55. FGFR4 Antibody to Treat Cardiac Death in CKD

(Lead Discovery Center)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Antibody
Disease Area	Genitourinary Disease
Indication	Chronic Kidney Disease
Current Stage	Lead identification
Target	FGF23/FGFR4
MoA	FGFR4-Ab prevents (i) FGF23/FGFR4 interaction, and (ii) LVH
Brief Description	• Chronic kidney disease (CKD) is a worldwide public health threat that increases risk of death due to cardiovascular complications, including left ventricular hypertrophy (LVH). • Novel therapeutic targets are needed to design treatments to alleviate the cardiovascular burden of CKD. • FGF23 exclusively activates FGFR4 on cardiac myocytes to stimulate phospholipase Cg/calcineurin/nuclear factor of activated T cell signaling. • A specific FGFR4-blocking antibody inhibits FGF23-induced hypertrophy of isolated cardiac myocytes and attenuates LVH in rats with CKD. • Mice lacking FGFR4 do not develop LVH in response to elevated FGF23, whereas knockin mice carrying an FGFR4 gain-of-function mutation spontaneously develop LVH. • FGF23 promotes LVH by activating FGFR4, thereby establishing FGFR4 as a pharmacological target for reducing cardiovascular risk in CKD.
Intellectual Property	WO2012177481A2
Publication	Activation of Cardiac Fibroblast Growth Factor Receptor 4 Causes Left Ventricular Hypertrophy. Cell Metabolism, (2015)
Inventors	Christian FAUL, Myles Wolf

Highlights

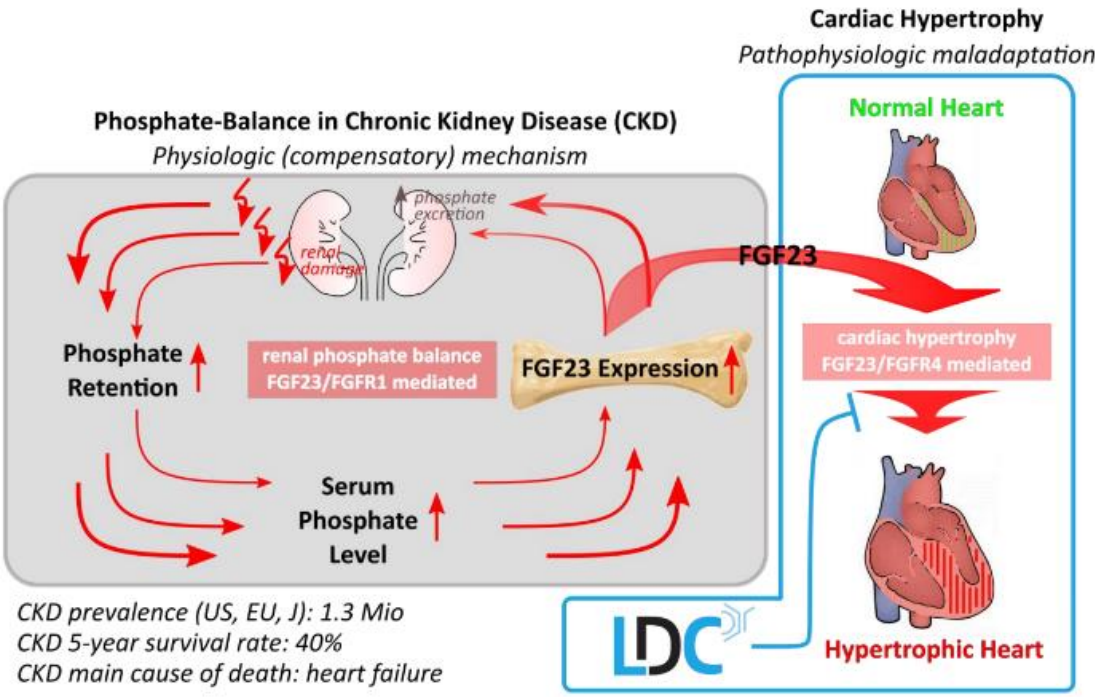
- In the absence of a-klotho, FGF23 induces binding of FGFR4 to PLCγ
- FGF23 activates calcineurin/NFAT signaling in cardiac myocytes via FGFR4
- FGFR4 blockade protects CKD rats with high serum FGF23 from cardiac hypertrophy
- Knockin mice carrying a FGFR4 gain-of-function mutation develop cardiac hypertrophy

55. FGFR4 Antibody to Treat Cardiac Death in CKD

(Lead Discovery Center)

Key Data

FGFR4 Antibody & Heart Failure in CKD

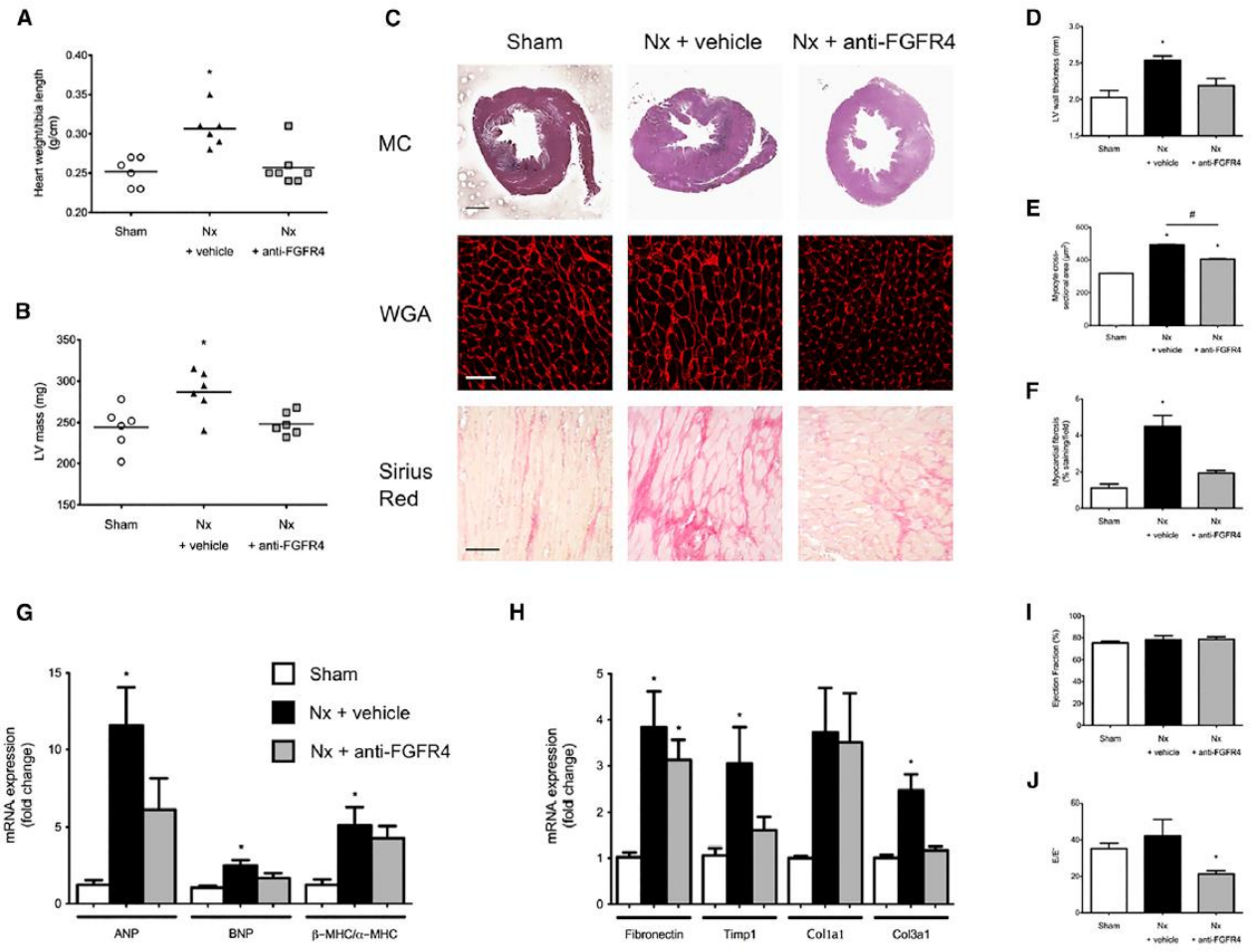


55. FGFR4 Antibody to Treat Cardiac Death in CKD

(Lead Discovery Center)

Key Data

Pharmacological Inhibition of FGFR4 Attenuates LVH in a Rat Model of CKD



(A and B) Compared with sham nephrectomy, 5/6 nephrectomy (Nx) in rats' results in increased ratio of heart weight to tibia length (A) and increased left ventricular mass (LVM) by echocardiography (B) at day 14 post-surgery. Each of these effects is attenuated by administering an FGFR4-specific blocking antibody (anti-FGFR4) (*p < 0.05 compared with Sham). (C) Representative gross pathology sections (H&E stain; original magnification, 32.5; scale bar, 2 mm), wheat germ agglutinin (WGA)-stained sections (original magnification, 363; scale bar, 50 mm), and picrosirius red stainings (original magnification, 310; scale bar, 100 mm) from the left ventricular mid-chamber (MC) at day 14 after 5/6 nephrectomy. (D–F) Compared with vehicle, anti-FGFR4 attenuates the effects of 5/6 nephrectomy to increase left ventricular (LV) wall thickness (by gross pathology, (D), cross-sectional area of individual cardiac myocytes (E), and myocardial fibrosis (F). All values are mean ± SEM (n = 6–14 rats per group; *p < 0.001 compared with Sham; #p < 0.01 compared with 5/6 nephrectomy treated with vehicle). (G and H) Quantitative PCR analysis of cardiac tissue shows that expression levels of hypertrophic markers (ANP, BNP, and b-MHC) (G) and of some fibrotic markers (TIMP metallopeptidase inhibitor 1, Timp1; collagen type 1 alpha 1, Col1a1; collagen type 3 alpha 1, Col3a1) (H) are significantly elevated in 5/6 nephrectomy rats that were treated with vehicle, but not in anti-FGFR4 treated rats (n = 6 rats per group; *p < 0.05 compared with Sham). (I and J) Echocardiography shows no significant differences in ejection fraction among the three groups (I), but anti-FGFR4 significantly improves diastolic function (E/E') in 5/6 nephrectomy rats compared to vehicle-treatment (J) (n = 6–8 rats per group; *p < 0.05 compared with vehicle-injected 5/6 nephrectomy).

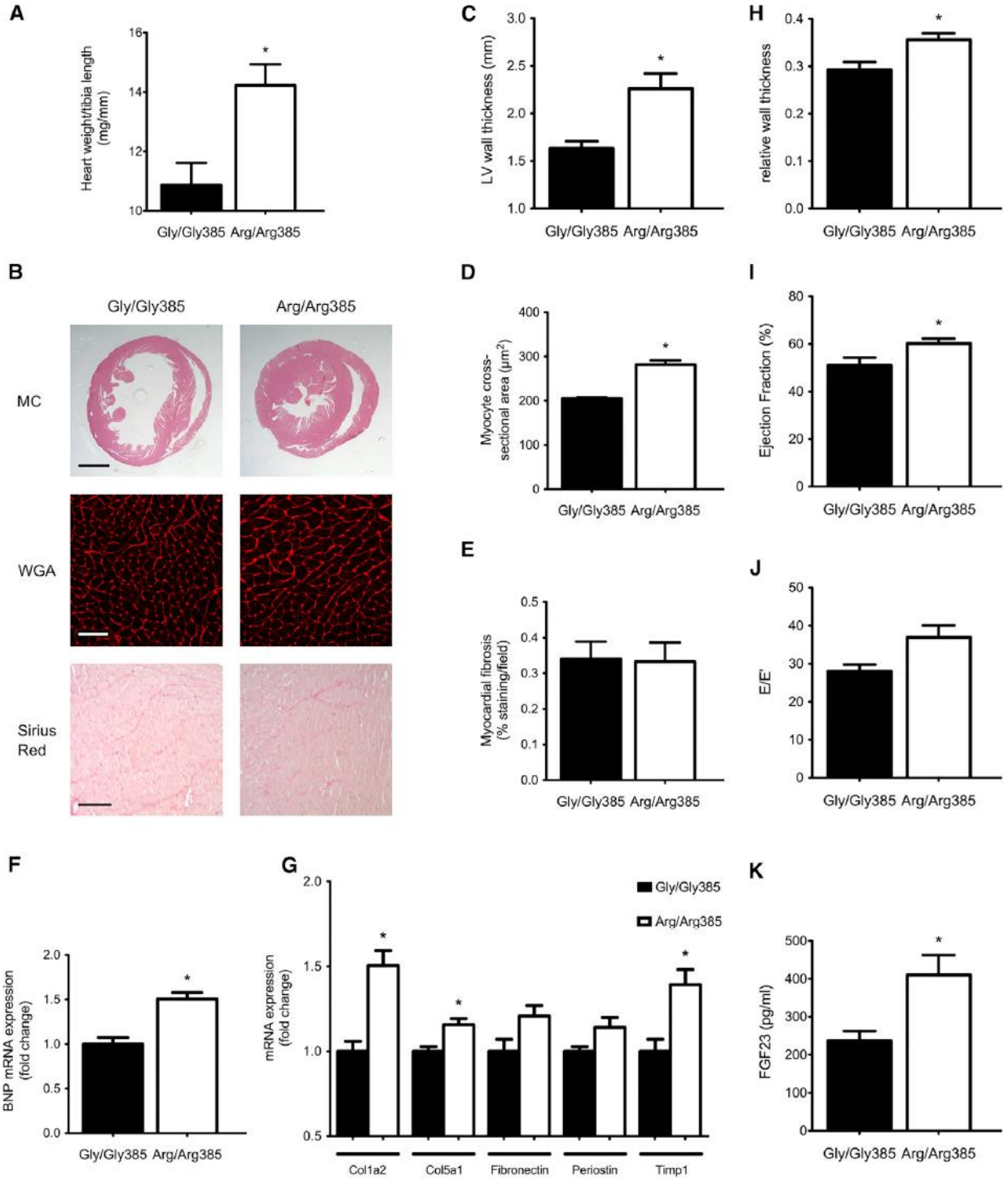
Source: https://pubmed.ncbi.nlm.nih.gov/26437603/

55. FGFR4 Antibody to Treat Cardiac Death in CKD

(Lead Discovery Center)

Key Data

Knockin Mice with an FGFR4 Gain-of-Function Mutation Spontaneously Develop LVH



To be continued

55. FGFR4 Antibody to Treat Cardiac Death in CKD

(Lead Discovery Center)

Key Data

Knockin Mice with an FGFR4 Gain-of-Function Mutation Spontaneously Develop LVH

(A) Six-month old homozygous knockin mice carrying the Arg385 substitution in FGFR4 (FGFR4Arg/Arg385) manifest significant increases in the ratio of heart weight to tibia length compared with wild-type littermates (FGFR4Gly/Gly385) (mean ± SEM; n = 9–12 mice per group; *p < 0.01).
(B) Representative gross pathology of mid-chamber (MC) sections of the heart (H&E stain; original magnification, 35; scale bar, 2 mm) and wheat germ agglutinin (WGA)-stained sections (original magnification, 363; scale bar, 50 mm) demonstrate LVH in FGFR4Arg/Arg385 mice but lack of myocardial fibrosis by picrosirius red staining (original magnification, 3100; scale bar, 100 mm).
(C–E) Compared with wild-type, FGFR4Arg/Arg385 mice develop significant increases in left ventricular (LV) wall thickness (mean ± SEM; n = 9–12 mice per group; *p < 0.01) (C) and cross-sectional area of individual cardiac myocytes (mean ± SEM; n = 100 cells per group; *p < 0.0001) (D), but no difference in collagen deposition (mean ± SEM; n = 9–12 mice per group) (E).
(F) Quantitative PCR analysis of total hearts from mice reveals significantly elevated BNP expression in 6-month-old FGFR4Arg/Arg385 mice compared with wildtype (n = 4–6 mice per group; *p < 0.01).
(G) Quantitative PCR analysis of cardiac tissue shows that expression levels of some fibrotic markers (TIMP metallopeptidase inhibitor 1, Timp1; collagen type 1 alpha 2, Col1a2; collagen type 5 alpha 1, Col5a1) are significantly elevated in FGFR4Arg/Arg385 mice compared to wild-type mice (n = 6 mice per group; *p < 0.01).
(H–J) Echocardiography shows that compared to wild-type mice, relative wall thickness (H), ejection fraction (I) and diastolic dysfunction (E/E′) (J) are increased in FGFR4Arg/Arg385 mice (n = 5–9 mice per group; *p < 0.05).
(K) FGFR4Arg/Arg385 mice demonstrate increased serum FGF23 levels compared with wild-type littermates (mean ± SEM; n = 9–12 mice per group; *p < 0.05).

Source: https://pubmed.ncbi.nlm.nih.gov/26437603/