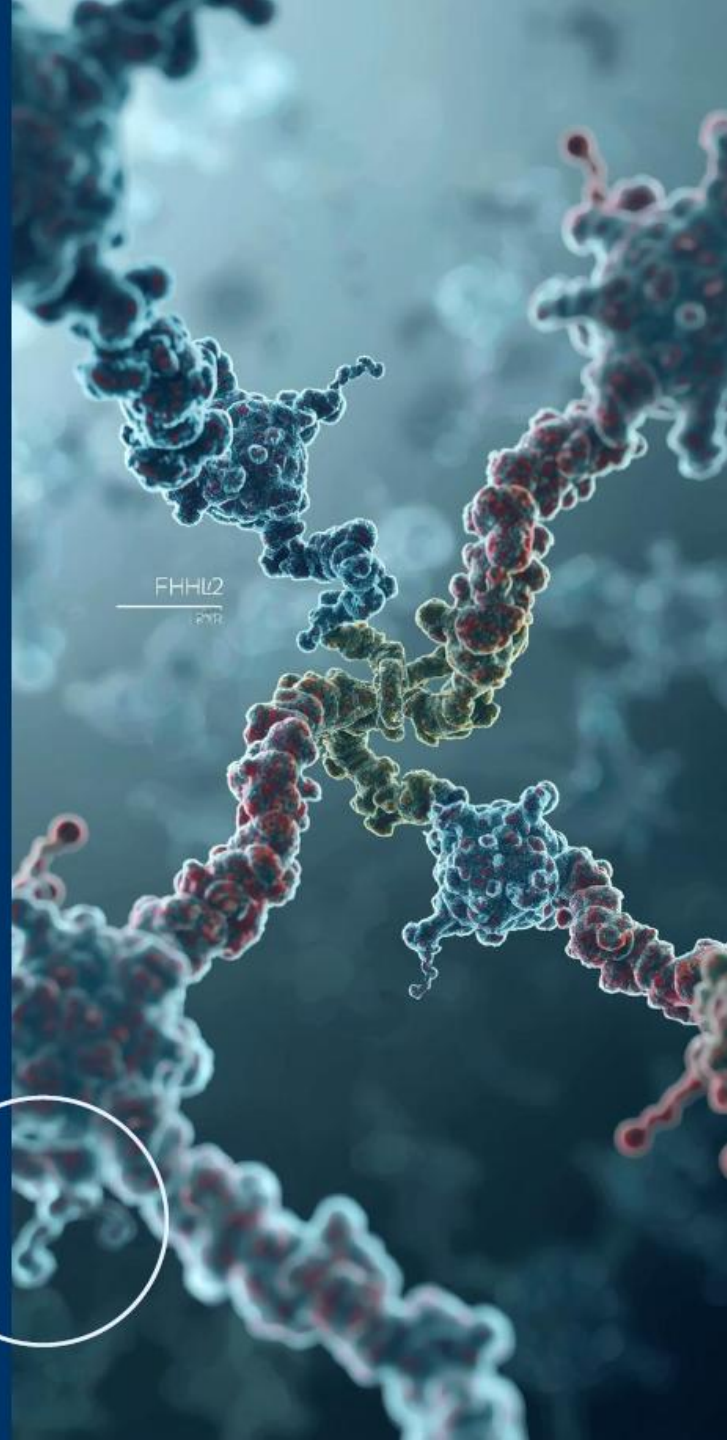
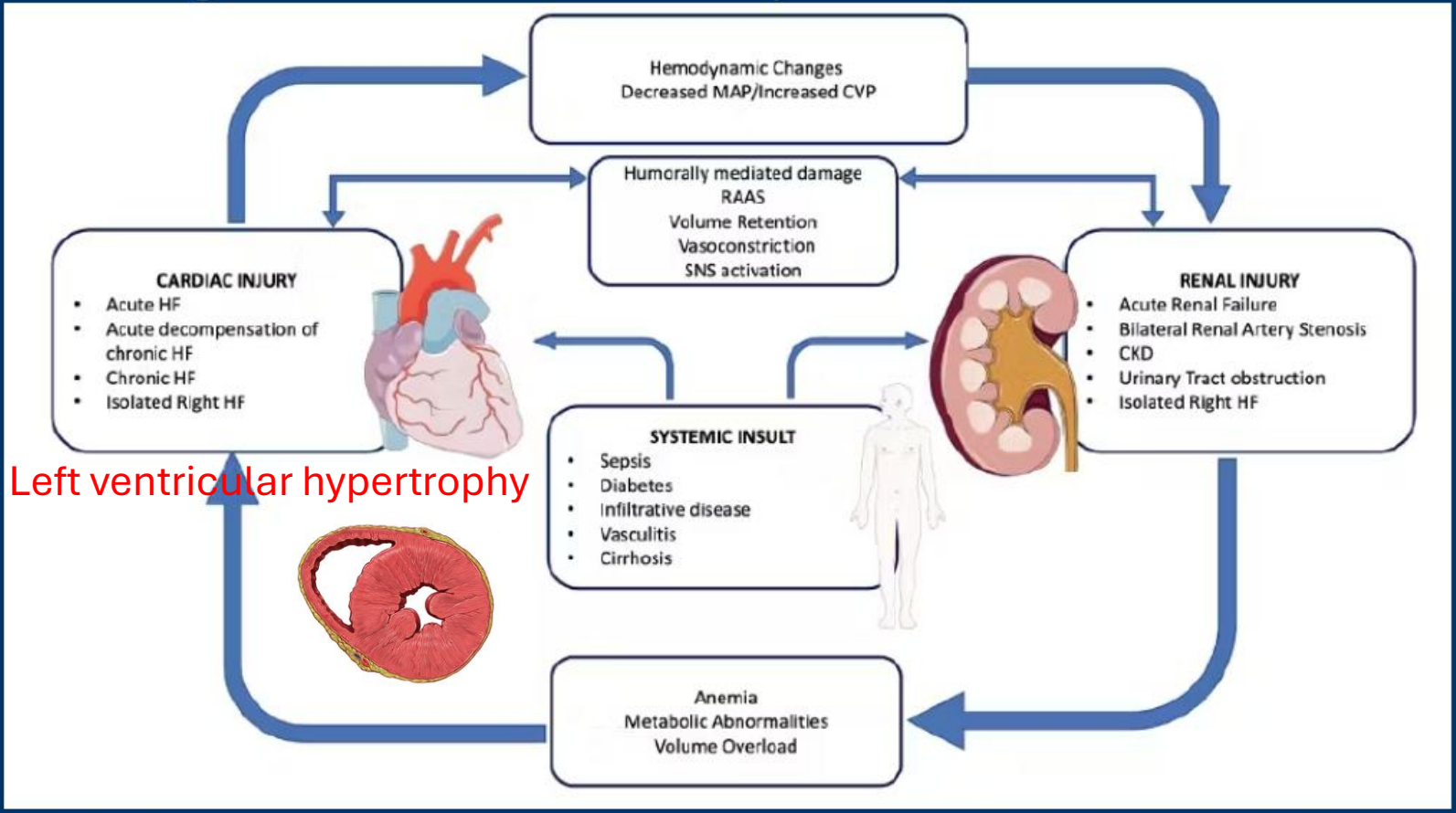
FHL2 is a cofactor of RXR to regulate FGF23 in CKD



陽交大附醫腎臟科
陽交大臨醫所 牛志遠 , Chih-Yuan Niu

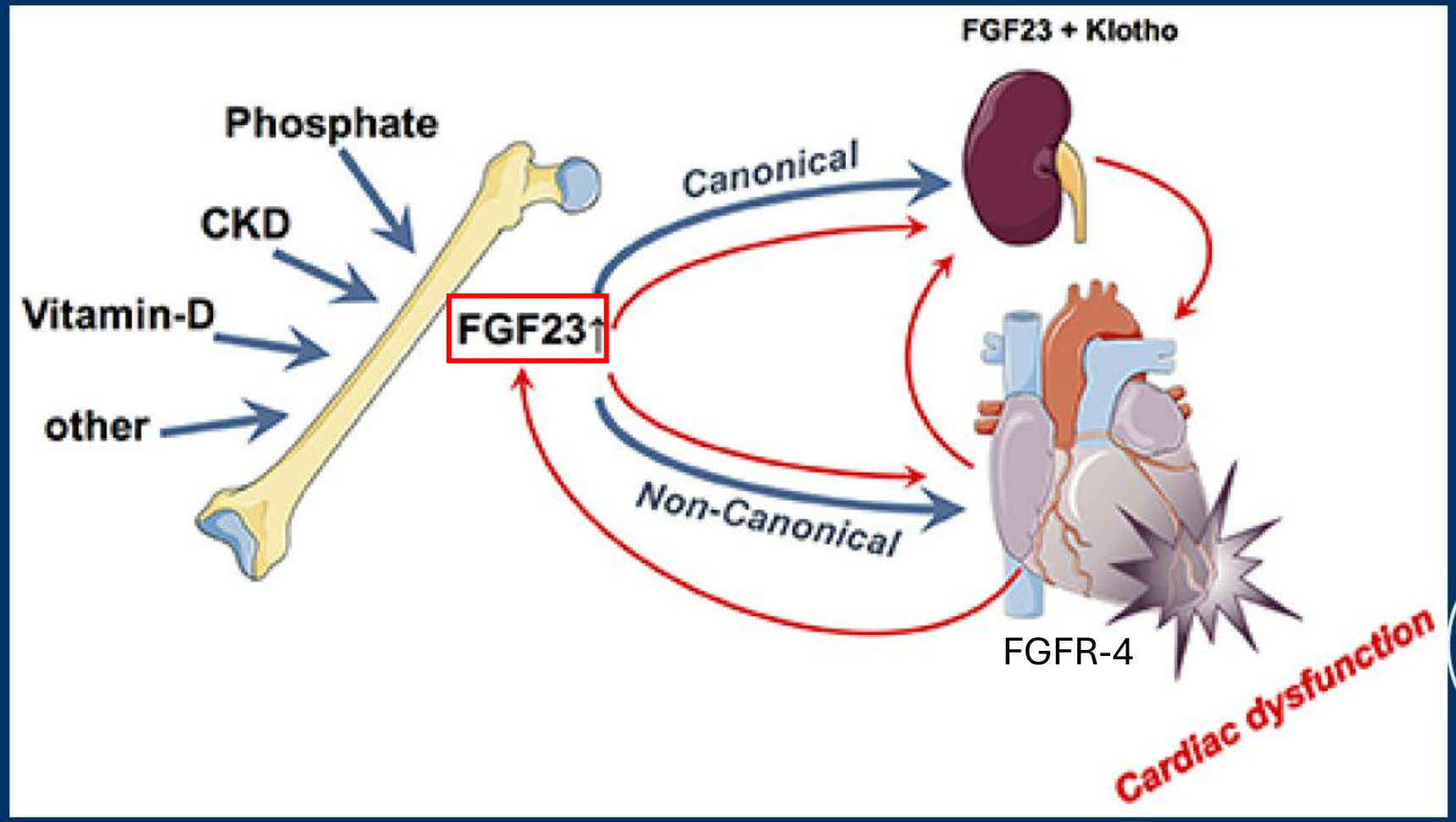
Introduction to Cardiorenal Syndrome

Understanding Cardiovascular Mortality in CKD



CKD, FGF23, and Cardiac Remodeling

FGF23 is a **critical mediator** connecting CKD-MBD and cardiac remodeling, influencing cardiovascular outcomes through its effects on mineral metabolism and cardiac function.

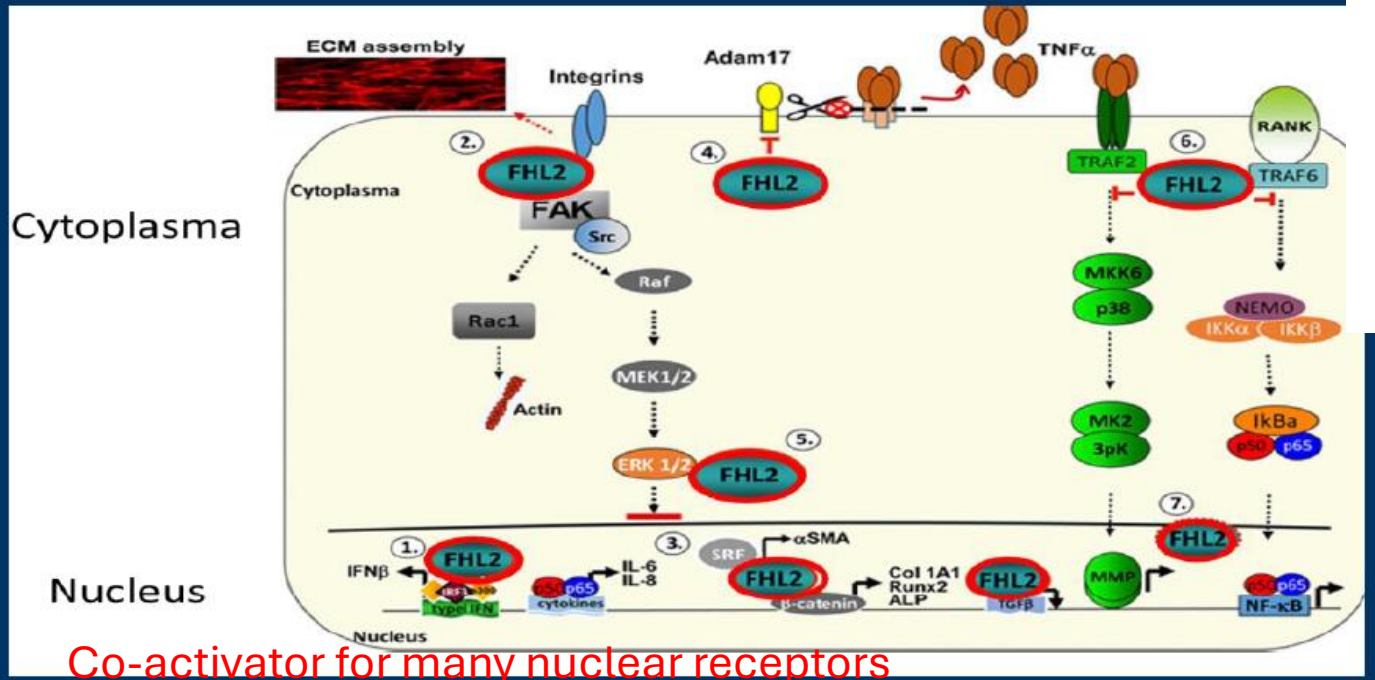


FHL2 as Co-activator of NRs

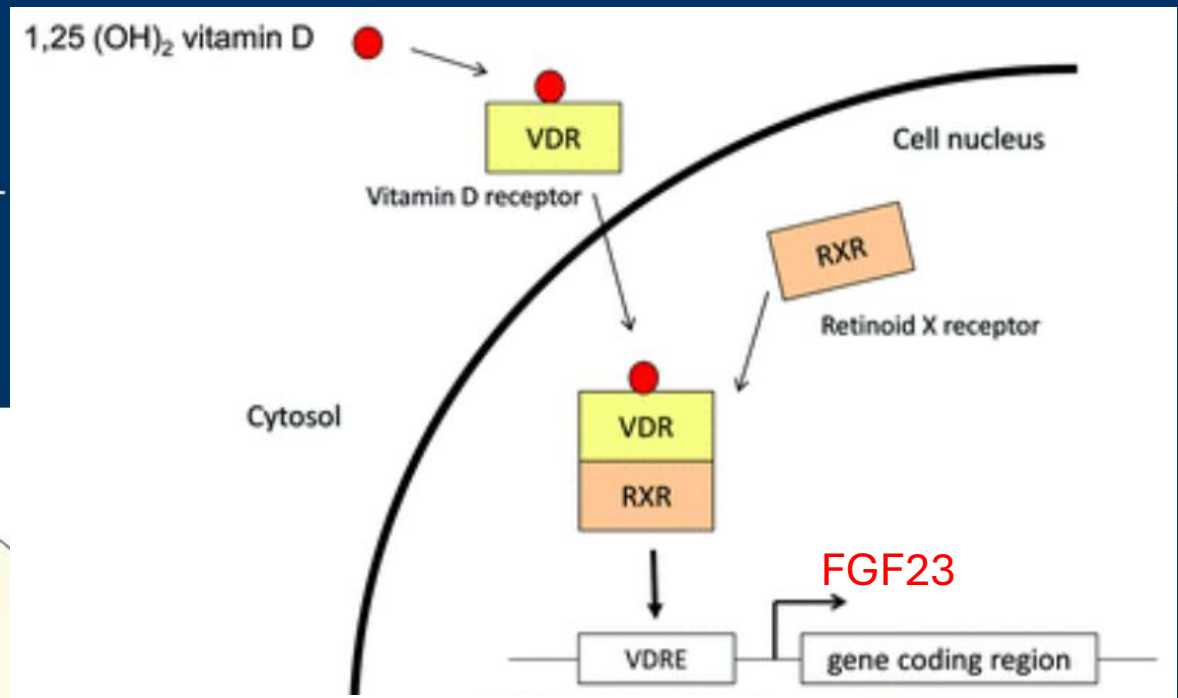
FHL2 Role

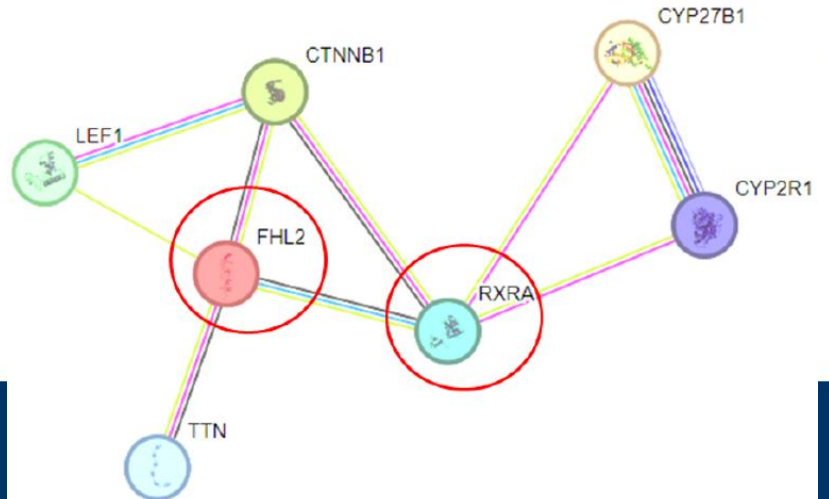
FHL2 can translocate into cytosol after stimluation, where it acts as a co-activator to many nuclear receptor and transcription factor

FHL2 (Four and a Half LIM Domains Protein 2)



Co-activator for many nuclear receptors

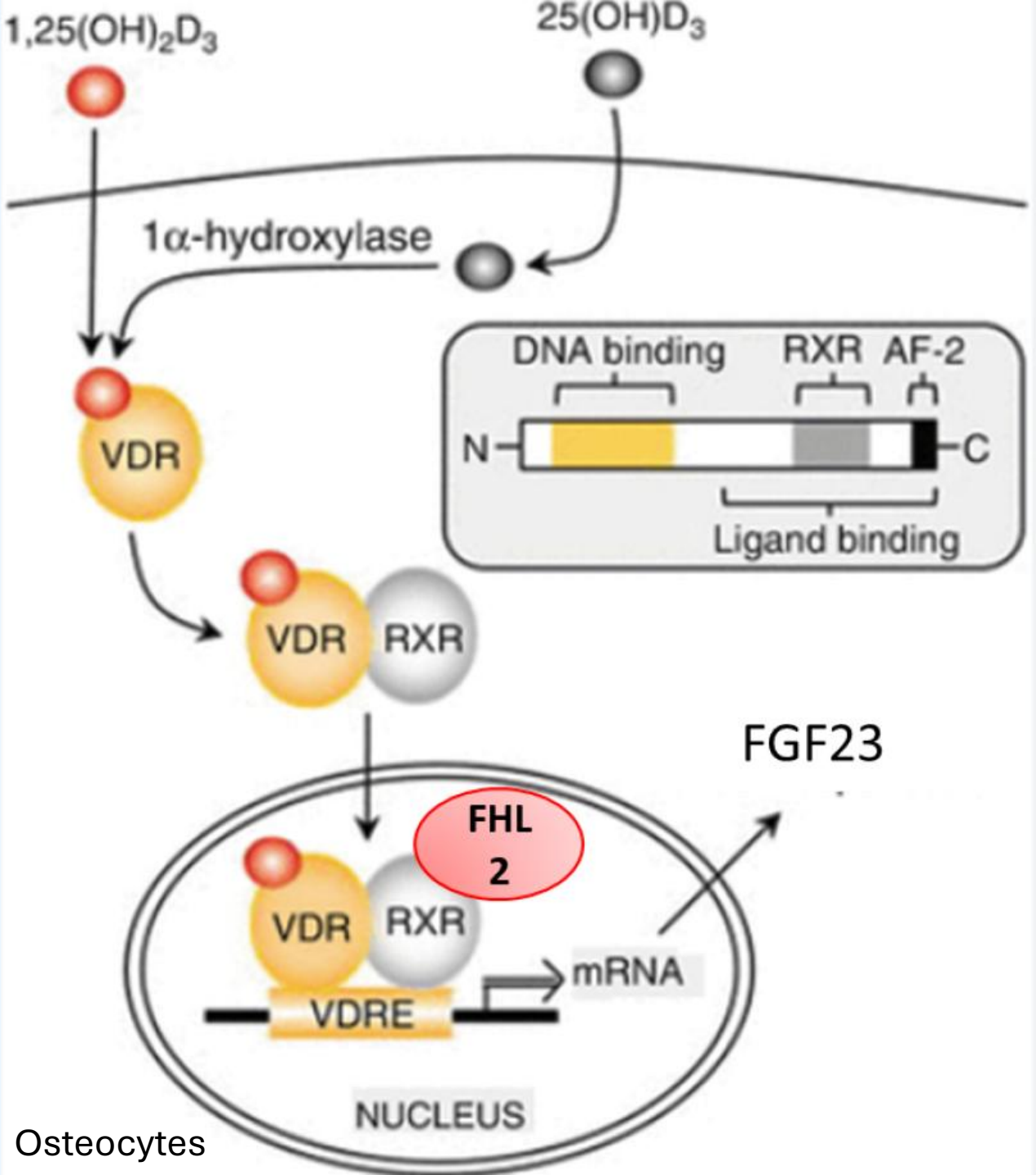




Hyposed FHL2–RXR–FGF23 Axis

Understanding the Interaction Pathway

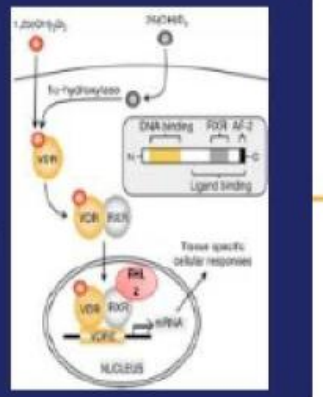
The schematic illustrates the **complex interactions** between FHL2, RXR, and FGF23, highlighting the regulatory role of FHL2 as a co-activator in the VDR/RXR–FGF23 axis involved in CKD pathophysiology.



Experiment Design

FHL2-RXR-FGF23 axis

FHL2 is a cofactor of RXR in osteocyte



①  Cell experitment
- CO-IP
- CO-ChIP
- Functional study

②  FGF23 and LVH in CKD animal models
- circulating FGF23 concentration
- Echocardiograhy
- Cardiac fibrosis

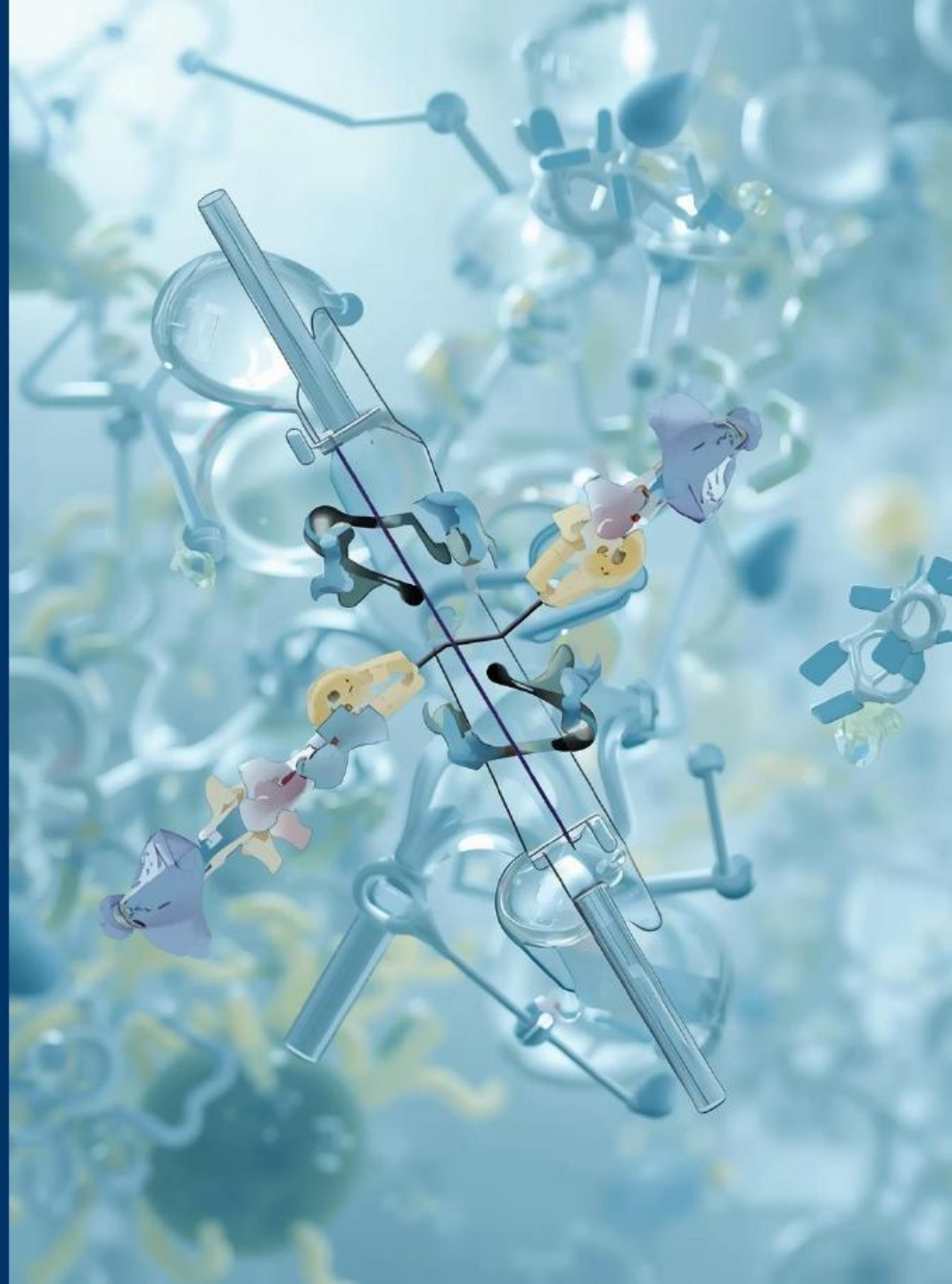
5/6 nephrectomy

③  Safety of FHL2 inhibition on bone health
- Micro-CT scan
- Osteoblast/ Osteoclast maturation
- Long-term effect

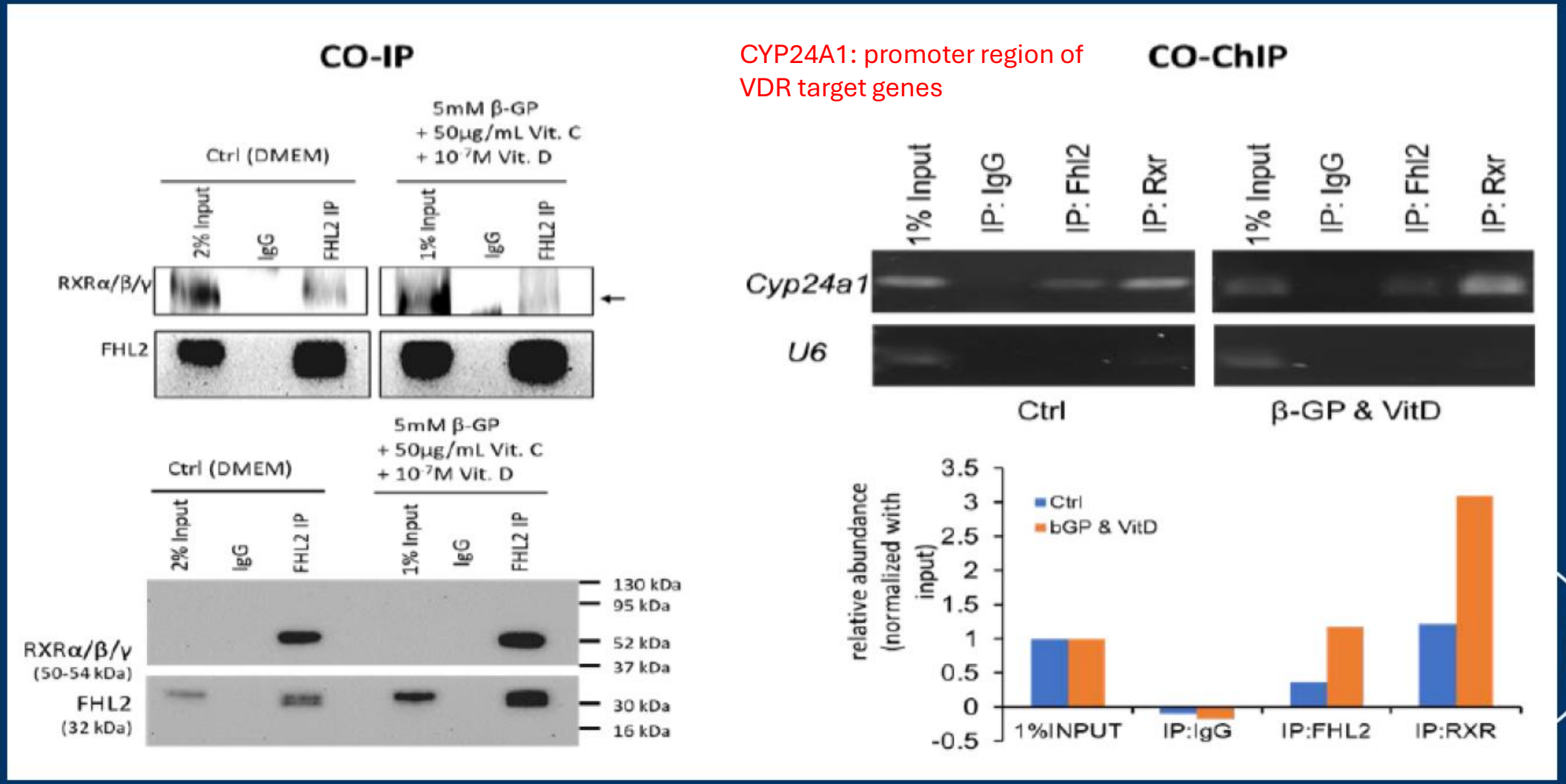
Co-IP and ChIP Results

Confirming FHL2–RXR Binding Interactions

The Co-IP and ChIP assays demonstrated a strong **interaction between FHL2 and RXR**, highlighting the role of vitamin D in enhancing promoter occupancy, which is crucial for FGF23 regulation in cardiac tissues.



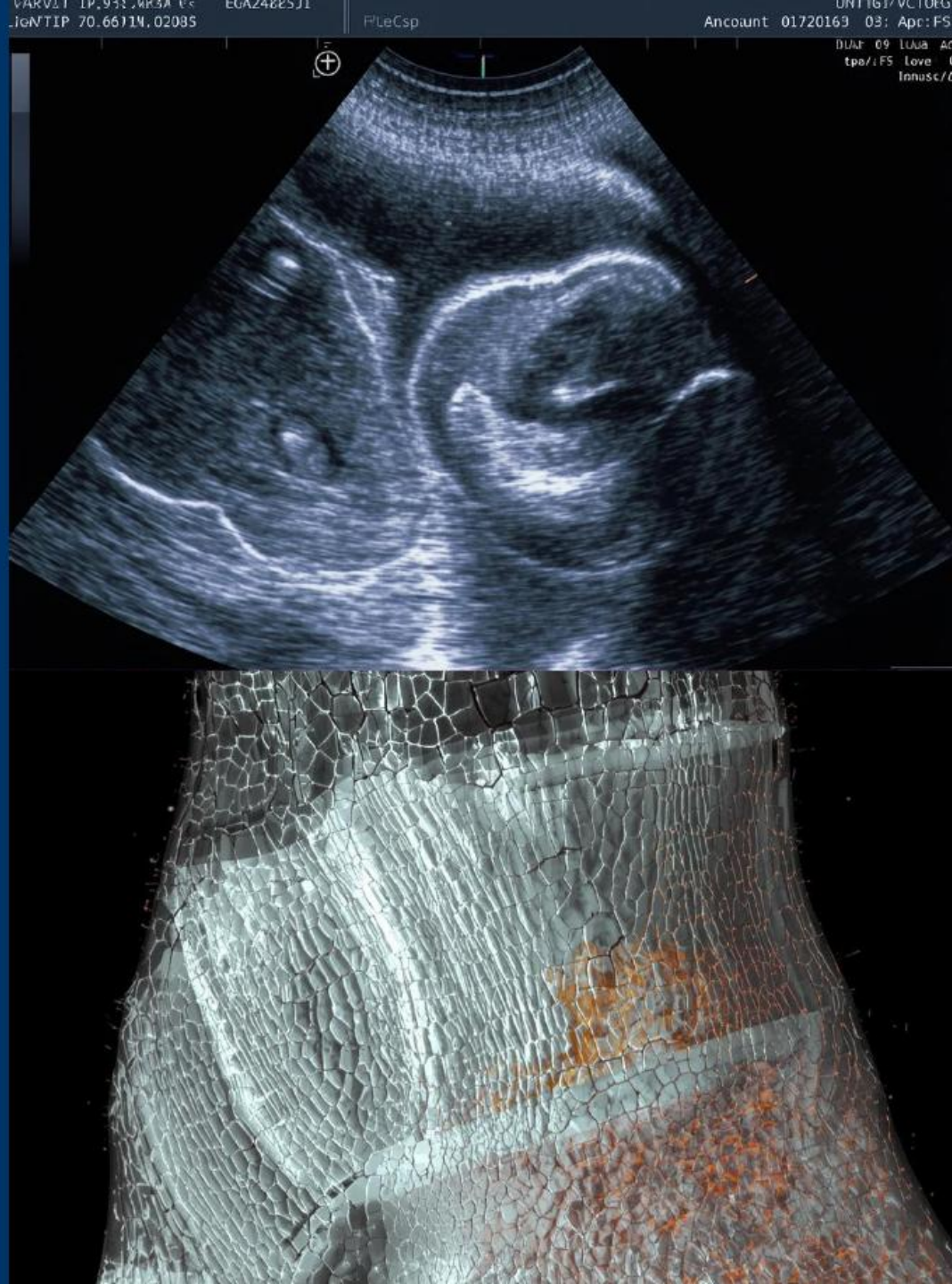
Co-immunoprecipitation and CO-ChIP confirms FHL2 physically binds to RXRα/β/γ proteins under both baseline and vitamin D-induced conditions.



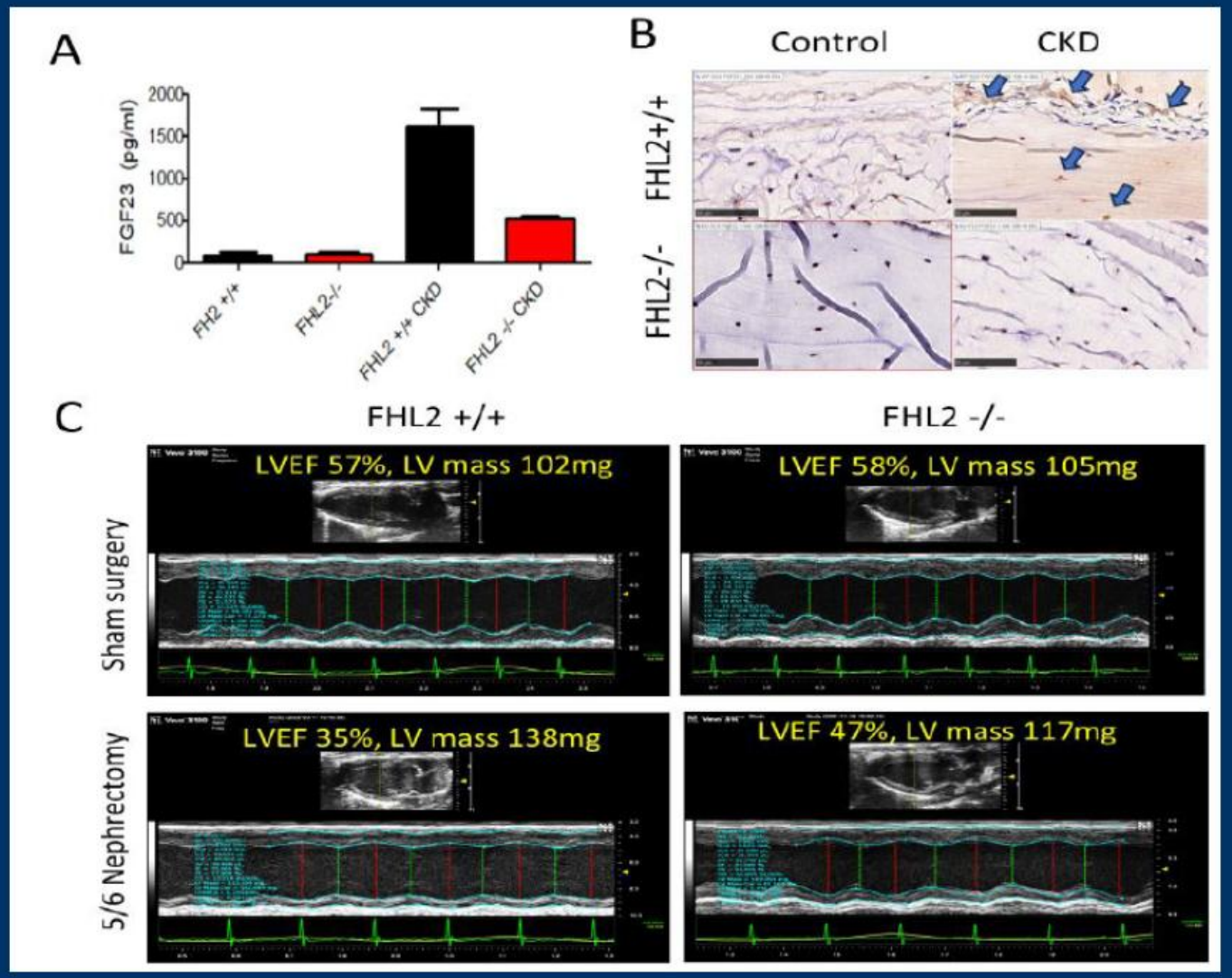
In Vivo Effects on CKD

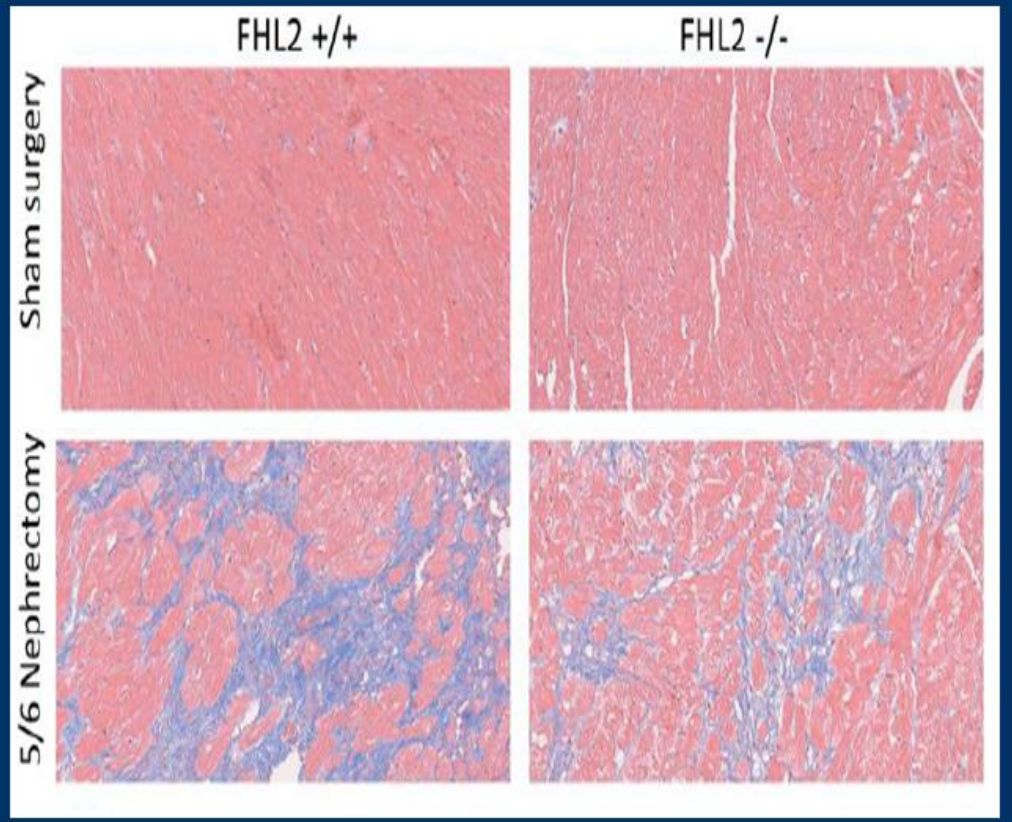
Echocardiography and Histology Findings

The echocardiography results demonstrate significant improvements in cardiac function, while histological analysis reveals reduced cardiac fibrosis in FHL2 knockout mice, highlighting the protective role of FHL2 inhibition in CKD.



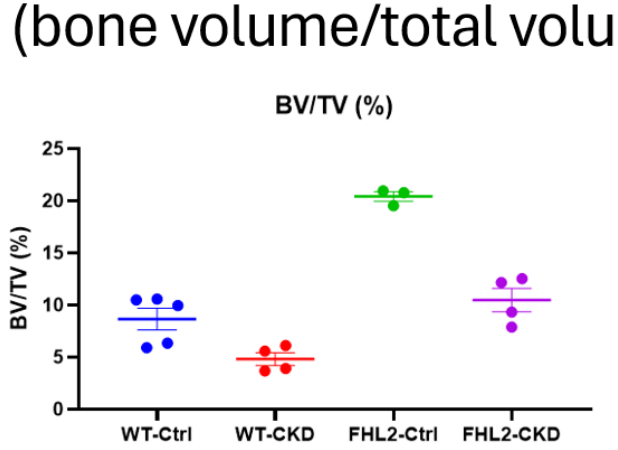
FHL2 KO mice have a lower FGF23 level and and attenuated LVH after CKD

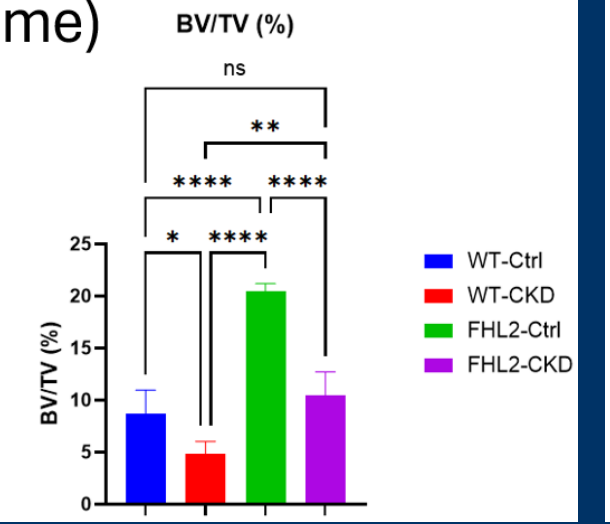




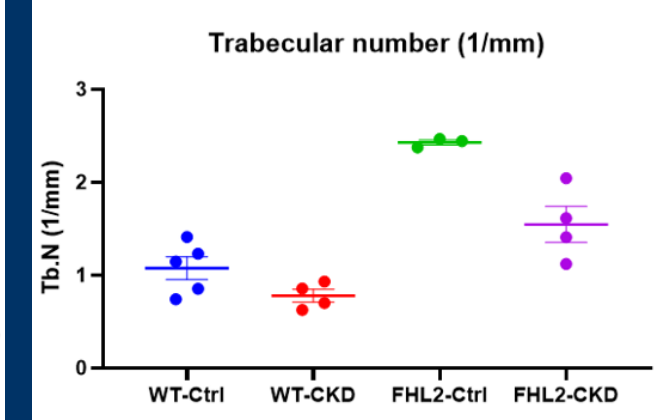
FHL2 KO mice have a higher bone density

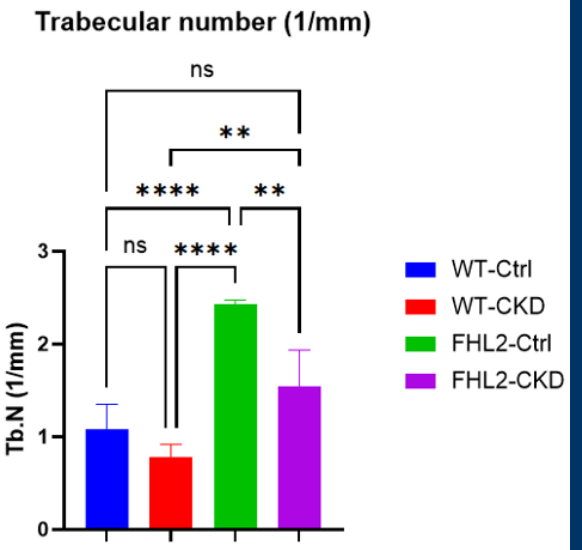
Percent bone volume (bone volume/total volume)





Trabecular number





Summary

. To conclude, our data establish FHL2 as a critical co-activator of RXR, driving pathological FGF23 expression.

. Inhibiting FHL2 safely and effectively attenuates elevated FGF23 and subsequent left ventricular hypertrophy and cardiac fibrosis in CKD.

. The fact that FHL2 inhibition is associated with improved bone density and structural integrity strengthens its therapeutic potential.

. We anticipate that FHL2 inhibitors could be developed into small molecule drugs for the treatment of renocardiac syndrome.