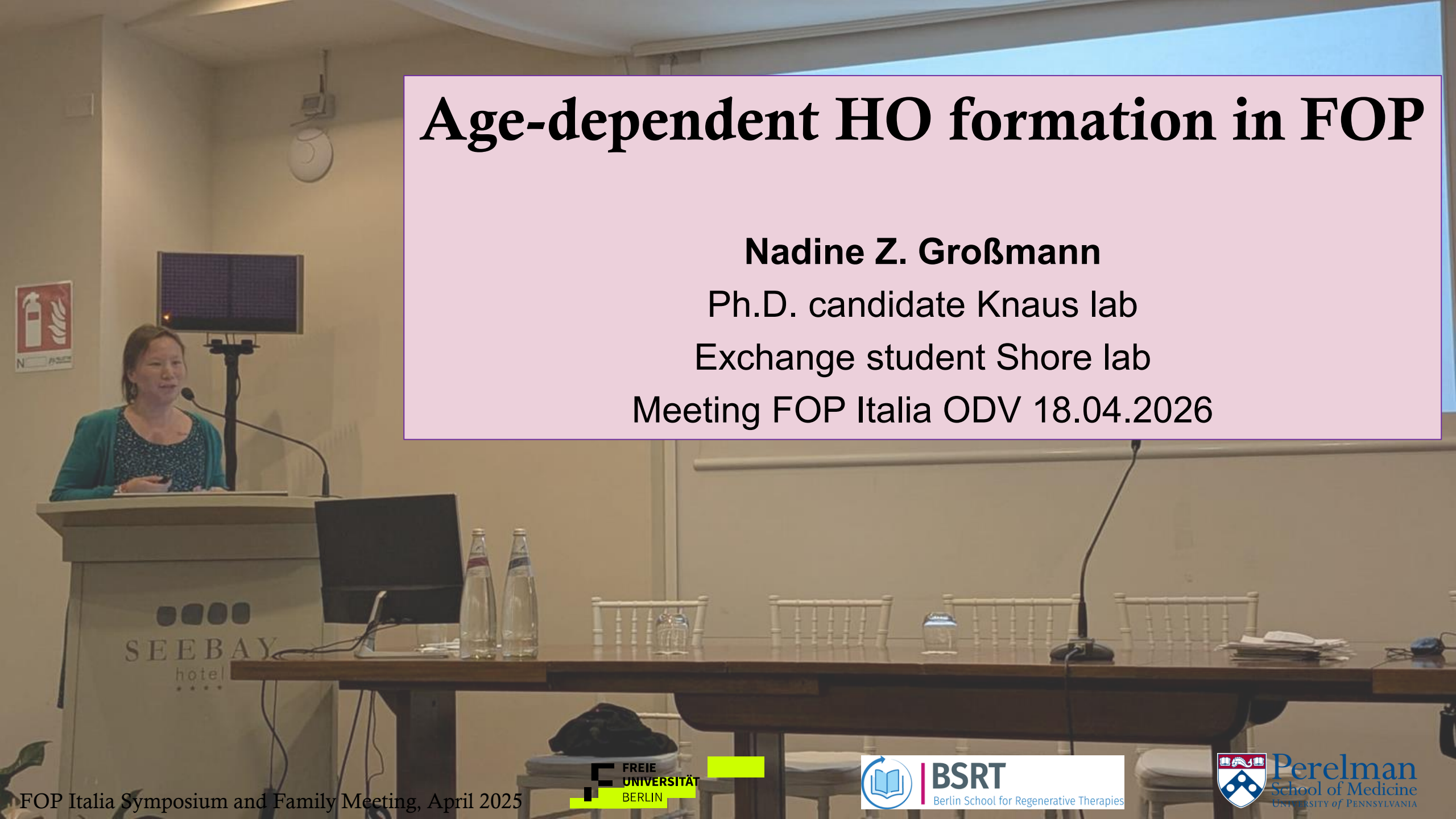


Age-dependent HO formation in FOP

Nadine Z. Großmann

Ph.D. candidate Knaus lab

Exchange student Shore lab

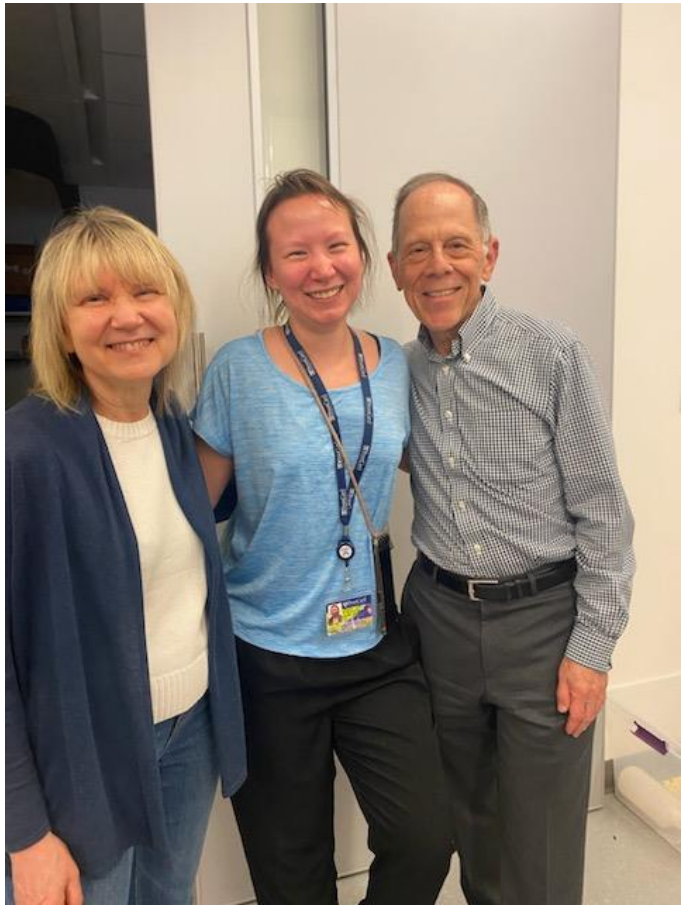
Meeting FOP Italia ODV 18.04.2026

FREIE UNIVERSITÄT BERLIN

BSRT Berlin School for Regenerative Therapies

Perelman School of Medicine University of Pennsylvania

Exchange change at the University of Pennsylvania in the Shore lab



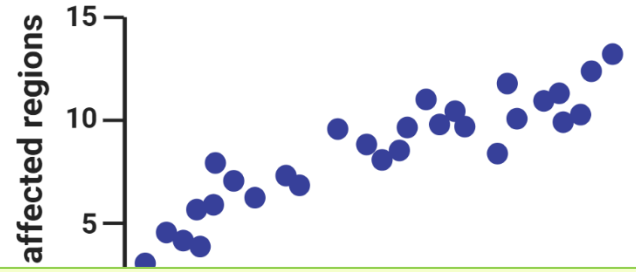
> J Bone Miner Res. 2016 Mar;31(3):650-6. doi: 10.1002/jbmr.2728. Epub 2015 Nov 14.

The Natural History of Flare-Ups in Fibrodysplasia Ossificans Progressiva (FOP): A Comprehensive Global Assessment

Robert J Pignolo [1 2 3], Christopher Bedford-Gay [4], Moira Liljesthröm [4], Blythe P Durbin-Johnson [5 6], Eileen M Shore [2 3 7], David M Rocke [5 6], Frederick S Kaplan [1 2 3]

Affiliations + expand

PMID: 27025942 PMCID: PMC4829946 DOI: 10.1002/jbmr.2728



→ Most body regions are affected before reaching the age of 30

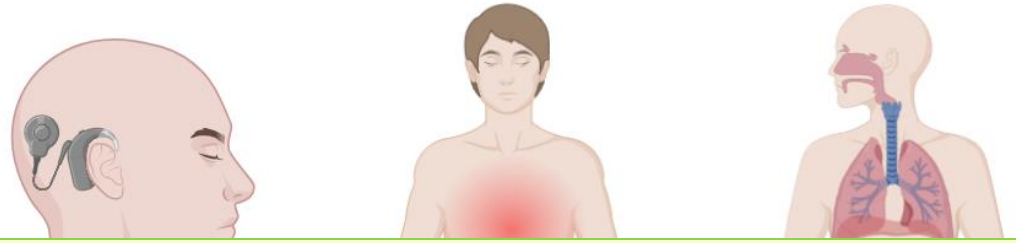
Review > Front Endocrinol (Lausanne). 2020 Jan 10:10:908. doi: 10.3389/fendo.2019.00908. eCollection 2019.

Fibrodysplasia Ossificans Progressiva (FOP): A Segmental Progeroid Syndrome

Robert J Pignolo [1 2 3], Haitao Wang [1 2 3], Frederick S Kaplan [4 5 6]

Affiliations + expand

PMID: 31998237 PMCID: PMC6966325 DOI: 10.3389/fendo.2019.00908



→ FOP displays segmental progeroid features

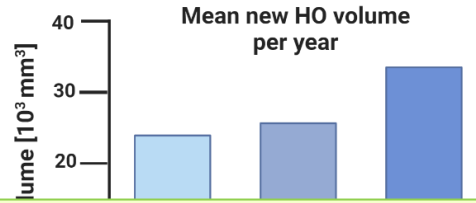
> Genet Med. 2022 Dec;24(12):2422-2433. doi: 10.1016/j.gim.2022.08.013. Epub 2022 Sep 24.

The natural history of fibrodysplasia ossificans progressiva: A prospective, global 36-month study

Robert J Pignolo [1], Geneviève Baujat [2], Matthew A Brown [3], Carmen De Cunto [4], Edward C Hsiao [5], Richard Keen [6], Mona Al Mukaddam [7], Kim-Hanh Le Quan Sang [2], Amy Wilson [8], Rose Marino [8], Andrew Strahs [8], Frederick S Kaplan [9]

Affiliations + expand

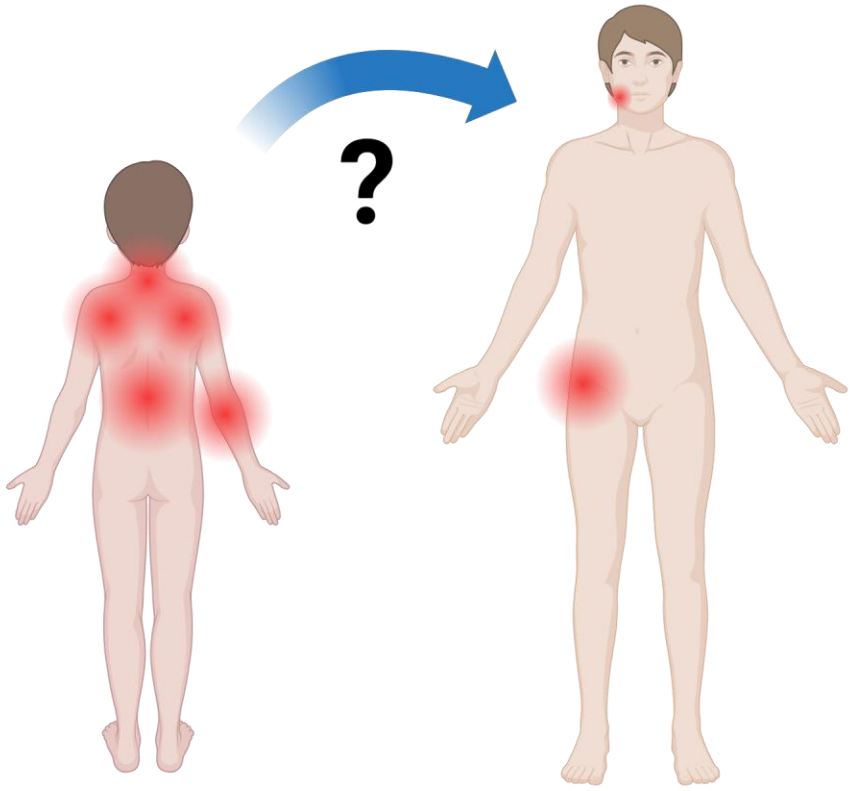
PMID: 36152026 DOI: 10.1016/j.gim.2022.08.013



→ Greatest accumulation of new HO occurs during childhood and early adulthood

Research question

Why is HO formation and disease progression more pronounced in children living with FOP compared with adults?



- Better understanding of pathomechanism
- Development of treatments tailored to age groups
- More targeted research and clinical studies
- New insights into disease progression
- Strengthening the perspective of affected individuals

uCT to quantify HO volume

JBMR Plus, 2025, **9**, ziaf123
https://doi.org/10.1093/jbmrpl/ziaf123
Advance access publication: July 29, 2025
Research Article

An inducible knock-in mouse model of fibrodysplasia ossificans progressiva shows spontaneous formation of heterotopic ossification

Salin A. Chakkalakal[1,2], Nadine Z. Großmann[1,2,3,4], Loreilys Mejías Rivera[1,2], Douglas W. Roberts[1,2], Maurizio Pacifici[5], Foteini Mourkioti[1,6,7], Eileen M. Shore[1,2,8,*]

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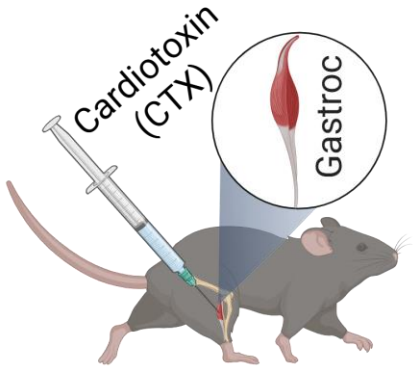
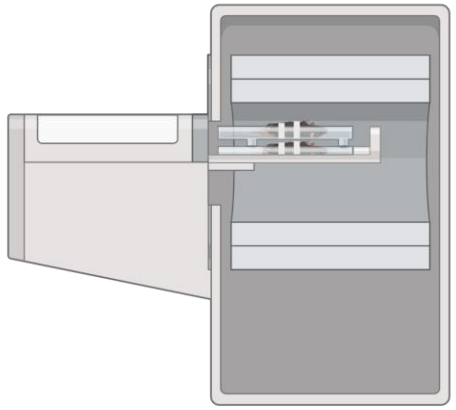
[2]The Center for Research in FOP and Related Disorders, Department of Orthopaedic Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, United States
[3]Department of Biology, Chemistry, Pharmacy, Freie Universität Berlin, 14195 Berlin, Germany
[4]Berlin School for Regenerative Therapies, 13353 Berlin, Germany
[5]Division of Orthopaedic Surgery, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, United States
[6]Department of Cell and Developmental Biology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, United States
[7]Penn Institute for Regenerative Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, United States
[8]Department of Genetics, Perelman School of Medicine at the University of Pennsylvania, Clinical Research Building, 415 Curie Blvd, Philadelphia, PA 19104, United States

*Corresponding author: Eileen M. Shore, Department of Orthopaedic Surgery, University of Pennsylvania, 309A Stemmler Hall, 3450 Hamilton Walk, Philadelphia, PA 19104, United States (shore@pennmedicine.upenn.edu).



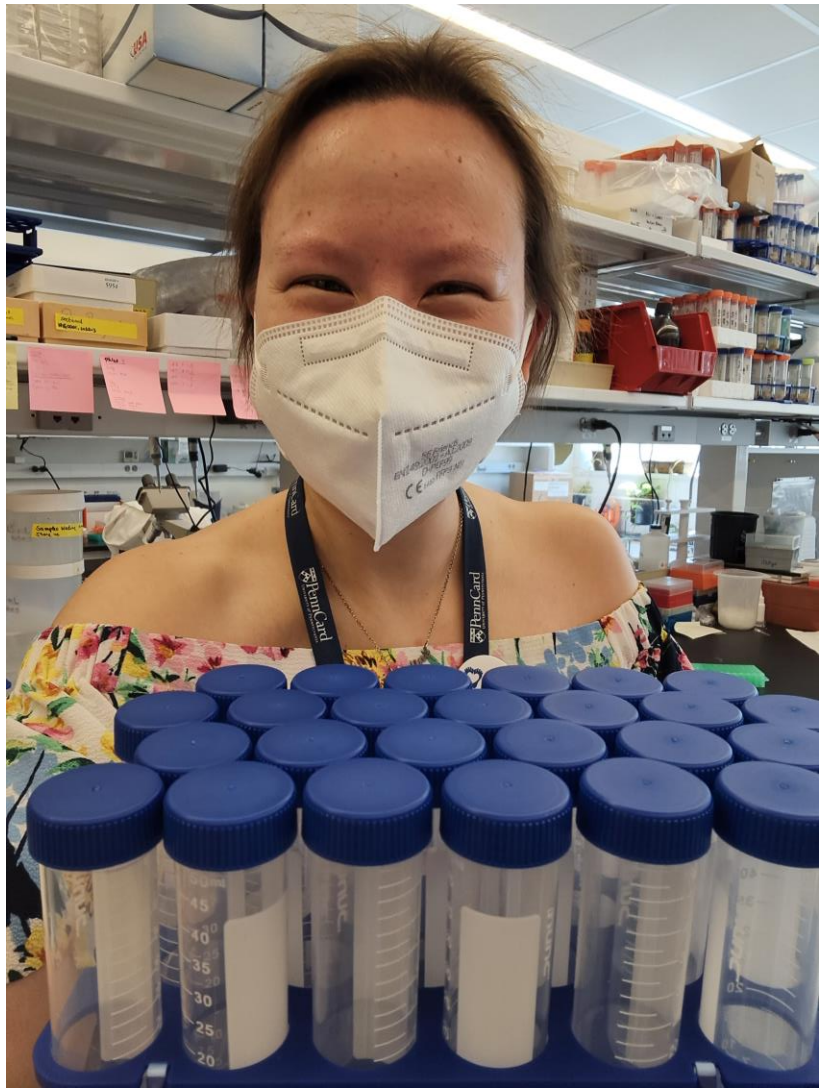
3, 7, 21 days
postinjury (dpi)

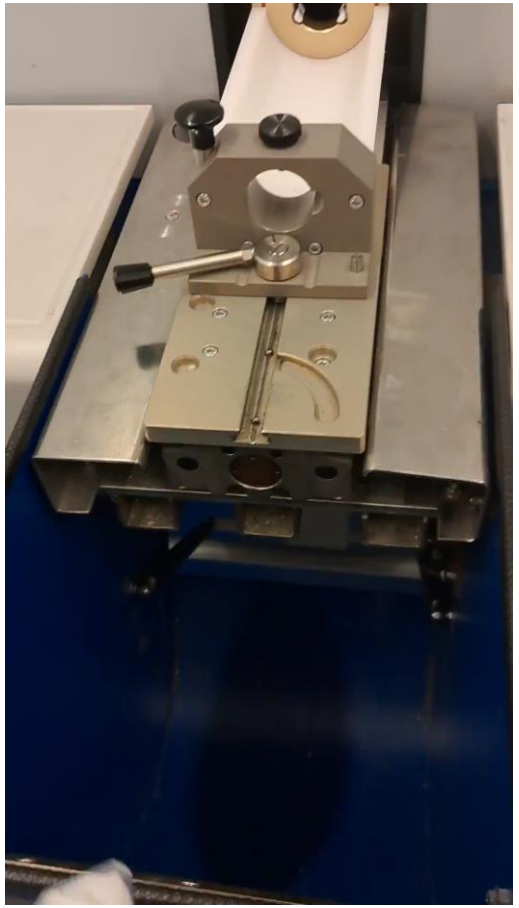


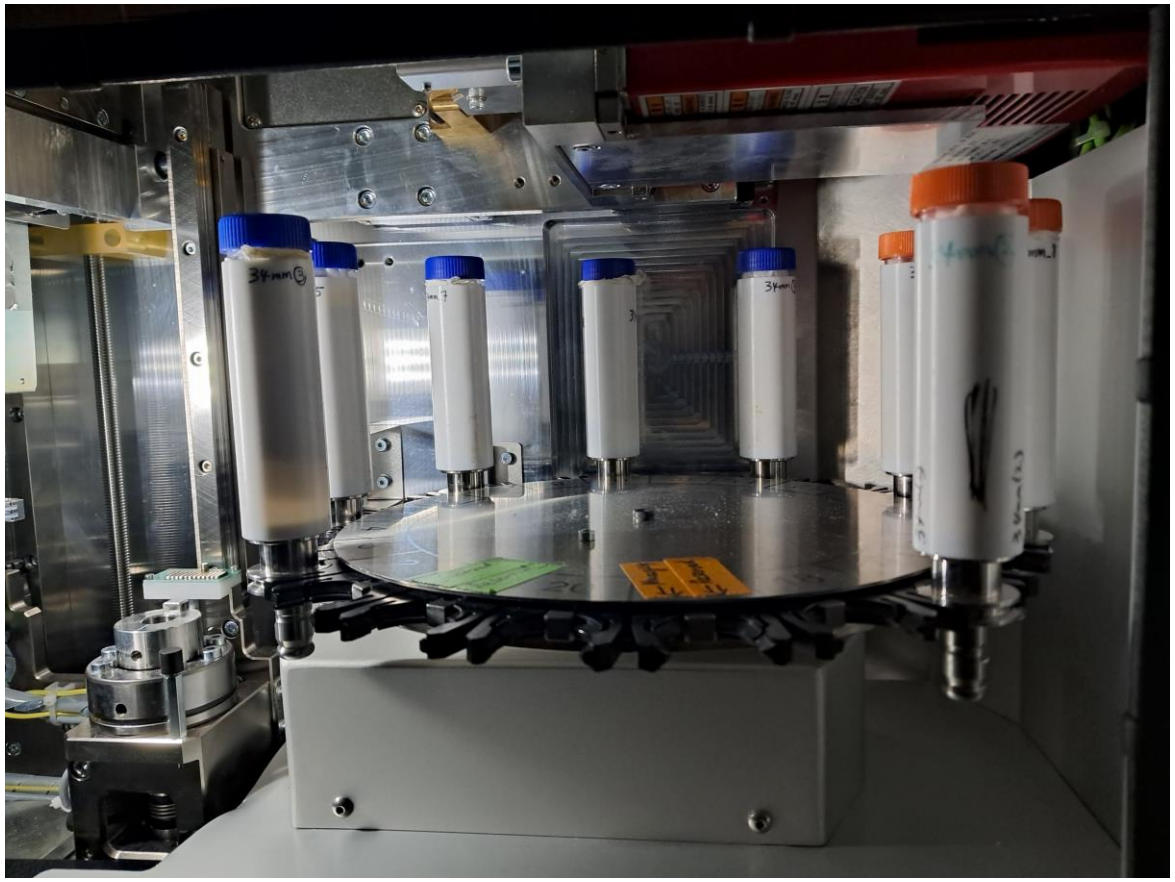
WT-*Acvr1*$^{+/+}$ or FOP-*Acvr1*$^{R206H/+}$
1.5/4/10-month-old

3 dpi = inflammation
7 dpi = chondrogenesis
21 dpi = mineralized bone

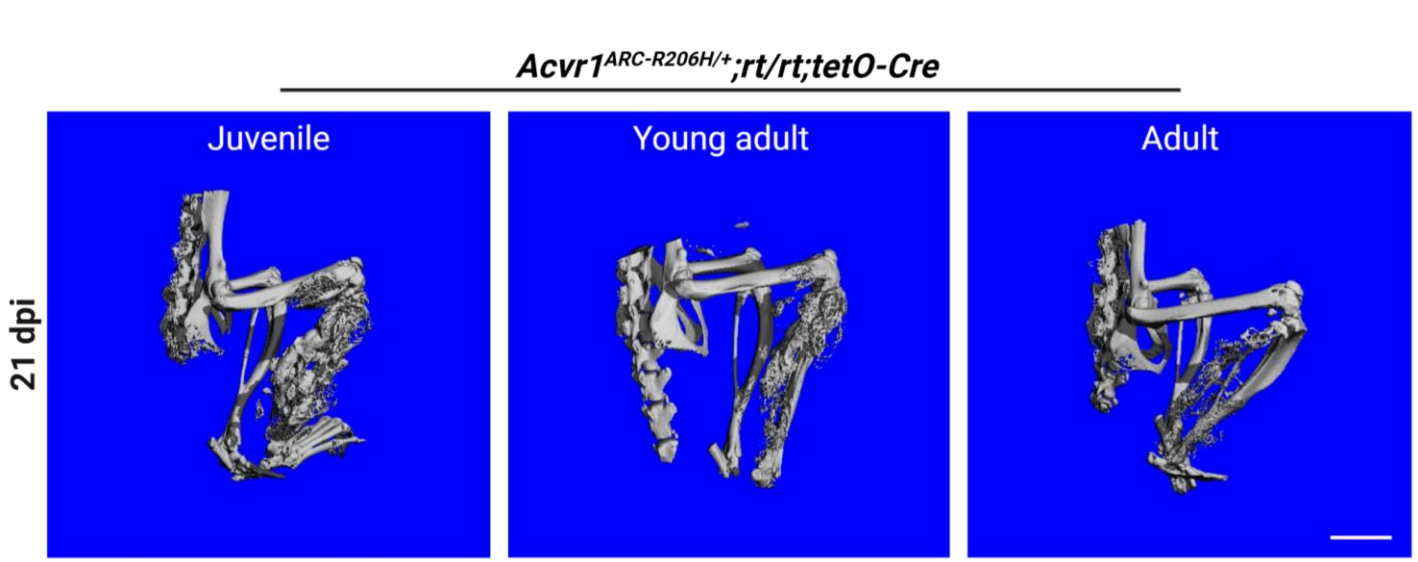
microCT & quantification
of HO volume

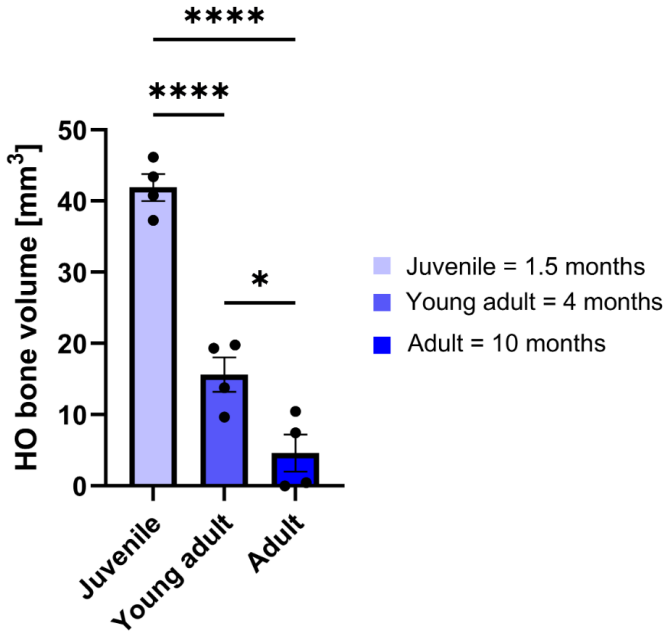

PennCard
PennCard





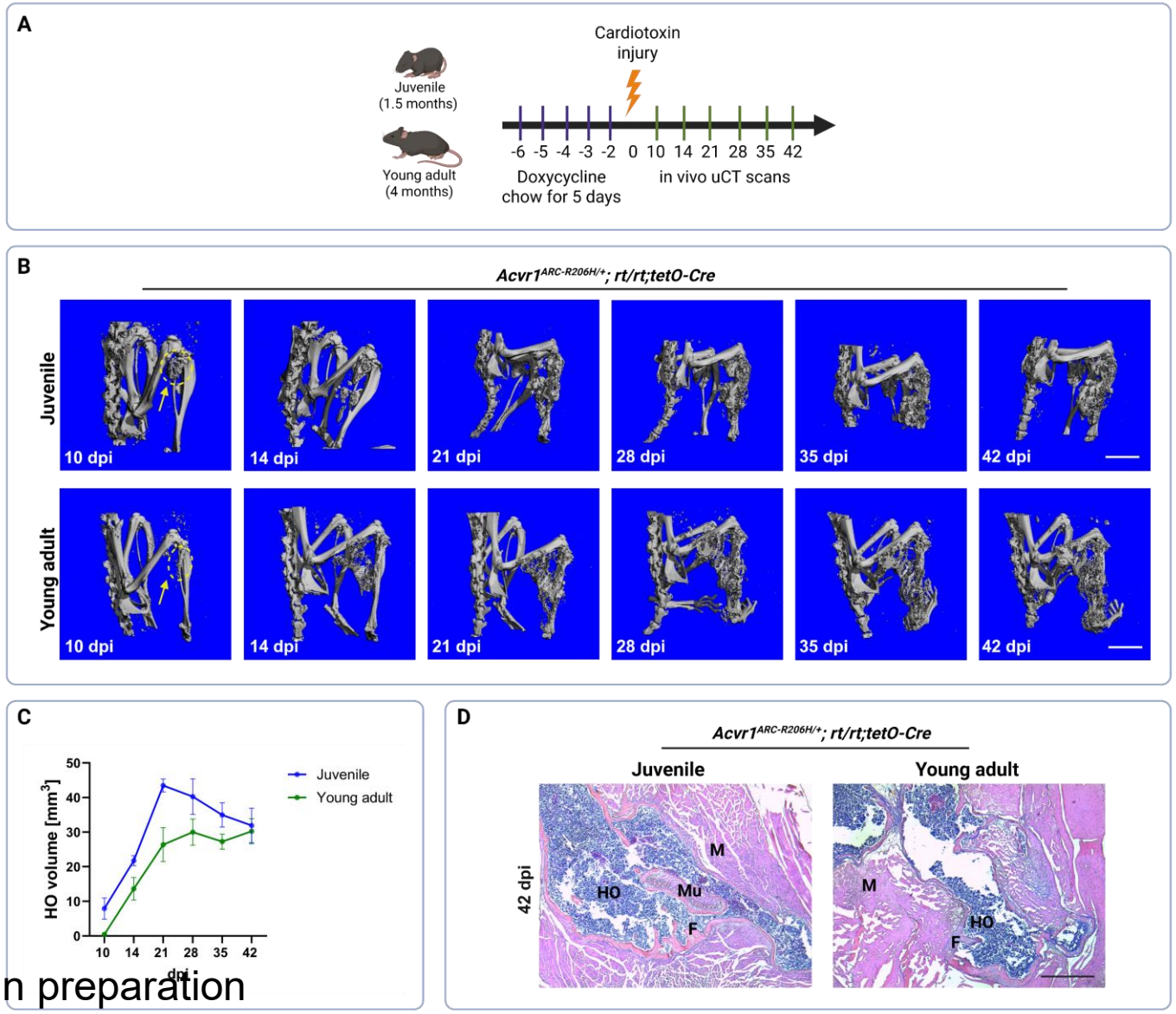
Juvenile FOP-mice form significantly more HO than adults at 21 dpi





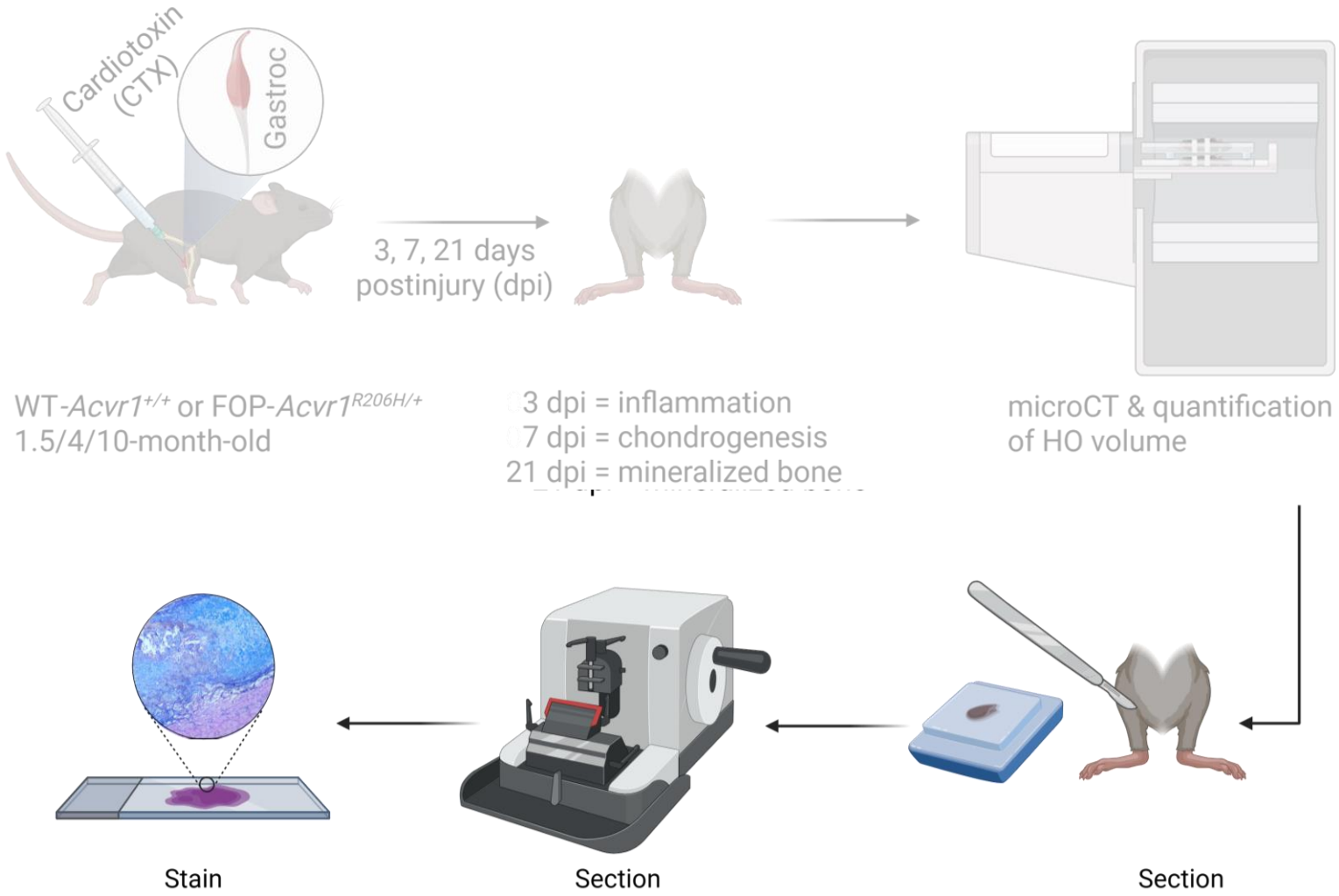
Großmann et al., in preparation

HO formation is detected earlier in juvenile FOP-mice relative to adult

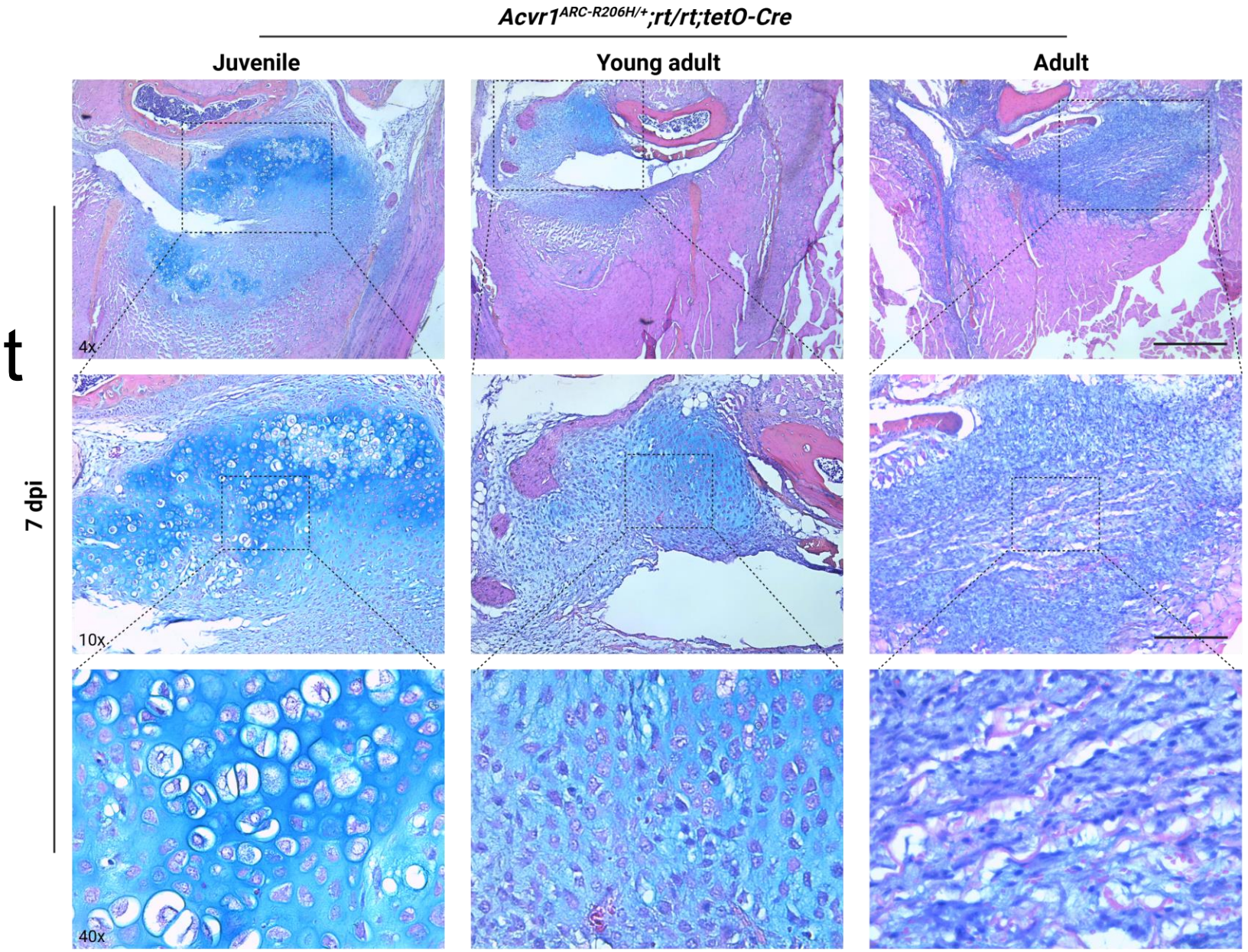


Großmann et al., in preparation

Histologic analysis to visualize structure and organization of muscle tissue



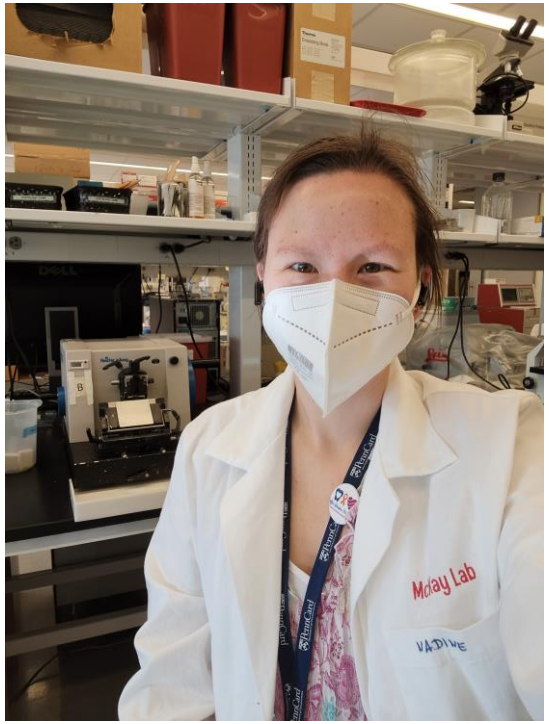
Adult FOP tissue sections show delayed chondrogenesis at 7 dpi



Scale bars: 0.5 mm,0.2 mm, 0.05 mm

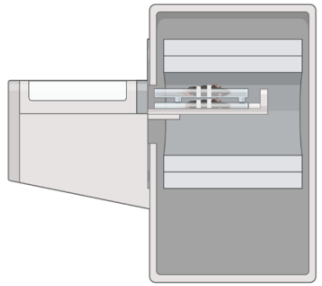
Juvenile = 1.5 mths; Young adult = 4 mths; Adult: 10 mths

Großmann et al., in preparation

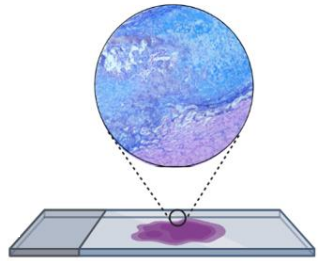

Mcfay Lab

Summary

- Youngest FOP-*Acvr1*$^{R206H/+}$ mice formed an significantly **increased volume of endochondral HO** compared to adult FOP-*Acvr1*$^{R206H/+}$ mice
- In vivo uCT scans showed **earlier onset of HO formation** in juvenile FOP-*Acvr1*$^{R206H/+}$ mice
- At 7 dpi, adult FOP-*Acvr1*$^{R206H/+}$ tissue sections reveal persisting presence of fibroblasts → **delayed muscle regeneration**



microCT & quantification of HO volume

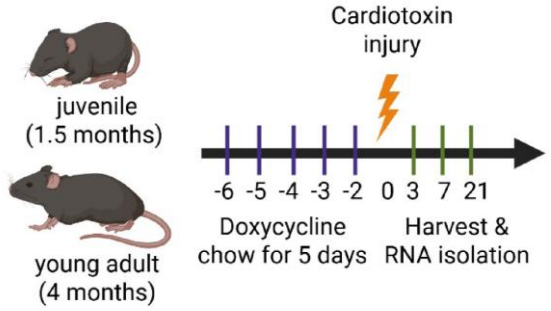


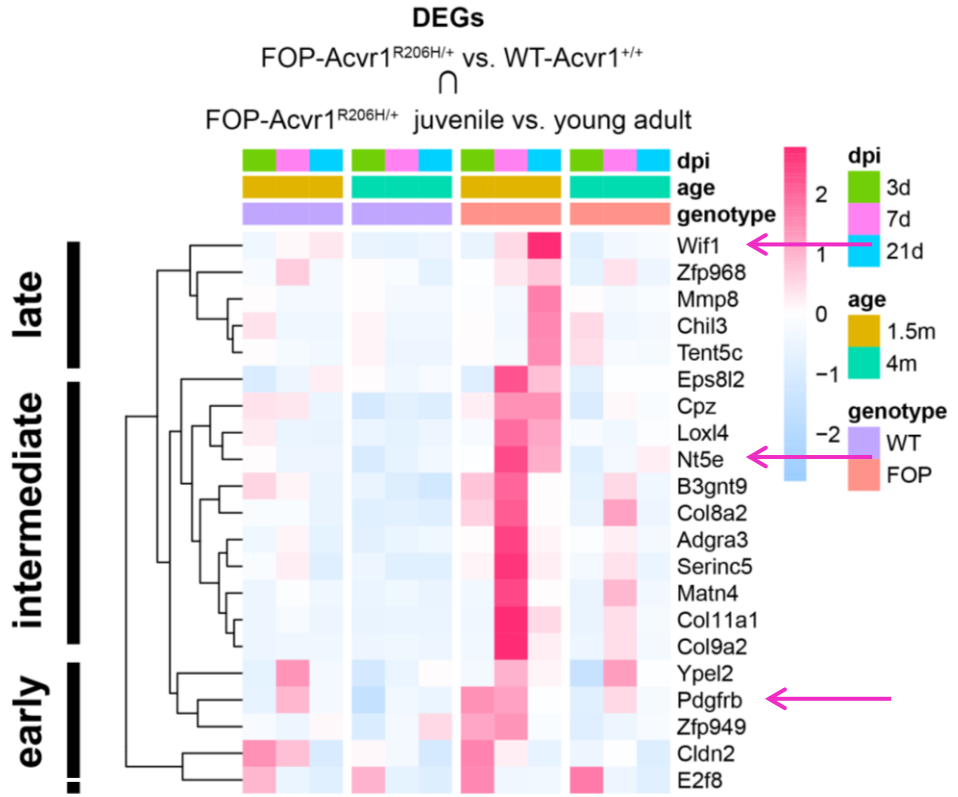
H&E/Alcian Blue staining

→ Age affects formation of HO

Backup

At 7 dpi juvenile FOP-mice showed an enhanced expression of genes related to components



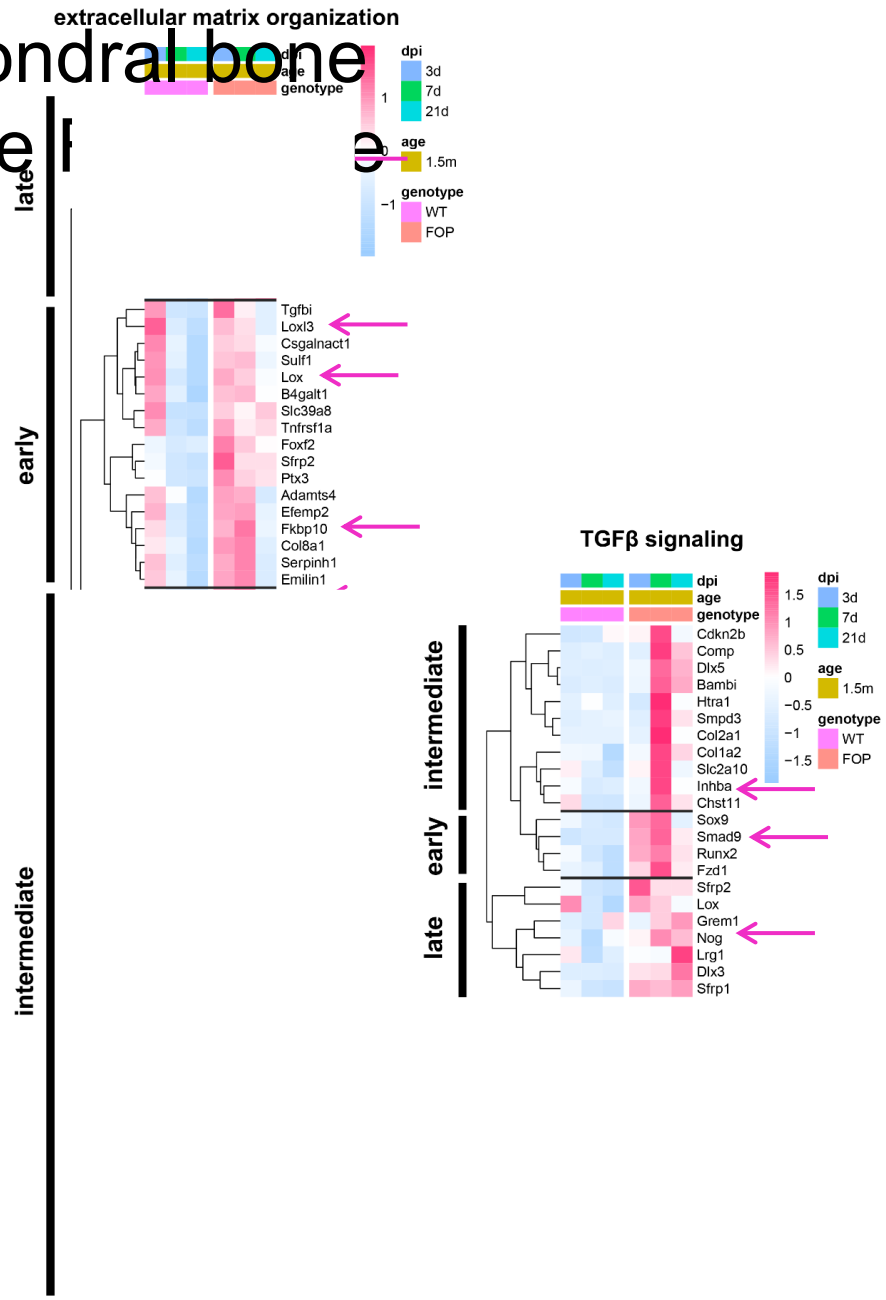


- Early: ***Pdgfrb*** (angiogenesis and migration)
- Intermed.: ***Nt5e*** (mutations can cause rare arterial and joint calcification)
- Late: ***Wif1*** (antagonist of the Wnt signaling pathway)

Großmann et al., in preparation

ECM organization, TGFβ signaling, and endochondral bone morphogenesis pathways are enriched in juvenile F e

- Genes enriched at an early (3 dpi) intermediate (7 dpi) or late (21 dpi) stage
- ECM organization:
  - Early: ***Lox*** (crosslinks collagen and elastin in the ECM), ***Fkbp10*** (crucial for collagen synthesis, folding, and ECM assembly, mutations cause OI Type XI)
  - Intermed.: ***Sox9*** (essential for chondrocyte differentiation and cartilage formation), ***Ihh*** (promotes chondrocyte differentiation and regulates osteoblast differentiation)
  - Late: ***Mmp9 (***involved in endochondral osteogenesis)
- TGFβ signaling:
  - Early: ***Smad9***
  - Intermed.: ***Inhba***
  - Late: ***Nog, Grem1*** (BMP antagonists)
- Endochondral bone morphogenesis:
  - Early: ***Sox9***
  - Intermed.: ***Comp*** (chondrocyte proliferation)
  - Late: ***Mmp13*** (degrades type II collagen)



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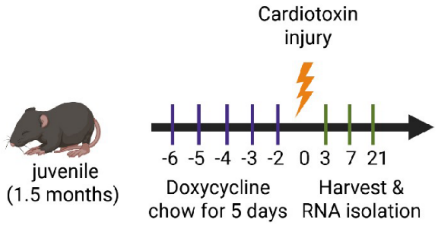

- Number of upregulated DEGs increases over time
- Only a single term, circulatory system development, was enriched starting at 3 dpi and remained enriched through 21 dpi
- From 7 dpi onward, enrichment was observed for genes associated with vascular development, chondrogenesis, osteogenesis, and inflammatory responses
- Genes related to the TGFβ superfamily signaling pathway showed peak expression at 7 dpi