Diagnosis and Treatment of Fibrous Dysplasia/McCune-Albright Syndrome

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Disclosures

The NIDCR receives support from:

Amgen for studies of denosumab in fibrous dysplasia

Ultragenyx/Kyowa Kirin for studies in fibrous dysplasia

FD/MAS is a complex skeletal and endocrine disease





Skeleton

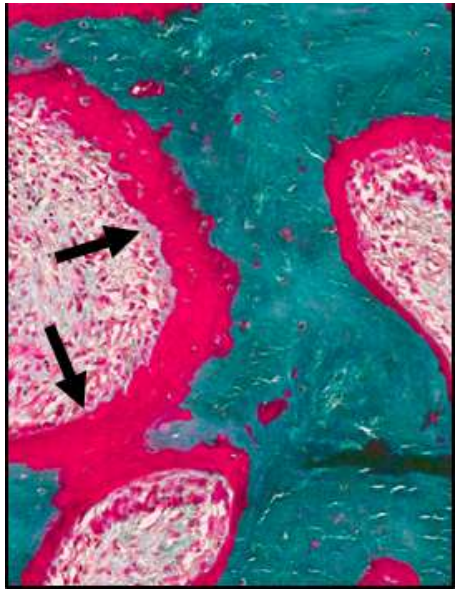
- Craniofacial
- Axial
- Appendicular

Consequences

- Deformity
- Fractures
- Pain

FD/MAS is a complex multisystem disease

Rickets

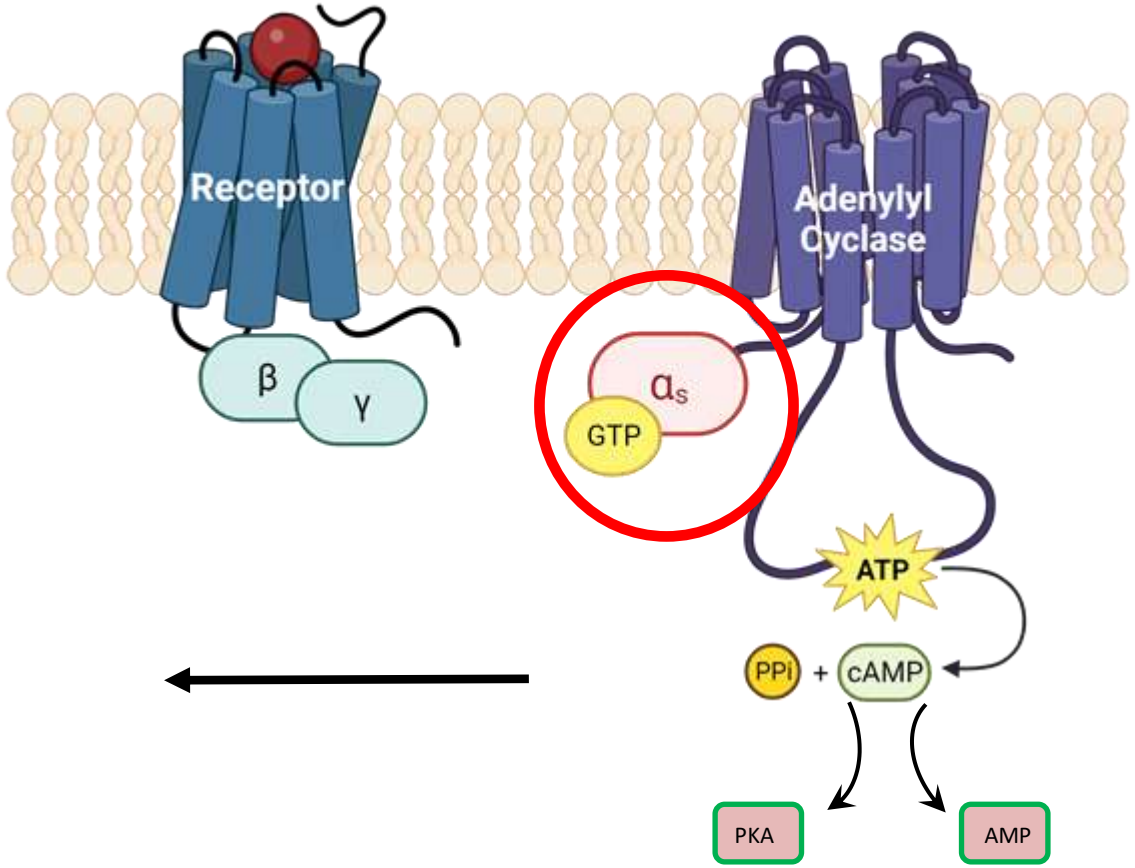


Osteomalacia

Intraductal papillary mucinous neoplasms

FD/MAS is caused by activating mutations in $G\alpha_s$ leading to ligand-independent signaling in many G-protein coupled receptors

Receptors
Melanocortin, LHCG, TSH, GHRH, etc.



Tissues
Melanocytes, Gonads, Thyroid, Pituitary, etc

Effectors
Melanin, Estradiol, Thyroxine, GH, etc

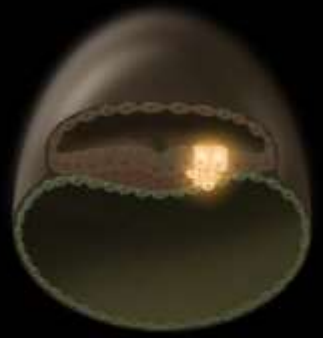
Weinstein, Shenker et al NEJM, 1991

Somatic Mosaicism Explains the Phenotype

blastocyst

Stem cell with
Gαs mutation arises

gastrula



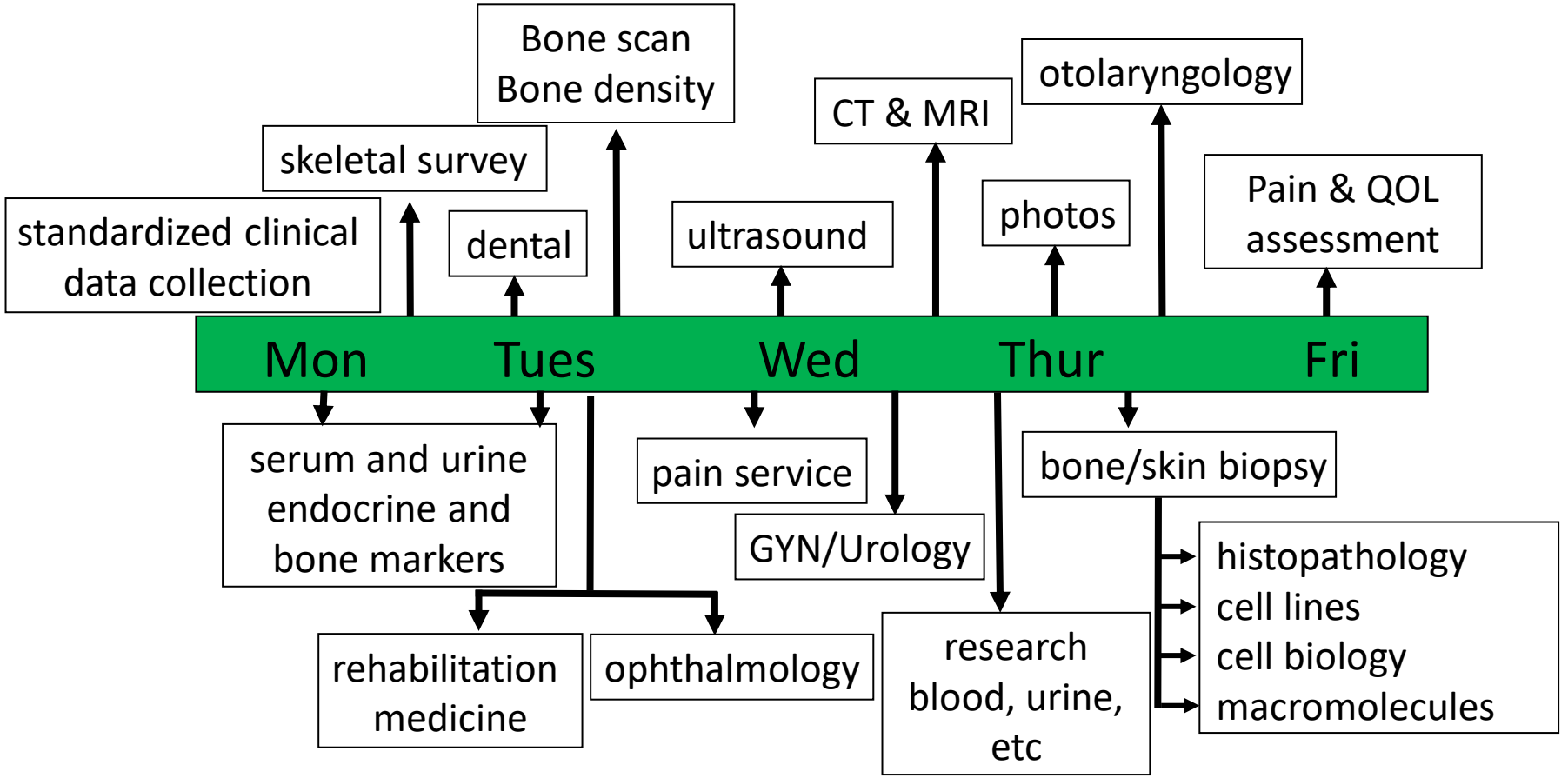
embryo

ectoderm, mesoderm, endoderm

skin – bone - thyroid

MAS: the map of affected tissues is charted in utero

NIDCR FD/MAS Study: complex disease/complex evaluation



- **25-year prospective cohort study, standardized collection of data & specimens**
- **Retrospective/prospective analyses: spectrum & natural history, standard of care**
- **312 subjects, age 1-102**

Prevalence of findings in NIH cohort

Findings	Prevalence (%)
Fibrous dysplasia	99
Café-au-lait	89
Gonads	
male (U/S or PP)	77
female (PP)	78
Thyroid	69
Phosphate wasting	48
requiring treatment	17
Growth hormone excess	18
Cushing's	7

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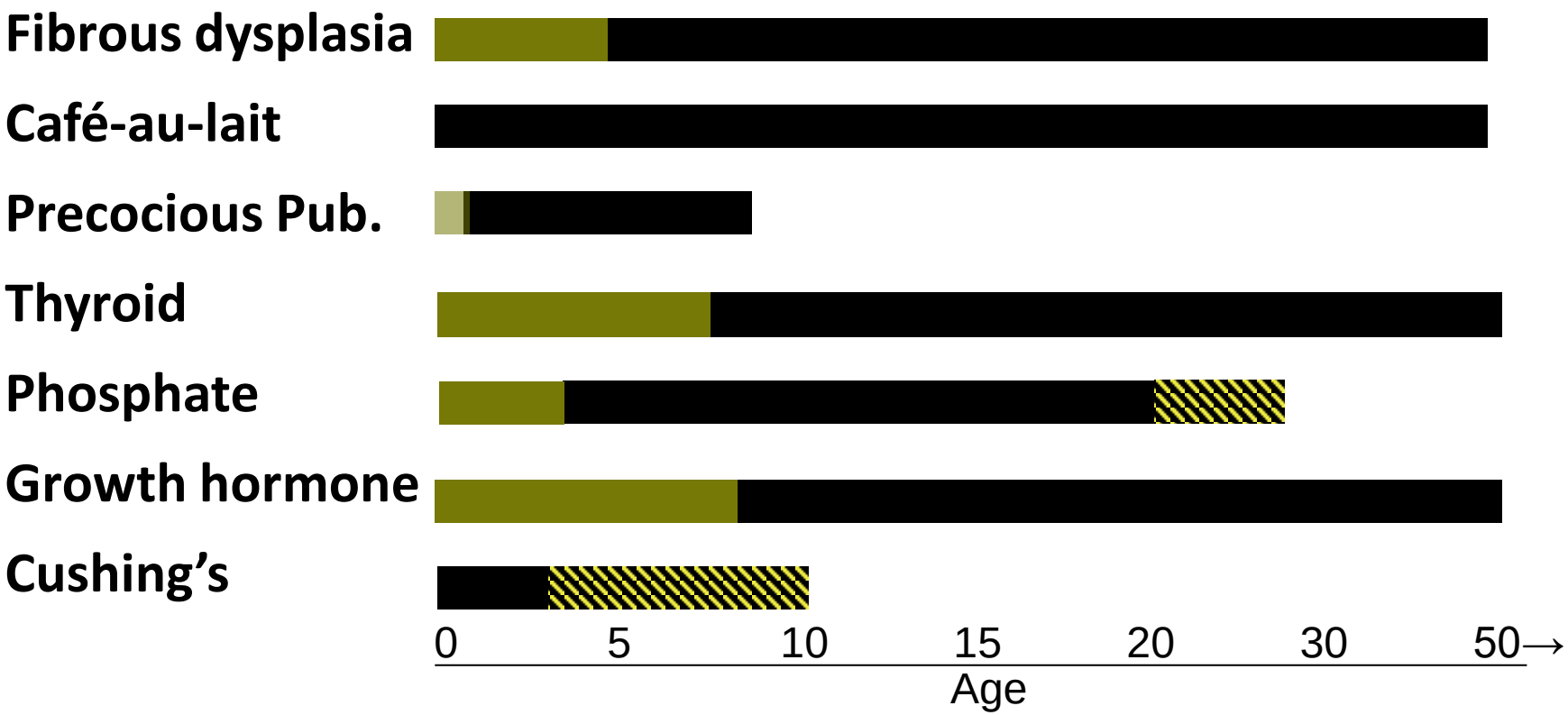
U/S = ultrasound; PP = precocious puberty

Other organs

- **GI tract**
  - **Reflux**
  - **Polyps: stomach and small bowel**
  - **Liver: hepatitis (infancy)**
  - **Pancreas (33-50%)**
- **Muscle: myxomas (Mazabraud's syndrome)**
- **Heart: tachycardia**
- **Brain:**
  - **learning deficits**
  - **ADHD-like syndrome**

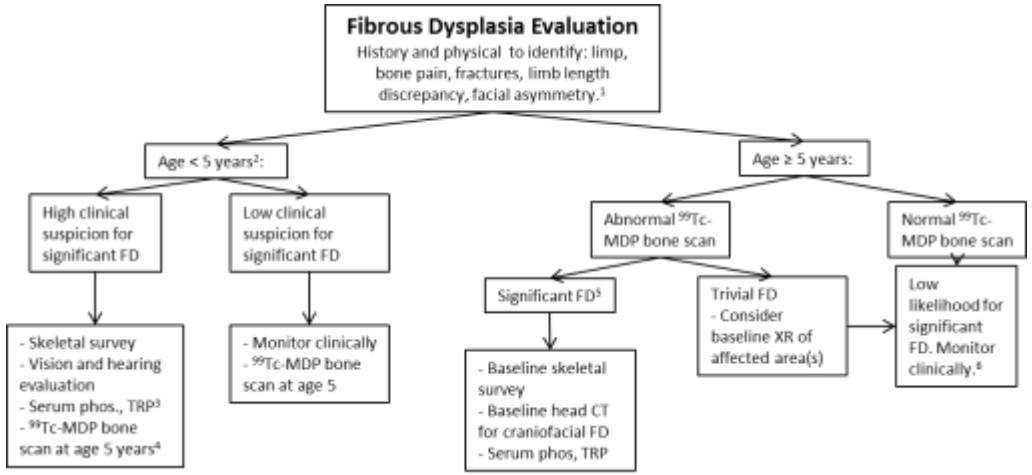
Approximate onset/offset of in affected tissues

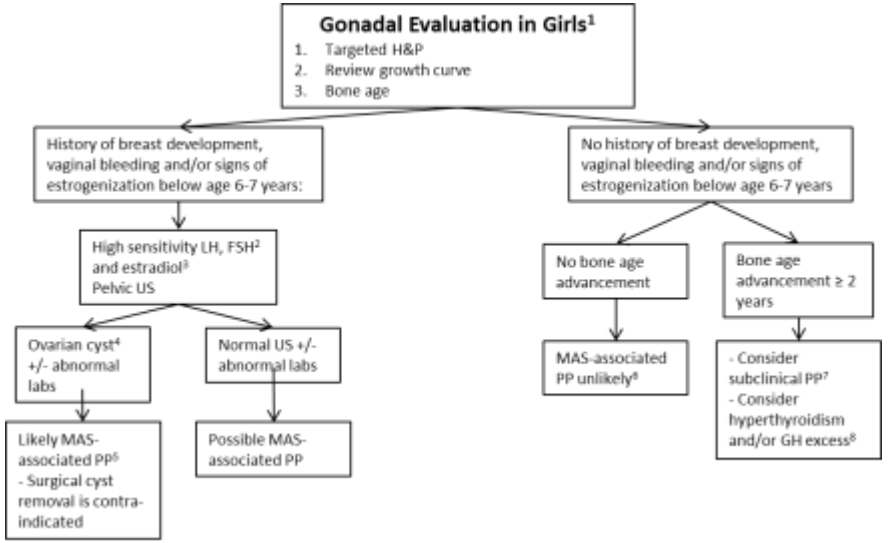


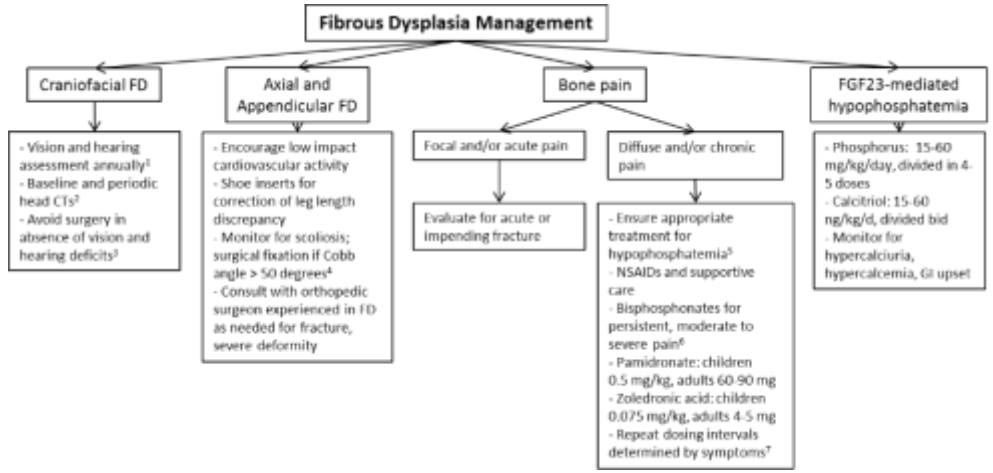
complete staging after age 5+ allows for determination of all affected and unaffected tissues

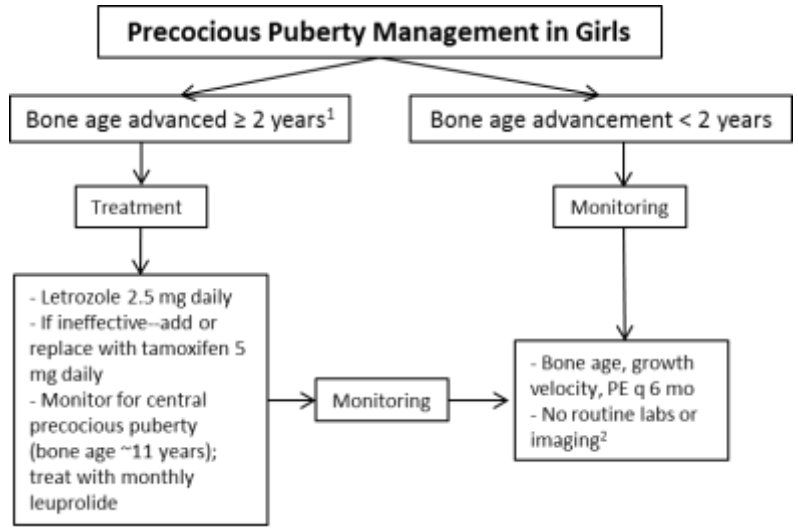
Diagnosis and Treatment of FD/MAS: NIH Algorithms

- Evidence-based and expert opinion
- Simple, user-friendly algorithms
- Distillation of 57 publications
- Expanded in 2019, 85 publications



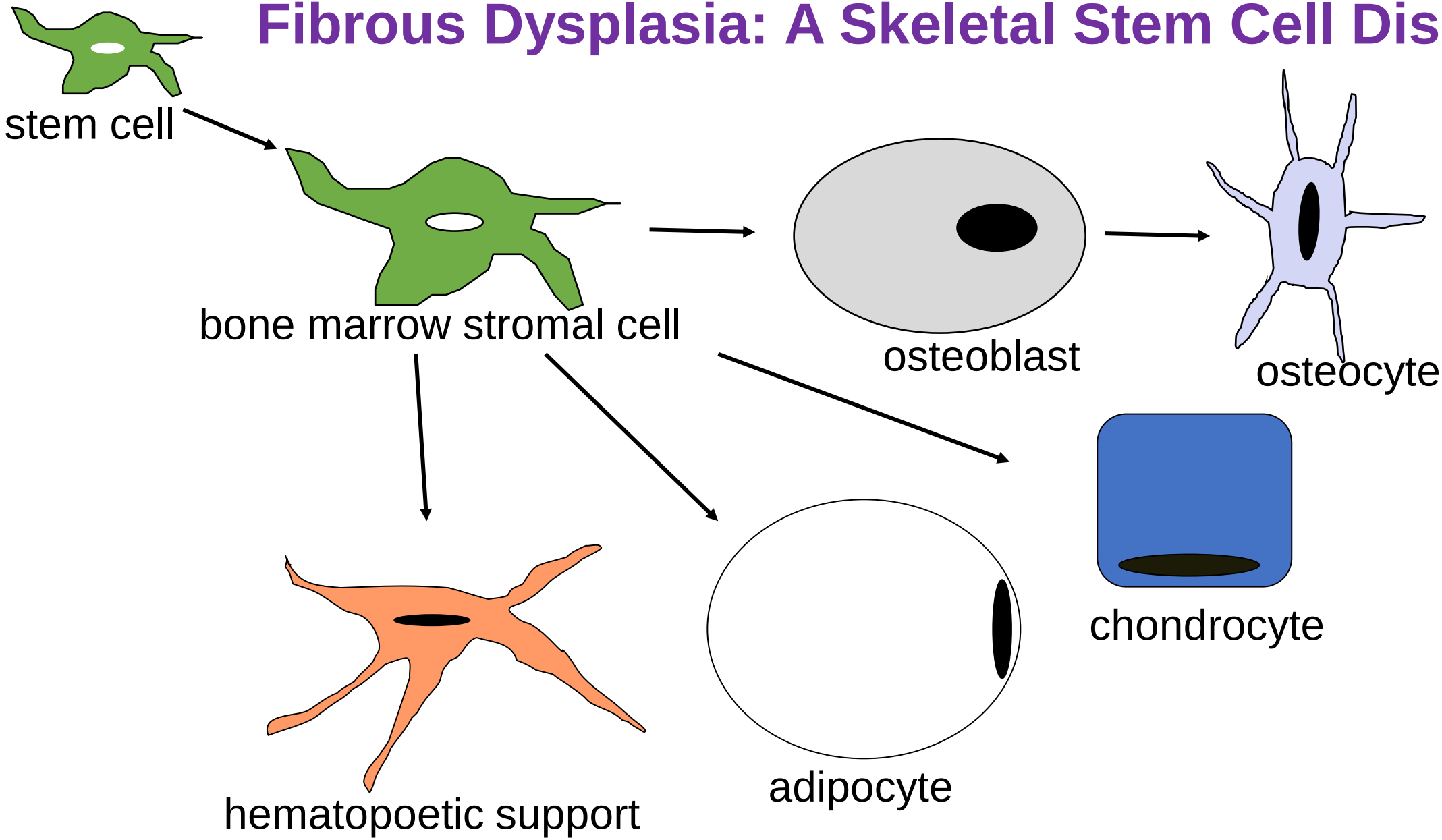




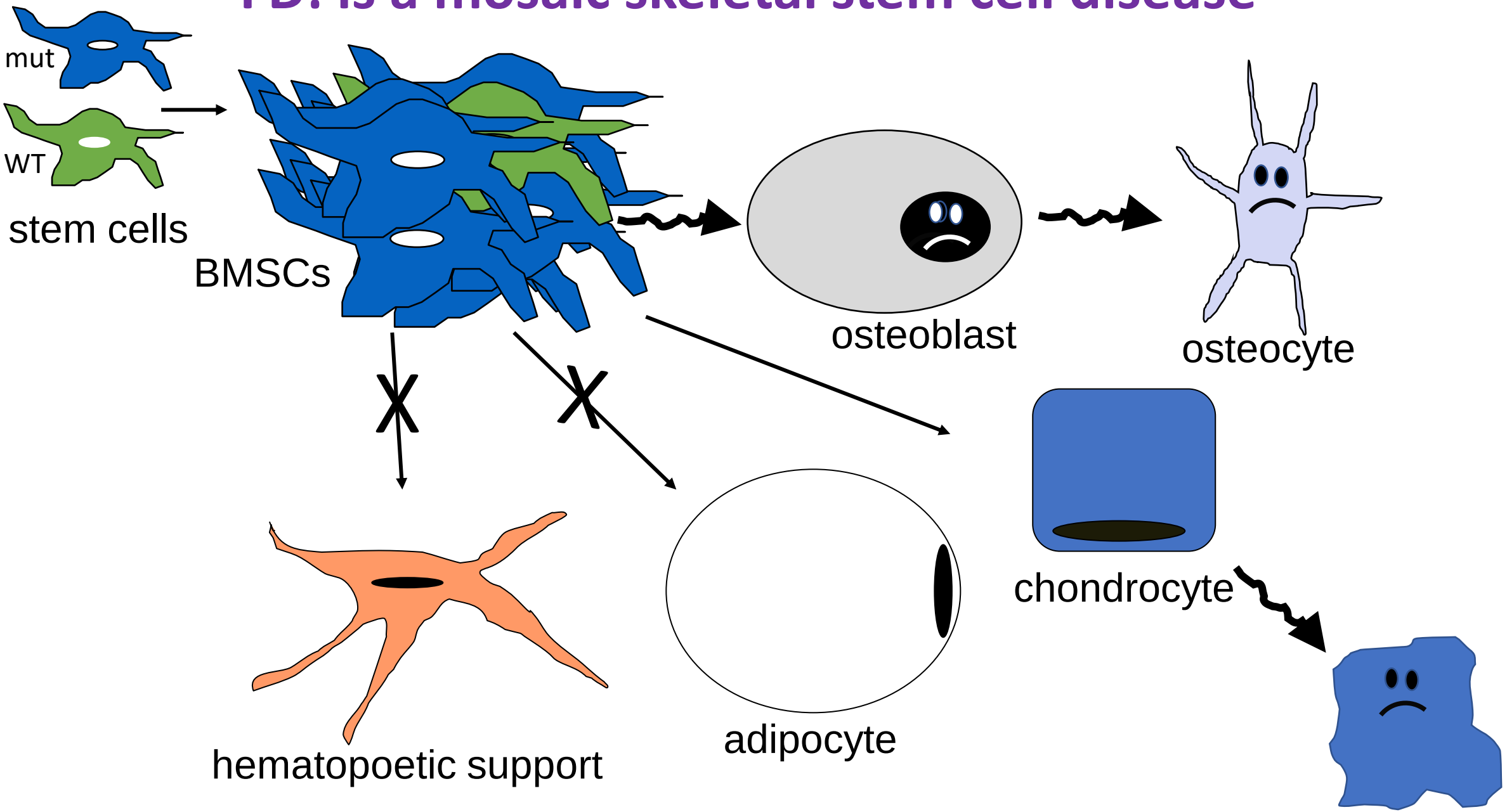


Boyce…Collins, GeneReviews 2015, updated 2019

Fibrous Dysplasia: A Skeletal Stem Cell Disease

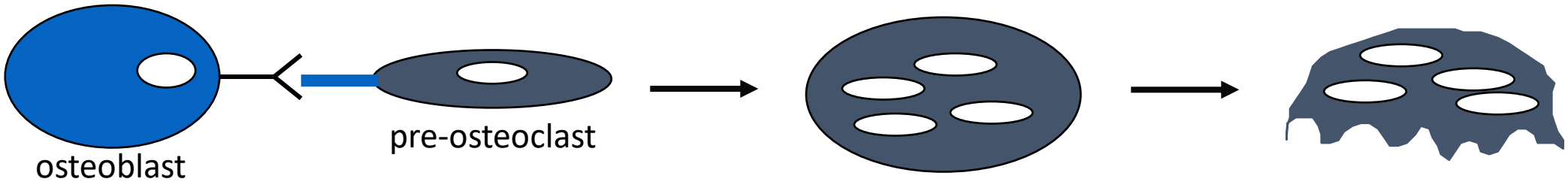


FD: is a mosaic skeletal stem cell disease



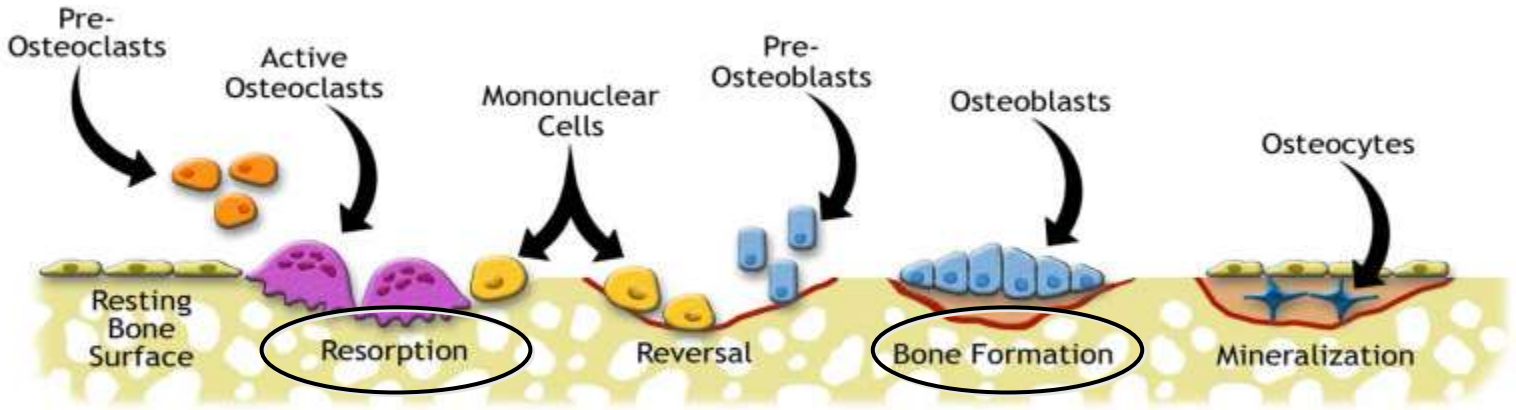
Riminucci, AJP 1997; Riminucci, JP 1999; Bianco, JBMR 2000, Collins, JBMR 2001

Bone Physiology – Remodeling Cycle – Disrupted in FD



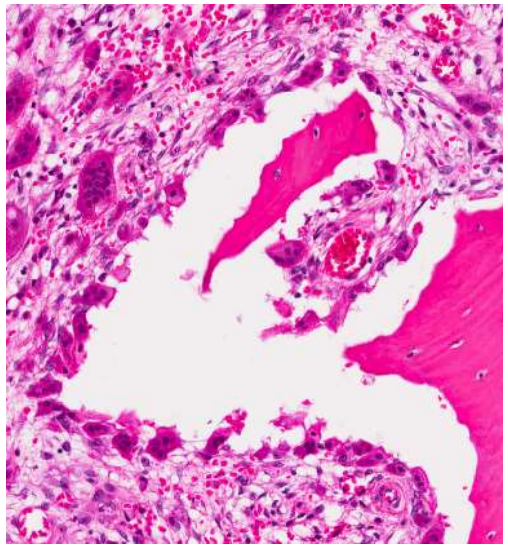
RANK

RANKL

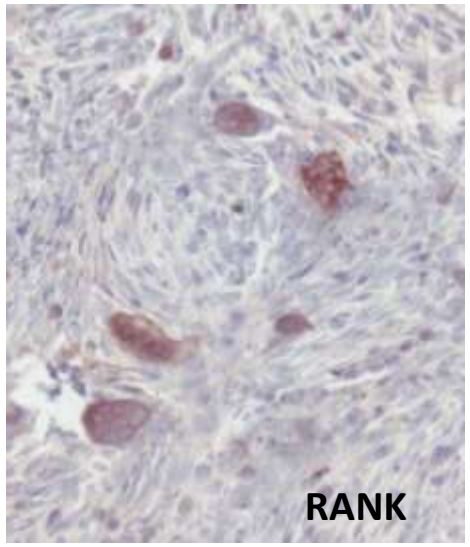


Bone Resorption and Formation are coupled processes

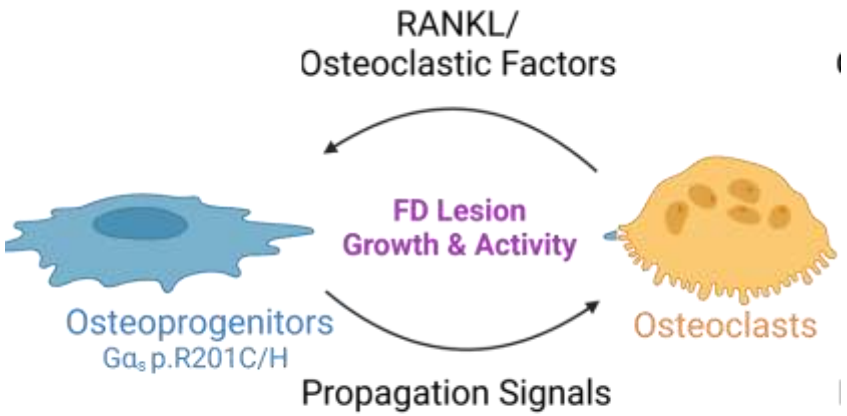
RANK/RANKL-mediated osteoclastogenesis in the pathogenesis of FD



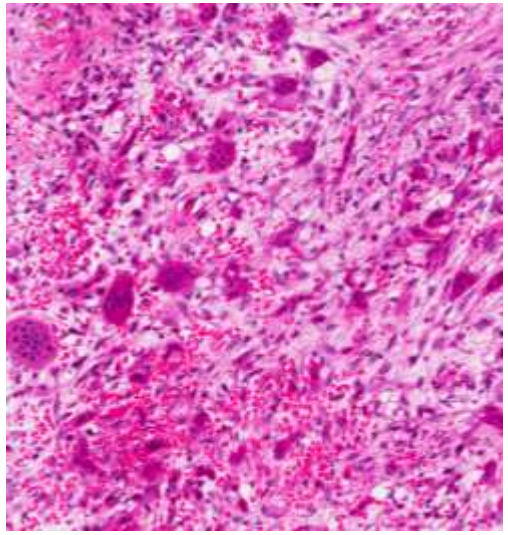
osteoclast osteolysis



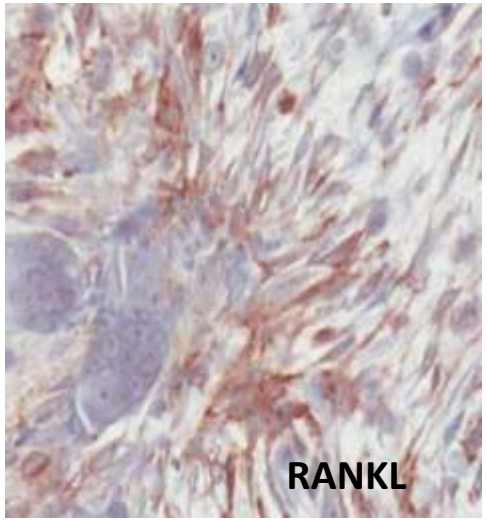
RANK/RANKL-mediated

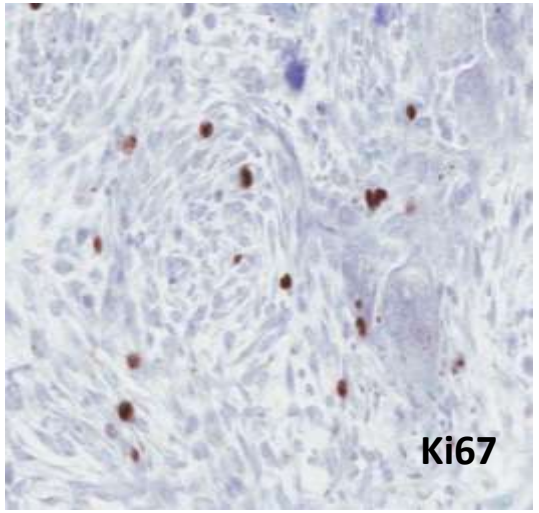


de Castro Bone Res, 2024



osteoclasts without resorption

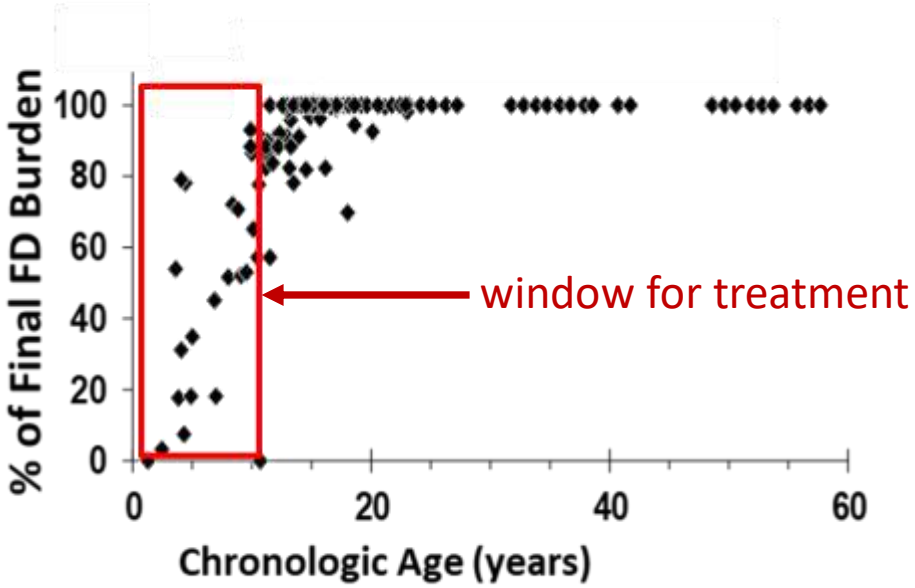




OCs in highly proliferative regions

FD Has an Age-related Phenotype

FD lesions are established in childhood & adolescence

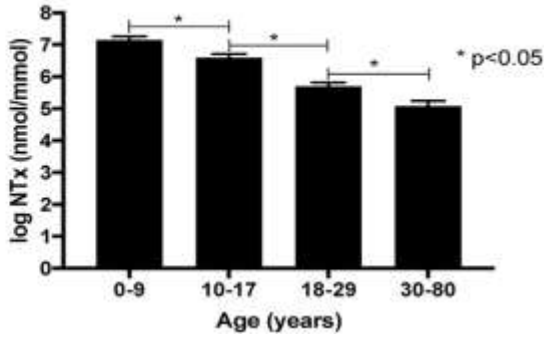


Age	Total FD present
5.7	50%
10.7	75%
15.0	90%

Collins, JBMR 2005; Hart, JBMR 2007

FD lesion activity decreases in adulthood

Decline in bone turnover markers



Florenzano JBMR 2019

Partial normalization of histology in patients >35 years

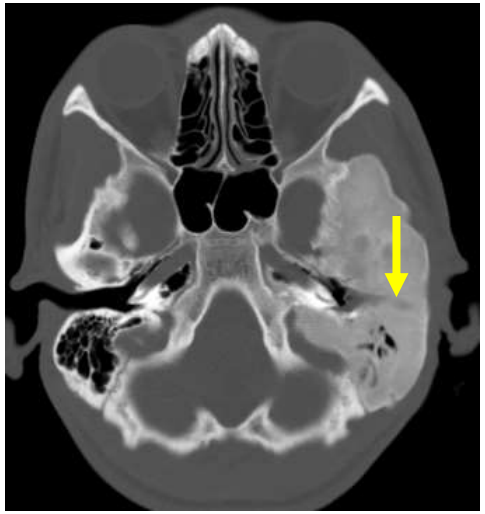
Kuznetsove JBMR 2008;; Szymczuk, JBMR 2022

Clinical sequelae – Craniofacial FD

nasal obstruction

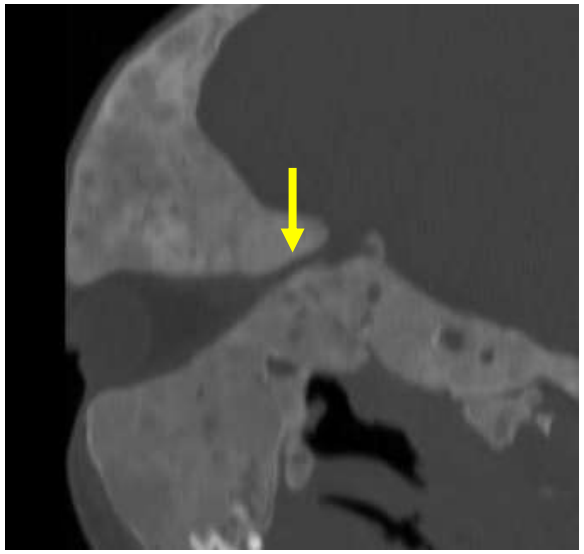
malocclusion

hearing impairment

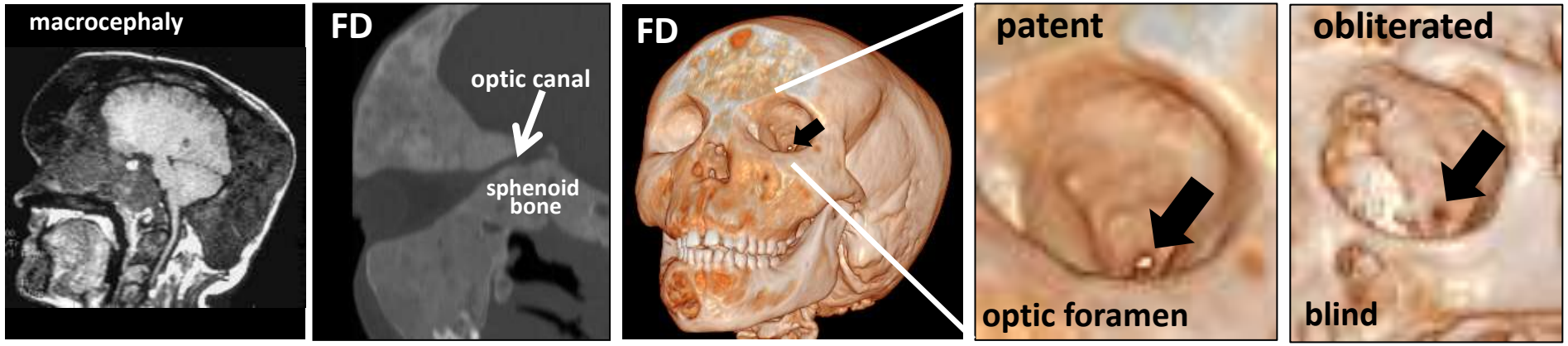


facial asymmetry

visual changes



Management of Skull-Based FD



Prophylactic optic nerve decompression is not indicated

Lee, NEJM, 2002 (n=38)

⬇

Watchful waiting is superior to surgery (meta-analysis)

Amit, PLos ONE 2011

⬇

GH excess is a risk factors for vision loss

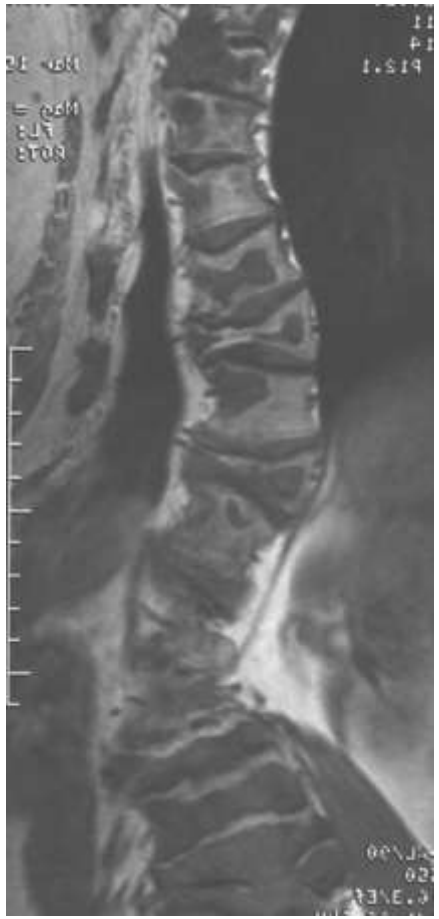
Cutler, Neurosurgery, 2006

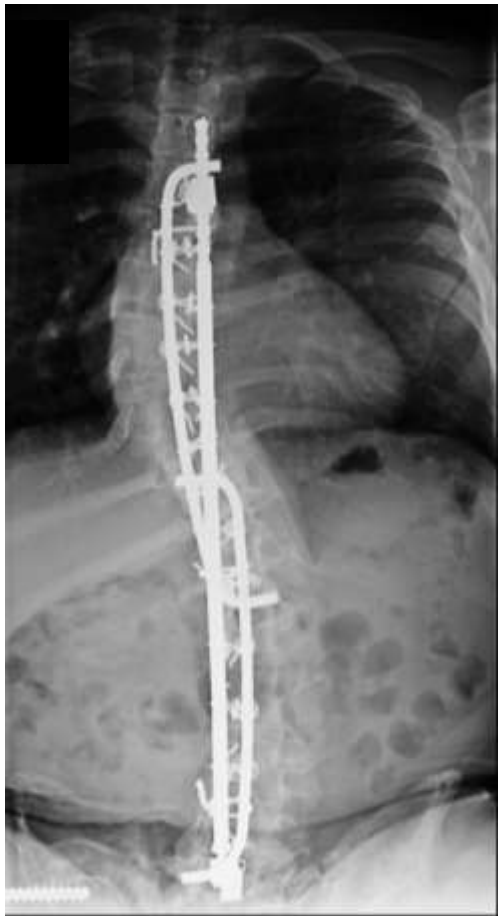
⬇

Early diagnosis & treatment of GH excess prevents vision loss

Boyce, JCEM, 2015

Axial Fibrous Dysplasia – Scoliosis





Common – Can be progressive and potentially lethal
Durable response to surgery

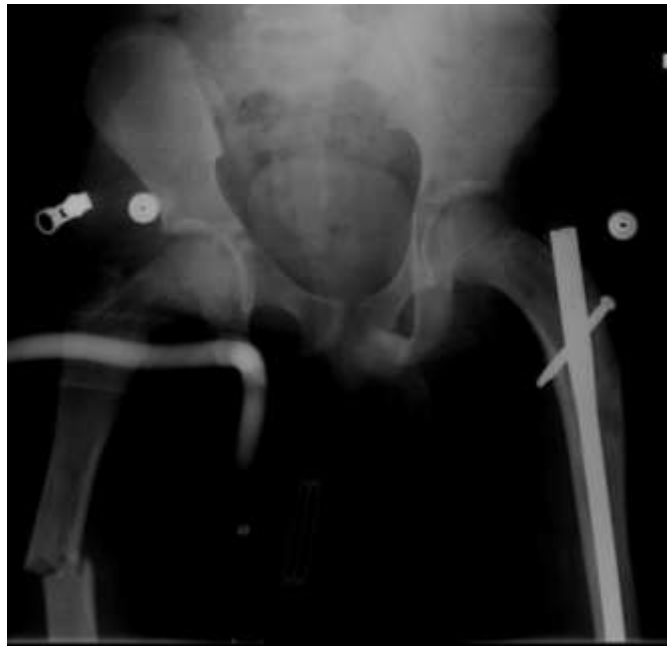
Appendicular Skeleton - Clinical sequelae

Deformity, Pain, Limp, Fractures, Disability

wind-swept deformity

shepherd's crook ground glass

normal



fragility fractures

Surgical management of appendicular FD

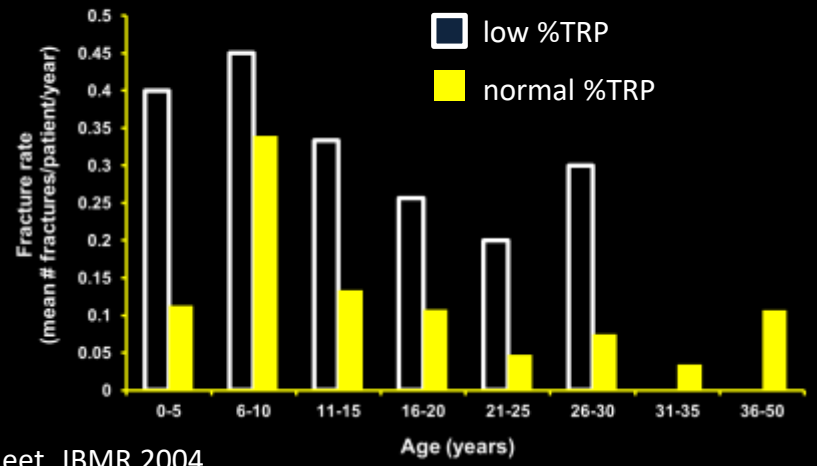
- **Surgical indications:**
  - **weight-bearing pain,**
  - **deformity that impairs gate**
- **Curettage & grafting futile**
- **Intramedullary rods superior**
- **Operate neck angle <110˚**

normal femoral neck shaft angle

Leet, JBJS, 2016

Endocrinopathies Increase Skeletal Morbidity in Fibrous Dysplasia

Hypophosphatemia: Fractures



Leet, JBMR 2004
N=35

Hyperthyroidism, Hypophosphatemia: Basilar Invagination

Pan, JBMR 2018
N=158

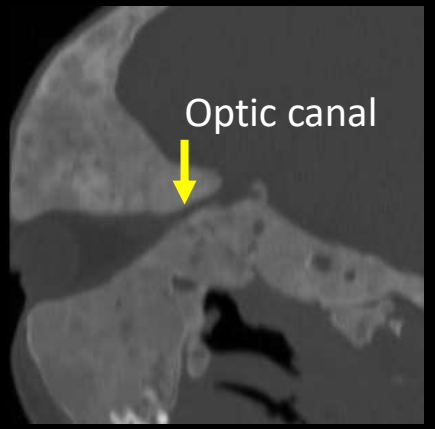
Normal skull base

FD: Displaced cervical vertebrae

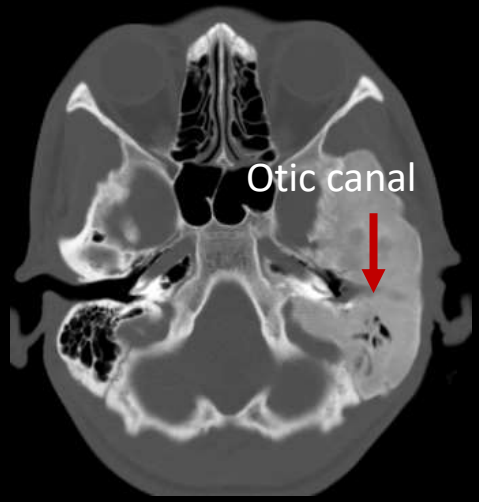
Hyperthyroidism, Hypophosphatemia: Scoliosis

Berglund, JBMR 2018
N=138

GH Excess: Vision loss, Hearing loss



Amit, PLOS One 2011
N=122



Boyce, JAMA-Oto 2017
N=130

Pain: Prevalence and Treatment

	Adults (n=35)		Children (n=43)	
Mean Pain Scores				
Prevalence	81%		49%	
Average Pain	**4.1 ***		2.8	
Treatments in subjects reporting pain:	% that used treatment	% relief reported	% that used treatment	% relief reported
No treatment	26%		**44%**	
NSAIDs	57%	56%	56%	50%
Bisphosphonates	26%	73%	17%	75%
Alternative Treatments	17%	52%	11%	No report

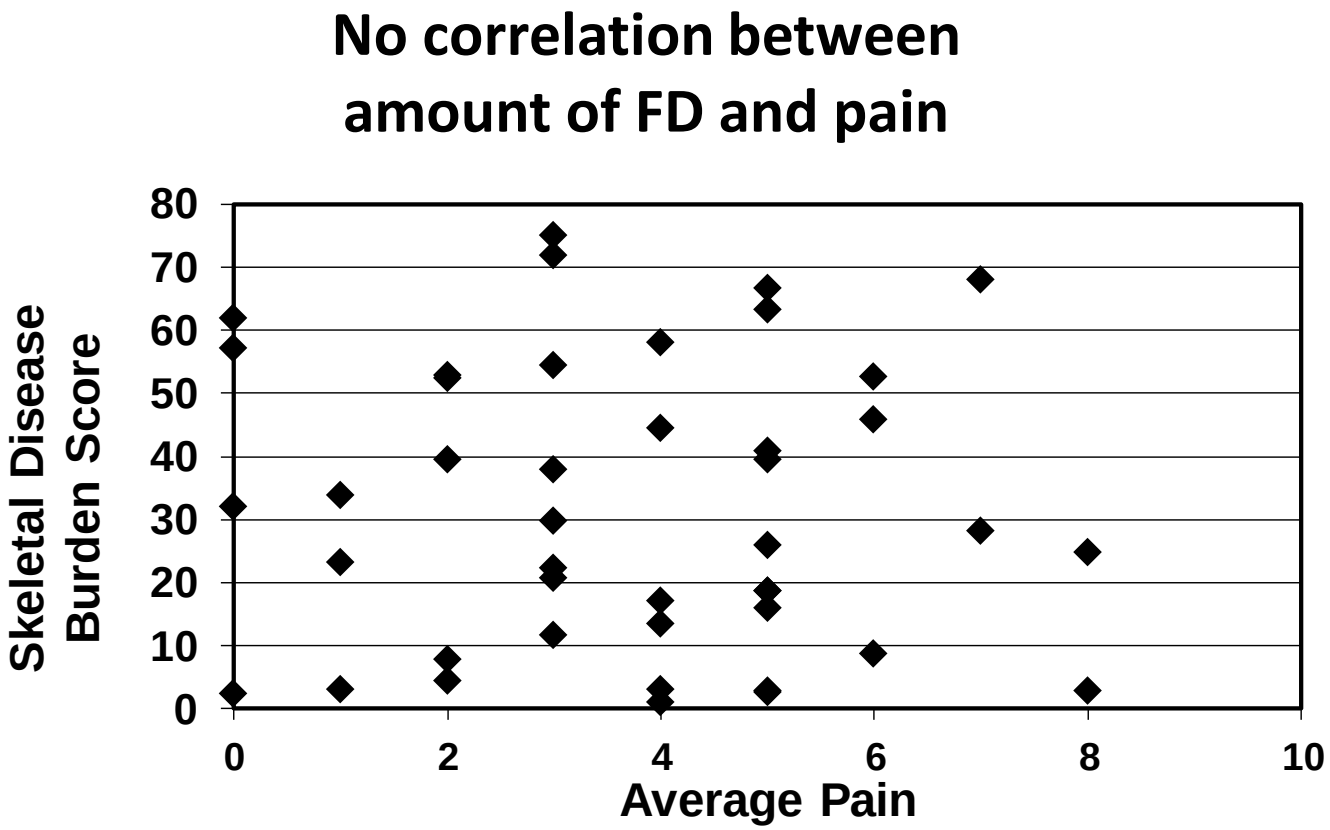
Kelly, Osteoporosis Int, 2008

Age-related increase in pain

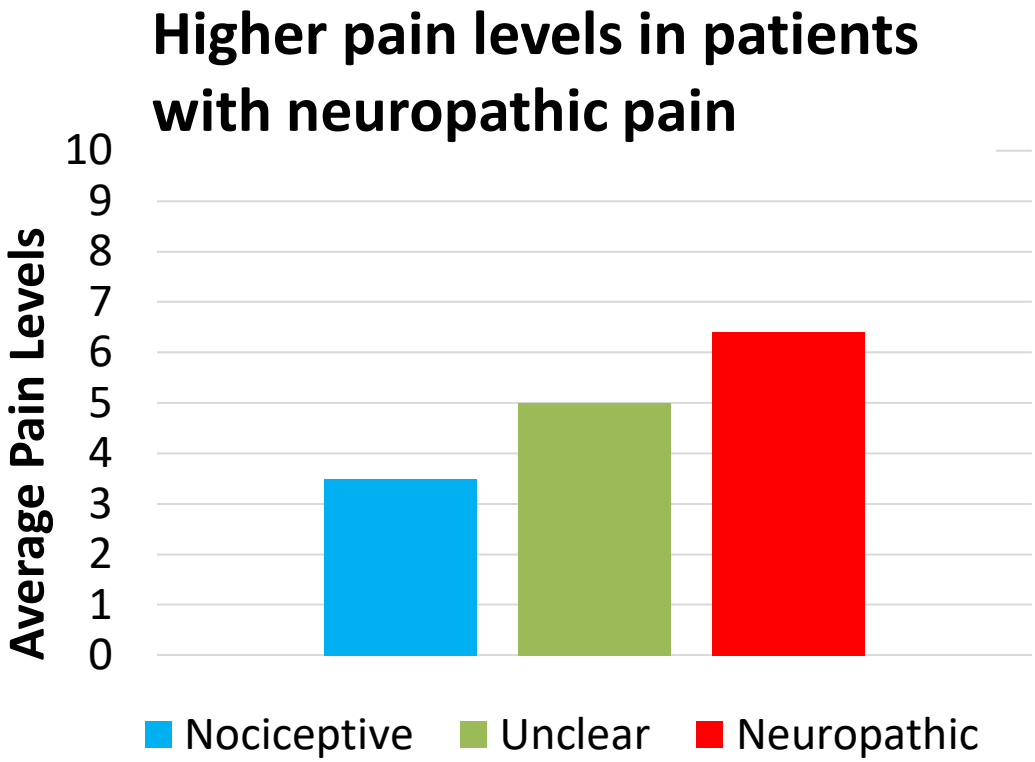
Pain is undertreated in children

Bisphosphonates have good efficacy

Pain and FD



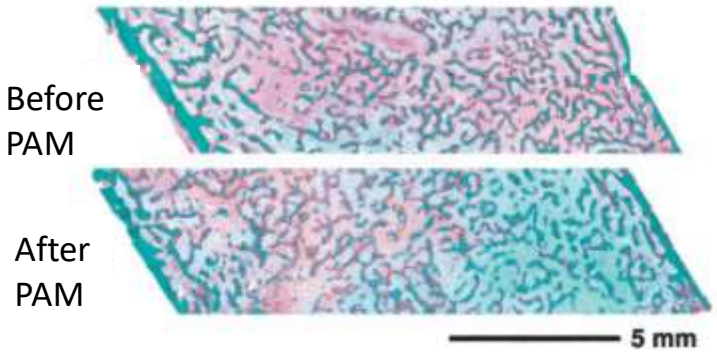
Kelly, Osteoporosis Int, 2007



Spencer, JCEM, 2022

Bisphosphonates in FD

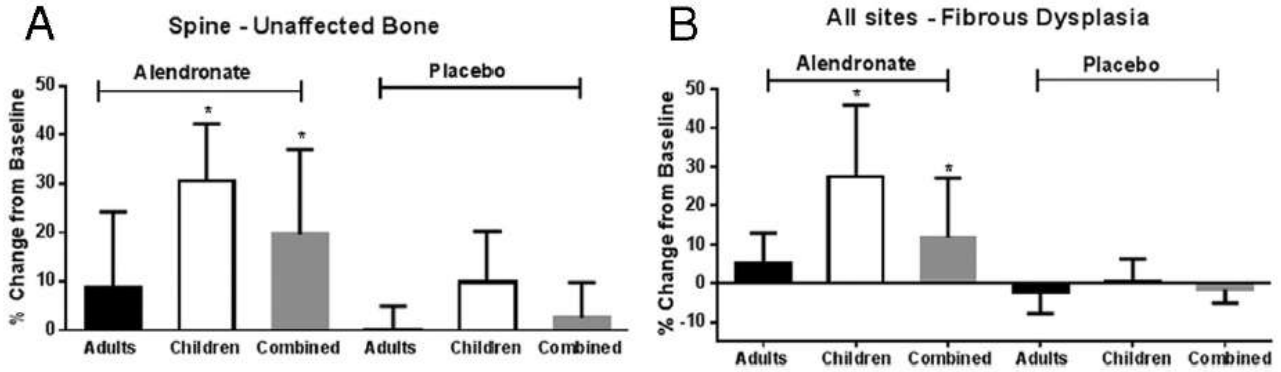
No effect on histology or histomorphometry of FD lesions



IV pamidronate; open label; 18 patients; age 4-17 yr; treated 1-9 yr

Plotkin, JCEM 2003

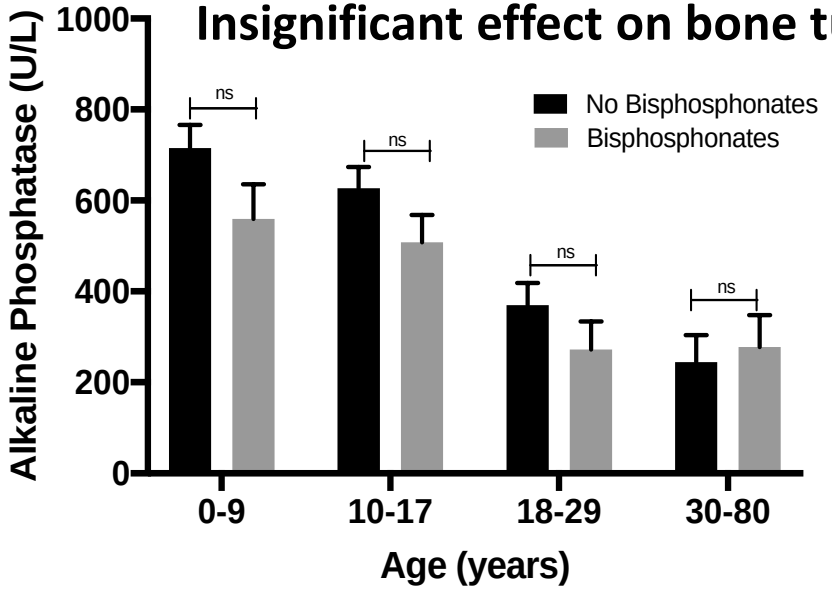
Increased density on DXA



Oral high dose alendronate; Placebo controlled; 36 pt; treated 24 mo;
No effect on pain; BMD effect only in children

Boyce, JCEM 2012

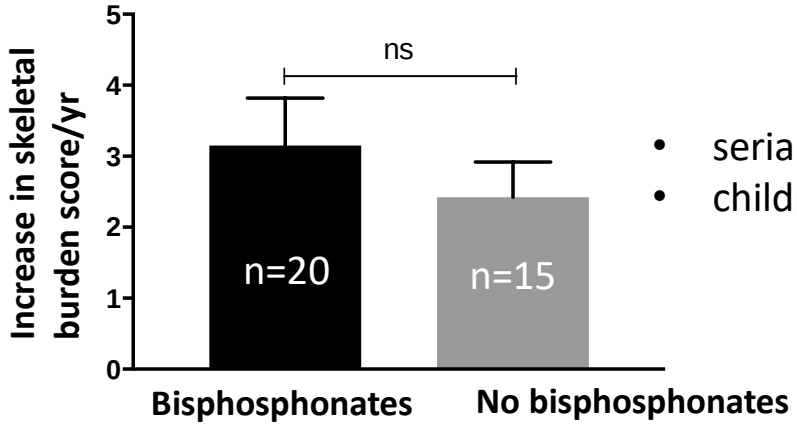
Insignificant effect on bone turnover markers



- Retrospective;
- Open label
- Matched controls
- Treated/untreated
- Did not prevent lesions

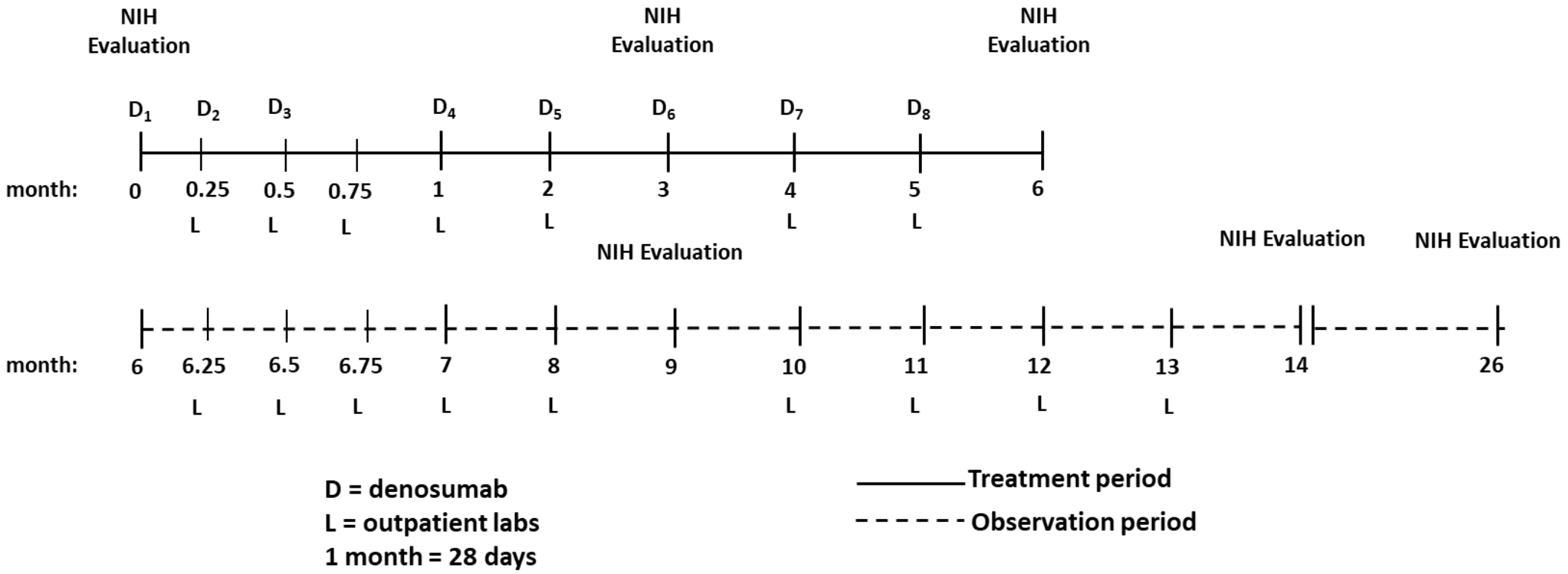
Florenzano, JBMR 2019

No difference in FD lesion formation or expansion



- serial bone scans
- children ≤ age 15

Phase 2 Study, High Dose Denosumab in Adults with FD (NCT03571191)



Primary endpoint: Bone turnover markers (P1NP, CTX)

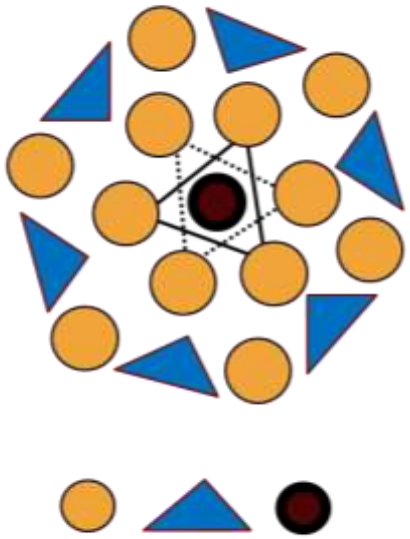
Secondary endpoints: lesion activity (18F NaF PET/CT), pain & function, FD bone biopsies

deCastro et al NEJM 2023

18F NaF PET/CT quantification of mineralizing tissues

Repurposing an old tracer for metabolic bone disease

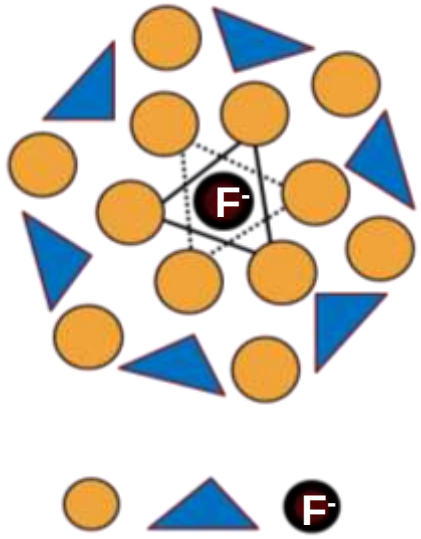
Hydroxyapatite



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

97% of enamel
70% of bone

Fluorapatite



Basis for
^{18}F NaF PET/CT scans

CT
Hounsfield Units, HU

PET
Standardized Uptake Values, SUV

CT

CT/PET
Fusion

CT = relative bone density

PET = metabolic activity

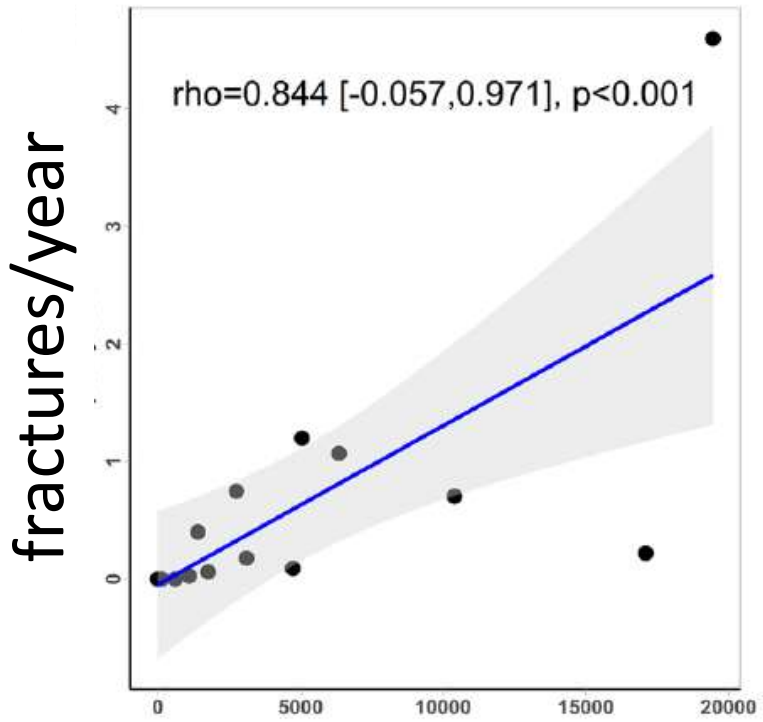
18F NaF PET/CT to Quantify Burden/Outcomes in FD

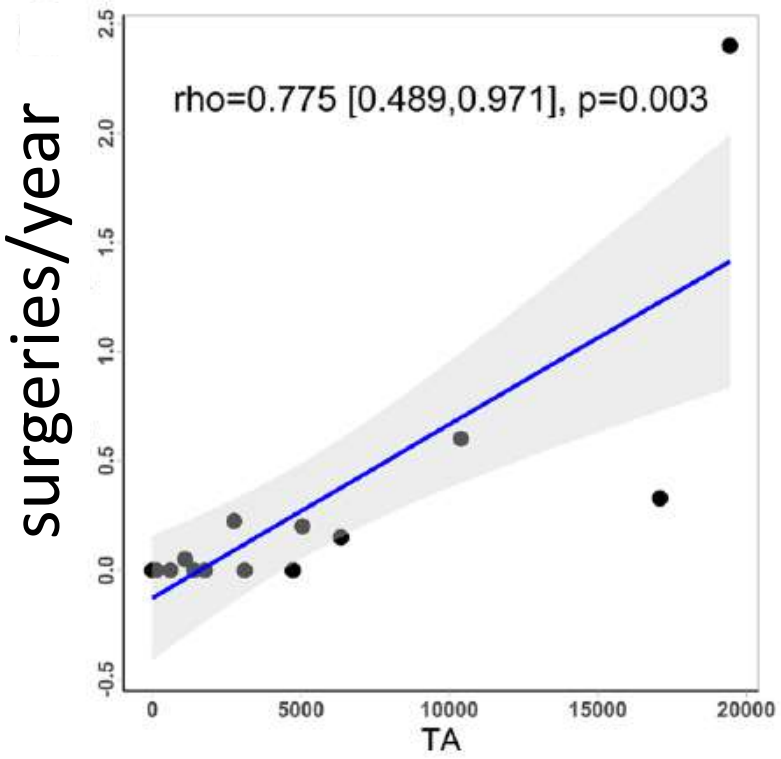
fibrous dysplasia

PET

metabolic activity
(SUV)

metabolic activity and FD volume
correlate with clinical outcomes in FD

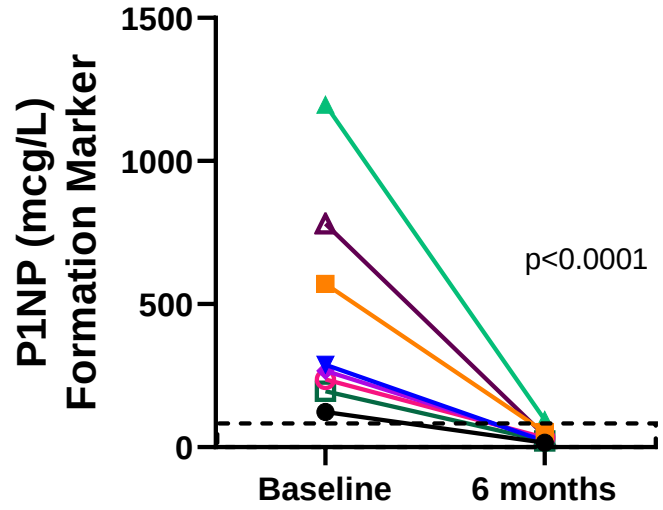


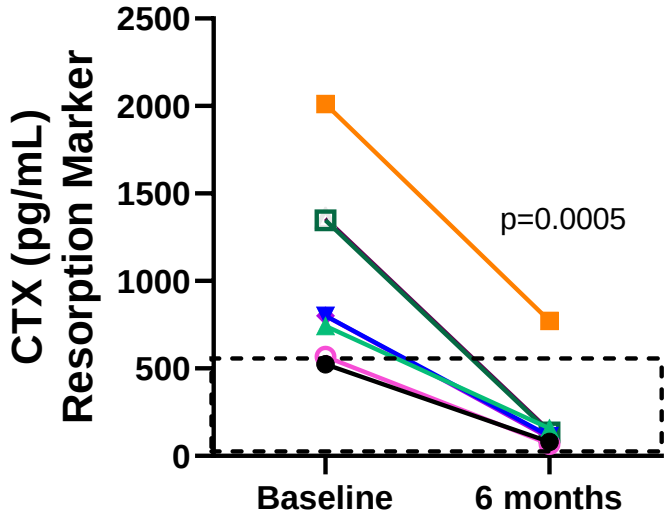


Papadakis JBMR 2019

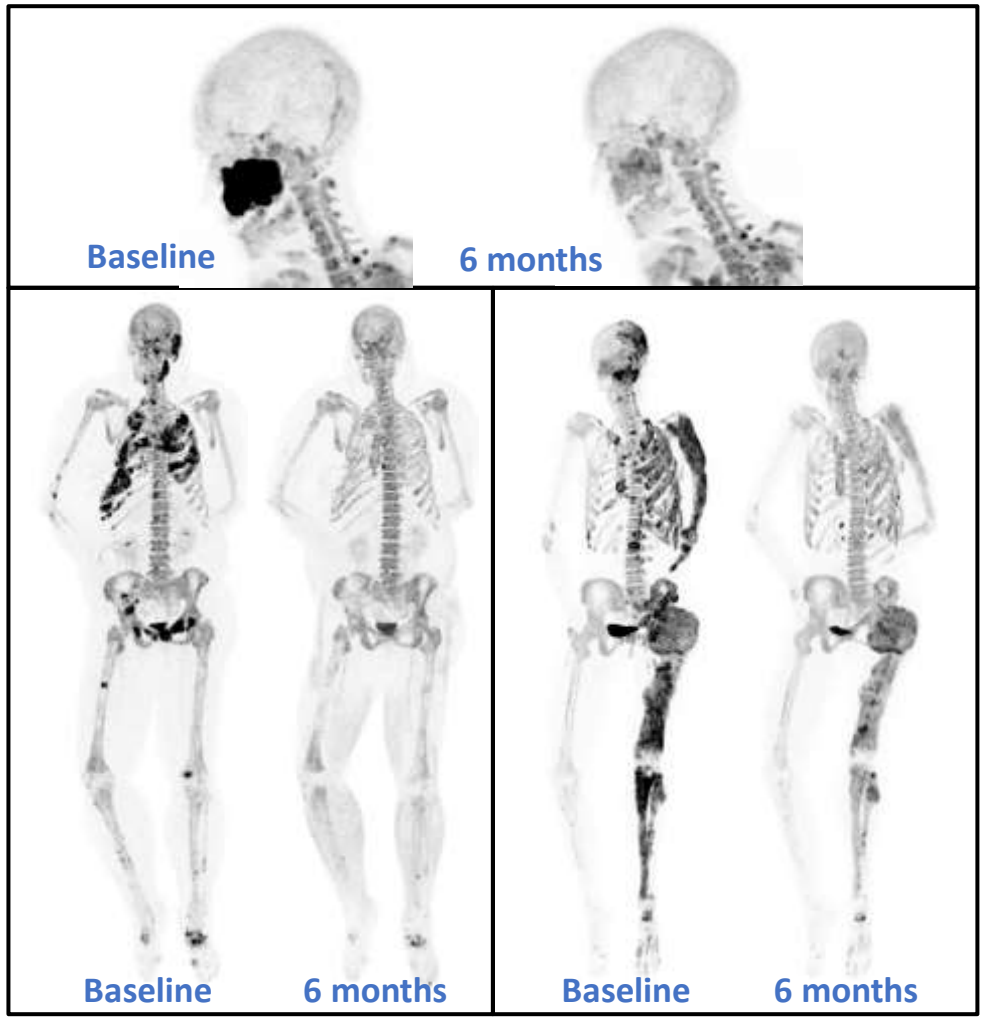
Denosumab Reduced FD Lesion Activity

Bone Turnover Markers





^{18}F-NaF PET/CT

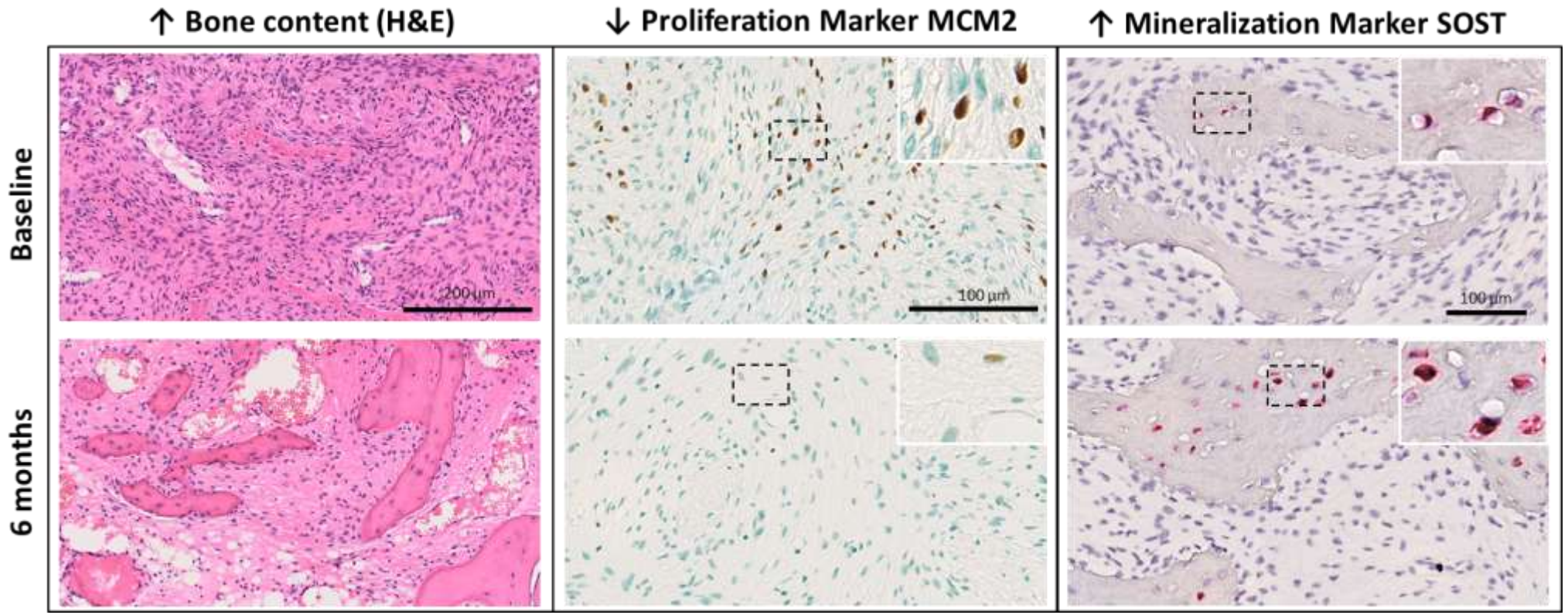


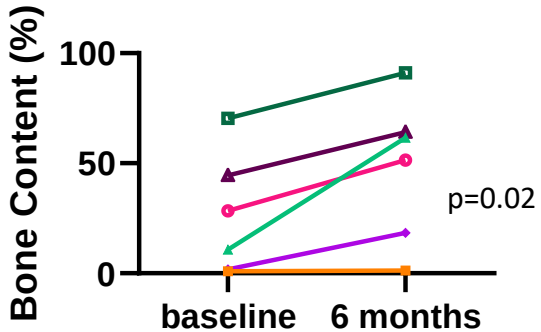
Improvements in pain & physical function

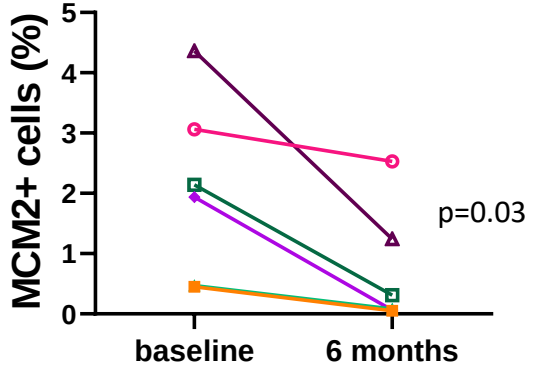
de Castro et al, NEJM 2023

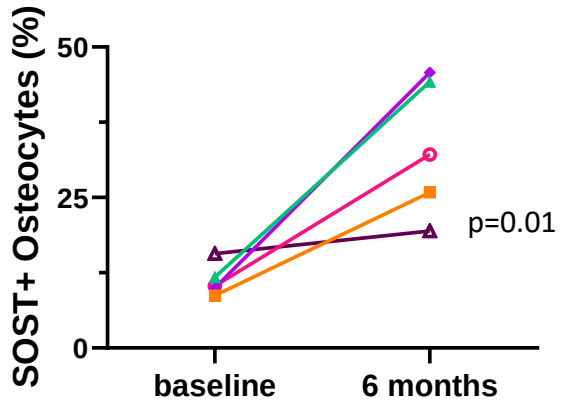
Denosumab Reduced FD Cell Proliferation & Increased Mineralization

Pre- and post-treatment, same site biopsies



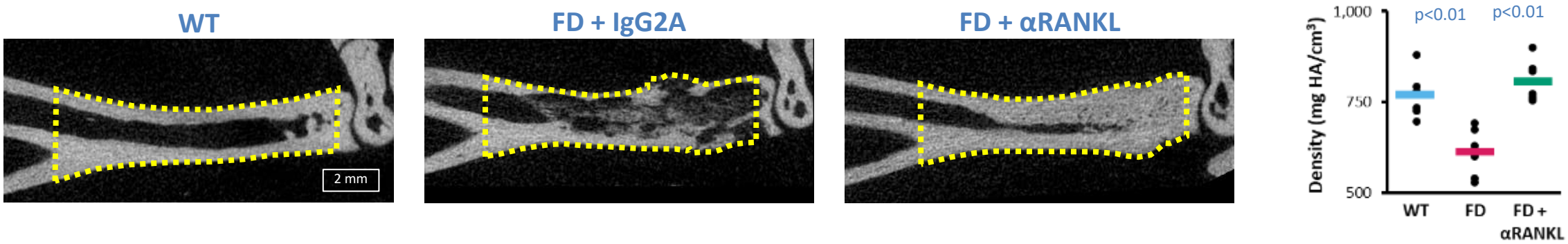




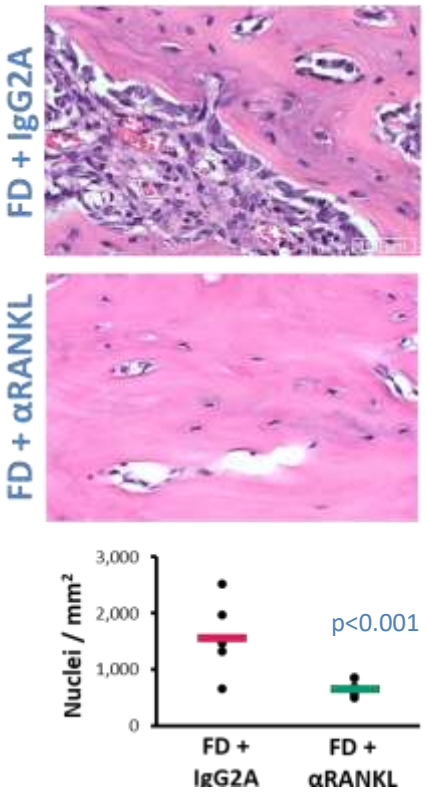


de Castro et al, NEJM 2023

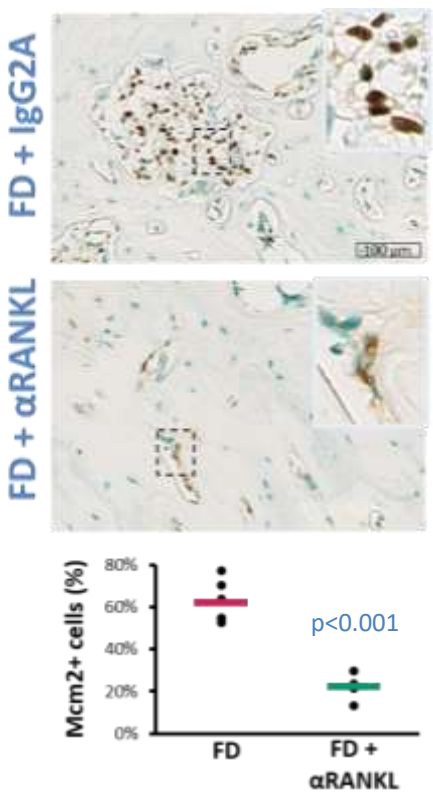
RANKL Inhibition Increases Mineralization in an FD Mouse Model



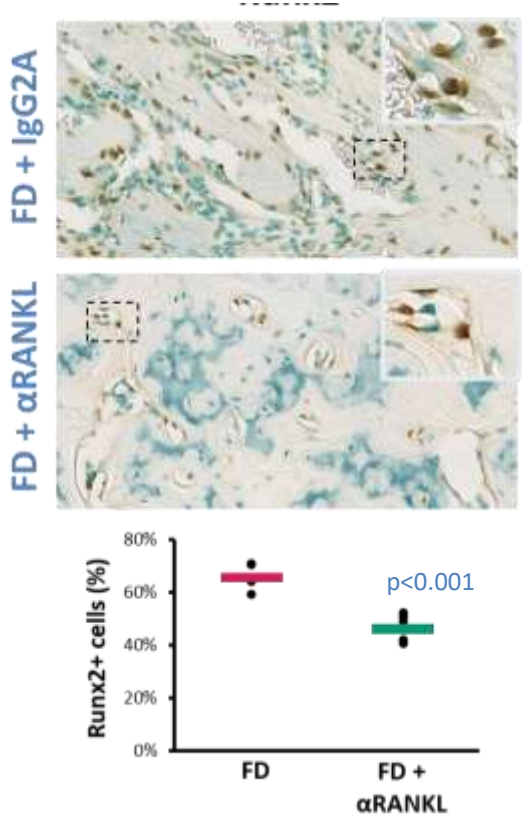
Decreased Cellularity

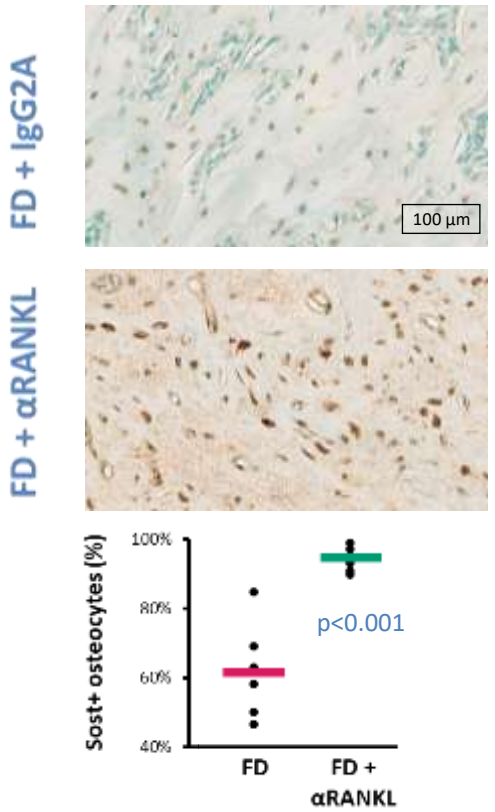


Decreased Proliferation



Promoted Differentiation

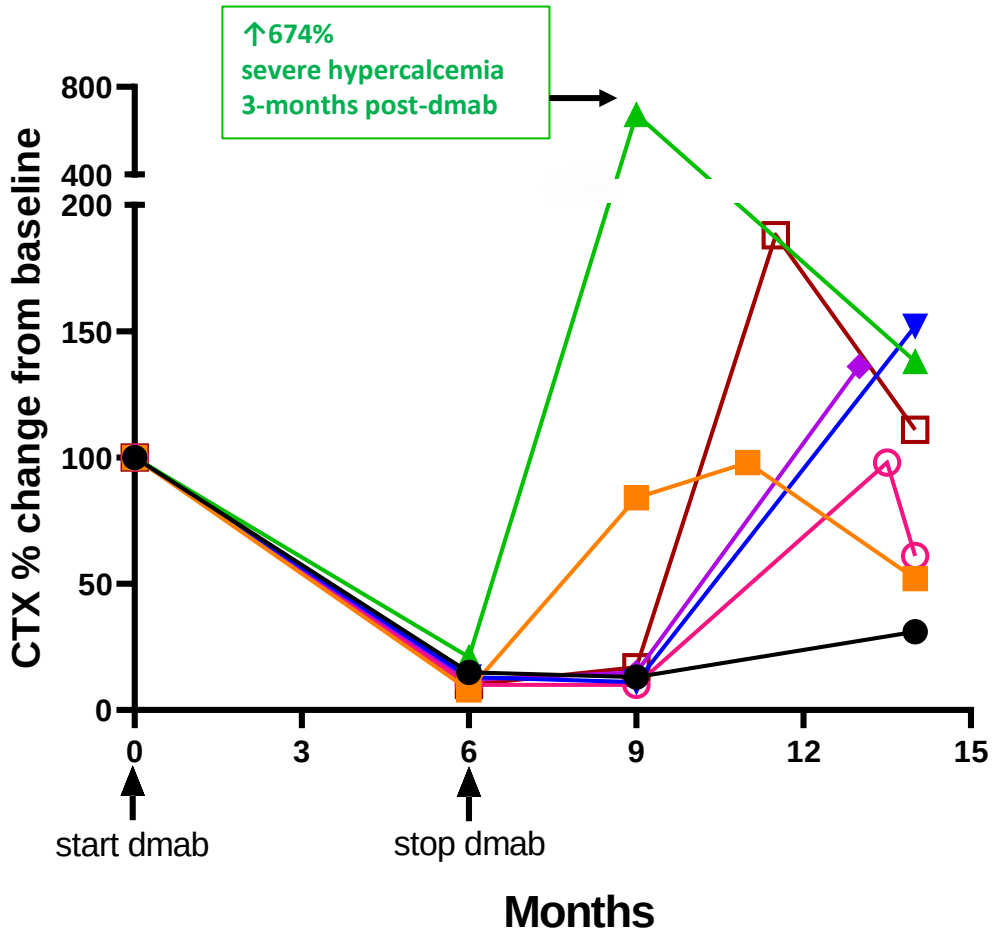


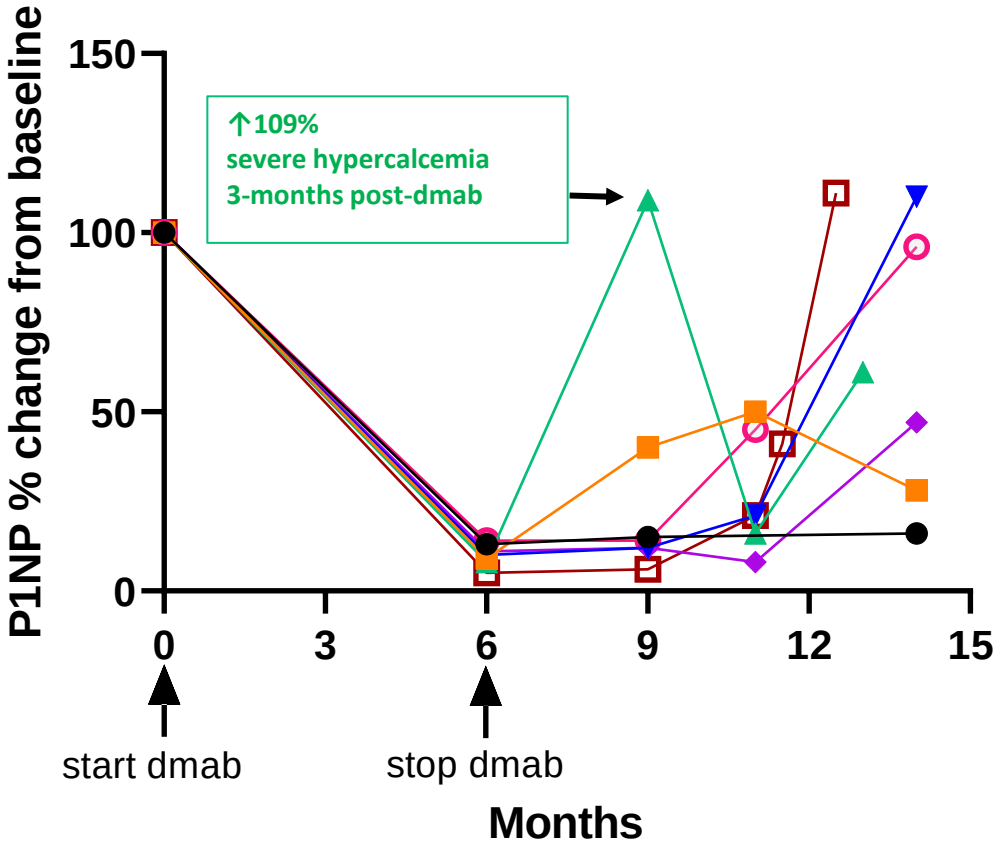


de Castro Bone Res 2024

Bone Turnover Rebound After Denosumab Discontinuation

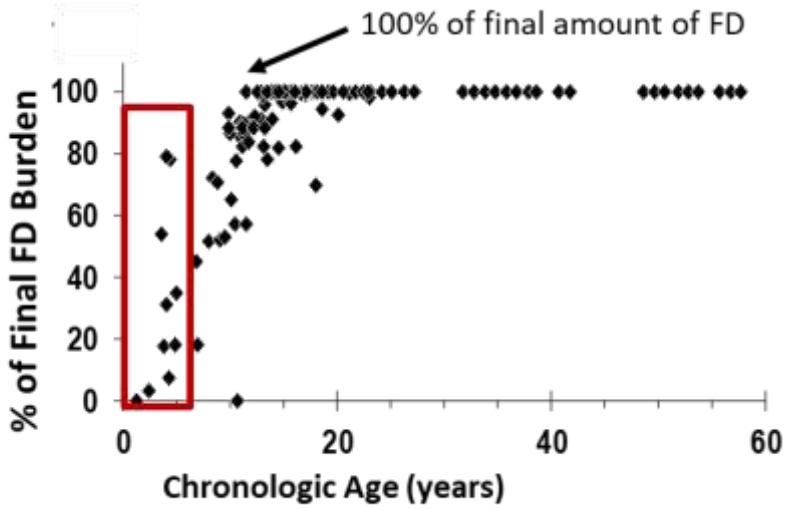
- All patients received zoledronate at denosumab discontinuation
- In 4 patients, CTX rebounded to above pre-treatment levels
- 1 subject developed severe hypercalcemia: **23 mg/dL** (normal range 8.6-10.4)

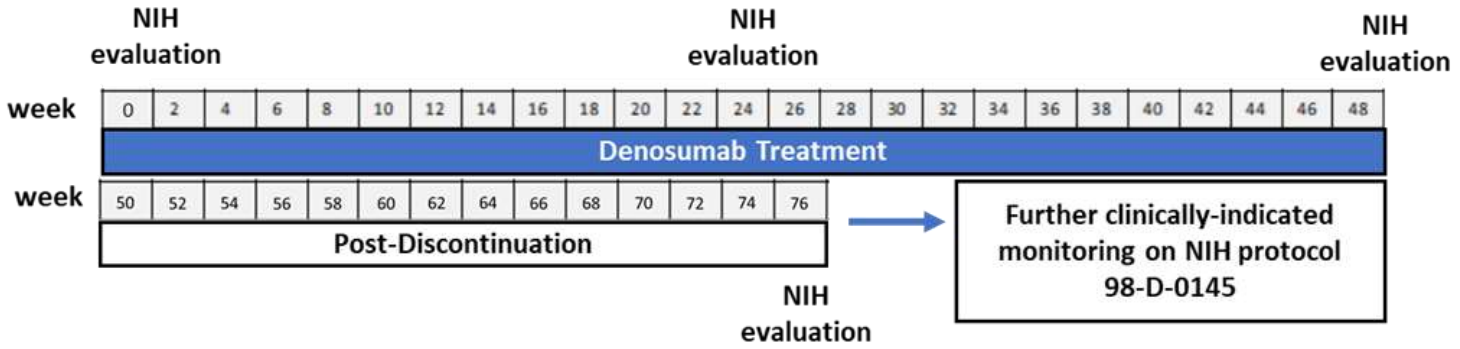




de Castro et al, NEJM 2023

Phase 2 study of denosumab to prevent FD progression in children (NCT05419050) – study underway – early results promising





Alison Boyce, MD and Vivian Szymczuk, MD

- 15 patients, age 4-14
- Primary endpoint: Change in FD lesion expansion compared to historical control patients
- Low/frequent dose: 0.25 mg/kg/month (12x lower than adult study)
- Enrolling – early results promising

RANK/RANKL and anti-RANKL in FD

- RANK/RANKL is central to the pathophysiology of FD
  - Precise cellular and molecular mechanisms TBD
- Anti-RANKL appears to have direct, natural history-changing beneficial effects
- Severe post-discontinuation hypercalcemia in a subset of patients
- Who should we treat? How long? What dose? - TBD
- Further study is needed to determine the clinical utility in children with progressive FD

25 years of Skeletal Disorders and Mineral Homeostasis Section Research

Current Group

Rachel Gafni
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Iris Hartley
Babak Saboury
Karen Pozo
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Scott Paul, Rehab
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Bill Chong, FDA
Iris Hartley, NIH

NICHD Pediatric Endo.

Alison Boyce, NIH
Cemre Robinson, Sanofi
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Elizabeth, Theng, UCLA
Sri Paravastu, U MO/KC
Natalia Wojnowski, NWU
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Paolo Bianco, Rome
Mara Riminucci, Rome
Brian Kobilka, Stanford
Charlie Hoffman, BC
Alfredo Molinolo, UCSD
Silvio Gutkind, UCSD
Laura Tosi, CNMC
Harald Jueppner, MGH
Tom Gardella, MGH

NIH National Institute of Dental and Craniofacial Research


In 2024, after 25 years at the NIDCR, I’ll be leaving for new horizons

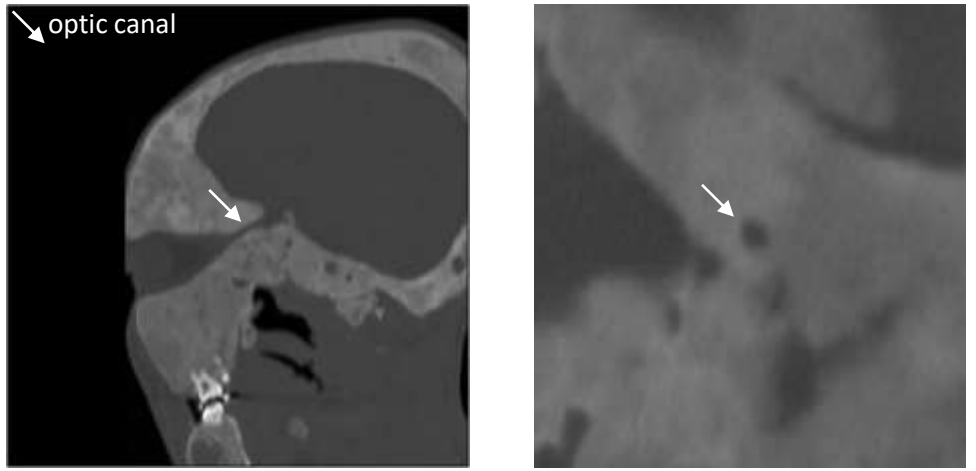
The Vexing Problem of Skull Base FD and the Optic Nerve

- Skull base is the most commonly involve bone
- Optic nerve passes through the skull base
- Prevailing thinking:
  - progressed to blindness
  - prophylactic surgical decompression is indicated
- Our observations suggested otherwise

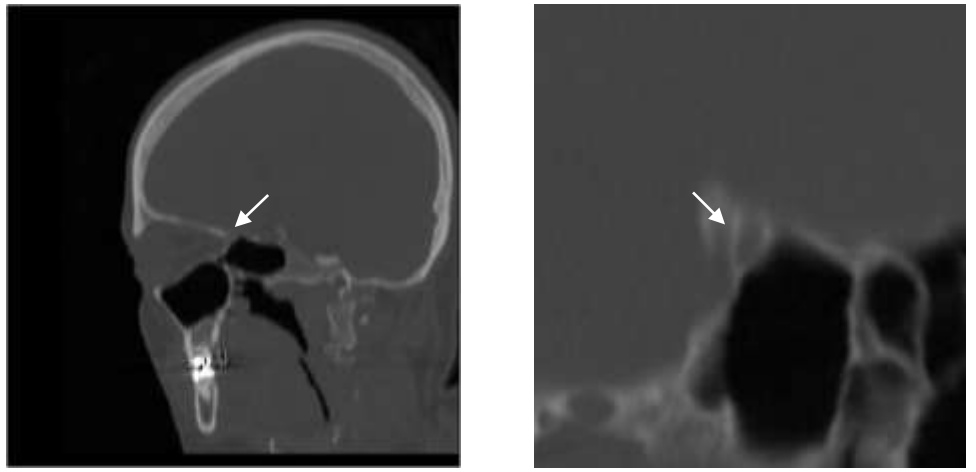
- Retrospective review of 38 patients
- FD canals narrowed: 10 vs 12 cm^2
- Vision was not impaired
- Narrowing was not age-related

Prophylactic decompression is contraindicated

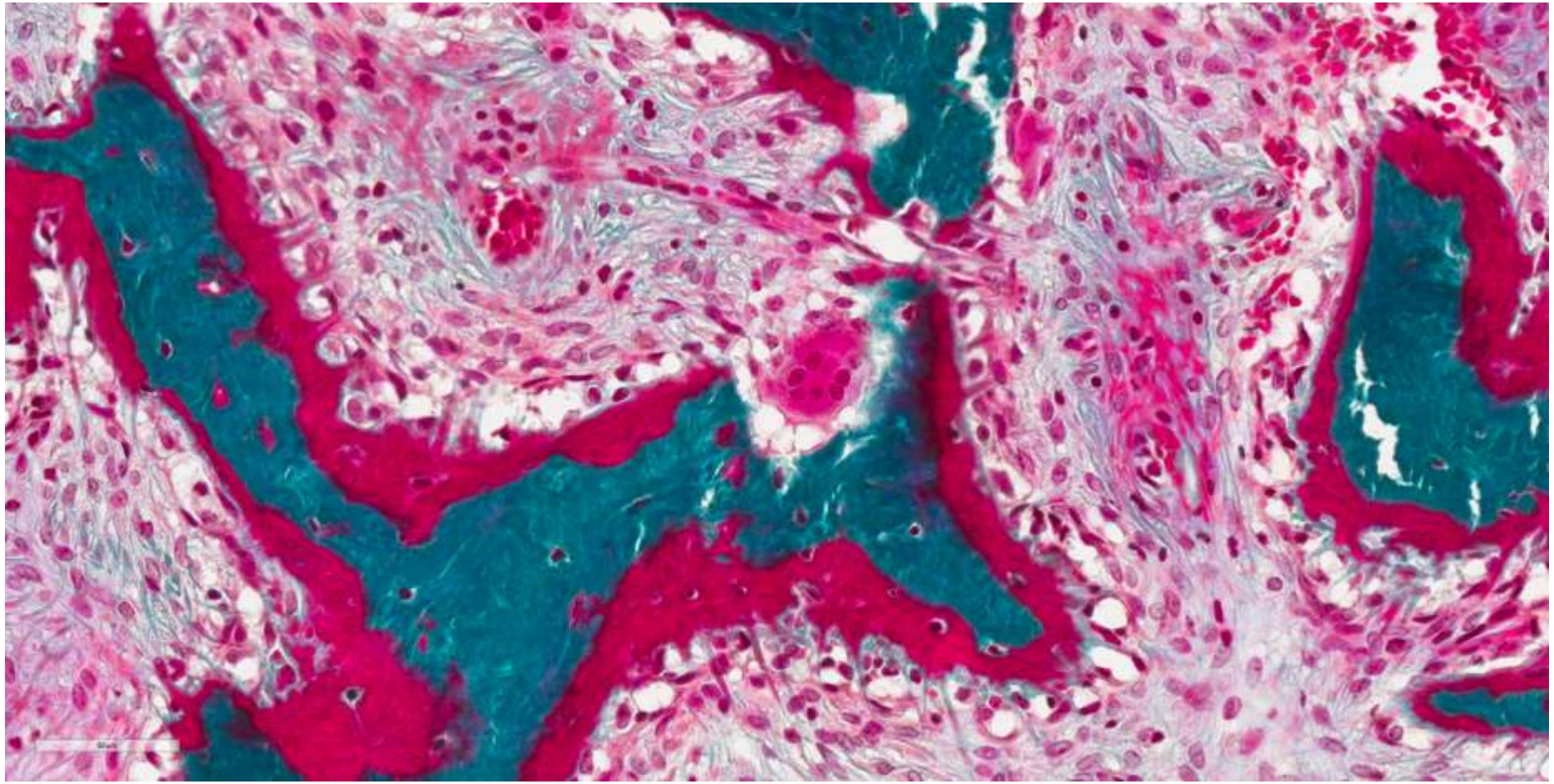
fibrous dysplasia

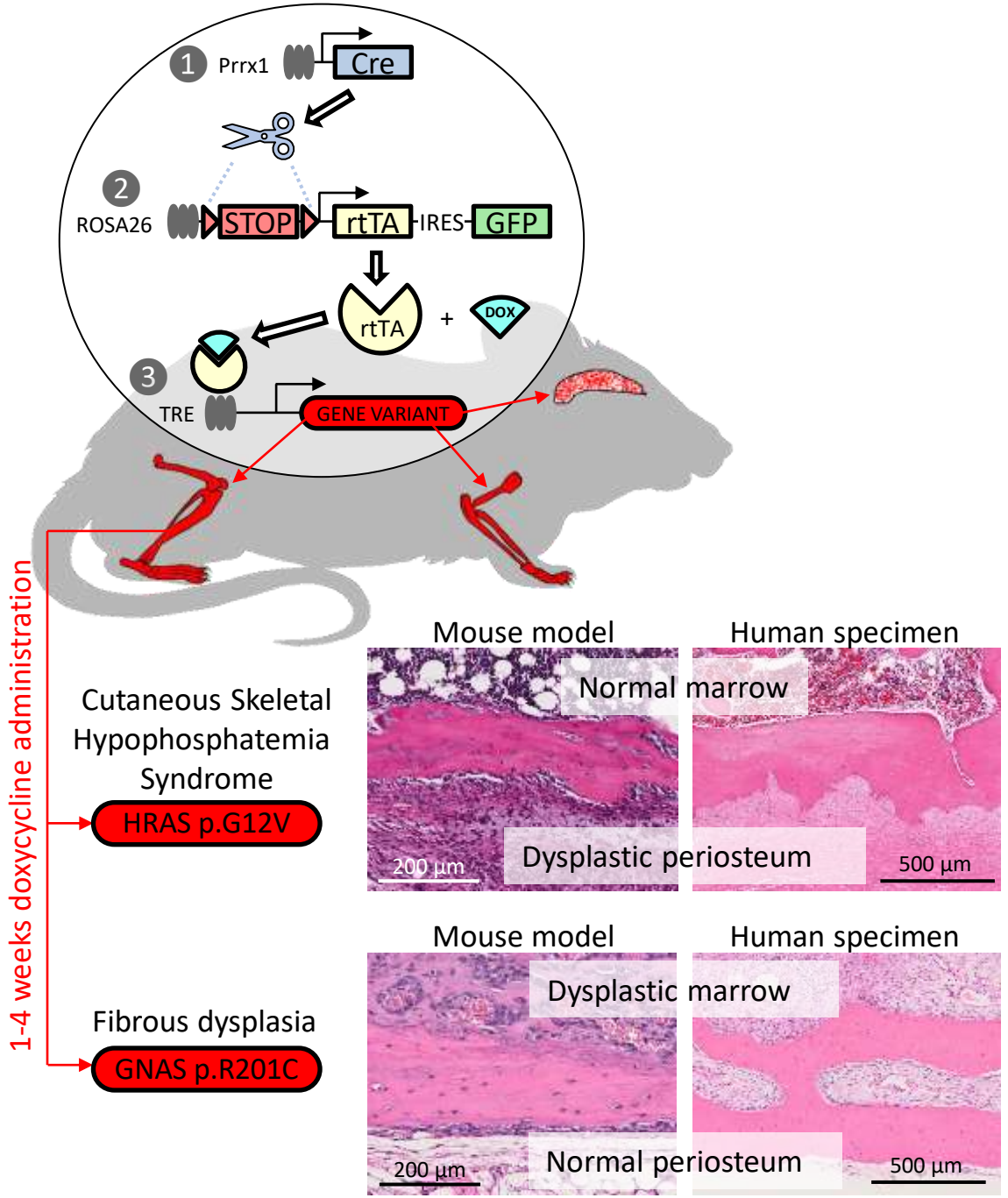


control



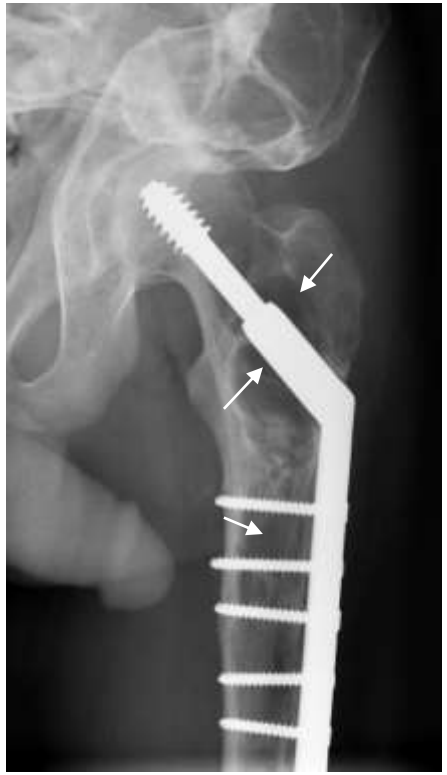
Lee et al NEJM 2002




1
Prrx1
Cre
2
ROSA26
STOP
rtTA
IRES
GFP
rtTA
+
DOX
3
TRE
GENE VARIANT
1-4 weeks doxycycline administration
Cutaneous Skeletal Hypophosphatemia Syndrome
HRAS p.G12V
Fibrous dysplasia
GNAS p.R201C
Mouse model
Human specimen
Normal marrow
Dysplastic periosteum
200 µm
500 µm
Mouse model
Human specimen
Dysplastic marrow
Normal periosteum
200 µm
500 µm

The Question of Curettage and Grafting in Fibrous Dysplasia

- Prevailing thinking:
  - remove & replace dysplastic bone with graft improves outcomes
- 23 patients, 20 y follow-up, 52 grafts
- Graft was regularly resorbed
- More resorption in younger patients



Curettage and Grafting are of Limited Value in FD

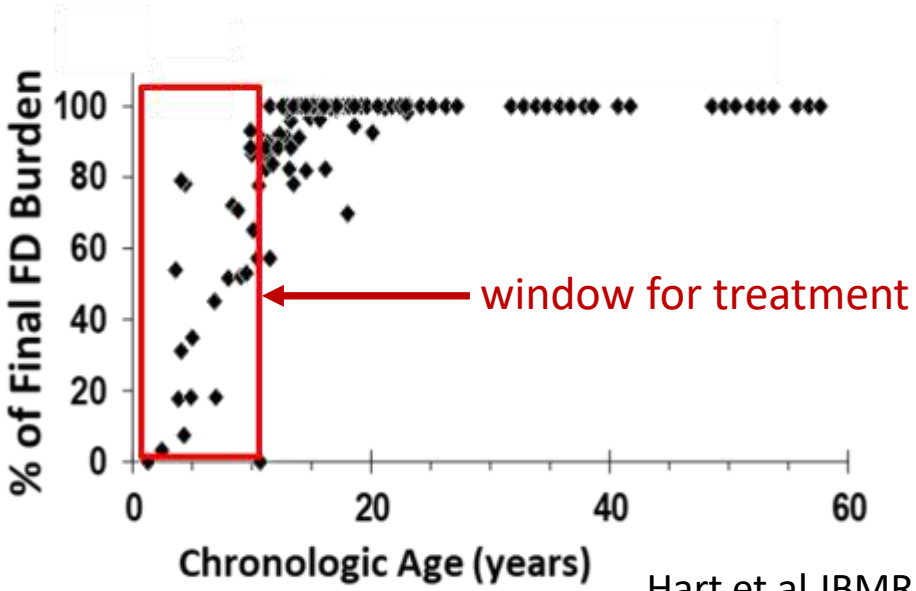
Arabella Leet, et al, JBJS 2016

FD Lesions are Acquired in Childhood

- Serial bone scans, 109 patients, followed up to 32 y
- Validated instrument, skeletal disease burden score

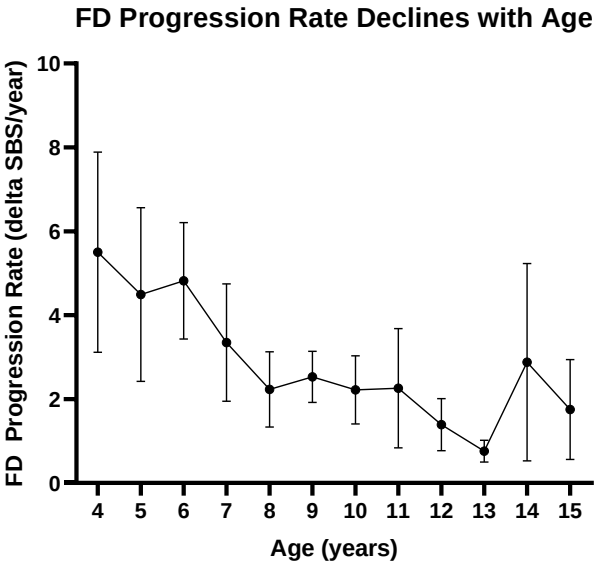
Age	region	disease present
3.4	craniofacial	90%
10.7	appendicular	75%
15.0	axial	90%

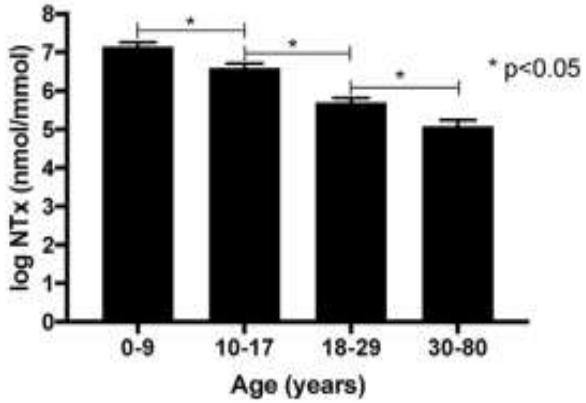
Collins et al JBMR 2005



Hart et al JBMR 2007

Progression slows with Age

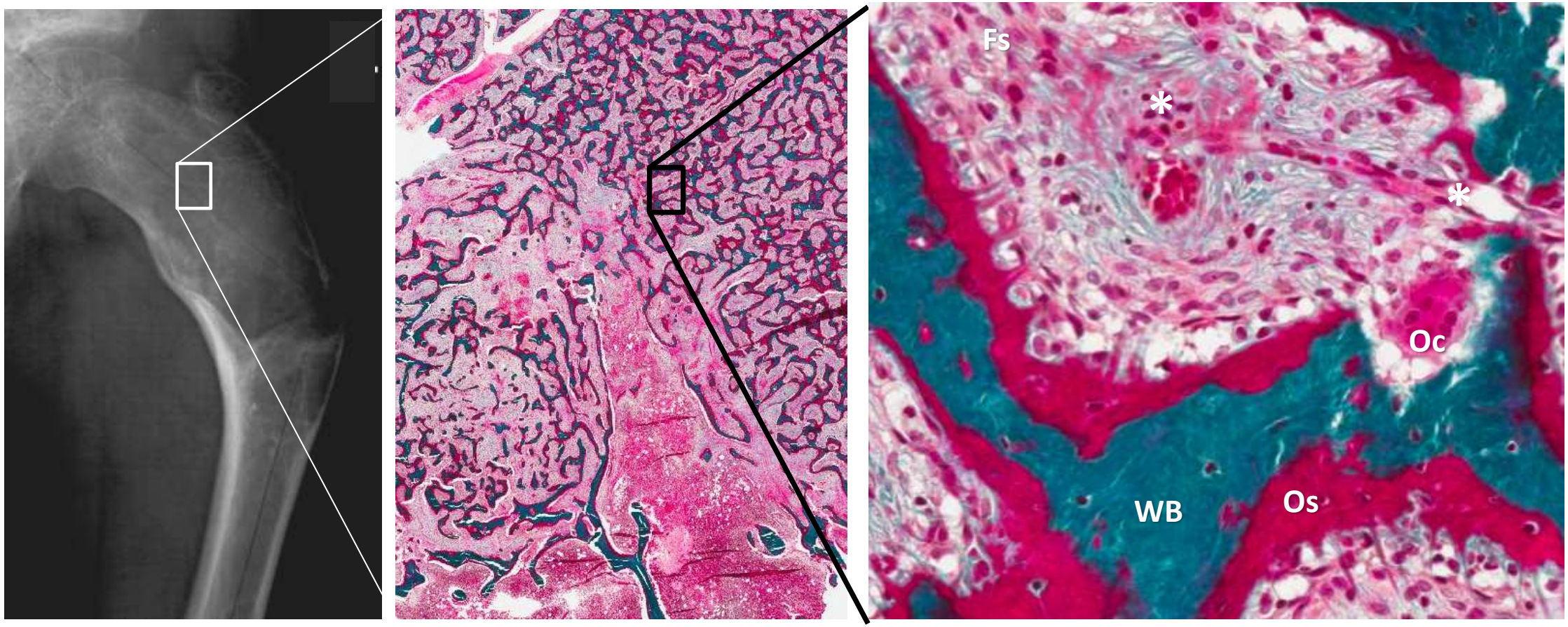




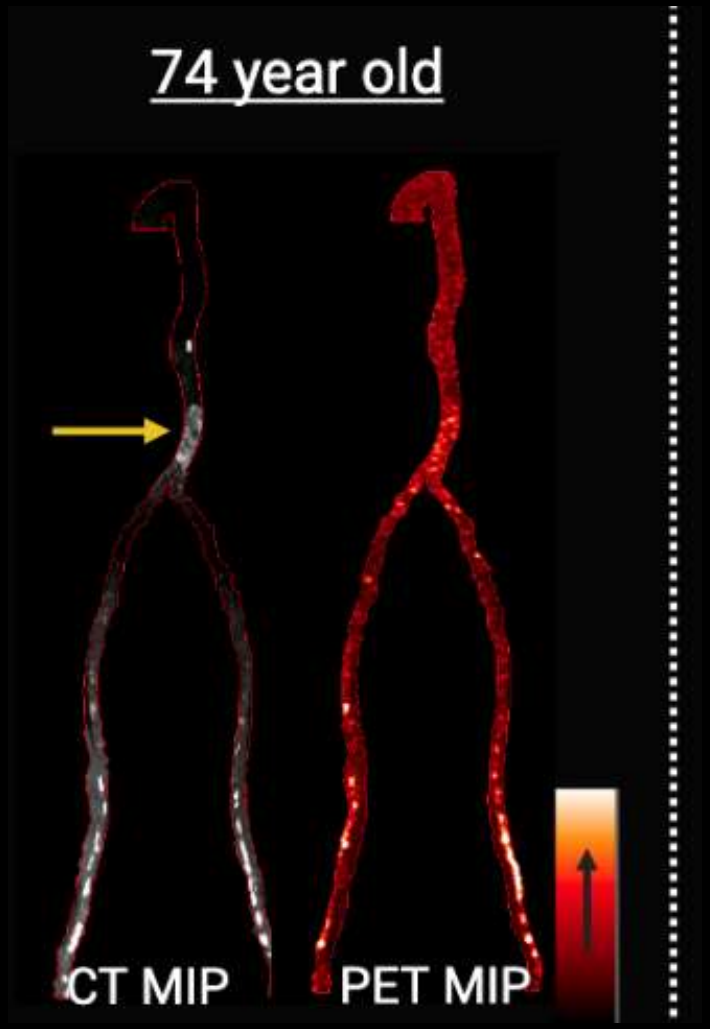
Florenzano JBMR 2019; Szymczuk, JBMR 2022

Cellular & tissue level features of fibrous dysplasia

- fibroosseous disease
- replacement of marrow, marrow fibrosis (Fs)
- massive de novo bone formation/resorption/formation
- unnmineralized matrix (osteoid, Os)
- woven, poorly mineralized bone (WB)
- high vascularity, venous pooling*
- osteoclasts/giant cells (Oc)

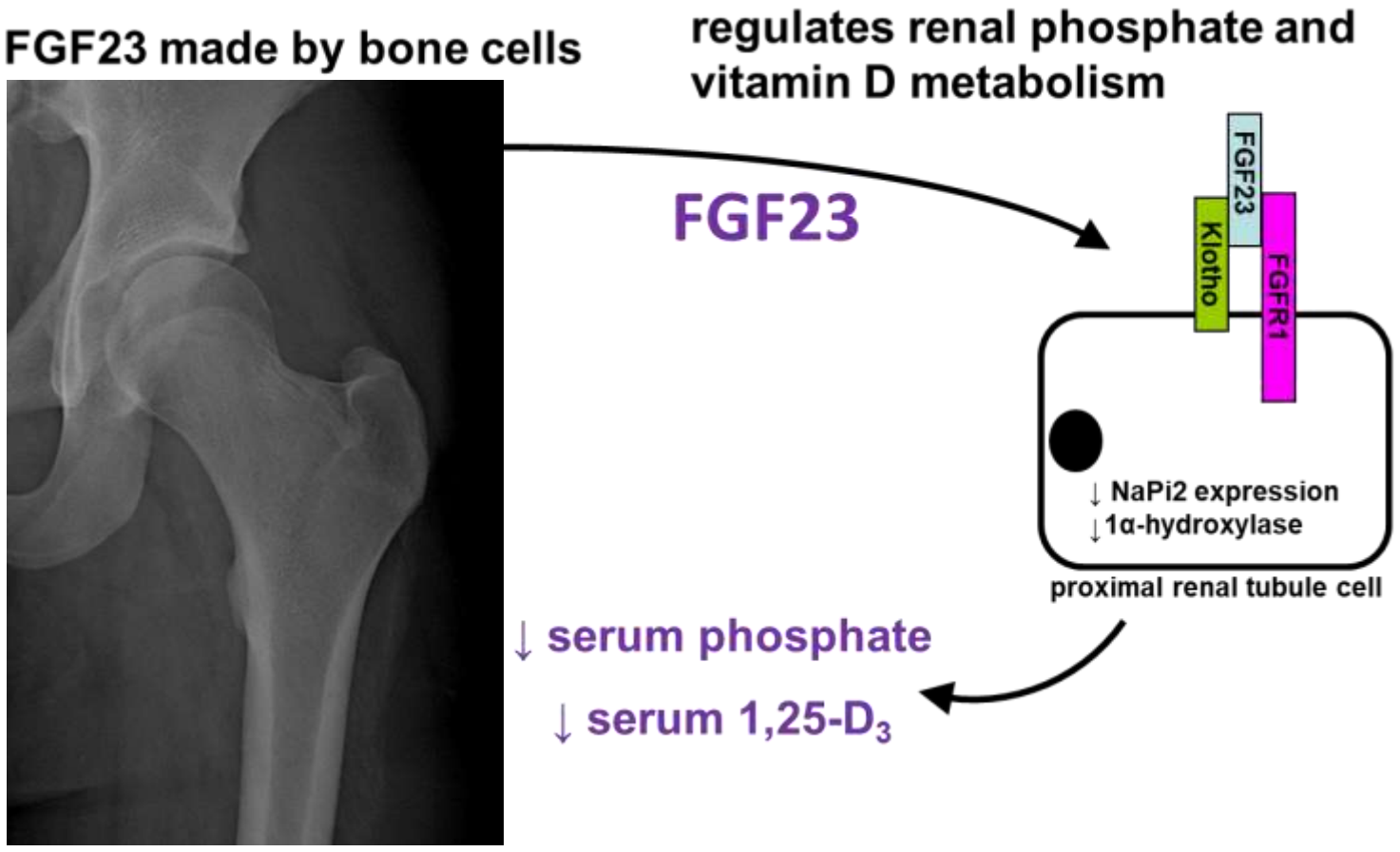


CT and PET Differential Quantification of Vascular Calcification
(hyperphosphatemic familial tumoral calcification)

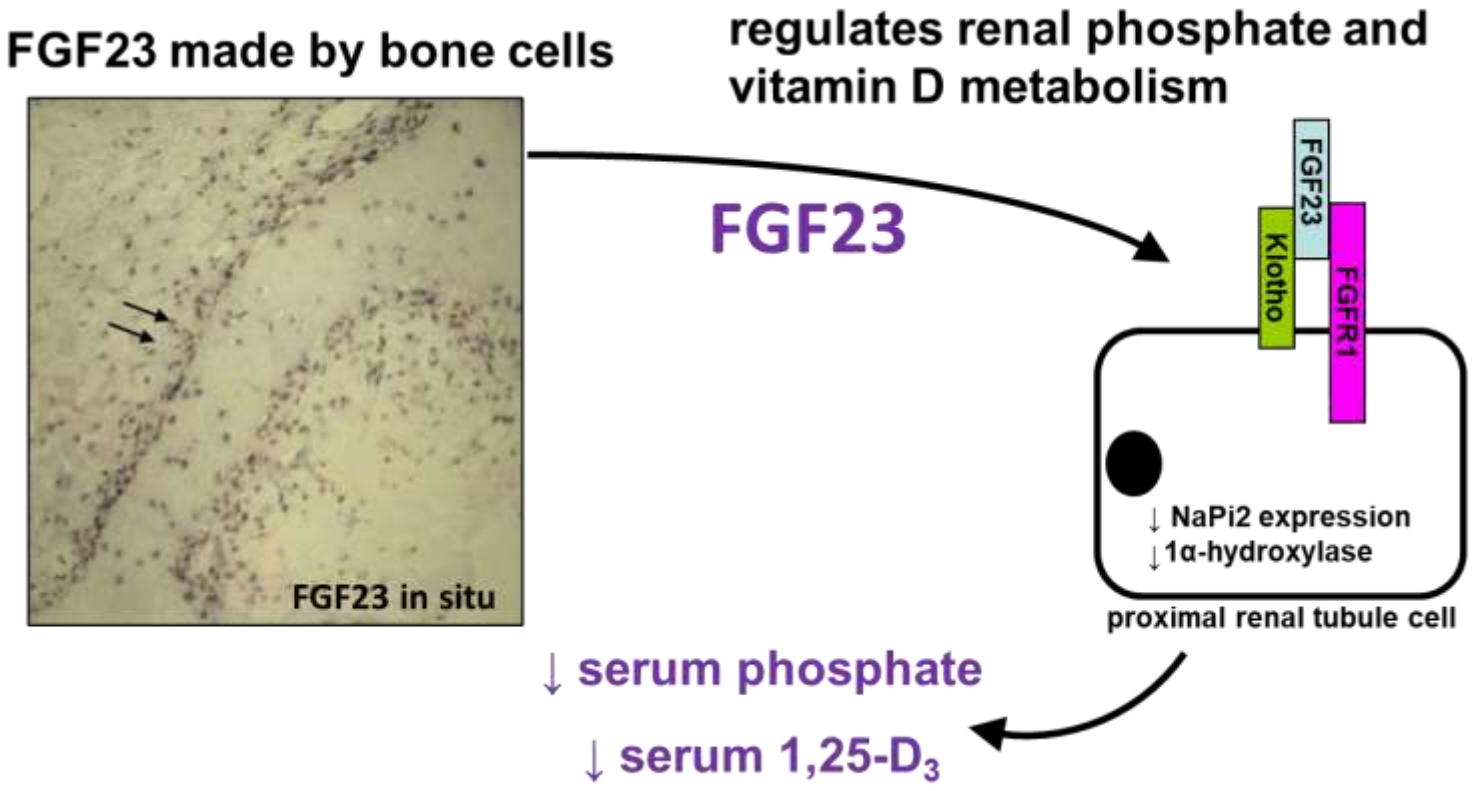


Sheppard…Saboury, in revision

FGF23 Physiology

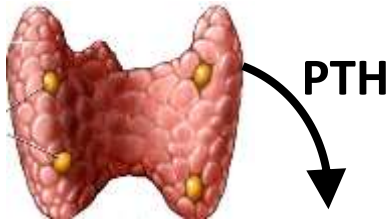


FGF23 excess is common in FD; worsens disease

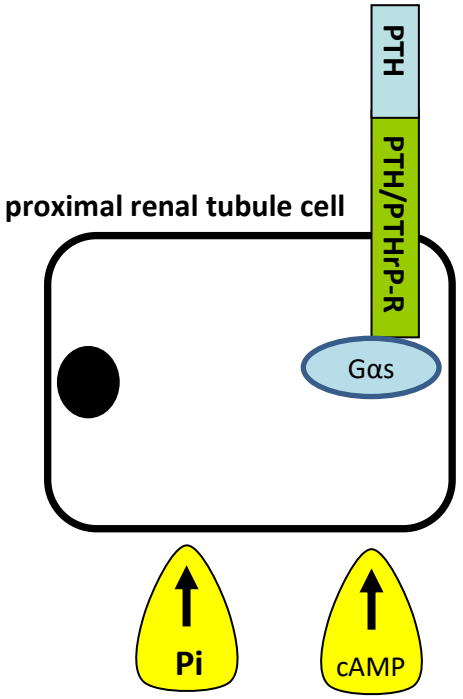


Hypophosphatemia and FD

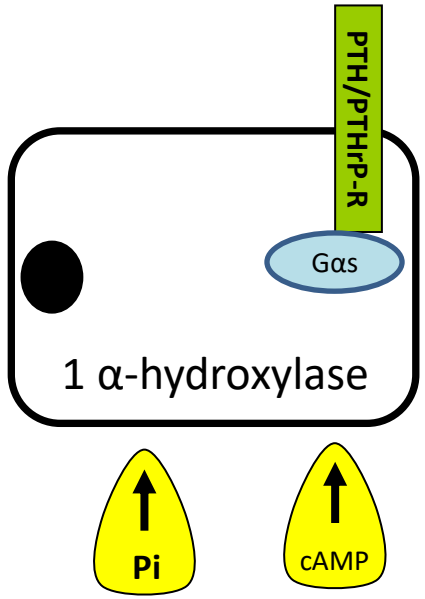
- Phosphate needed to mineralize bone
- Low levels associated with:
  - rickets, bowing, earlier and more fractures, scoliosis
- Assumption Gαs mutation in kidney was cause



PTH

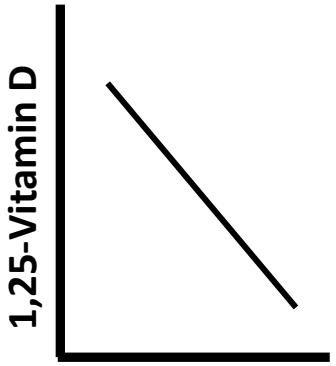


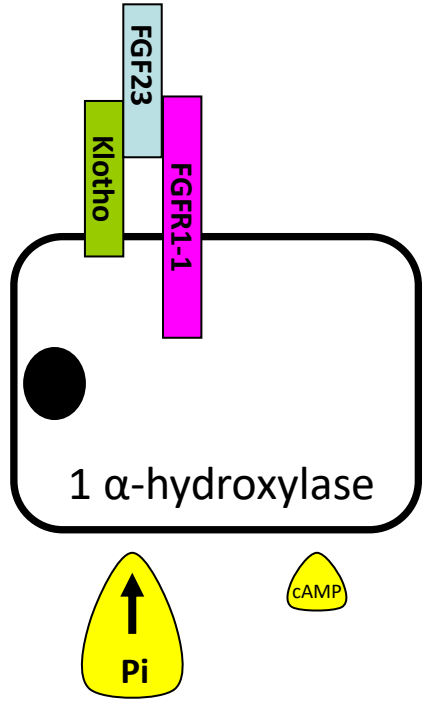
Hypothesis in MAS:
Gαs, Ligand-Independent

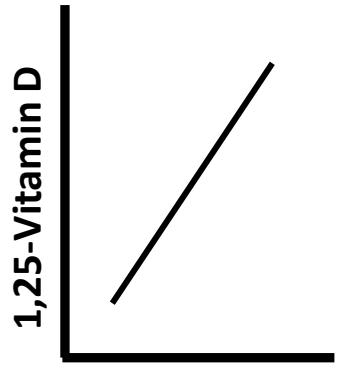


- Alternative hypothesis; FGF23-mediated
- Normal nephrogenous cAMP

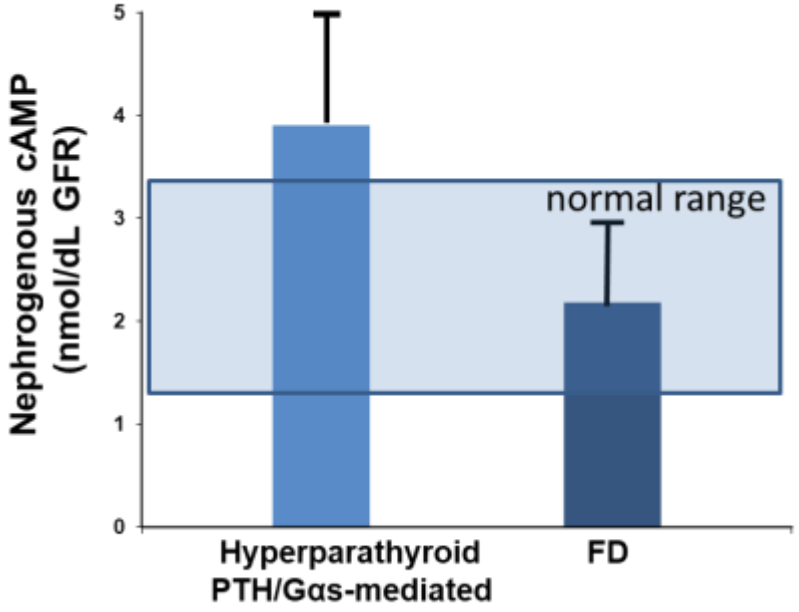
FGF23-Mediated

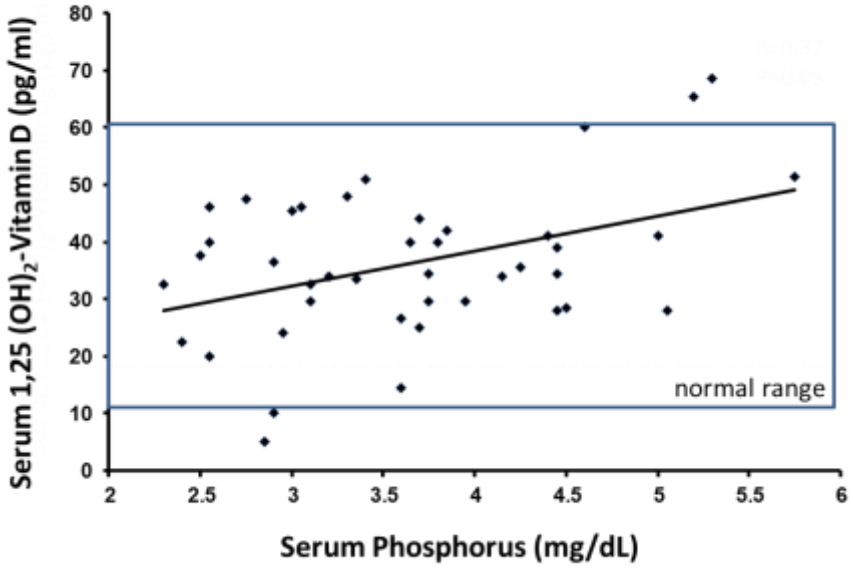


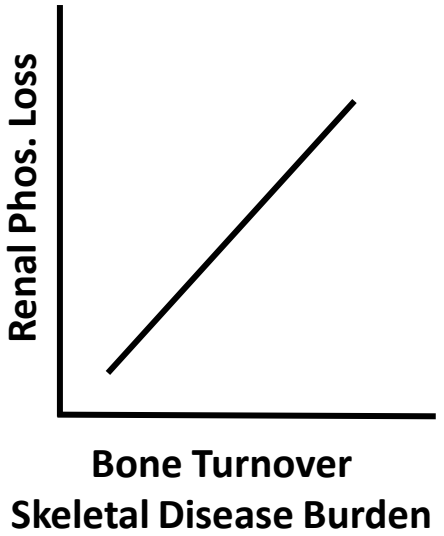




Mineral Metabolism Defect in FD is FGF23, Not Renal Gαs-Mediated



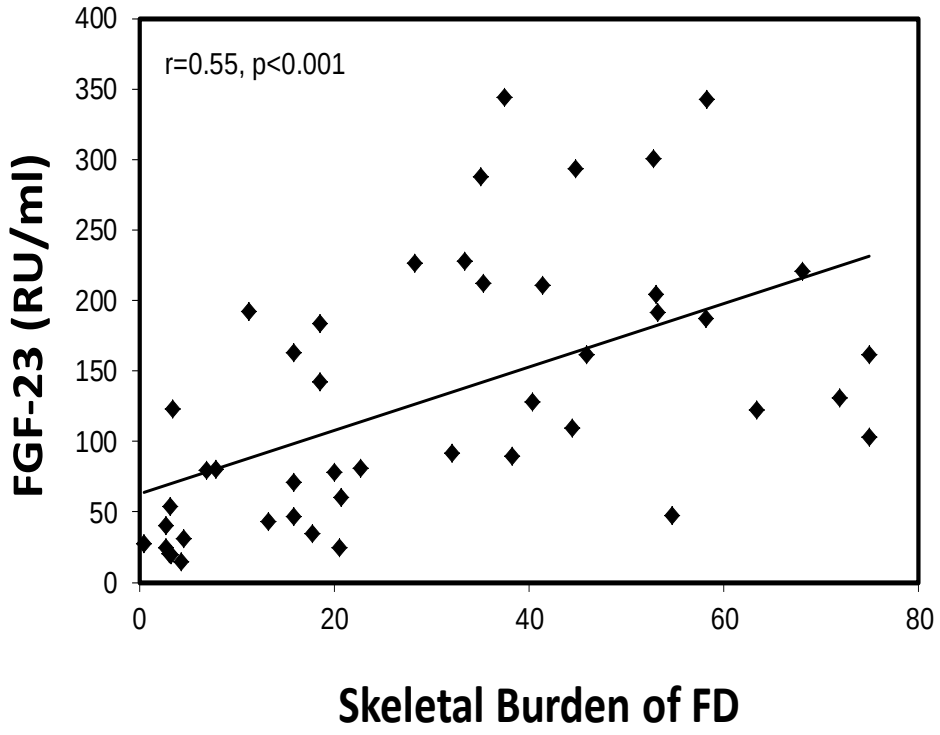


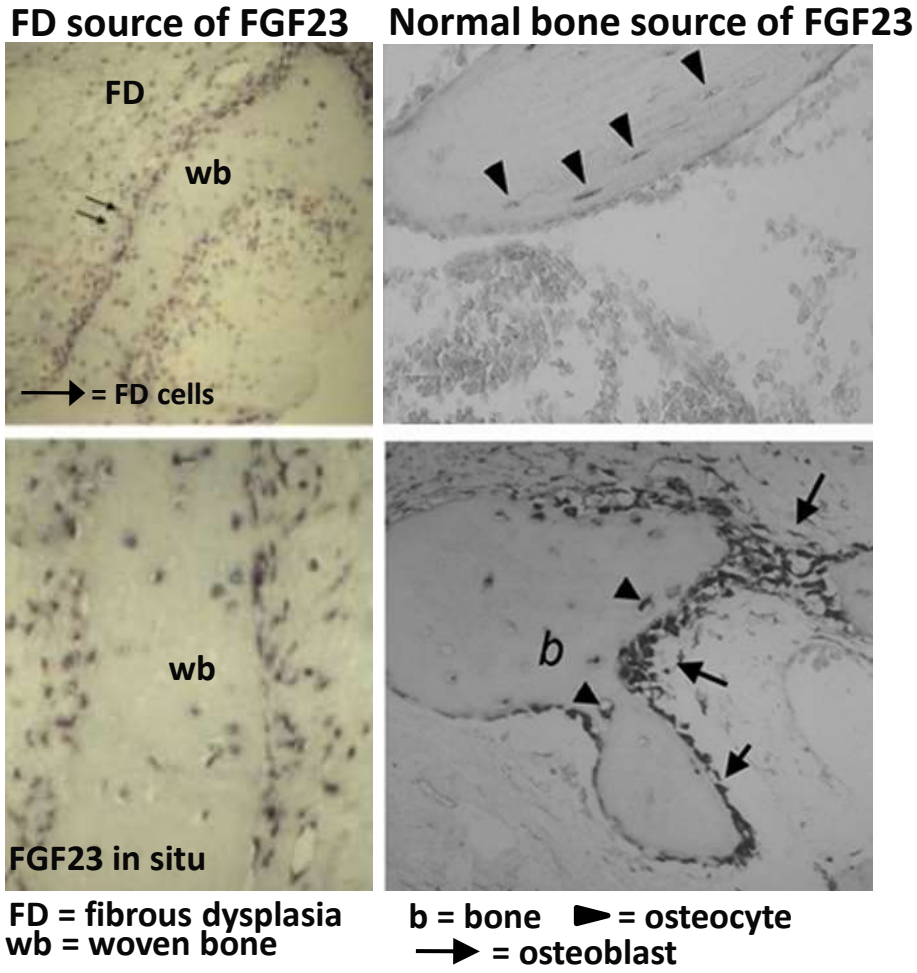


Pointed to FD Bone as the Source of FGF23

Collins et al, JBMR, 2001

Tissue Source of FGF23: FD & Normal Bone





Riminucci, et al JCI, 2003

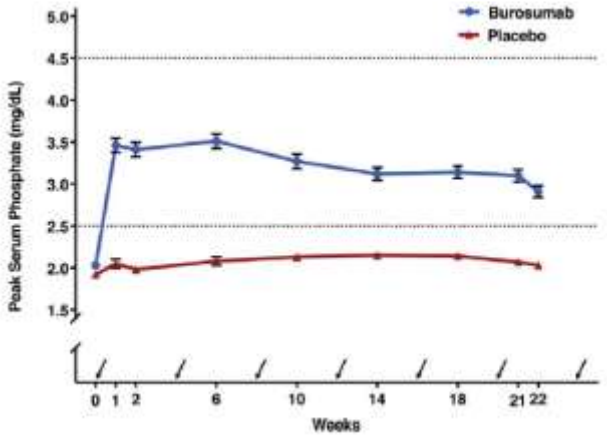
Medical Therapies for FGF23 excess

"Conventional" therapy

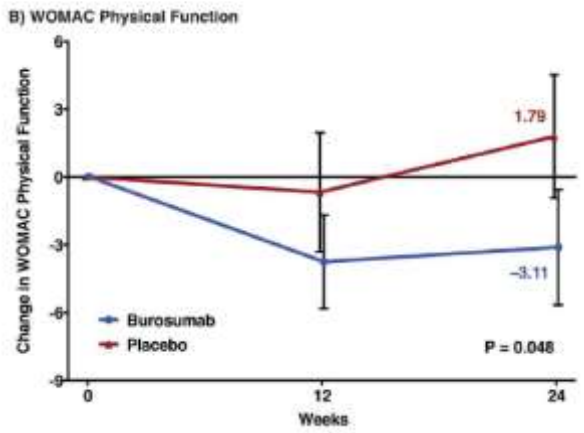
- **Oral Phosphate**
  - **3-5 X/day as tolerated → diarrhea**
  - **causes secondary hyperparathyroidism**
- **Active Vitamin-D (calcitriol or alfacalcidol)**
  - **prevent secondary hyperparathyroidism**
  - **causes hypercalciuria**
- **Cinacalcet**
  - **adjuvant**
  - **hypercalciuria**

Anti-FGF23 mAb (burosumab): approved for X-linked hypophosphatemia, tumor-induced osteomalacia

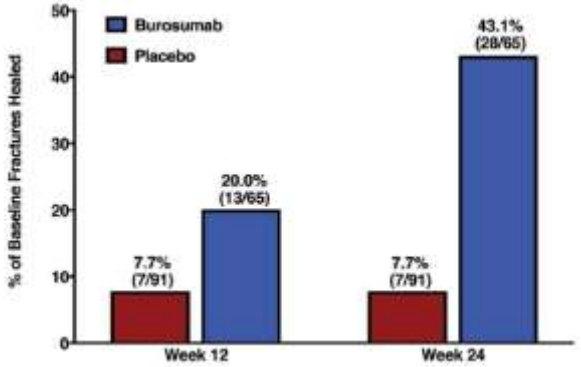
Corrects hypophosphatemia



Improves function



Heals fractures

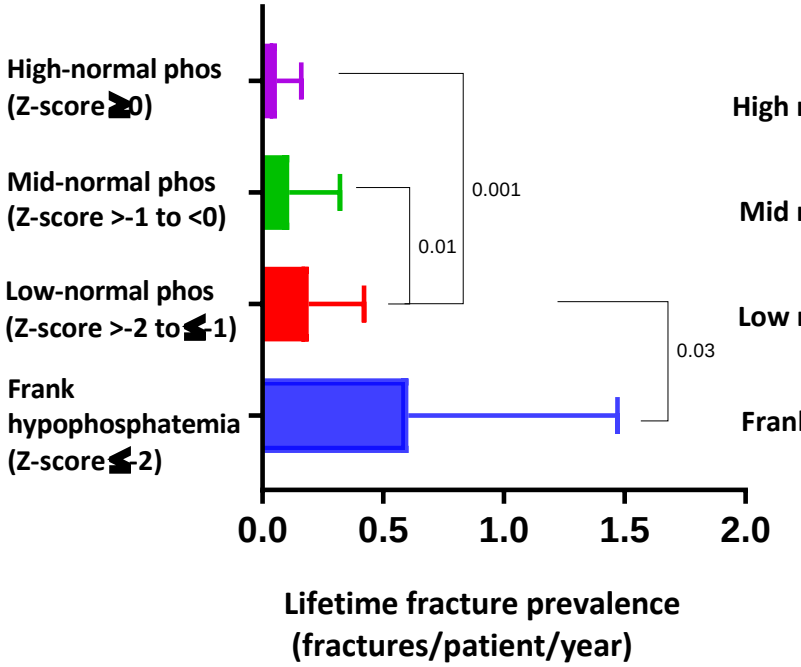


- **Effective**
- **Safe**
- **Expensive - $200K/y**

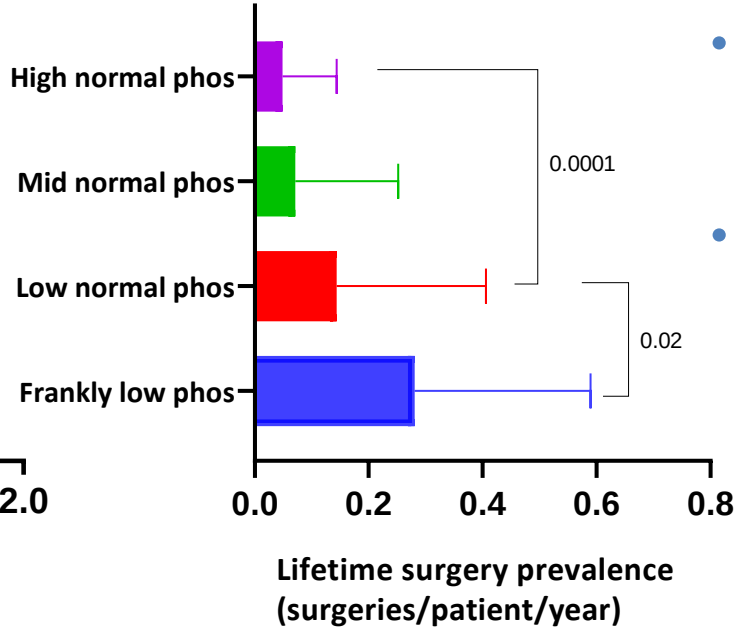
Insogna et al, JBMR 2018
Carpenter et al, NEJM 2018

FD & Hypophosphatemia: Higher Risk for Skeletal Morbidity

Fractures



Surgeries



- Even low-normal phos levels associated with ↑ FD-related complications
- FD is likely more vulnerable to hypophosphatemia than normal bone

Gun, JCEM 2023
N=240

Phase 2 Burosumab for FGF23-mediated Hypophosphatemia in FD NCT0550959

- N=15, age ≥1 year, hypophosphatemia & increased FGF23
- Primary endpoint: subjects achieving serum target phosphate levels (Z-score -1 to +2) at Week 48

	NIH evaluation								NIH evaluation														NIH evaluation		
-2	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Washout period	Burosumab Treatment																								

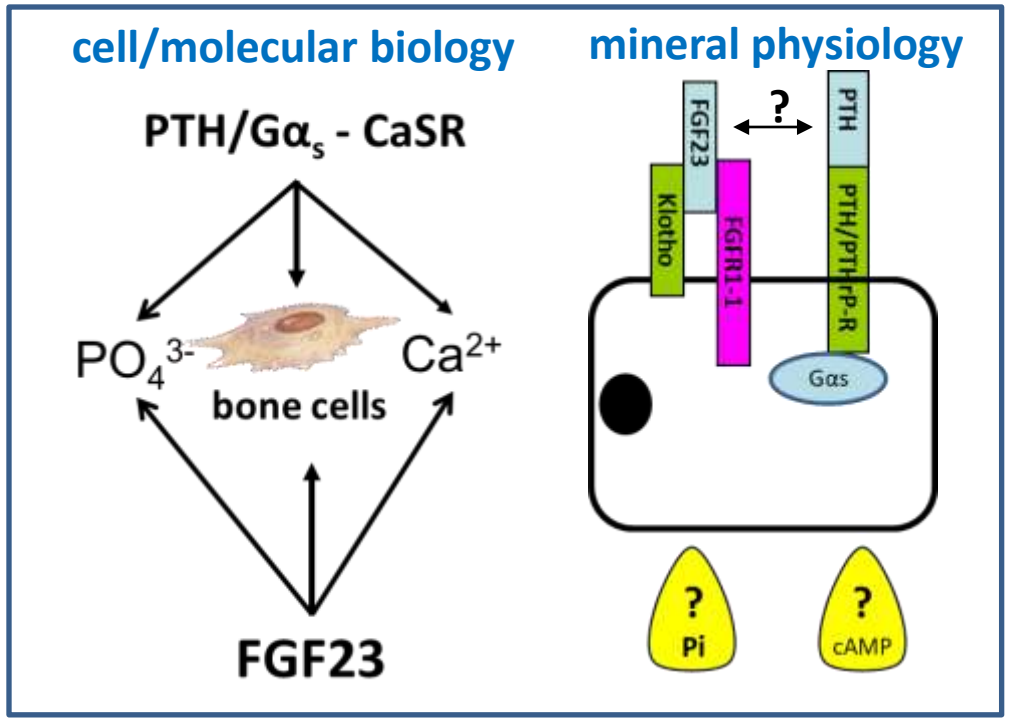
Model Diseases of Dysregulated Bone and Mineral Homeostasis

Fibrous dysplasia/ McCune-Albright syndrome

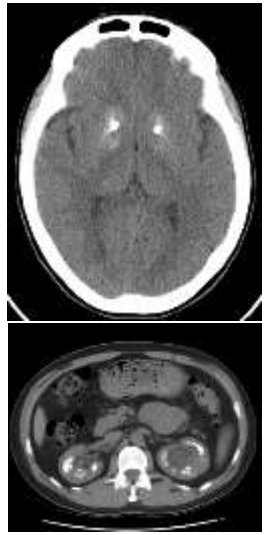
$G\alpha_s$ – FGF23

Tumor-induced osteomalacia

FGF23 excess



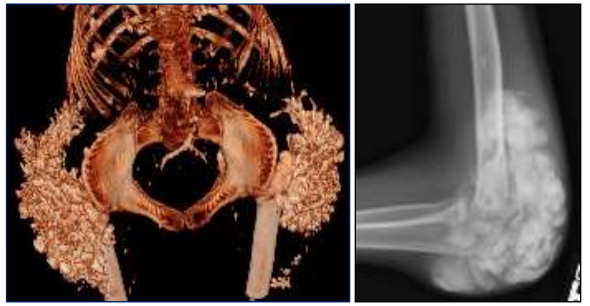
Hypoparathyroidism



PTH – CaSR – FGF23

Cutaneous skeletal hypophosphatemia syndrome

FGF23 excess



Familial tumoral calcinosis

FGF23 deficiency

CaSR=calcium-sensing receptor

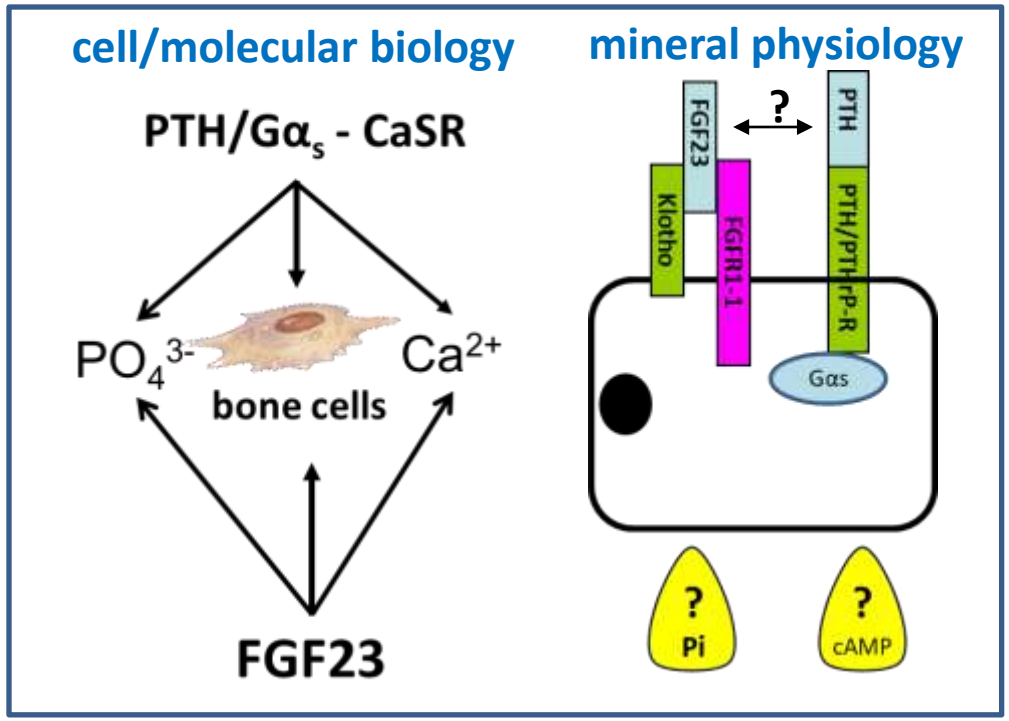
Model Diseases of Dysregulated Bone and Mineral Homeostasis

Fibrous dysplasia/ McCune-Albright syndrome

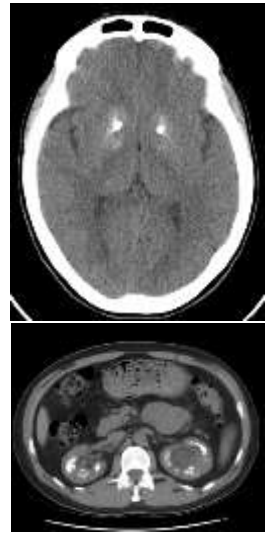
$G\alpha_s$ – FGF23

Tumor-induced osteomalacia

FGF23 excess



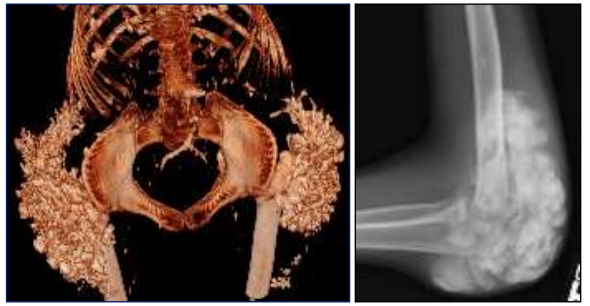
Hypoparathyroidism



PTH - CaSR

Cutaneous skeletal hypophosphatemia syndrome

FGF23 excess



Familial tumoral calcinosis

FGF23 deficiency

CaSR=calcium-sensing receptor

15 yo Boy Segmental Multisystem Disorder, Hypophosphatemia: Is this FD?

- 5 patients, somatic variants in the GTPase domain of *N/HRAS*
- ***Cutaneous Skeletal Hypophosphatemia Syndrome***
- Suggests role of RAS signaling in bone development and phosphate homeostasis

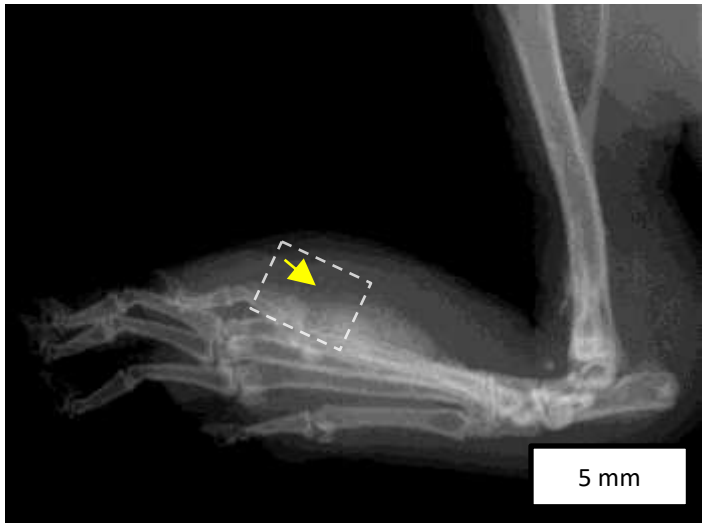
Debate: skin vs bone as the source of FGF23?

Lim et al Hum Mol Genet, 2014

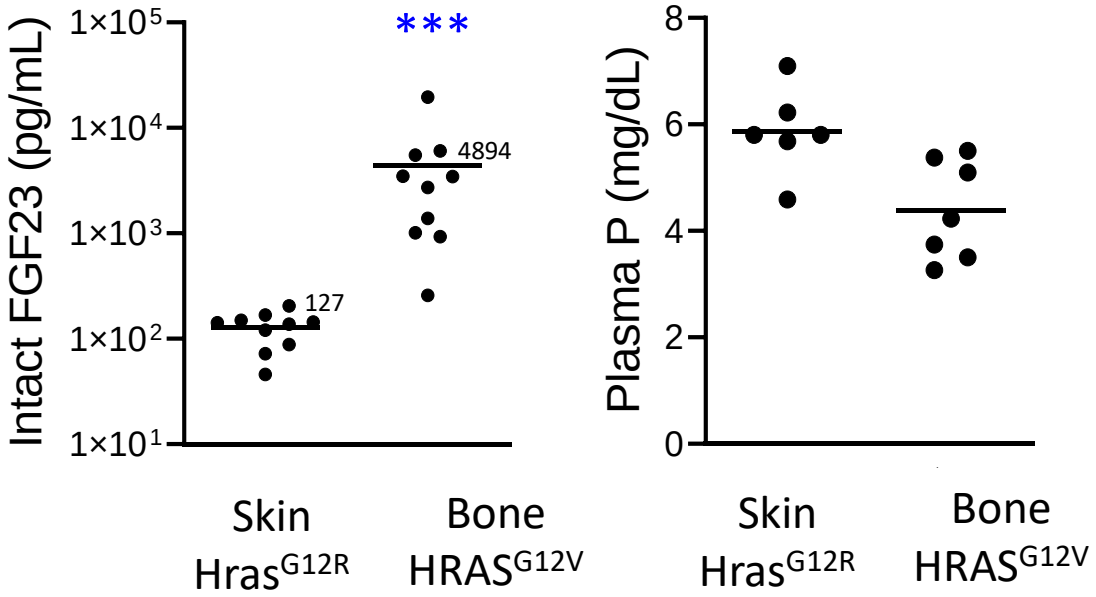
FD/MAS Community Meeting, 2013

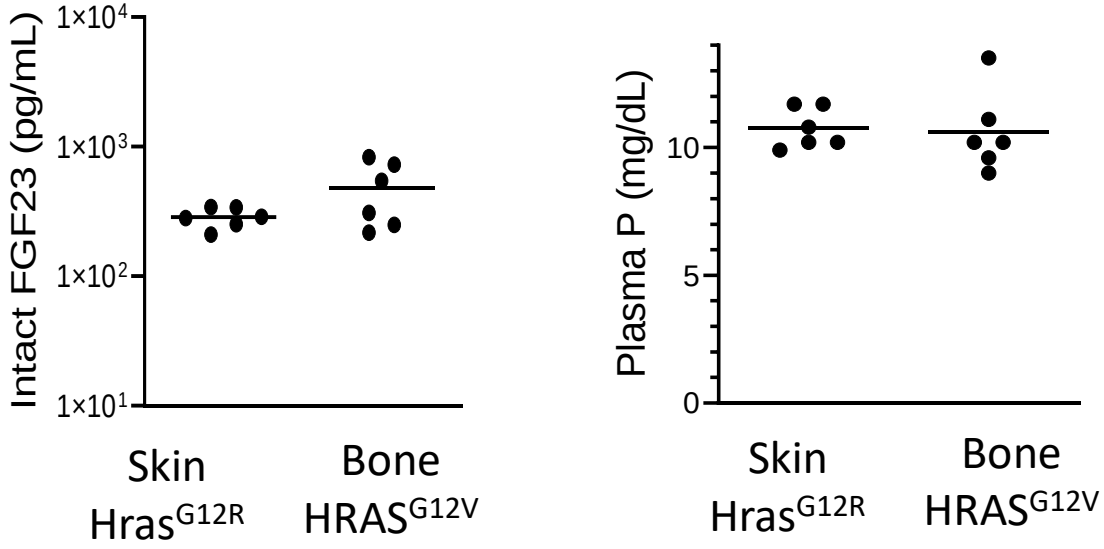
Bone, Not Skin is the Source of FGF23 in CSHS

Bone HRAS^{G12V}



Skin Hras^{G12R}





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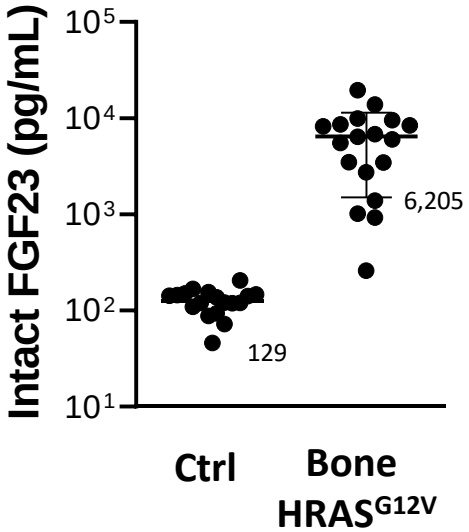
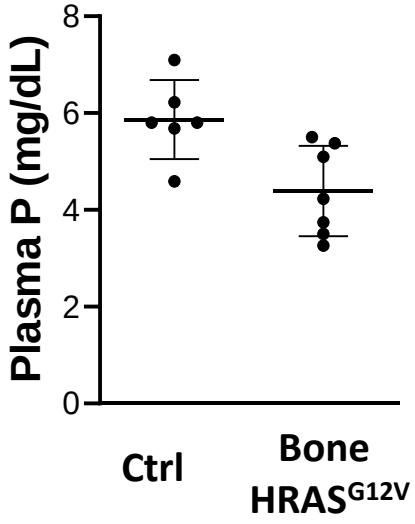
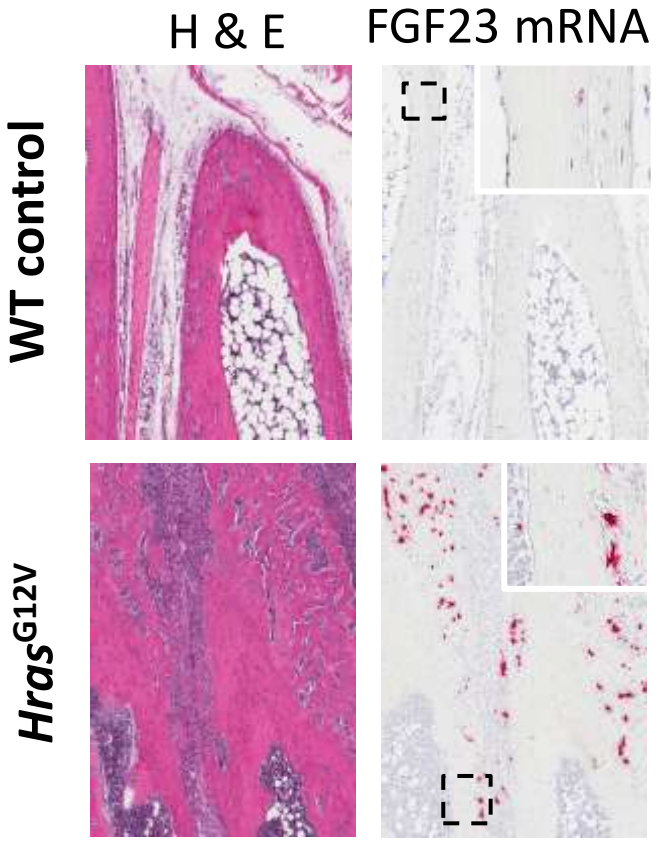
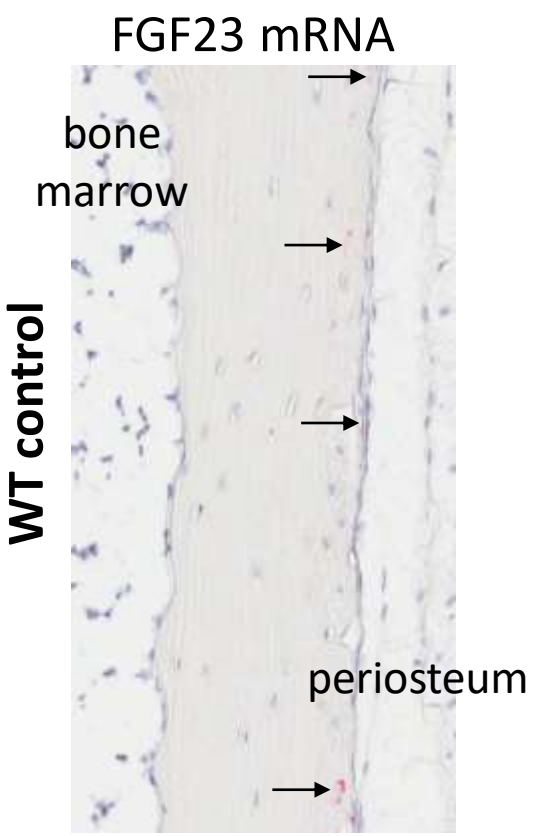
Skeletal Stem Cell HRAS^{G12V} Expression: Periosteal Dysplasia, ↑FGF23

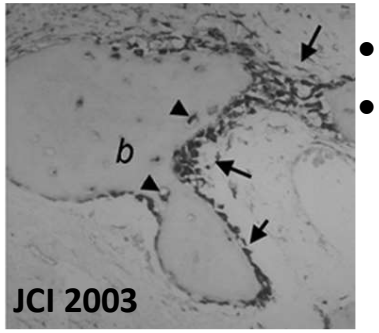








FGF23 expression appears confined to periosteal-derived bone cells



- normal fracture callus
- periosteal cell-derived

Ovejero…de Castro, JCI 2023

Luis Fernandez de Castro Diana Ovejero