



Treatment for Fibrous Dysplasia: RANKL and Beyond

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Disclosure

No conflicts of interest to declare.

My Scientific Journey to FD Study



BSD, PhD

West China School of Stomatology, Sichuan University
2008 – 2018



Visiting PhD student

NIH, UCSD, UMB
2014 – 2018



MSOB, Orthodontic Resident

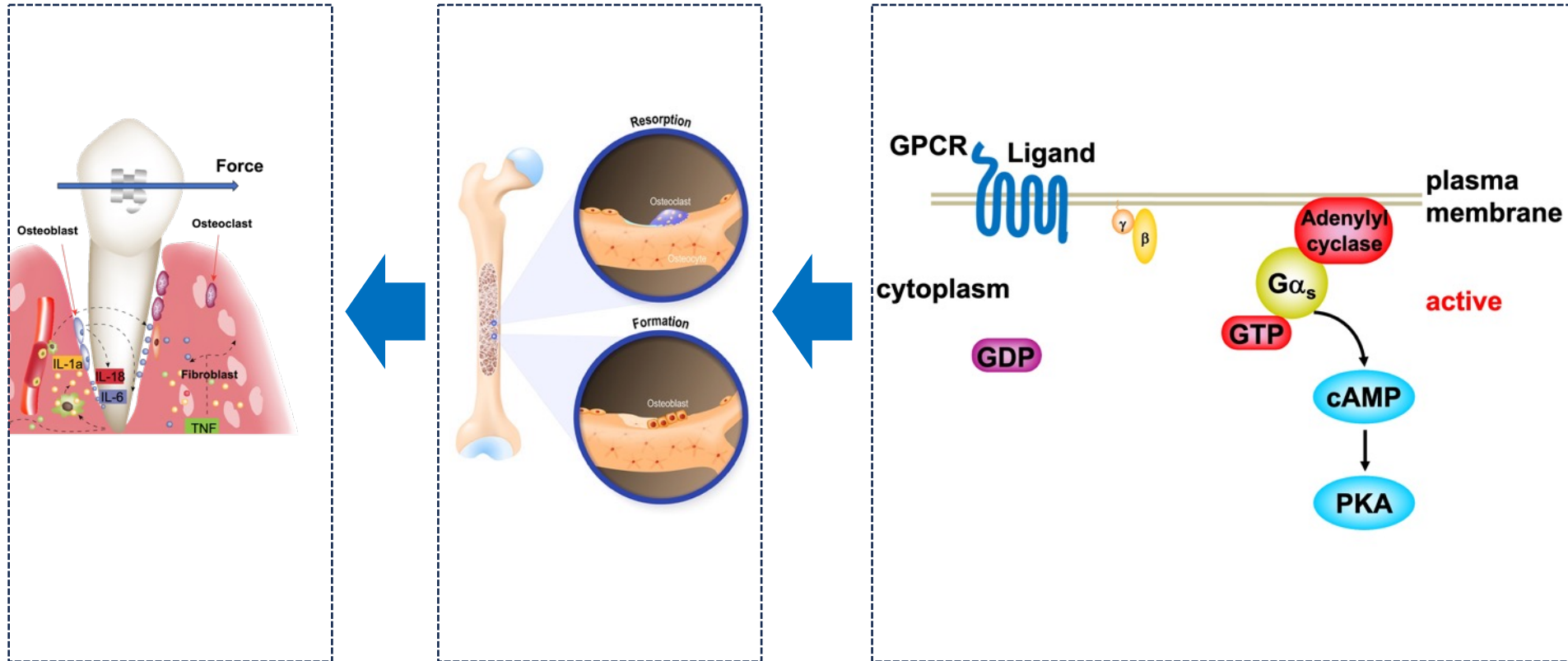
School of Dental Medicine, University of Pennsylvania
2018 – 2021

Orthodontics



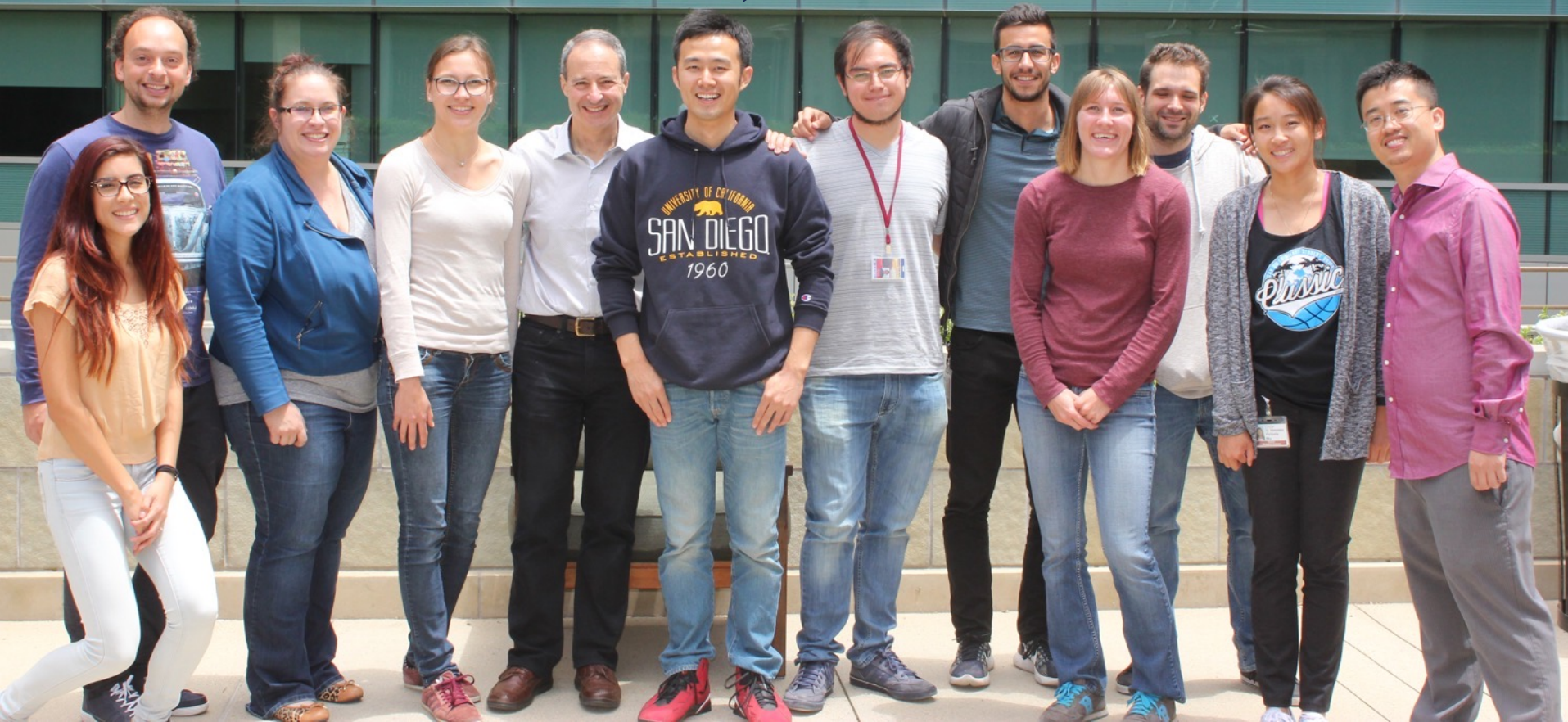
Orthodontics

Bone remodeling: The biological basis of orthodontic tooth movement



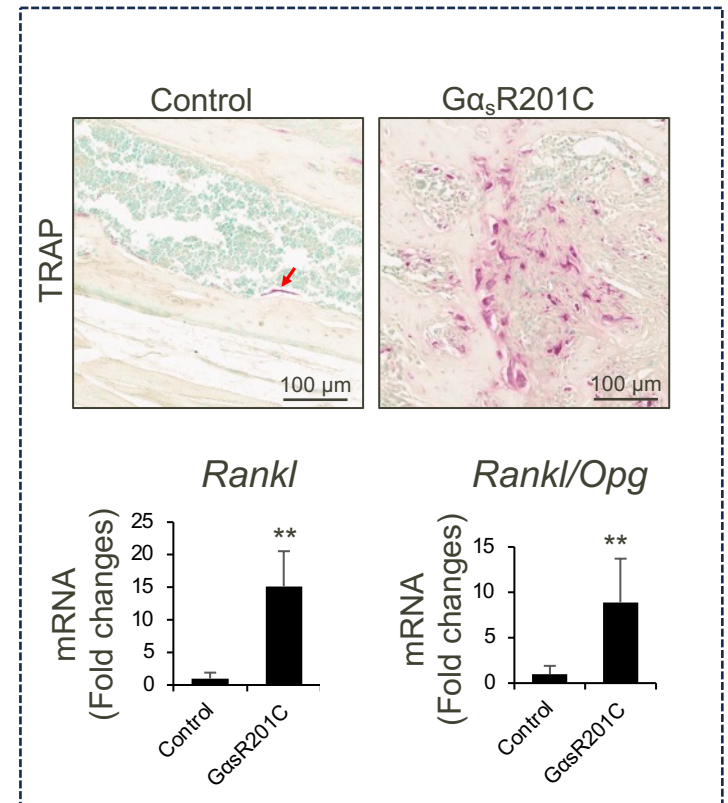
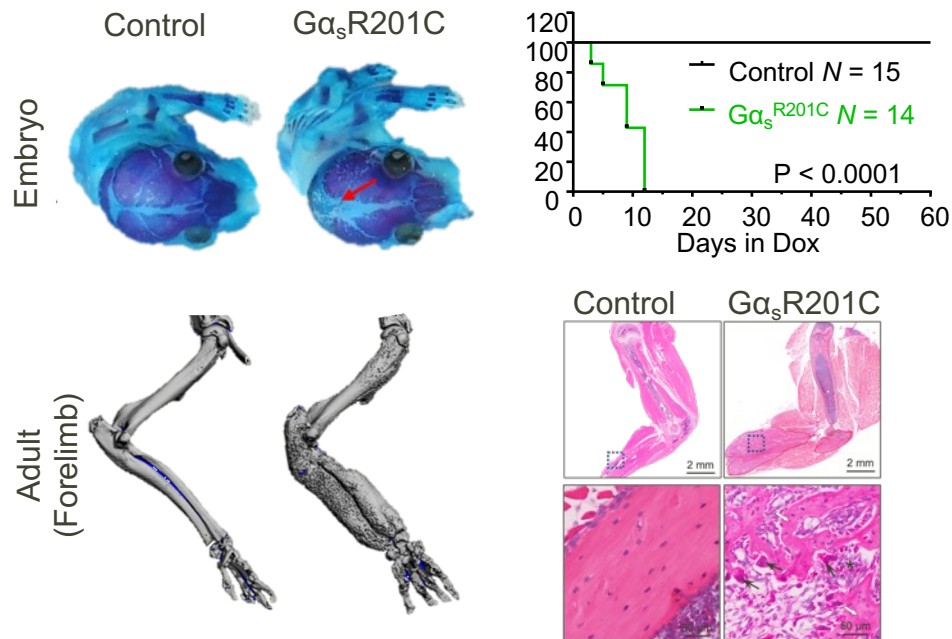
Dr. Gutkind

Xuefeng



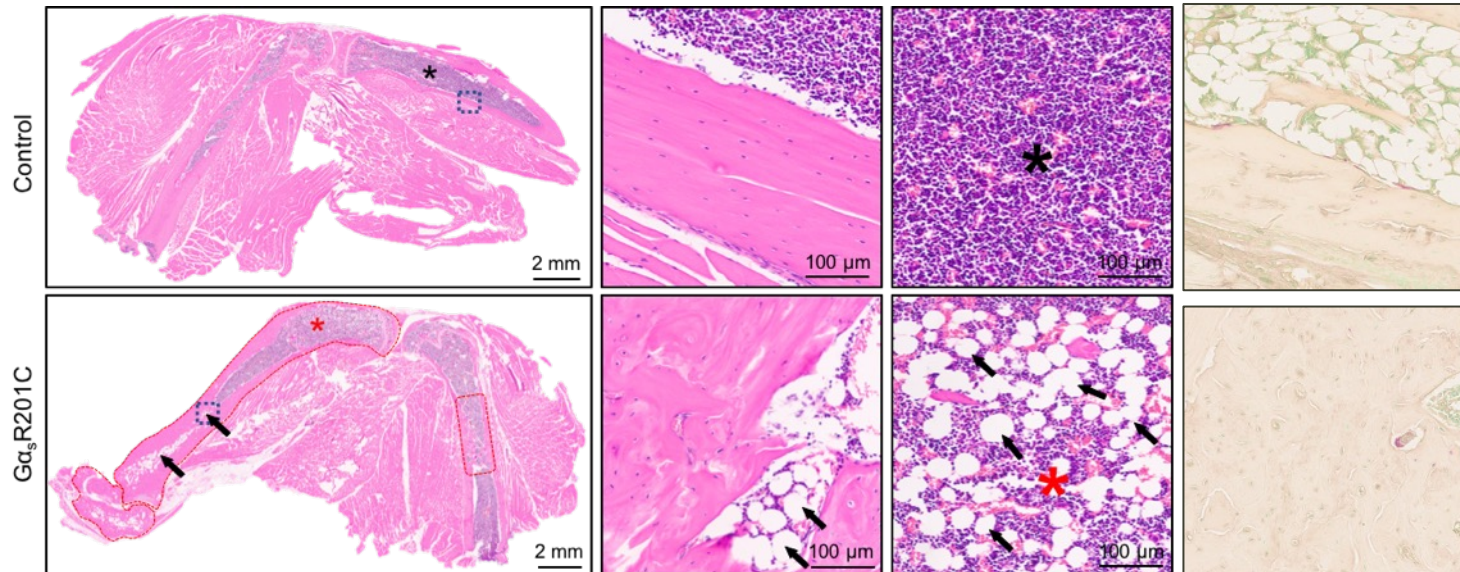
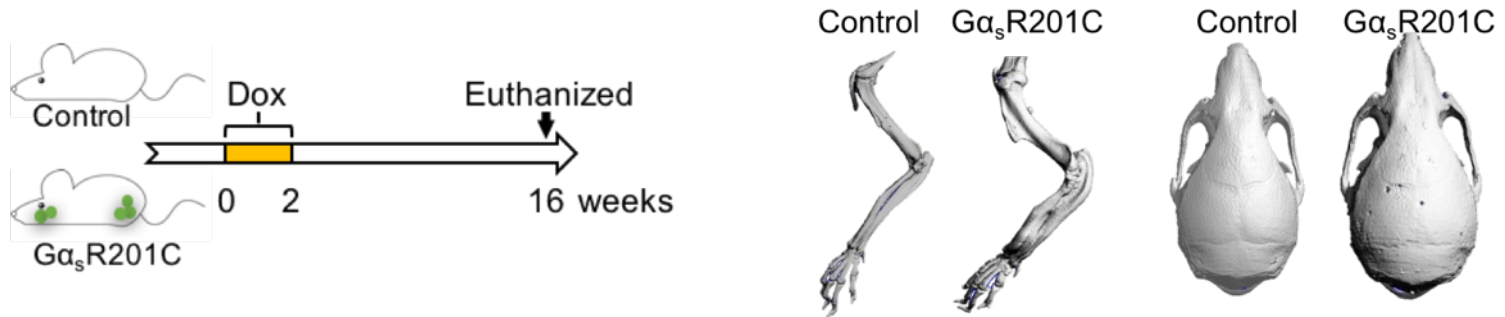
Transgenic Mouse Model of FD

Prrx1-Cre/LSL-rtTA-IRES-GFP/Tet- $G_{\alpha_s}^{R201C}$

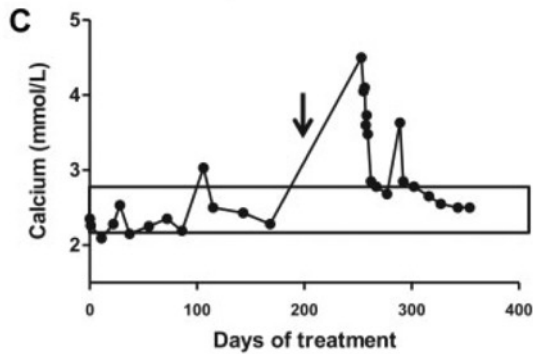
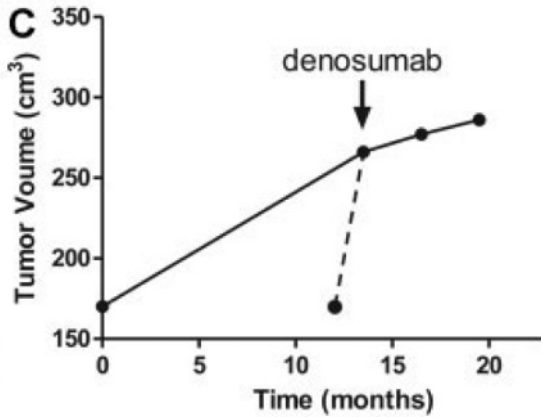


Transgenic Mouse Model of FD

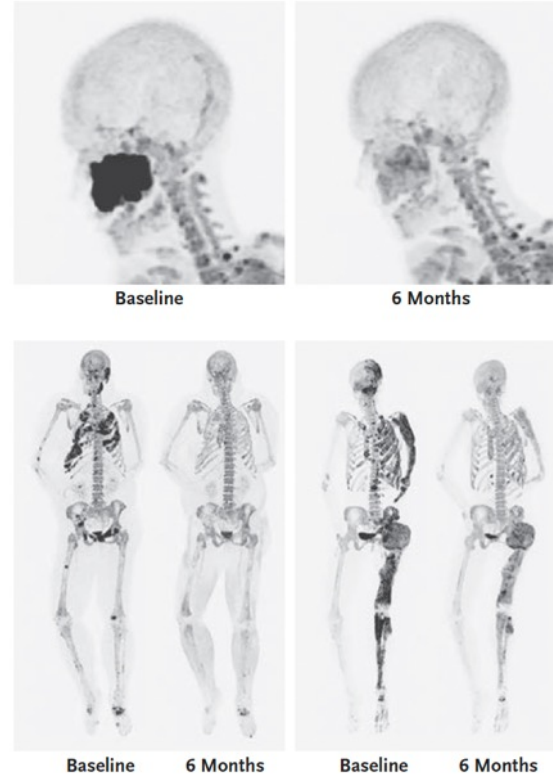
Prrx1-Cre/LSL-rtTA-IRES-GFP/Tet- $G_{\alpha_s}^{R201C}$



RANKL Inhibition Treatment for FD



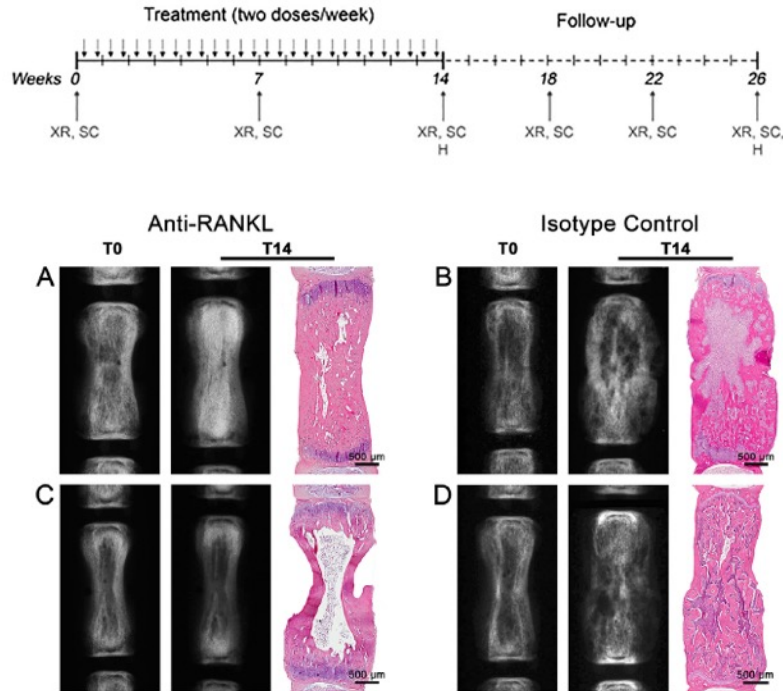
B PET-CT



Alison *et al.*, JBMR 2012, NEJM 2023

- Denosumab reduces FD expansion and bone pain
- Significant bone-turnover rebound with hypercalcemia may happen to pt after discontinuation

RANKL Inhibition Treatment for FD



Biagio *et al.*, JBMR 2019

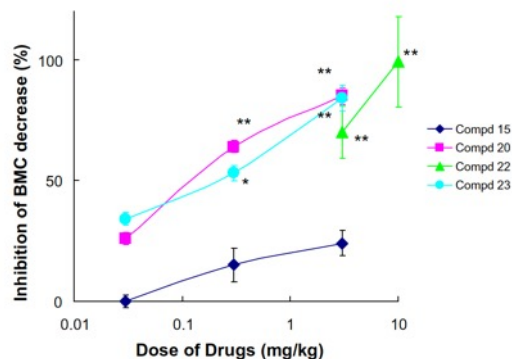
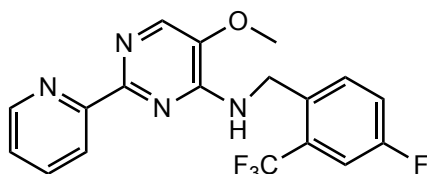
Unpublished data

Safer, more effective and convenient therapeutic options?

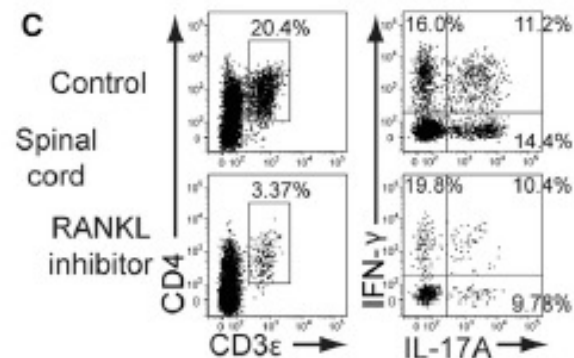
RANKL-Induced Osteoclastogenesis Inhibitors

AS2676293 (4-pyrrolidino-2- (pyridin-2-yl) pyrimidine)

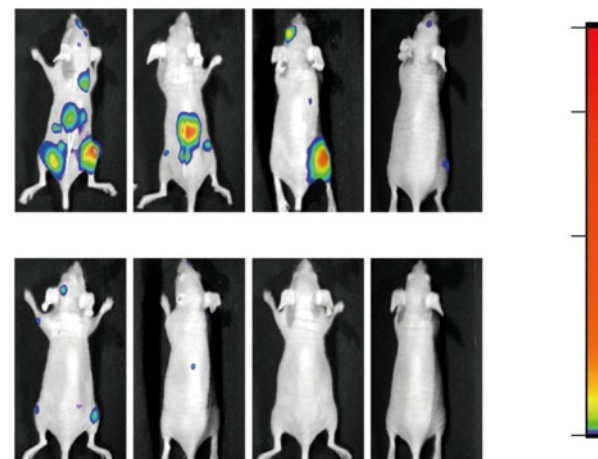
- Orally bioavailable
- Robust potency in RANKL-induced osteoclastogenesis inhibition
- Metabolic stable



Junji M. *et al*, Bioorganic & Medicinal Chemistry Letters, 2012

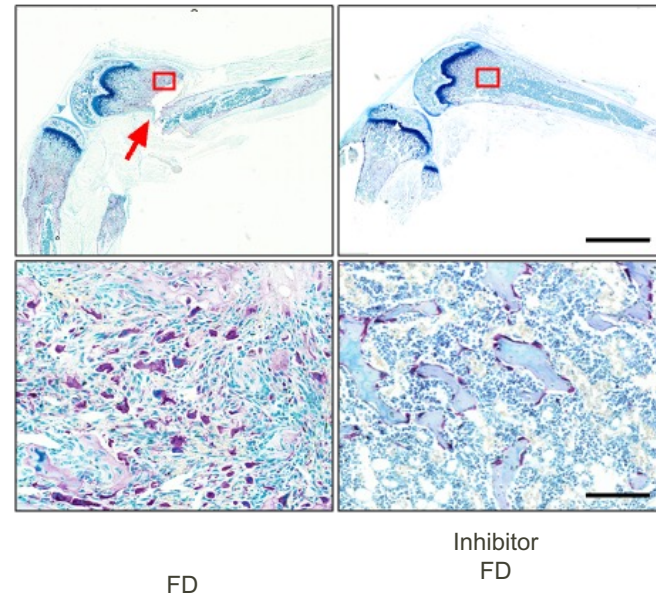
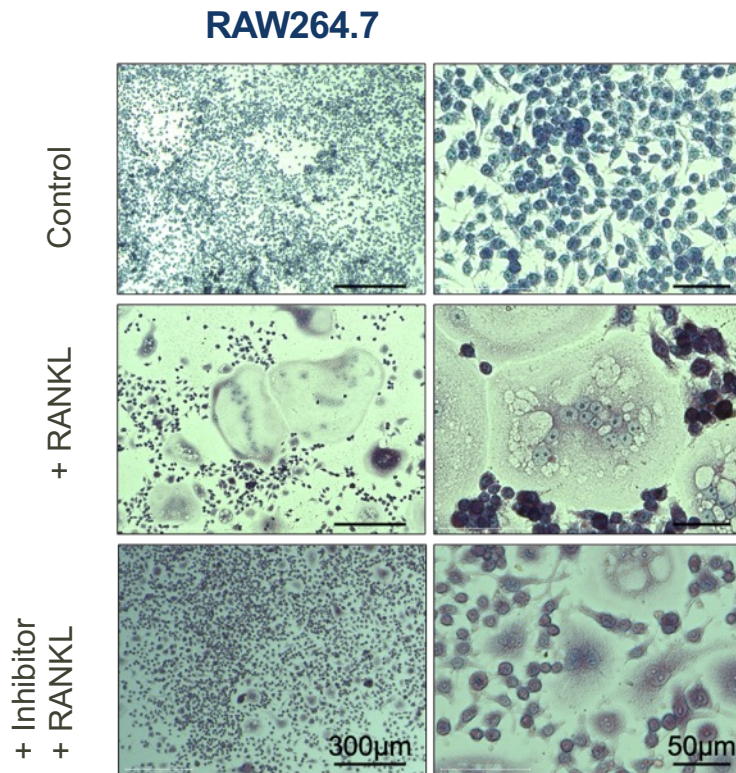


Matteo M. *et al*, Immunity, 2015

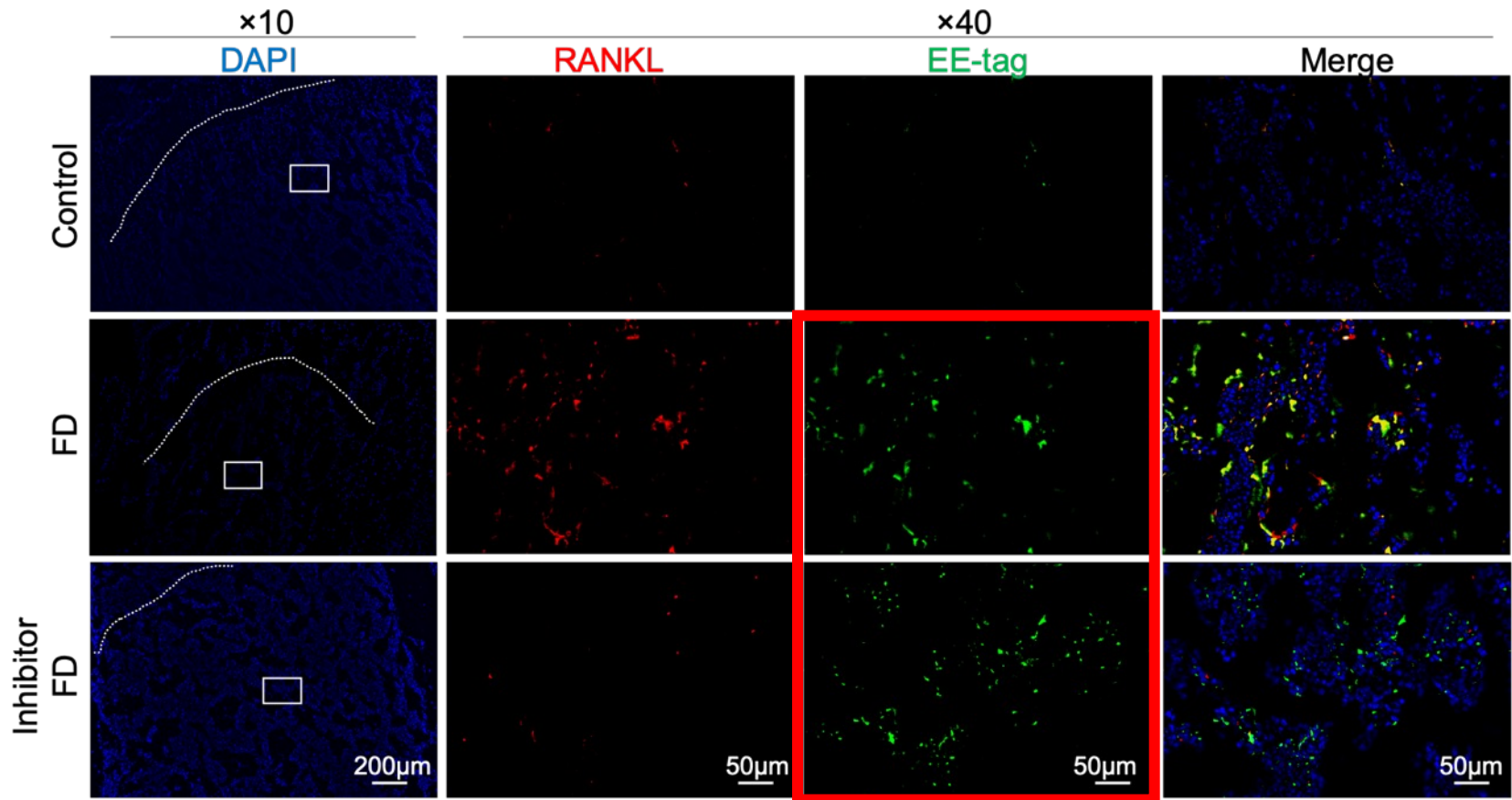


Yuta *et al*, Bone Research, 2019

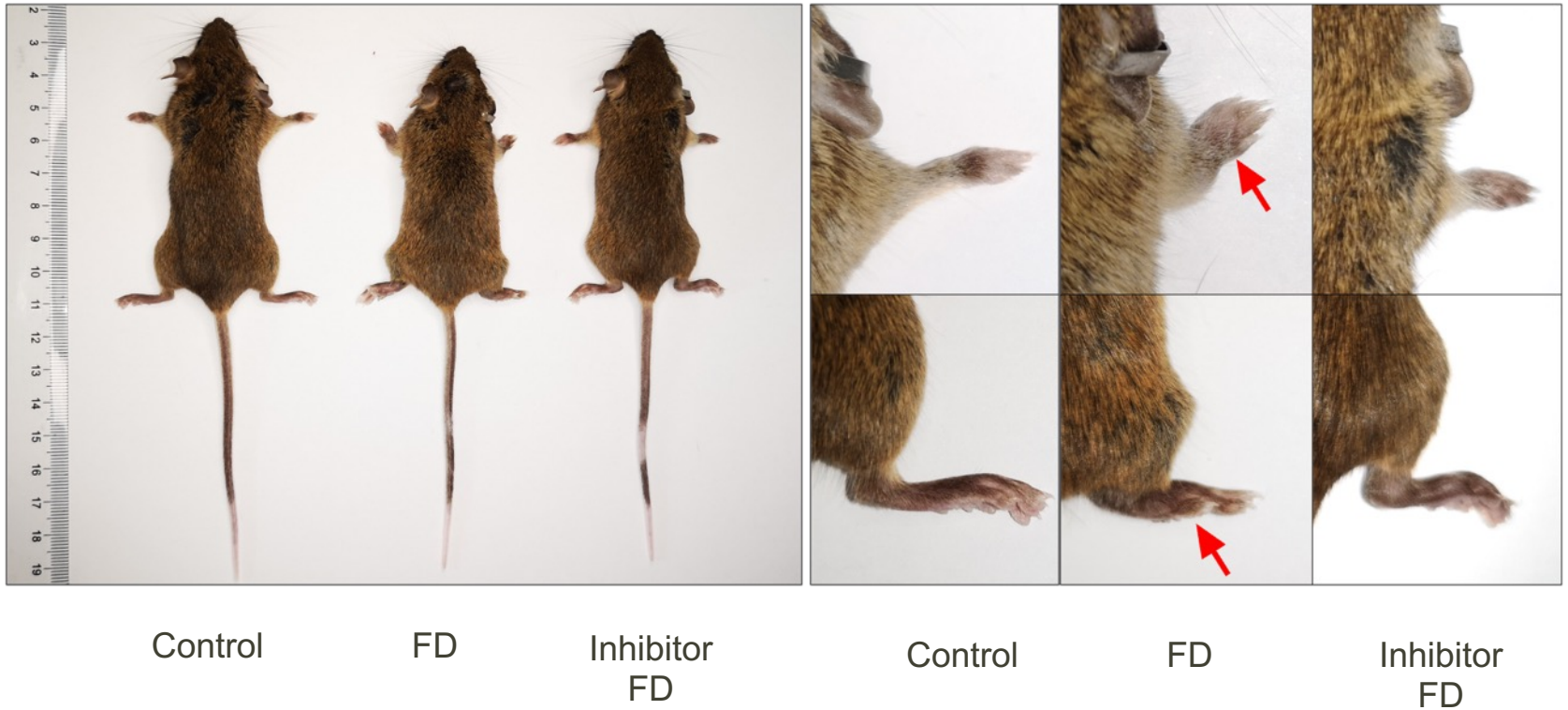
AS2676293 suppresses RANKL-Induced Osteoclastogenesis



AS2676293 suppresses RANKL-Induced Osteoclastogenesis



AS2676293 halts the progression of FD lesions



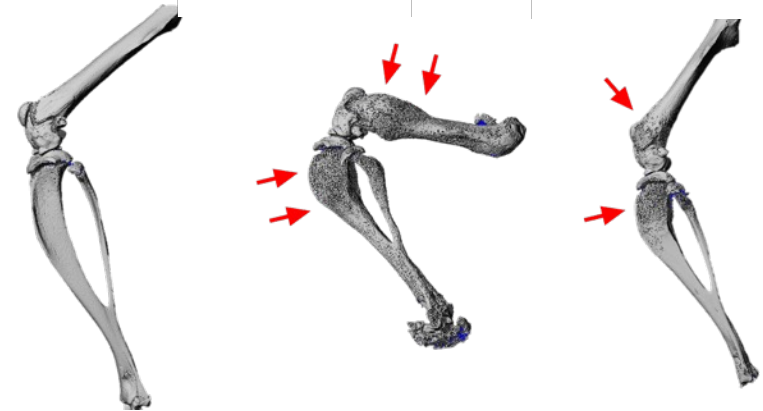
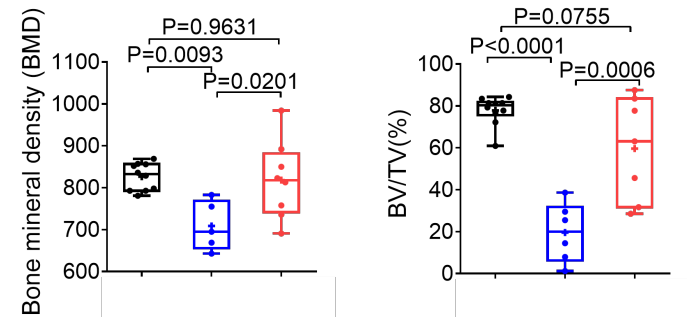
AS2676293 halts the progression of FD lesions



Control

FD

Inhibitor
FD

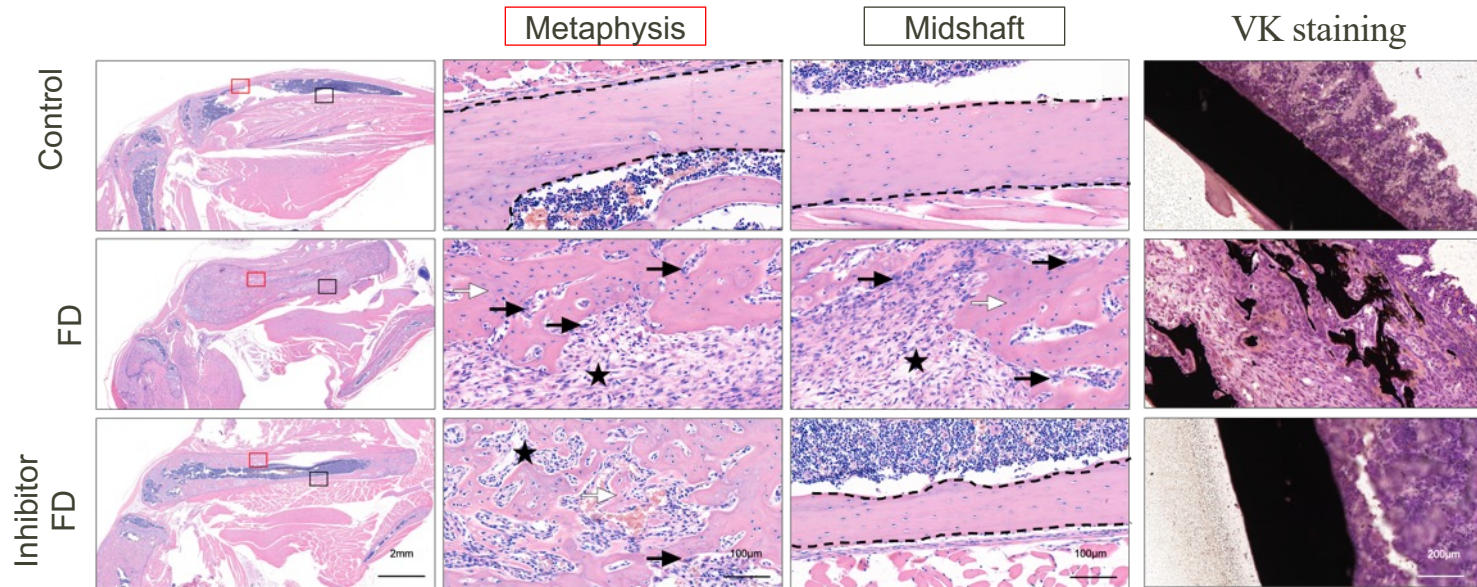


Control

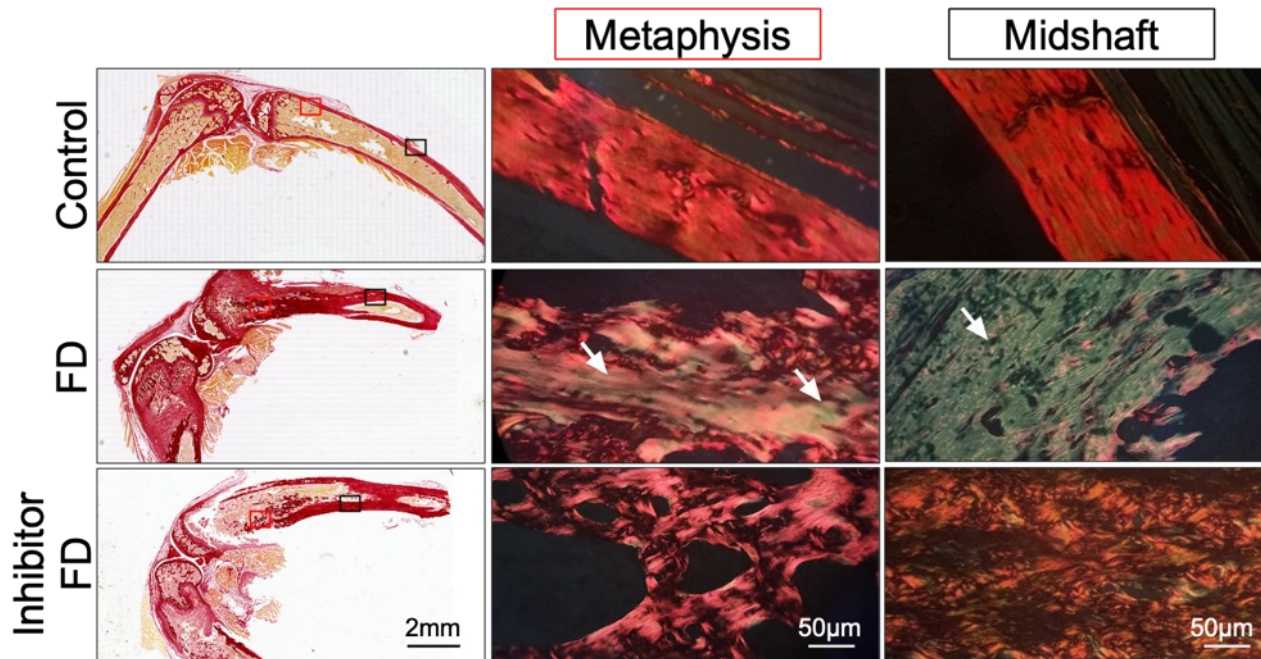
FD

Inhibitor
FD

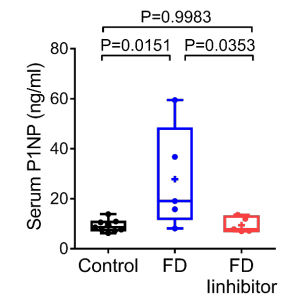
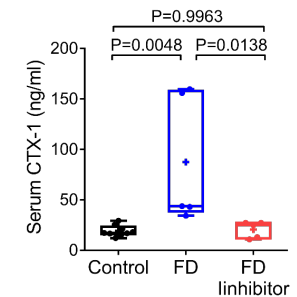
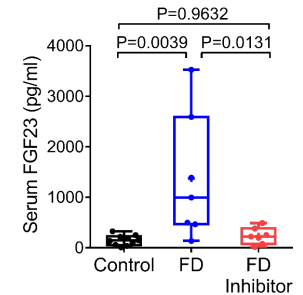
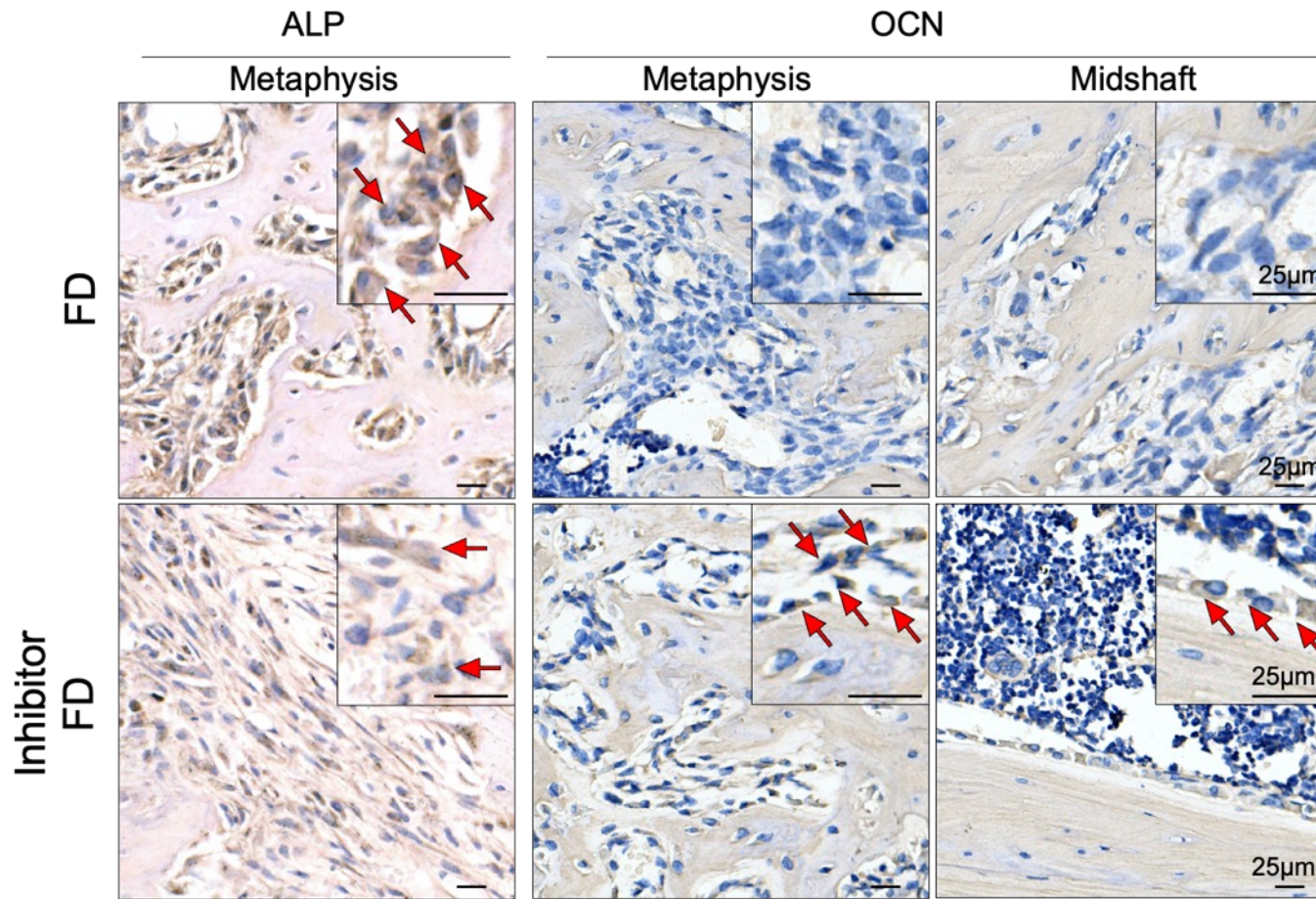
AS2676293 promotes bone remineralization



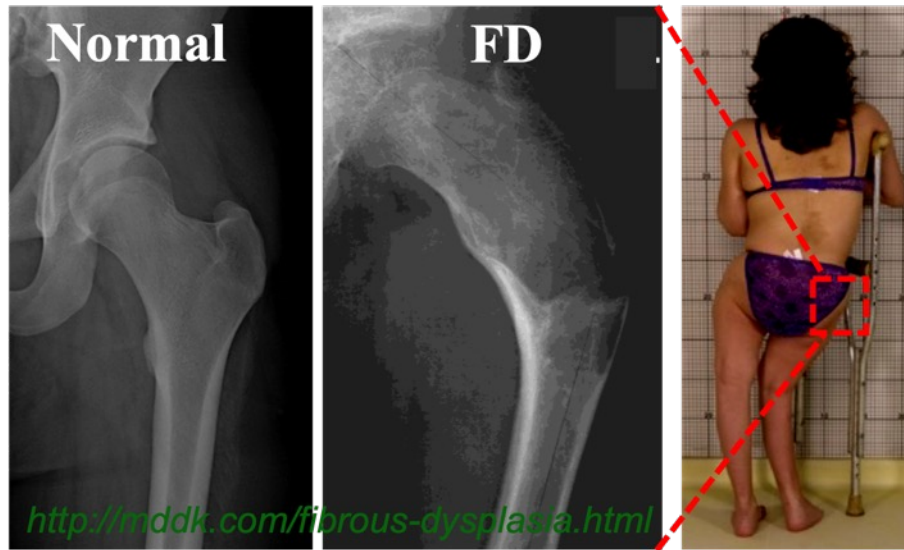
AS2676293 promotes bone remineralization



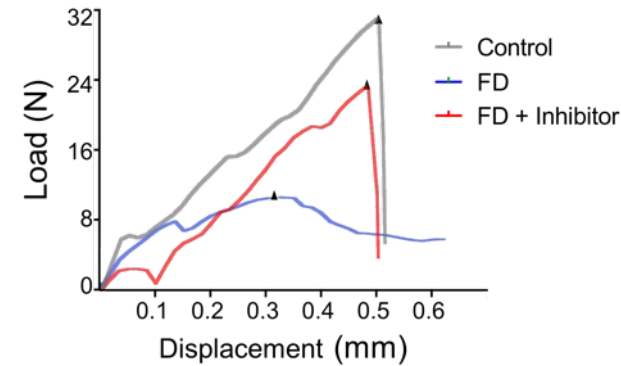
AS2676293 promotes bone remineralization



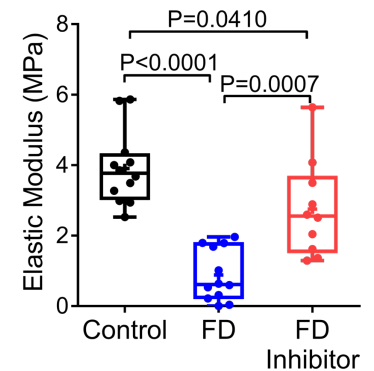
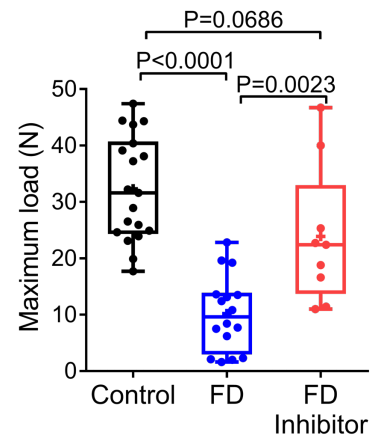
AS2676293 promotes bone remineralization

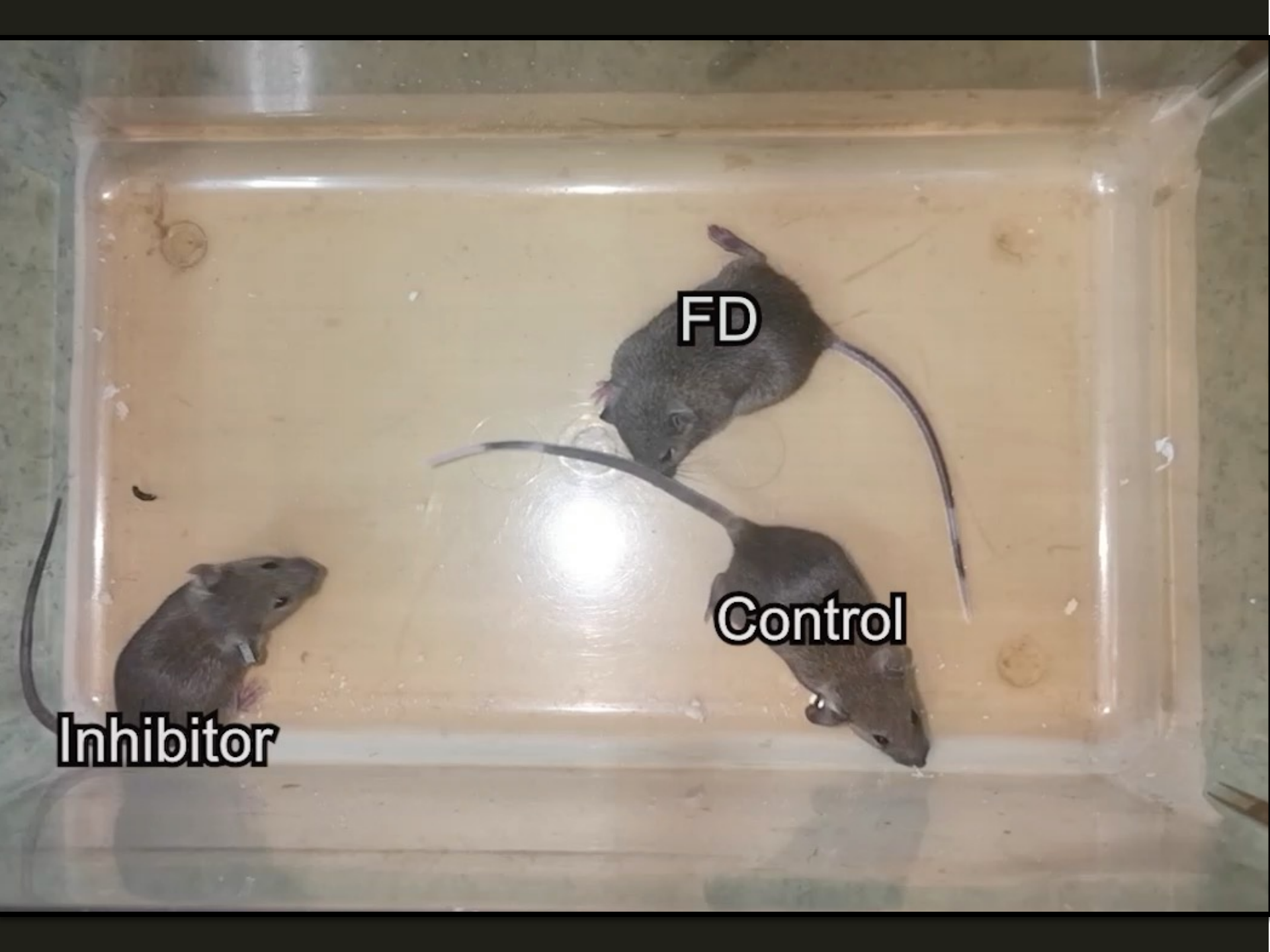


Load-displacement curve



Biomechanical analysis





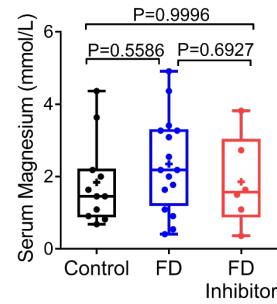
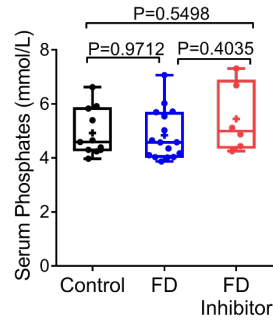
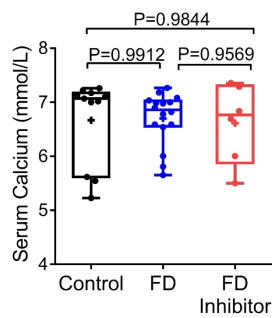
FD

Control

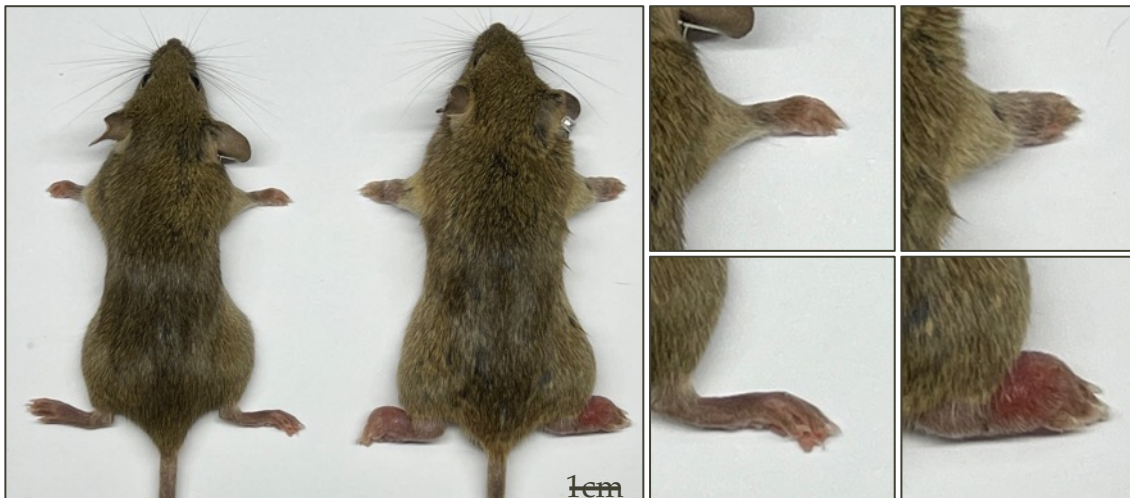
Inhibitor

Safety of AS2676293

- Safety evaluation



Liu *et al*, Bone, 2022



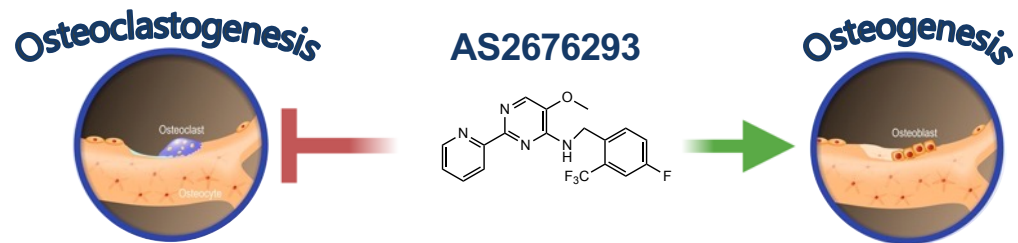
Control

FD mice after AS2676293 withdrawal

Unpublished data

Next

- Mechanism study of AS2676293 ?



Fighting FD: We Are in Action



- The prevalence of FD is 10~30/10,00,000, the most common (38.42%) benign bone disease

王军等，中国矫形外科杂志. 2018

- MAS was included in the *First Catalog of Rare Disease in China*

First Catalog of Rare Disease in China, 2018

- FD/MAS Care Center founded in 2021
 - 284 registered patients
 - Online data base program launched in 2022
 - Join FD/MAS Alliance in 2022
 - Established collaboration with 5 hospitals
 - Medical committee board established
 - ~ 20 online/on site conference

国家卫生健康委员会
科学技术部
工业和信息化部文件
国家药品监督管理局
国家中医药管理局

国卫医发〔2018〕10号

关于公布第一批罕见病目录的通知



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Qianming Chen
Ding Bai
Xianglong Han
Zhongyu Liu

Mingxu Zhou and family

FD/MAS Care Center

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骨力(FD/MAS)关爱中心