kidney mass, which is due to underlying disease. Kidney hypertrophy may be compensatory, for loss of kidney tissue function. For example, hypertrophy is frequently observed in patients with a solitary functional kidney. Krill *et al.*, 2012, J. UROLOGY, 188supp:1613-1617. Cell hypertrophy can be assessed by total protein/cell and electronic volume. See Huang *et al.*, 2014, MOLECULAR AND CELLULAR ENDOCRINOLOGY, 390:45-53.

[0038] For purposes of the present invention, a subject is considered to be suffering from chronic kidney disease if they experience renal hypotrophy, hypoplasia, or significant decrease in kidney mass. Renal hypotrophy can be assessed, for example, by magnetic resonance imaging. See Chang *et al.*, 2007, J. UROLOGY, 178:2550-2554.

[0039] In particular embodiments of the present invention, the subject exhibits one or more additional symptoms of chronic kidney disease. This may include one or more of the following indicators of chronic kidney disease, renal failure or kidney dysfunction: increased serum creatinine levels, decreased serum bilirubin levels, increased urine albumin concentration, increased urinary creatinine levels, increased urinary albumin-to-creatine ratio (albumin-to-creatinine ratio of 25 mg/g or higher in women and 17 mg/g or higher in men, with a value of 30 mg/g indicative of serious CKD), increased urinary protein-to-creatinine ratio (protein-to-creatinine ratio of 200 mg/g is considered to be too high and indicative of CKD), hypertension (defined as systolic blood pressure of 140 mm Hg or above; diastolic blood pressure of 90 mm Hg or above; or undergoing current antihypertensive drug treatment), diabetes mellitus (defined as fasting glucose level of 126 mg/dL or higher; or the use of insulin or oral hypoglycemic medications); appearance of cystatin C in the urine or plasma, urinary C-reactive protein (uCRP), urinary retinol-binding protein (uRBP), hepcidin, increased serum levels of creatinine, hemojuvelin; uric acid and/or urea; beta trace protein; kidney injury molecule-1 (KIM-1); urinary N-acetyl-beta-(D)-glucosaminidase (NAG); urinary interleukin-18 (uIL-18); liver fatty acid binding protein-1 (L-FABP-1); blood urea nitrogen (BUN); micro-RNA 21 (miRNA-21); and electrolytes.

[0040] In certain embodiments, useful biomarkers indicative of renal dysfunction include one or more of the following: cystatin C in the urine or plasma; urinary C-reactive protein (uCRP); urinary retinol-binding protein (uRBP); neutrophil gelatinase-associated lipocalin (NGAL); hepcidin; creatinine; hemojuvelin; uric acid and/or urea; beta trace protein; kidney injury molecule-1 (KIM-1); urinary N-acetyl-beta-(D)-glucosaminidase (NAG); urinary interleukin-18 (uIL-18); liver fatty acid binding protein-1 (L-FABP-1); blood urea nitrogen (BUN); micro-RNA 21 (miRNA-21); and electrolytes.

[0041] In addition, retention of potentially toxic solutes, including phosphates, dimethyarginines (asymmetric, or ADMA, and symmetric, or SDMA), uric acid, parathyroid

hormone (PTH), fibroblast growth factor 23 (FGF23), beta-2 microalbumin (B2M), interleukin-6 (IL-6), protein-bound indoxyl sulfate (IS) and p-cresol and its conjugates, p-cresylsulfate (PCS) and p-cresylglucuronide (PCG), may be indicative of decreased renal function or a renal disorder, *e.g.*, "uremic syndrome." See, Liabeuf *et al.*, 2014, SEMIN NEPHROL, 34(2):164-179, http://dx.doi.org/10.1016/j.semnephro.2014.02.008.

[0042] Subjects with abnormal levels of these biomarkers may be candidates for treatment with GDF15 modulators. In some embodiments, the clinician will use one or more of the above characteristics in combination with other observations, such as family history of kidney disease, or whether the subject has had, or has been diagnosed as requiring renal intervention, such as kidney transplant or dialysis.

[0043] The above renal-related characteristics and biomarkers 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 renal disorder, such as chronic kidney disease (CKD), has previously been treated with a known renal treatment, such as dialysis, 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 renal-related characteristics, and may also avoid or reduce the need for further renal treatments, by administering to the subject a GDF15 inhibitor.

[0044] 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 renal disorder or dysfunction.

[0045] 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 renal disease or dysfunction, for example, CKD, and may be determined at a pre-specified cutoff of, for example, the 75^{th} percentile (*i.e.*, upper quartile or 25%); 90^{th} percentile (*i.e.*, upper 10%); or 95^{th} 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 renal disease or dysfunction, for example, CKD. See, for example, Brown *et al.*, 2002, THE LANCET 359:2159-2163; Kempf *et al.*, 2011, NATURE MEDICINE, 17:581-588.

[0046] 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, for example, 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.

[0047] 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.

II. Comorbidities of Chronic Kidney Disease

[0048] Chronic kidney disease 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 CKD. Among the frequent comorbidities of CKD are cachexia, chronic or congestive heart failure, anemia, diabetes and hypertension. Accordingly, the present invention includes methods of increasing renal function in a subject in need thereof, the method comprising administering an effective amount of a composition comprising a GDF15 inhibitor to increase renal function in a subject who. For example, the subject suffering from renal dysfunction or CKD may exhibit a comorbidity of cachexia, chronic or congestive heart failure, anemia, diabetes or hypertension.

III. GDF15 Modulators

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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)

[0053] 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)

[0054] Exemplary anti-GDF15 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 CKD or another kidney-related disease or disorder who exhibits symptoms of CKD or who is diagnosed as having CKD or at risk of having CKD. In some embodiments, the antibodies reverse a symptom or characteristic of CKD or another kidney-related disease or disorder by at least 2%, 5%, 10%, 15%, 20%, 25%, 30% or 35%.

[0055] In a preferred embodiment, an anti-GDF15 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-GDF15 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.

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
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

[0056] It is understood that the antibodies described herein can be designed, tested, and formulated using techniques known in the art.

[0057] 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
```

[0058] 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
```

[0059] 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
```

[0060] 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
```

[0061] 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
```

[0062] 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
```

[0063] 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
```

[0064] 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
```

[0065] 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
```

[0066] 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
```

[0067] 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
```

[0068] 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
```

[0069] 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
```

[0070] 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
```

[0071] 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
```

[0072] 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
```

[0073] 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
```

[0074] 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
```

[0075] 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
```

[0076] 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
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[0077] 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
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[0078] 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
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[0079] 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
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[0080] 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
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[0081] 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
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[0082] 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
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[0083] 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
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[0084] 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
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[0085] 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
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[0086] 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
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[0087] 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
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[0088] 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
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[0089] 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
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[0090] 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
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[0091] 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.

[0092] 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.

[0093] 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).

[0094] 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.

[0095] 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.

[0096] 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).

[0097] 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).

[0098] 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.

[0099] 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).

[00100] Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of an antibody.

[00101] 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).

[00102] 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).

[00103] 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

[00104] 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.

[00105] 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.

[00106] 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, a GDF15 modulator (*e.g.*, an antibody) is lyophilized, and then reconstituted in buffered saline, at the time of administration.

[00107] For therapeutic use, a GDF15 modulator (*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.

[00108] 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.

[00109] 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 a GDF15 modulator (*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 GDF15 modulator (*e.g.*, an antibody), and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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.

[00115] 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.

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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).

[00120] 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.

[00121] 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.

[00122] 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.

[00123] 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.

[00124] 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.

[00125] 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.

[00126] 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).

[00127] 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.

[00128] 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.

[00129] 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.

[00130] 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.

[00131] 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.

[00132] 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.

[00133] 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: Administration of Recombinant mFc-GDF15 Increases Blood Urea Levels

[00134] ICR SCID (spontaneous mutant T&B cell deficient) mice were injected intraperitoneally with a PBS solution (control) or 40 μg of a murine, recombinant Fc-GDF15 protein. Body weight, and molecular markers for muscle degradation (Atrogin, MurF1), adipogenesis (Glut4, Leptin, C/EPBβ) and lipid accumulation (Stearoyl-CoA desaturase, Fatty acid synthase) were measured after injection.

[00135] **FIG. 1** shows that mice injected with Fc-GDF15 exhibited significant body weight loss. Similarly, mice injected with Fc-GDF15 exhibited significant loss of gonadal mass (**FIG. 2A**) and gastroc mass (**FIG. 2B**). The treated mice also exhibited upregulation of markers for muscle degradation (Atrogin, MurF1) and downregulation of markers of adipogenesis (Glut4, leptin) and lipid accumulation (stearoyl-CoA desaturase; fatty acid synthase).

[00136] Mice treated with Fc-GDF15 also exhibited lower levels of liver enzymes (alanine aminotransferase (ALT), alkaline phosphatase (ALK); and an increase in urea levels in blood (urea nitrogen, a marker of kidney impairment) (**FIG. 3**), consistent with a role of GDF15 in kidney function.

EXAMPLE 2: Treatment of Renal Hypotrophy in an HT-1080 Xenograft Tumor Model

[00137] This Example demonstrates the treatment of renal hypotrophy (as indicated by kidney weight loss) by an anti-GDF15 antibody (01G06) in an HT-1080 fibrosarcoma xenograft model. 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 x 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 via intraperitoneal injection: murine IgG control, murine 01G06 dosed at 2 mg/kg on day 1 and day 7. 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. Treatment with anti-GDF15 antibody 01G06 resulted in body weight increase to initial weight or 100% ($p<0.001$) (**FIG. 4A**), and in kidney weight increase (**FIG. 4B**).

[00138] As shown in **FIG. 4B**, 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 anti-GDF15 antibody 01G06. In addition, mice treated with anti-GDF15 antibody 01G06 displayed significant liver and gonadal muscle gain compared to the baseline group (**FIG. 4B**).

[00139] The data in **FIGS. 4A-B** indicate that an anti-GDF15 antibody can reverse kidney weight loss in an HT-1080 fibrosarcoma xenograft model. Similarly, the results indicate that an anti-GDF15 antibody can reverse the loss of organ mass, such as kidney mass, loss of muscle mass, loss of fat and involuntary weight loss in an HT-1080 xenograft tumor model.

EXAMPLE 3: Treatment with Anti-GDF15 Antibody Reverses Elevated Levels of Urea Seen in Mice Bearing HT-1080 Human Tumor Xenographs

[00140] ICR SCID (spontaneous mutant T&B cell deficient) mice bearing HT-1080 human tumor xenografts, as in Example 2, exhibit cachexia. Systemic administration of 10 mg/kg of an anti-GDF15 antibody (Hu01G06-127) but not human IgG reversed the body weight loss observed in mice bearing HT-1080 human tumor xenografts (**FIG. 5A**), as well gonadal weight loss (**FIG. 5B**). Administration of the anti-GDF15 antibody also reversed elevated levels of urea observed in mice bearing HT-1080 human tumor xenografts (**FIG. 6**).

EXAMPLE 4: *In Vivo* Model of Chronic Kidney Disease

[00141] Sub-total nephrectomy, mimics the progressive renal failure after loss of renal mass in humans. As described in Ma and Fogo, 2003, KIDNEY INTERNATIONAL, 64:350-355, one kidney is removed and approximately 2/3 of the remaining kidney is ablated, resulting in reduced kidney functional relevant to progressive kidney disease. Animals are dosed with either anti-GDF15 antibody or control at the time of treatment. Animals are assessed for body and kidney size and weight, glomerular filtration rate, serum creatinine and other markers for kidney disease.

EXAMPLE 5: Ureteral Obstruction Model of Progressive Renal Disease.

[00142] Unilateral ureteral obstruction (UUO) in animals, as described in Chevalier *et al.*, 2009, KIDNEY INTERNATIONAL, 75:1145-1152, is a model of renal fibrosis and chronic kidney injury. Ureteral obstruction can be accomplished by ligation, or by placement of a reversible obstruction. Animals are dosed with either anti-GDF15 antibody or control at the time of treatment. Animals are assessed for body and kidney size and weight, glomerular filtration rate, systolic blood pressure, atrophy of the tubules and tubular apoptosis. Glomerular filtrate rate can be measured following relief of UUO using standard clearance techniques.

EXAMPLE 6: Treatment of Subjects Previously Treated with Other Renal Interventions

[00143] Subjects exhibiting renal hypotrophy who have previously been treated with known renal interventions, but who exhibit at least one characteristic of chronic kidney disease, are treated with an anti-GDF15 antibody. Treatment with an anti-GDF15 antibody lasts for a duration of 3 months, during which kidney size, creatinine levels, glomerular filtration rate, and renal output are monitored at regular intervals.

INCORPORATION BY REFERENCE

[00144] The entire disclosure of each of the patent documents and scientific articles referred to herein, including U.S. Patent Application Serial No. 62/015,093, filed June 20, 2014, is incorporated by reference for all purposes.

EQUIVALENTS

[00145] 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.

[00146] In a first embodiment there is provided a method of increasing renal function in a subject in need thereof, the method comprising administering an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to increase renal function in the subject, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

[00147] In a second embodiment there is provided a method of treating a subject having a renal disorder or renal dysfunction in need thereof, the method comprising administering an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to ameliorate a symptom of the renal disorder or renal dysfunction, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of

SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

[00148] In a third embodiment there is provided a method of reducing or reversing renal hypotrophy in a subject in need thereof wherein the subject has one or more symptoms of chronic kidney disease, the method comprising administering an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to reduce or reverse renal hypotrophy in the subject, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

[00149] In a fourth embodiment there is provided a method of treating or preventing chronic kidney disease (CKD) in a subject in need thereof, the method comprising administering to the subject an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to treat or prevent CKD in the subject, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

[00150] In a fifth embodiment there is provided the use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for increasing renal function, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

[00151] In a sixth embodiment there is provided the use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for ameliorating a symptom of renal disorder or renal dysfunction in need thereof, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

[00152] In a seventh embodiment there is provided the use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for reducing or reversing renal hypotrophy in a subject in need thereof, wherein the subject has one or more symptoms of chronic kidney disease, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence

of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

[00153] In an eighth embodiment there is provided the use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for treating or preventing chronic kidney disease (CKD) in a subject in need thereof, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21

[00154] In the present specification and claims, the word 'comprising' and its derivatives including 'comprises' and 'comprise' include each of the stated integers but does not exclude the inclusion of one or more further integers.

[00155] The reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

Claims

1. A method of increasing renal function in a subject in need thereof, the method comprising administering an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to increase renal function in the subject, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

2. A method of treating a subject having a renal disorder or renal dysfunction in need thereof, the method comprising administering an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to ameliorate a symptom of the renal disorder or renal dysfunction, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID

NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

3. A method of reducing or reversing renal hypotrophy in a subject in need thereof wherein the subject has one or more symptoms of chronic kidney disease, the method comprising administering an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to reduce or reverse renal hypotrophy in the subject, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

4. A method of treating or preventing chronic kidney disease (CKD) in a subject in need thereof, the method comprising administering to the subject an effective amount of a composition comprising an anti-GDF15 antibody that decreases or inhibits GDF15 activity thereby to treat or prevent CKD in the subject, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

5. The method of any one of claims 1-4, wherein the subject has an elevated blood level of GDF15.

6. The method of any one of claims 1-5, wherein the subject exhibits a glomerular filtration rate (GFR) below 90 ml creatinine/minute/1.73m^2 body-surface area.

7. The method of any one of claims 1-6, wherein the subject exhibits albuminuria.

8. The method of claim 7, wherein the subject exhibits urinary excretion of albumin in excess of 30 mg per day, 30 mg per liter of urine, and/or 30 μg/mg of creatinine in urine.

9. The method of any one of claims 1-8, wherein the subject exhibits hyperuricemia.

10. The method of claim 9, wherein the subject exhibits a serum uric acid level of at least 6.3 mg/dL.

11. The method of any one of claims 1-10, wherein the subject exhibits iron deficiency.

12. The method of claim 11, wherein the subject exhibits transferrin saturation of below 25% and a low ferritin level.

13. The method of any one of claims 1-12, wherein the subject has been diagnosed as having chronic kidney disease.

14. The method of claim 15, wherein the anti-GDF15 antibody is humanized or human.

15. The method of any one of claims 1-14, wherein the anti-GDF15 antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 47 and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 30.

16. The method of any one of claims 1-14, wherein the anti-GDF15 antibody comprises (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 1, a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 7,

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and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 13; and (ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 16, a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 18, and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 22.

17. Use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for increasing renal function, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

18. Use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for ameliorating a symptom of renal disorder or renal dysfunction in need thereof, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID

NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

19. Use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for reducing or reversing renal hypotrophy in a subject in need thereof, wherein the subject has one or more symptoms of chronic kidney disease, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

20. Use of an anti-GDF15 antibody that decreases or inhibits GDF15 activity, in the manufacture of a medicament for treating or preventing chronic kidney disease (CKD) in a subject in need thereof, wherein the antibody is selected from:

(a) an antibody comprising the heavy chain sequence of SEQ ID NO:47 or 49 and the light chain sequence of SEQ ID NO:30;

(b) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, 45, 46, or 48 and the light chain sequence of SEQ ID NO:29;

(c) an antibody comprising the heavy chain sequence of SEQ ID NO:41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:28;

(d) an antibody comprising the heavy chain sequence of SEQ ID NO:39, 40, 41, 42, 43, 44, or 45 and the light chain sequence of SEQ ID NO:27;

(e) an antibody comprising the heavy chain sequence of SEQ ID NO:38 and the light chain sequence of SEQ ID NO:26;

(f) an antibody comprising the heavy chain sequence of SEQ ID NO:37 and the light chain sequence of SEQ ID NO:25;

(g) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:7 or 9, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:22;

(h) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, 5, 6, or 8, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(i) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(j) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4 or 5, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21;

(k) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21; and

(l) an antibody comprising a heavy chain CDR_{H1} sequence of SEQ ID NO:1, a heavy chain CD_{H2} sequence of SEQ ID NO:4, and a heavy chain CDR_{H3} sequence of SEQ ID

NO:13; and

a light chain CDR_{L1} sequence of SEQ ID NO:16, a light chain CDR_{L2} sequence of SEQ ID NO:18, and a light chain CDR_{L3} sequence of SEQ ID NO:21.

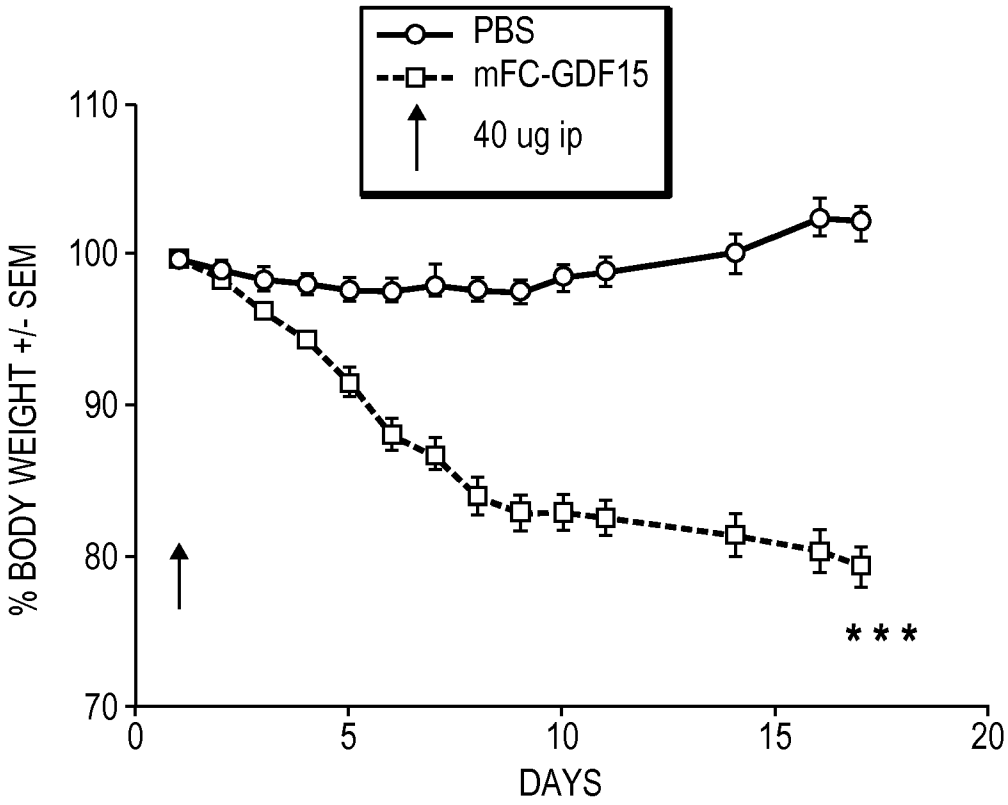
PBS
mFC-GDF15
40 ug ip
110
100
90
80
70
% BODY WEIGHT +/- SEM
0
5
10
15
20
DAYS
* * *

FIG. 1

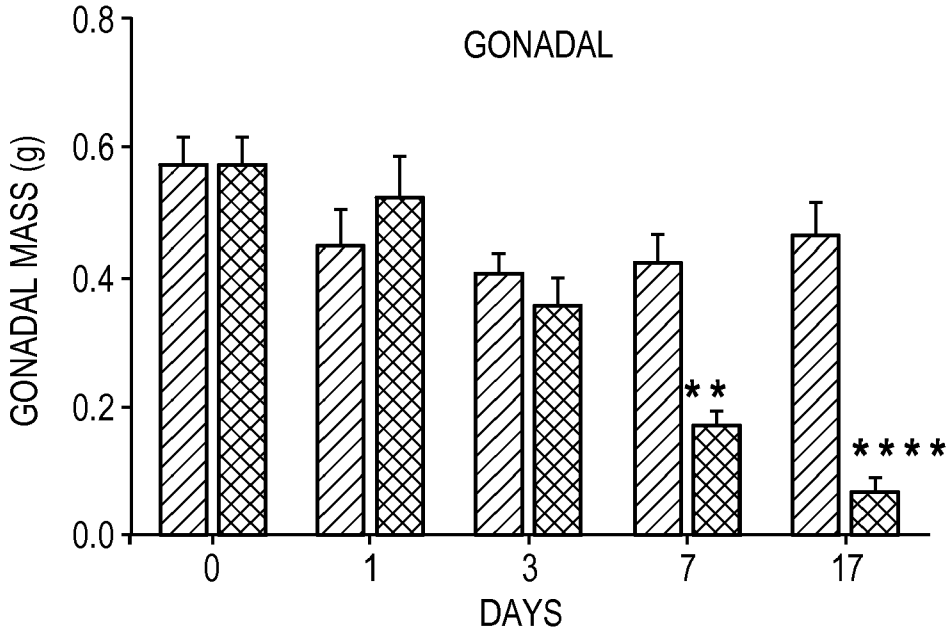
GONADAL
GONADAL MASS (g)
0.8
0.6
0.4
0.2
0.0
0
1
3
7
17
DAYS
**
****

FIG. 2A

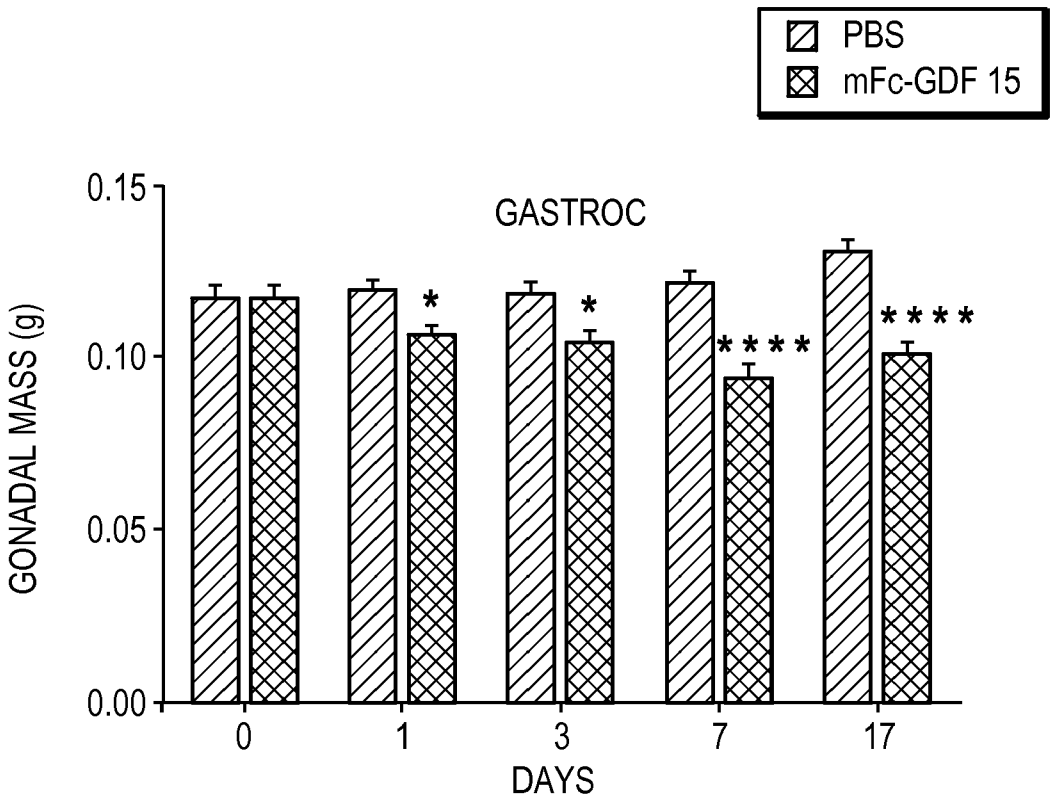
PBS
mFc-GDF 15
GASTROC
GONADAL MASS (g)
0.15
0.10
0.05
0.00
0
1
3
7
17
DAYS
*
*
****
****

FIG. 2B

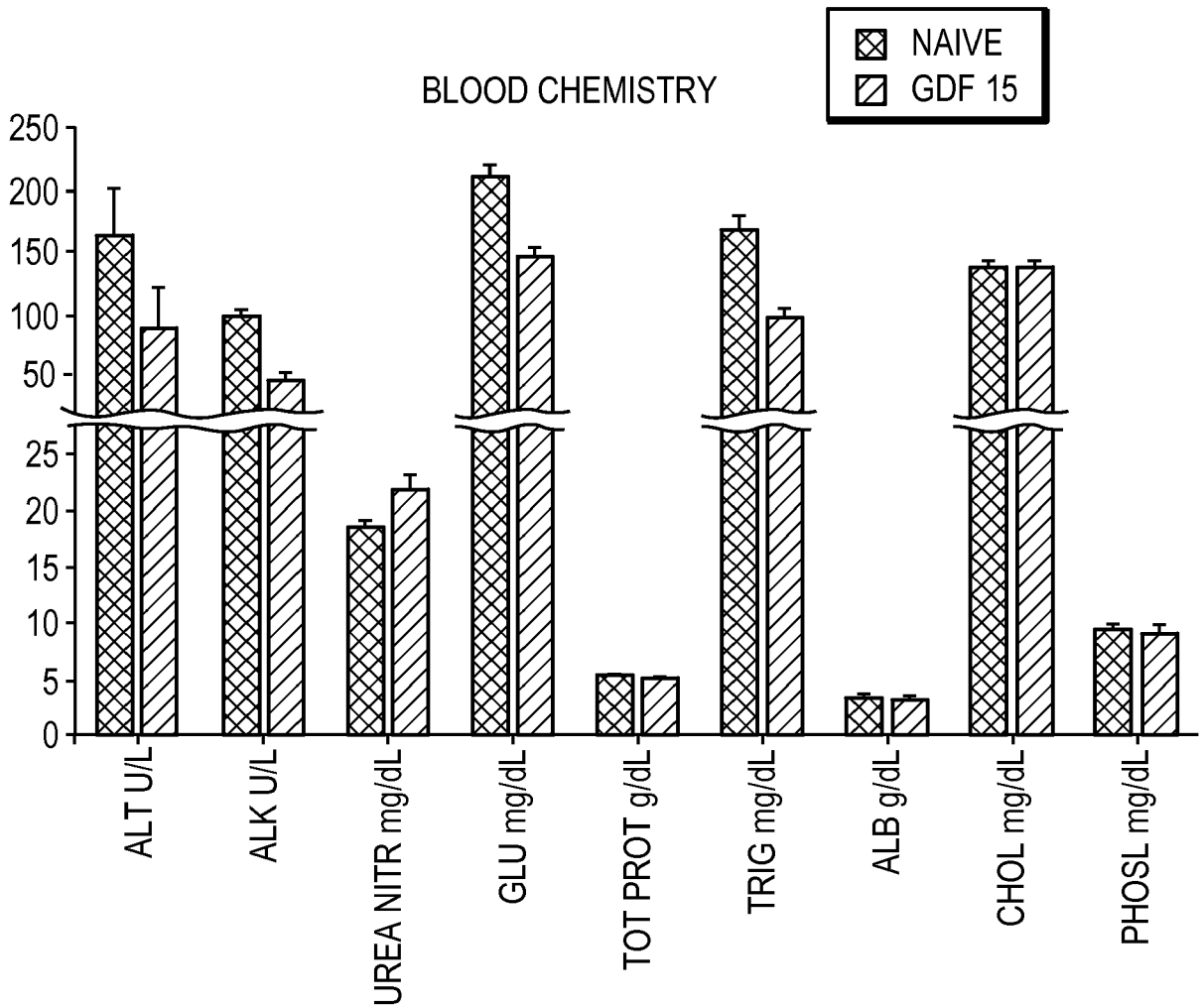
BLOOD CHEMISTRY
NAIVE
GDF 15
250
200
150
100
50
25
20
15
10
5
0
ALT U/L
ALK U/L
UREA NITR mg/dL
GLU mg/dL
TOT PROT g/dL
TRIG mg/dL
ALB g/dL
CHOL mg/dL
PHOSL mg/dL

FIG. 3

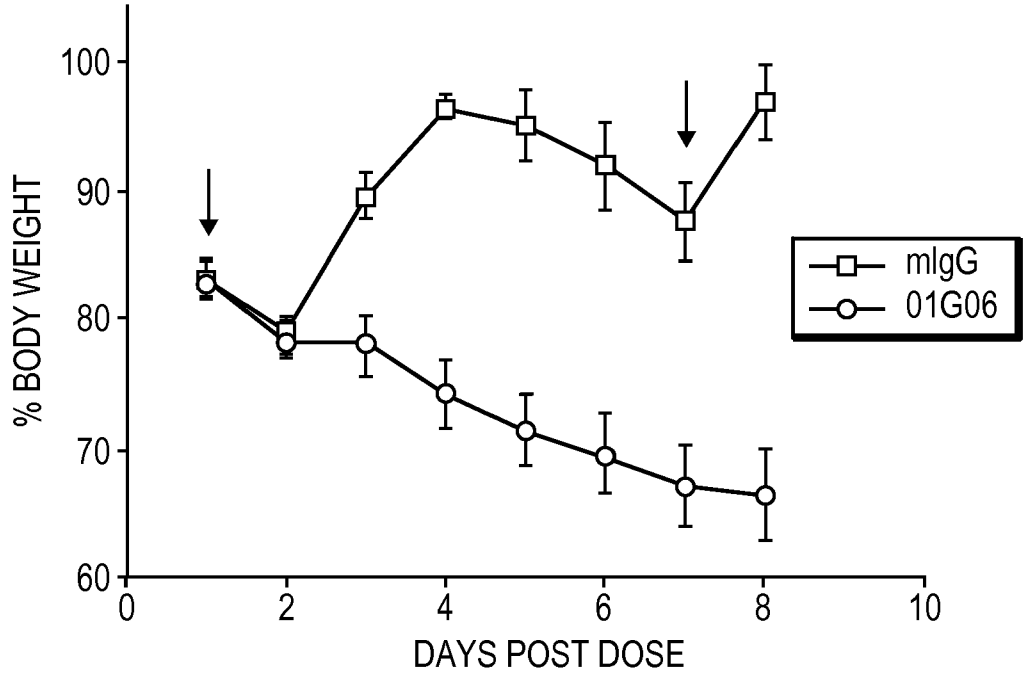
% BODY WEIGHT
100
90
80
70
60
0
2
4
6
8
10
DAYS POST DOSE
mIgG
01G06

FIG. 4A

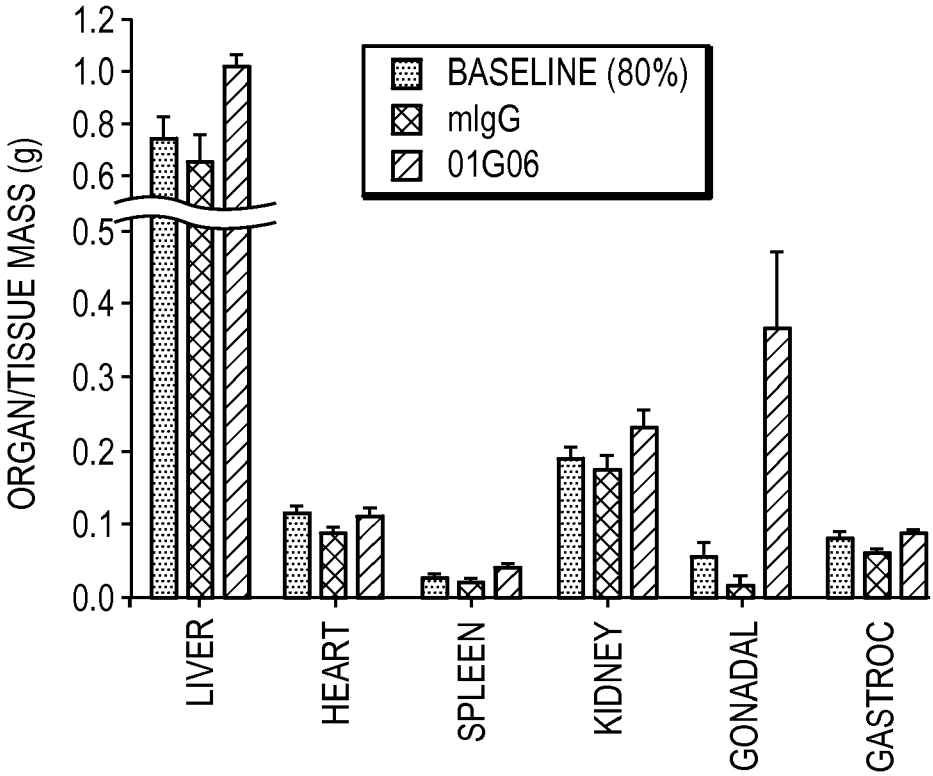
ORGAN/TISSUE MASS (g)
1.2
1.0
0.8
0.6
0.5
0.4
0.3
0.2
0.1
0.0
BASELINE (80%)
mIgG
01G06
LIVER
HEART
SPLEEN
KIDNEY
GONADAL
GASTROC

FIG. 4B

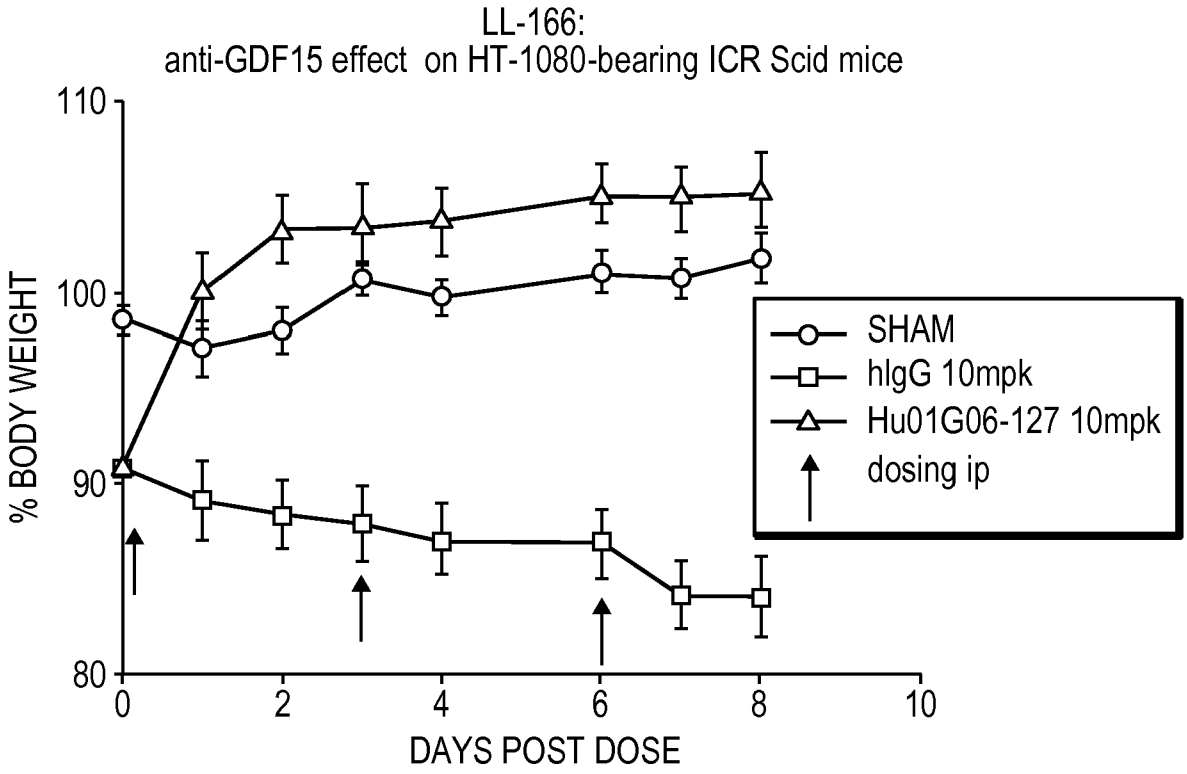
LL-166:
anti-GDF15 effect on HT-1080-bearing ICR Scid mice
% BODY WEIGHT
110
100
90
80
0
2
4
6
8
10
DAYS POST DOSE
SHAM
hIgG 10mpk
Hu01G06-127 10mpk
dosing ip

FIG. 5A

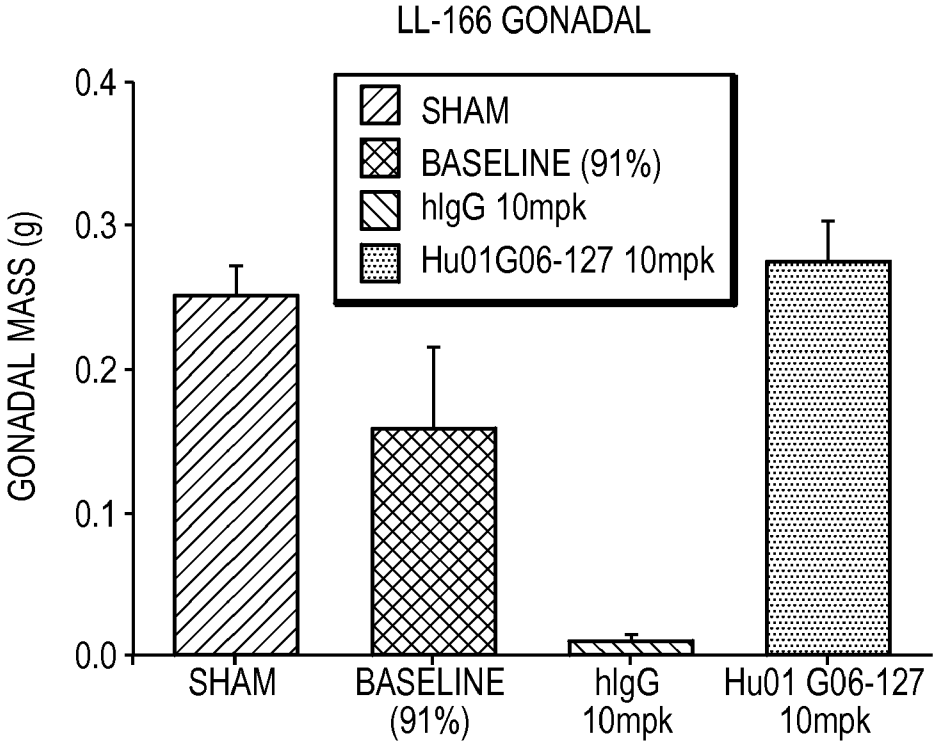
LL-166 GONADAL
GONADAL MASS (g)
0.4
0.3
0.2
0.1
0.0
SHAM
BASELINE (91%)
hIgG 10mpk
Hu01G06-127 10mpk
SHAM
BASELINE (91%)
hIgG 10mpk
Hu01 G06-127 10mpk

FIG. 5B

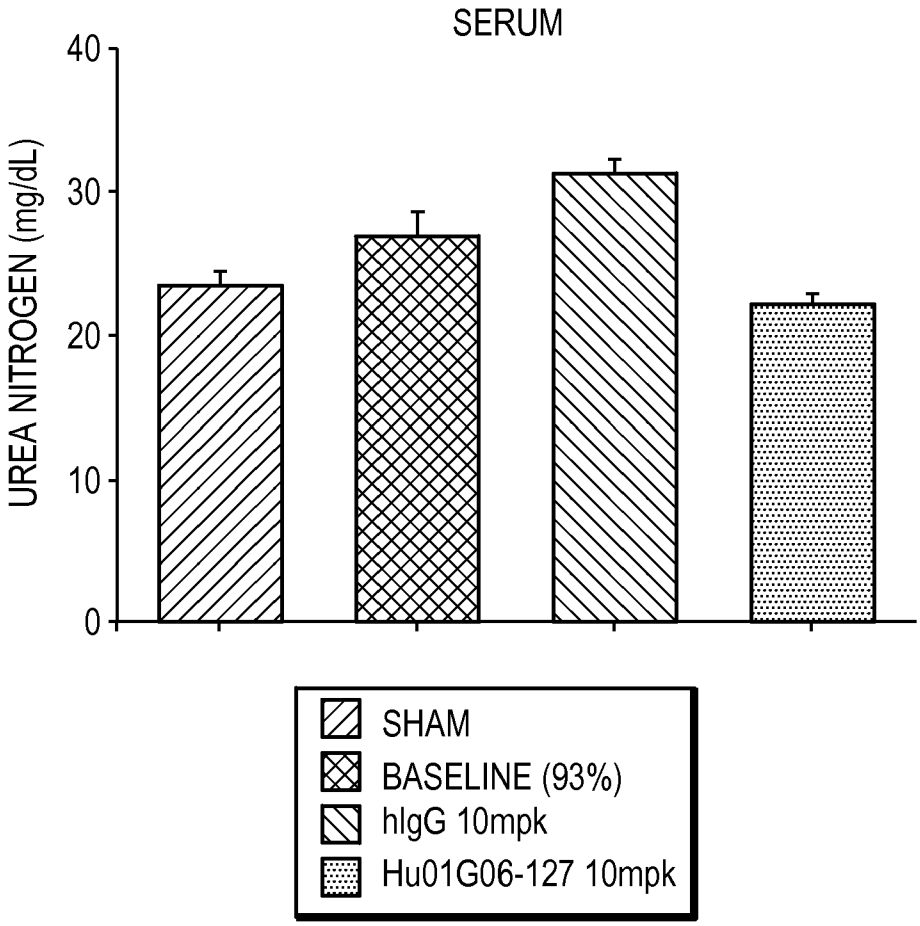
SERUM
UREA NITROGEN (mg/dL)
40
30
20
10
0
SHAM
BASELINE (93%)
hIgG 10mpk
Hu01G06-127 10mpk

FIG. 6