Endocrine Disorders of FGF23

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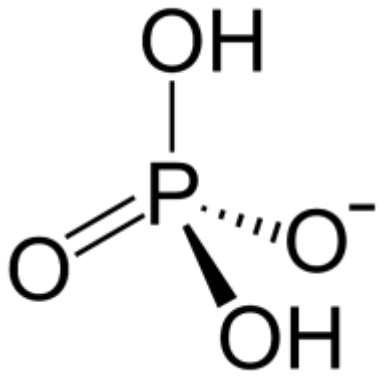
National Institutes of Health

NIH National Institute of Dental and Craniofacial Research

XXXI CONGRESO DE LA SOCIEDAD CHILENA DE OSTEOLOGÍA Y METABOLISMO MINERAL - SCHOMM

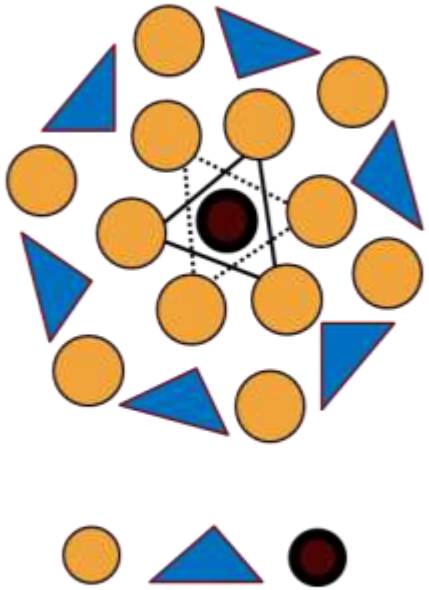
26 y 27 DE ABRIL 2024

FGF23 is the Primary Regulator of Phosphate
Why do we care about phosphate?



- **Energy: ATP**
- **Nucleic acids: DNA, RNA**
- **Membranes: phospholipids**
- **Signaling: cAMP, phosphorylation**

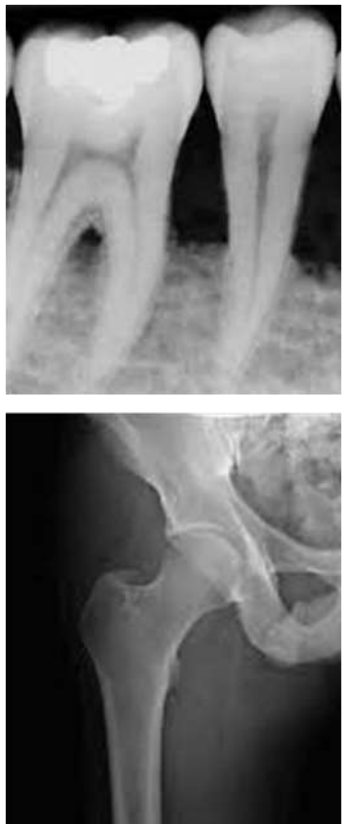
Hydroxyapatite



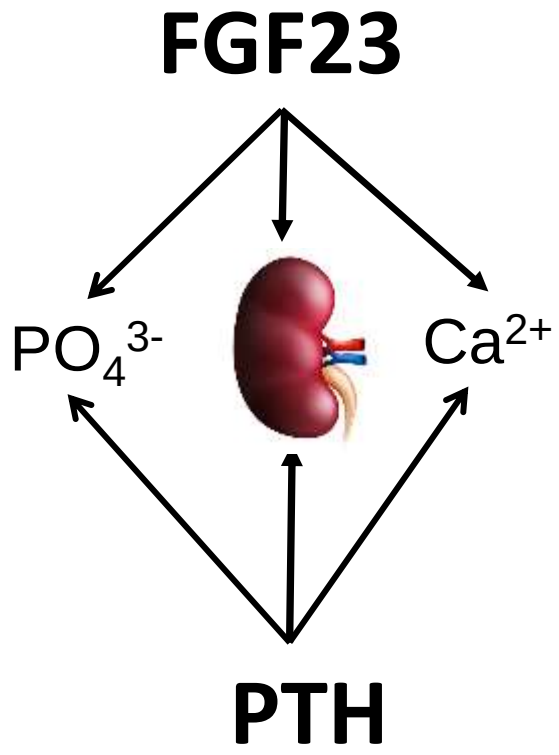
$Ca_{10}(PO_4)_6(OH)_2$

97% of enamel
70% of bone

Mineralized tissues

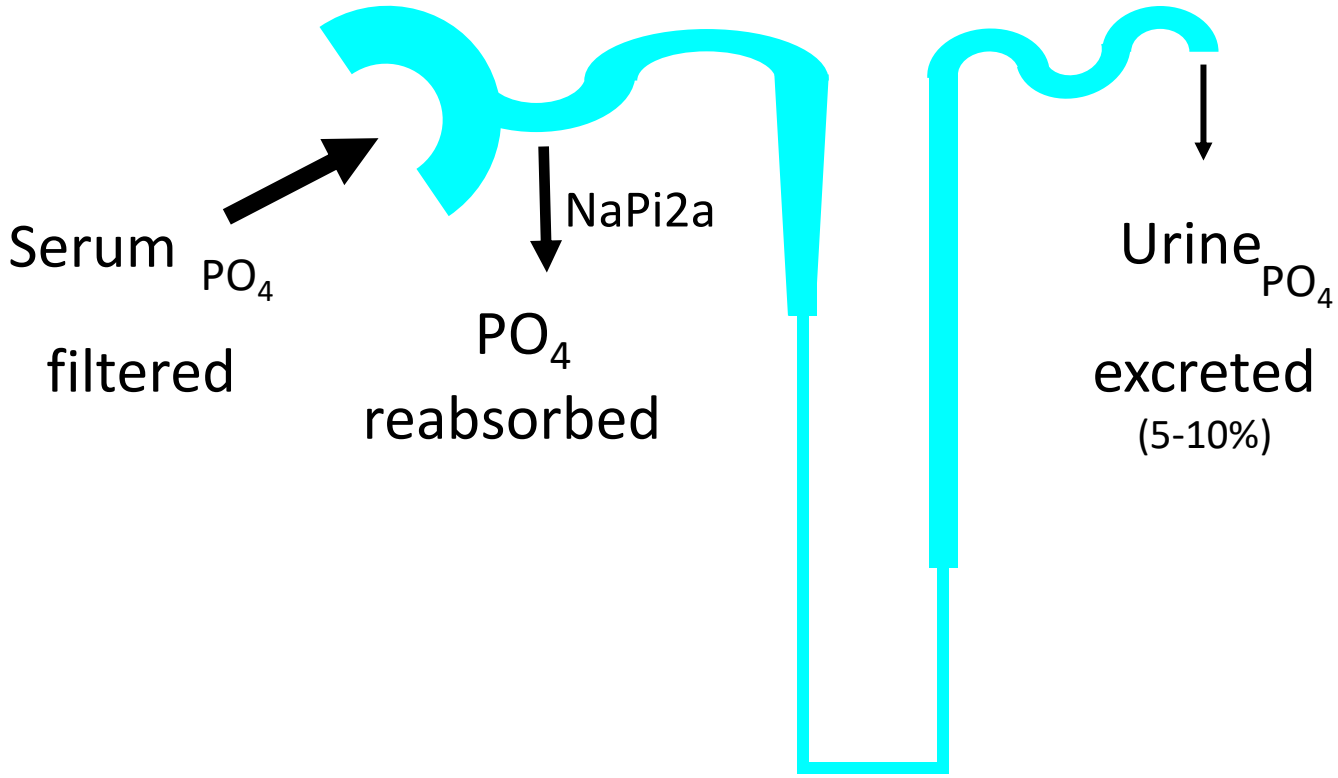


Mineral homeostasis

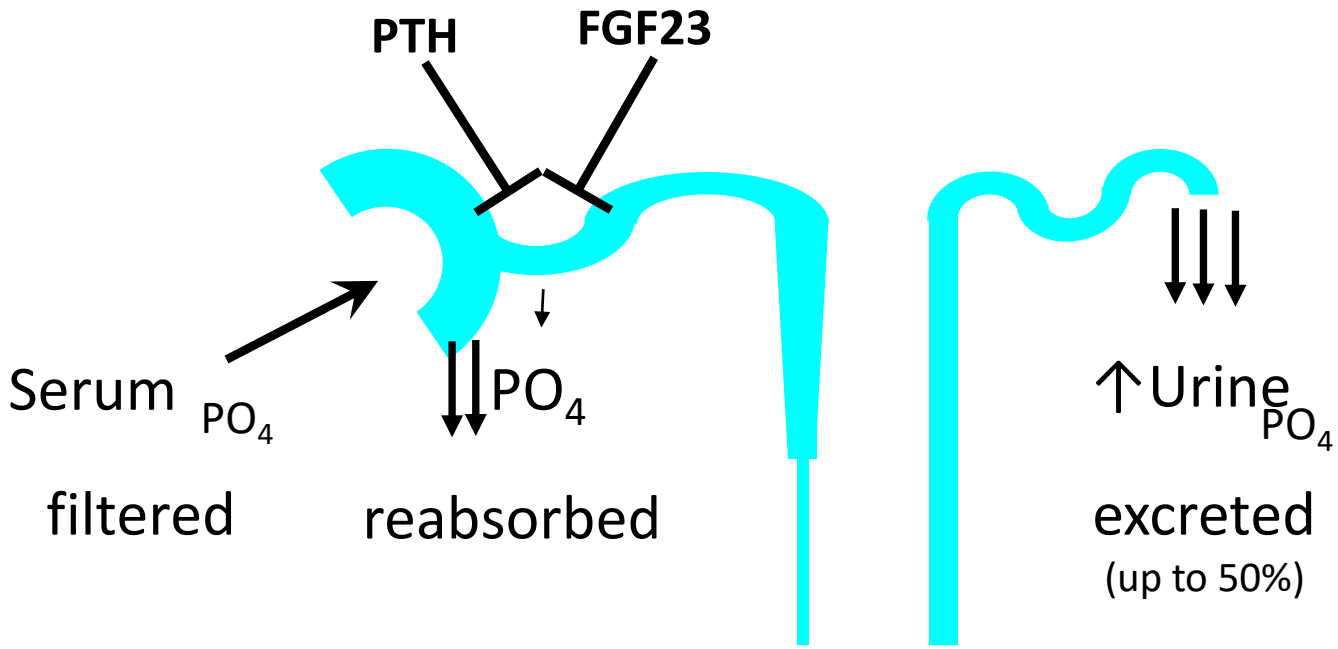


PTH= parathyroid hormone
FGF23 = fibroblast growth factor 23

Mineral Physiology – Phosphate



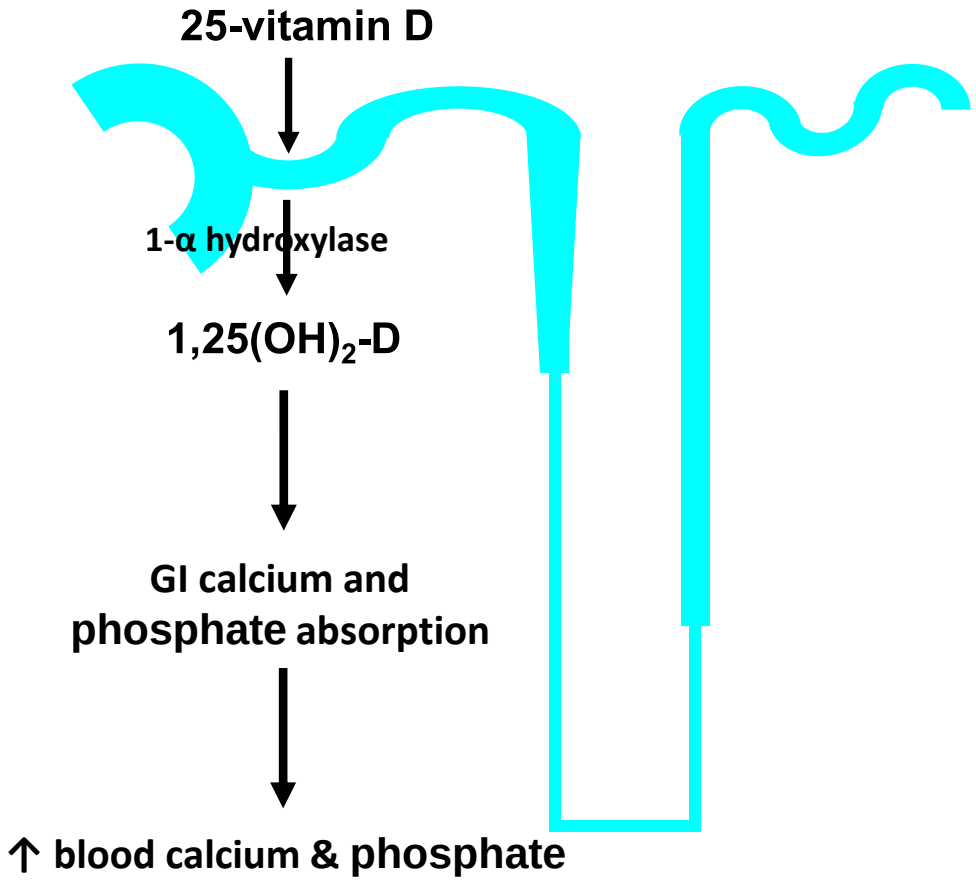
FGF23 & PTH protect against hyperphosphatemia; synergize to increase urinary PO4 excretion



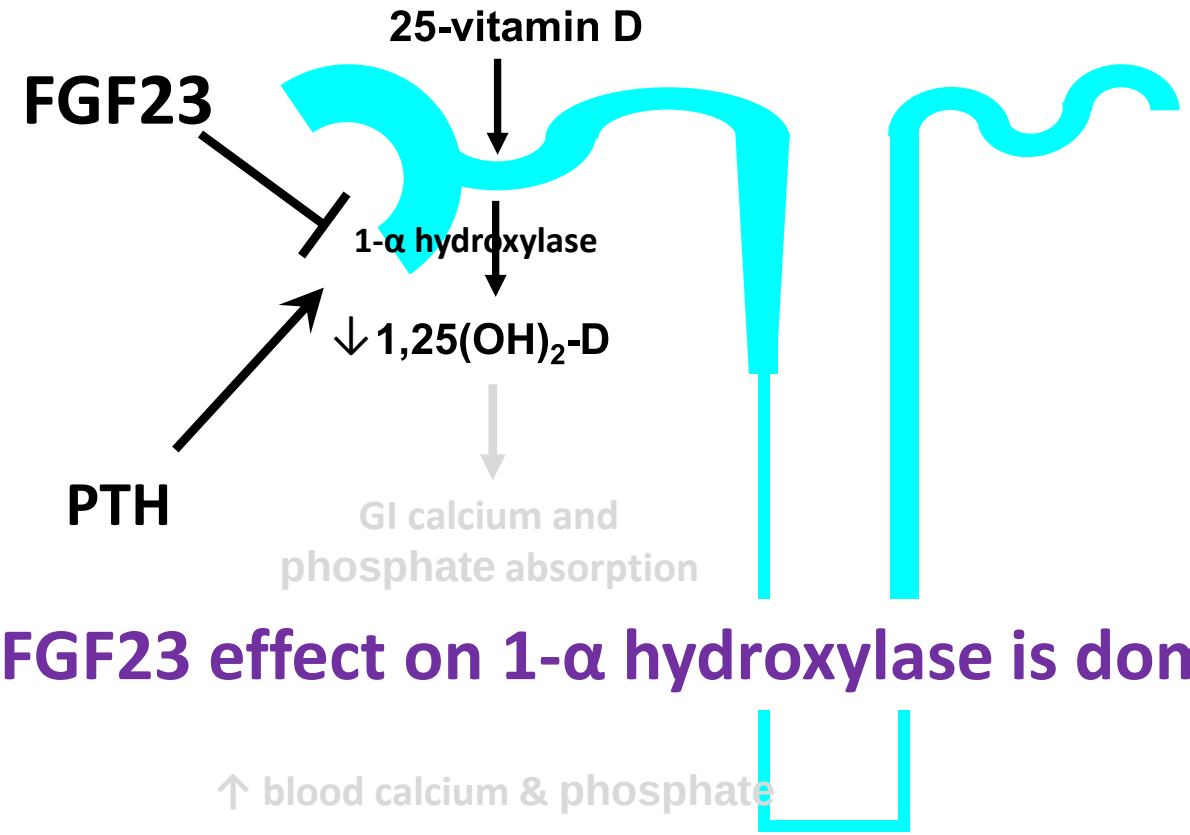
FGF23 and PTH actions are mutually dependent

(for either to fully work, both FGF23 and PTH must be present)

Vitamin D Physiology



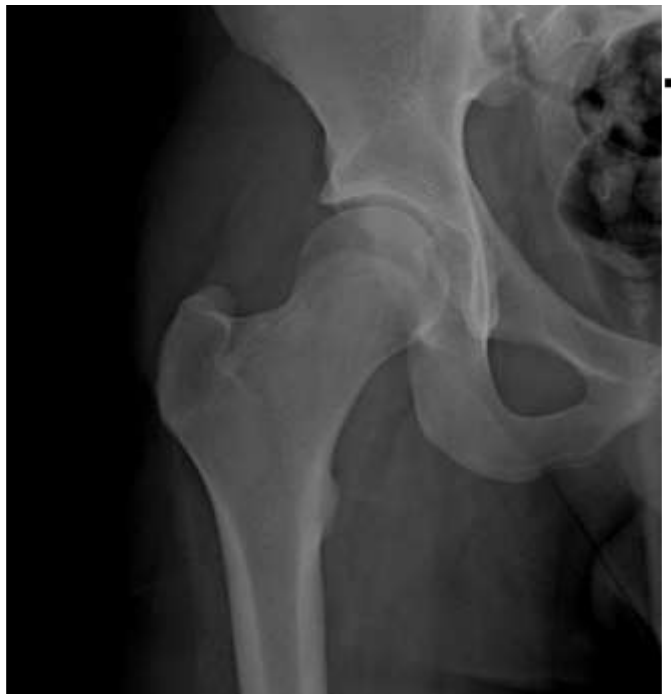
FGF23 Inhibits 1,25-D Production
PTH Stimulates 1,25-D Production



FGF23 effect on 1-α hydroxylase is dominant

FGF23 Action and Regulation

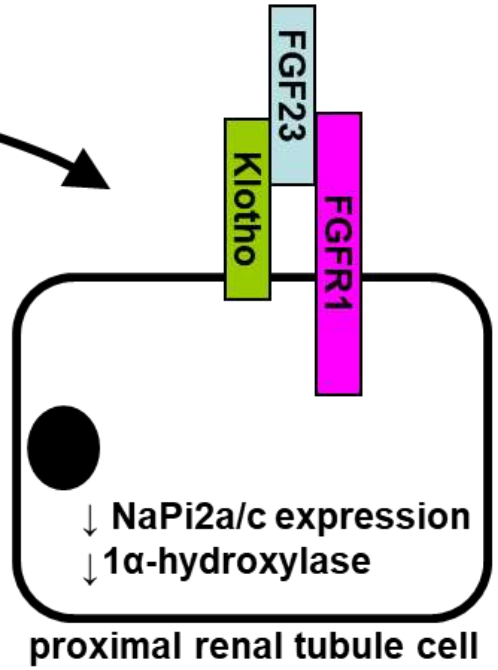
FGF23 is made by bone cells



Collins, JBMR, 2001
Riminucci, Collins, J Clin Invest 2003
Sitara et al, Matrix Biology, 2004
Mirams et al, Bone, 2004

regulates renal phosphate and vitamin D metabolism

FGF23



↓ serum phosphate

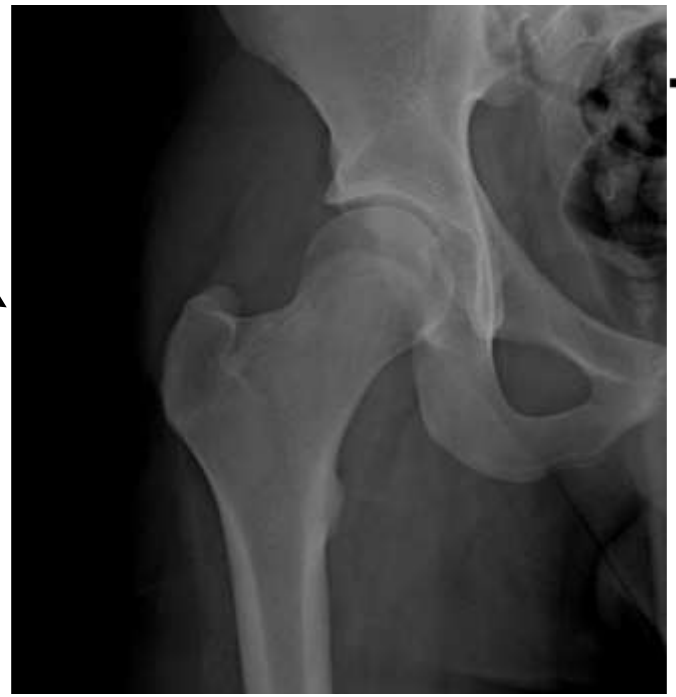
↓ serum 1,25-vitamin D_3

phosphate

Shimada, JBMR, 2004

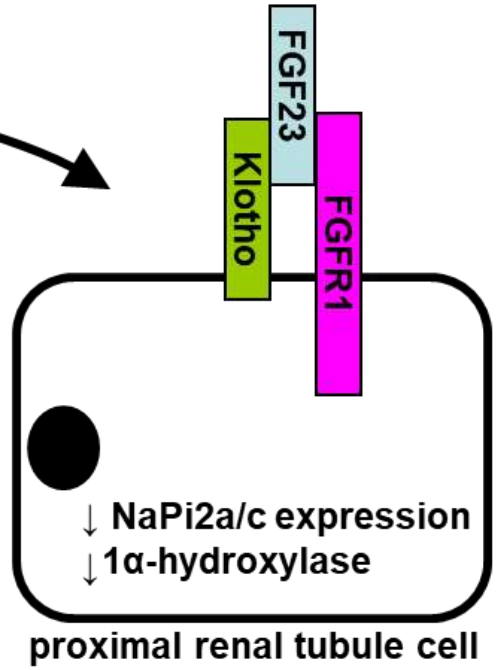
FGF23 Action and Regulation

↑Phosphorus
↑1,25-Vit D
↑ Ca^{2+} + Pi
(HIF/Epo/Fe)



regulates renal phosphate and vitamin D metabolism

FGF23



↓ serum phosphate

↓ serum 1,25-vitamin D_3

phosphate

Phosphorus
- Ferrari JCEM 2005
- Antoniucci JCEM 2006
- Burnett JBMR 2006
- DiIorio CJASN 2012
- Roszko JBMR 2020

1,25-vit. D:
- Collins JBMR, 2005
- Kolek A J Gastr Liver Phys 2005
- Barthel J Ster Mol Bio 2006
- Liu A J Soc Nephr 2006

Phosphorus + Ca:
- Quinn AJPEM, 2012

FGF23-Mediated Diseases

	Condition	Abbreviation	Gene(s)	FGF23
FGF23 Excess	Tumor-induced osteomalacia	TIO	*FN-FGFR1 (FGF23-secreting tumors)*	↑↑
	X-linked hypophosphatemic rickets	XLH	*PHEX*	↑
	FD/McCune-Albright syndrome	FD/MAS	*GNAS (mosaic)*	↑
	Autosomal recessive hypophosphatemic rickets	ARHR1	*DMP-1*	↑
	Autosomal recessive hypophosphatemic rickets/ENPP1 Deficiency	ARHR2/ENPP1 def	*ENPP1*	↑
	Cutaneous skeletal hypophosphatemia syndrome	CSHS	*RAS (mosaic)*	↑
	Autosomal dominant hypophosphatemic rickets	ADHR	*FGF23*	↑
FGF23 Deficiency	Hyperphosphatemic familial tumoral calcinosis	HFTC (1,2,3)	*GALNT3; FGF23; Klotho*	↓
	Autoimmune tumoral calcinosis (FGF23 resistance)	ATC	FGF23 Autoantibodies	↑↑
	Renal Failure	CRF	*N/A*	↑↑

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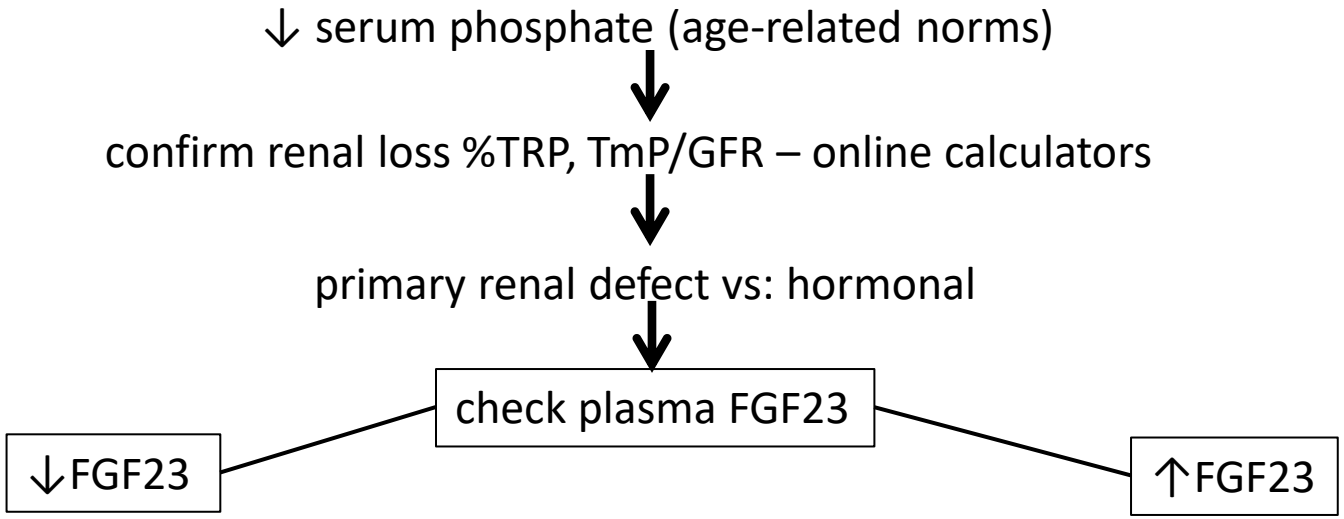
	Autoimmune tumoral calcinosis (FGF23 resistance)	ATC	FGF23 Autoantibodies	↑↑	
	Renal Failure	CRF	*N/A*	↑↑	

Evaluation of FGF23-Mediated Hypophosphatemia



renal dysfunction

Fanconi-type tubulopathy

- aminoaciduria
- proteinuria (low MW)
- bicarbonaturia (acidosis)
- calciuria

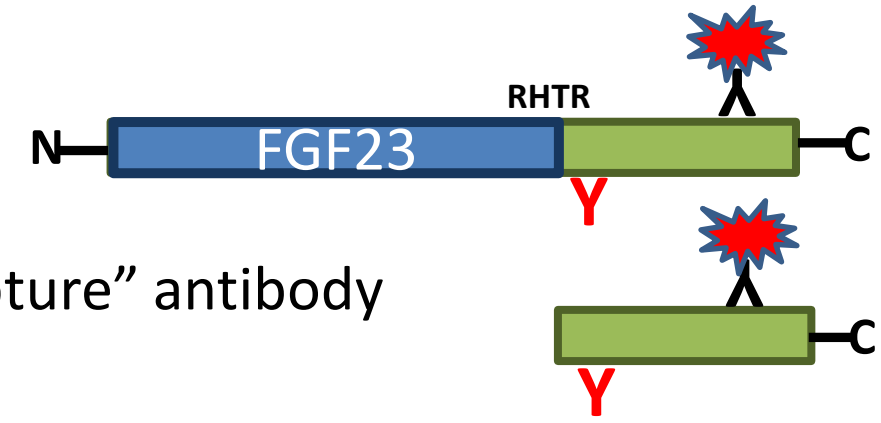
Acquired (Fanconi syndrome)

- Toxins (lead, cadmium, etc)
- Drugs (**tenofovir,** chemotherapy)

TRP = tubular reabsorption of phosphate
TmP/GFR tubular maximum reabsorption of phosphate

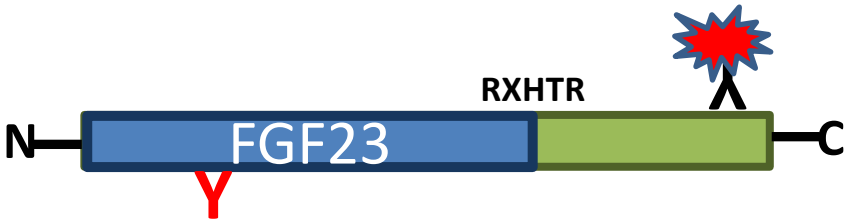
FGF23 ELISA assays

= "signal" antibody



Y = "capture" antibody

"C-terminal" assay:
detects intact and C-terminal FGF23
reported in RU/mL (Immutopics, others)
(normal <180)

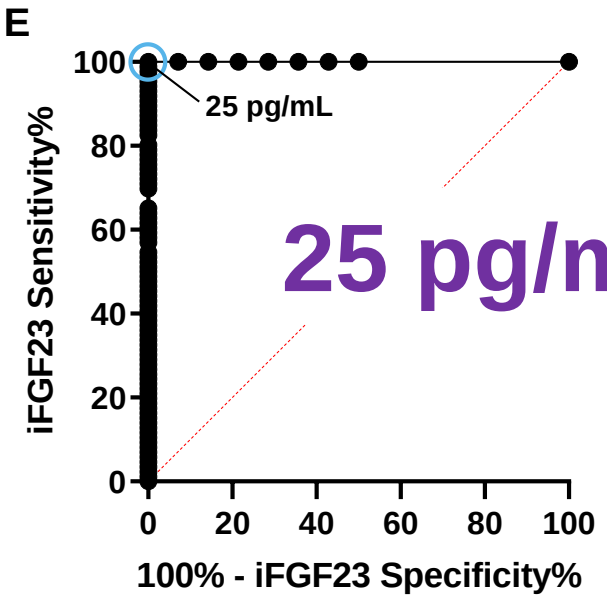


"Intact" assay:
detects only intact FGF23
reported in pg/mL (Kainos or Immutopics, others)
(normal <108pg/ml)

"C-terminal" assay measures both C-terminal *AND* intact molecule

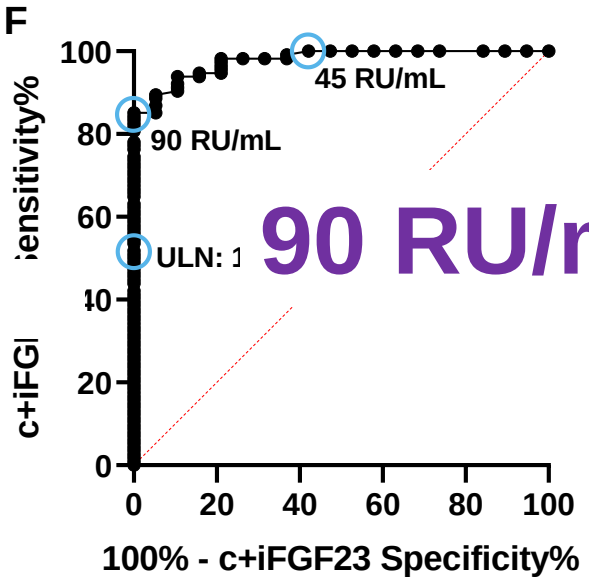
What is the FGF23 Upper Limit in Hypophosphatemia?

intact FGF23
(normal <108pg/ml)



25 pg/ml

C-terminal FGF23
(normal <180)



90 RU/ml

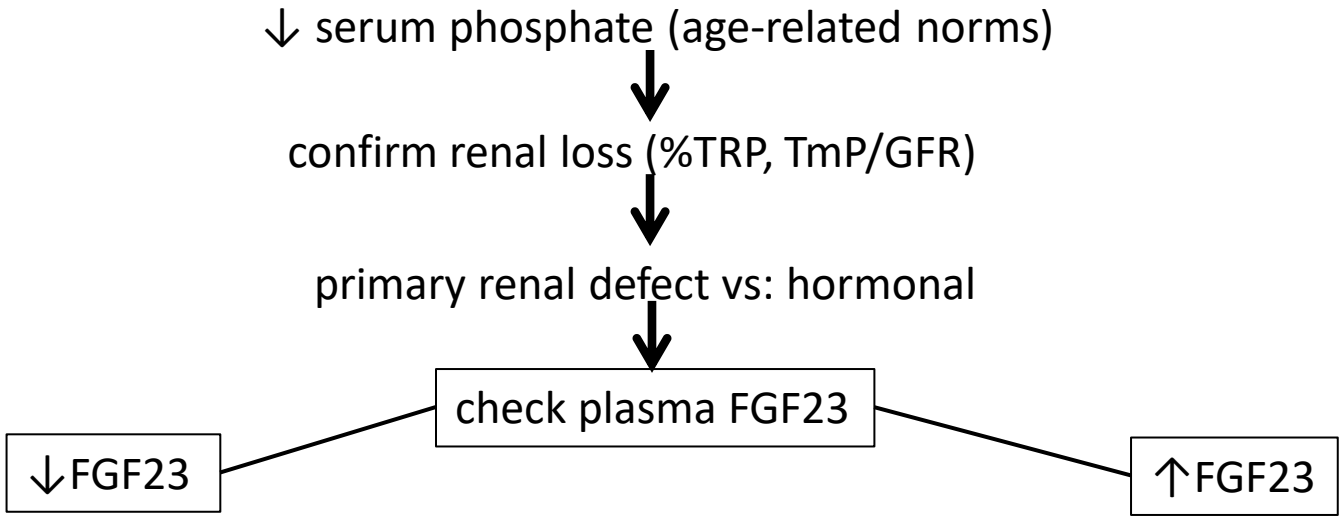
In hypophosphatemia

25 pg/ml = upper limit intact FGF23

90 RU/ml = upper limit C-terminal FGF23

Hartley, JBMR, 2023

FGF23 Excess - Evaluation of Hypophosphatemia



Fanconi-type tubulopathy

- aminoaciduria
- proteinuria (low MW)
- bicarbonaturia (acidosis)
- calciuria

Acquired Fanconi syndrome

- Toxins (lead, cadmium, etc)
- Drugs (**tenofovir,** chemotherapy)
  tenofovir alafenamide fumarate

Genetic

same treatment

- X-linked (*PHEX*)
- MAS (*GNAS*)
- ARHR1(*DMP1*)
- CSHS (*RAS*)
- ADHR (*FGF23*)
- ARHR2 (ENPP1)

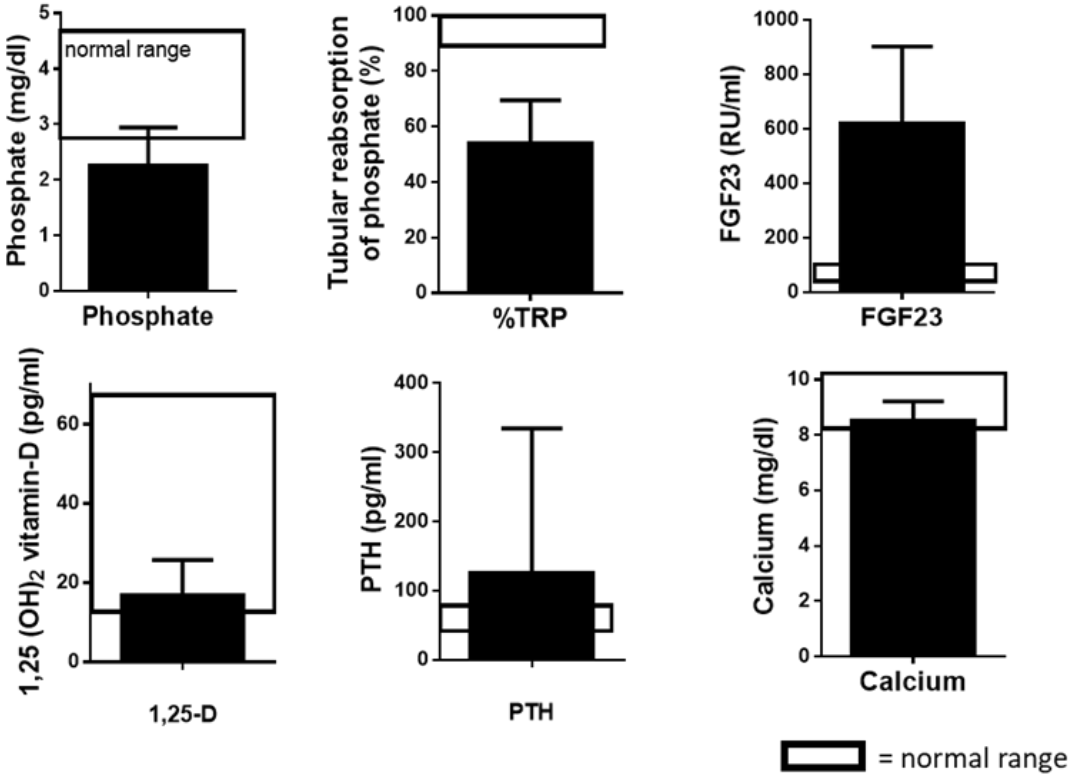
start in childhood

Acquired

- TIO
- Metastatic cancers (esp. prostate)

FGF23 excess - Tumor-induced osteomalacia

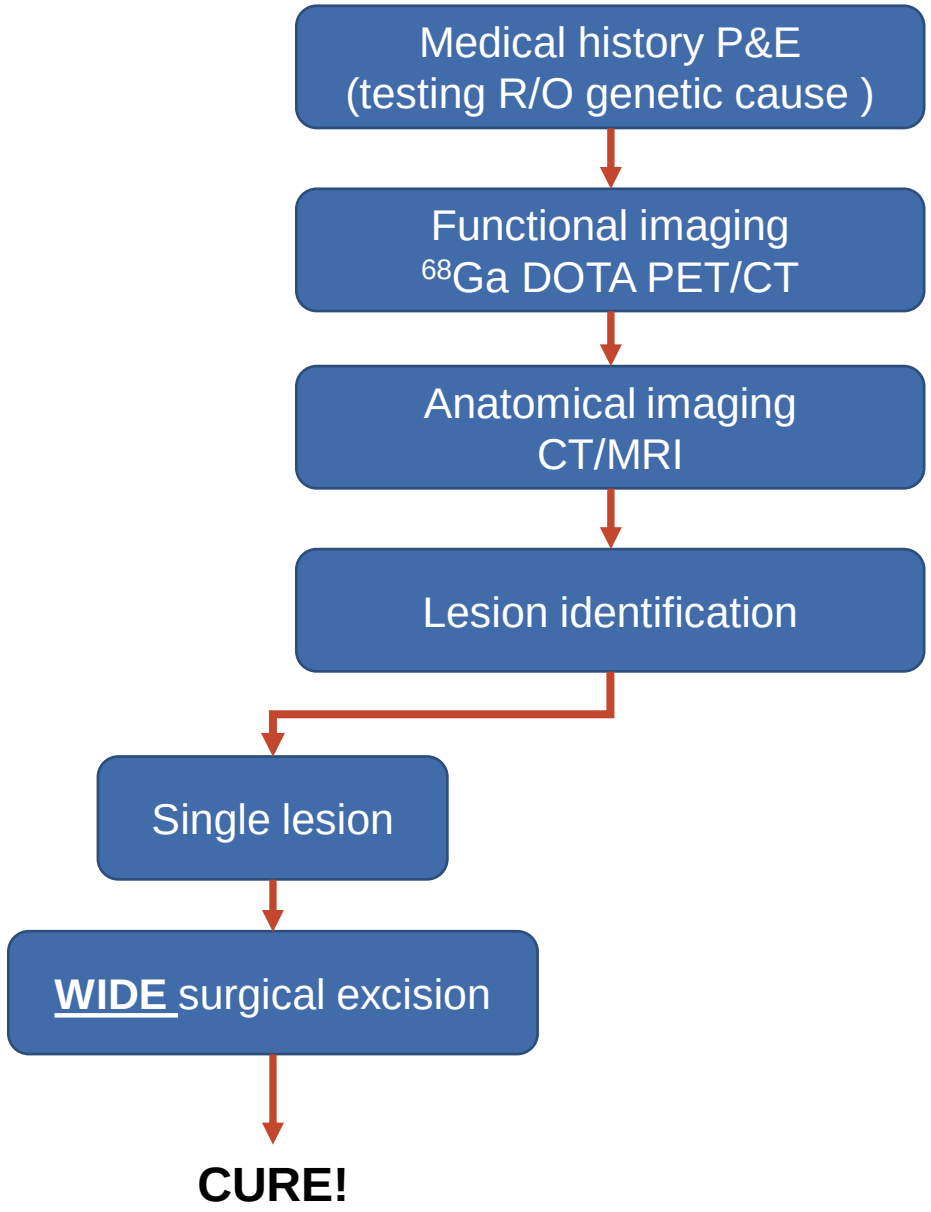
- adult onset, previous nl phos
- pain, fractures, weakness



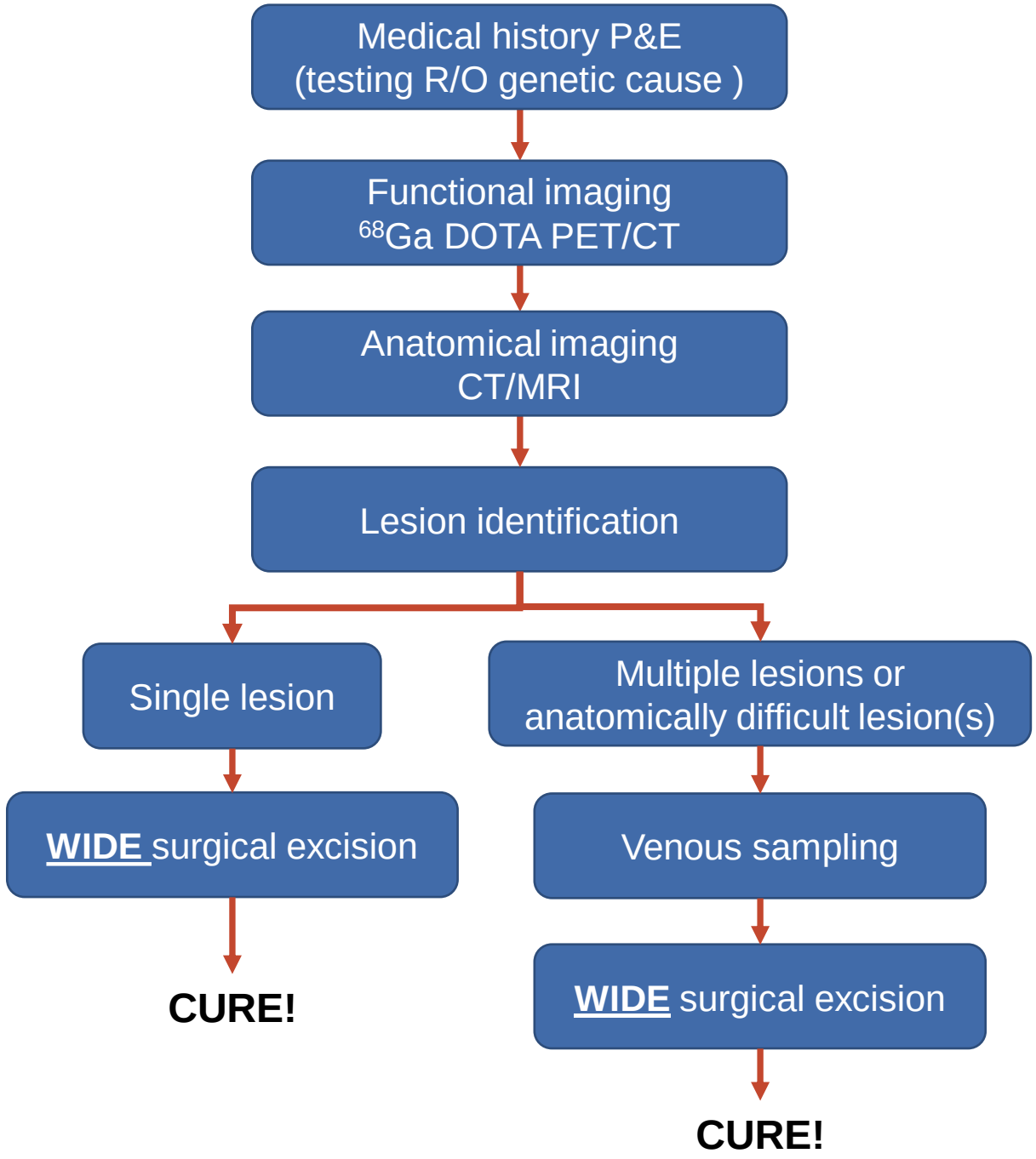
- small, difficult to locate tumors
- avoid biopsy, complete resection

Chong, JBMR, 2013

Approach to TIO



Approach to TIO



Approach to TIO

Medical history P&E
(testing R/O genetic cause)

Functional imaging
^{68}Ga DOTA PET/CT

Anatomical imaging
CT/MRI

Lesion identification

Single lesion

WIDE surgical excision

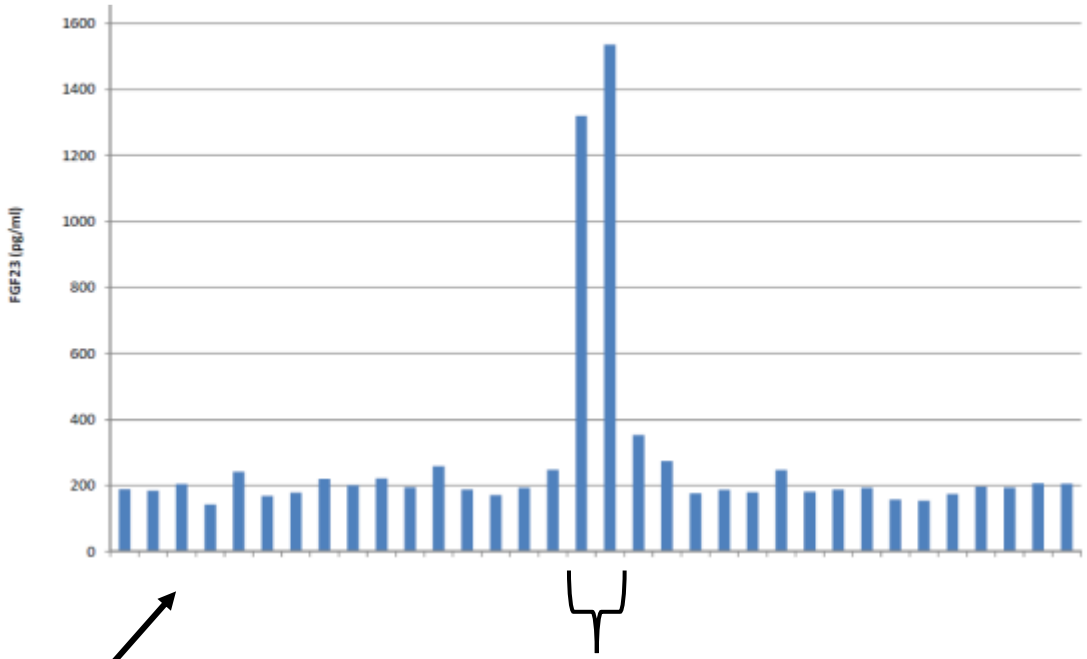
CURE!

Multiple lesions or
anatomically difficult lesion(s)

Venous sampling

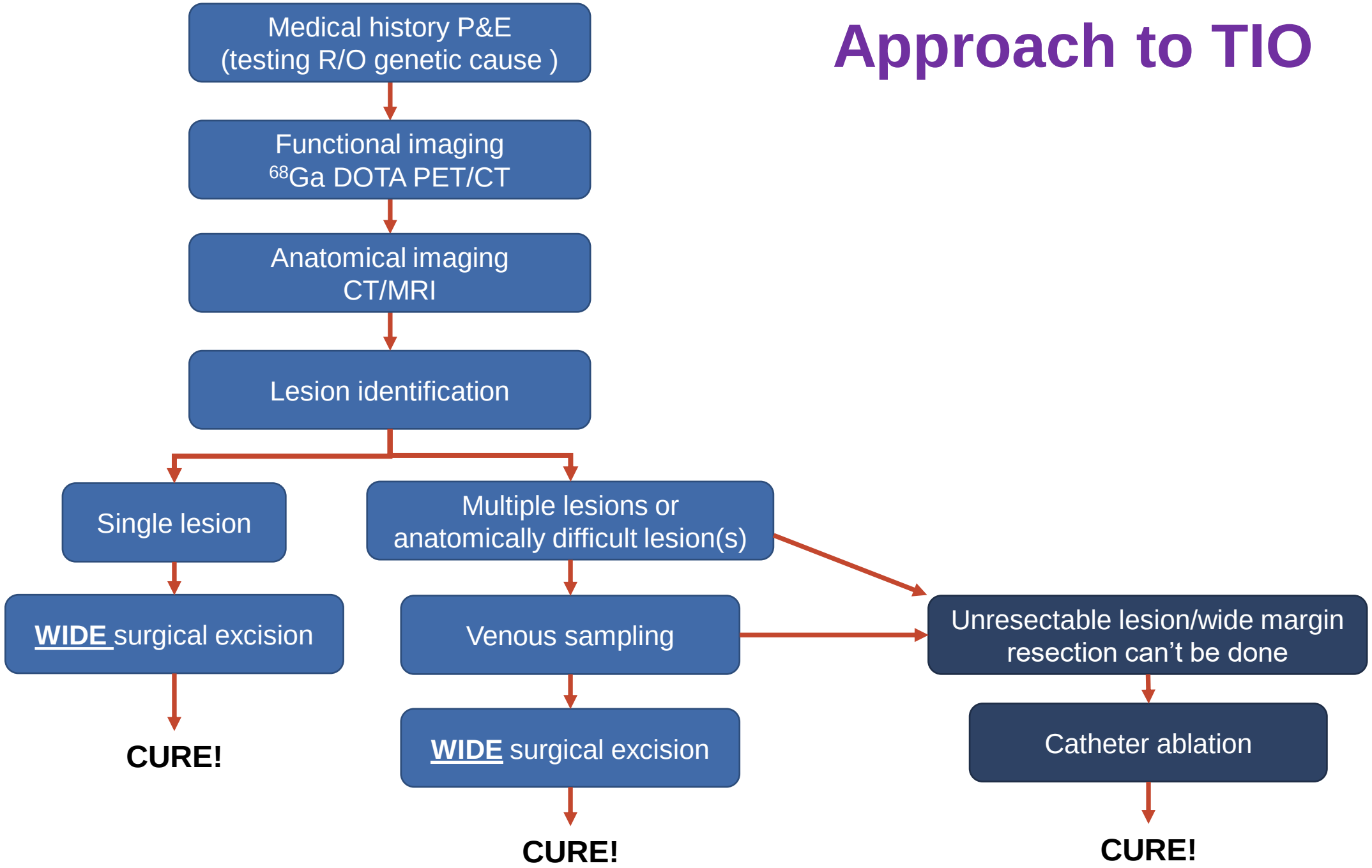
WIDE surgical excision

CURE!

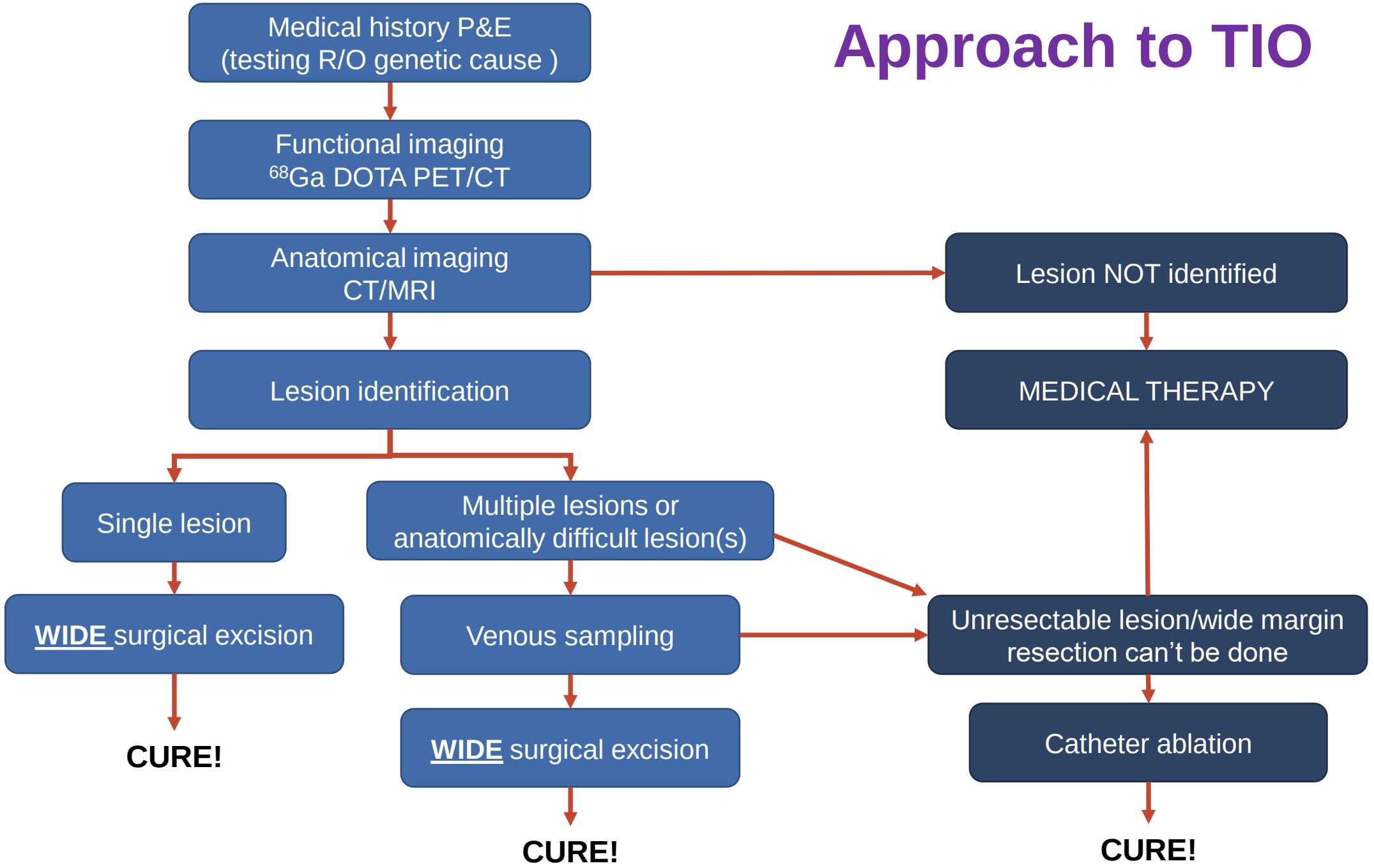


veins draining tumor
confirm tumor site

Approach to TIO

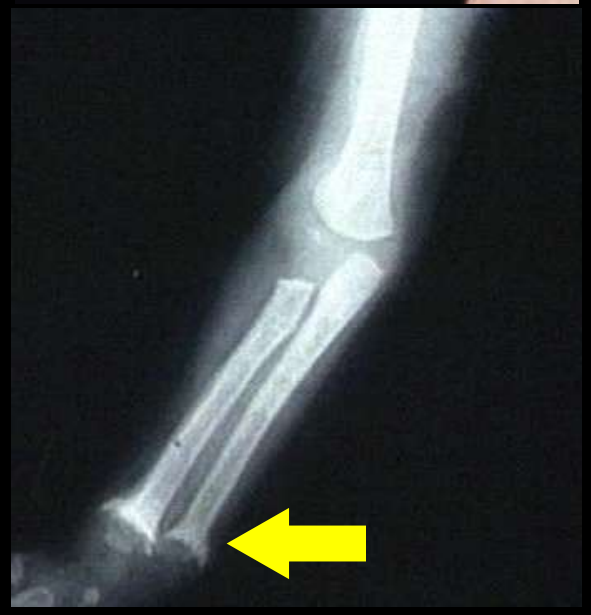


Approach to TIO



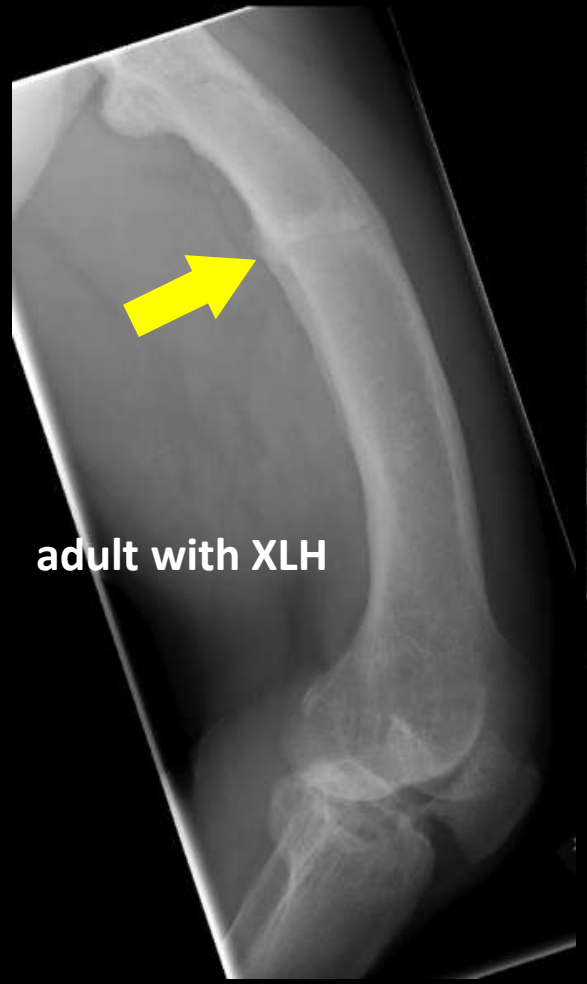
Findings in XLH

rickets



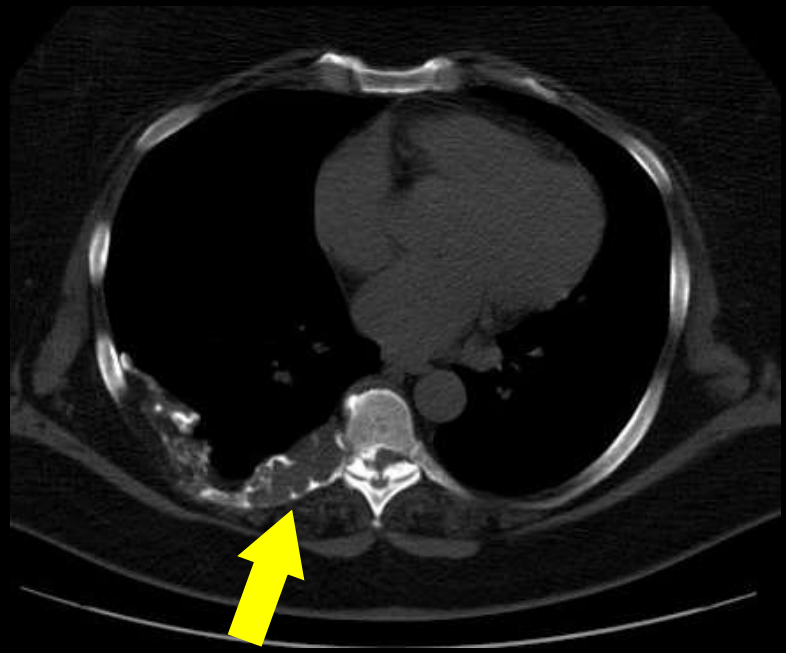
child with XLH

bowing & rickets



adult with XLH

pseudofractures

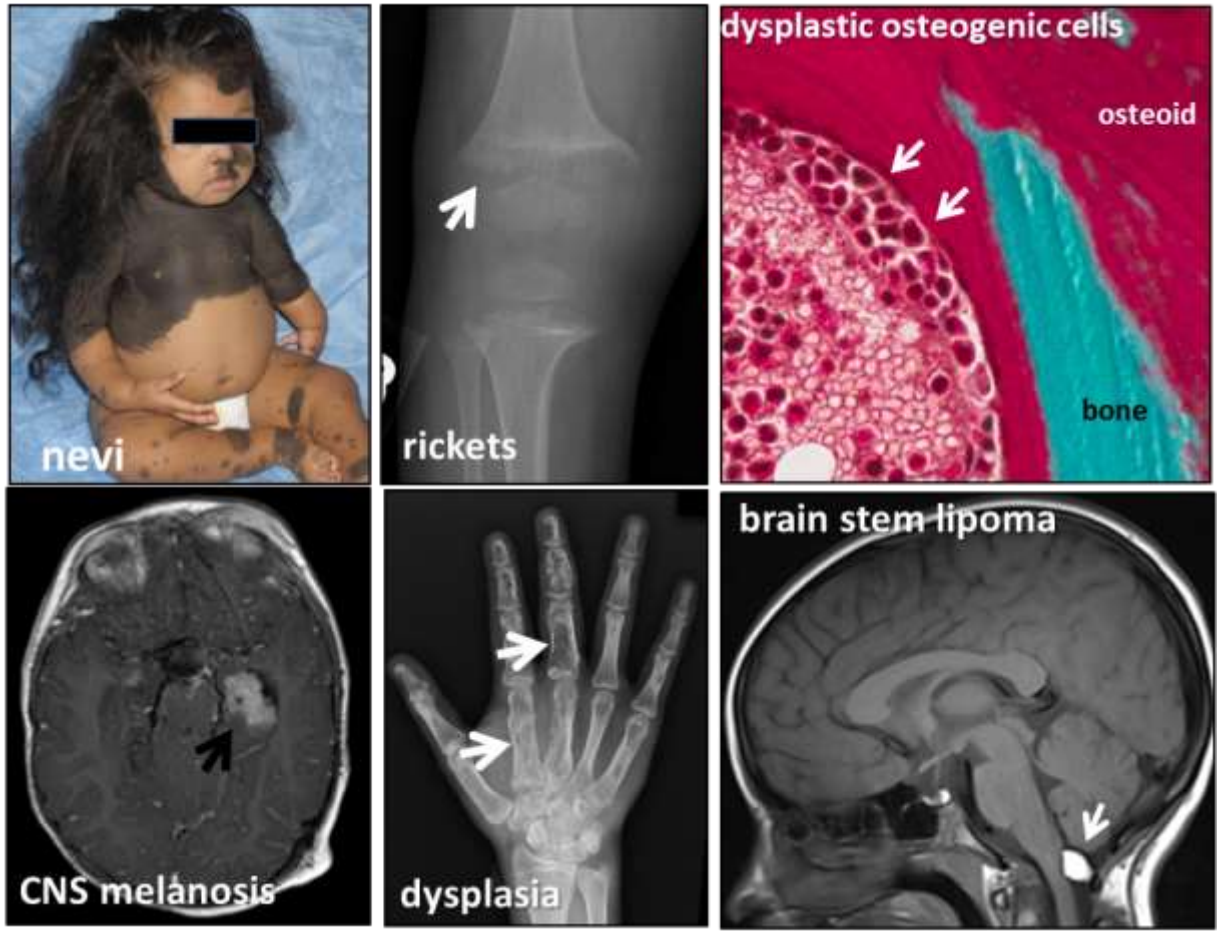


brown tumor
prolonged, secondary/tertiary hyperparathyroidism

Mosaic diseases of FGF23 excess

McCune-Albright Syndrome (somatic gain-of-function mutations in *GNAS)*

Cutaneous Skeletal Hypophosphatemia Syndrome (somatic gain-of-function mutations in *RAS)*



Boyce & Collins, Endo Rev, 2020

Lim, Hum Mol Gen, 2014

Dysplastic Bone is the Source of FGF23

FGF23 Excess Treatment - Phosphate Replacement

- 15-60 mg/kg elemental phosphate/day; 3-6 doses/day
- GI upset/diarrhea common
- Target remineralization (normalization of alkaline phosphatase), not necessarily ‘normal’ phosphate level
- secondary hyperparathyroidism common

FGF23 Excess Disorders

Genetic

- X-linked (*PHEX*)
- ARHR1/2 (*DMP1/ENPP1*)
- MAS (*GNAS*)
- CSHS (*RAS*)

Acquired

- TIO
- Metastatic cancers

Florenzano, Calcif Tissue Int. 2020.

1,25 dihydroxyvitamin D Replacement

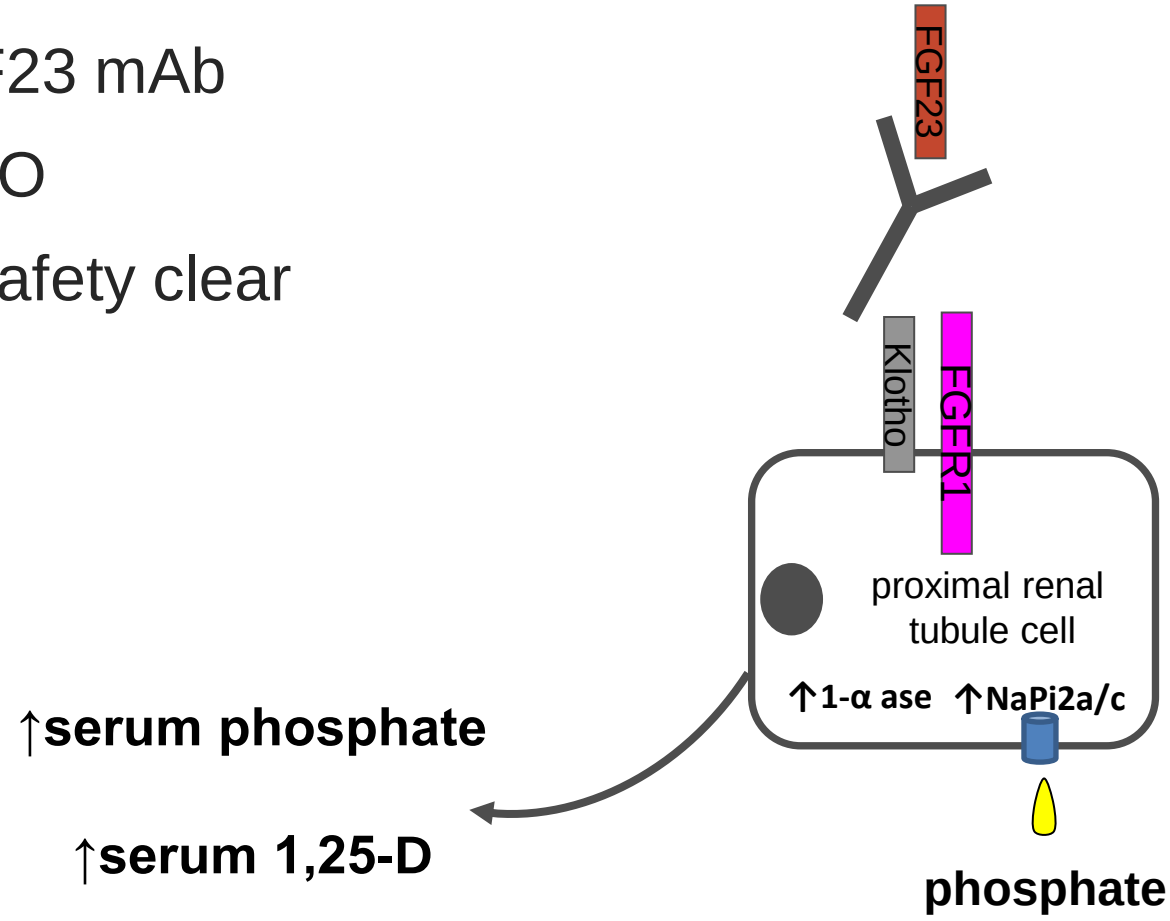
Active vitamin D (calcitriol or alfacalcidol)

- 15-60 ng/kg/day
- Improves GI calcium (and phosphate) absorption
- Prevents/controls secondary hyperparathyroidism
- Can cause hypercalciuria (monitor 24-hour urine calcium)
- Target: PTH in the normal range without hypercalciuria

Florenzano, Calcif Tissue Int. 2020.

Burosumab (Crysvita) Medical for FGF23 Excess

- Burosumab – anti-FGF23 mAb
- Approved for XLH & TIO
- Short term efficacy & safety clear
- Expensive ($200K/y)

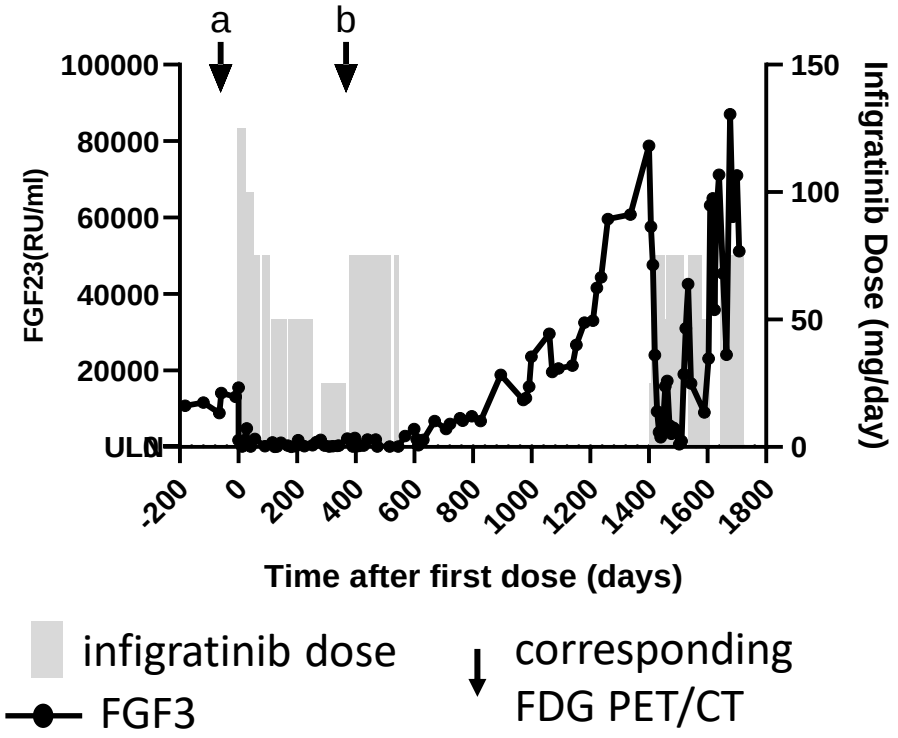


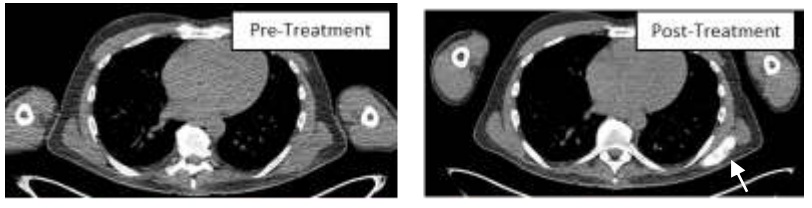
Imel, Lancet, 2019 RCT children XLH
Insogna, JBMR, 2018, RCT adults XLH
Carpenter, NEJM, 2018, Open, children XLH
Imanishi, JBMR, 2020, TIO
Jan de Beur, JBMR, 2020, TIO

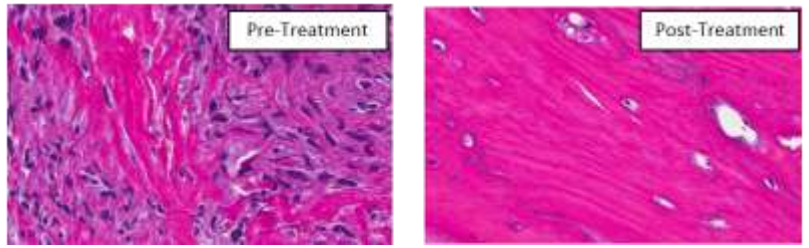
FGFR Blockade in Tumor-Induced Osteomalacia

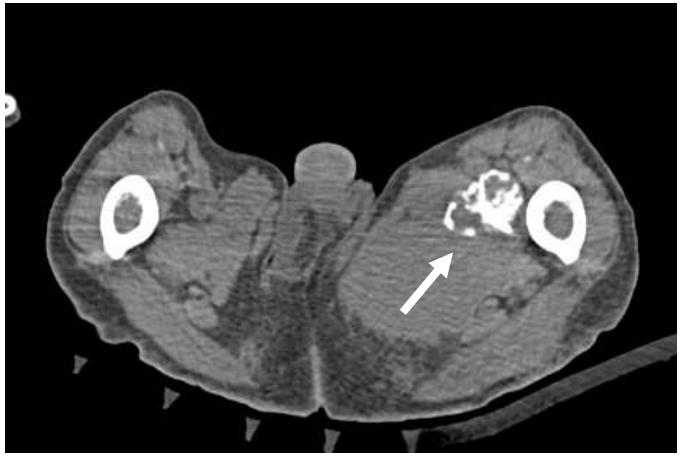
Infigratinib:

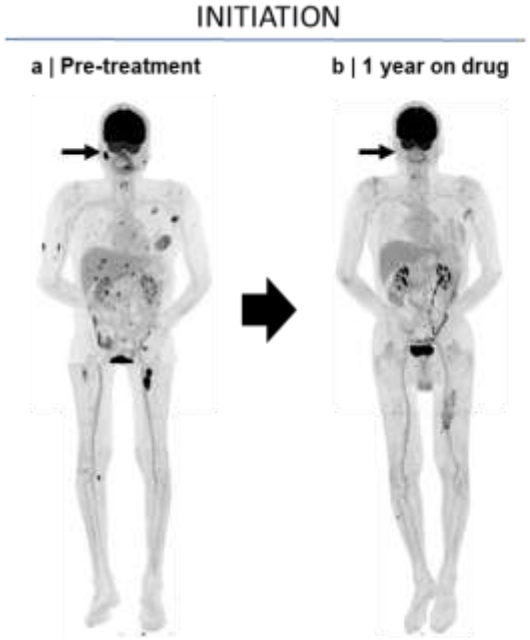
- **pan-FGFR inhibitor**
- **decreased FGF23**
- **tumorostatic**
- **metaplastic differentiation**











Hartley, NEJM, 2020

FGF23 Deficiency -HFTC

	Condition	Abbreviation	Gene(s)	FGF23
FGF23 Excess	Tumor-induced osteomalacia	TIO	*FN-FGFR1 (FGF23-secreting tumors)*	↑↑
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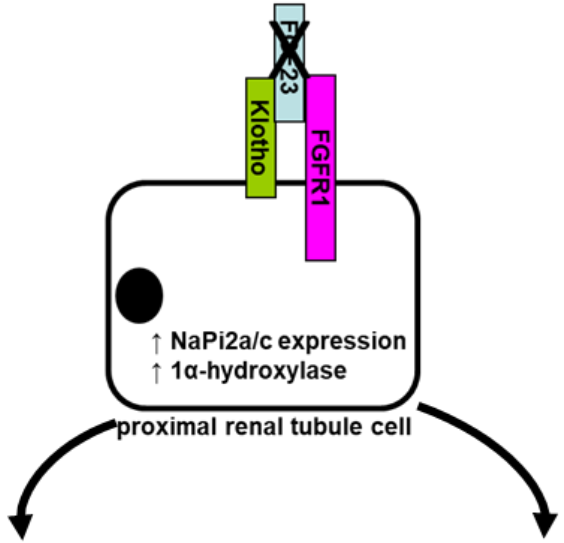
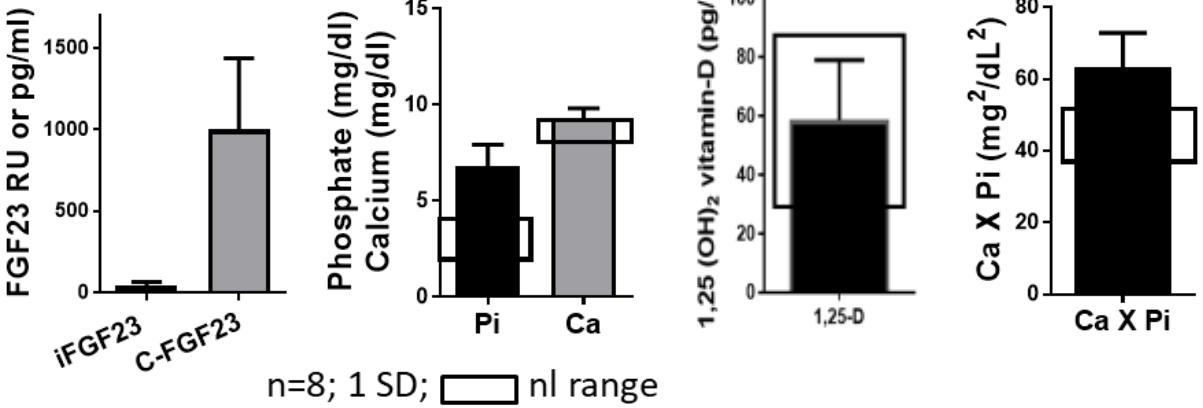
	Autoimmune tumoral calcinosis (FGF23 resistance)	ATC	FGF23 Autoantibodies	↑↑
	Renal Failure	CRF	*N/A*	↑↑

FGF23 Deficiency – Hyperphosphatemic Tumoral Calcinosis



↑ phosphate

↑ Ca x Pi product

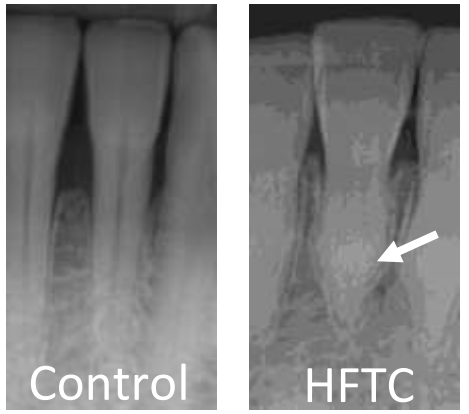


n=8; 1 SD; ▭ nl range

Ramnitz, JBMR, 2016

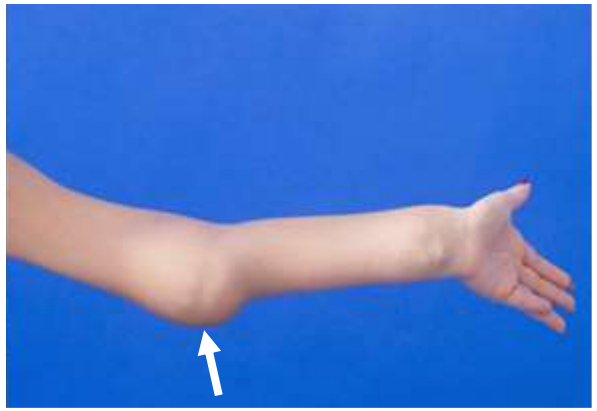
92%

Dental calcification



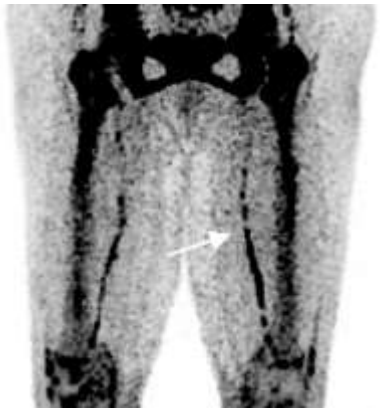
82%

Soft tissue calcification



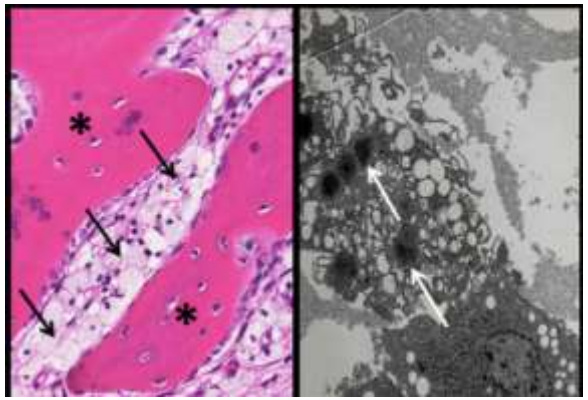
59%

Vascular calcification



47%

Inflammation (CRP)



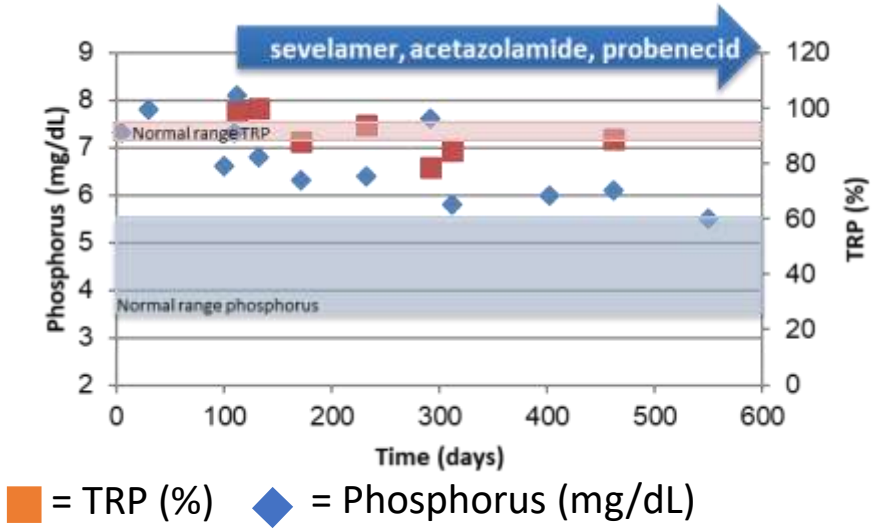
Lee et all JBMRPlus 2022

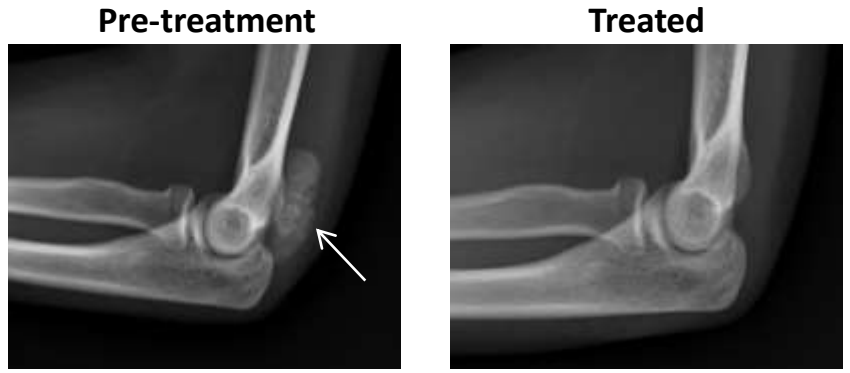
Treatment Possibilities: lower phosphate, inhibit mineralization

Sometimes work

Existing drugs

- Decrease GI phosphate absorption
  - sevelamer, aluminum hydroxide
- Promote renal phosphate excretion
  - acetazolamide, probenecid
- Target inflammation
  - anakinra, canakinumb
- Chelate phosphate
  - topical thiosulfate





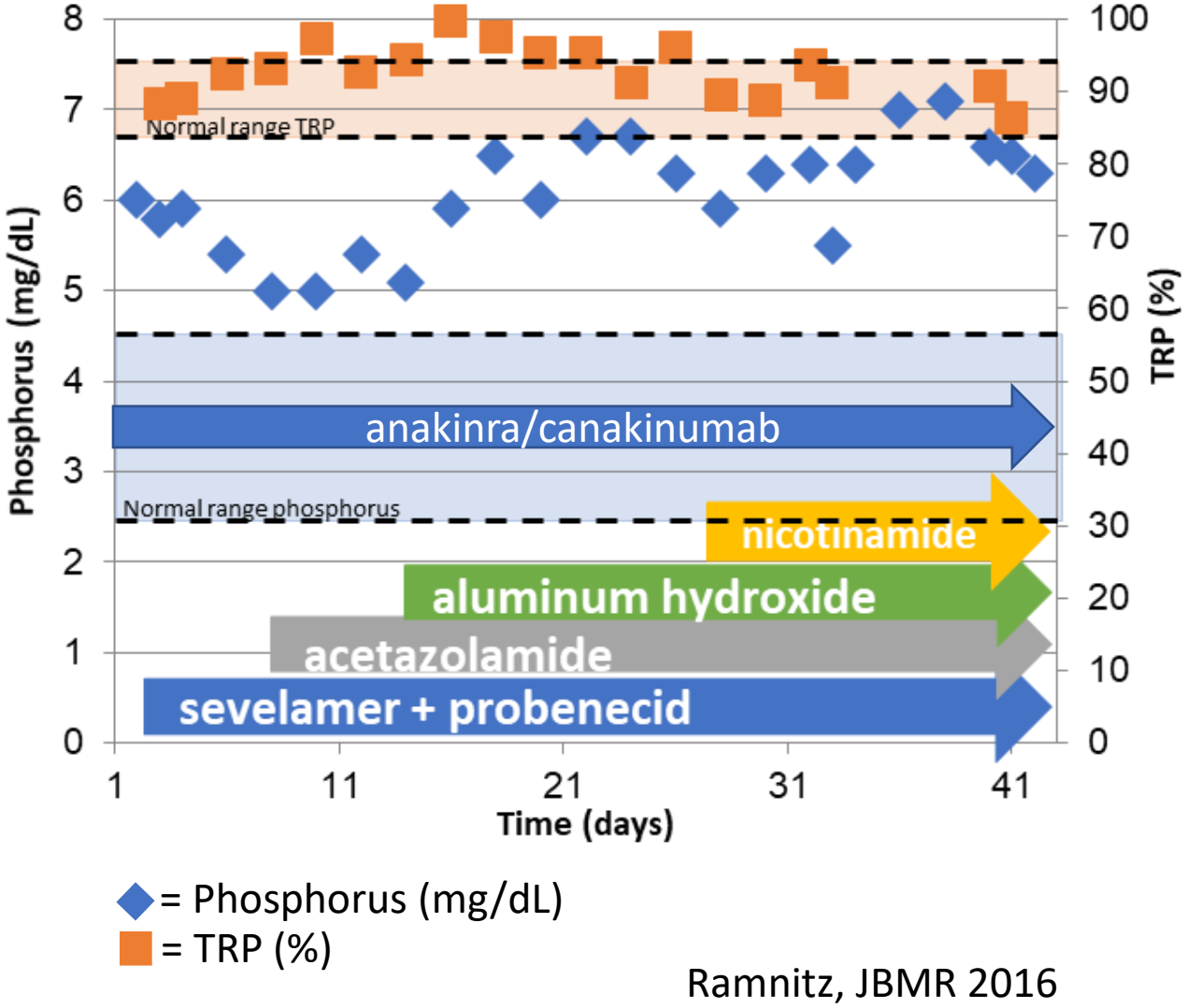
Ramnitz, JBMR 2016

Treatment Possibilities: lower phosphate, inhibit mineralization

Existing drugs

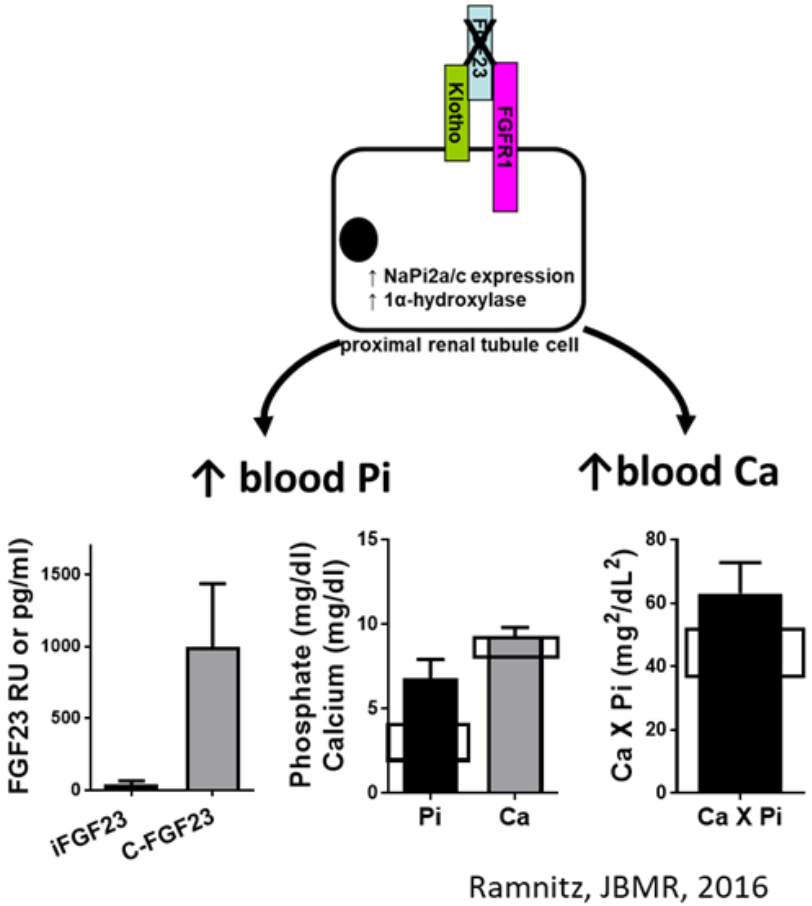
- Decrease GI phosphate absorption
  - Sevelamer, aluminum hydroxide
- Promote renal phosphate excretion
  - acetazolamide, probenecid
- Target inflammation
  - anakinra, canakinumb
- Chelate phosphate
  - topical thiosulfate

But usually don't



Ramnitz, JBMR 2016

HFTC Treatment – What's Next?



Ramnitz, JBMR, 2016

Potential targets

- Tenapanor – decrease Pi GI absorption
- FGF23 replacement - Ultragenyx
- Promote renal phosphate excretion
  - NaPi2a inhibitor
  - several companies

FGF23-Mediated Diseases

	Condition	Abbreviation	Gene(s)	FGF23	Treatment
FGF23 Excess	Tumor-induced osteomalacia	TIO	*FN-FGFR1* *(FGF23-secreting tumors)*	↑↑	Surgery
	X-linked hypophosphatemic rickets	XLH	*PHEX*	↑	Burosumab*
	FD/McCune-Albright syndrome	FD/MAS	*GNAS (mosaic)*	↑	Burosumab*
	Autosomal recessive hypophosphatemic rickets	ARHR1	*DMP-1*	↑	Burosumab*
	Autosomal recessive hypophosphatemic rickets/ENPP1 Deficiency	ARHR2/ENPP1 def	*ENPP1*	↑	Burosumab*
	Cutaneous skeletal hypophosphatemia syndrome	CSHS	*RAS (mosaic)*	↑	Burosumab*
	Autosomal dominant hypophosphatemic rickets	ADHR	*FGF23*	↑	Iron replacement
FGF23 Deficiency	Hyperphosphatemic familial tumoral calcinosis	HFTC (1,2,3)	*GALNT3; FGF23; Klotho*	↓	Pi binder Phosphaturia Anti-IL1
	Autoimmune tumoral calcinosis (FGF23 resistance)	ATC	FGF23 Autoantibodies	↑↑	
	Renal Failure	CRF	*N/A*	↑↑	Pi binder

* or conventional (phosphate + active vitamin D)

Skeletal Disorders and Mineral Homeostasis Section

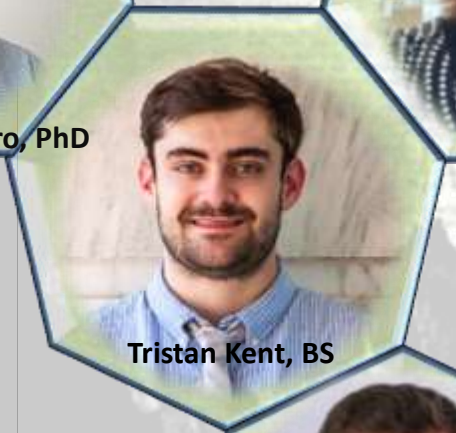
Rachel Gafni, MD

Michael T. Collins, MD

Luis Fernandez De Castro, PhD

Rebeca Galisteo

Fiona Obiezu, BS



Tristan Kent, BS

Karen Pozo
Research Nurse

Kelly Roszko, MD PhD

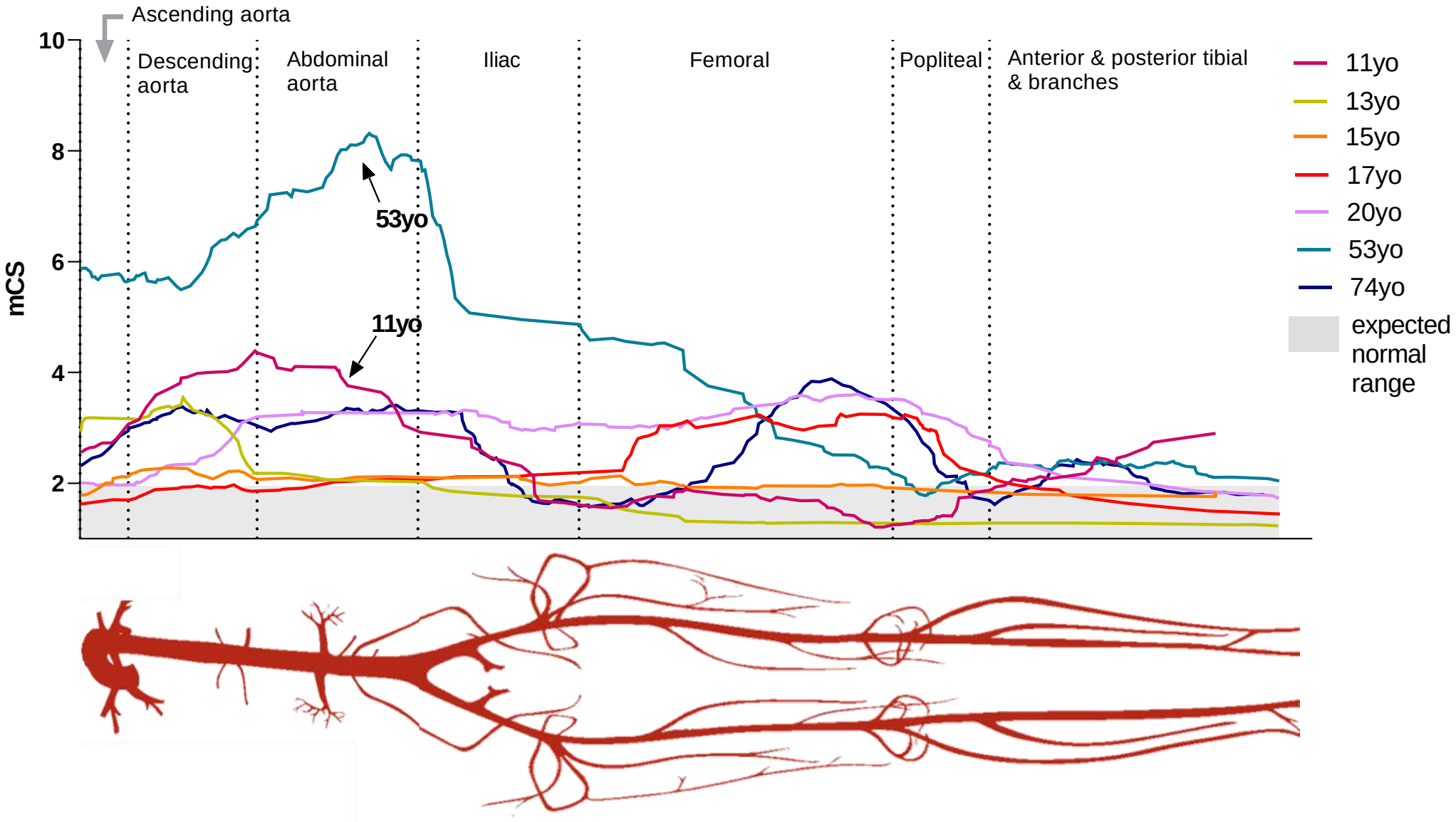
Will Bryant, BS

Rita Meadows, PhD

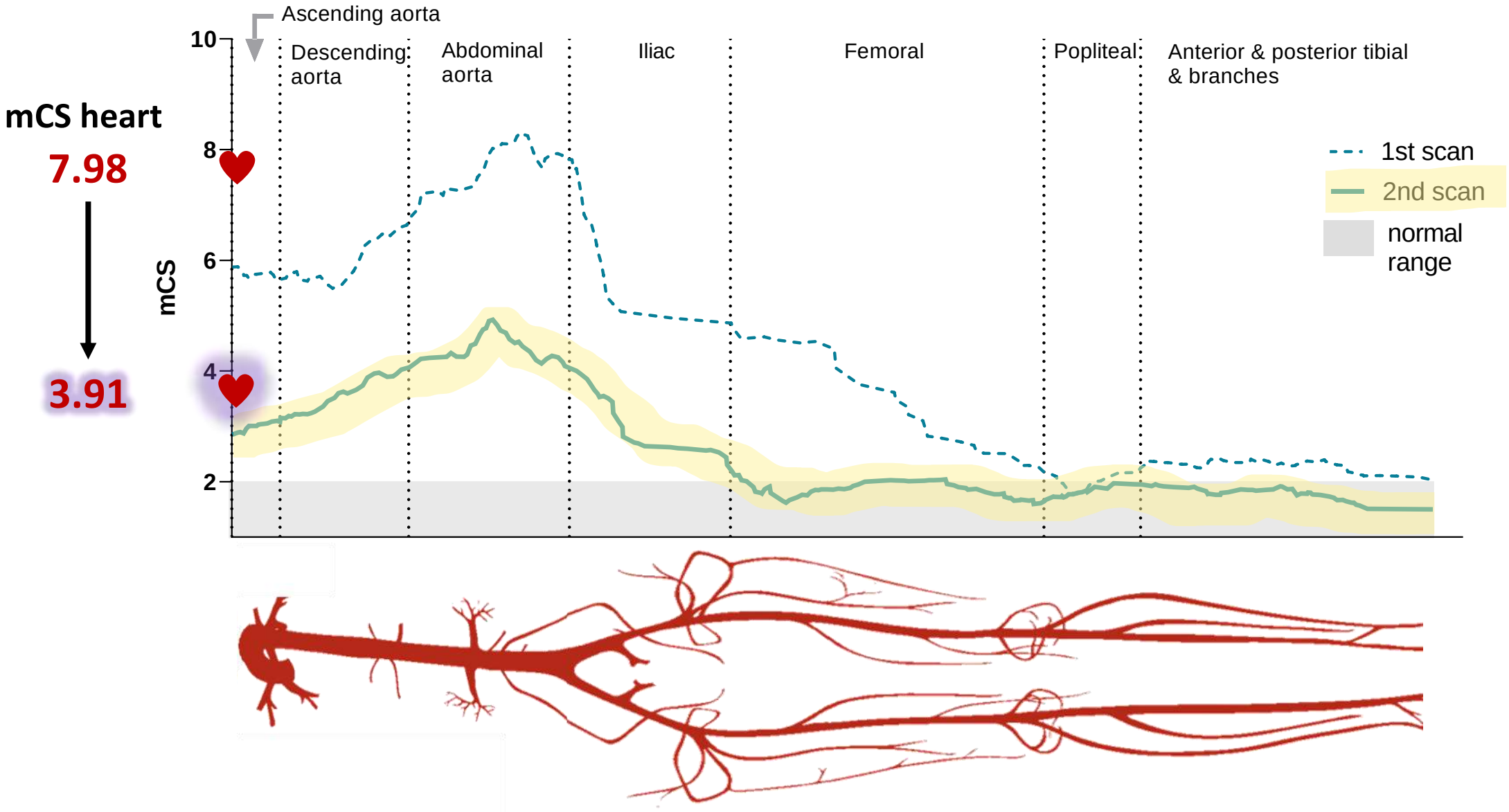
Kimberly Ampuero, BS

Iris Hartley, MD

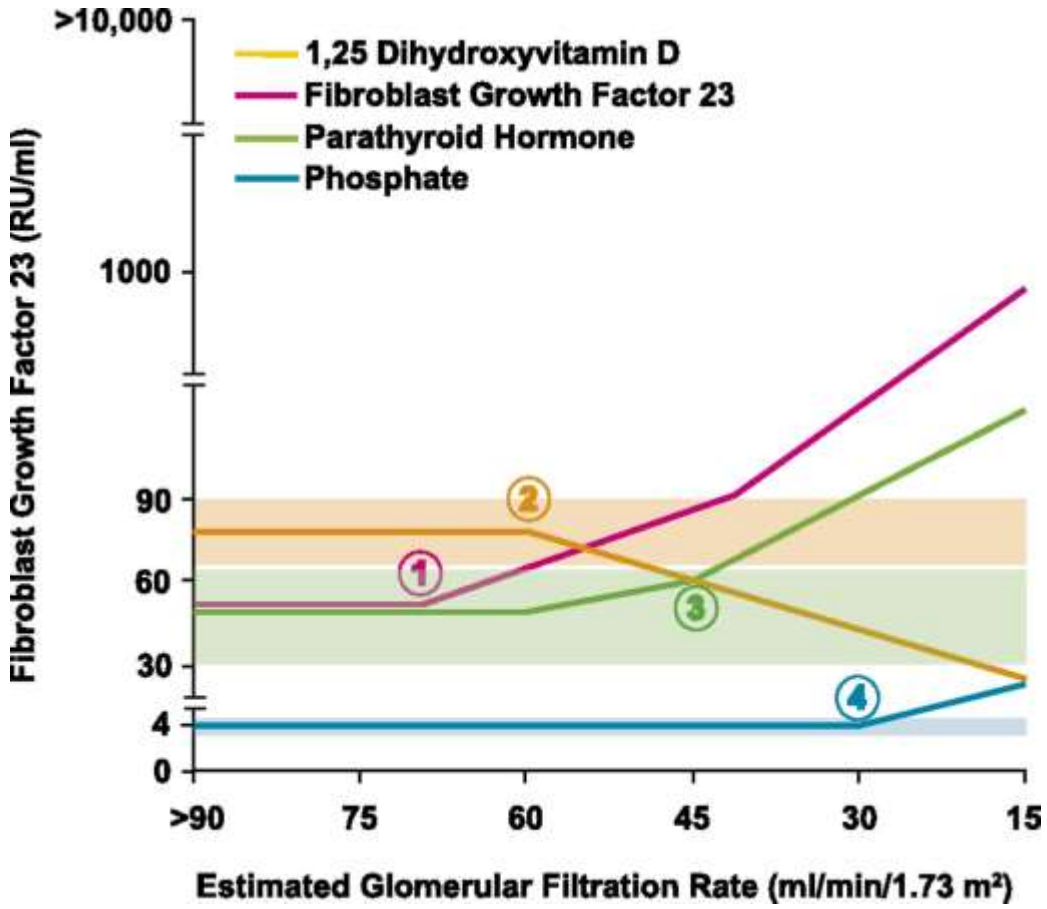
Vascular atlas of microcalcification score in HFTC patients



Vascular atlas of mCS of a 53,54yo HFTC pt before & after 15-months on anakinra



Renal Failure, Hyperphosphatemia and CKD-MBD



Isakova, JASN 2015

CKD-MBD = chronic kidney disease – metabolic bone disease

FGF23 Effects in CRF

- FGF23-dependent ↑ mortality
  - Cardiovascular

Causes of ↑ FGF23

- Renal damage
  - Glycerol-3-phosphate; Simic…Rhee, JCI, 2020
- FGF23 rises to control Pi → eventually overwhelmed
  - Cystinosis, Florenzano, JASN, 2020
- **Both**

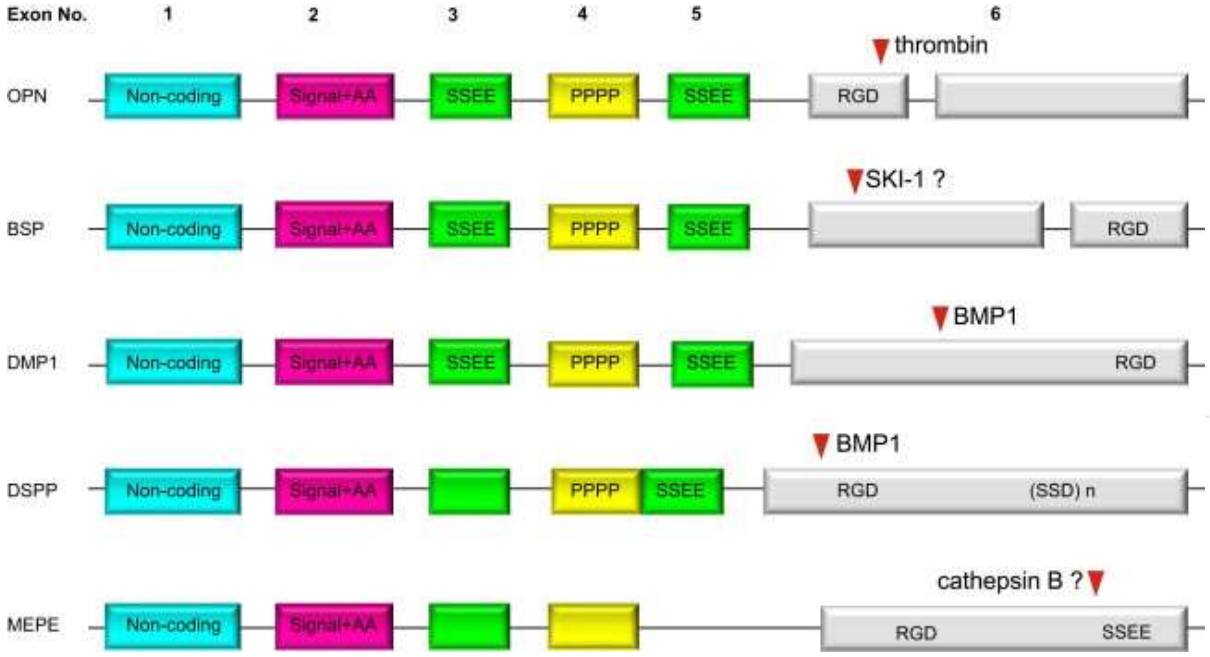
Treatment implications

- FGFR blockade (failed preclinical studies)
- Pi binder, Ferric citrate, (↓FGF23/morbidity)
  - Block, JASN, 2019
- NaPi2a inhibitors
  - Thomas, J Am Soc Neph, 2019
  - Clerin…Juppner, JCI, 2020

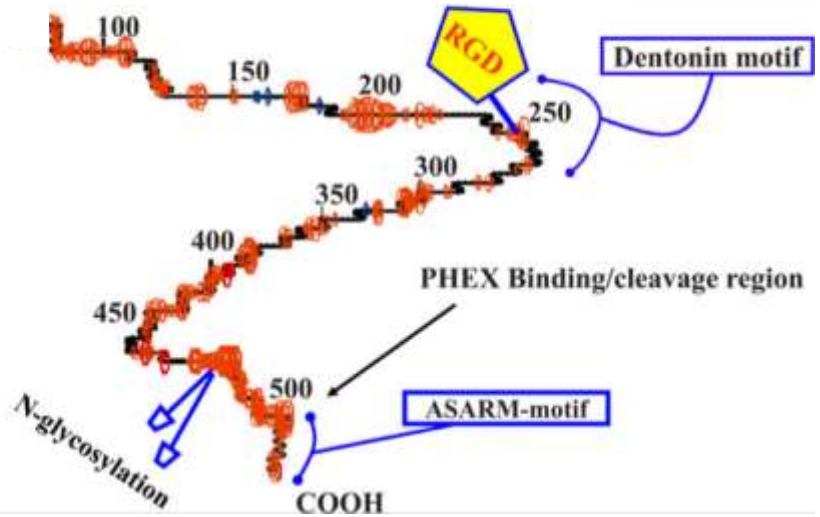
Sibling Protein ASARM-Mediated Regulation of FGF23 and Mineralization

SIBLING Genes/Proteins (Larry Fisher, NIDCR)

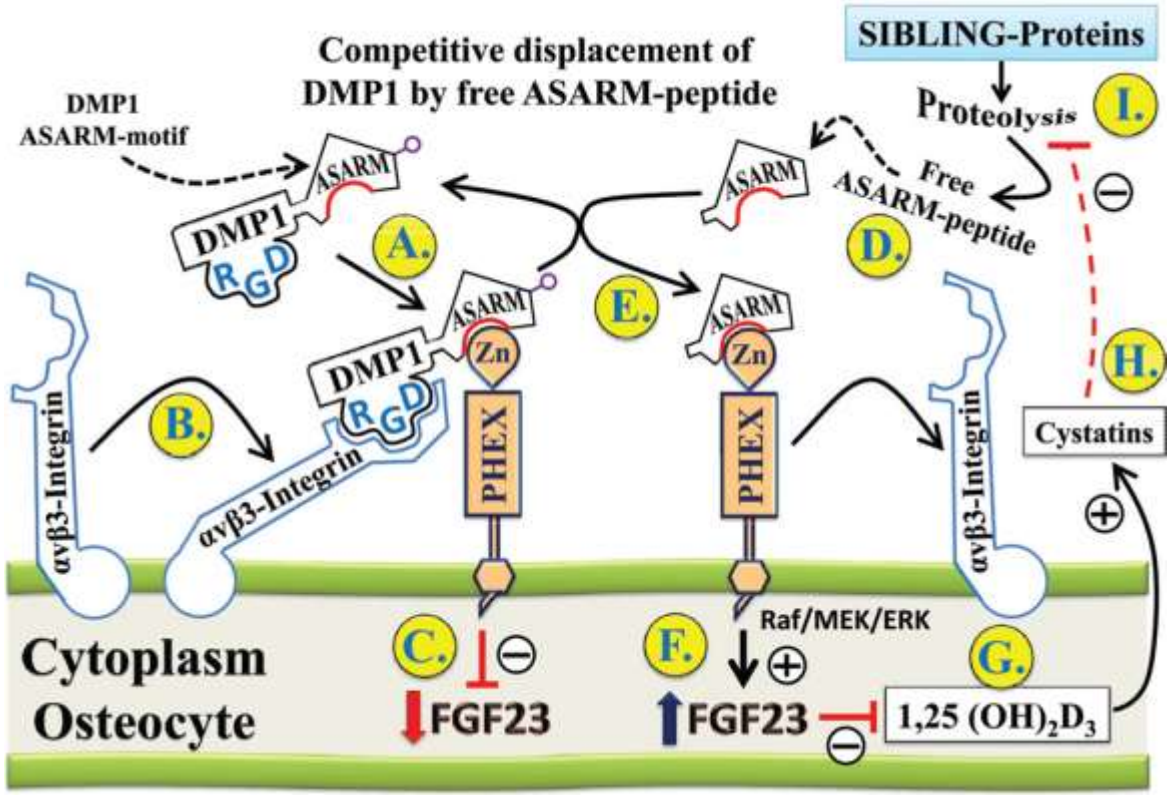
- **s**mall **i**ntegrin-**b**inding **li**gand, **N**-linked **g**lycoprotein
- highly expressed in ECM of mineralized tissues
- unifying feature is an Acidic Serine Aspartate Rich MEPE associated **motif** (**ASARM**)



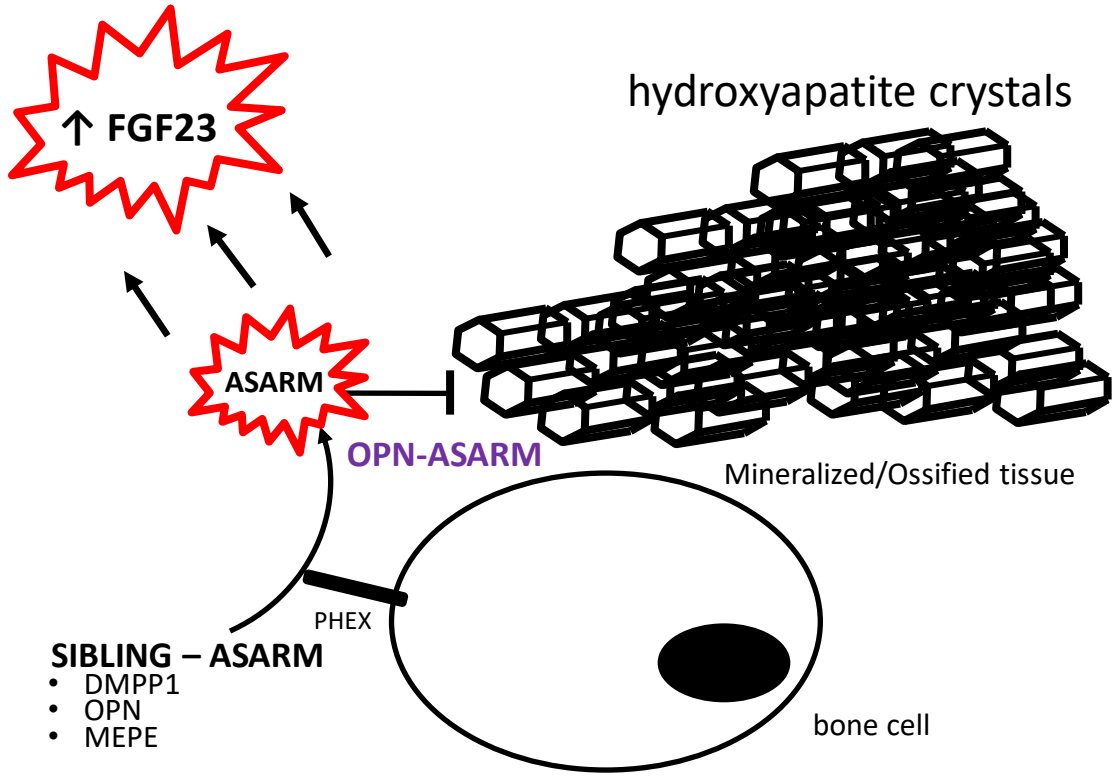
MEPE Secondary Structure



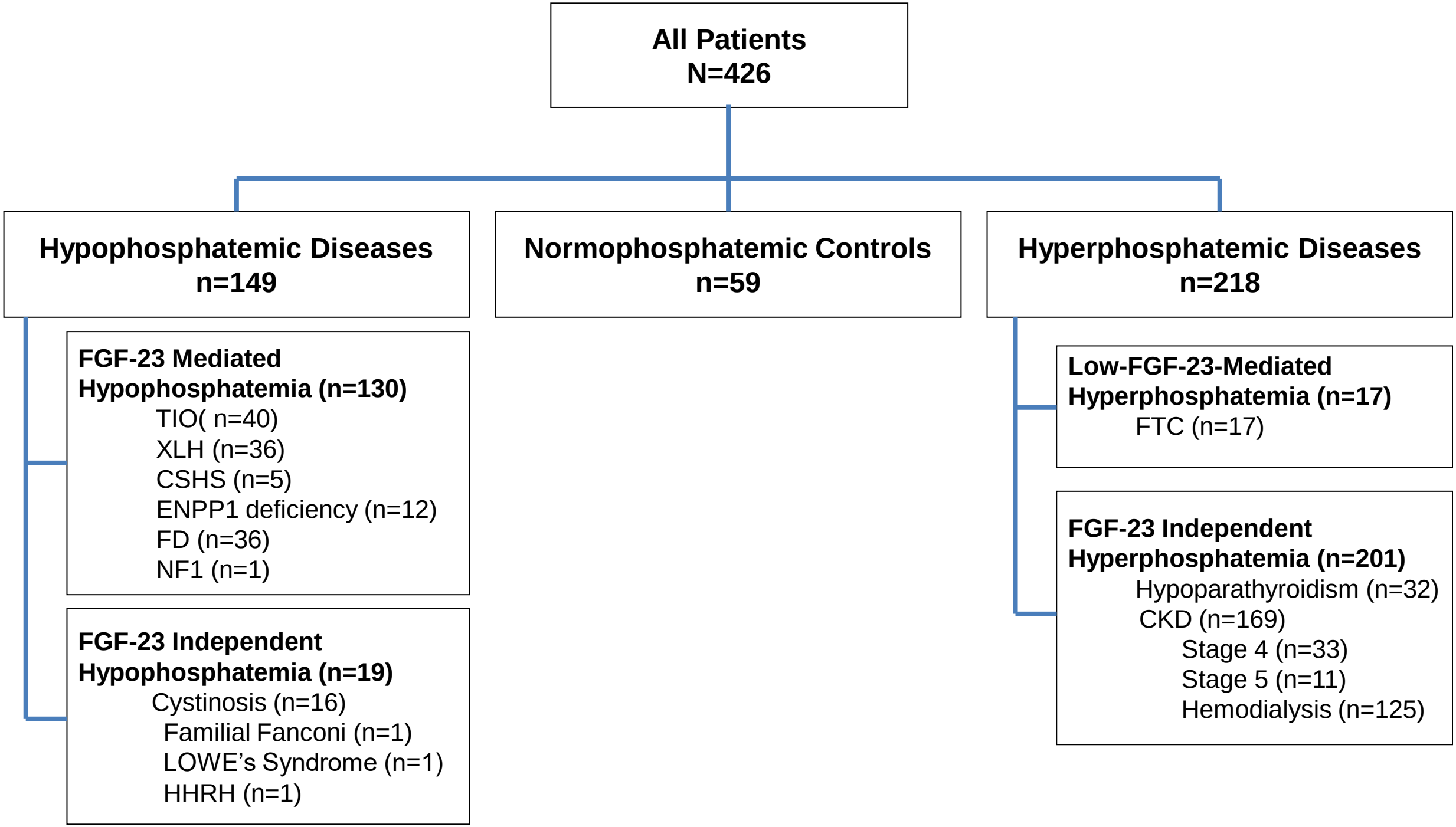
Sibling Protein ASARM-Mediated Regulation of FGF23 and Mineralization

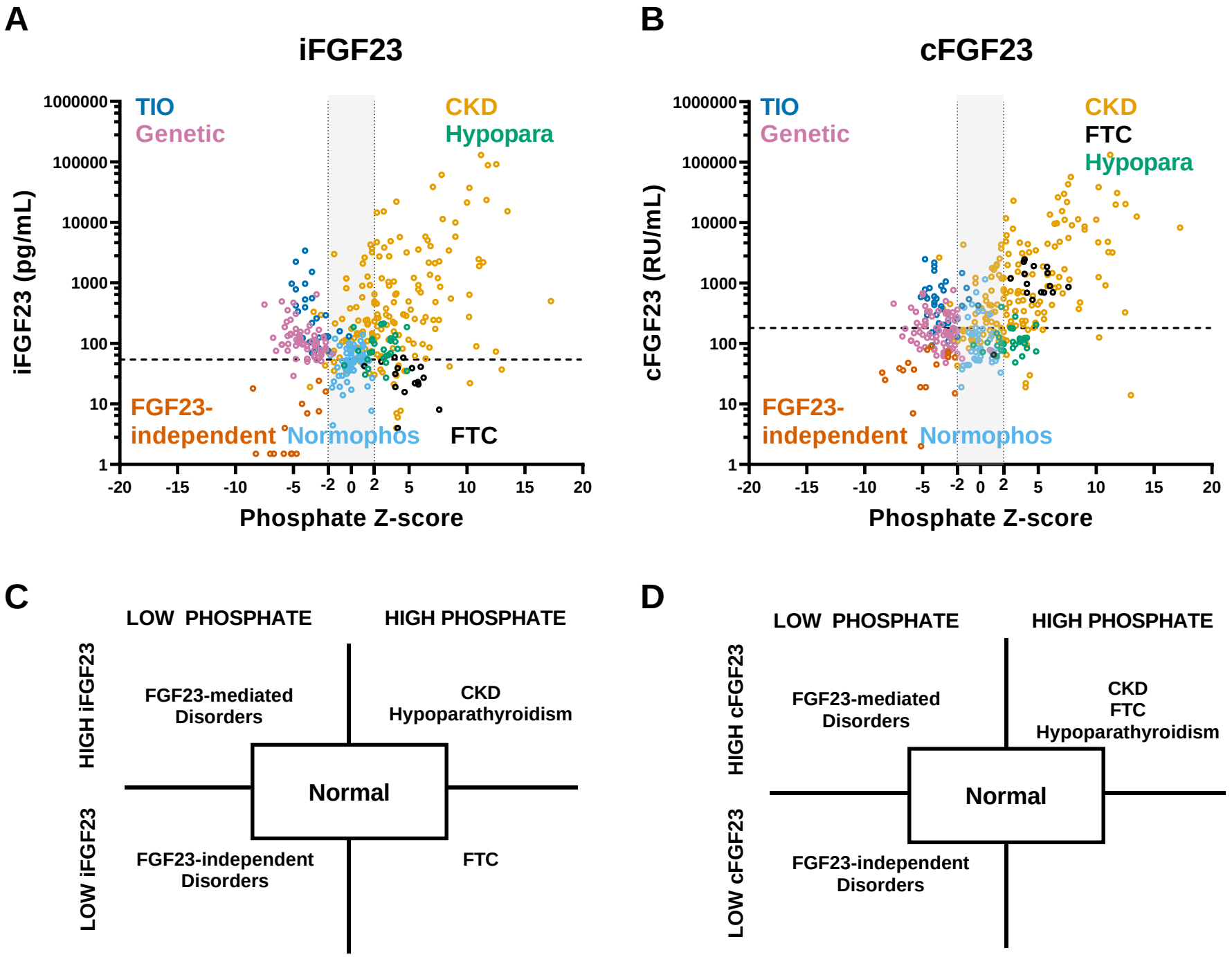


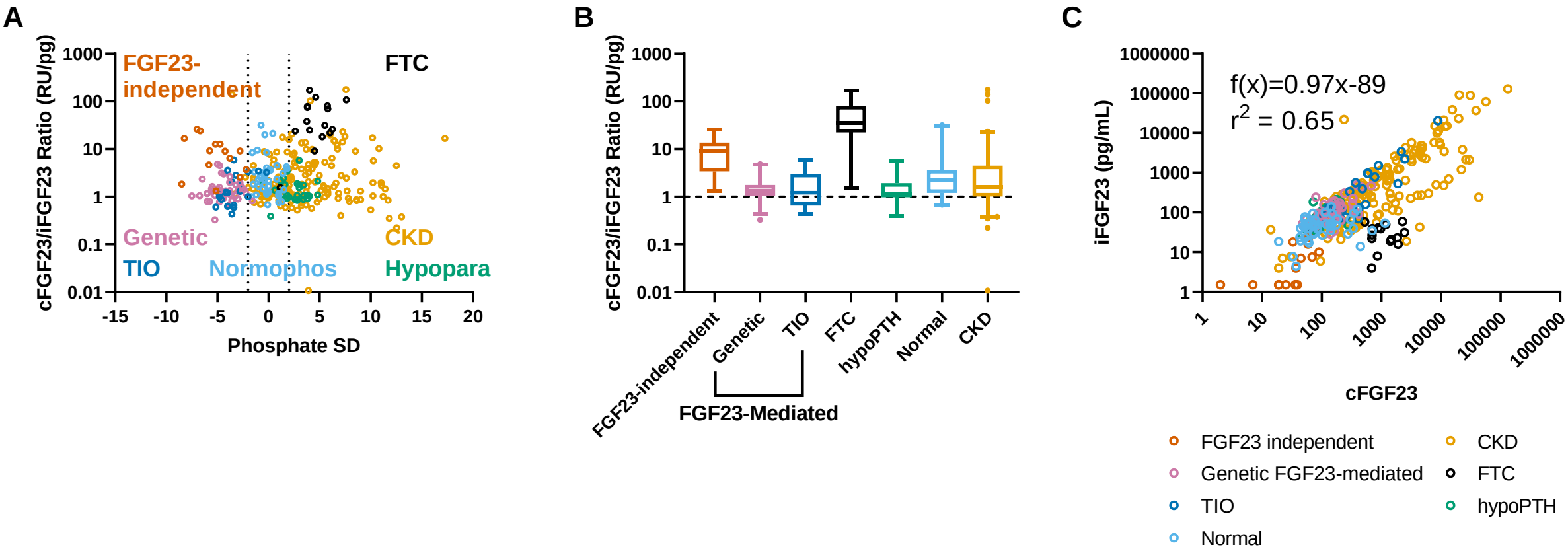
Martin…Rowe, Endo, 2018
Bresler…Rowe, J Endo, 2004

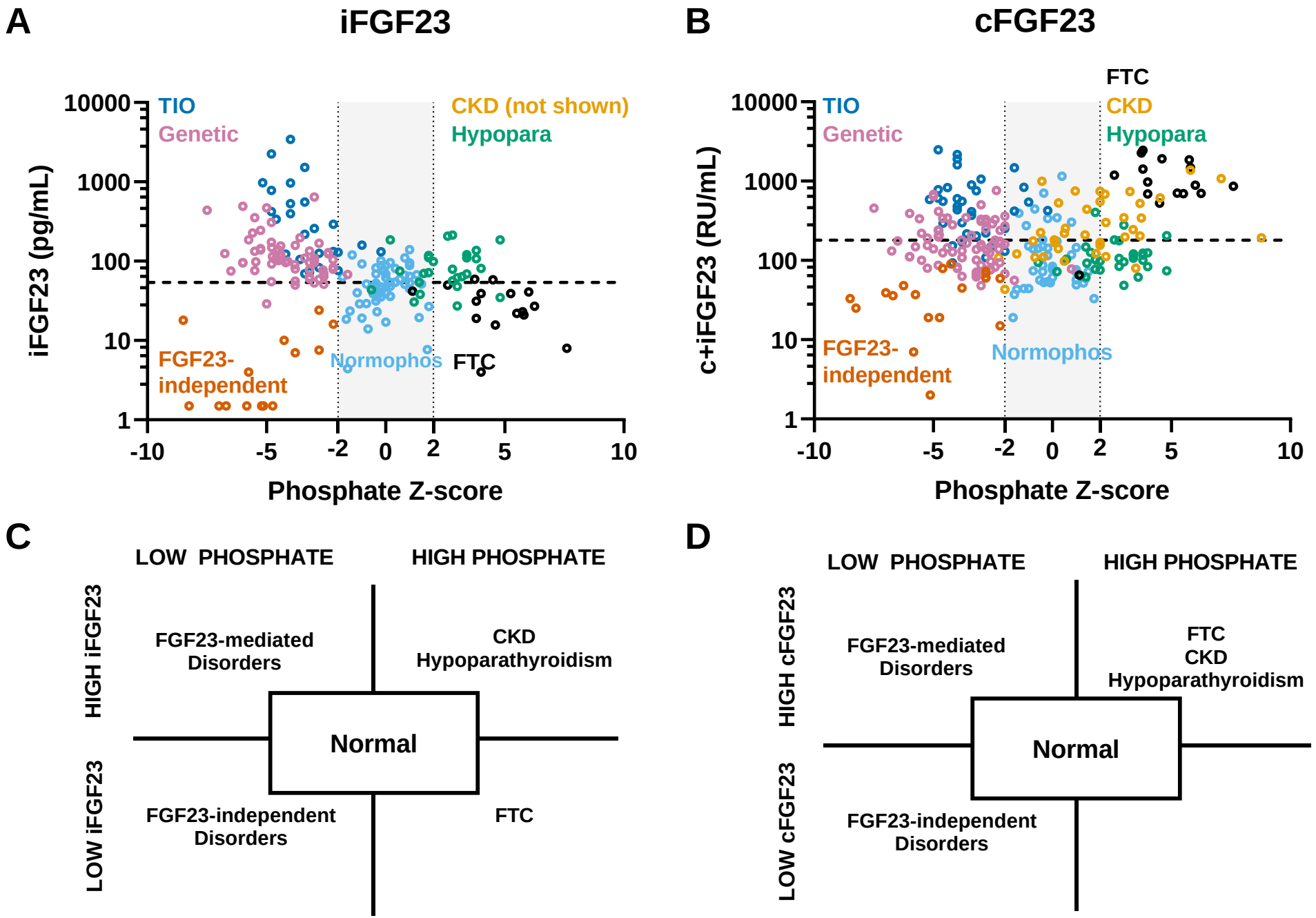


Addison…McKee, JBMR, 2008
Addison…McKee, JBMR, 2010
Chien…McKee, J Struc Bio, 2018

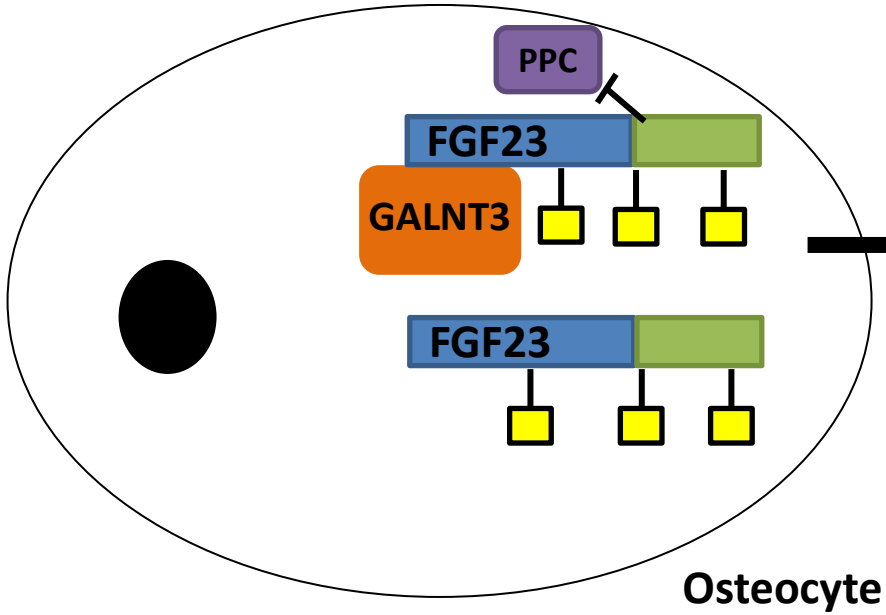

All Patients
N=426
Hypophosphatemic Diseases
n=149
Normophosphatemic Controls
n=59
Hyperphosphatemic Diseases
n=218
FGF-23 Mediated
Hypophosphatemia (n=130)
TIO(n=40)
XLH (n=36)
CSHS (n=5)
ENPP1 deficiency (n=12)
FD (n=36)
NF1 (n=1)
FGF-23 Independent
Hypophosphatemia (n=19)
Cystinosis (n=16)
Familial Fanconi (n=1)
LOWE's Syndrome (n=1)
HHRH (n=1)
Low-FGF-23-Mediated
Hyperphosphatemia (n=17)
FTC (n=17)
FGF-23 Independent
Hyperphosphatemia (n=201)
Hypoparathyroidism (n=32)
CKD (n=169)
Stage 4 (n=33)
Stage 5 (n=11)
Hemodialysis (n=125)


A
iFGF23
TIO
Genetic
CKD
Hypopara
FGF23-
independent
Normophos
FTC
iFGF23 (pg/mL)
Phosphate Z-score
B
cFGF23
TIO
Genetic
CKD
FTC
Hypopara
FGF23-
independent
Normophos
cFGF23 (RU/mL)
Phosphate Z-score
C
LOW PHOSPHATE
HIGH PHOSPHATE
HIGH iFGF23
LOW iFGF23
FGF23-mediated
Disorders
CKD
Hypoparathyroidism
Normal
FGF23-independent
Disorders
FTC
D
LOW PHOSPHATE
HIGH PHOSPHATE
HIGH cFGF23
LOW cFGF23
FGF23-mediated
Disorders
CKD
FTC
Hypoparathyroidism
Normal
FGF23-independent
Disorders

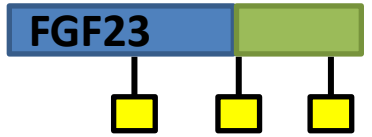

A
cFGF23/iFGF23 Ratio (RU/pg)
1000
100
10
1
0.1
0.01
-15
-10
-5
0
5
10
15
20
Phosphate SD
FGF23-
independent
FTC
Genetic
TIO
Normophos
CKD
Hypopara
B
cFGF23/iFGF23 Ratio (RU/pg)
FGF23-independent
Genetic
TIO
FTC
hypoPTH
Normal
CKD
FGF23-Mediated
C
iFGF23 (pg/mL)
1000000
100000
10000
1000
100
10
1
f(x)=0.97x-89
r2 = 0.65
cFGF23
FGF23 independent
Genetic FGF23-mediated
TIO
Normal
CKD
FTC
hypoPTH


A
iFGF23
iFGF23 (pg/mL)
10000
1000
100
10
1
TIO
Genetic
CKD (not shown)
Hypopara
FGF23-
independent
Normophos
FTC
-10
-5
-2
0
2
5
10
Phosphate Z-score
B
cFGF23
c+iFGF23 (RU/mL)
FTC
CKD
C
LOW PHOSPHATE
HIGH PHOSPHATE
HIGH iFGF23
LOW iFGF23
FGF23-mediated
Disorders
CKD
Hypoparathyroidism
Normal
FGF23-independent
Disorders
FTC
D
HIGH cFGF23
LOW cFGF23

Raine syndrome: FGF23 phosphorylation → degradation



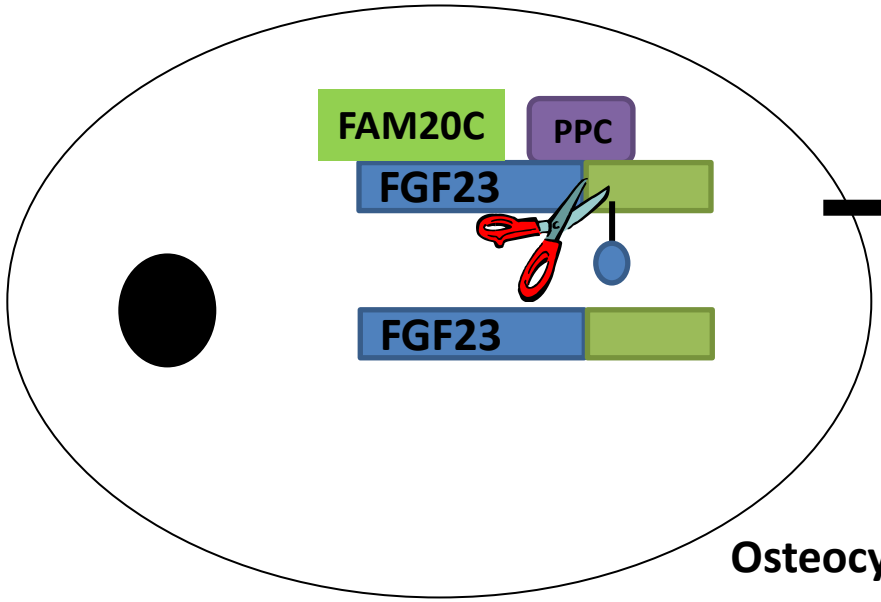
Formation of active or intact FGF23 (iFGF23)



= glycosylation

or

= phosphorylation



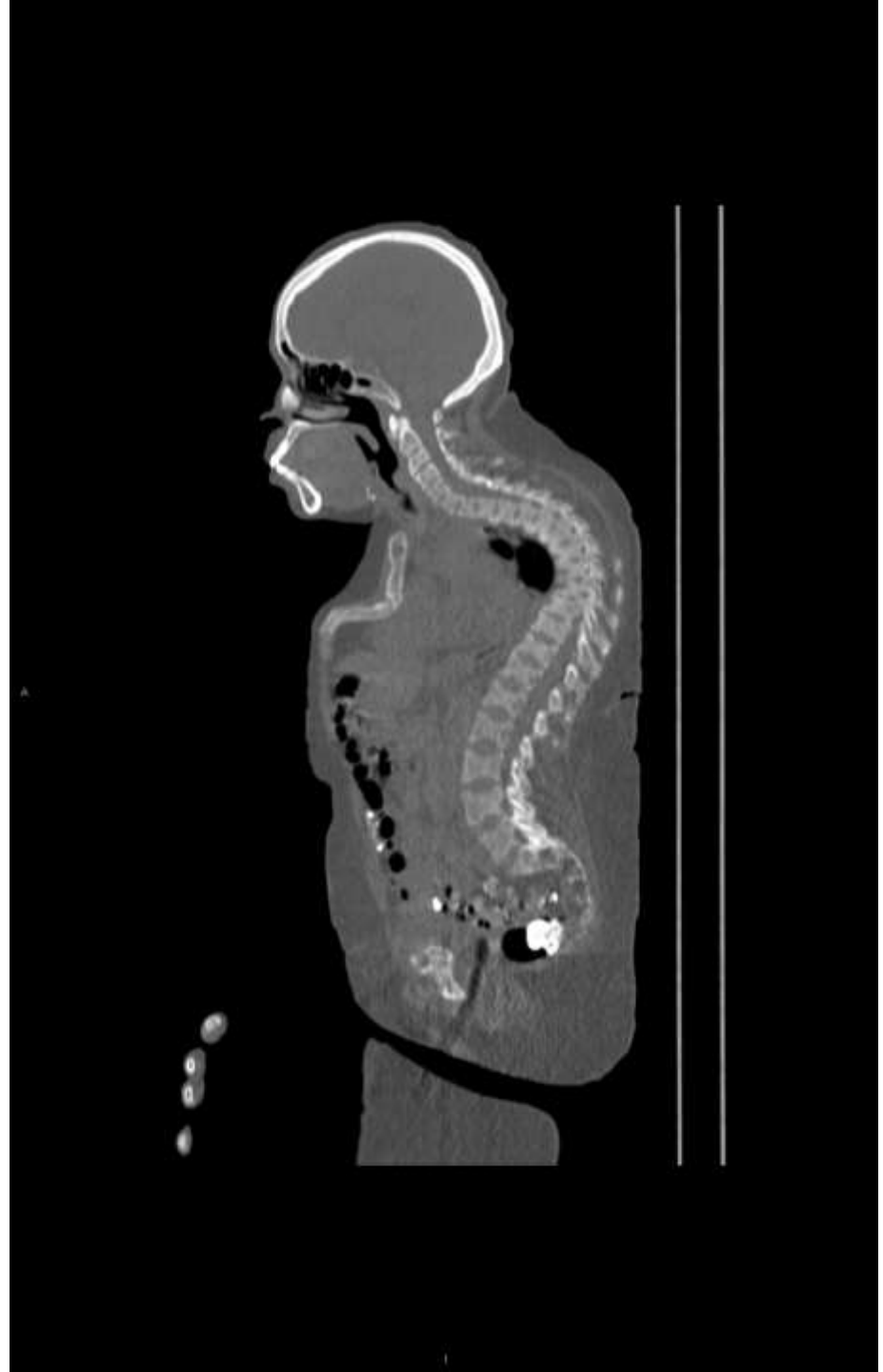
Formation of inactive or C-terminal FGF23 (cFGF23)

= phosphorylation

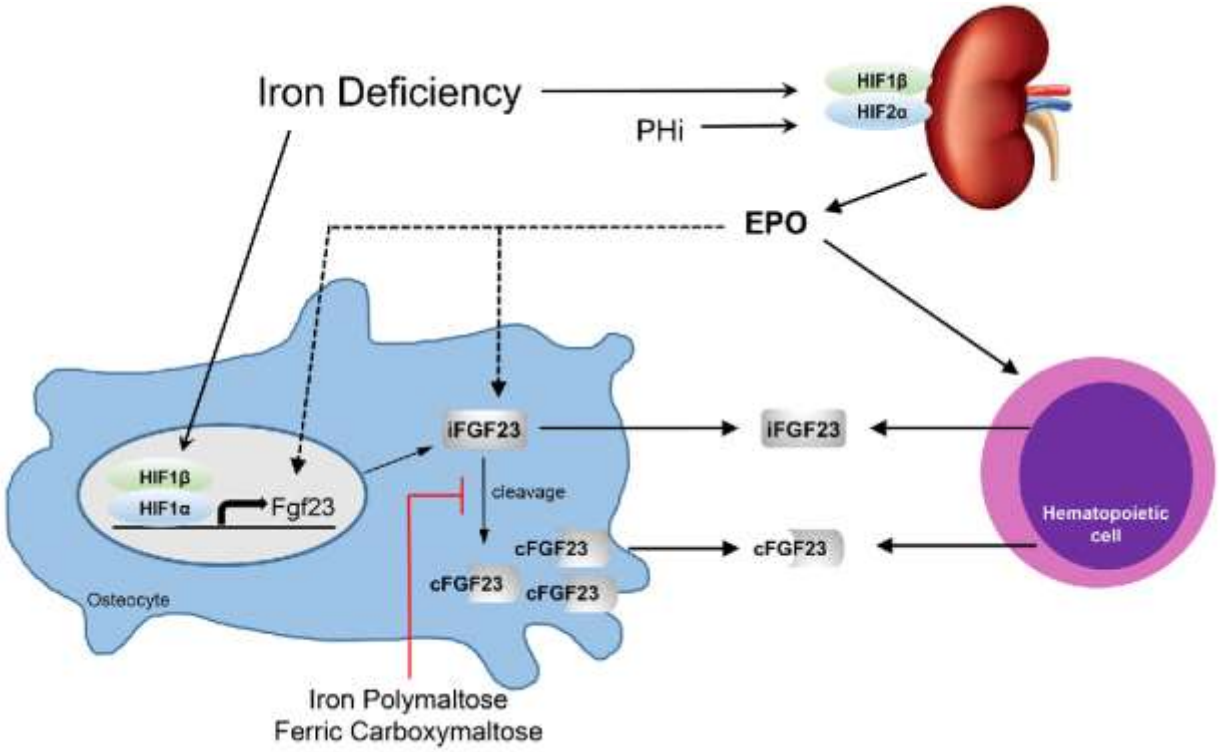
GALNT3 = polypeptide N-acetylgalactosaminyltransferase 3

= glycosylation

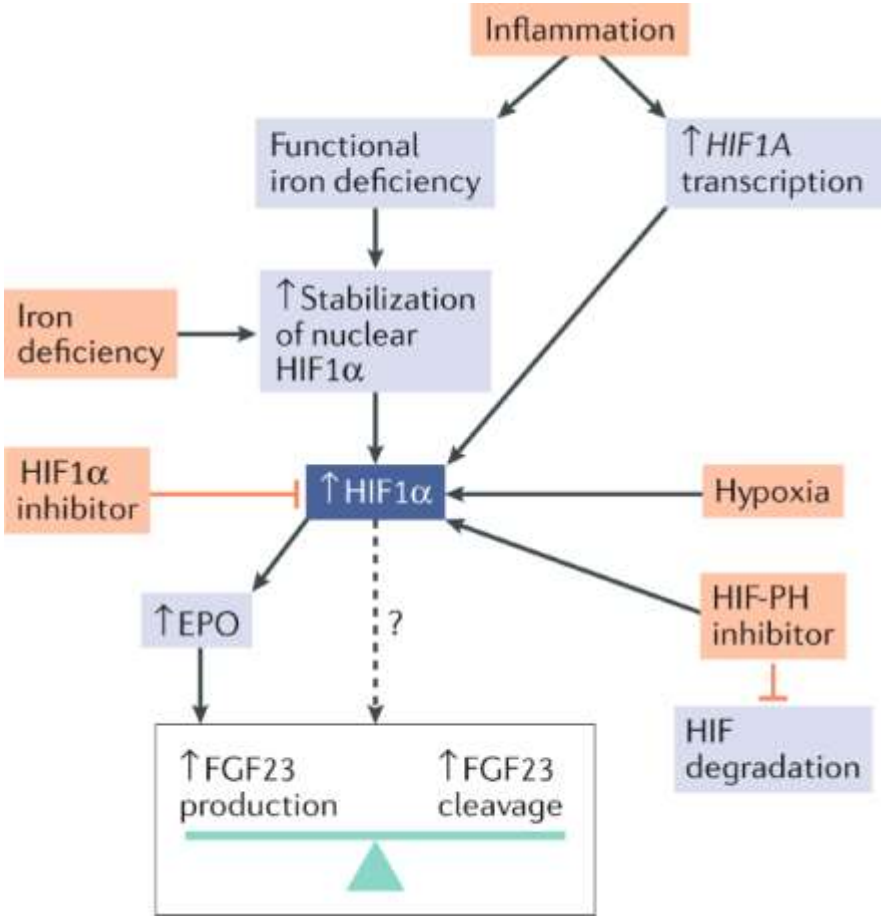
PPC = proprotein convertase (furin)



Fe/HIF/EPO in FGF23 Transcription, Translation, Posttranslational Regulation



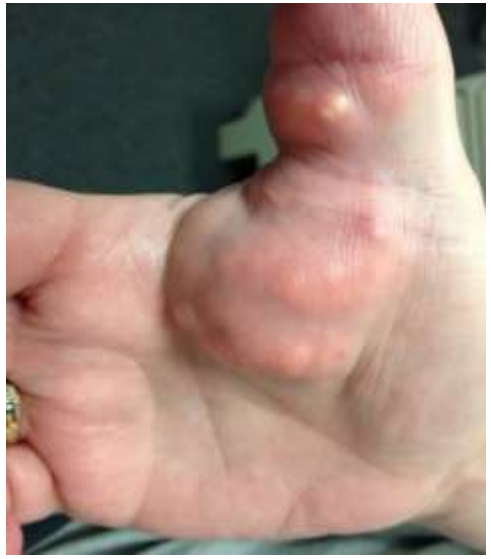
Wheeler & Clinkenbeard, Curr Mol Biol Rep, 2019

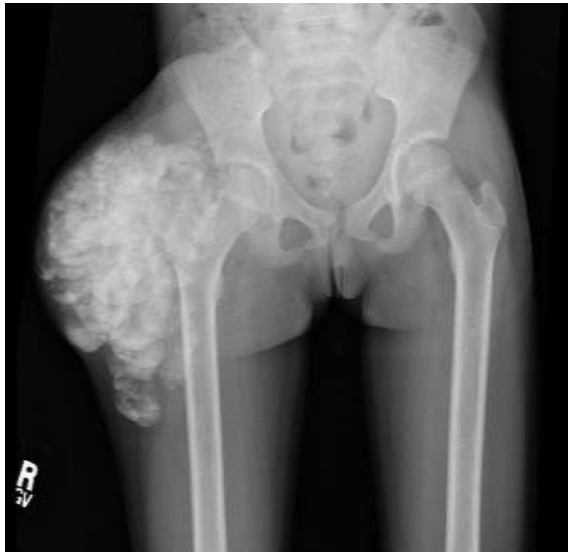


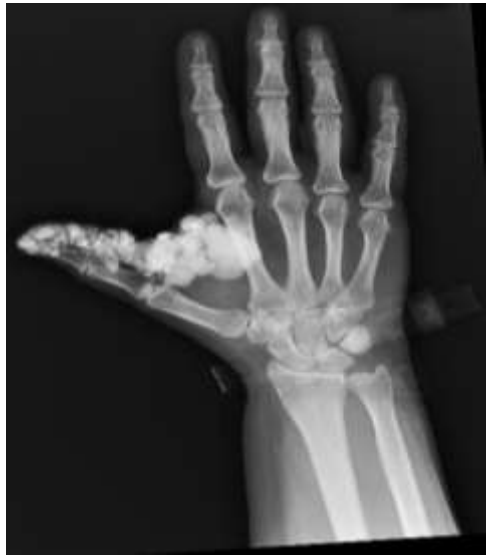
Edmonston & Wolf, Nat Rev Neph, 2019

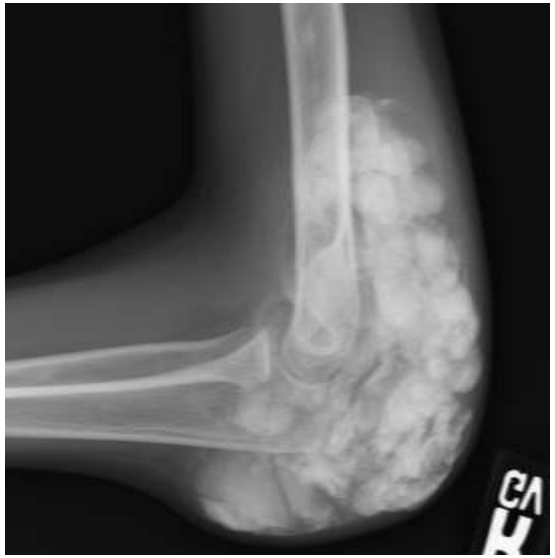
Nicolae David, Despina Sitara, Marc Hanudel, Mara Cristov, Luis Toro, others

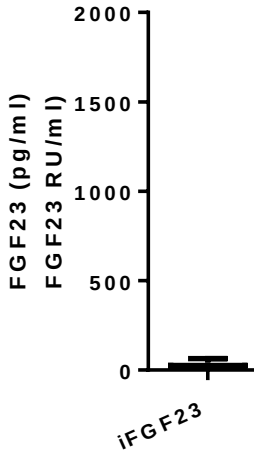
Findings in FGF23 deficiency: Hyperphosphatemic tumoral calcinosis

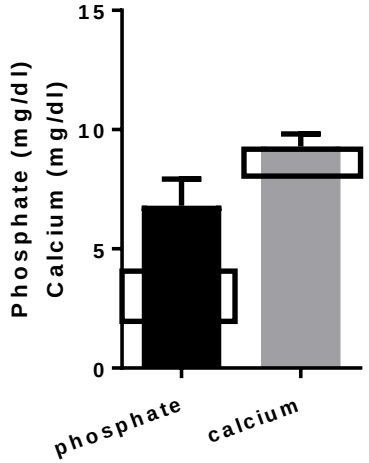


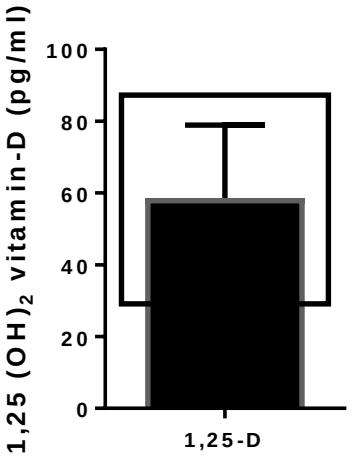


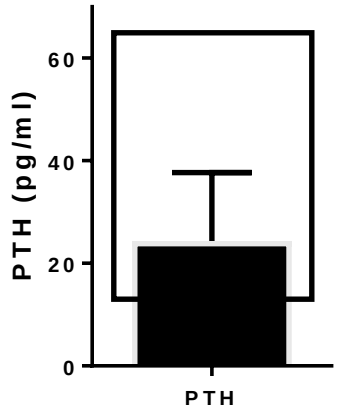








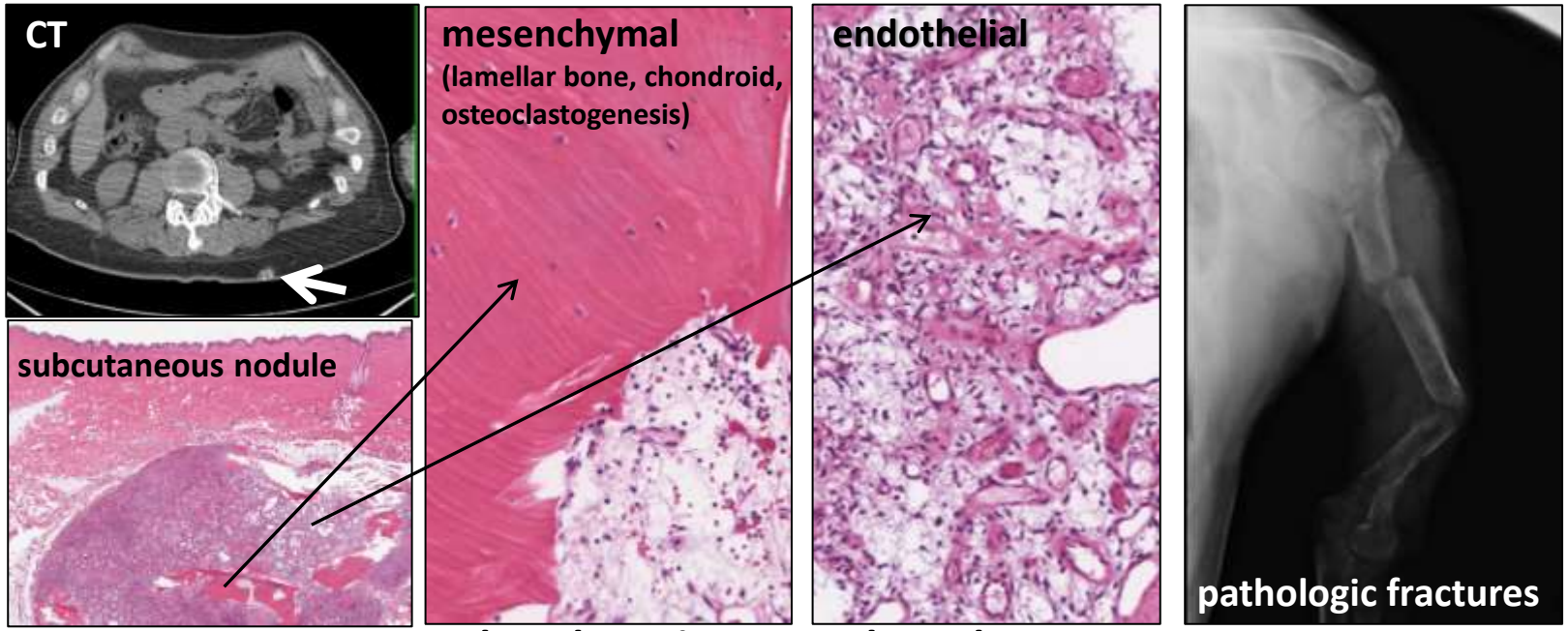




Ramnitz, JBMR 2016

FGF23 excess - Tumor-induced osteomalacia

- FGF23-secreting mesenchymal tumors
- small, difficult to locate
- osteomalacia, pain, fractures
- removal is curative



phosphaturic mesenchymal tumors

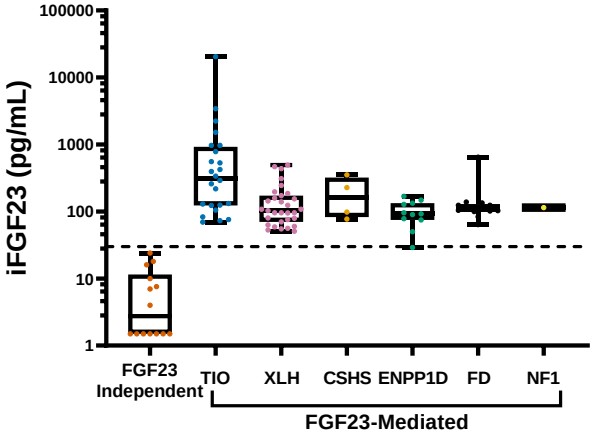
intact FGF23

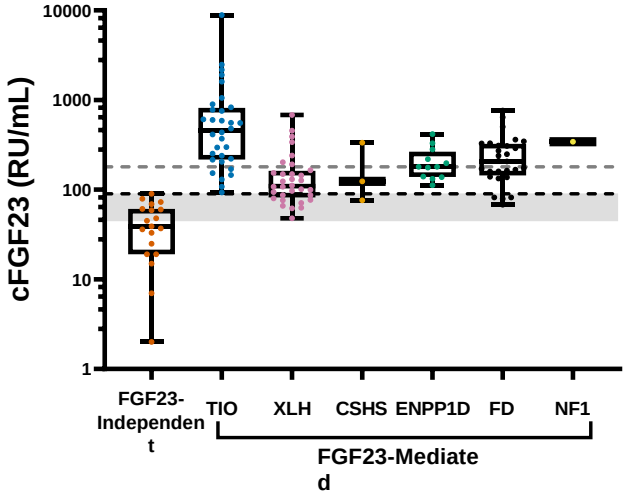
intact FGF23

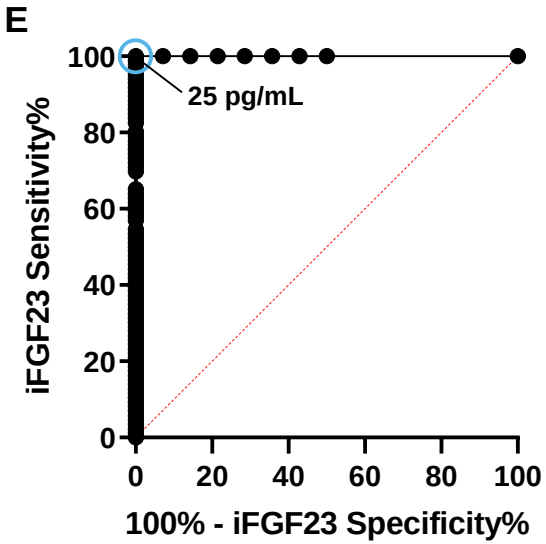
C-terminal FGF23

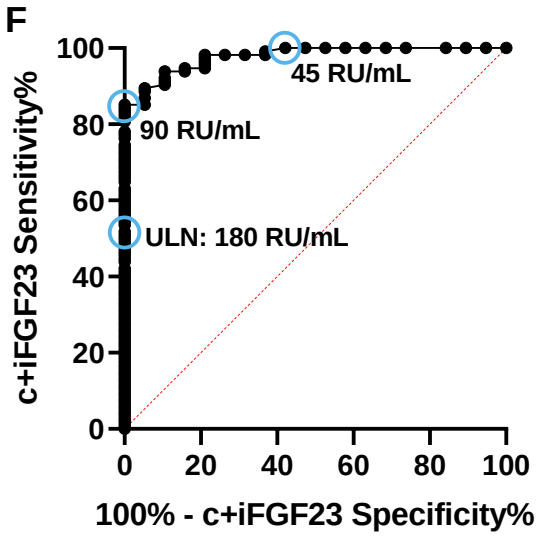
What FGF23 Level is Excess in Hypophosphatemia?

C-terminal FGF23







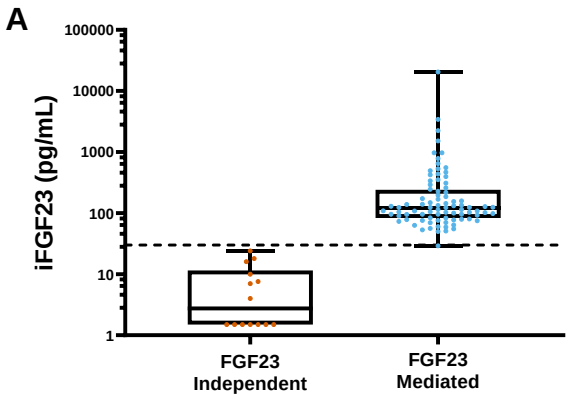


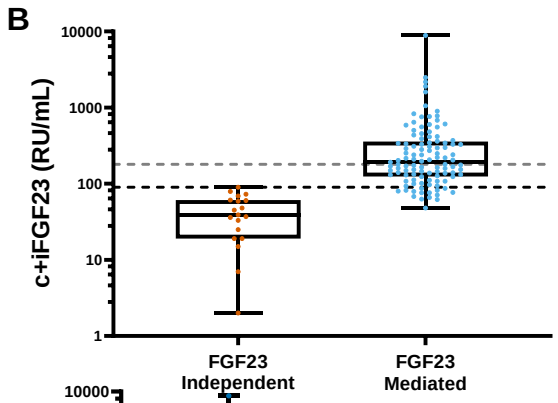
Iris Hartley, unpublished

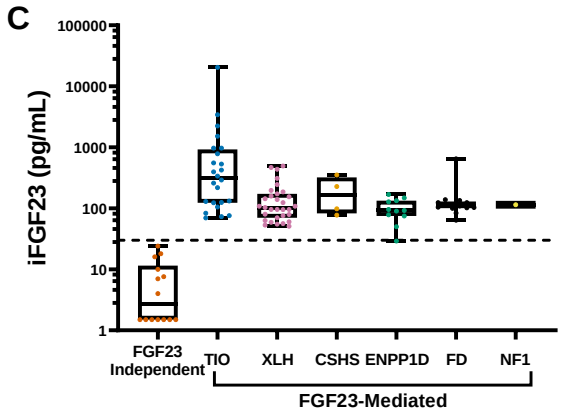
What FGF23 Level is Excess in Hypophosphatemia?

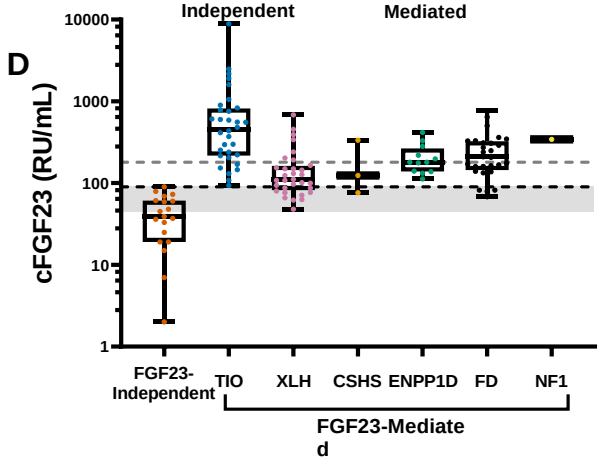
intact FGF23

C-terminal FGF23

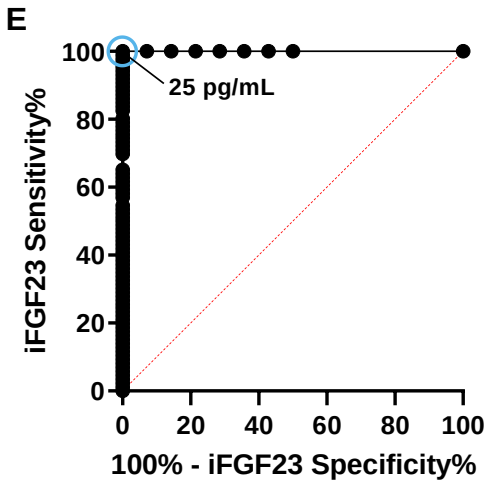




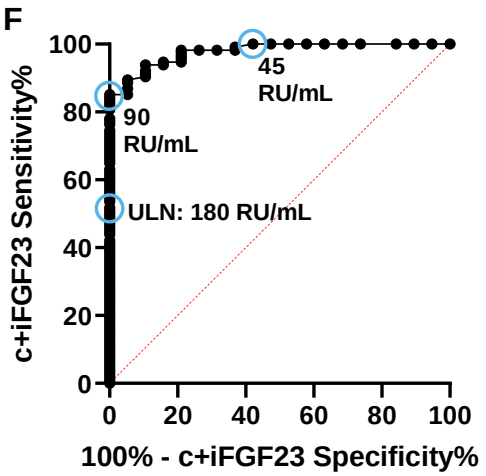




intact FGF23



C-terminal FGF23



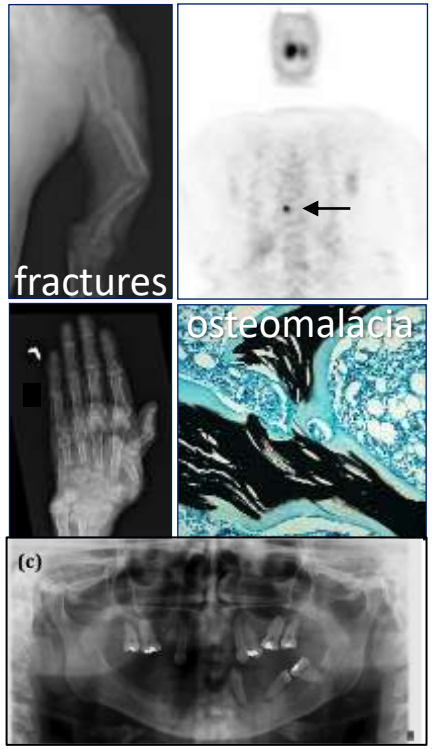
N = 426 (disease + control)
FGF23-independent =
Cystinosis (n=16)
Familial Fanconi (n=1)
LOWE's Syndrome (n=1)
HHRH (n=1)

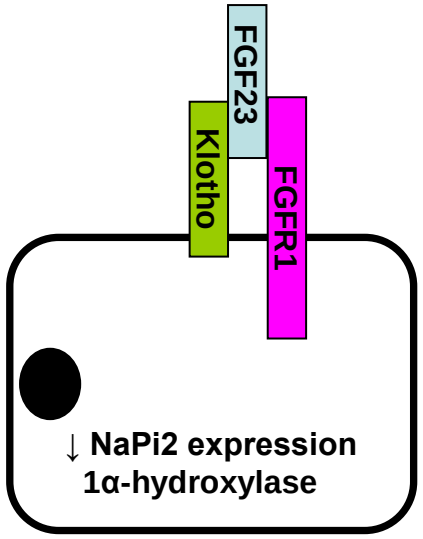
TIO = tumor-induced osteomalacia
XLH = X-linked hypophosphatemic rickets
CSHs = cutaneous hypophosphatemic rickets
ENPP deficiency
FD = fibrous dysplasia
NF1 = neurofibromatosis type 1

Iris Hartley, unpublished

FGF23 Excess

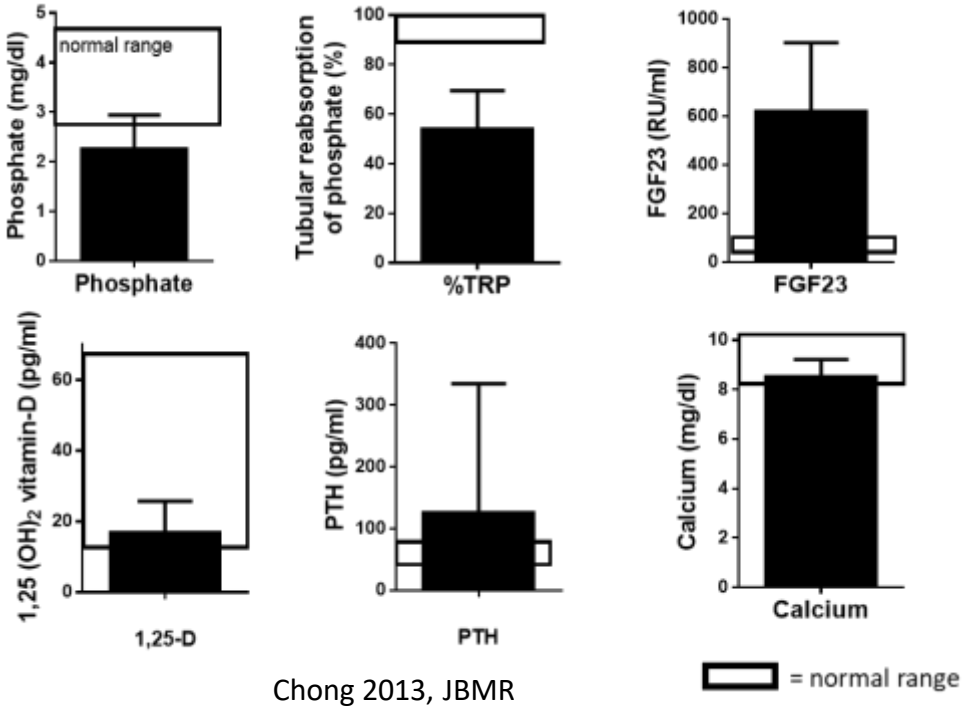
Tumor-induced osteomalacia





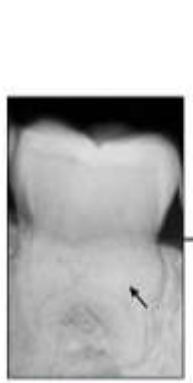
↓ serum phosphate

↓ serum 1,25-D_3



Chong 2013, JBMR

Signs of Hyperphosphatemic Familial Tumoral Calcinosis (HFTC)



Ocular involvement (rare)

Calcification of eyelids/conjunctiva/cornea, retinal angioid streaks, vision loss

Dental pathology (most common phenotypic feature)

Pulp calcification and thistle-shaped roots

Systemic inflammation (common, especially with new lesion formation)

Recurrent fevers, fatigue, anemia, polyarthritis, increased C-reactive protein and/or erythrocyte sedimentation rate

Ectopic calcification (common)

Lateral hips, elbows, shoulders, hands, pressure/trauma points

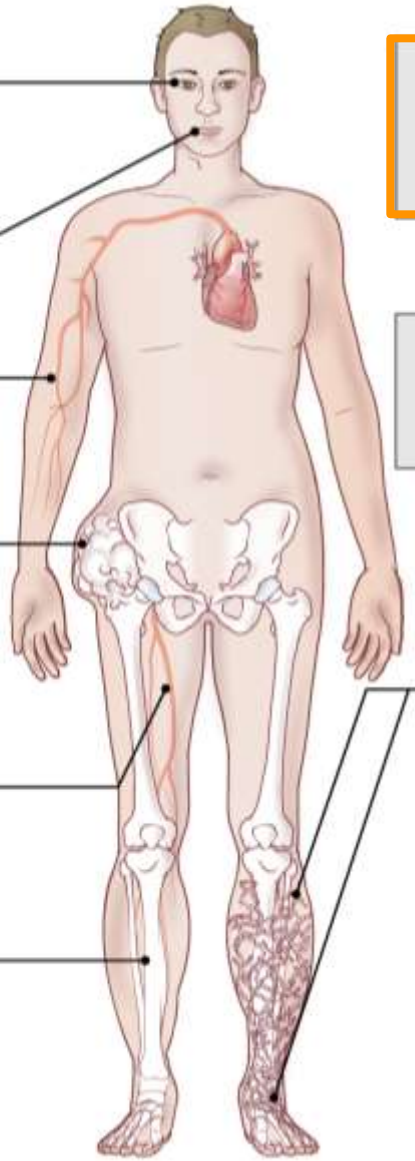
An area of ectopic calcification (C) and bone formation (B) associated with macrophages (M) causing inflammation

Vascular calcification

Femoral/iliac arteries, aorta, carotids, cerebral vasculature

Hyperostosis (childhood only, often presenting symptom)

Tibiae (common, arrows), rarely ulnae, radii, and/or metacarpals



Biochemical findings (common – requisite for diagnosis)

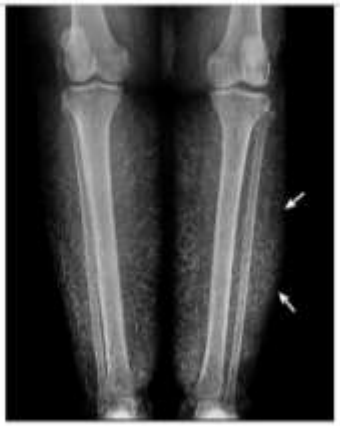
- High serum phosphorus
- High C-terminal FGF23
- Low/normal intact FGF23

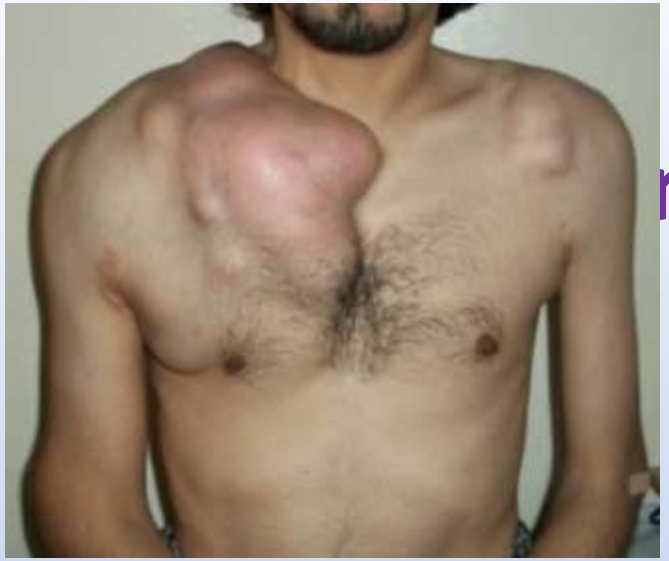
Other extracutaneous tissue calcifications

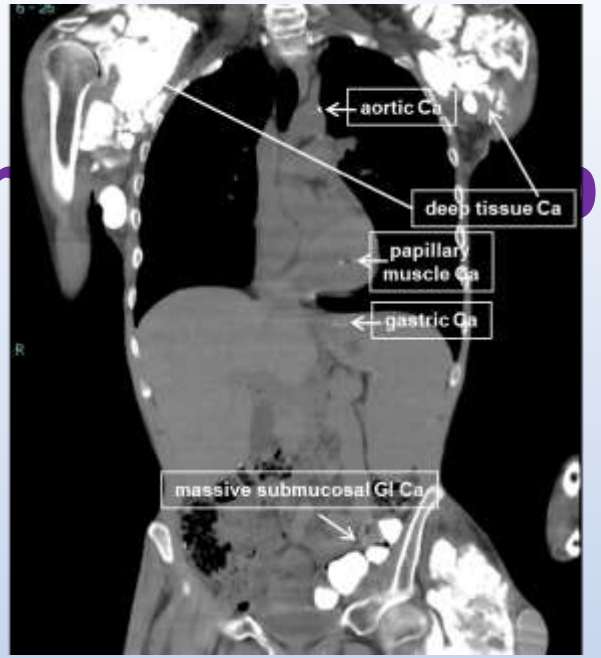
Dura, tongue, submucosal GI tract, testicular, nephrocalcinosis, other

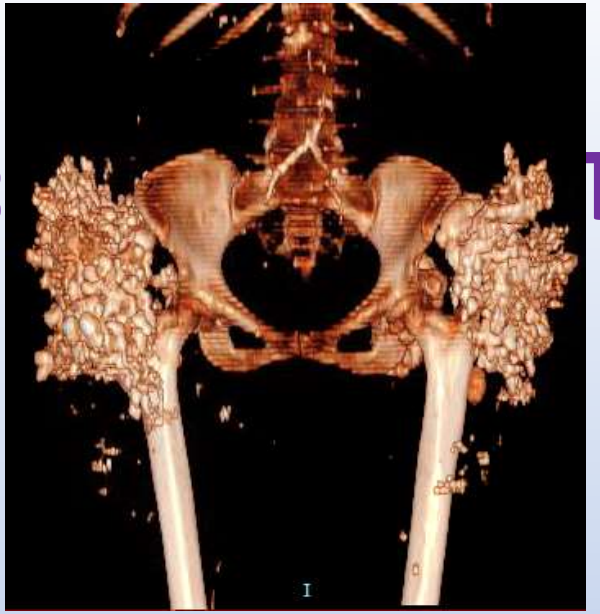
Stocking foot calcification (Age-related/late finding)

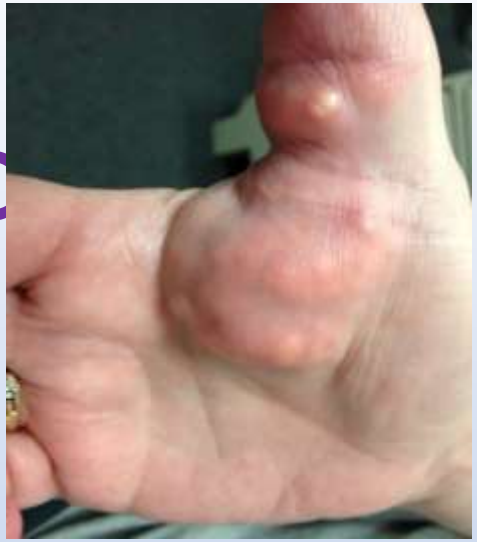
Feet and legs

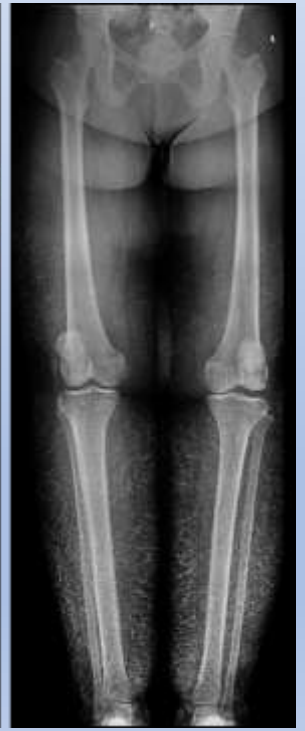


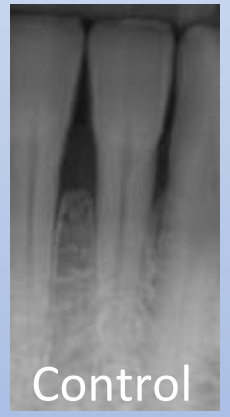


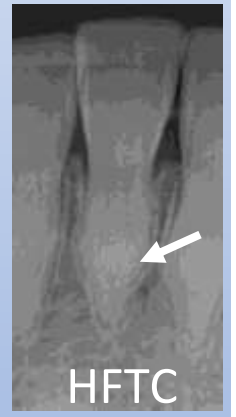


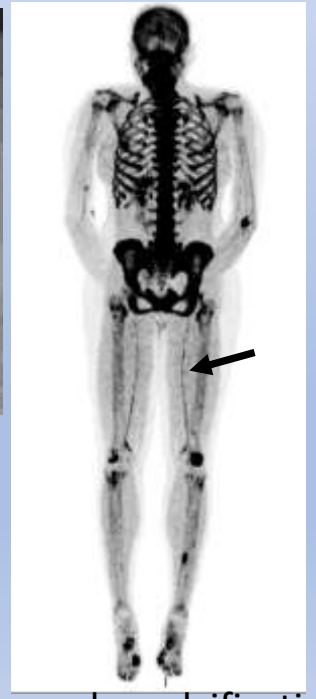




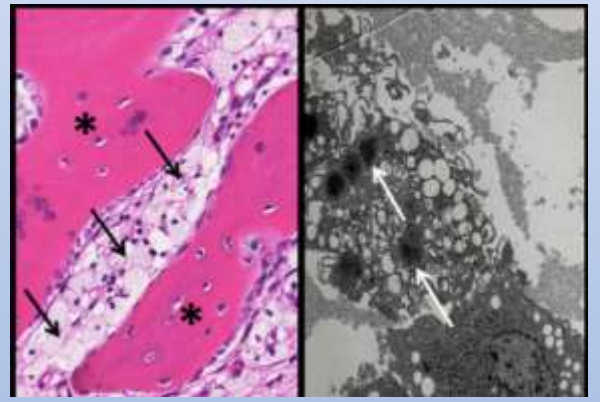




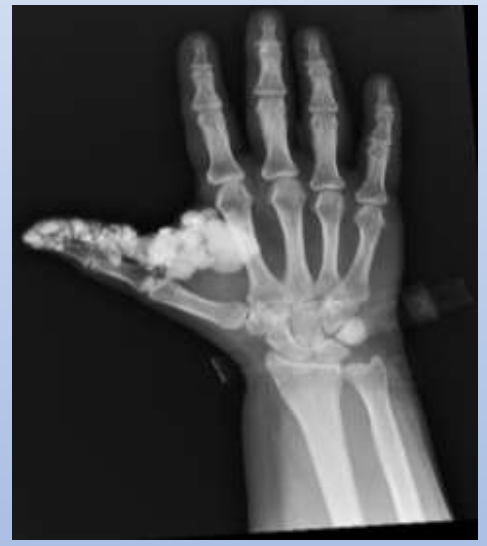


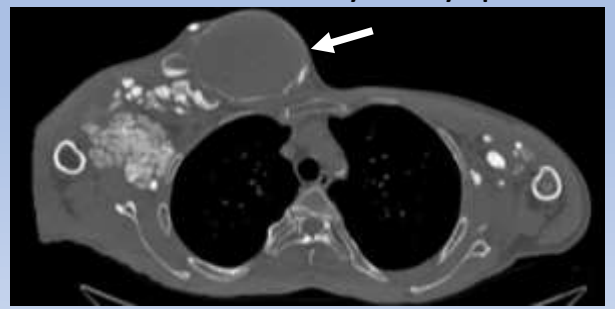


vascular calcification



inflammation macrophages with hydroxyapatite





FGF23-Mediated Diseases

FGF23 Excess

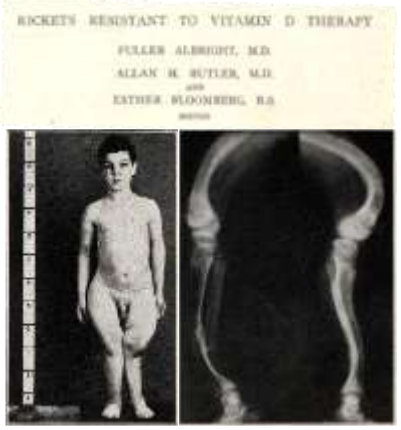
FGF23 Deficiency

Post-Translational Regulation

Condition	Abbreviation	Gene(s)	FGF23
Tumor-induced osteomalacia	TIO	*FN-FGFR1 (FGF23-secreting tumors)*	↑↑
X-linked hypophosphatemic rickets	XLH	*PHEX*	↑
Autosomal recessive hypophosphatemic rickets	ARHR1	*DMP-1*	↑
Autosomal recessive hypophosphatemic rickets/ENPP1 Deficiency	ARHR2/ENPP1 def	*ENPP1*	↑
Cutaneous skeletal hypophosphatemia syndrome	CSHS	*RAS (mosaic)*	↑
FD/McCune-Albright syndrome	FD/MAS	*GNAS (mosaic)*	↑
Autosomal dominant hypophosphatemic rickets	ADHR	*FGF23*	↑
Hyperphosphatemic familial tumoral calcinosis	HFTC (1,2,3)	*GALNT3; FGF23; Klotho*	↓
Autoimmune tumoral calcinosis (FGF23 resistance)	ATC	FGF23 Autoantibodies	↑↑
Renal Failure	CRF	*N/A*	↑↑

A Brief History of FGF23

first disease of FGF23


RICKETS RESISTANT TO VITAMIN D THERAPY

FULLER ALBRIGHT, M.D.

ALLAN M. BUTLER, M.D.

AND

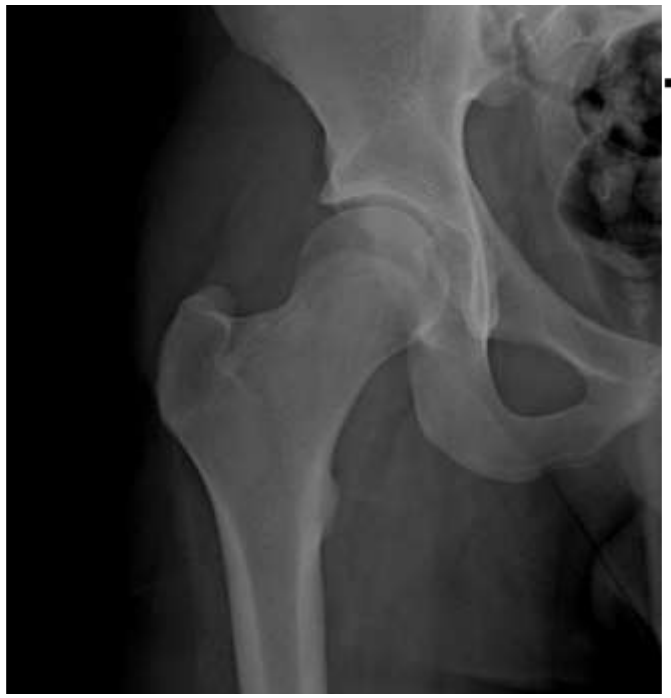
ESTHER BLOOMBERG, B.S.

1937

Rickets resistant to Vitamin D therapy (VDRR, Albright)

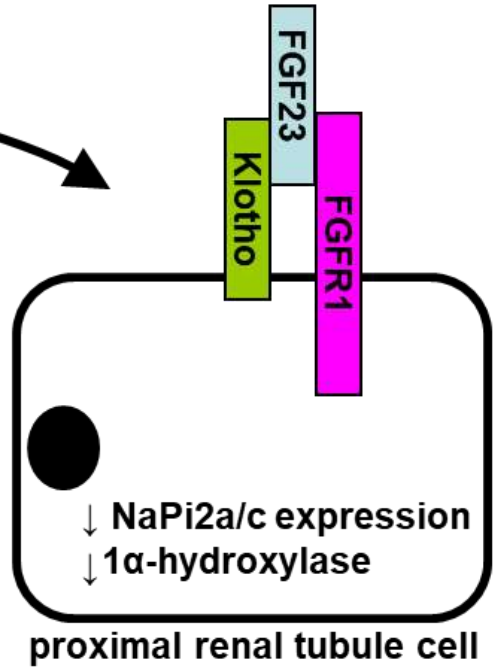
FGF23 Action and Regulation

?



regulates renal phosphate and vitamin D metabolism

FGF23



↓ serum phosphate

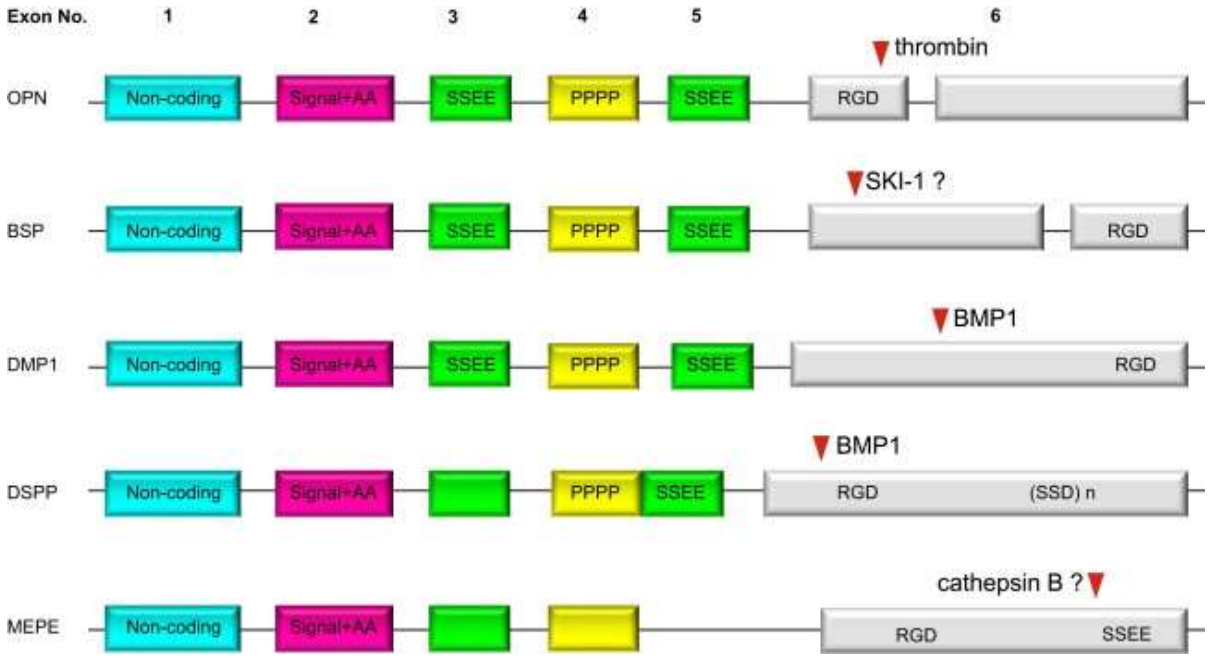
↓ serum 1,25-vitamin D_3

phosphate

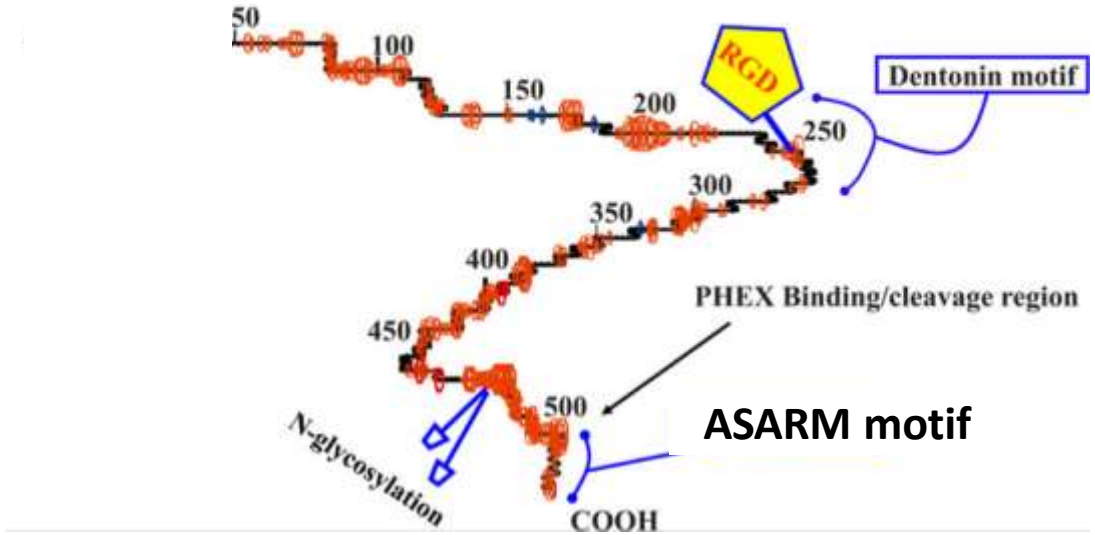
Sibling Protein ASARM-Mediated Regulation of FGF23 and Mineralization

SIBLING Genes/Proteins (Larry Fisher, NIDCR)

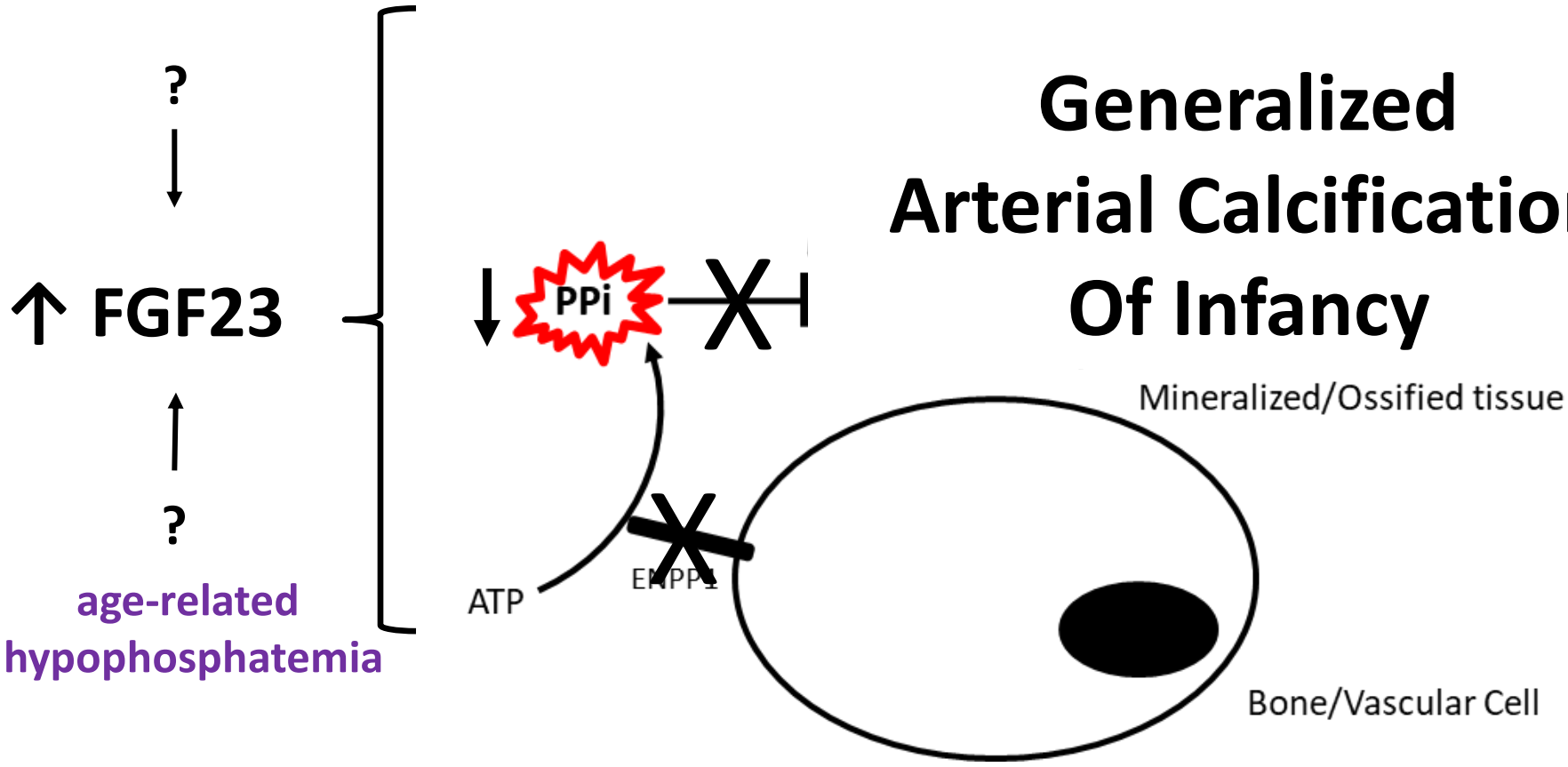
- **s**mall **i**ntegrin-**b**inding **li**gand, **N**-linked **g**lycoprotein
- highly expressed in ECM of mineralized tissues
- unifying feature is an Acidic Serine Aspartate Rich (**ASARM**)



Pathogenic Sibling-derived ASARMs



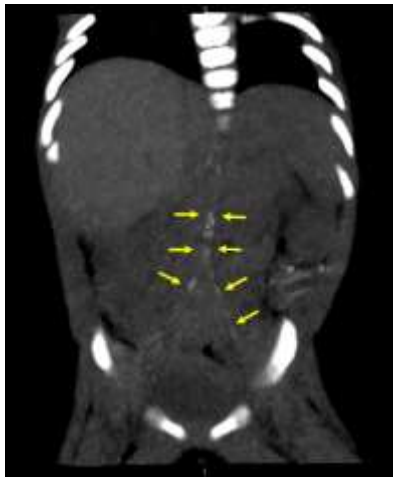
ENPP1 Mutations Cause ADHR2 (ENPP1 Deficiency Syndrome)

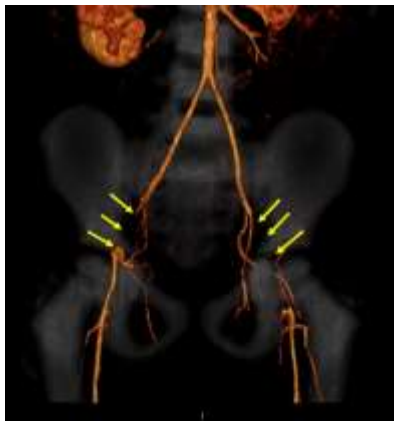


Generalized Arterial Calcification Of Infancy

ENPP1 = ectonucleotide pyrophosphatase/phosphodiesterase 1

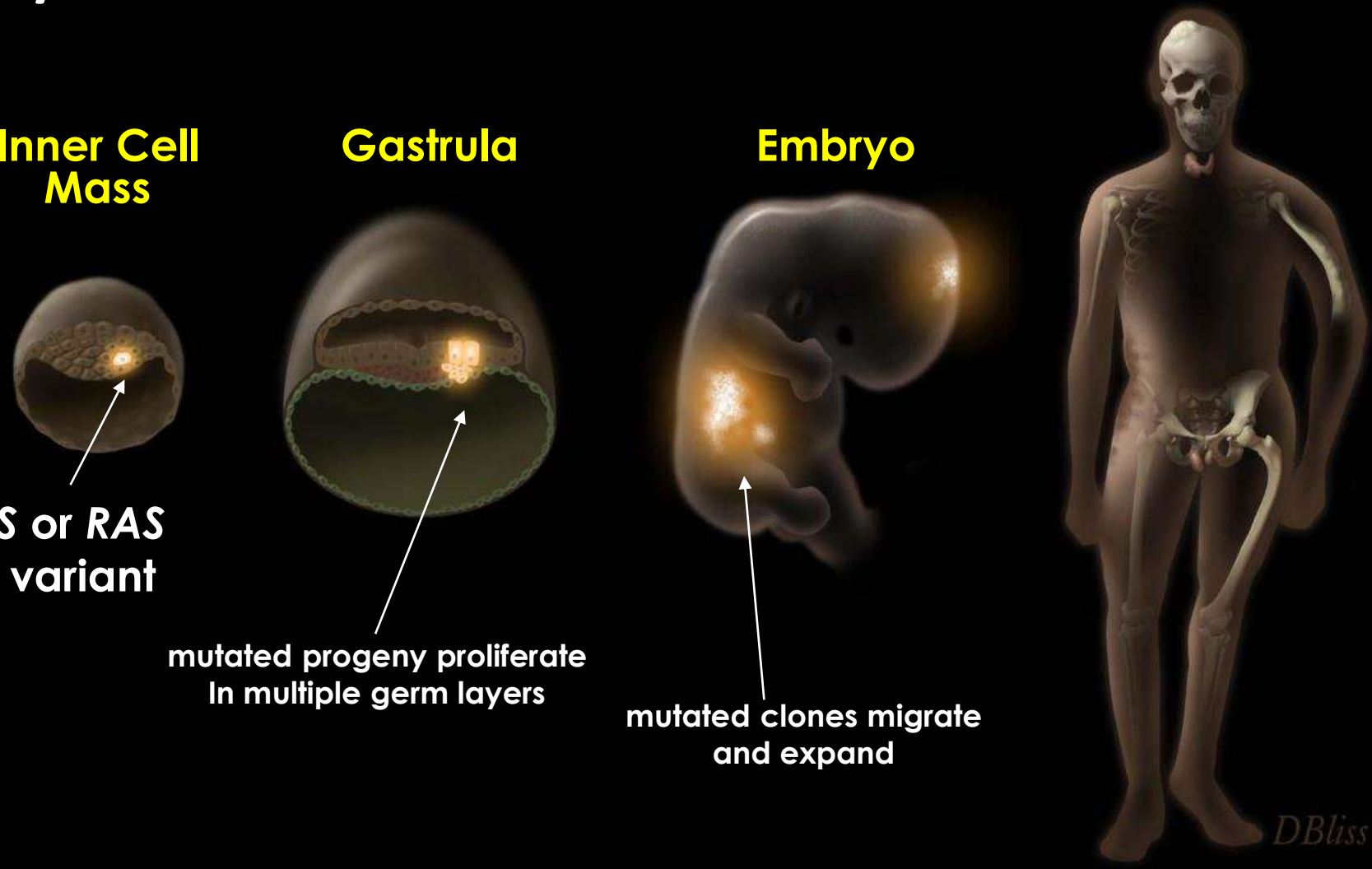
ENPP1 Replacement
(Inozyme Pharma)





Carlos Ferreira

FD/MAS and CSHS Mosaic FGF23 disorders

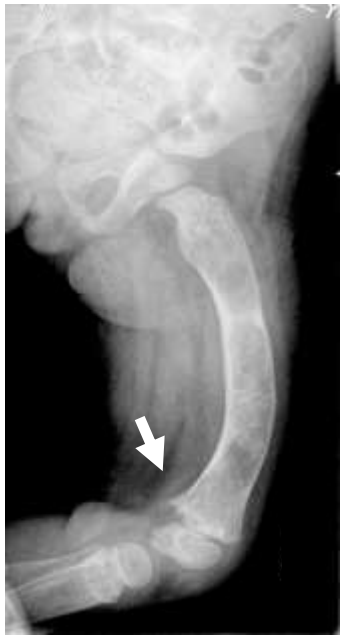


Phenotype involves tissues derived from ectoderm, mesoderm, and endoderm

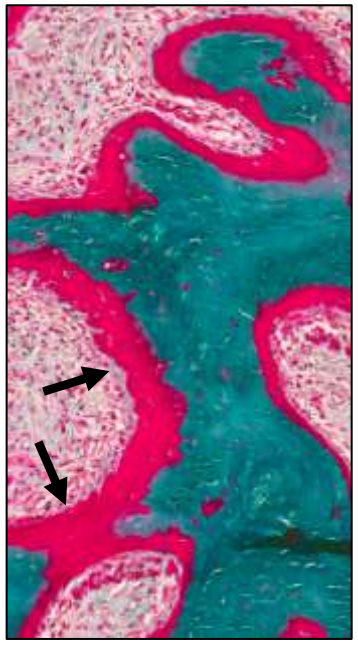
Bone cells are the source of FGF23 in FD

↑FGF23 in fibrous dysplasia ⟶ FD makes FGF23 ⟶ Normal bone makes FGF23

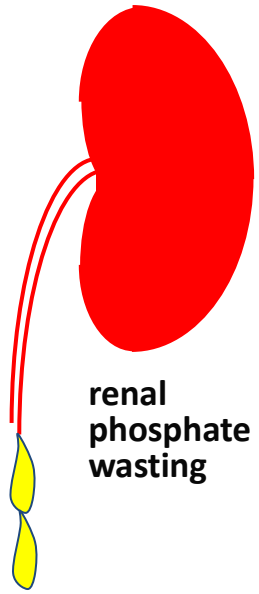
rickets



osteomalacia

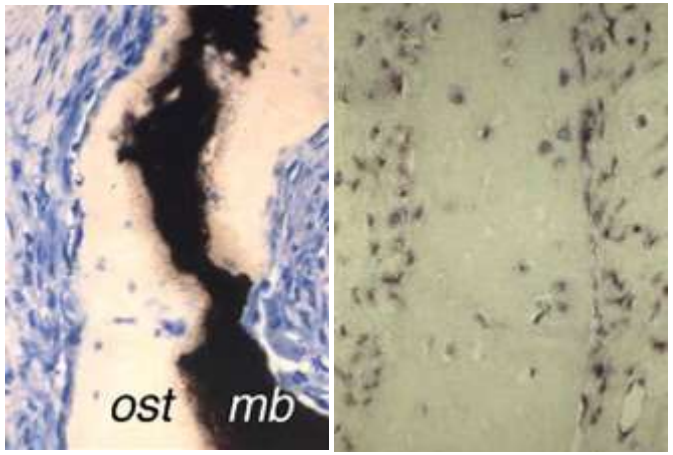


hypo-phosphatemia



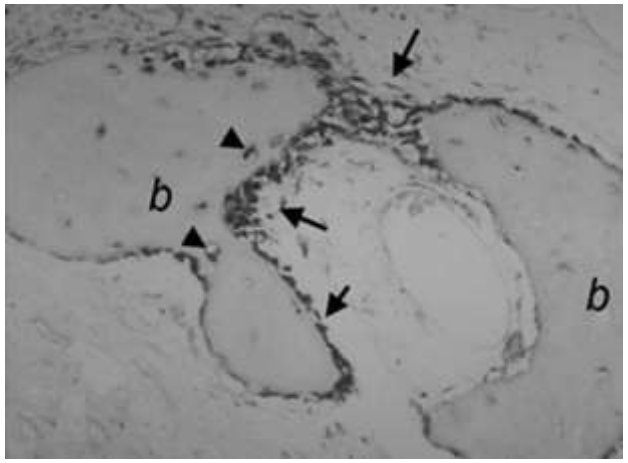
renal phosphate wasting

FGF23 *in situ* hybridization



fibrous dysplasia of bone

FGF23 *in situ* hybridization



normal bone

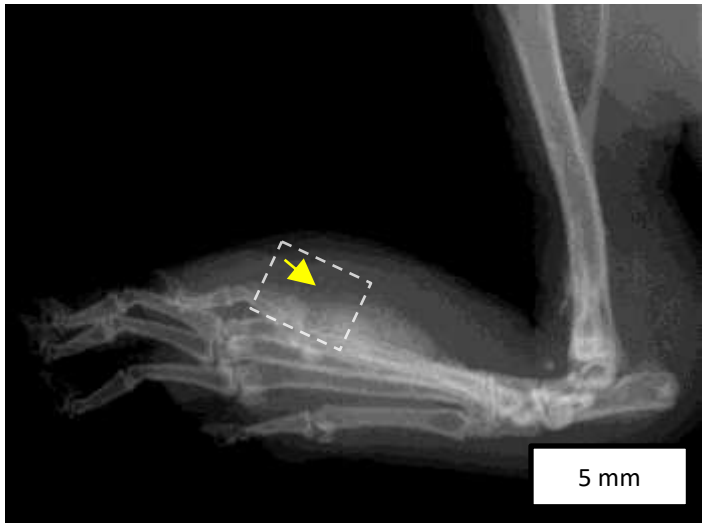
osteoblasts and osteocytes are the physiological source of FGF23

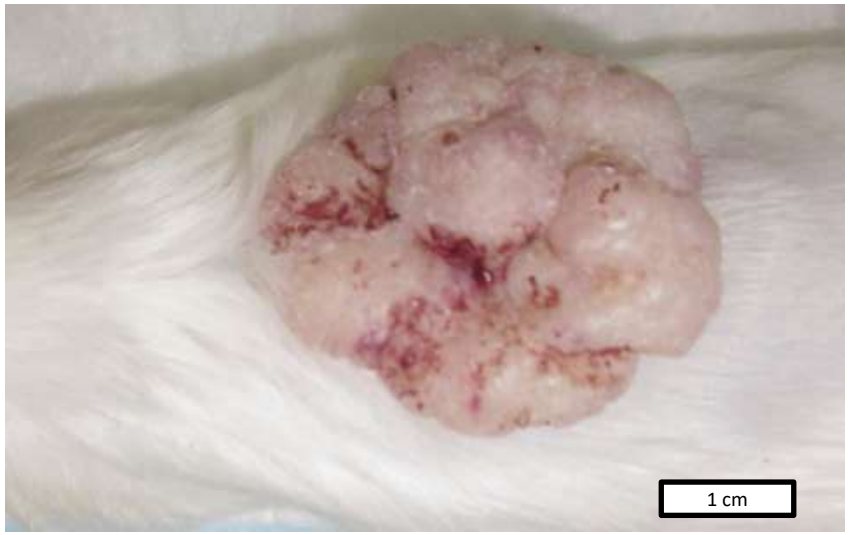
Collins, JBMR, 2001
Corsi, JBMR, 2003

Riminucci, Collins, J Clin Invest 2003
Sitara et al, Matrix Biology, 2004
Mirams et al, Bone, 2004

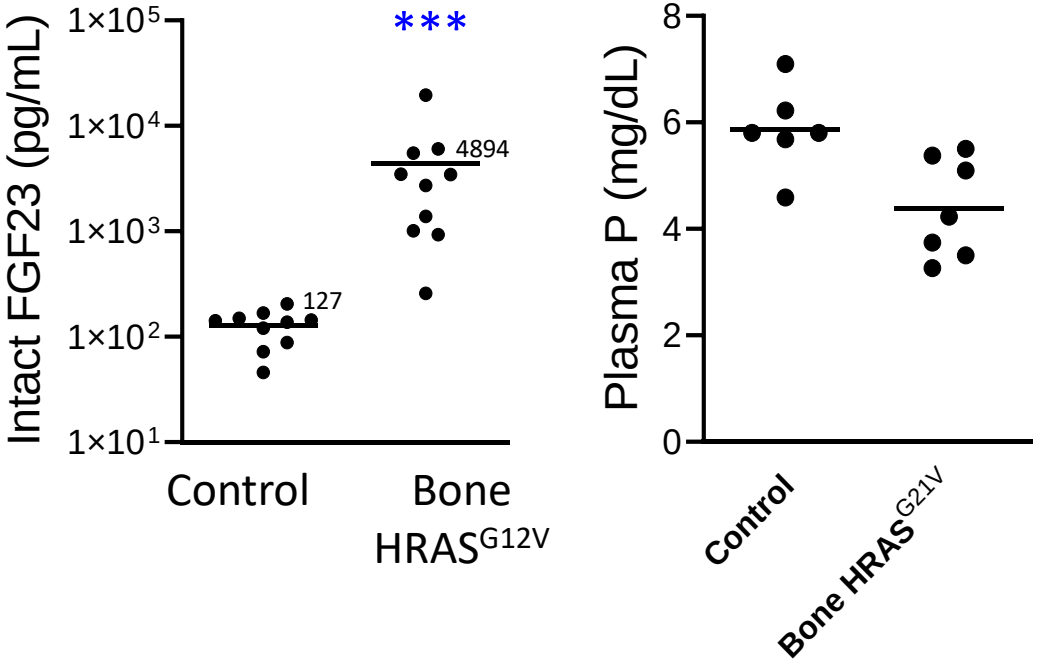
Bone, Not Skin is the Source of FGF23 in CSHS

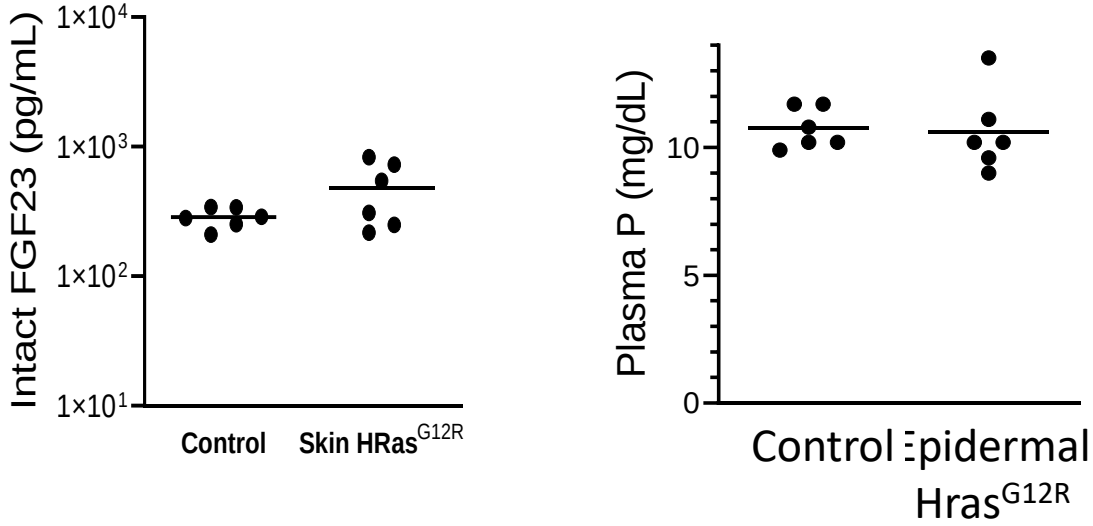
Bone HRAS^{G12V}





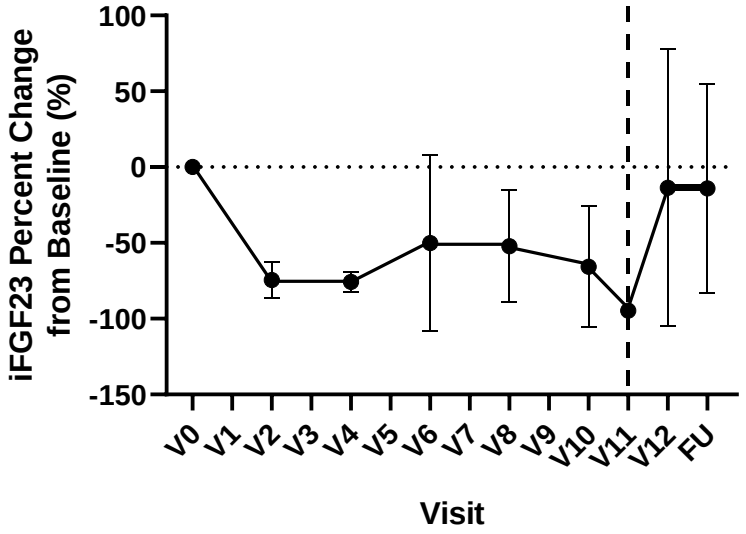
Skin Hras^{G12R}

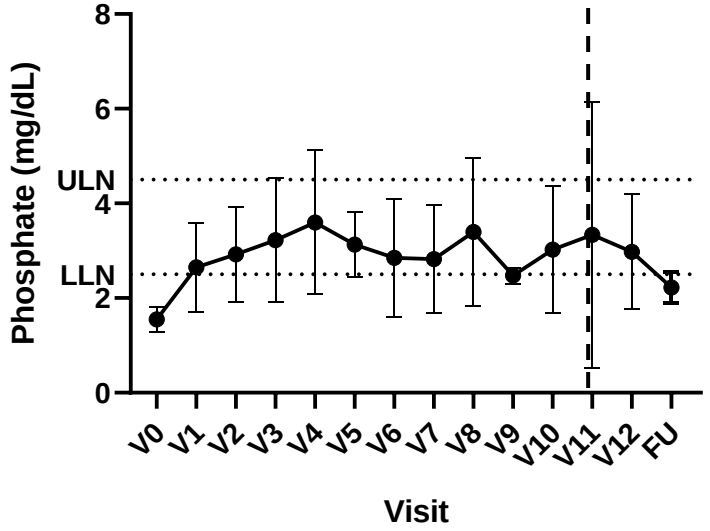




Luis Fernandez de Castro, JCI (in revision)

Infigratinib in Benign TIO

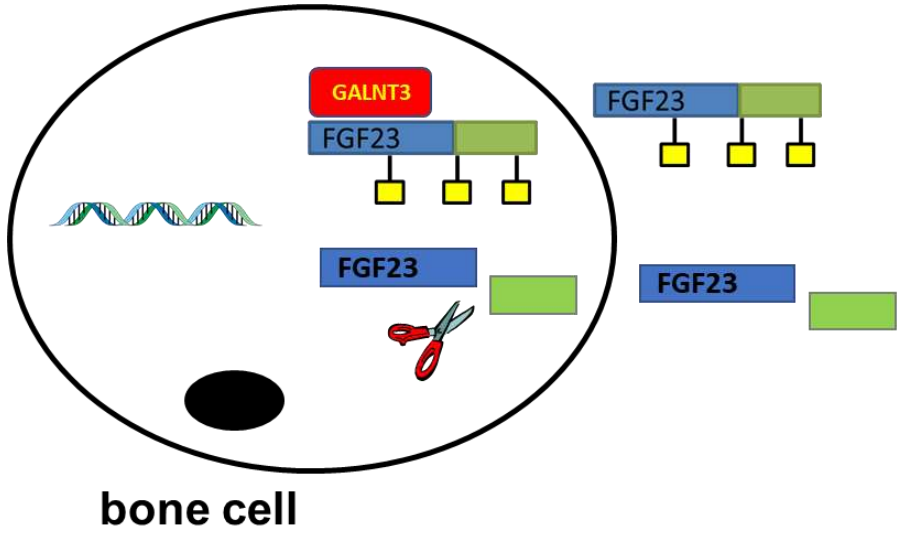




- 1° objective: **persistent** biochemical remission
- 24 weeks treatment infigratinib, n= 4
- Results:
  - FGF23 decreased, phosphate increased
  - **No persistent remission**
  - **Substantial adverse side effects**
  - Study ended early
- Need more specific, less toxic drug!

Hartley, JBMR-plus, 2022

Is Posttranslational regulation a regulated process?

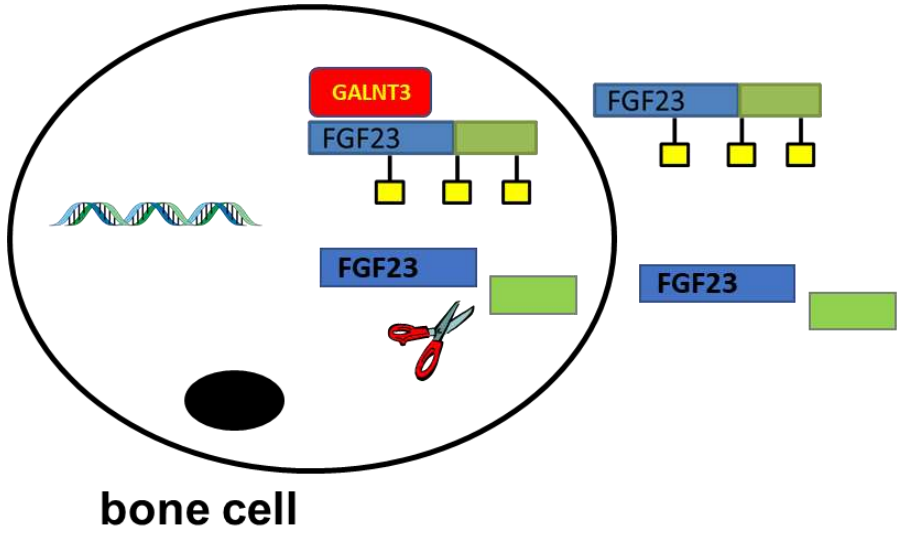


Two pieces of information suggest yes, and that the HIF/Epo/Fe pathway is involved

1. **Patients with ADHR1 (FGF23 mutations alter FGF23 glycosylation) only become hypophosphatemic when anemic**
2. **HIF1α is activated in tumor-induced osteomalacia**

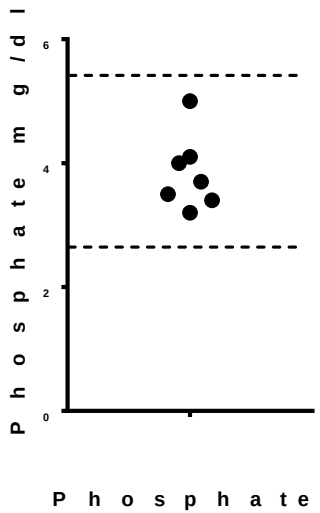
Imel & Econs, JCEM 2011
Zhang, Collins, Bone Res, 2016

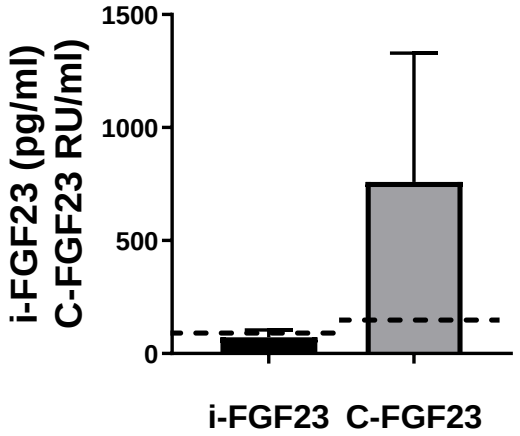
Is Post-translational regulation a HIF-related process?

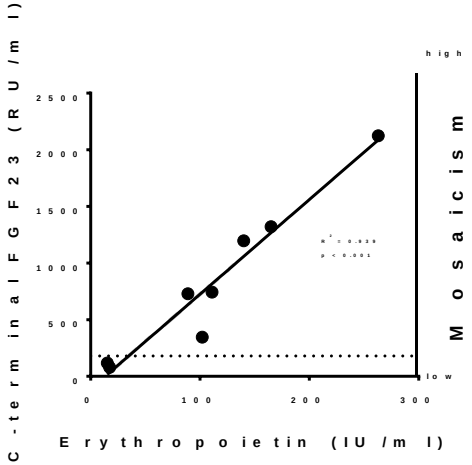


Paragangliomas due to gain-of-function, somatic mutations in HIF2α, ↑↑ EPO → polycythemia

Zhuang, NEJM 2012







Roszko, JBMR, 2020

↑ HIF2α

↑↑ EPO

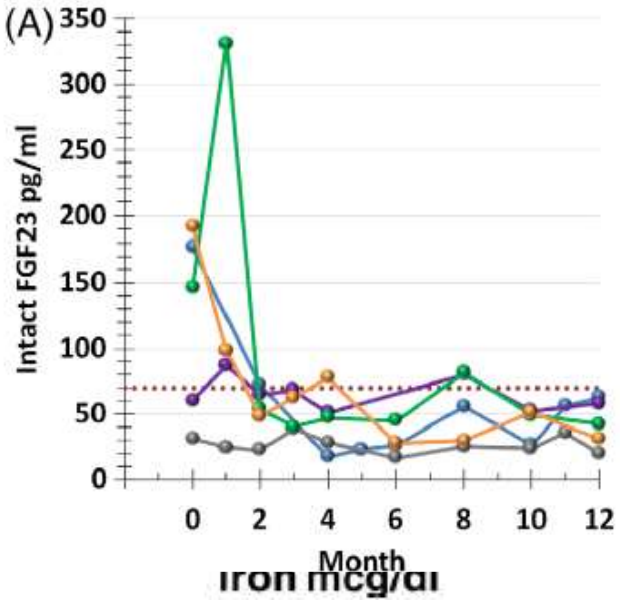
↑↑ FGF23 transcription/translation

↑↑ posttranslational regulation (GALNT3/furin)

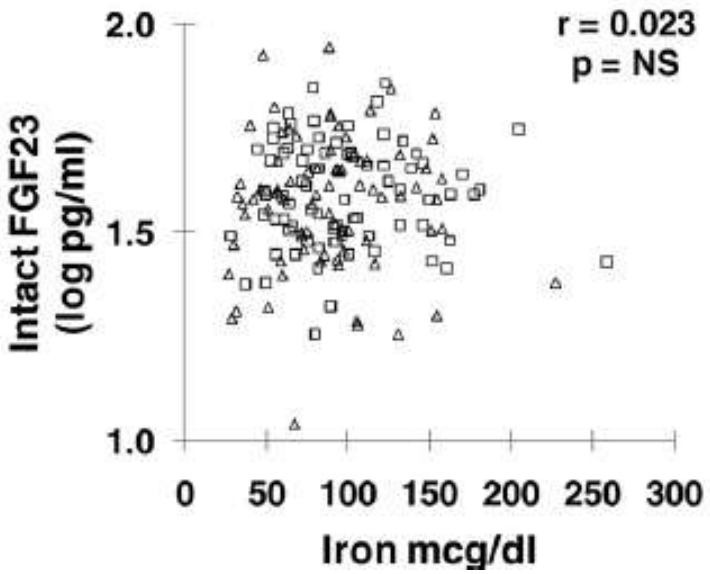
ADHR (mutations in FGF23): FGF23 Elevation Occurs During Anemia

Fe replacement treatment in ADHR1

ADHR

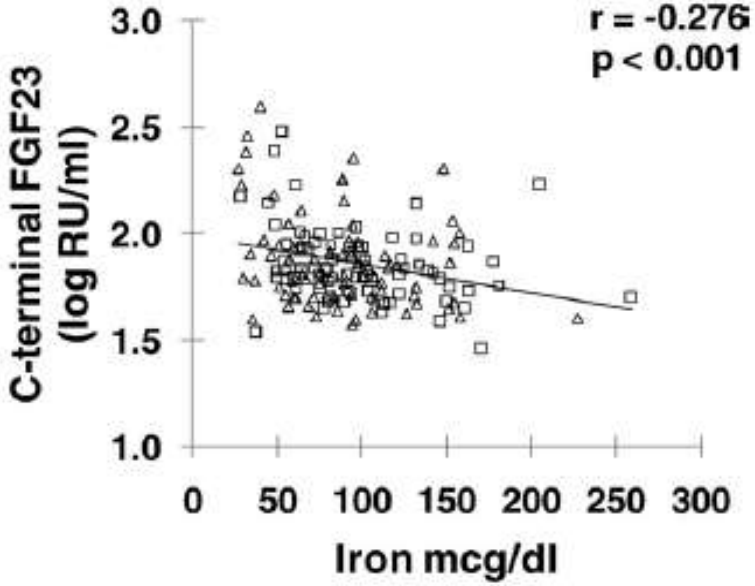


Controls



↑processing in Controls

(FGF23 posttranslational modification is a regulated process)



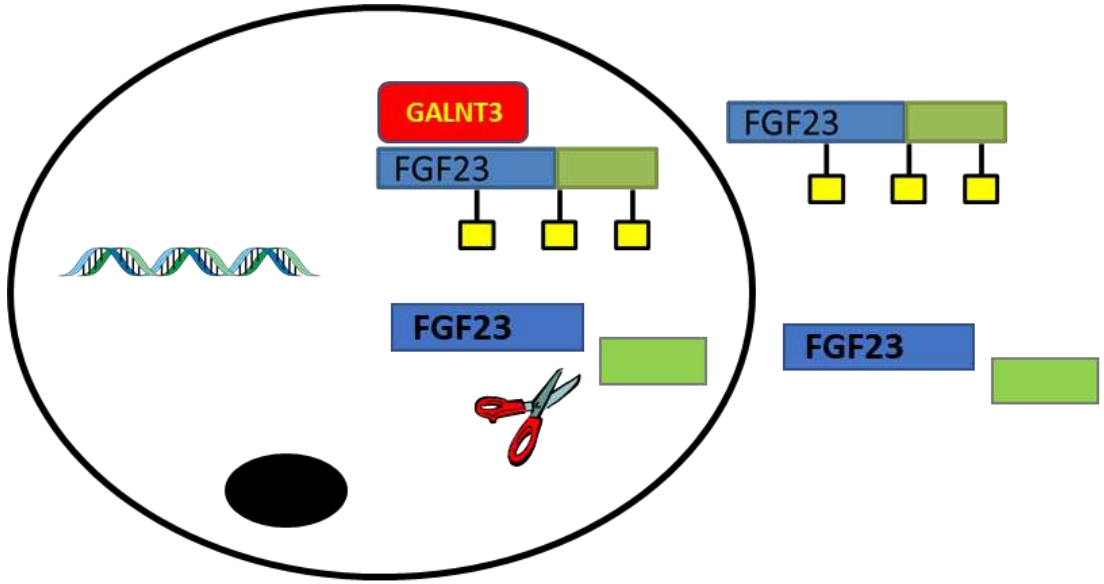
Imel, JBMR, 2019

Imel, JCEM, 2011

FGF23 Regulation

Phos
1,25-D
Ca
PTH
GNAS
RAS
PHEX
DMP1
ENPP1
FGFR1

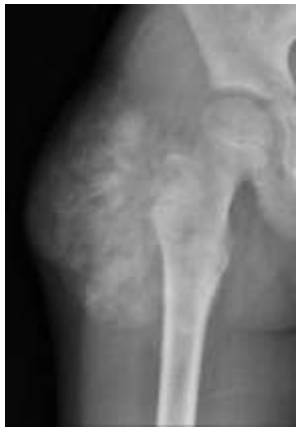
Transcriptional/
Translational



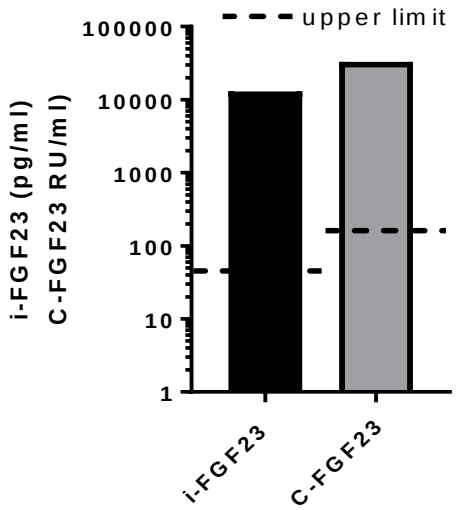
Iron
HIF*
EPO

Posttranslational

Novel Form of Tumoral Calcinosis

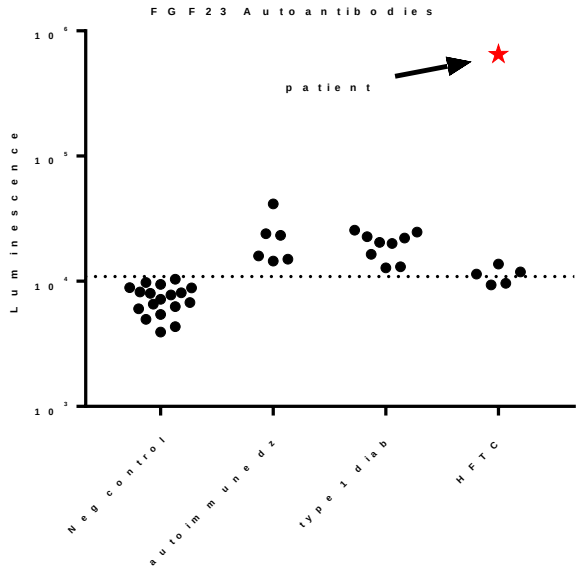


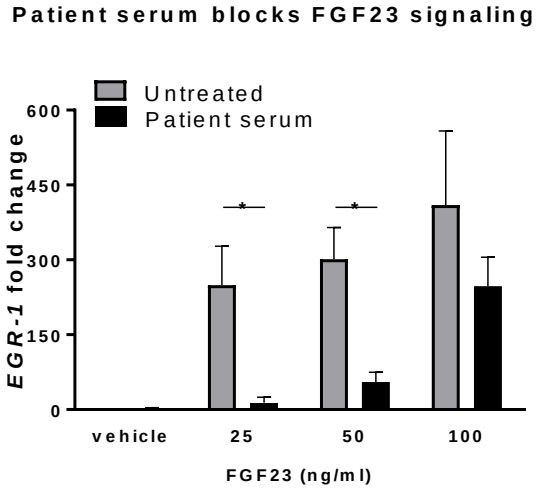
FGF23 Resistance



- 7-year-old boy ↑Pi and ↑Ca X Pi; c/w FTC
- WES; mutations in *KL, GALNT3, FGF23, FGFRs* excluded

Autoimmune Tumoral Calcinosis

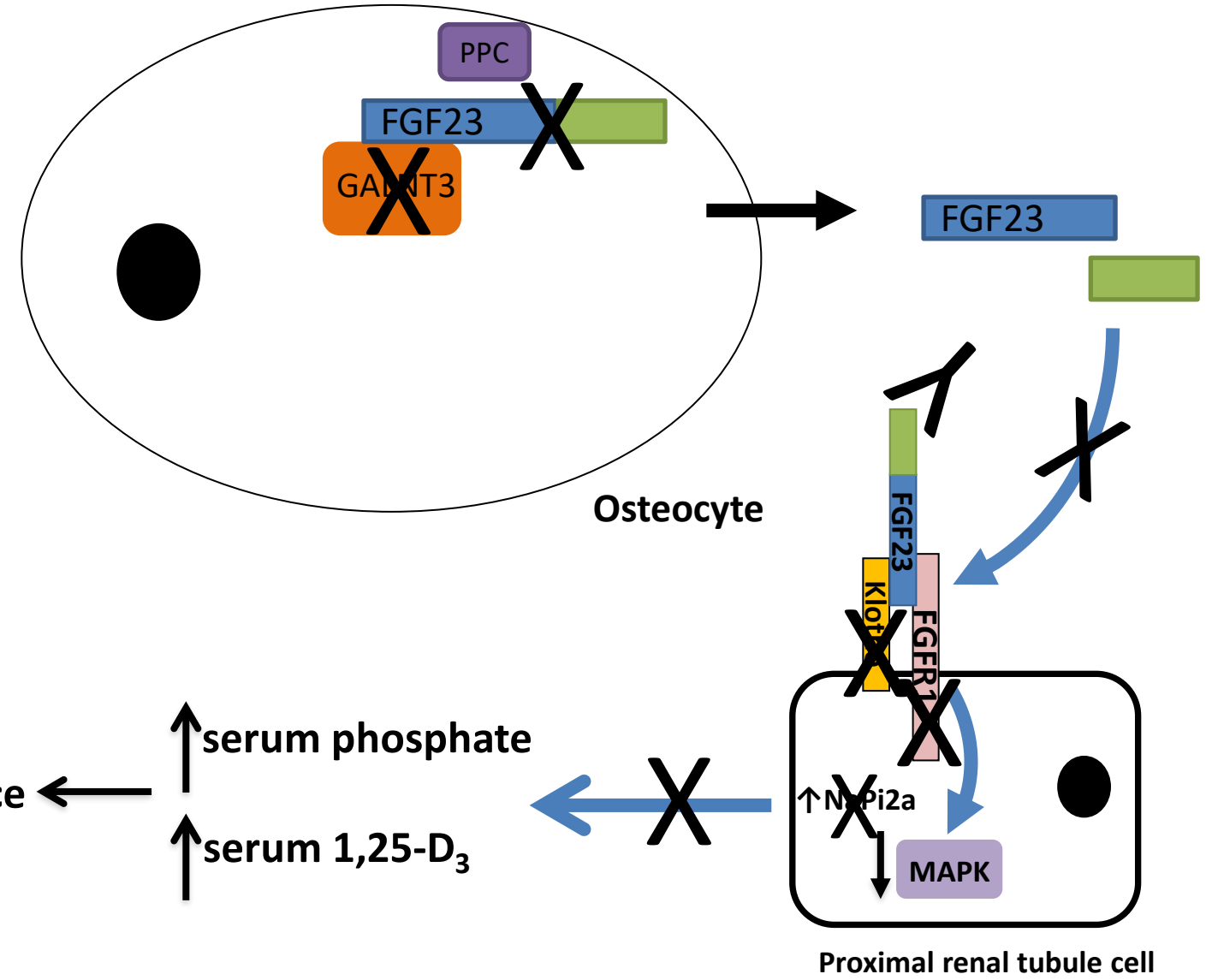


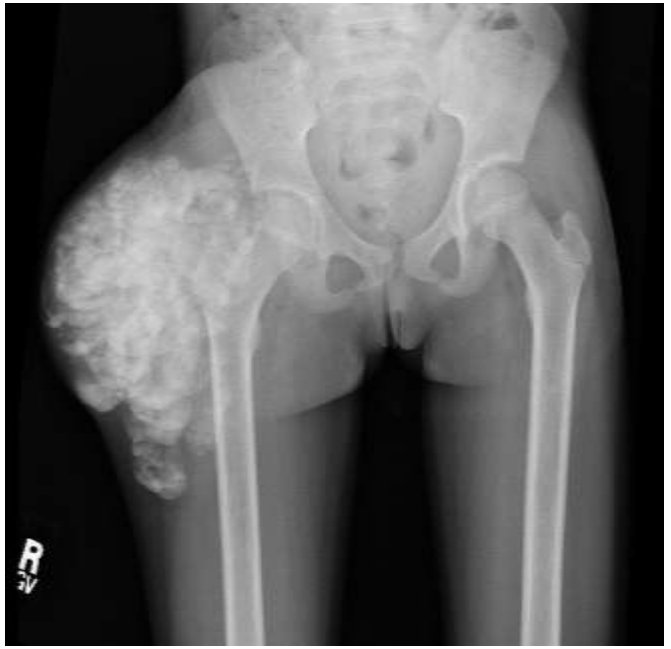


- Developed type 1 diabetes under observation

Roberts, JCI, 2018

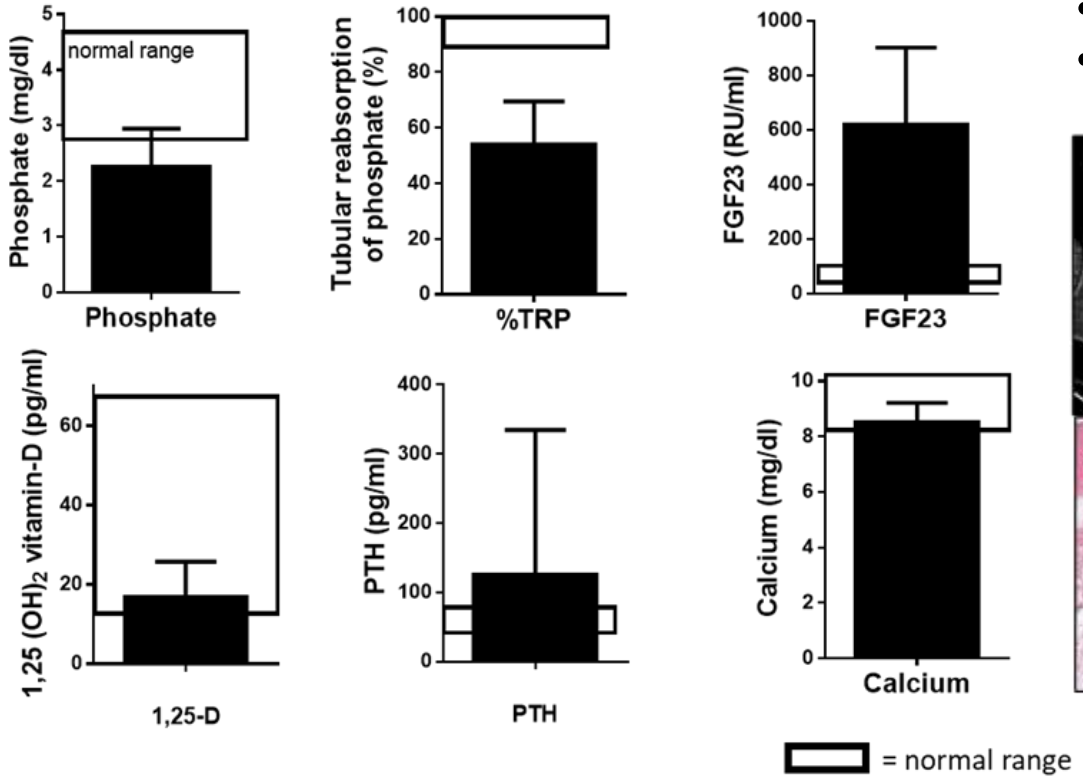
FGF23 Action → Tumoral Calcinosis



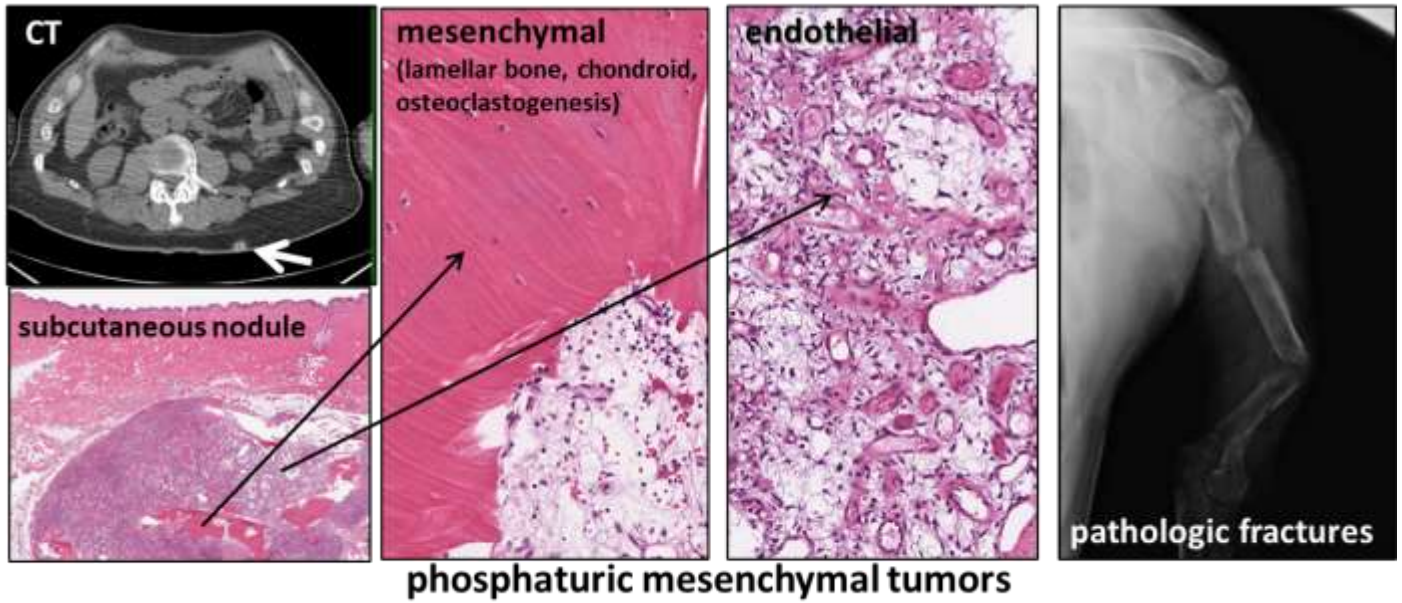


Topaz, Nat Gen, 2004
Benet-Pages Hum Mol Gen, 2005
Ichikawa, JCI, 2007, n=1
Prasad, Am J Med Gen, 2016, n=1
Roberts, JCI, 2018, n=1

FGF23 excess - Tumor-induced osteomalacia

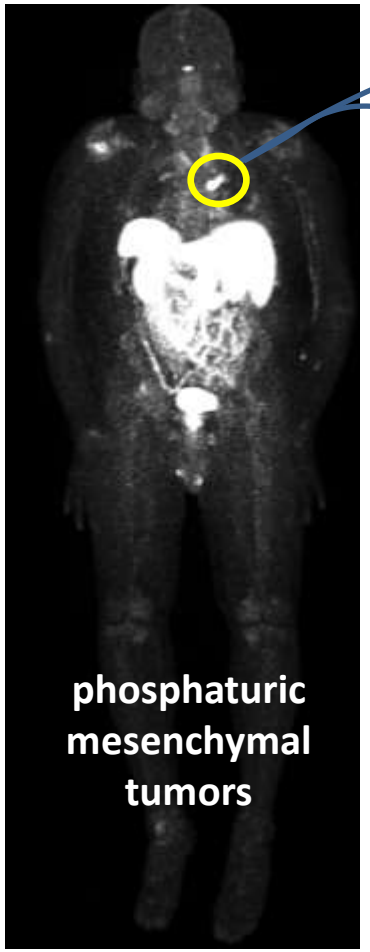


- FGF23-secreting mesenchymal tumors
- small, difficult to locate
- osteomalacia, pain, fractures
- removal is curative



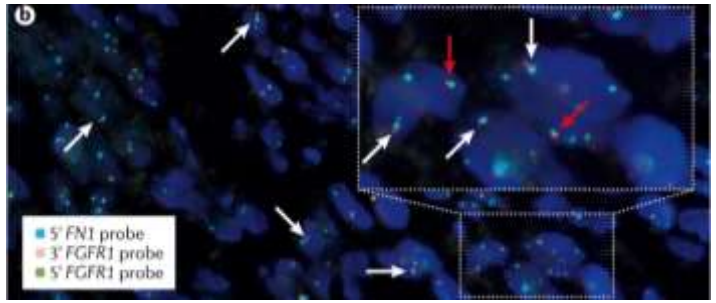
Chong, JBMR, 2013

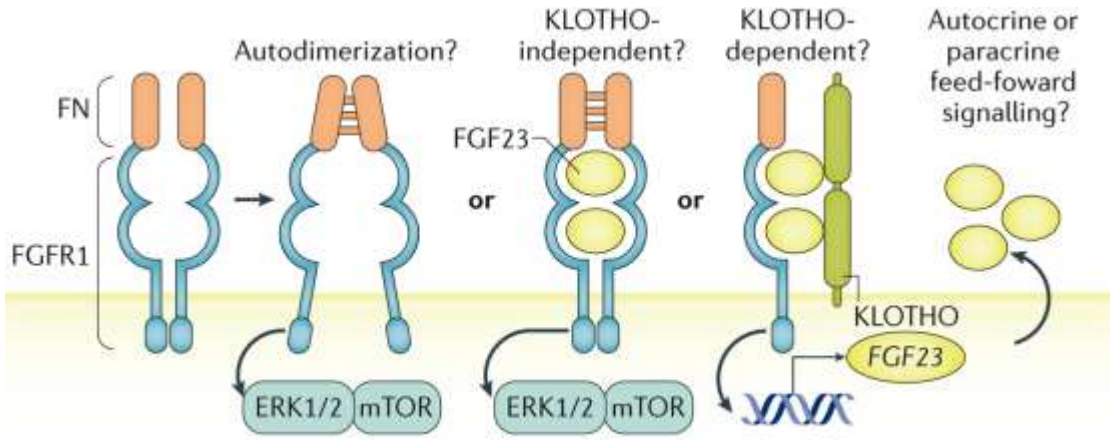
Tumor-Induced Osteomalacia



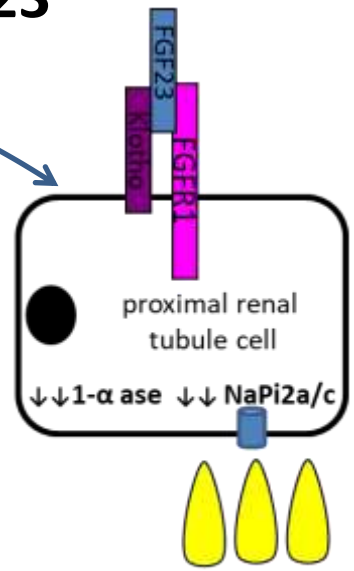
68Ga DOTA PET/CT

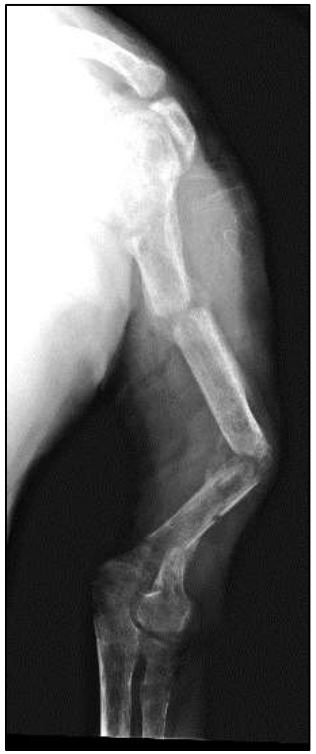
Fibronectin 1/FGFR1 translocations





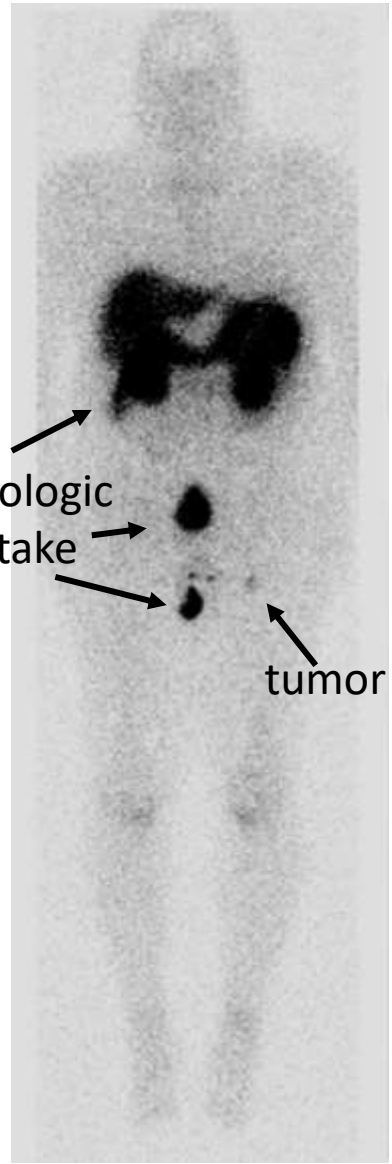
↑↑FGF23



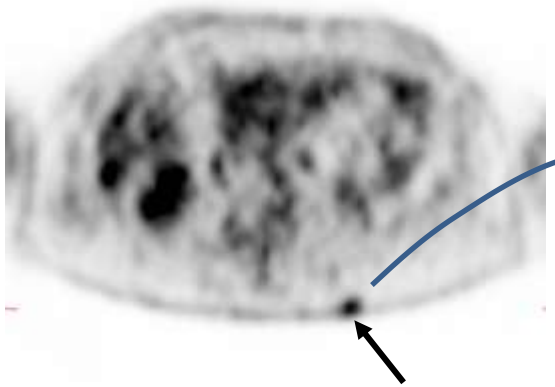


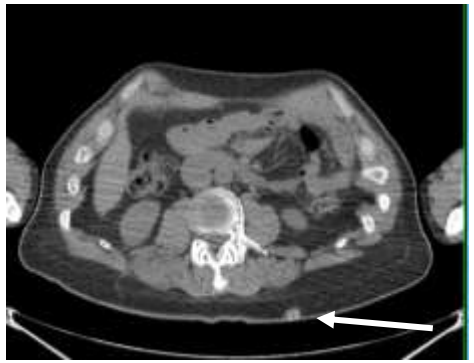
Lee JC, Mod Pathol, 2016
Minisola, *Nat. Rev. Dis. Primers, 2017*

Tumor-Induced Osteomalacia



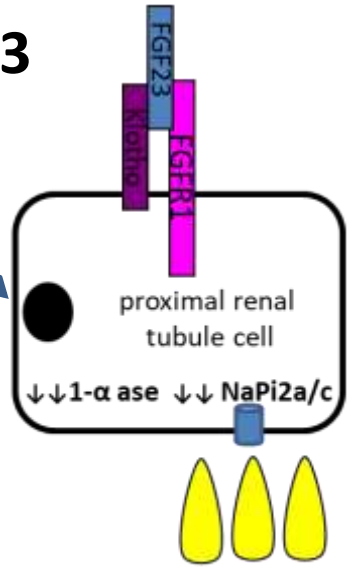
octreoscan



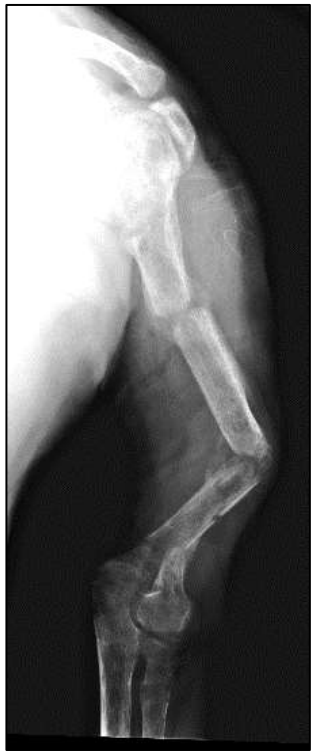


PET/CT scan

↑↑FGF23



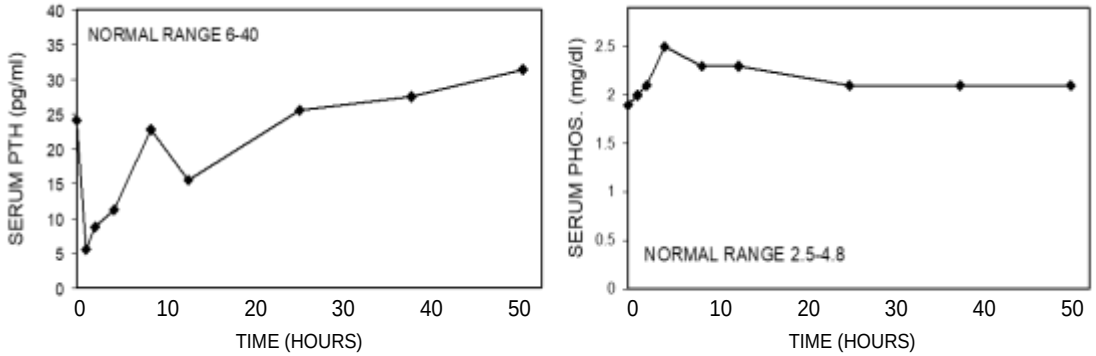
phosphate



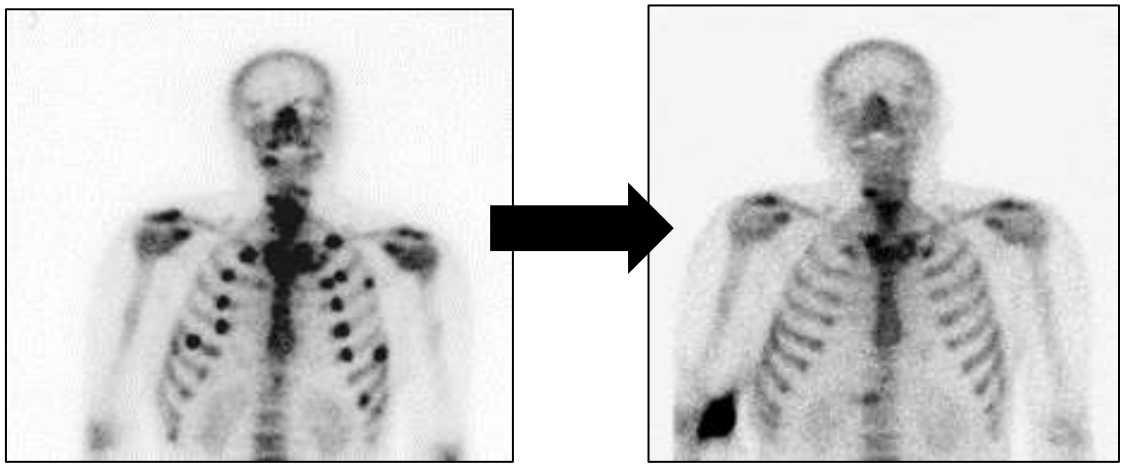
Cinacalcet Adjuvant for Treatment of TIO*

- FGF23 action is PTH-dependent
- Adjuvant to calcitriol + phosphate
- No effect on FGF23 levels
- **Cause/worsen hypercalciuria**

Cinacalcet decreases PTH, increases phosphate

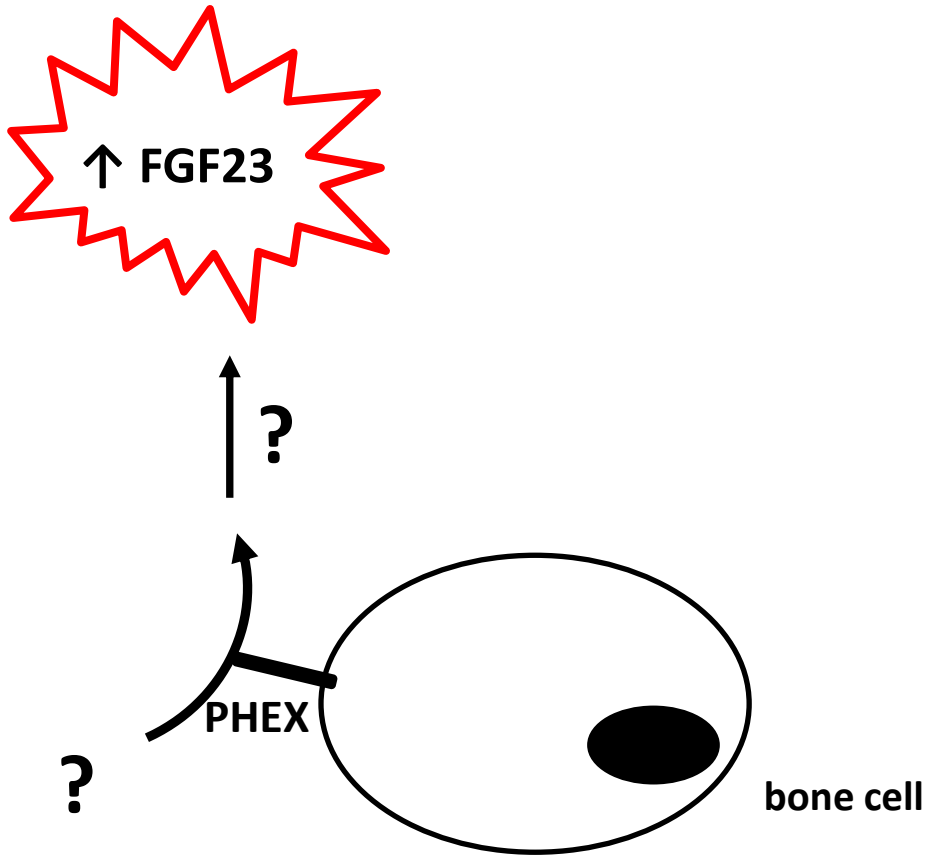


Cinacalcet heals osteomalacia



*off-label treatment

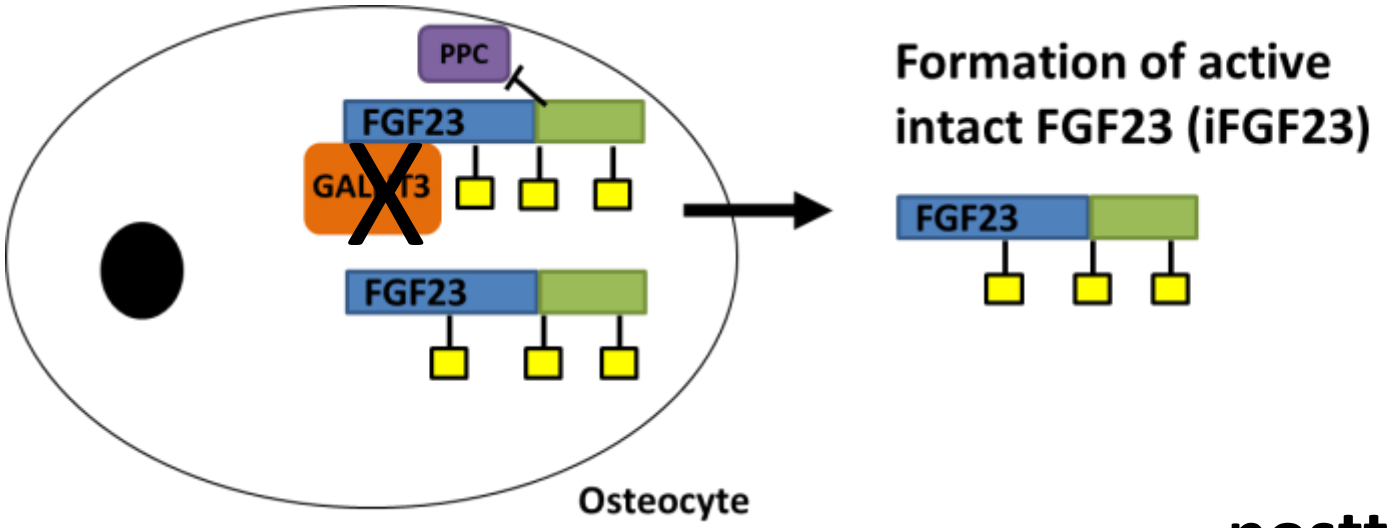
Mechanism of X-linked Hypophosphatemia



PHEX = Phosphate-regulating neutral endopeptidase, X-linked

HYP Consortium, Nat Gen, 1995

FGF23 Physiology

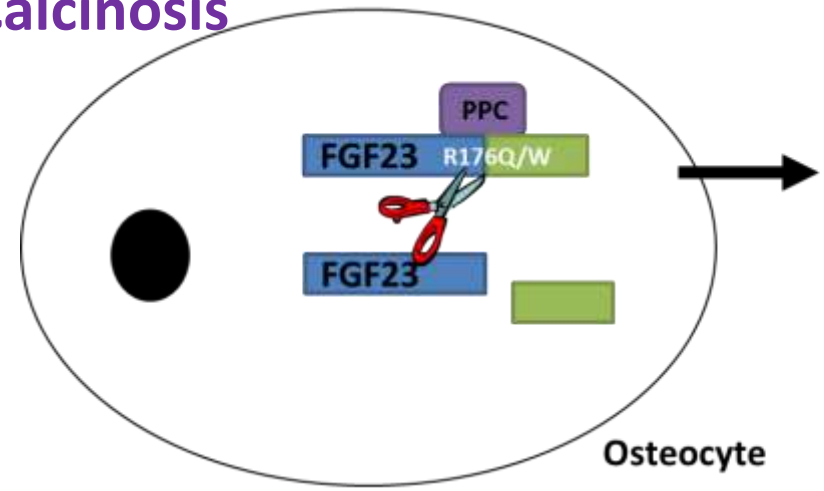


Formation of active intact FGF23 (iFGF23)

transcription and translation

posttranscription regulation

Hyperphosphatemic Tumoral Calcinosis



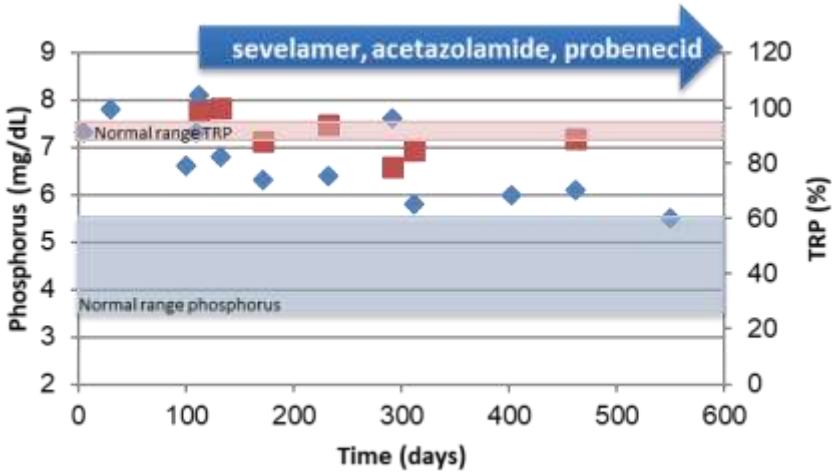
Formation of inactive or C-terminal FGF23 (cFGF23)

GALNT3 = polypeptide N-acetylgalactosaminyltransferase 3

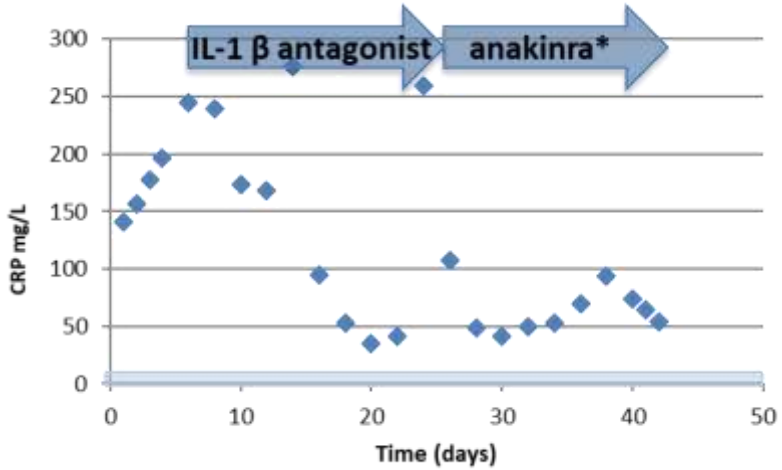
= glycosylation

PPC = proprotein convertase (furin)

Effective Treatment Responses

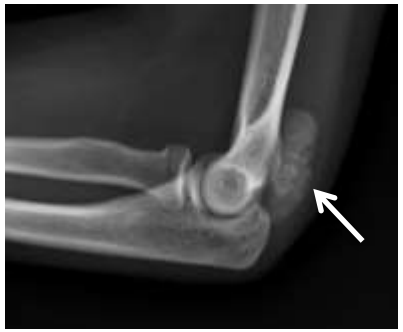


■ = TRP (%) ◆ = Phosphorus (mg/dL)

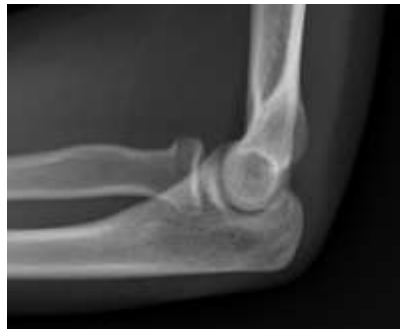


***IL-1R mAb**

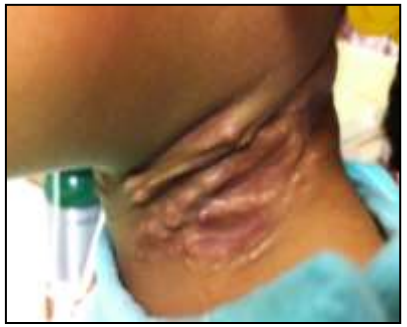
Pre-treatment



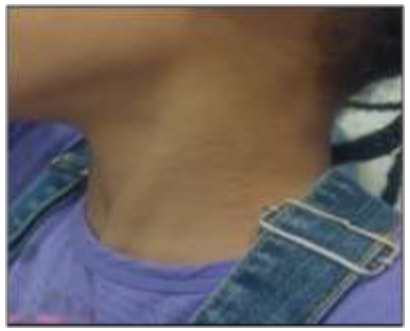
Treated



Pre-treatment



Treated



Ramnitz, JBMR 2016