(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2012 (02.02.2012)

PCT

(10) International Publication Number
WO 2012/015674 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61P 9/10* (2006.01)
A61K 39/395 (2006.01) *A61P 13/12* (2006.01)
A61P 3/00 (2006.01)

(21) International Application Number:
PCT/US2011/044913

(22) International Filing Date:
22 July 2011 (22.07.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/367,600 26 July 2010 (26.07.2010) US

(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BREYER, Matthew, Douglas** [US/US]; c/o Eli Lilly and Company, P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **KHARITONENKOV, Alexei** [US/US]; c/o Eli Lilly and Company, P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US). **SMITH, Rosamund, Carol** [US/US]; c/o Eli Lilly and Company, P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(74) Agents: **CASTETTER, Andrea, M.** et al.; Eli Lilly and Company, P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2012/015674 A1

(54) **Title**: THERAPEUTIC USES OF AN FGFR1c ANTIBODY

(57) **Abstract**: The present invention relates to therapeutic uses of an FGFR1c antibody, such as treating or preventing hyperphosphatemia or calcinosis, chronic renal disease or chronic renal failure, tissue and vascular calcification, or albuminuria and proteinuria in a patient.

THERAPEUTIC USES OF AN FGFR1c ANTIBODY

The present invention relates to therapeutic uses of an FGFR1c antibody.

There are many disease conditions in which mineral ion homeostasis, particularly dysregulation of serum phosphate levels, is disturbed contributing to a variety of complications including those of the skeletal and vascular systems.

FGF23 is a key regulator of phosphate homeostasis. FGF23 is a phosphaturic hormone that is induced in bone under conditions of hyperphosphatemia and released into the circulation where it acts to induce actions in the kidney (and other tissues) to result in increased phosphate excretion and normalization of serum phosphate levels. FGF23 appears to signal *in vivo* principally through FGFR1 and its co-receptor, α-Klotho (Klotho). Stimulation of the FGF23/Klotho/FGFR1 pathway either by overexpression of soluble Klotho or FGF23 results in hypophosphatemia.

An antibody specific to the FGFR1 subtype c (FGFR1c) is able to induce dramatic body weight loss through an inhibition of food intake in mice and monkeys. International Patent Applications WO 2005/037235 and WO 2004/083381 disclose FGFR1c antibodies and uses of the antibodies in therapeutic and diagnostic methods.

An objective of the present invention is to provide novel therapeutic uses of an FGFR1c antibody. The present examples demonstrate that an FGFR1c antibody delivered *in vivo* results in a lowering of phosphate levels. Furthermore, the present examples demonstrate that an FGFR1c antibody delivered *in vivo* results in an up-regulation of endogenous FGF23 levels. Together these results illustrate that an FGFR1c antibody modulates the FGF23/Klotho/FGFR1c pathway.

The present invention is that an FGFR1c antibody will be useful as a therapeutic agent where serum phosphate is elevated, and/or FGF23 serum levels are unbalanced from normal. These conditions include kidney disease, tissue and vascular calcifications, hyperphosphatemia, osteopenia (particularly loss of BMD of cortical bone), and diseases or conditions exhibited by Klotho or FGF23 knockout mice, including arteriosclerosis, infertility, short life span, pulmonary emphysema, skin atrophy, anemia, thymic atrophy, ectopic calcifications including those of the kidney and vasculature, accumulation of renal interstitial matrix, glomerulosclerosis, and neuronal degeneration.

Additional examples of diseases where an FGFR1c antibody may have therapeutic benefit include cancer, diabetes, metabolic syndrome, obesity, heart disease, vascular disease, lung disease, bone disease, Parkinson's Disease, Alzheimer's Disease, Multiple Sclerosis, cachexia and Muscular Dystrophy.

The present invention provides a method of treating or preventing hyperphosphatemia or calcinosis, chronic renal disease or chronic renal failure, tissue and vascular calcification, or albuminuria and proteinuria in a patient, comprising administering an effective amount of an FGFR1c antibody to a patient.

In a further aspect, the present invention provides a method of reducing blood pressure and calcific atherosclerotic plaque burden in a patient, comprising administering an effective amount of an FGFR1c antibody to a patient.

In a further aspect, the present invention provides a method of lowering serum phosphate levels in a patient, comprising administering an effective amount of an FGFR1c antibody to a patient.

In a further aspect, the present invention provides a method of increasing FGF23 in a patient, comprising administering an effective amount of an FGFR1c antibody to a patient.

In a further aspect, the present invention provides a method of increasing phosphate clearance by the kidney in a patient, comprising administering an effective amount of an FGFR1c antibody to a patient.

Furthermore, the present invention provides the use of an FGFR1c antibody in the manufacture of a medicament for treating or preventing hyperphosphatemia or calcinosis, chronic renal disease or chronic renal failure, tissue and vascular calcification, or albuminuria and proteinuria.

In a further aspect, the present invention provides the use of an FGFR1c antibody in the manufacture of a medicament for reducing blood pressure and calcific atherosclerotic plaque burden.

In a further aspect, the present invention provides the use of an FGFR1c antibody in the manufacture of a medicament for lowering serum phosphate levels.

In a further aspect, the present invention provides the use of an FGFR1c antibody in the manufacture of a medicament for increasing FGF23.

In a further aspect, the present invention provides the use of an FGFR1c antibody in the manufacture of a medicament for increasing phosphate clearance by the kidney.

Furthermore, the present invention provides an FGFR1c antibody for use in treating or preventing hyperphosphatemia or calcinosis, chronic renal disease or chronic renal failure, tissue and vascular calcification, or albuminuria and proteinuria.

In a further aspect, the present invention provides an FGFR1c antibody for use in reducing blood pressure and calcific atherosclerotic plaque burden.

In a further aspect, the present invention provides an FGFR1c antibody for use in lowering serum phosphate levels.

In a further aspect, the present invention provides an FGFR1c antibody for use in increasing FGF23.

In a further aspect, the present invention provides an FGFR1c antibody for use in increasing phosphate clearance by the kidney.

The FGFR1c antibody comprises a light chain and a heavy chain, wherein the light chain comprises a light chain variable region (LCVR) and the heavy chain comprises a heavy chain variable region (HCVR), wherein the LCVR comprises amino acid sequences LCDR1, LCDR2, and LCDR3, and the HCVR comprises amino acid sequences HCDR1, HCDR2, and HCDR3, wherein LCDR1 is SEQ ID NO:5, LCDR2 is SEQ ID NO:6, LCDR3 is SEQ ID NO:7, HCDR1 is SEQ ID NO:8, HCDR2 is SEQ ID NO:9, and HCDR3 is SEQ ID NO:10. Preferably, the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3. More preferably, the FGFR1c antibody comprises a light chain with the amino acid sequence of SEQ ID NO: 2, and a heavy chain with the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 11.

The following definitions are provided to aid those of ordinary skill in the art in understanding the disclosure herein. These definitions are intended to be representative of those known in the art, and are therefore not limited to the specific elements presented, but encompass concepts and features disclosed in cited and/or contemporary publications or patents.

The term “treating” (or “treat” or “treatment”) means slowing, stopping, reducing, or reversing the progression or severity of a symptom, disorder, condition, or disease.

The term "preventing" (or "prevent" or "prevention") refers to a decrease in the occurrence of a symptom, disorder, condition, or disease or decrease in the risk of acquiring a symptom, disorder, condition, or disease or its associate symptoms in a subject.

A "patient" is a mammal, preferably a human.

The term "effective amount" refers to the amount or dose of FGFR1c antibody upon which single or multiple dose administration to a patient, provides the desired treatment.

Example 1

Effects of an FGFR1c antibody in Normal Mice

The *in vivo* effects of treatment with an FGFR1c antibody comprising a light chain with the amino acid sequence of SEQ ID NO: 2, and a heavy chain with the amino acid sequence of SEQ ID NO: 1 ("FGFR1c antibody Ab21") on body weight, serum phosphate, calcium and FGF23 are examined.

The study is conducted in 8-9 week-old female C57BL/6 mice. For baseline serum data, a group of 3 untreated mice is sacrificed at time 0. Remaining mice are randomized into two study groups of 12 mice each, based on body weight (n=3/group/time point). FGFR1c antibody Ab21 or isotype control IgG1 is administered subcutaneously to these mice at a single dose of 1 mg/kg in a total volume of 100 µL/mouse. At each time point (6, 24, 48 and 96 hours post administration), 3 mice from each study group are anesthetized by isoflurane for orbital bleeding and sacrificed. Serum samples are prepared from the collected blood at each time point and frozen at -80°C until the time of assay. Body weights for the mice in the 2 study groups are collected at time 0 (used as baseline), 24, 48 and 96 hour time points. A portion of the serum is analyzed for calcium and inorganic phosphorous. These samples are centrifuged at 3000 RPM for 10 minutes at room temperature prior to analysis in a Beckman Allegra 6R centrifuge. Calcium levels are determined by a colorimetric method in which o-cresolphthalein complexone reacts with calcium in the sample at alkaline pH to form calcium-o-cresolphthalein complex. The calcium concentration is directly proportional to the color intensity of this complex and is photometrically measured with an automated chemistry analyzer. Inorganic phosphorous combines with ammonium molybdate under

acidic conditions to form an ammonium molybdate complex. The concentration of this complex is also measured photometrically. Roche Calcium and Inorganic Phosphorous reagent kits are utilized for this analysis, as well as either a Hitachi 912 or Hitachi Modular Analytics Chemistry analyzer (Roche Diagnostics).

A separate portion of serum is used to measure intact FGF23 levels using a commercially-available human intact FGF23 ELISA kit (Kainos Laboratories, catalog # CY-4000). Manufacturer's instructions are followed. Sera are diluted at various concentrations such that the values are within the range of the standard curve for quantification. Standard curve ranges from 3-800 pg/ml. The assumption is made that the ELISA has 100% cross-reactivity to mouse FGF23. The absorbance of the wells is read on a Molecular Devices SpectraMax250 plate reader. The absorbance from the wells is determined and back-calculations for dilutions are made. Results are summarized in Table 1 below.

Table 1

Effects of administration of FGFR1c antibody Ab21 on body weight, serum phosphate, calcium and FGF23 in normal mice

Group	Body Weight (g)	Phosphate (mg/dL)	Calcium (mg/dL)	FGF23 (pg/mL)
0 Hours				
Untreated	--	7.90 (0.44)	10.33 (0.21)	81 (39)
IgG Control	18.71 (0.27)	ns	ns	ns
Treated	18.85 (0.26)	ns	ns	ns
6 Hours				
IgG Control	not measured	6.67 (0.15)*	9.93 (0.25)	46 (9)
Treated	not measured	8.00 (0.70)	10.10 (0.10)	132 (16)*
24 Hours				
IgG Control	18.54 (0.35)	7.07 (0.51)	10.37 (0.12)	75 (17)
Treated	18.07 (0.33)$^{+}$	6.87 (0.46)$^{+}$	10.53 (0.06)	993 (214)*$^{+}$
48 Hours				
IgG Control	18.60 (0.36)	7.70 (0.26)	10.40 (0.10)	74 (26)
Treated	17.67 (0.42)*$^{+}$	6.23 (0.51)*$^{+}$	10.37 (0.15)	2036 (250) *$^{+}$
96 Hours				
IgG Control	18.77 (0.2)	7.37 (0.58)	10.20 (0.40)	55 (41)
Treated	17.60 (0.30)*$^{+}$	5.17 (0.06)*$^{+}$	9.63 (0.40)	825 (386)*
average (standard deviation), n = 3, Student's t-test used				
* denotes statistical significance vs. IgG control within the same time point, $p < 0.05$				
$^{+}$ statistical significance vs. respective time 0, $p < 0.05$				
ns denotes no serum drawn at this time point from these mice				
-- data not applicable for this analysis				

A statistically significant decrease in body weight was observed as early as 24 hours in the group treated with FGFR1c antibody Ab21, and the effect reached a plateau by 48 hours, with a maximum decrease of 6-7%. Serum levels of phosphate begin to decrease with statistical significance at 24 hours with treatment with FGFR1c antibody Ab21, and they continued to decrease over time (maximum decrease was 35%). No statistically significant differences in serum calcium were observed with treatment. Serum levels of FGF23 were statistically significantly increased compared to IgG control as early as 6 hours, and FGF23 continued to be elevated for the duration of the study. The maximal increase in FGF23 in the treatment group was observed at 48 hours in this study (28-fold increase, compared to IgG control).

The study demonstrated that administration of FGFR1c antibody Ab21 in normal animals induced a decrease in serum phosphate and an increase in serum FGF23.

Example 2

Effects of an FGFR1c antibody in Diet-Induced Obese Mice

The *in vivo* effects of treatment with FGFR1c antibody Ab21 on body weight, serum phosphate, calcium, FGF23 and PTH, and the fractional excretion of phosphate in urine are examined.

Thirty-six diet-induced obese (DIO), C57/Bl6 male mice (Taconic Farms, NY) are maintained *ad libitum* on a high fat diet (Teklad 95217, 40% fat). Water is also available *ad libitum*. Mice are housed in a temperature-controlled room (74°F) with a 12:12 hour light:dark cycle (lights off at 10:00 AM).

One week prior to experiment start, mice are placed into metabolic cages for adaptation. Following this period, all mice are weighed and are block randomized to 6 groups based on body weights. Saline (n=12) or FGFR1c antibody Ab21 (1 mg/kg, n=12) is delivered *ip* at a volume of 10 mL/kg at the initiation of the dark cycle on day 1 (time = 0). Half of the animals from each dosed group are euthanized 48 hours post-dose and the other half at 96 hours post-dose. Pair-fed control groups are included for each of the time points with food intake matched to the average daily food intake of the group treated with FGFR1c antibody Ab21. Urine is collected using a 1mL pipette and total volume determined. A portion is acidified with 5µl of 5N HCl and processed for calcium

and phosphate while another portion is assayed for creatinine. Blood is collected via cardiac puncture following CO2 exposure and a portion is processed for determination of serum analytes (creatinine, calcium, phosphate). Fractional excretion is calculated as follows: [Serum(PO4)/Serum(creatinine)] / [Urine(PO4)/Urine(creatinine)] * 100.

Separate portions of serum are used to measure intact FGF23 (as described above) and intact PTH. Intact PTH levels are measured using a commercially-available mouse intact PTH ELISA kit (Immutopics, catalog # 60-2300). Manufacturer's instructions are followed, with the exception that only 1 replicate is measured. Standard curve ranges from 36-3500 pg/ml. The absorbance of the wells is read on a Molecular Devices SpectraMax250 plate reader. Serum and urine phosphate and calcium are measured as described above. Serum and urine creatinine levels are determined by photometrically measuring the color intensity of the chromogen produced following a series of enzymatic reactions which convert creatinine to sarcosine. Hydrogen peroxide is liberated from sarcosine and reacts with a color substrate to form a quinone imine chromogen. This chromogen is measured photometrically with an automated chemistry analyzer. The color intensity is directly proportional to the creatinine concentration present in the specimen. Roche Creatinine Plus reagent kits are utilized for this analysis on the Hitachi Modular Analytics Chemistry Analyzer (Roche Diagnostics). Results are summarized in Tables 2 through 4, below.

Table 2

FGF23 and PTH levels in serum, following *ip* dosing of vehicle, FGFR1c antibody Ab21 (1 mg/kg), or pair-feeding

Group	FGF23 (pg/mL)	PTH (pg/mL)
48 Hours		
Vehicle	125 (34.6)	296 (125.3)
Pair-Fed	134 (14.2)	321 (120.6)
Treated	1516 (219.9)*	370 (91.1)
96 Hours		
Vehicle	100 (29.0)	588 (404.1)
Pair-Fed	150 (15.4)	302 (110.8)
Treated	1399 (184.3)*	332 (131.9)
average (standard deviation) listed, n = 3-6, Student's t-test used		
* denotes statistical significance vs. vehicle and pair-fed, $p < 0.05$		

Table 3

Body weight, cumulative weight change and food intake following *ip* dosing of vehicle, FGFR1c antibody Ab21 (1mg/kg), or pair-feeding

Group	Body weight (g)	Cumulative Weight Change (g)	Cumulative Food Intake (g)
48 Hours			
Vehicle	40.6 ± 1.1	1.0 ± 0.1	6.2 ± 0.2
Treated	37.0 ± 0.7*	-0.9 ± 0.2*	2.5 ± 0.3*
Pair-Fed	36.7 ± 0.9*	-0.7 ± 0.2*	2.5 ± 0.1*
96 Hours			
Vehicle	38.9 ± 1.1	0.1 ± 0.2	10.6 ± 0.4
Treated	35.3 ± 0.7*	-4.3 ± 0.3*	6.2 ± 0.3*
Pair-Fed	36.0 ± 0.7*	-3.6 ± 0.1*	5.6 ± 0.2*
Data presented are means ± SEM, $p<0.05$, 1-way ANOVA used			
* denotes statistical significance vs. vehicle within the same time point			

Table 4a

Serum levels of creatinine, calcium, and phosphate following *ip* dosing of vehicle, FGFR1c antibody Ab21 (1 mg/kg), or pair-feeding

Group	Serum		
	Creatinine (mg/dL)	Calcium (mg/dL)	Phosphate (mg/dL)
48 hour time point for serum collection			
Vehicle	0.16 ± 0.01	9.7 ± 0.4	10.2 ± 0.6
Treated	0.15 ± 0.01	10.0 ± 0.2	9.6 ± 0.7
Pair-Fed	0.17 ± 0.02	10.1 ± 0.2	9.9 ± 0.5
96 hour time point for serum collection			
Vehicle	0.16 ± 0.01	9.7 ± 0.2	10.4 ± 0.6
Treated	0.18 ± 0.02	9.5 ± 0.1	7.8 ± 0.4*
Pair-Fed	0.18 ± 0.02	10.5 ± 0.1*	10.5 ± 0.8
Data presented are means ± SEM			
* denotes statistical significance vs. vehicle and pair-fed within the same time point, $p<0.05$, 1-way ANOVA used			

5

Table 4b

Urine levels of creatinine, calcium, phosphate, and fractional excretion of phosphate following *ip* dosing of vehicle, FGFR1c antibody Ab21 (1 mg/kg), or pair-feeding

Group	Urine				
	Urine Volume (mL)	Creatinine (mg/dL)	Calcium (mg/dL)	Phosphate (mg/dL)	Fractional Excretion of Phosphate
48 hour time point for serum collection Urine collected during a period of 24 – 48 hours post dosing					
Vehicle	1.00 ± 0.13	50.9 ± 3.4	12.1 ± 1.5	257.8 ± 31.8	7.6 ± 0.1
Treated	1.00 ± 0.27	65.9 ± 14.5	11.5 ± 2.8	318.7 ± 72.6	7.3 ± 0.6
Pair-Fed	0.92 ± 0.22	65.1 ± 10.5	10.4 ± 1.2	325.6 ± 50.1	8.4 ± 0.6
96 hour time point for serum collection Urine collected during a period of 72 - 96 hours post dosing					
Vehicle	1.04 ± 0.25	51.9 ± 6.5	9.6 ± 0.8	264.6 ± 58.8	7.3 ± 0.8
Treated	1.06 ± 0.21	53.8 ± 7.6	9.7 ± 1.9	248.7 ± 43.4	10.8 ± 1.3*
Pair-Fed	1.03 ± 0.26	52.4 ± 10.1	12.2 ± 2.4	237.8 ± 51.5	7.4 ± 0.6
Data presented are means ± SEM,					
* denotes statistical significance vs. vehicle and pair-fed within the same time point, $p<0.05$, 1-way ANOVA used					

Male DIO mice *ip* dosed with FGFR1c antibody Ab21 illustrated statistically significant reductions in body weight and food intake at both time points, compared with vehicle-treated animals (Table 3). Mice treated with FGFR1c antibody Ab21 showed a statistically significant decrease in serum phosphate concomitant with a statistically significant increase in fractional excretion of phosphate in urine at 96 hours (Table 4a and Table 4b). Lack of a similar finding in the pair-fed group demonstrated that these effects are attributable to the antibody rather than to a decrease in food intake alone. A statistically significant increase in serum levels of FGF23 was observed with FGFR1c antibody Ab21 treatment at both 48 and 96 hour time points in this study, compared to vehicle or pair-fed mice (Table 2). Maximum observed increase was 14-fold over vehicle. No statistically significant changes in serum levels of PTH in the group treated with FGFR1c antibody Ab21 were seen in these conditions (Table 2).

The study demonstrated that administration of FGFR1c antibody Ab21 in diet-induced obese animals induced a decrease in serum phosphate and an increase in serum FGF23. Furthermore, the study illustrated an increase in renal phosphate excretion, as evidenced by the increase in fractional excretion of phosphate, in mice treated with FGFR1c antibody Ab21, compared to pair-fed controls.

Sequences

Complete heavy chain amino acid sequence. (SEQ ID NO: 1)

Q V Q L V Q S G A E V K K P G S S V K V S C K A S
G Q T F T G Y Y M H W V R Q A P G Q G L E W M G R
I I P I L G I A N Y A Q K F Q G R V T I T A D K S T S
T A Y M E L S S L R S E D T A V Y Y C A R G G D L
G G M D V W G Q G T T V T V S S A S T K G P S V F
P L A P S S K S T S G G T A A L G C L V K D Y F P E
P V T V S W N S G A L T S G V H T F P A V L Q S S G
L Y S L S S V V T V P S S S L G T Q T Y I C N V N H
K P S N T K V D K R V E P K S C D K T H T C P P C P
A P E L L G G P S V F L F P P K P K D T L M I S R
T P E V T C V V V D V S H E D P E V K F N W Y V D
G V E V H N A K T K P R E E Q Y N S T Y R V V S V
L T V L H Q D W L N G K E Y K C K V S N K A L P A
P I E K T I S K A K G Q P R E P Q V Y T L P P S R
E E M T K N Q V S L T C L V K G F Y P S D I A V E
W E S N G Q P E N N Y K T T P P V L D S D G S F F
L Y S K L T V D K S R W Q Q G N V F S C S V M H E
A L H N H Y T Q K S L S L S P G K

Complete light chain amino acid sequence. (SEQ ID NO: 2)

E I V L T Q S P L S L P V T P G E P A S I S C R S S
Q S L R H S N G Y N Y L D W Y L Q K P G Q S P Q L
L I Y L A S N R A S G V P D R F S G S G S G T D F T
L K I S R V E A E D V G V Y Y C M Q A L Q I P P T F
G P G T K V D I K G T V A A P S V F I F P P S D E Q
L K S G T A S V V C L L N N F Y P R E A K V Q W K
V D N A L Q S G N S Q E S V T E Q D S K D S T Y S
L S S T L T L S K A D Y E K H K V Y A C E V T H Q
G L S S P V T K S F N R G E C

Variable heavy chain amino acid sequence. (SEQ ID NO: 3)

Q V Q L V Q S G A E V K K P G S S V K V S C K A S
G Q T F T G Y Y M H W V R Q A P G Q G L E W M G R
I I P I L G I A N Y A Q K F Q G R V T I T A D K S T S
T A Y M E L S S L R S E D T A V Y Y C A R G G D L G
G M D V W G Q G T T V T V S S

Variable light chain amino acid sequence. (SEQ ID NO: 4)

E I V L T Q S P L S L P V T P G E P A S I S C R S S Q
S L R H S N G Y N Y L D W Y L Q K P G Q S P Q L L I
Y L A S N R A S G V P D R F S G S G S G T D F T L K
I S R V E A E D V G V Y Y C M Q A L Q I P P T F G P
G T K V D I K

Light Chain CDRs:

LC-CDR1: RSSQSLRHSNGYNYLD (SEQ ID NO: 5)
LC-CDR2: LASNRAS (SEQ ID NO: 6)
LC-CDR3: MQALQIPPT (SEQ ID NO: 7)

Heavy Chain CDRs:

HC-CDR1: GQTFTGYYMH (SEQ ID NO: 8)
HC-CDR2: RIIPILGIANYAQKFQG (SEQ ID NO: 9)
HC-CDR3: GGDLGGMDV (SEQ ID NO: 10)

Heavy Chain Amino Acid Sequence (human IgG4 PAA): (SEQ ID NO: 11)

QVQLVQSGAEVKKPGSSVKVSCKASGQTFTGYYMHWVRQAPGQGLEWMGRIIP
ILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGGDLGGMDV
WGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE
SKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG
LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT
QKSLSLSLG

WE CLAIM:

1. A method of treating or preventing hyperphosphatemia or calcinosis in a patient, comprising administering an effective amount of an FGFR1c antibody to the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

2. A method of treating or preventing chronic renal disease or chronic renal failure in a patient, comprising administering an effective amount of an FGFR1c antibody to the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

3. A method of treating or preventing tissue and vascular calcification in a patient, comprising administering an effective amount of an FGFR1c antibody to the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

4. A method of treating or preventing albuminuria and proteinuria in a patient, comprising administering an effective amount of an FGFR1c antibody to the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

5. A method of reducing blood pressure and calcific atherosclerotic plaque burden in a patient, comprising administering an effective amount of an FGFR1c antibody to

the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

6. A method of lowering serum phosphate levels in a patient, comprising administering an effective amount of an FGFR1c antibody to the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

7. A method of increasing FGF23 in a patient, comprising administering an effective amount of an FGFR1c antibody to the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

8. A method of increasing phosphate clearance by the kidney in a patient, comprising administering an effective amount of an FGFR1c antibody to the patient, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

9. The method of anyone of Claims 1 to 8, wherein the FGFR1c antibody comprises a light chain with the amino acid sequence of SEQ ID NO: 2 and a heavy chain with the amino acid sequence of SEQ ID NO: 1.

10. Use of an FGFR1c antibody in the manufacture of a medicament for treating or preventing hyperphosphatemia or calcinosis, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the

amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

11. Use of an FGFR1c antibody in the manufacture of a medicament for treating or preventing chronic renal disease or chronic renal failure, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

12. Use of an FGFR1c antibody in the manufacture of a medicament for treating or preventing tissue and vascular calcification, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

13. Use of an FGFR1c antibody in the manufacture of a medicament for treating or preventing albuminuria and proteinuria, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

14. Use of an FGFR1c antibody in the manufacture of a medicament for reducing blood pressure and calcific atherosclerotic plaque burden, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

15. Use of an FGFR1c antibody in the manufacture of a medicament for lowering serum phosphate levels, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of

SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

16. Use of an FGFR1c antibody in the manufacture of a medicament for increasing FGF23, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

17. Use of an FGFR1c antibody in the manufacture of a medicament for increasing phosphate clearance by the kidney, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

18. Use of an FGFR1c antibody in treating or preventing hyperphosphatemia or calcinosis, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

19. Use of an FGFR1c antibody in treating or preventing chronic renal disease or chronic renal failure, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

20. Use of an FGFR1c antibody in treating or preventing tissue and vascular calcification, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

21. Use of an FGFR1c antibody in treating or preventing albuminuria and proteinuria, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

22. Use of an FGFR1c antibody in reducing blood pressure and calcific atherosclerotic plaque burden, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

23. Use of an FGFR1c antibody in lowering serum phosphate levels, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

24. Use of an FGFR1c antibody in increasing FGF23, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

25. Use of an FGFR1c antibody in increasing phosphate clearance by the kidney, wherein the FGFR1c antibody comprises a light chain comprising a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO: 4, and a heavy chain comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO: 3.

26. The use of any one of Claims 10 to 25, wherein the FGFR1c antibody comprises a light chain with the amino acid sequence of SEQ ID NO: 2 and a heavy chain with the amino acid sequence of SEQ ID NO: 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/044913

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61K39/395 A61P3/00 A61P9/10 A61P13/12
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/083381 A2 (INDIANA UNIVERSITY ADVANCED RESEARCH & TECHNOLOGY INSTITUTE) 30 September 2004 (2004-09-30) cited in the application page 3, line 4 - line 6 page 3, line 12 - line 15 page 49, line 15 - line 20 page 55, line 17 - line 24 page 61, line 7 - line 15 page 62, line 14 - page 63, line 13 -----	1-26
Y	WO 2005/019427 A2 (CURAGEN CORPORATION) 3 March 2005 (2005-03-03) claims 17-25 examples 1,2 -----	1-26

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2011	15/09/2011

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/044913

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/037235 A2 (IMCLONE SYSTEMS INCORPORATED) 28 April 2005 (2005-04-28) cited in the application examples 13-16 claim 20 sequences 15,16 figures 2A,2B,20,24 -----	1-26
Y	H. SUN ET AL.: "Monoclonal antibody antagonists of hypothalamic FGFR1 cause potent but reversible hypophagia and weight loss in rodents and monkeys.", AMERICAN JOURNAL OF PHYSIOLOGY. ENDOCRINOLOGY AND METABOLISM, vol. 292, no. 3, March 2007 (2007-03), pages E964-E976, XP008085179, USA abstract page E975, left-hand column, paragraph 2 -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/044913

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004083381 A2	30-09-2004	NONE	
WO 2005019427 A2	03-03-2005	AU 2004258687 A1	24-03-2005
		CA 2501155 A1	03-03-2005
		EP 1664075 A2	07-06-2006
WO 2005037235 A2	28-04-2005	AT 506077 T	15-05-2011
		CA 2542638 A1	28-04-2005
		DK 1680140 T3	14-06-2011
		EP 1680140 A2	19-07-2006
		EP 2060270 A2	20-05-2009
		EP 2229955 A1	22-09-2010
		ES 2361917 T3	24-06-2011
		JP 4686465 B2	25-05-2011
		JP 2008501302 A	24-01-2008
		PT 1680140 E	31-05-2011
		US 2007274981 A1	29-11-2007