THE UNIVERSITY OF UTAH
DEPARTMENT OF
BIOMEDICAL ENGINEERING

The role of Fibroblast Growth Factor 21 in Heart Failure

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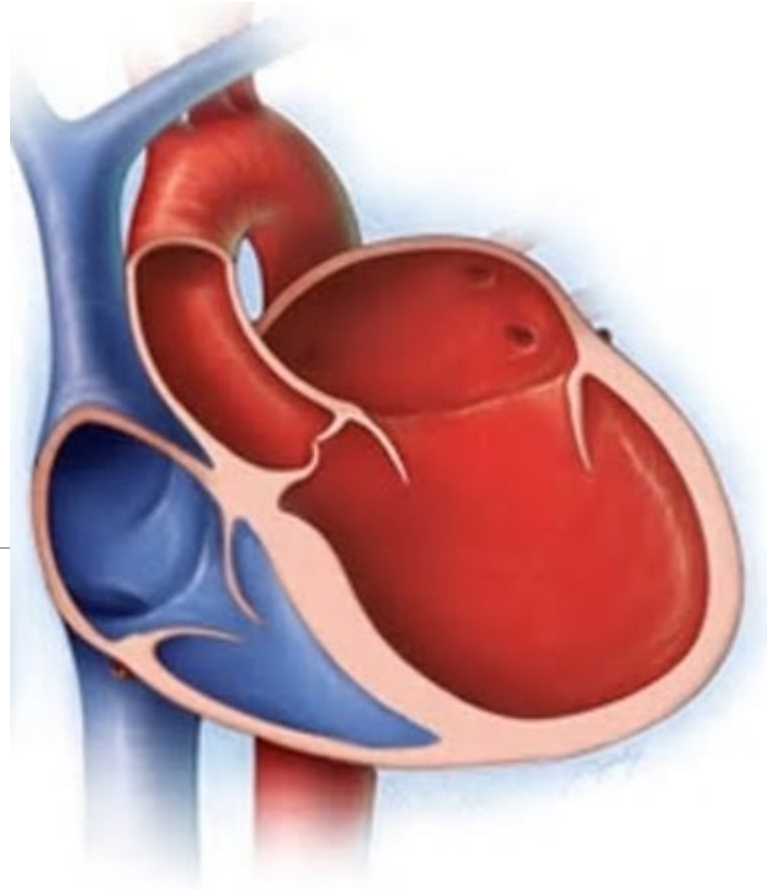
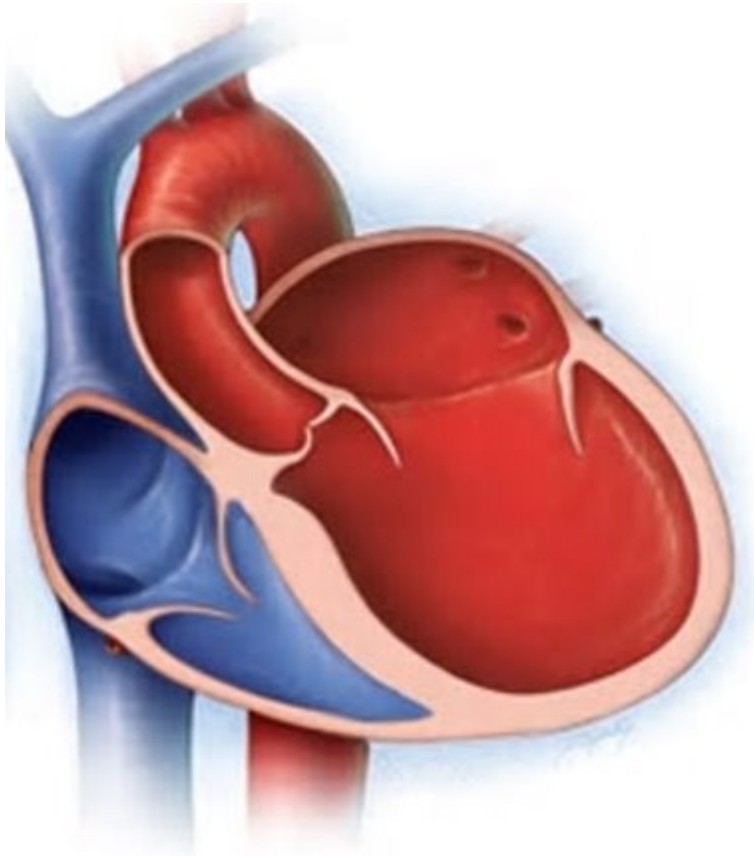


Google Images: mayoclinic.org (Dilated Cardiomyopathy)

Heart Failure (HF) is one of the leading causes of mortality worldwide[1]

- In 2017, 9.4% deaths in the U.S attributed to HF
- A syndrome characterized by the heart's inability to supply enough blood to the body
- In Dilated cardiomyopathy (DCM), the heart muscle begins to dilate, reducing muscle contractions
- Disease progression exhibits increased cell death and oxidative stress induction

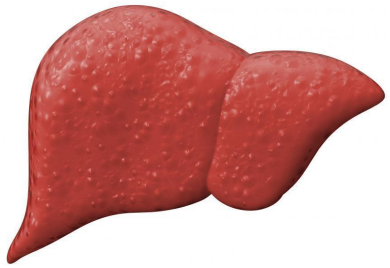


Google Images: mayoclinic.org (Dilated Cardiomyopathy)

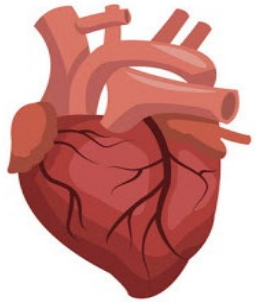
[1]Ahuja Preeti. *Circulation* . Vol. 127. 2013. pp. 1957-67.

Fibroblast Growth Factor 21 (FGF21) is secreted in response to oxidative stress in the body

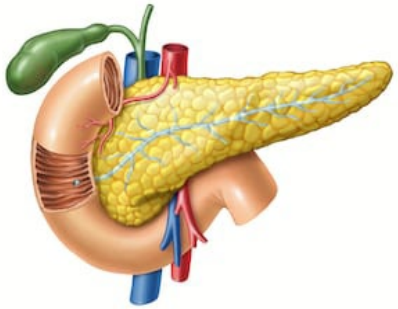
- A metabolic regulator that is produced in response to mitochondrial or oxidative stress in the body, which occurs a lot in DCM[1]
- Activation requires *β-Klotho (KLB)* and FGFR1
- Known production sites include:



Google Images: mayoclinic.org (liver)



Google Images: mayoclinic.org (Heart)

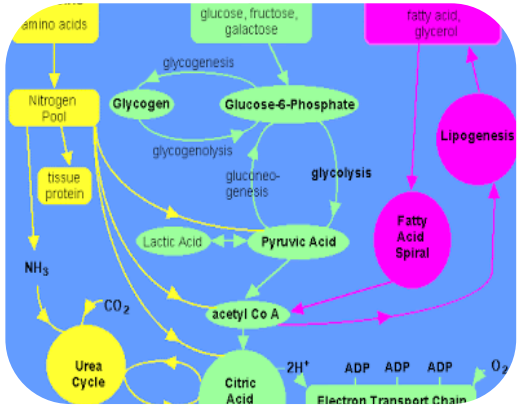


Google Images: mayoclinic.org (Pancreas)

Google Images: mayoclinic.org (Adipose tissue)

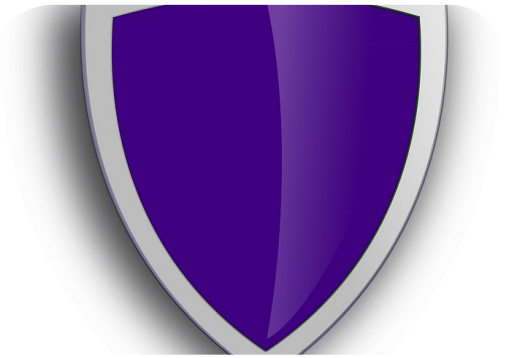
[1]Ahuja Preeti. *Circulation* . Vol. 127. 2013. pp. 1957-67.

FGF21 has multiple roles in the body but varies depending on the disease being studied



Metabolism

Homeostasis



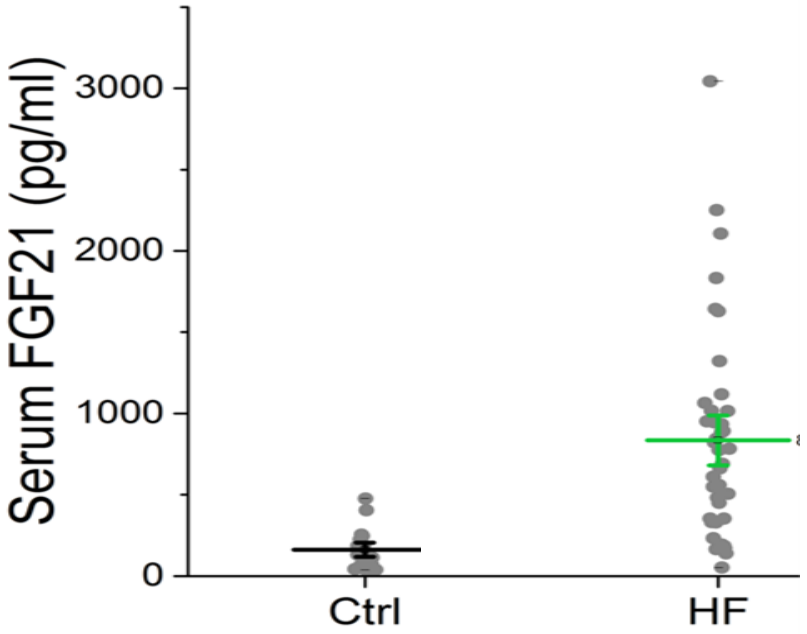
Cardioprotective effect

Biomarker for mitochondrial myopathies[1]

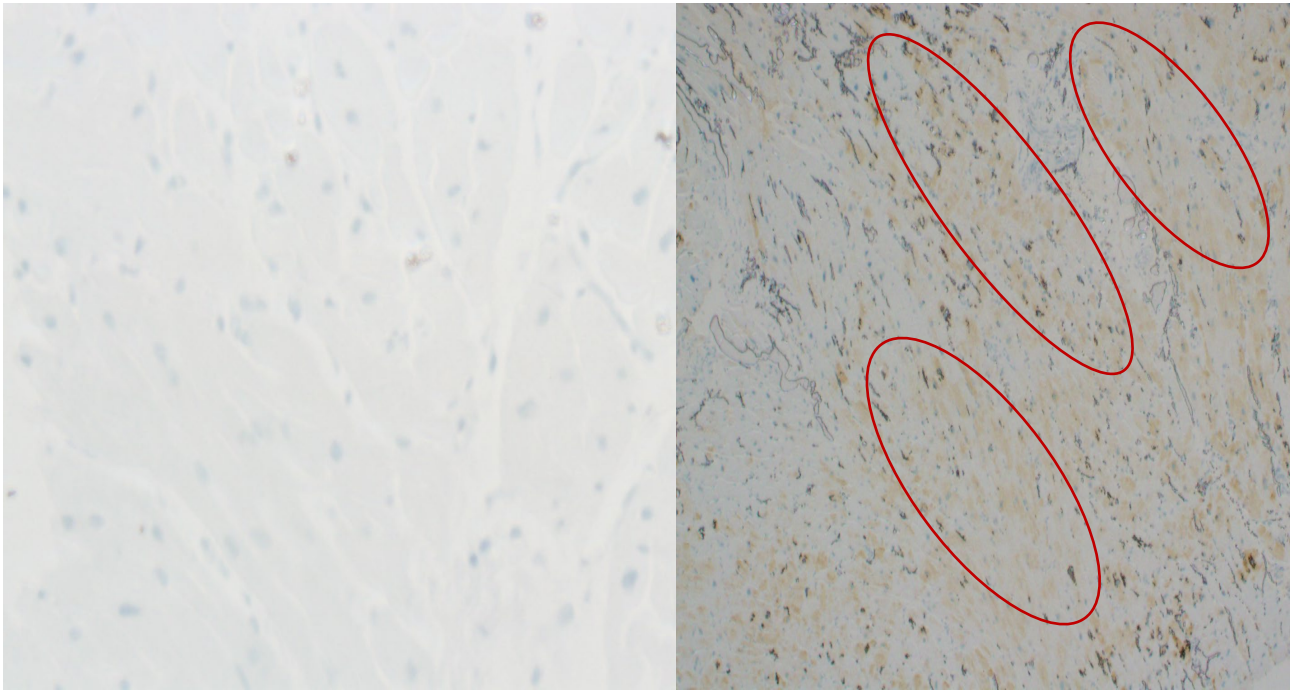
[1] https://n.neurology.org/content/87/22/2290

Previous lab results showed high levels of FGF21 in HF patients

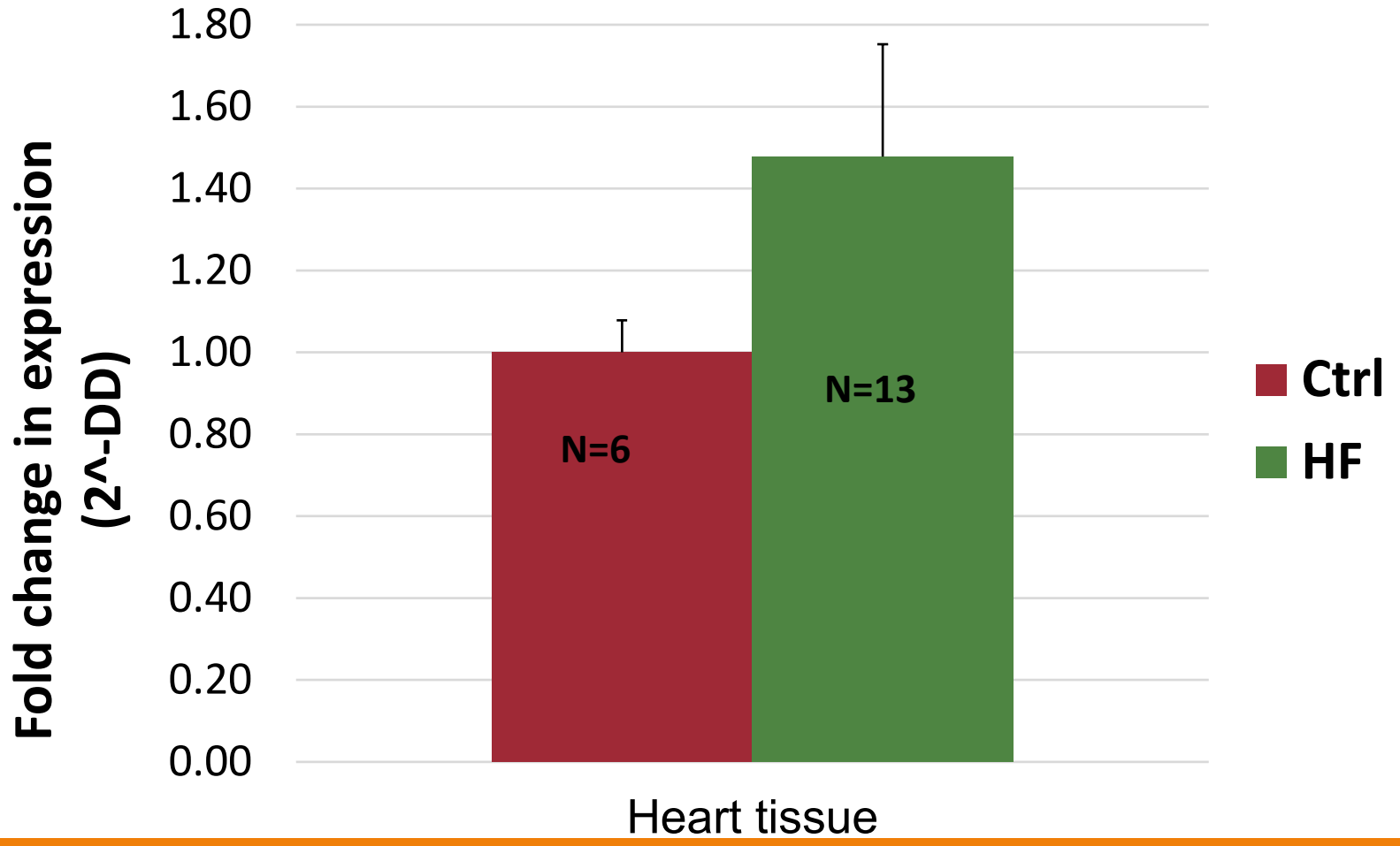
Serum FGF21 in HF patients vs. donors



Immunochemistry data (Donors-left, HF patients-right)



Upregulation of FGF21 gene expression was seen in HF patients

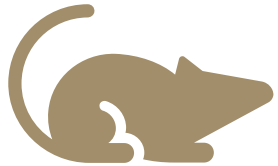


Is FGF21 being produced in other organs in response to cardiac stress?

Question

Where is FGF21 being produced during HF?

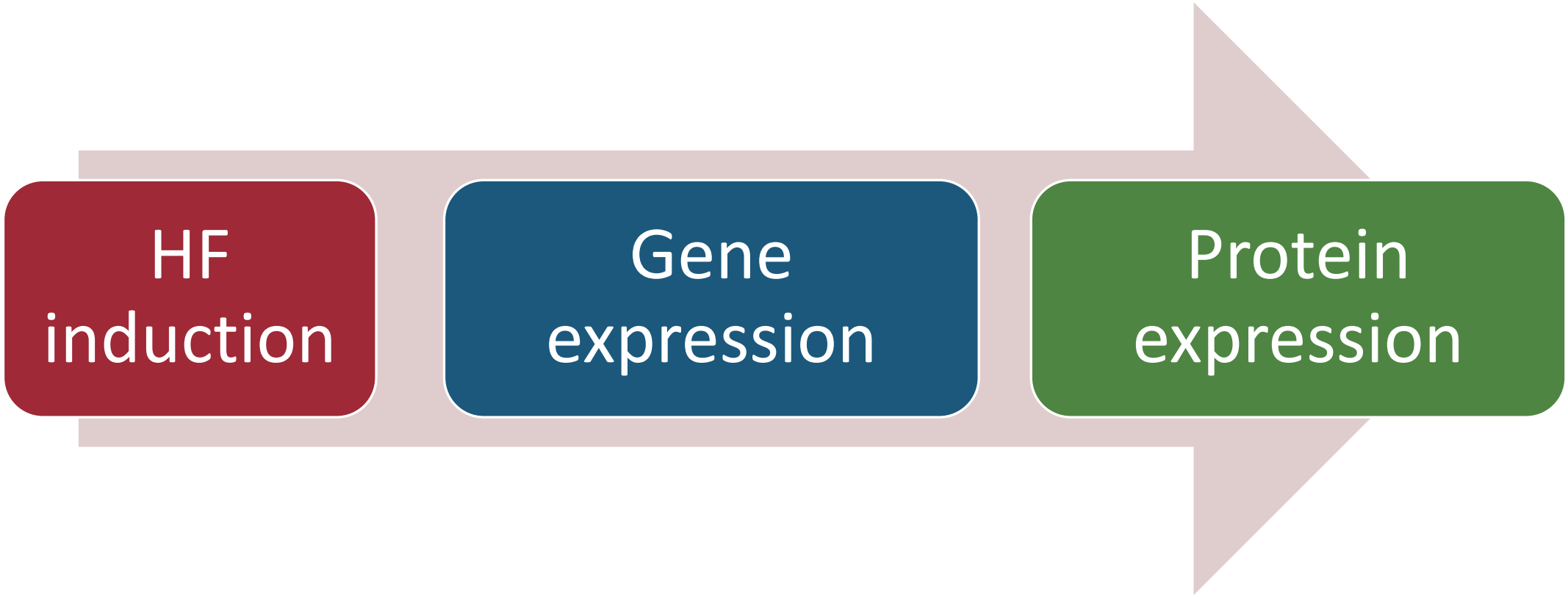
What is it targeting?



Hypothesis

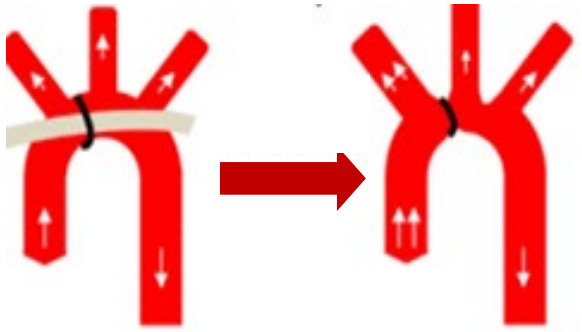
When cardiomyocytes experience oxidative stress, it leads to the production of FGF21 by other organs

To test our hypothesis, we induced HF in four mice and examined the gene and protein expression



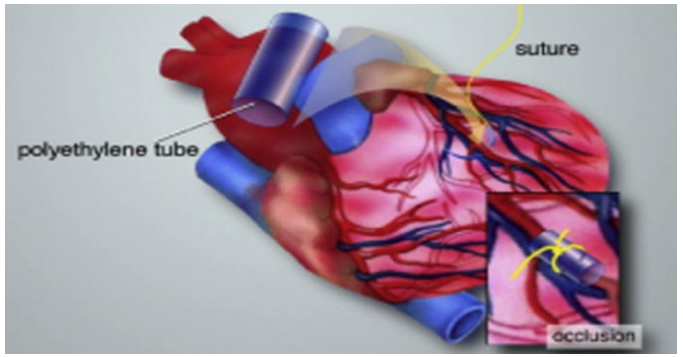
HF was induced in four mice via open heart surgery

Transverse Aortic Constriction (TAC)



Google Images: scintica.com (Transverse aortic constriction)

Coronary Artery Ligation



Google Images: sciencedirect.com (Coronary artery ligation)

Google Images: laboratoryequipment.com (mice)

FGF21 gene expression in mice was examined via quantitative PCR (qPCR)

Tissue Homogenization

Google Images: benchmarkscientific.com (beads)

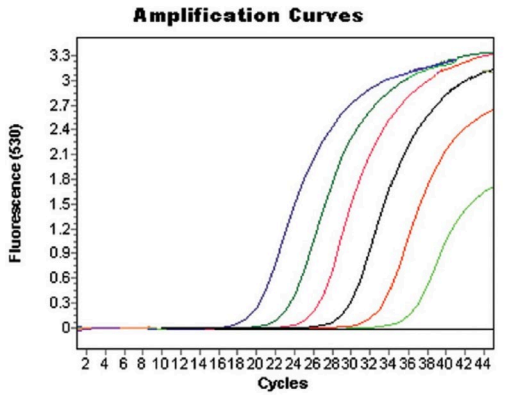
RNA Isolation

Google Images: bioscience.co.uk (RNA isolation)

qPCR

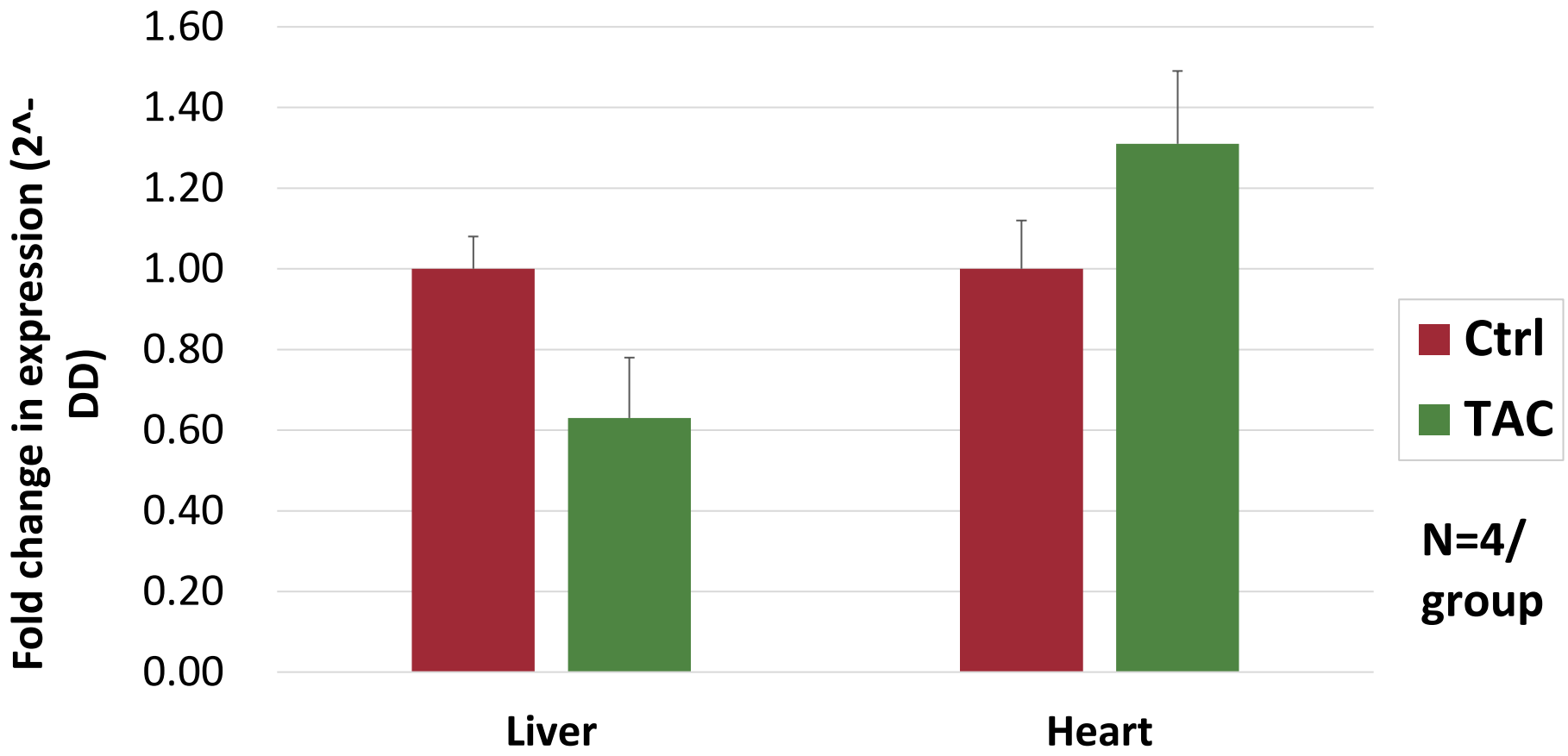
Google Images: biorad.com (PCR machine)

Analysis



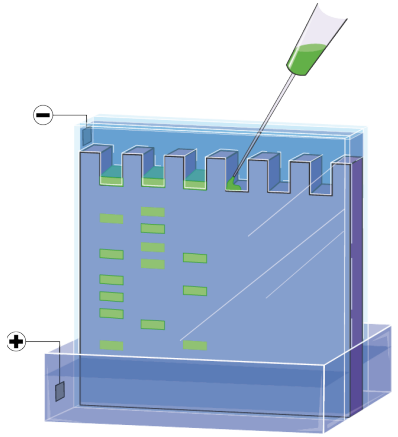
Google Images: jgid.org (qPCR)

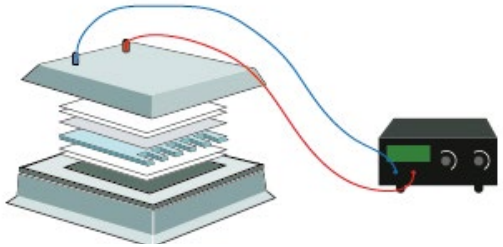
The FGF21 upregulations in TAC mice confirms the heart is an FGF21-target site

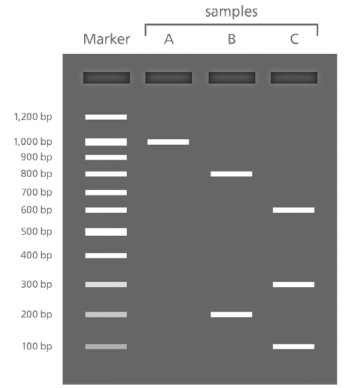


FGF21 protein expression was examined in mice via Western Blot (WB)

Sample Preparation → Electrophoresis → Transfer to membrane → Stain for Protein







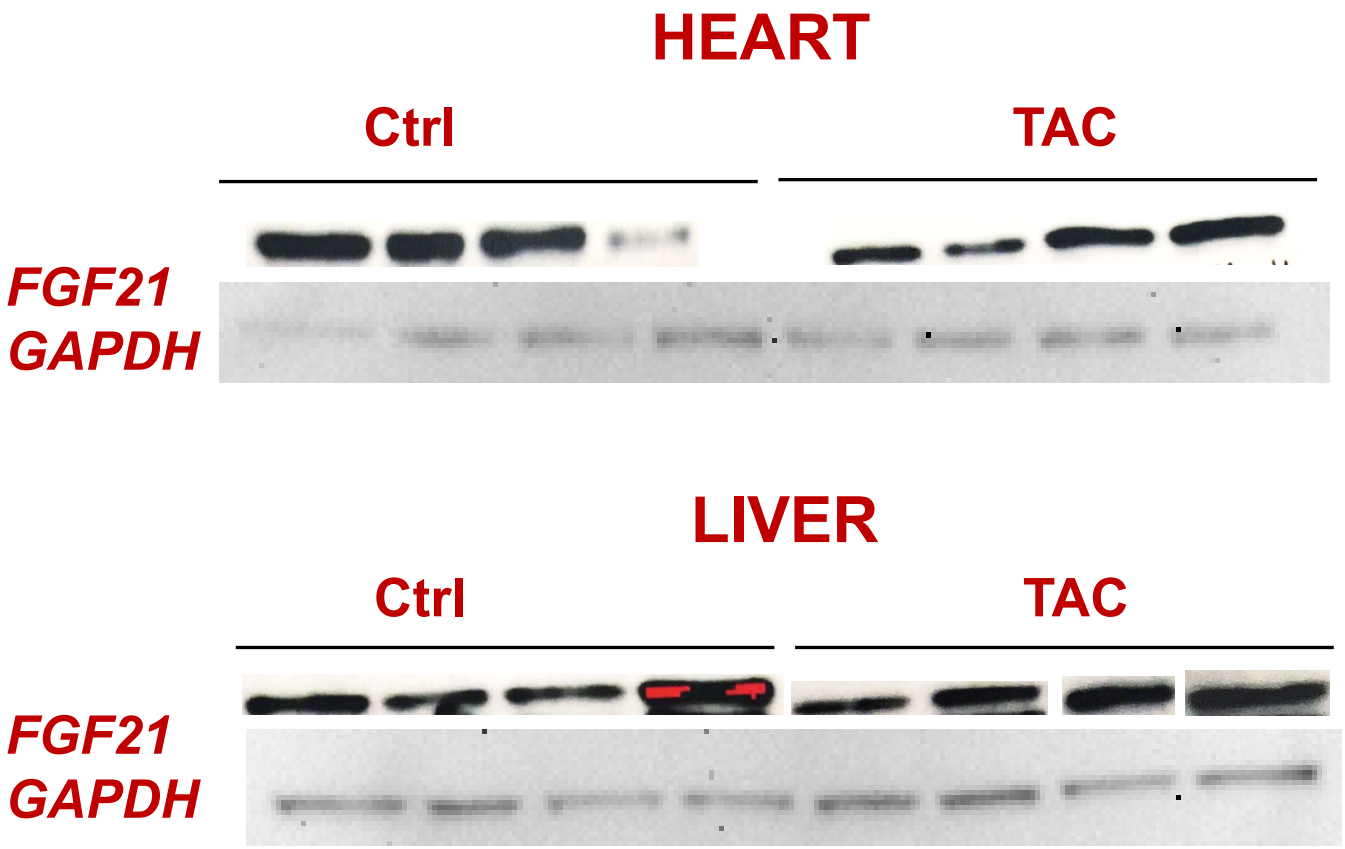
Google Images: biorad-antibodies.com (western blot)

Google Images: smart.servier.com (Electrophoresis)

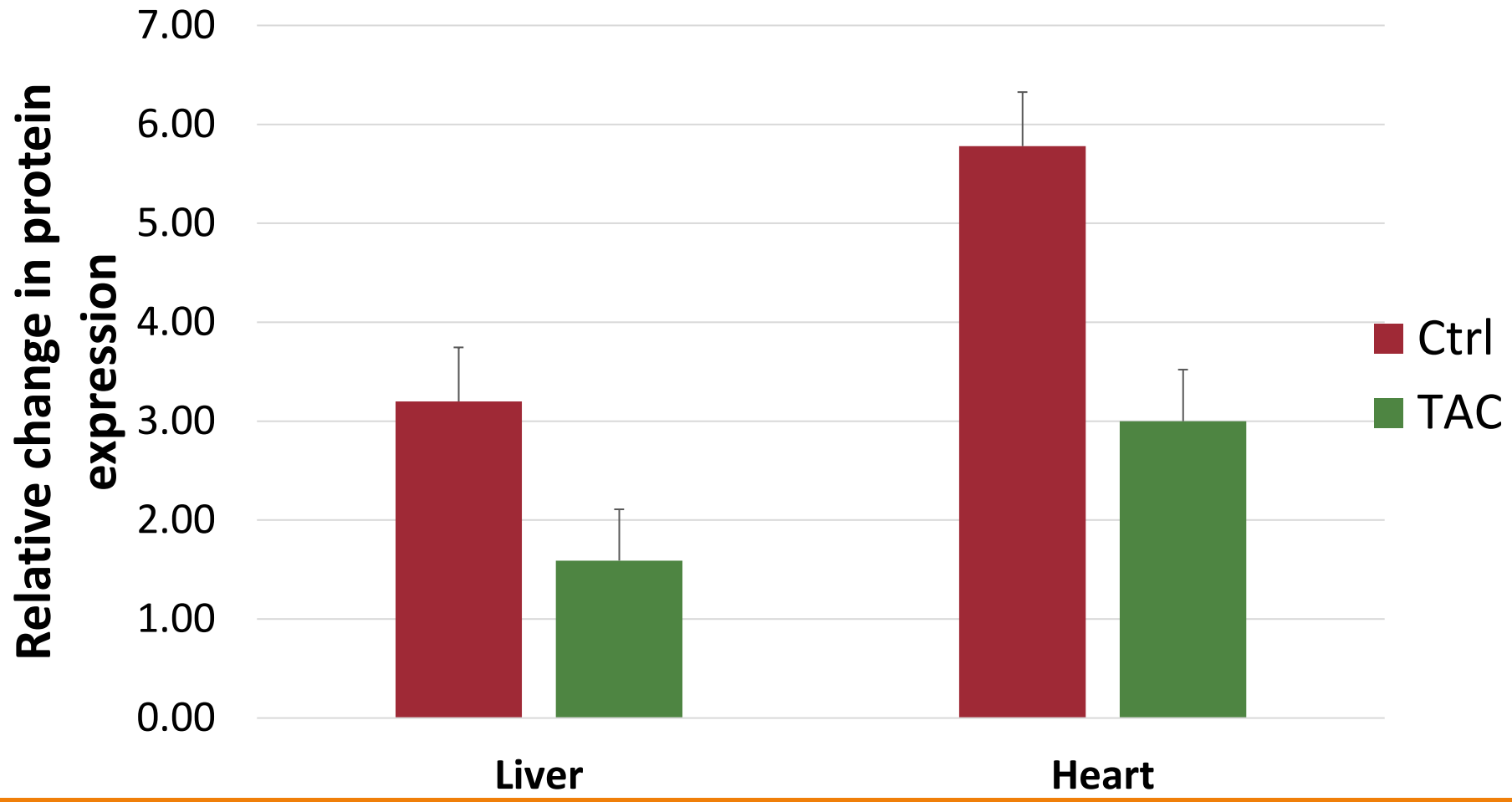
Google Images: angel.co (western blot)

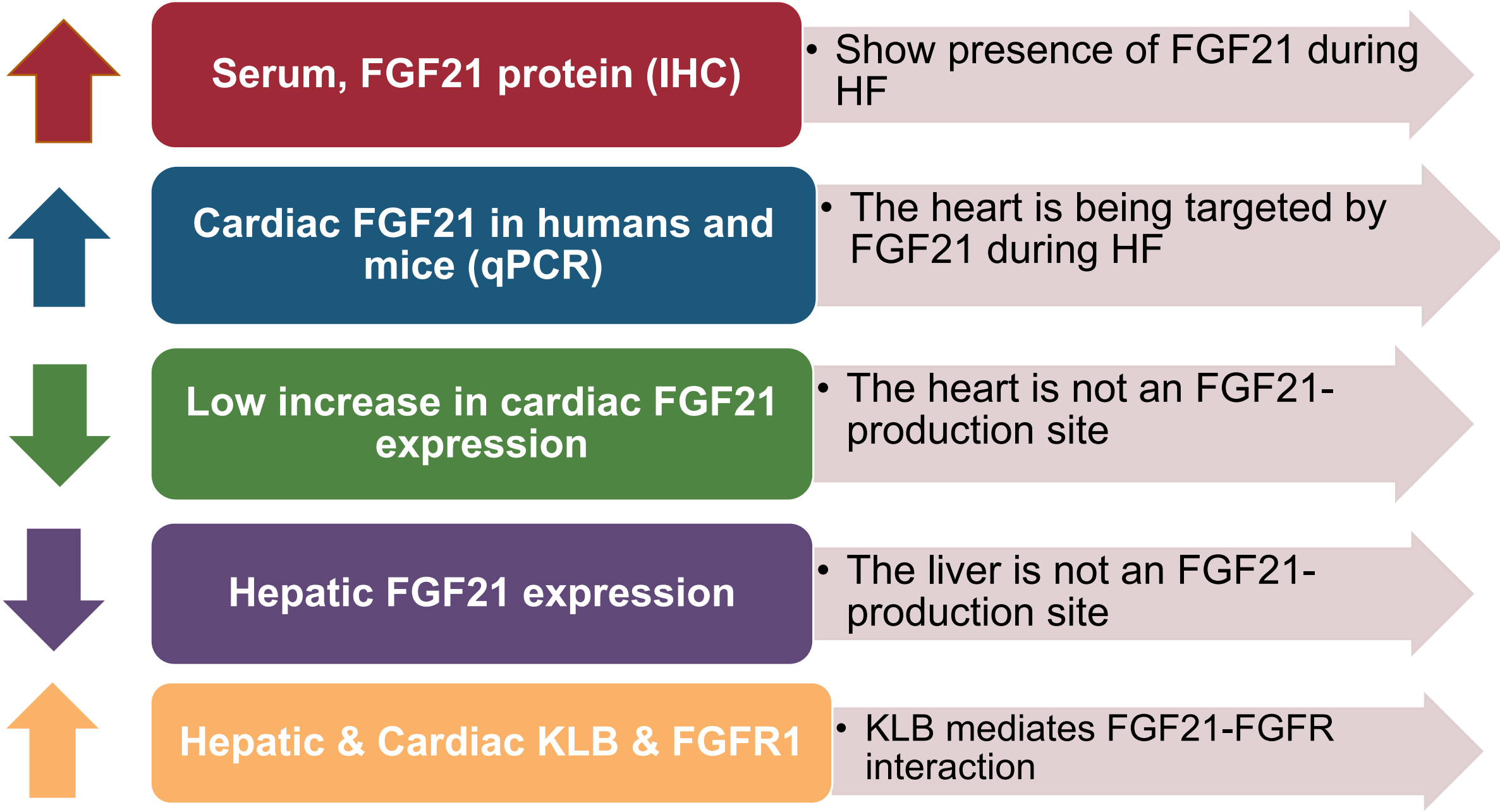
Google Images: yourgenome.org (western blot)

Qualitative WB data shows the presence of FGF21 in the heart and liver during HF



Downregulation of FGF21 protein expression was seen the TAC heart and liver tissues




Serum, FGF21 protein (IHC)
• Show presence of FGF21 during HF
Cardiac FGF21 in humans and mice (qPCR)
• The heart is being targeted by FGF21 during HF
Low increase in cardiac FGF21 expression
• The heart is not an FGF21-production site
Hepatic FGF21 expression
• The liver is not an FGF21-production site
Hepatic & Cardiac KLB & FGFR1
• KLB mediates FGF21-FGFR interaction

Limitations

- TAC is not a good model of ischemic HF
  - The gradual disease progression in patients isn't reflected by the acute increase in LV afterload[1]
- Small sample size

Future plans

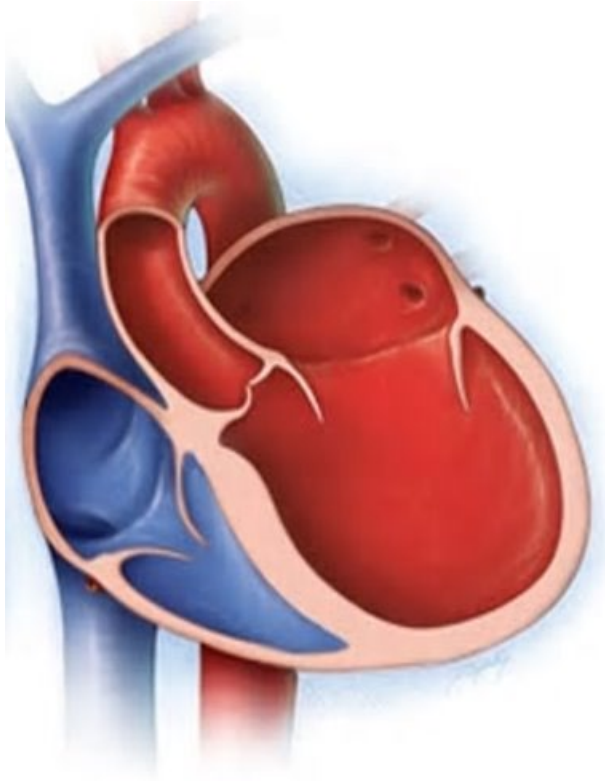
- Induce HF using a ascending aortic constriction procedure[1]
- The variability seen in the current study allows for a power analysis
- Re-examine FGF21 gene expressions

[1]Christian Riehle. *Cardiovascular Research* . Vol. 115. 2019. pp. 1838-1849.

Understanding the production site of FGF21 in DCM has multiple advantages

Clinical settings

- FGF21 as a metabolic stress biomarker for HF



Targeted therapy

- To prevent cardiac cell death during disease progression

Google Images: mayoclinic.org (Dilated Cardiomyopathy)