



Western
Bone & Joint Institute

Endogenous Mechanisms of Cartilage Healing

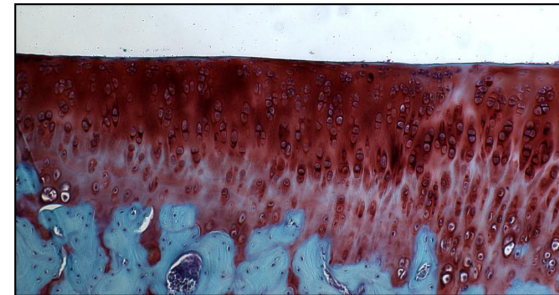
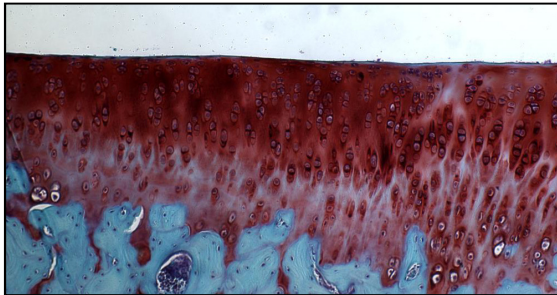
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Cartilage Regeneration in OA

Exogenous regeneration
Provide exogenous cells,
scaffolds, molecules to the joint

Endogenous regeneration
Stimulate cells in the joint to
regenerate joint tissues



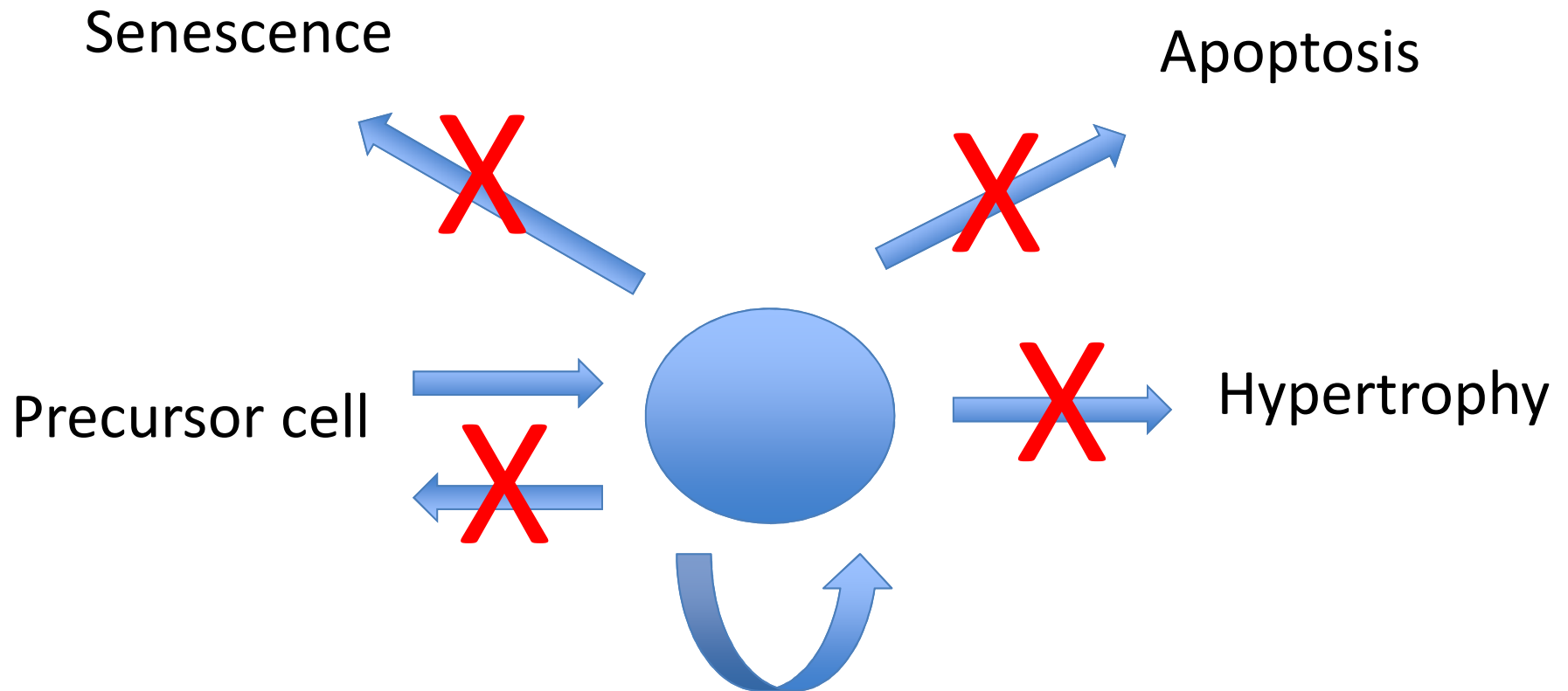
Correct OA stimulus

Correct OA stimulus

Can cartilage regenerate ?

- Evidence for precursor cells in cartilage and joint (reviewed in Jiang & Tan, NRR 2015)
- Repair of articular defects in mice is dependent on genetic background and age (Eltawil et al, OAC 2009)

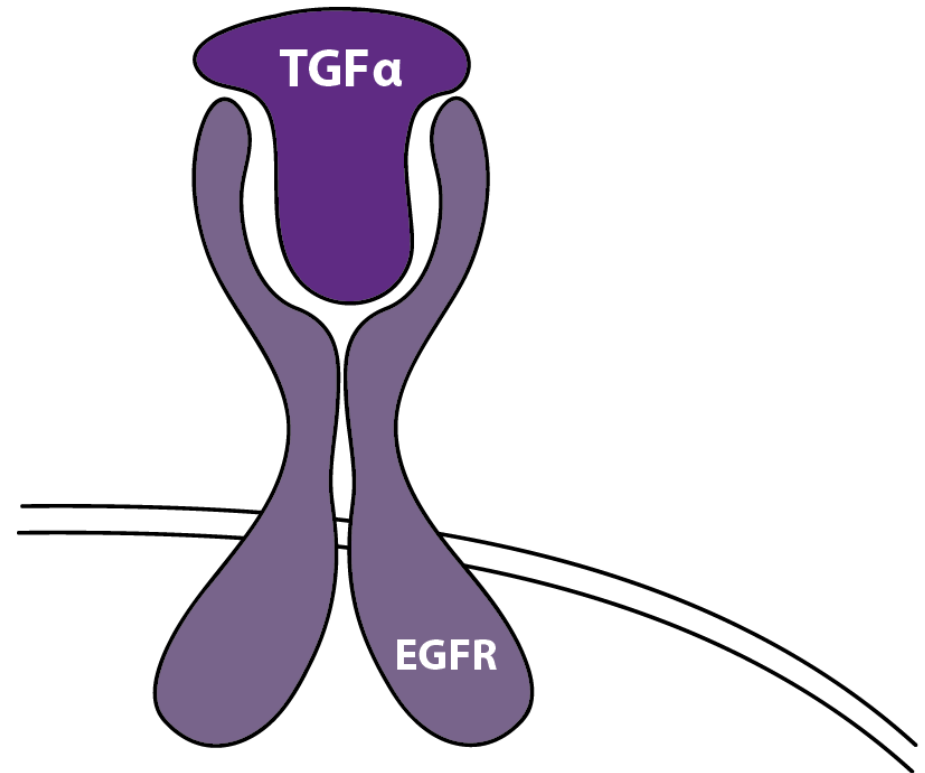
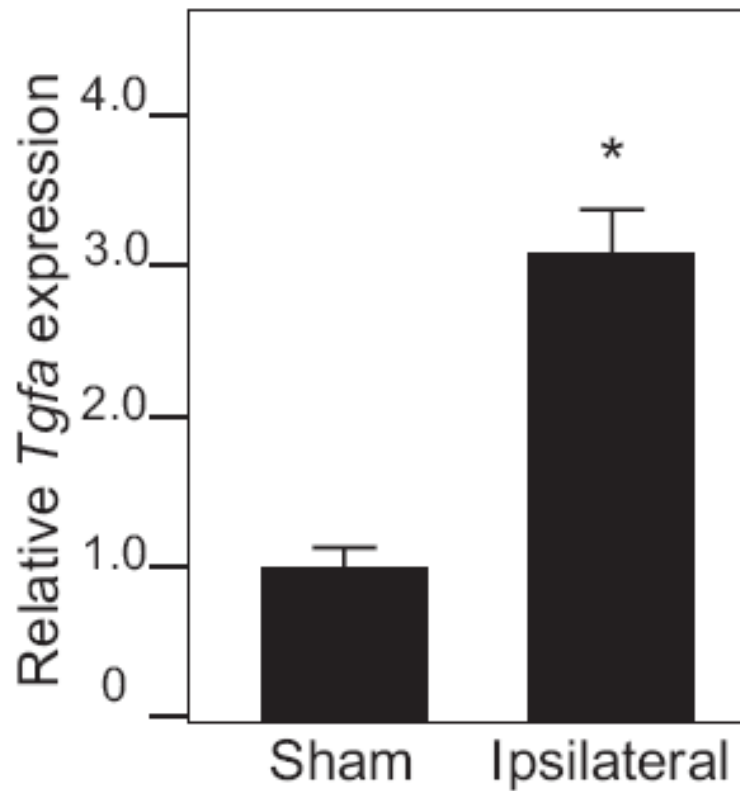
Control of chondrocyte phenotype



Challenges

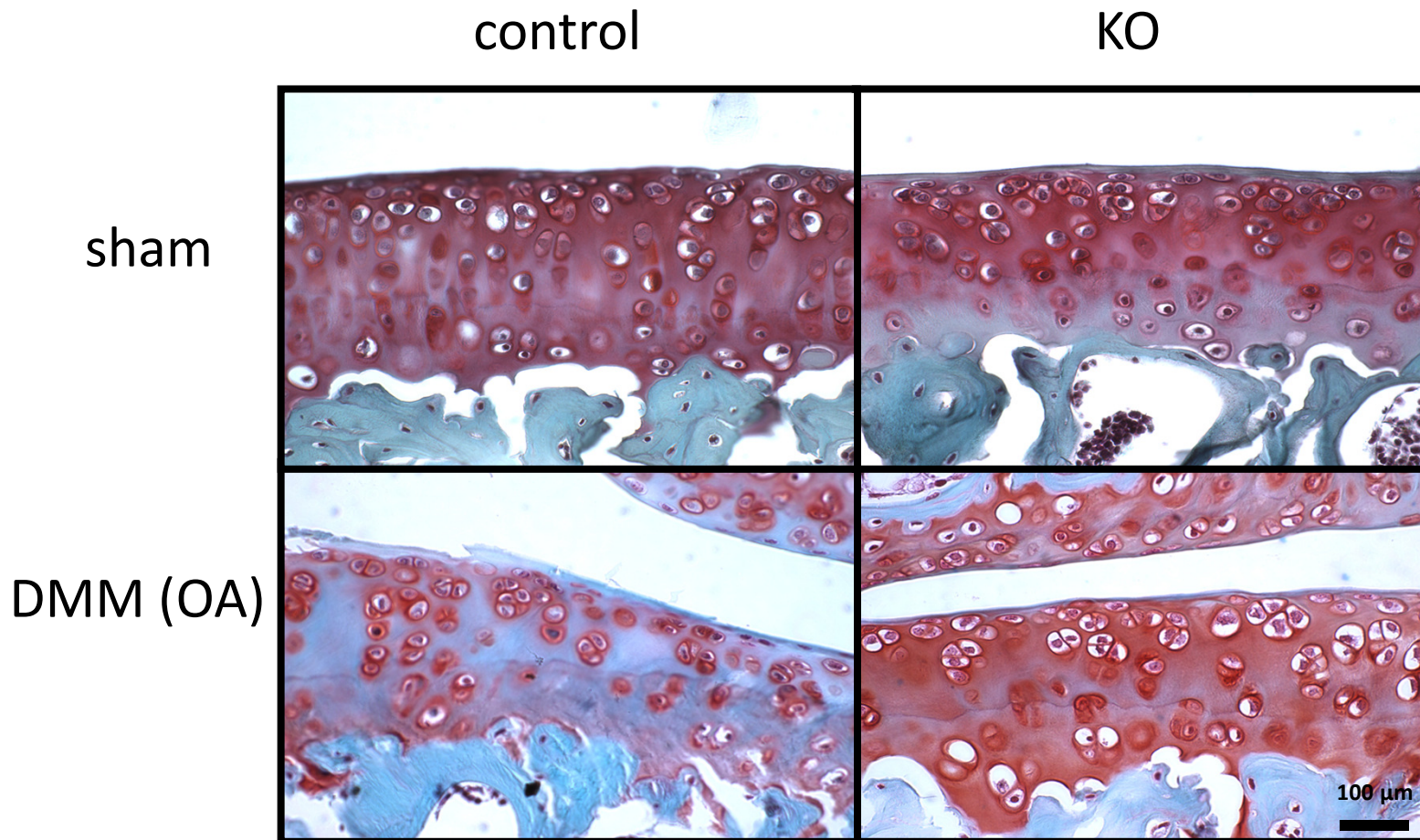
- Can we control cartilage regeneration while preventing hypertrophy, dedifferentiation etc?
- It will not be sufficient to generate more chondrocytes; need to create the right kind of chondrocyte (e.g. superficial vs deep) and proper cartilage organization
- This will require a better understanding of how articular cartilage is formed in the first place (during development)

The TGF α -EGFR pathway as promoter of OA



Appleton et al., 2007

Tgfa KO mice are protected in a surgical OA model



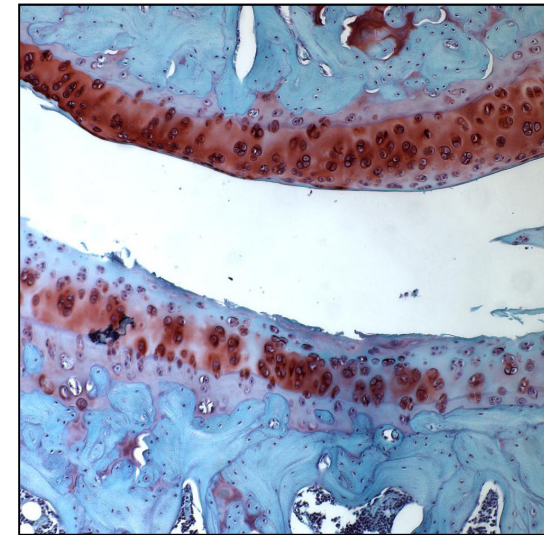
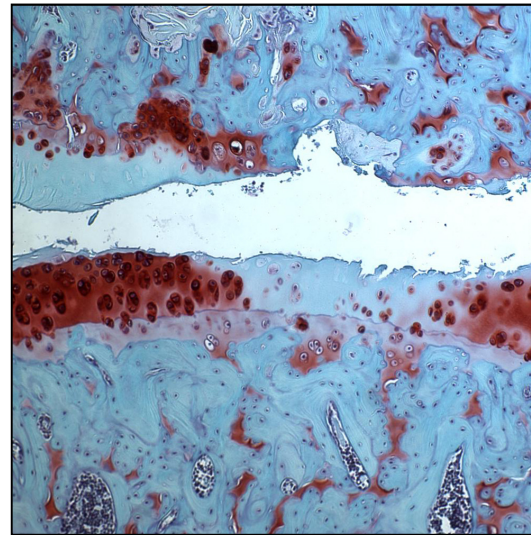
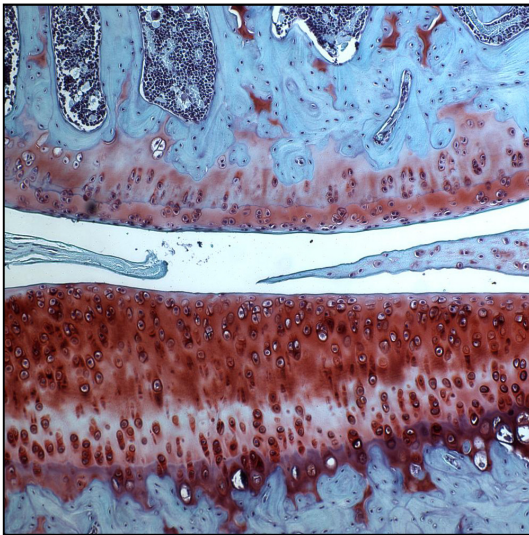
Usmani et al., in revision

EGFR inhibition (AG1478) reduces OA severity in a rat model of OA

Sham

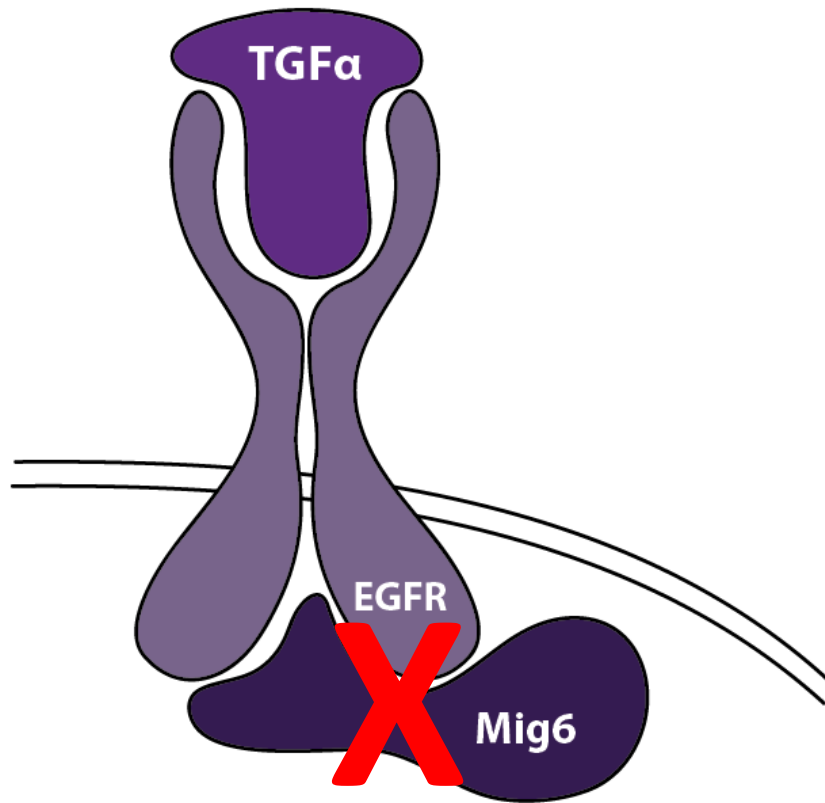
OA

OA + AG

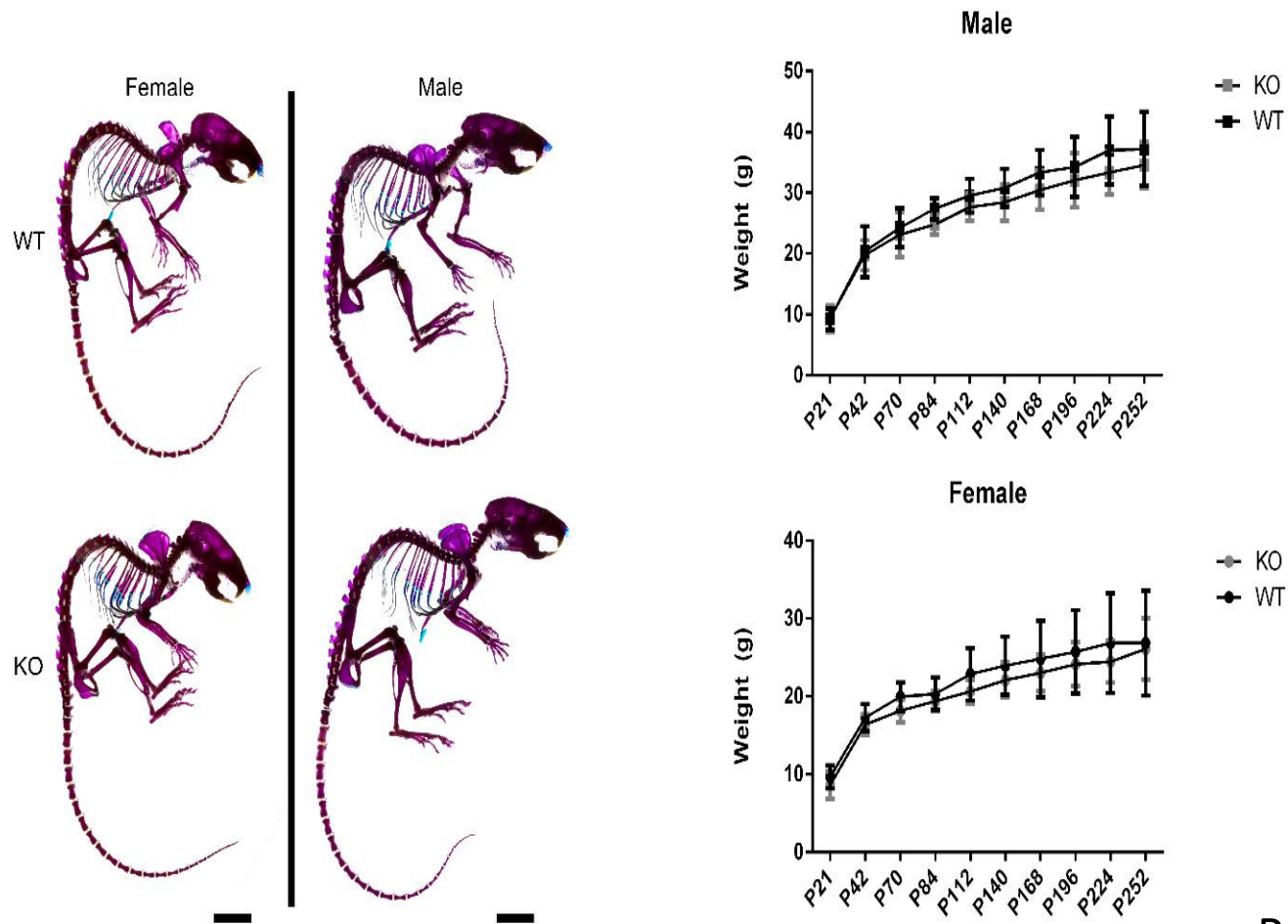


Appleton et al., in revision

Does EGFR activation cause OA? Cartilage-specific KO mice for Mig6

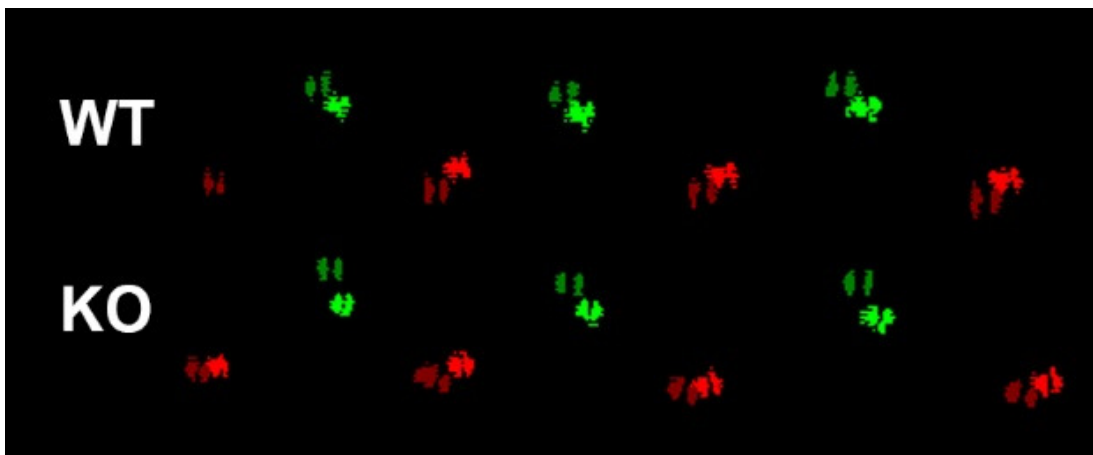


No overt phenotype in cartilage-specific Mig6 KO mice

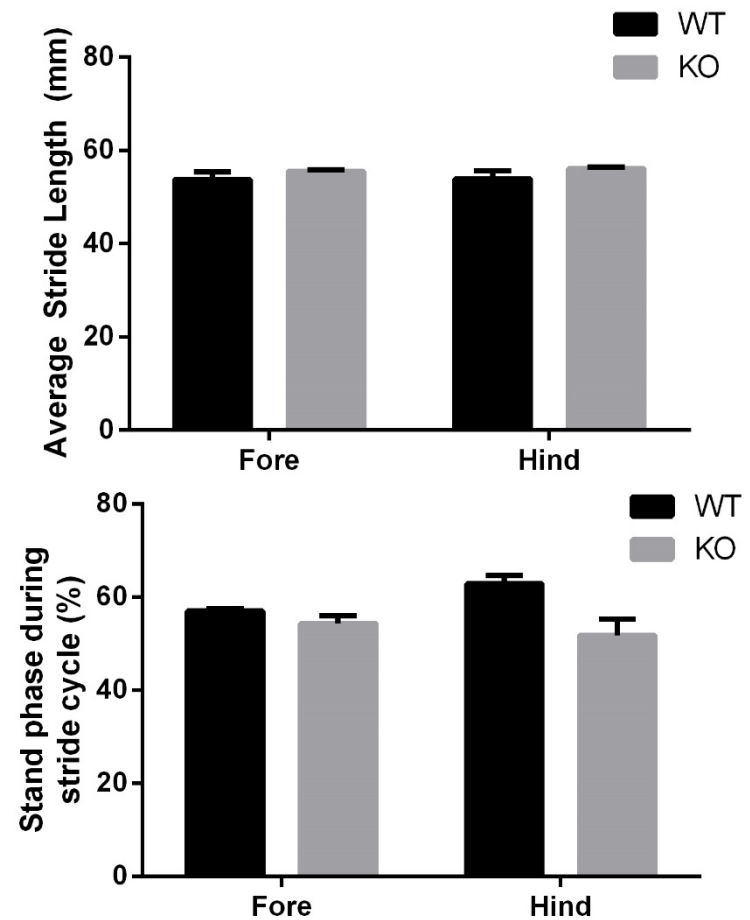


Pest et al., 2014

Gait is unaffected in KO animals



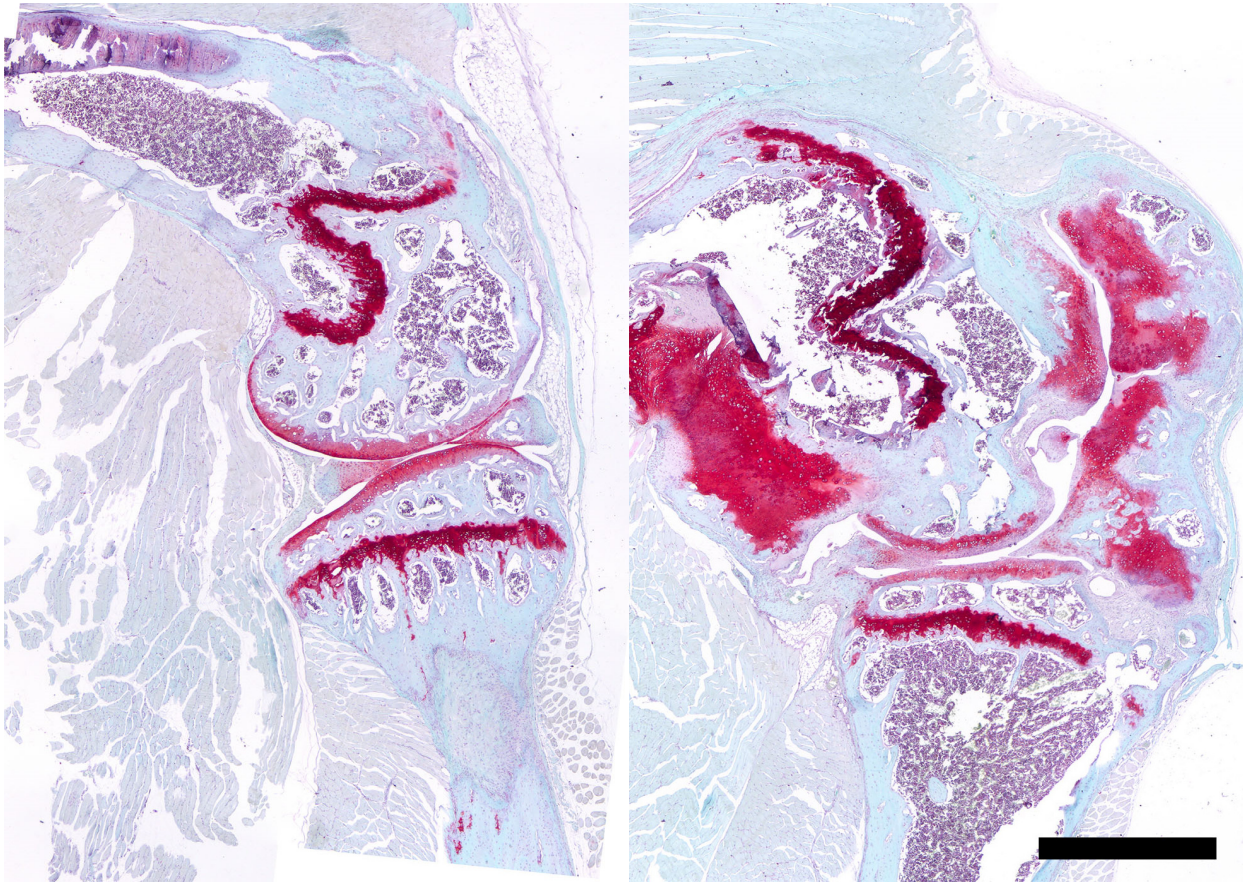
Catwalk Gait Analysis



Ectopic endochondral ossification in joint periphery of Mig6 KO knees

Control

KO

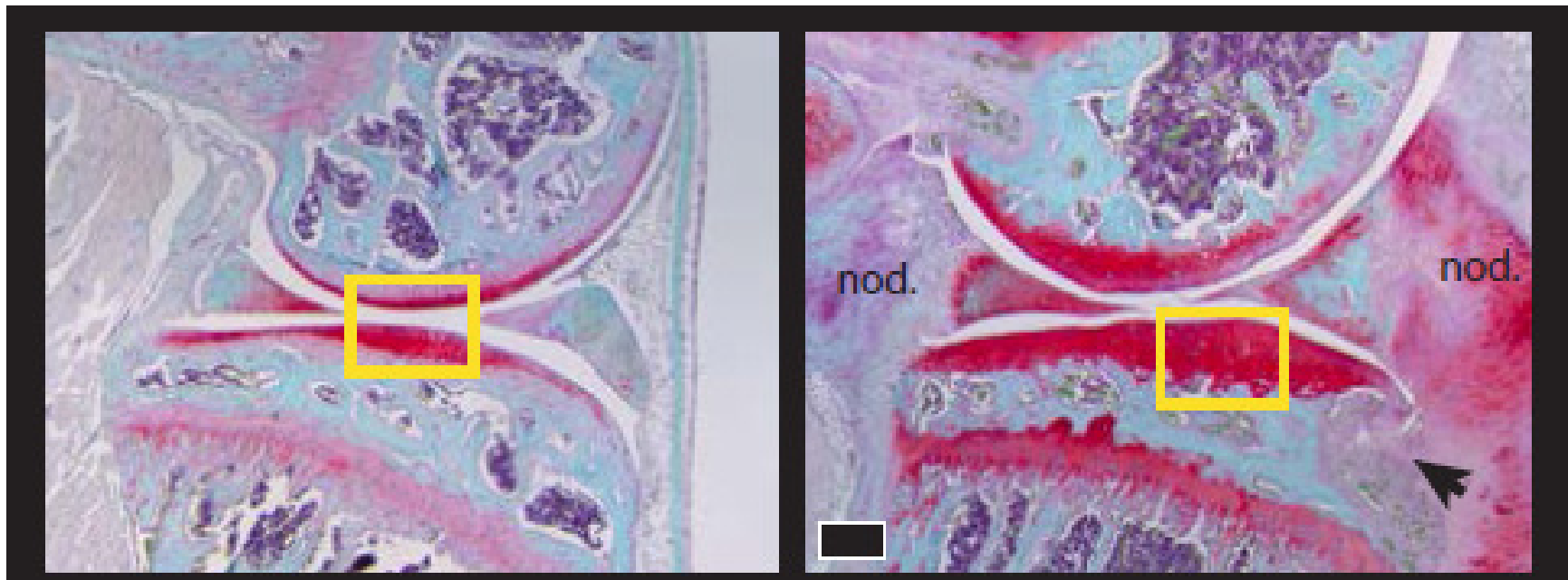


Pest et al., 2014

Increased articular cartilage thickness in cartilage-specific Mig6 KO mice

Control

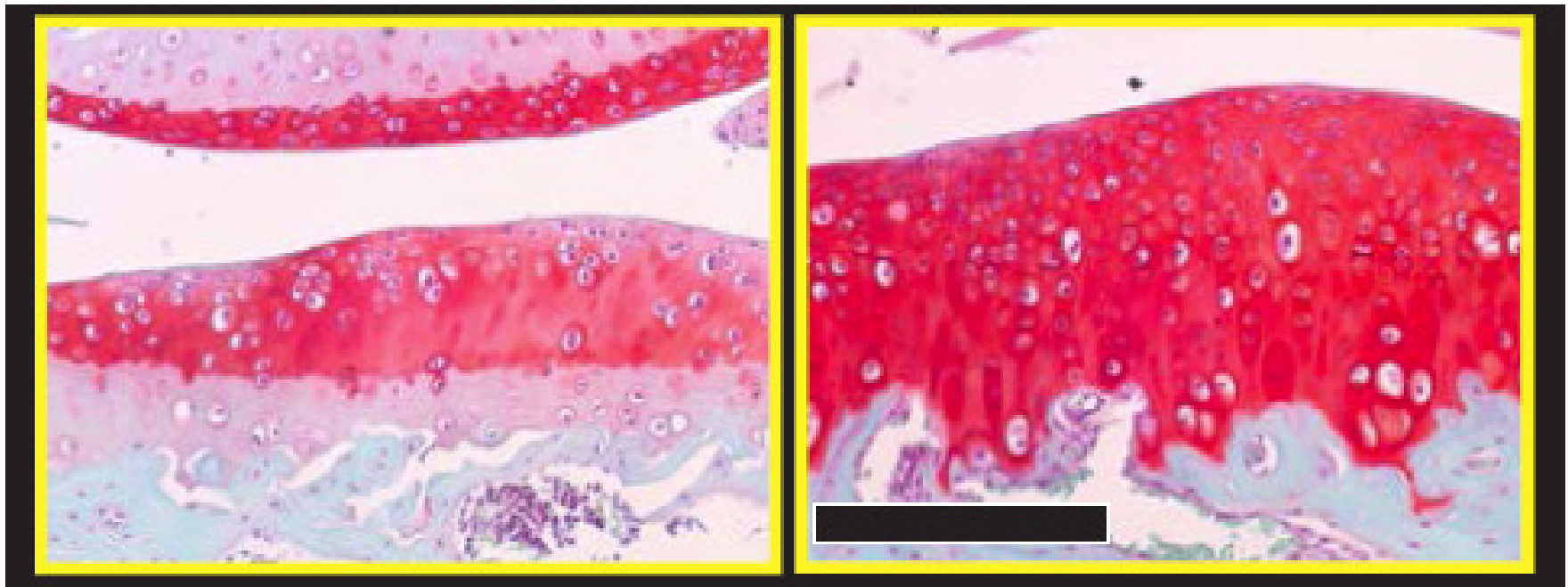
KO



Increased articular cartilage thickness in cartilage-specific Mig6 KO mice

Control

KO

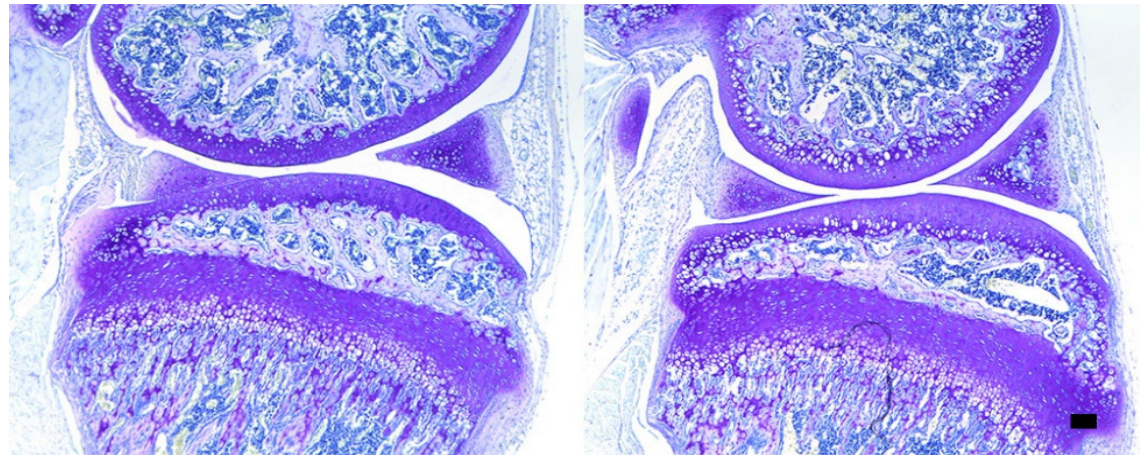


Articular cartilage thickness in Mig6 KO mice

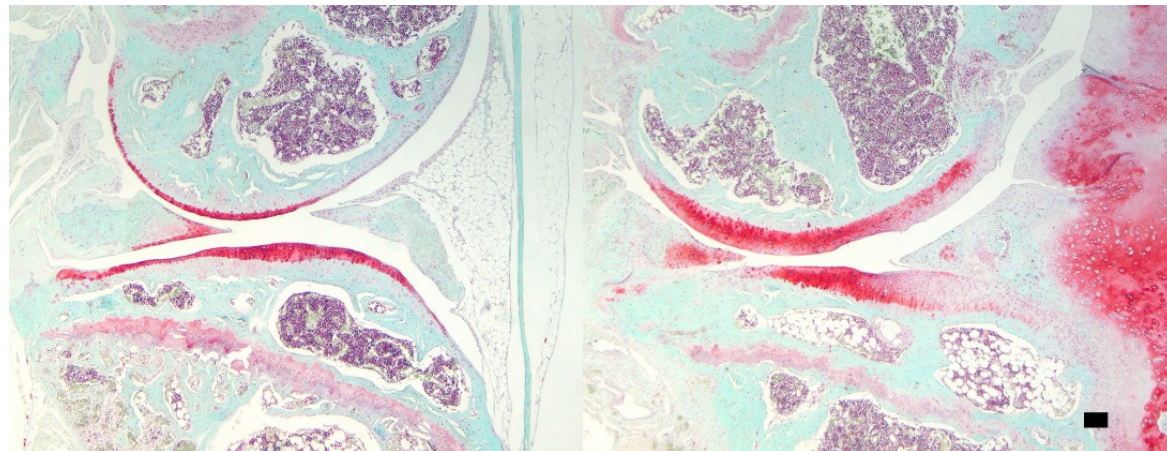
Control

KO

4 weeks



21 months

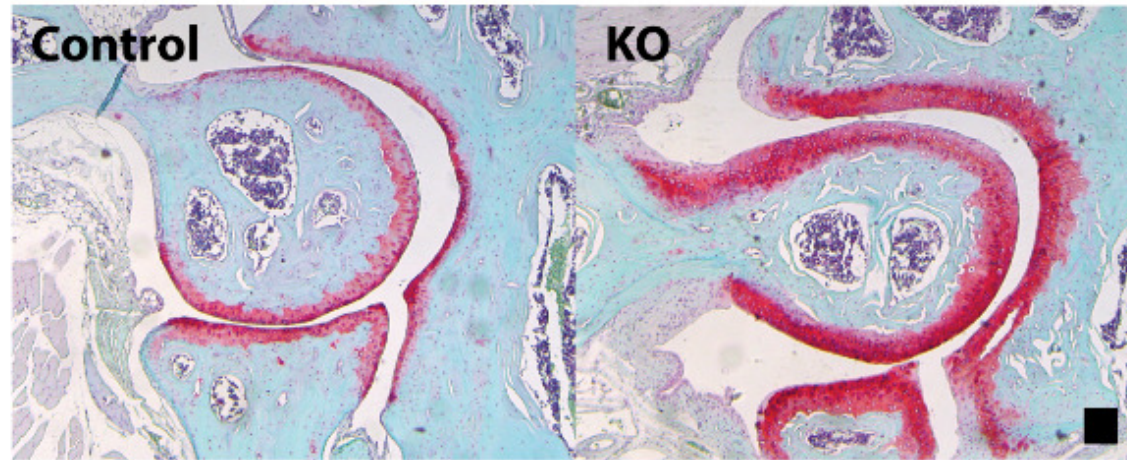


Articular cartilage thickness in Mig6 KO mice

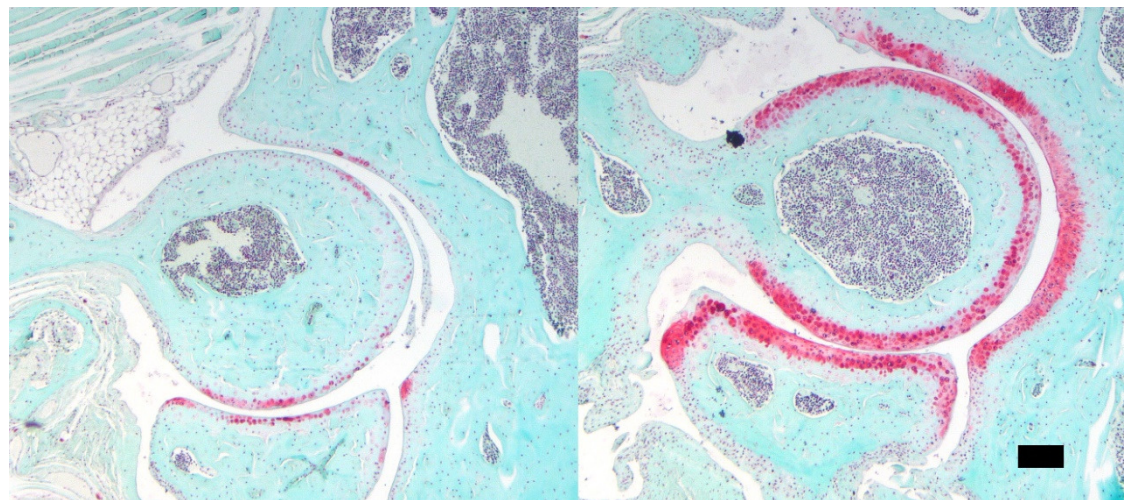
Control

KO

36 Weeks

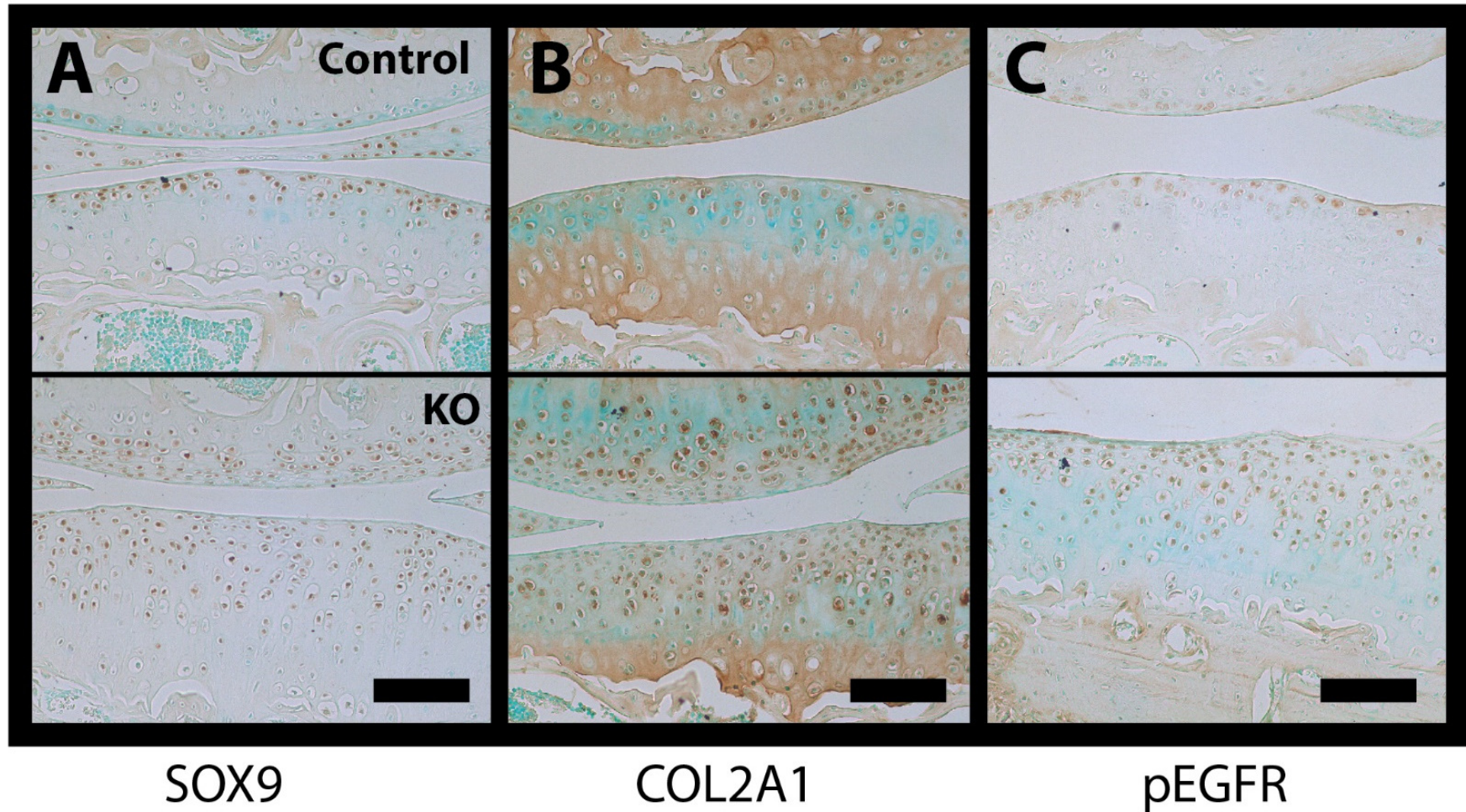


21 months

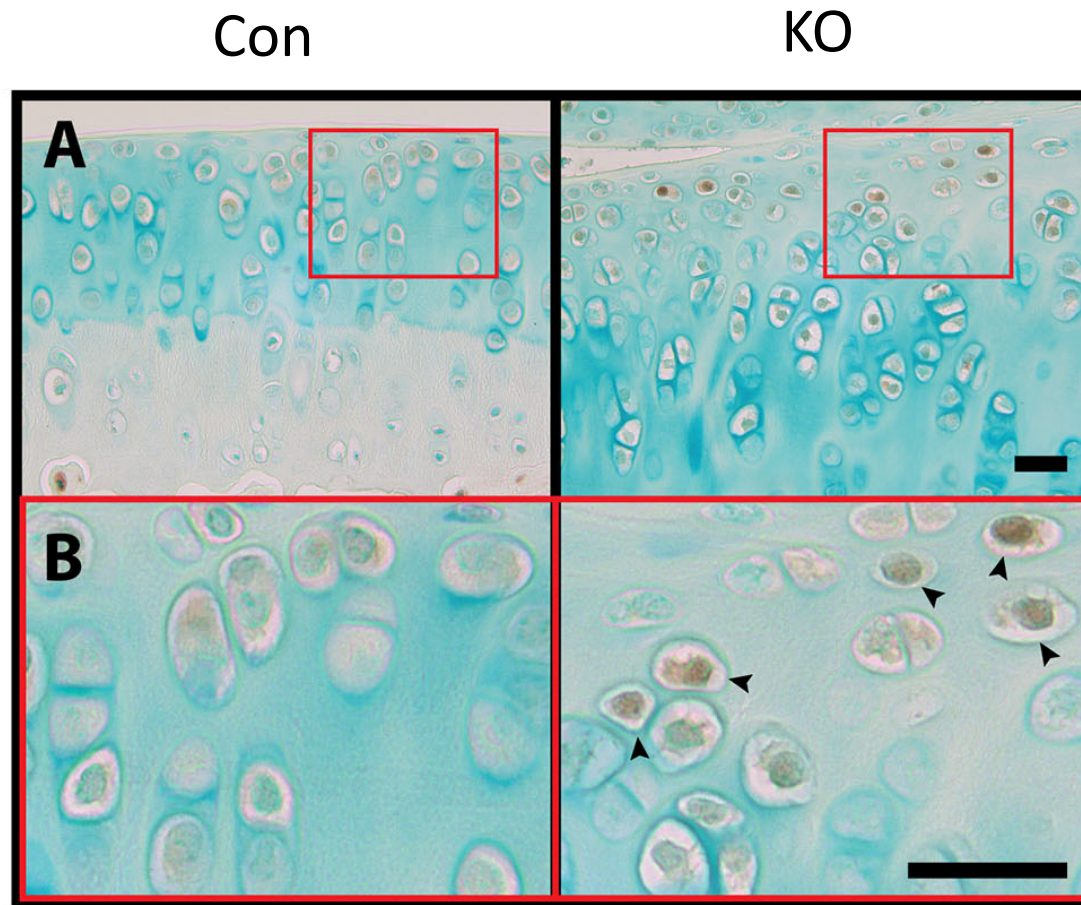


Cartilage markers in Mig6 KO mice

12 Weeks



Increased chondrocyte proliferation in cartilage-specific Mig6 KO mice

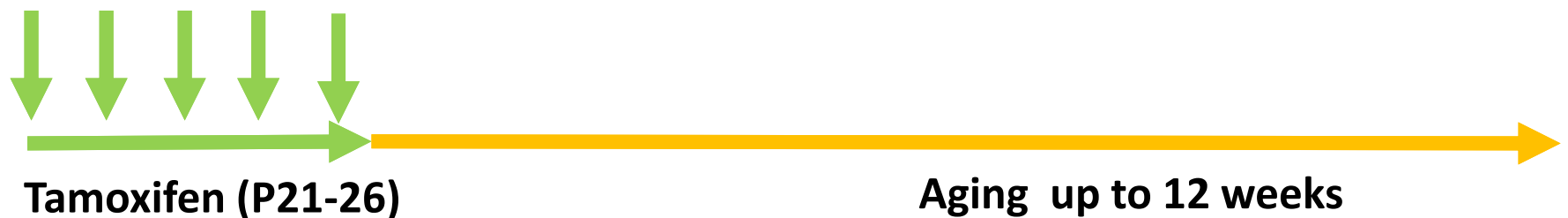


Conclusions so far

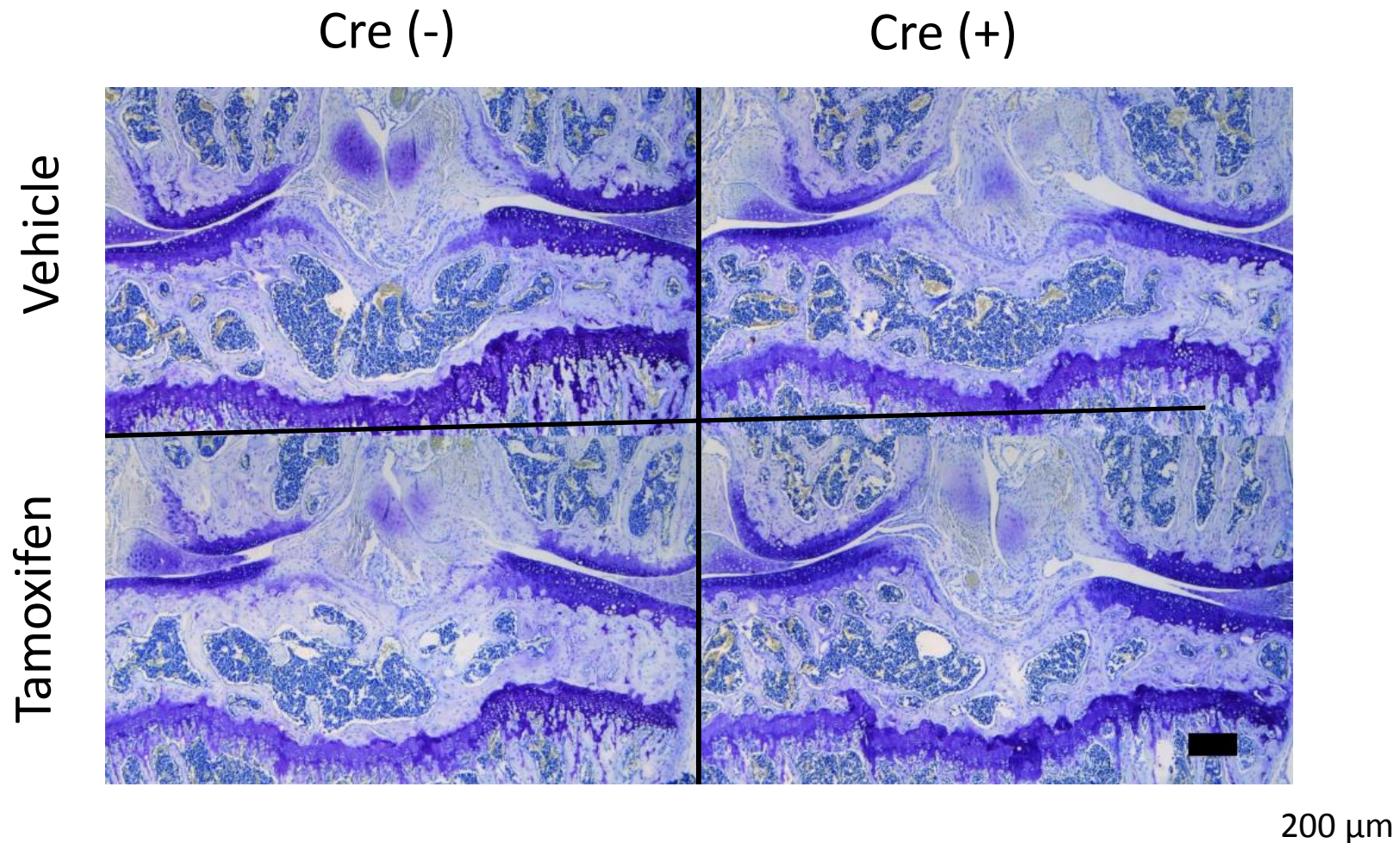
- Mig6 deletion in cartilage leads to increased proliferation of articular chondrocytes and increased articular cartilage thickness in multiple joints
- This appears at odds with the catabolic function of EGFR signaling in OA – time-/context-dependent effects? EGFR-independent effects?
- Mig6 deletion leads to endochondral ossification in peri-articular tissues of the knee, but not most other joints

Is inhibition of Mig6 a potential strategy to promote articular cartilage growth ?

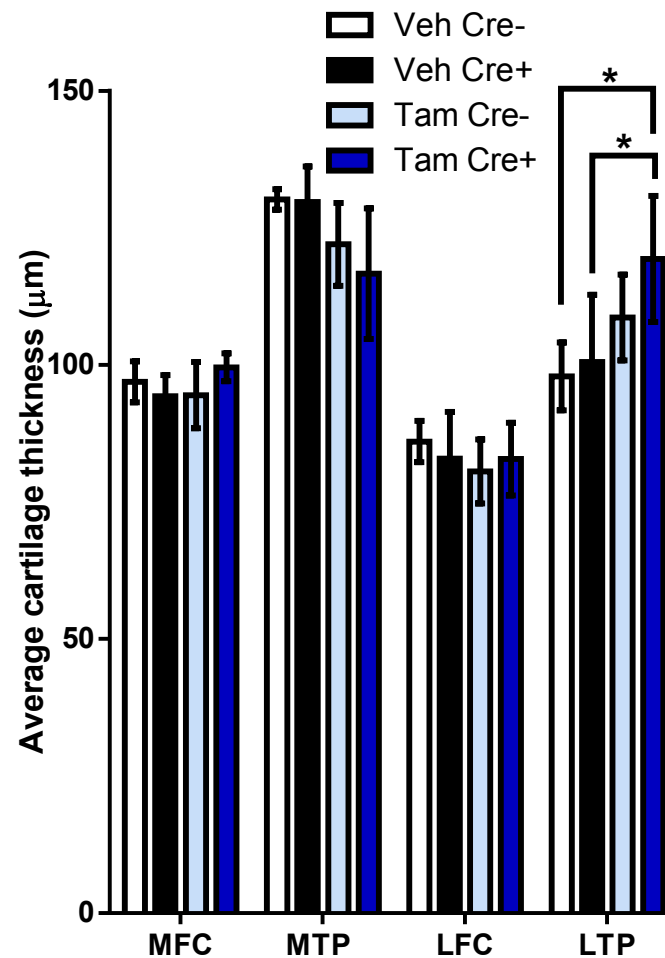
- Post-natal KO of the *Mig6* gene in cartilage
- Col2Cre-ER(T2) driver (Di Chen)
- induction of Cre activity in chondrocytes at 3 weeks of age



What happens when we delete Mig-6 from postnatal chondrocytes?



Not much happens when we delete Mig-6 from postnatal chondrocytes

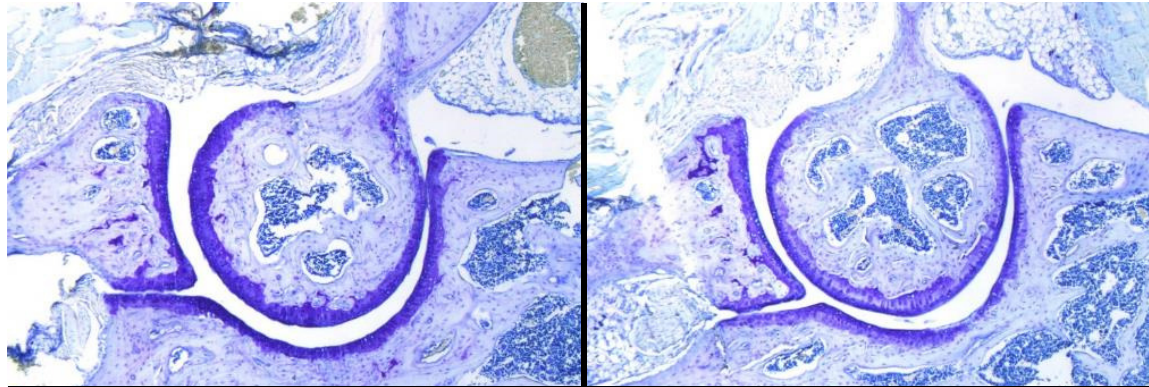


Nothing in the elbows either

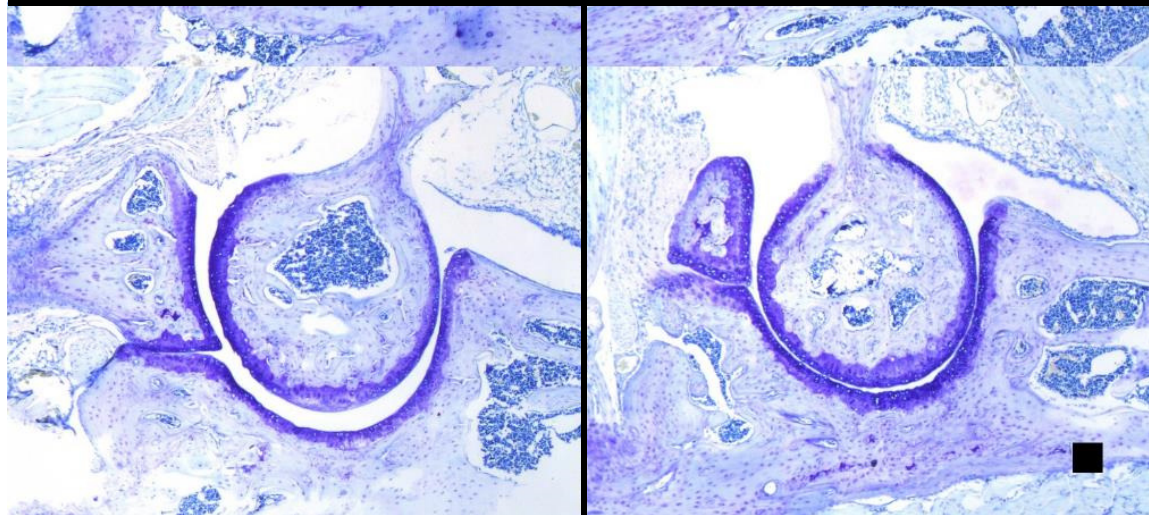
Cre (-)

Cre (+)

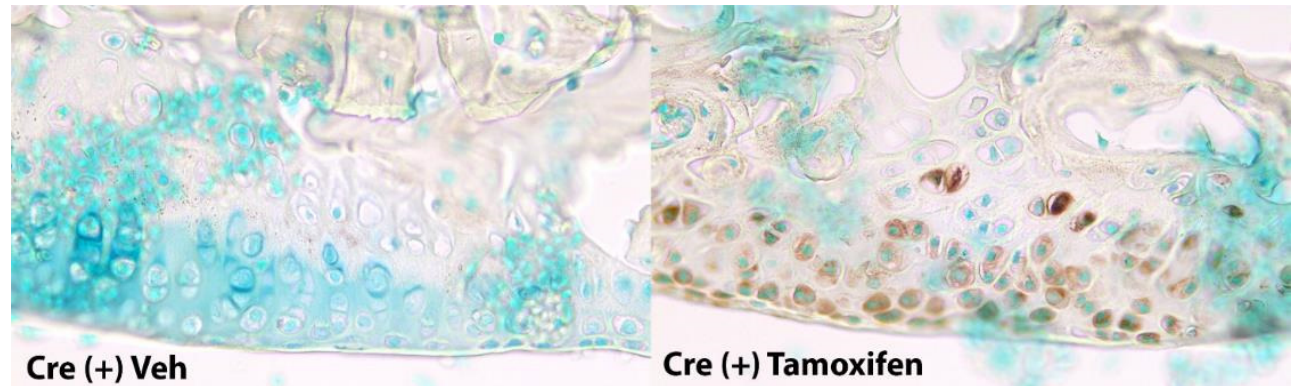
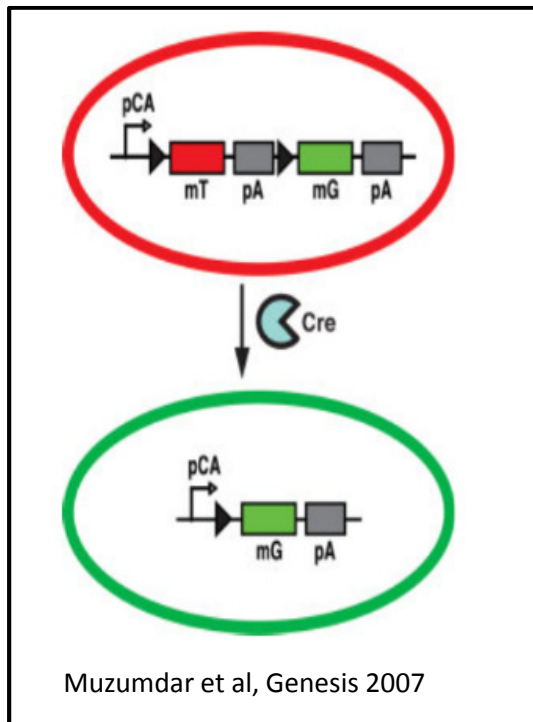
Vehicle



Tamoxifen



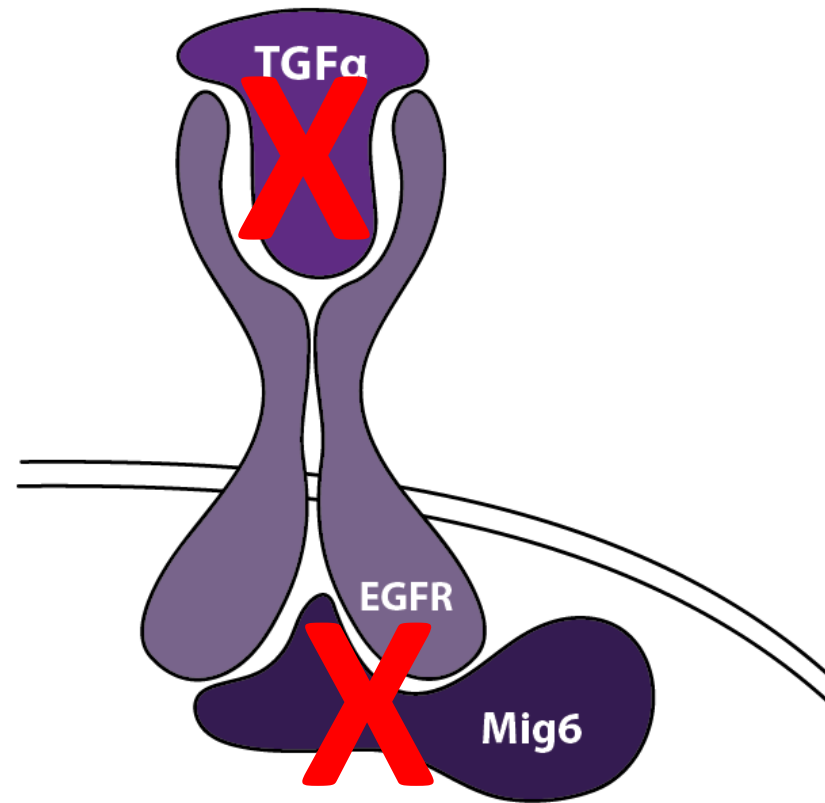
Recombination occurs, but not in all cells



→ Different tamoxifen time course ?

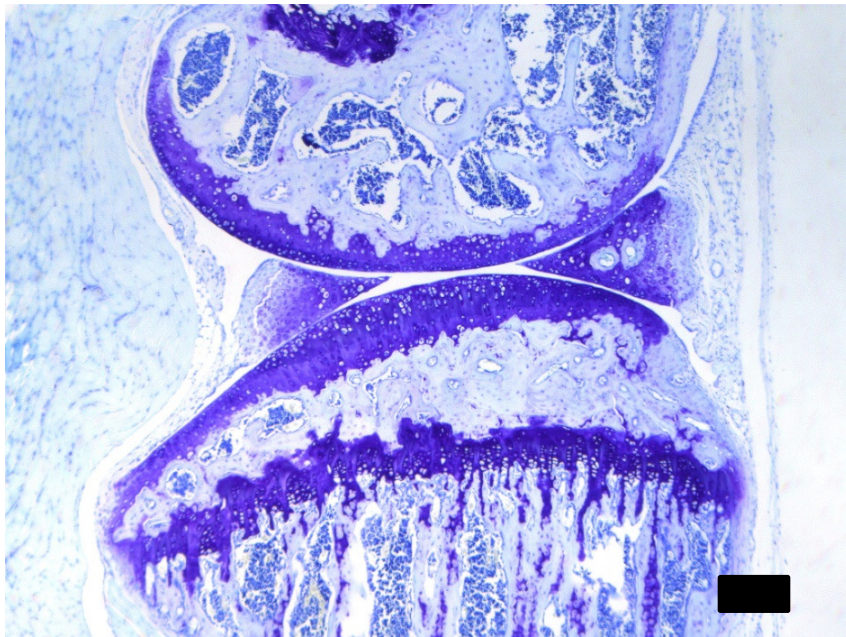
→ Aggrecan-CreER(T2) driver

Does deletion of TGF α counteract the effects of Mig6 loss?

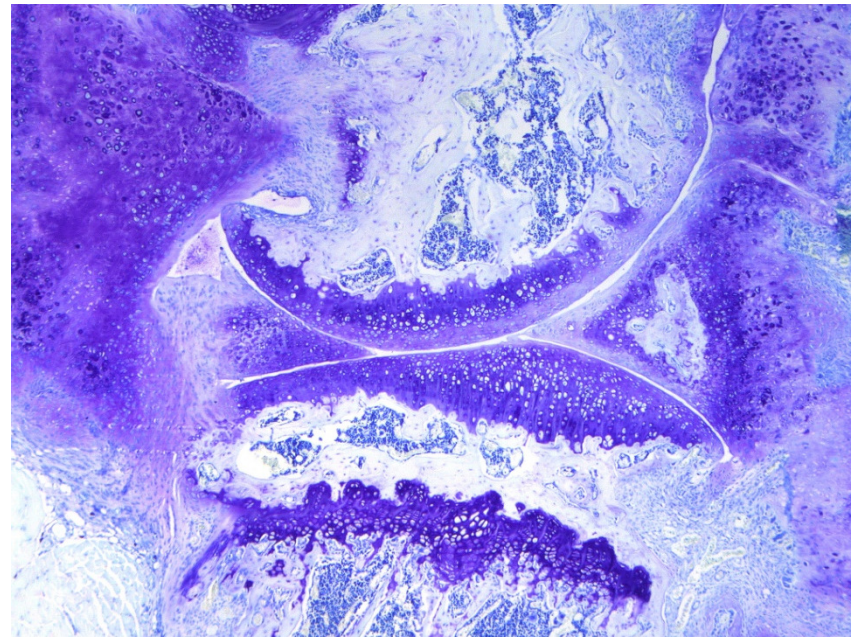


Anabolic effects of Mig6 deletion do not require TGFA α

Mig6^{fl/fl} Tgfa^{-/-}



Mig6^{fl/fl} Col2Cre Tgfa^{-/-}



Is Mig6 a potential target for cartilage repair ?

- Developmental deletion of Mig6 from cartilage promotes articular cartilage growth
- Transient suppression of Mig6 signaling might be one therapeutic avenue, but it is not clear yet whether this mechanism is effective in adult cartilage
- Data indicate that this role of Mig6 in cartilage might be independent of EGFR signaling
- Mig6 suppression can also promote ectopic endochondral ossification which is detrimental to articular cartilage
- Too early to say whether Mig6 is promising target; however, it is clearly an important player in joint and cartilage biology

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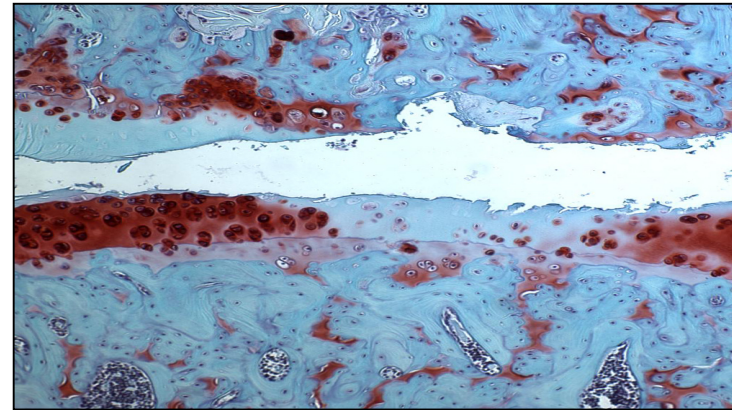
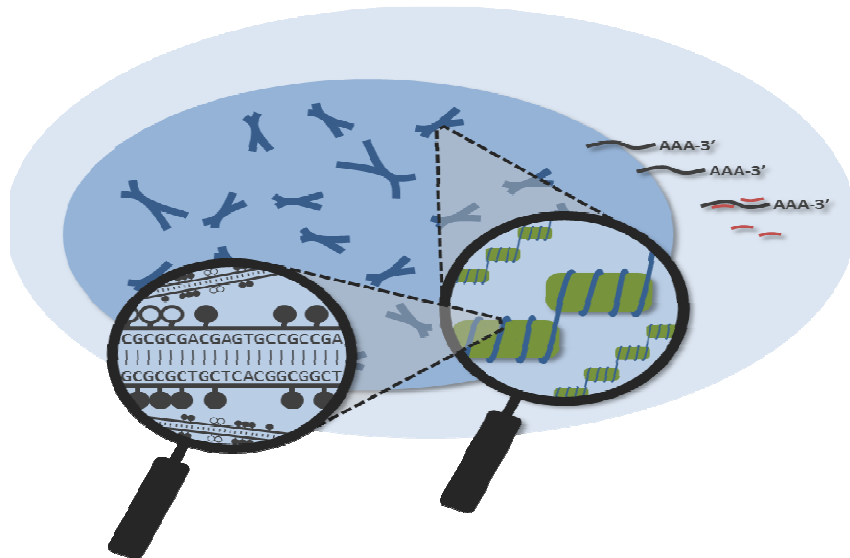


CIHR IRSC

1st Osteoarthritis Epigenetics Workshop

Amsterdam

October 20th-21st 2015



<http://www.molepi.nl/research/osteoarthritis/workshop>

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