Cartilage Regeneration – from Pediatric Growth Plate Injuries to Osteoarthritis

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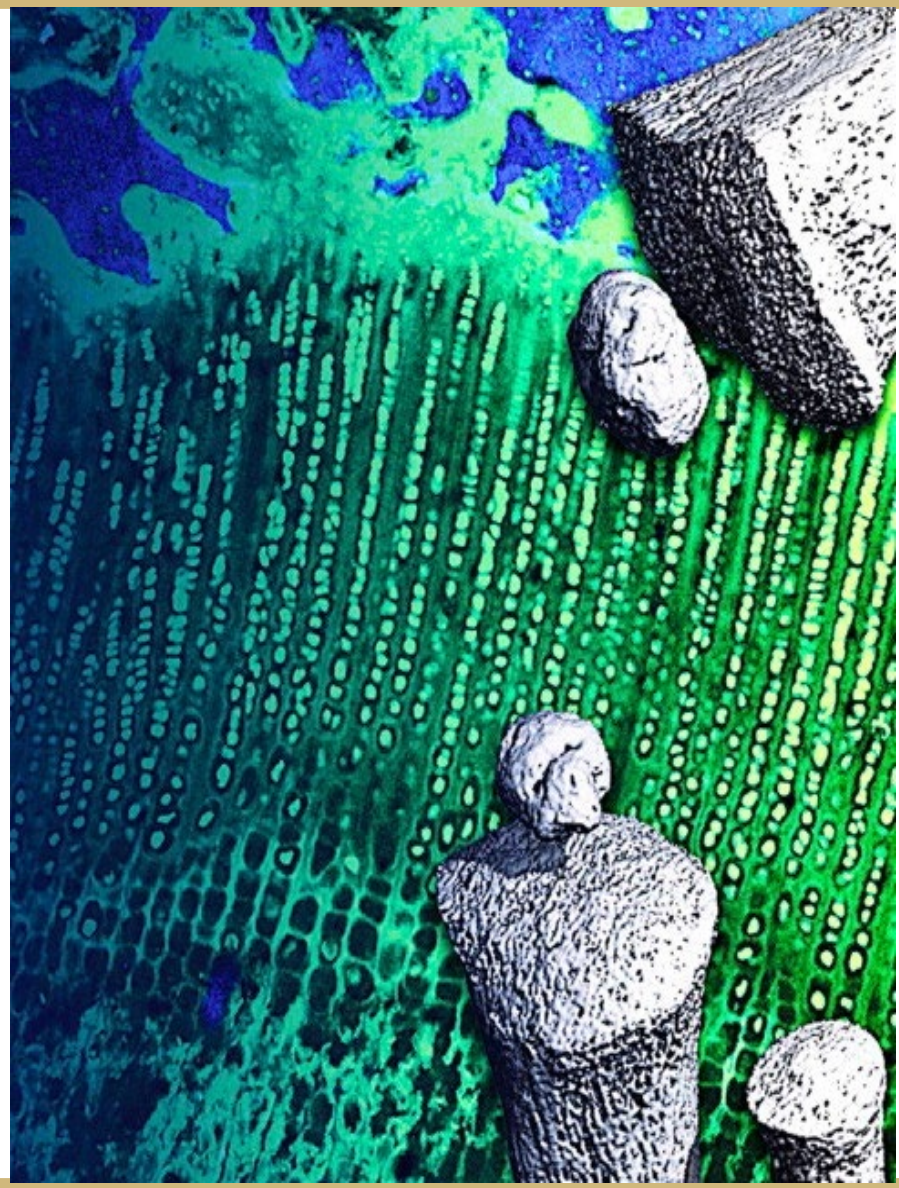


CU – CSU Summit

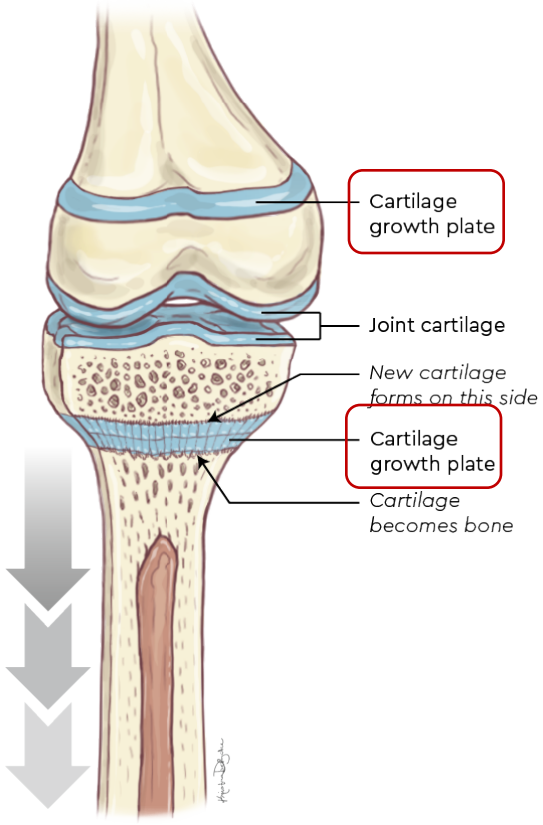
Chronic Disease Frontiers: Colorado Approach to Causes and Treatment

August 13, 2025

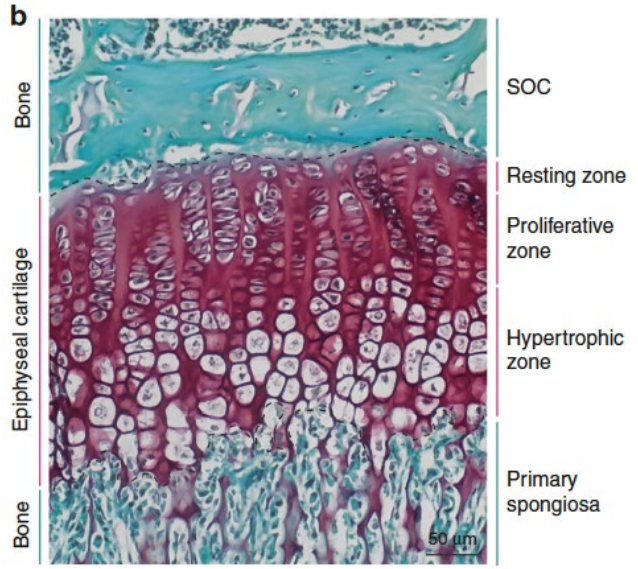
Disclosures

No disclosures

Growth Plate Cartilage and Articular Cartilage



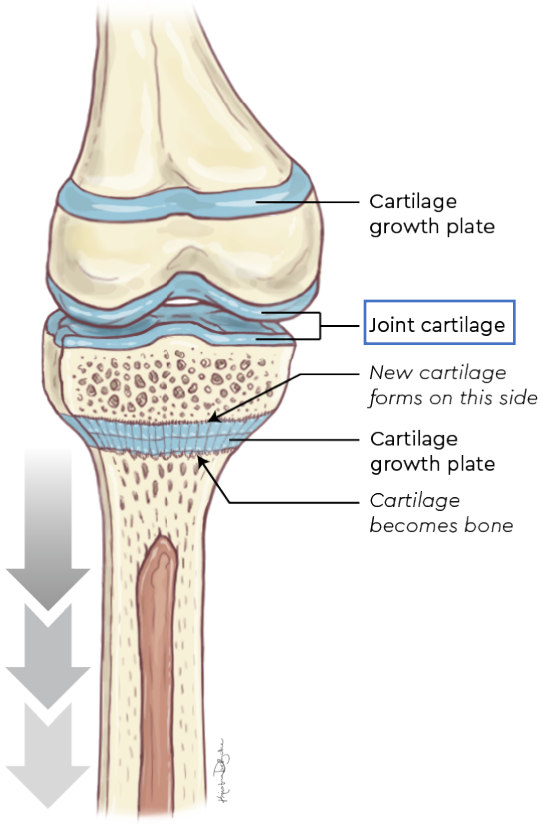
Feature	Growth Plate Cartilage
Location	Found at metaphysis of long bones in children
Function	Enables longitudinal bone growth during development
Structure	Hyaline cartilage organized into zones
Cell Types	Chondrocytes in columns (proliferative, hypertrophic)
Vascularization	Avascular
End Fate	Undergoes endochondral ossification
Regenerative Capacity	Active during growth; ceases after skeletal maturity
Clinical Relevance	Growth disorders, limb length discrepancies



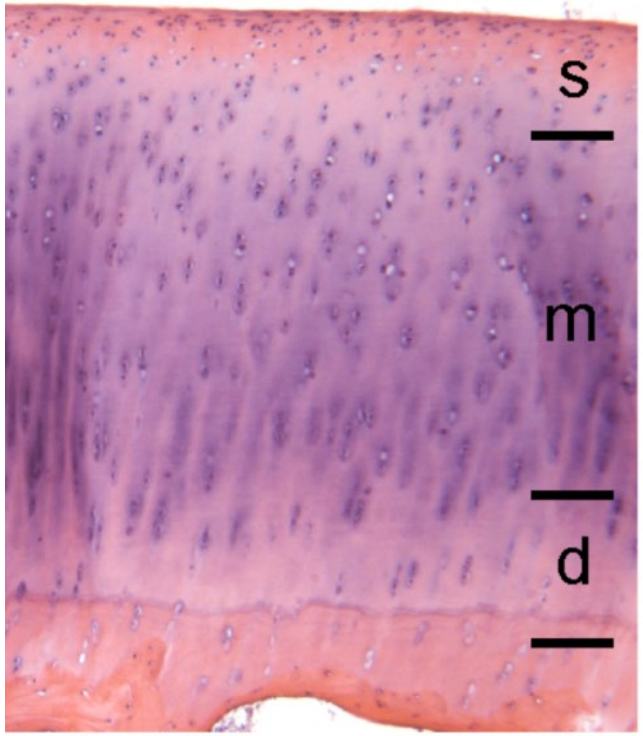
Chagin A.S. et al. *Pediatr Res* **87**, 986–990 (2020).

Longitudinal growth occurs by *endochondral ossification* – cartilage is gradually replaced by bone

Growth Plate Cartilage and Articular Cartilage

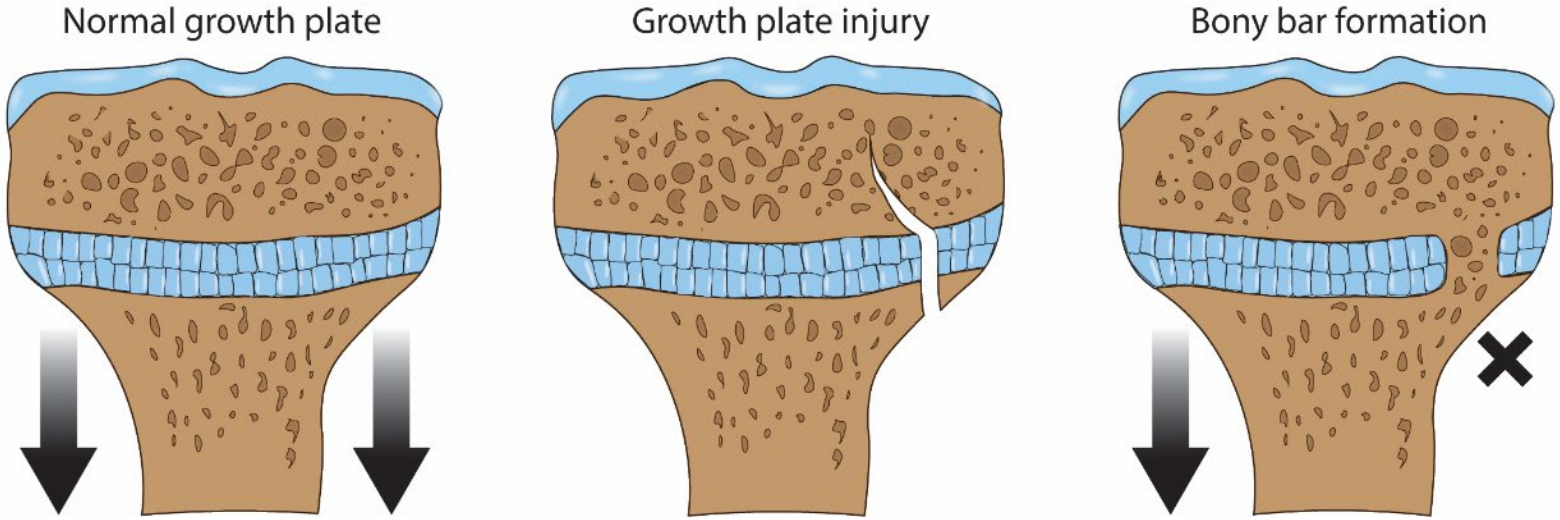


Feature	Articular Cartilage
Location	Covers ends of bones in synovial joints
Function	Facilitates smooth joint movement; absorbs shock
Structure	Hyaline cartilage with zonal organization
Cell Types	Chondrocytes in lacunae
Vascularization	Avascular
End Fate	Maintains structure throughout life
Regenerative Capacity	Limited to None
Clinical Relevance	Osteoarthritis, cartilage injury



Haltmayer E. et al. PLOS ONE. 14. e0214709. 10.1371.

Growth plate injuries can cause deformity



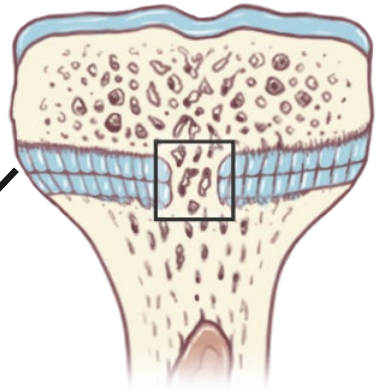
Bony bar formation prevents localized endochondral bone formation

Angular deformities

Limb length discrepancies

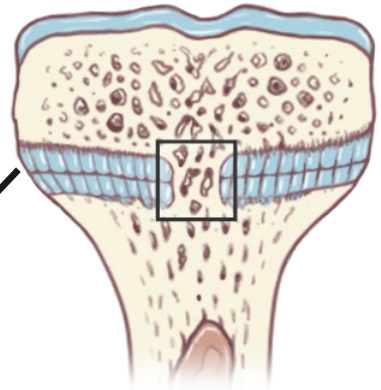
Devastating for patients and limited clinical treatments

Growth plate injuries: Current treatments



- bony bar spans <50% of growth plate volume
- 2 years or 2 cm of growth remaining

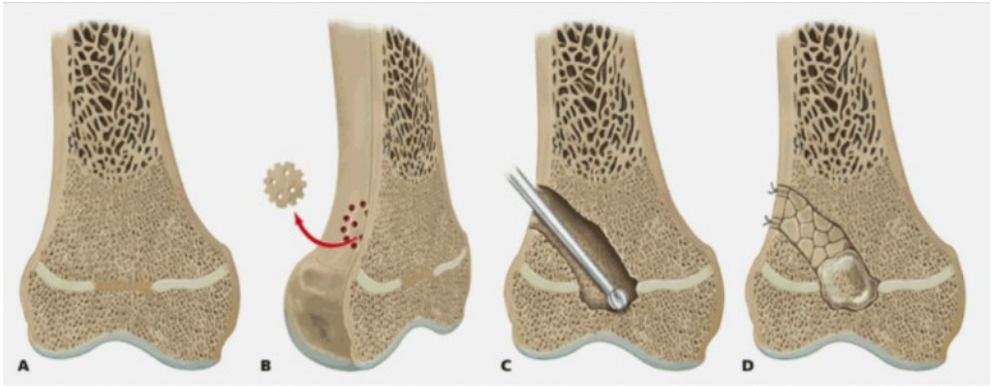
Growth plate injuries: Current treatments



- bony bar spans <50% of growth plate volume
- 2 years or 2 cm of growth remaining

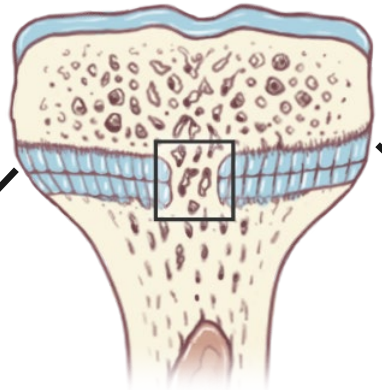
BONY BAR RESECTION

18-30% poor outcome



Paleyinstitute.org

Growth plate injuries: Current treatments



- bony bar spans <50% of growth plate volume
- 2 years or 2 cm of growth remaining

BONY BAR RESECTION
18-30% poor outcome

- bony bar spans >50% of growth plate volume

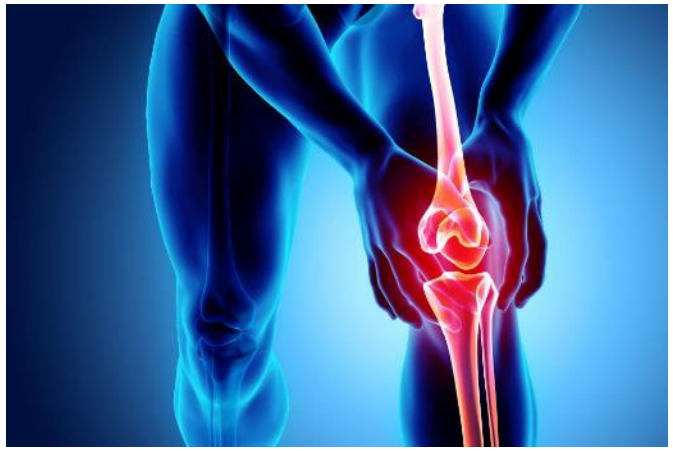
EPIPHYSIODESIS
Prone to infections, multiple hospitalizations

NO treatment is attempting to regenerate the growth plate cartilage

Cartilage injuries & lesions

- Individuals with cartilage injuries are 4.2X more likely to develop OA than those without an injury.
- Cartilage lesions do not heal on their own.

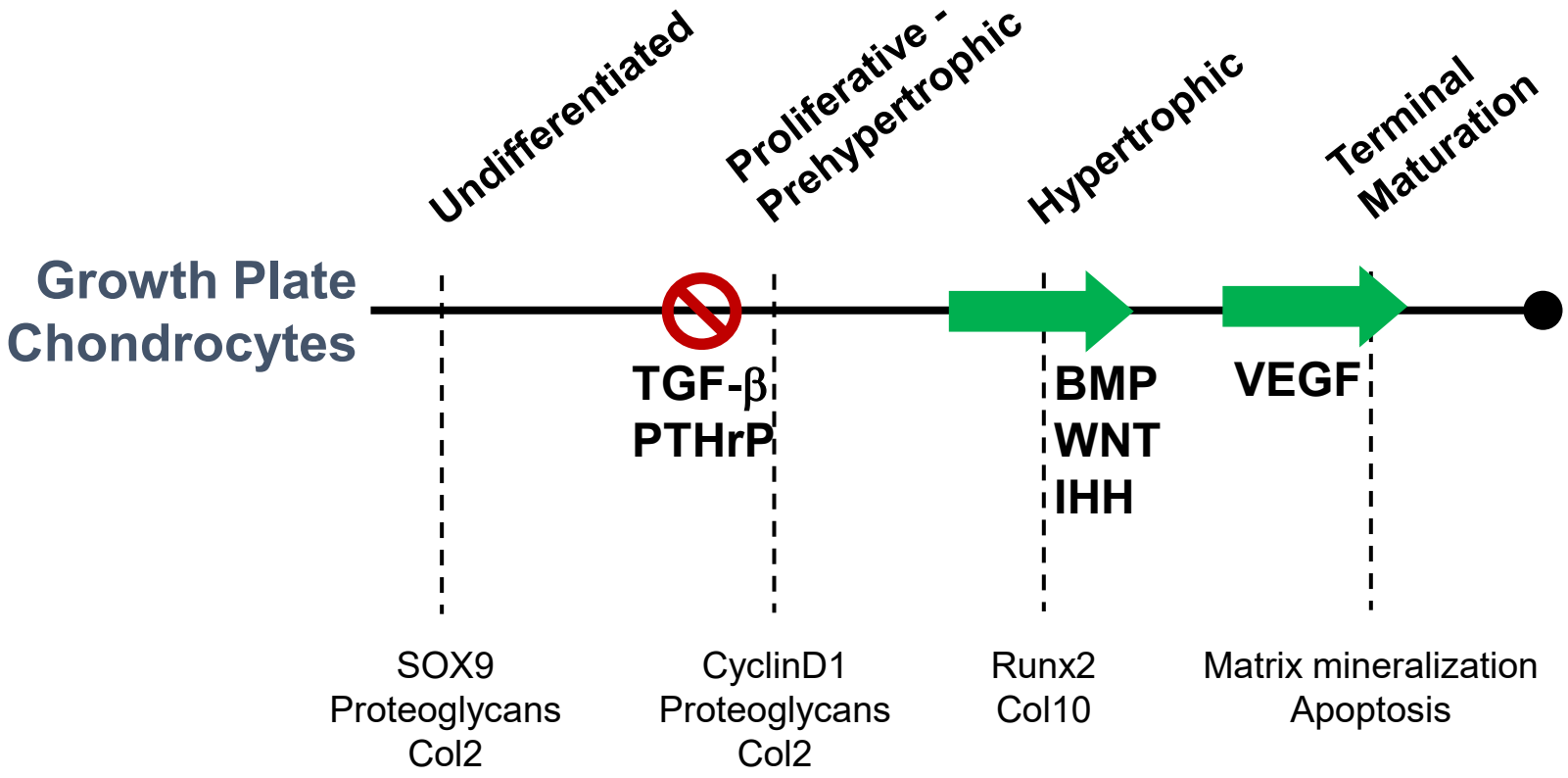
Osteoarthritis (OA) & lesions



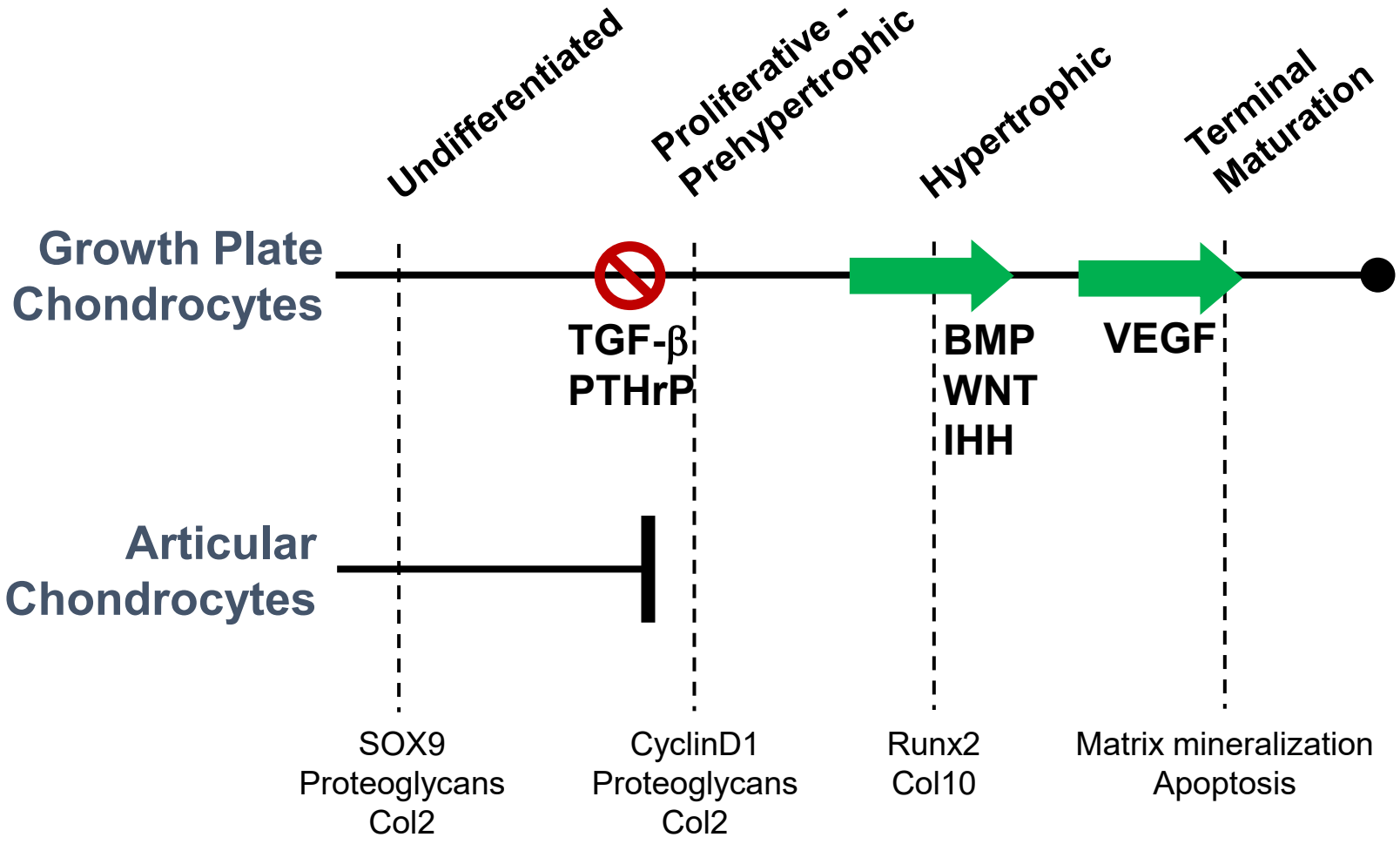
- OA is the #3 cause of disability in the U.S.
- Inflammation-associated OA leads to cartilage degeneration and formation of cartilage lesions.
- Cartilage lesions do not heal on their own.

No regenerative therapies exist for cartilage lesions in OA or non-OA patients.

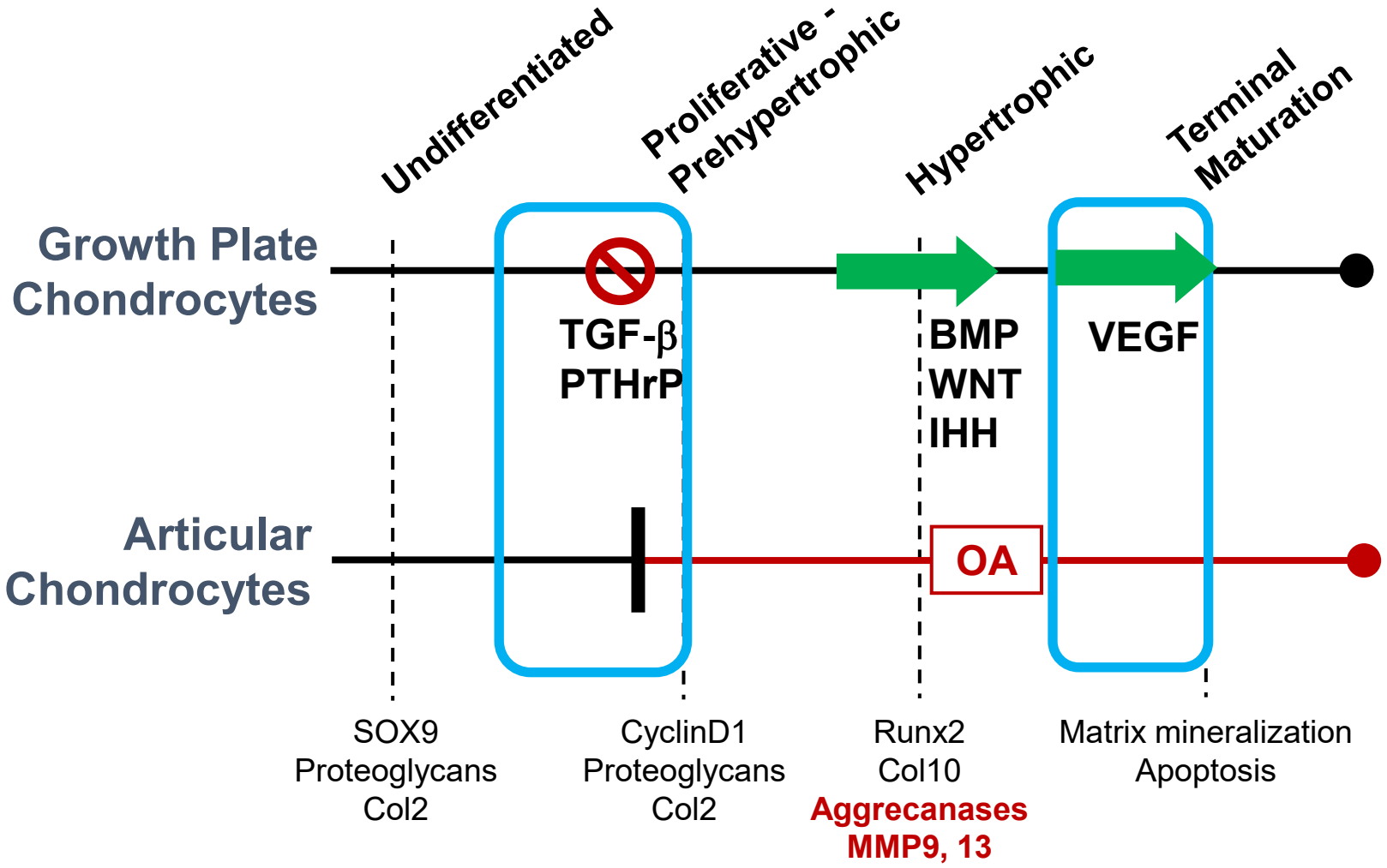
Growth Plate Chondrocyte Hypertrophy is an Orderly Differentiation Process



Articular Chondrocytes



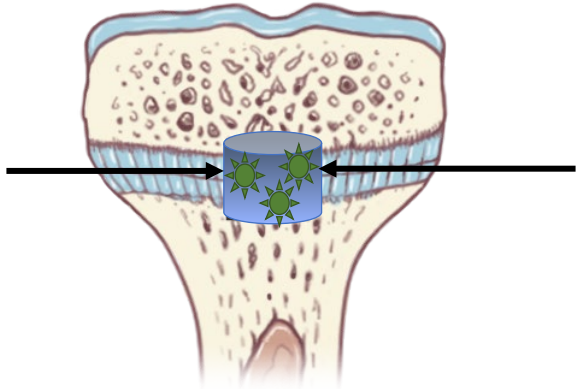
OA: Hypertrophy of Articular Chondrocytes



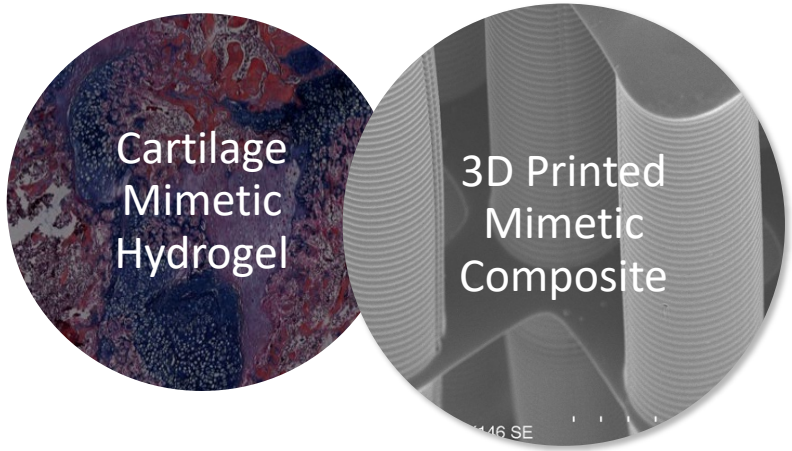
Research Program

To develop regenerative medicine approaches to treat growth plate injuries

Prevent Bony Bar Formation



Regenerate Growth Plate Cartilage



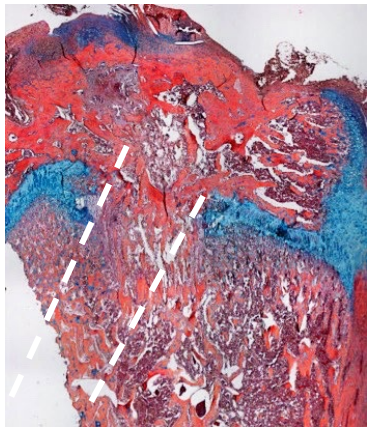
Restore Normal Bone Elongation

Rat model of growth plate injury: proximal tibia drill-hole defect

Rat tibia

Injury site

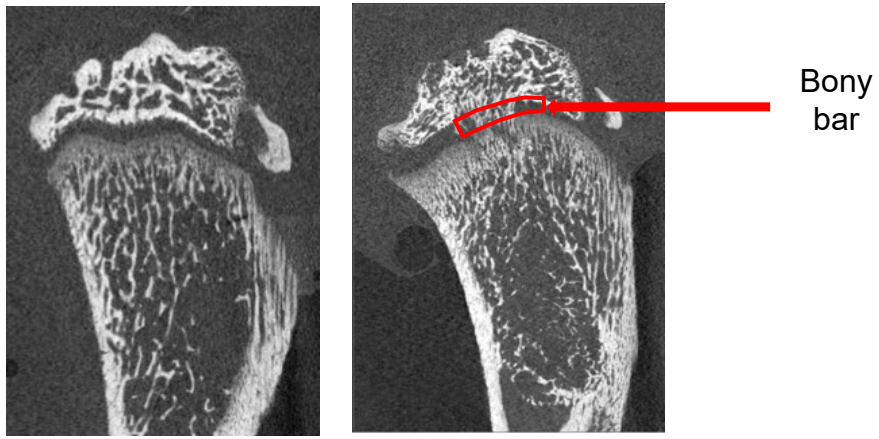
Drill track



ABH stain
Cartilage, Bone

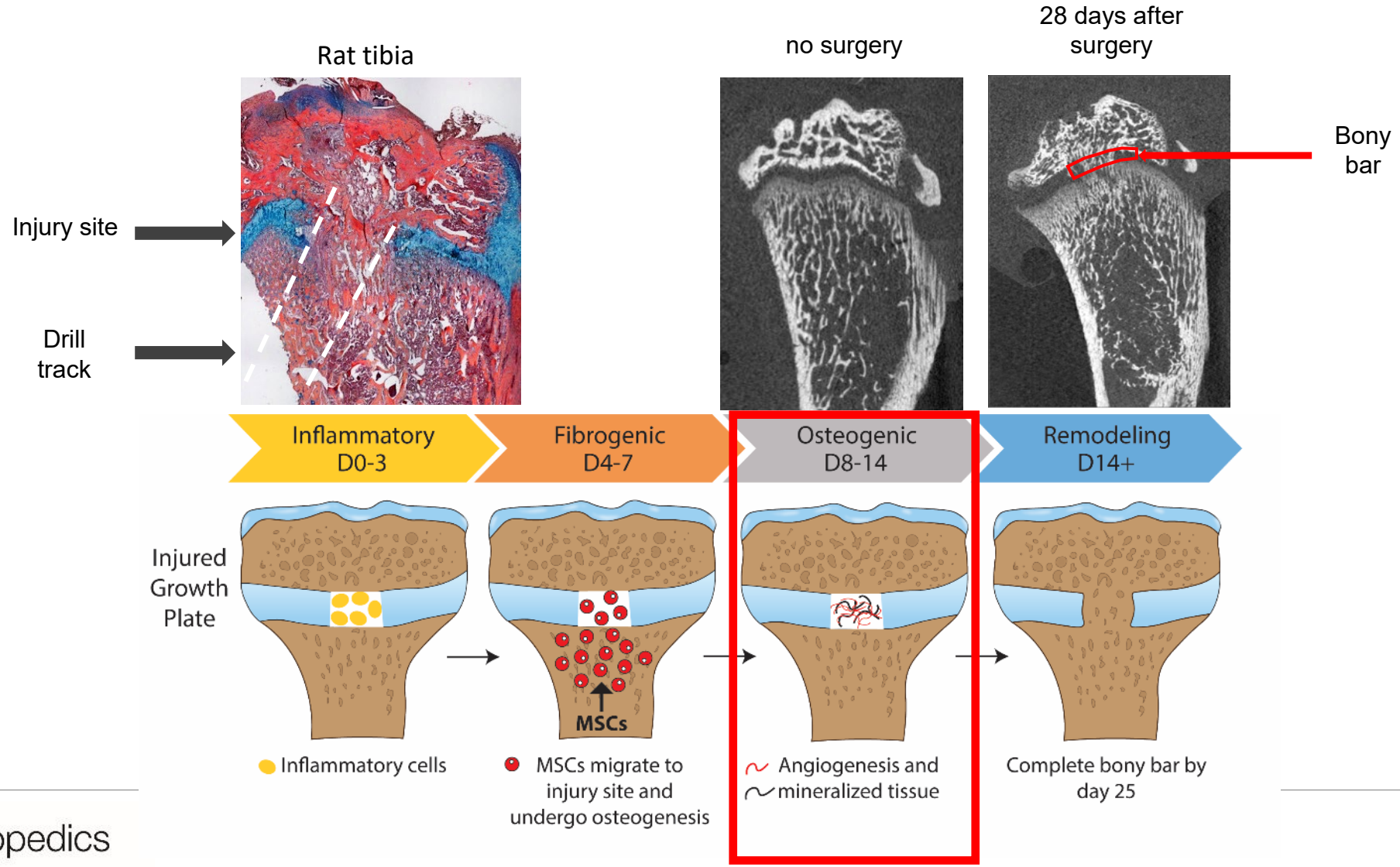
no surgery

28 days after surgery



Bony bar

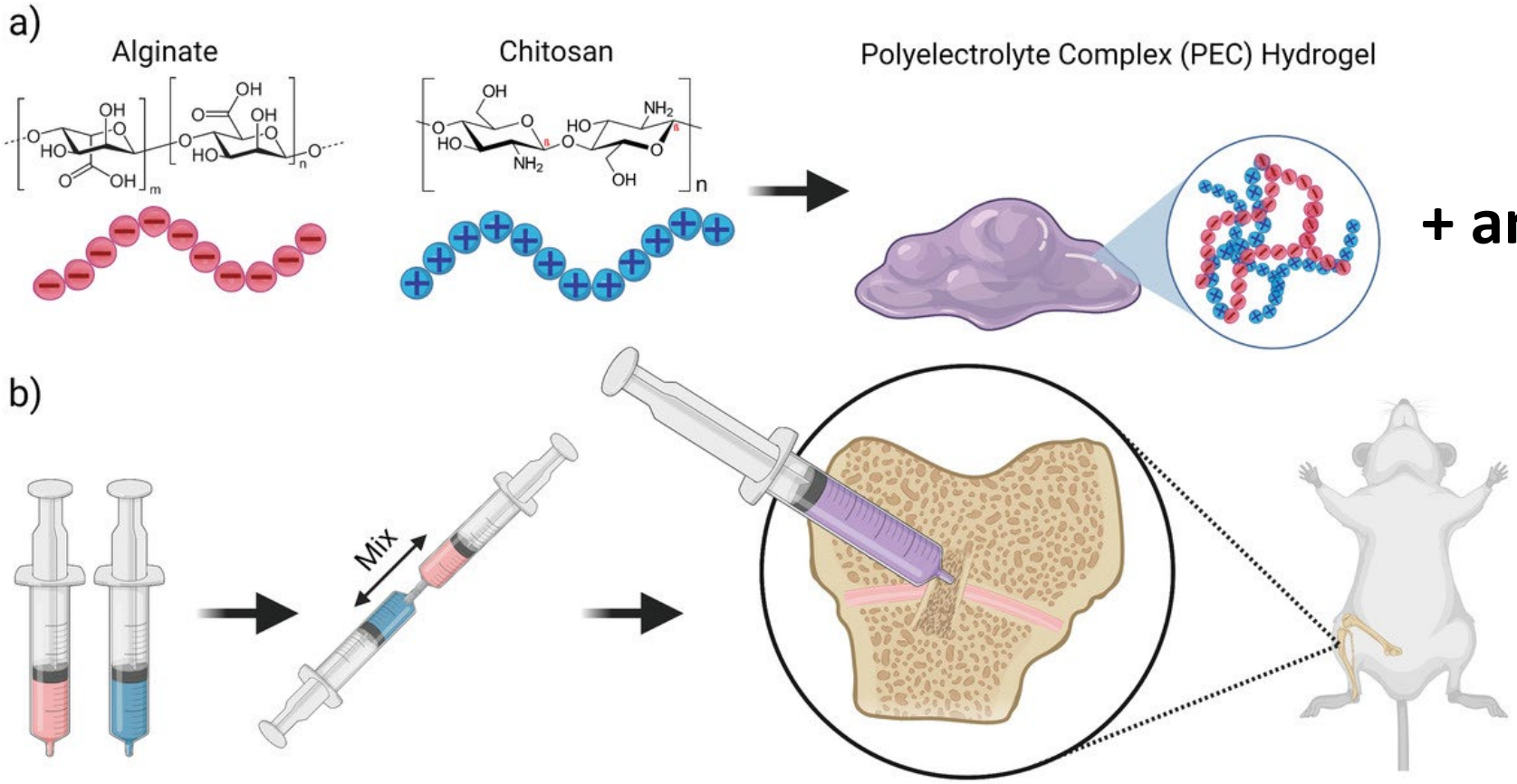
Rat model of growth plate injury: proximal tibia drill-hole defect



Local delivery of α-VEGF

COLORADO SCHOOL OF MINES

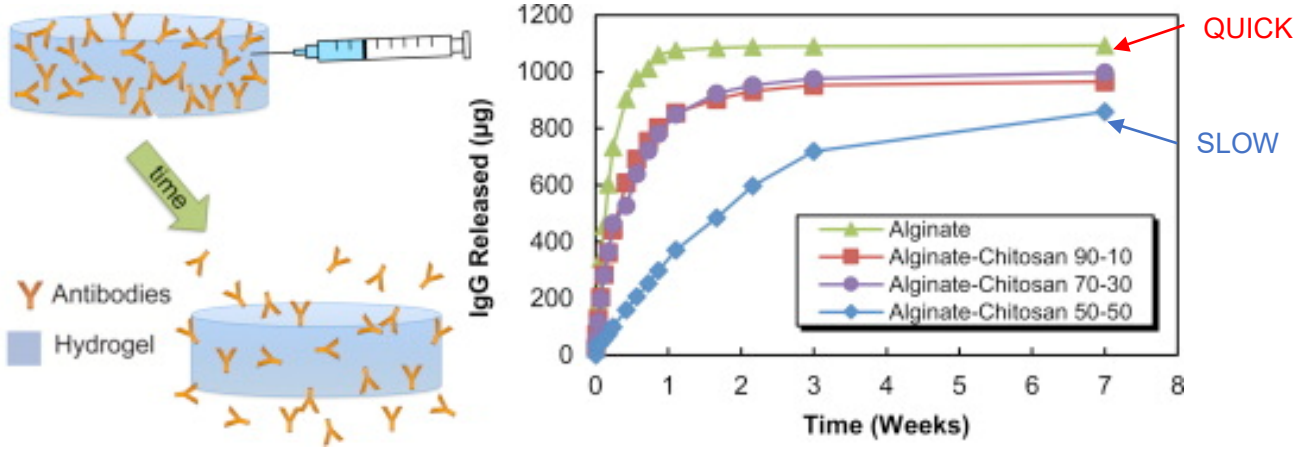
Collaboration with
Melissa Krebs, PhD



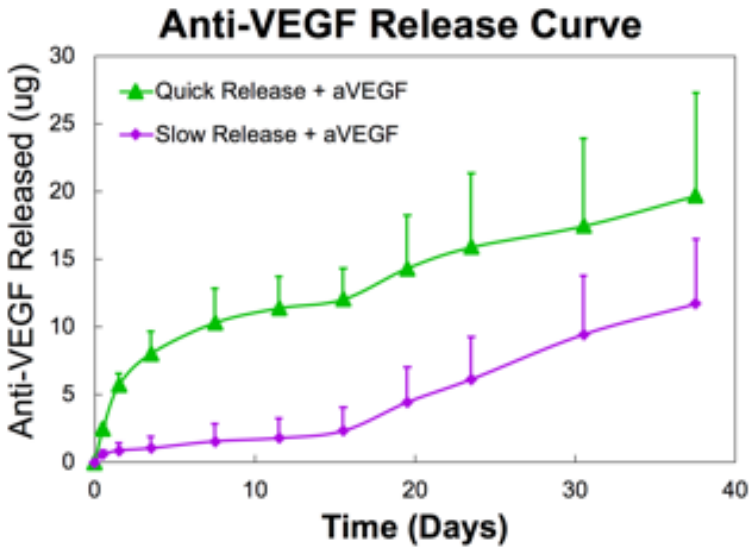
+ anti-VEGF Ab

M. A. Stager, et al. *Macromol. Biosci.* 2022, 22, 2200126.

Antibody release can be modulated in alginate-chitosan hydrogels



Fletcher N. et al. Mater. Sci. and Eng. C. 2016; 801-806.



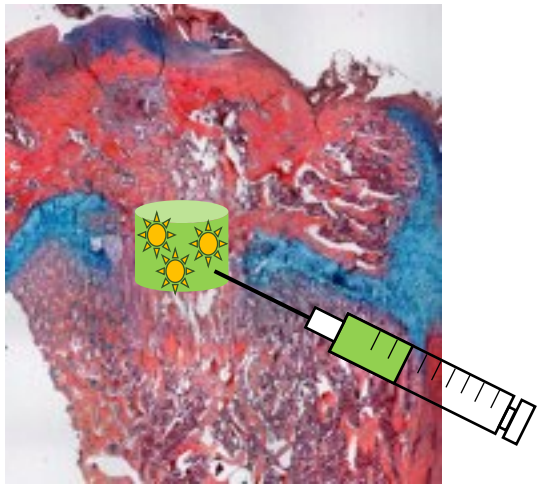
Quick Release = Alginate:chitosan 90:10

Slow Release = Alginate:chitosan 50:50

Erickson CB. et al. *J Orthop Res. 2021*;39(8):1658-1668

Study design

Chris Erickson, PhD

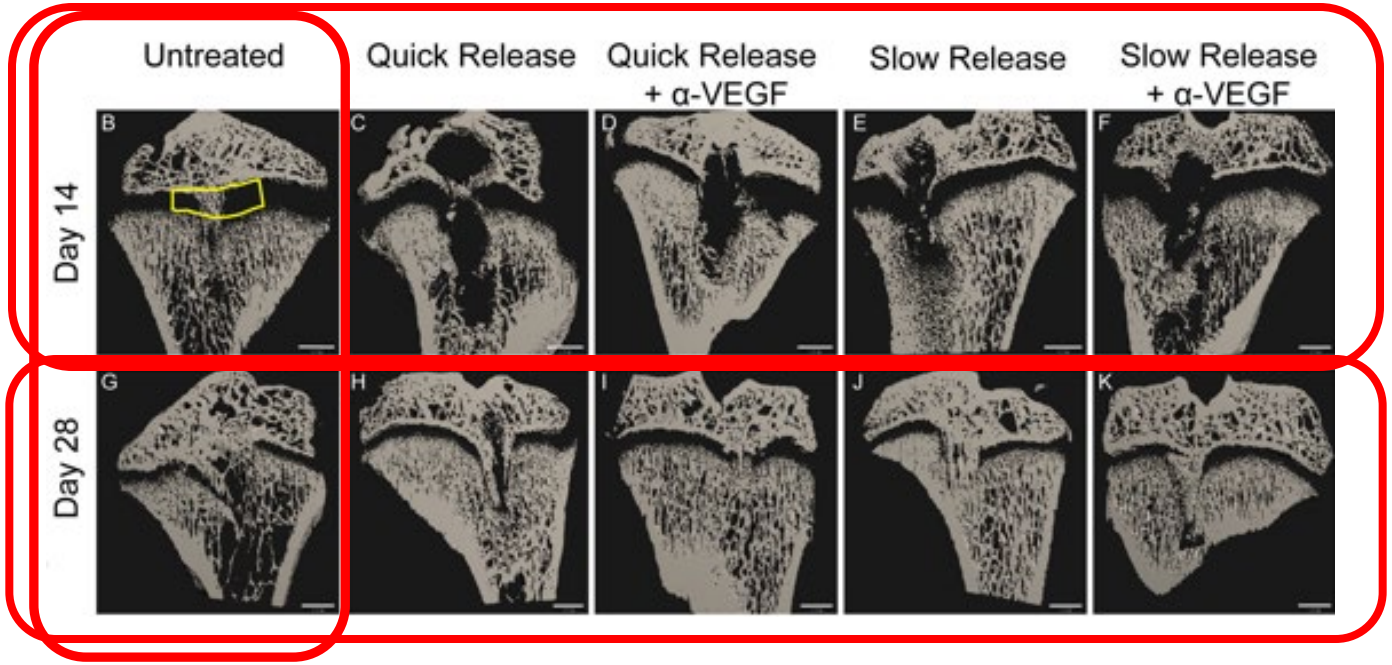


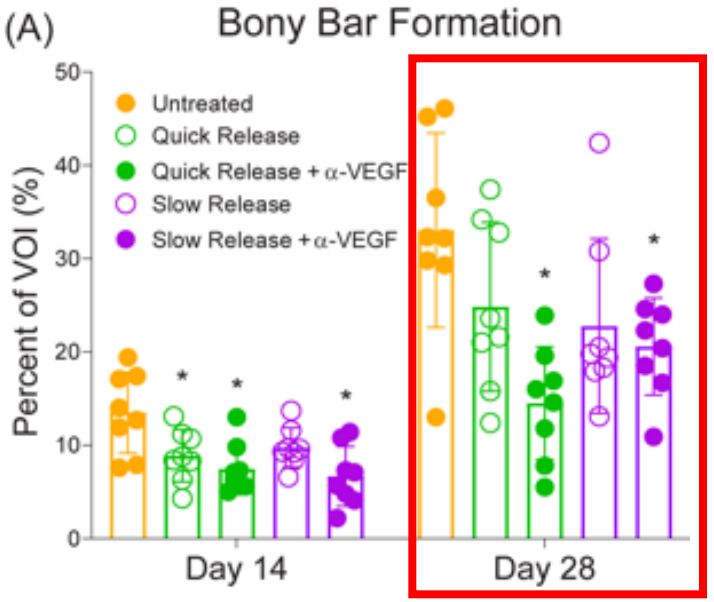
Alginate:Chitosan Hydrogel

Anti-VEGF Antibody
~7ug anti-VEGF$_{165}$

	Treatment groups	Hydrogel name	α-VEGF	Outcomes
1	Intact	-	-	• MicroCT, histology • Perfusion/Blood vessels • N = 8 limbs total (4 male, 4 female) per time point per outcome
2	Untreated	-	-	
3	Alginate:chitosan 90:10	Quick Release	-	
4	Alginate:chitosan 90:10 + anti-VEGF antibody	Quick Release + α-VEGF	+	
5	Alginate:chitosan 50:50	Slow Release	-	
6	Alginate:chitosan 50:50 + anti-VEGF antibody	Slow Release + α-VEGF	+	

Local delivery of α-VEGF reduces bony bar formation

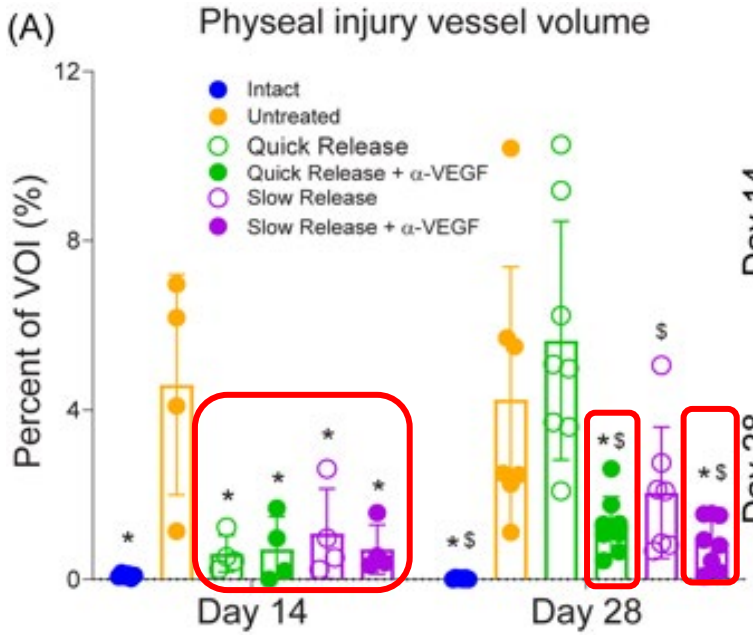


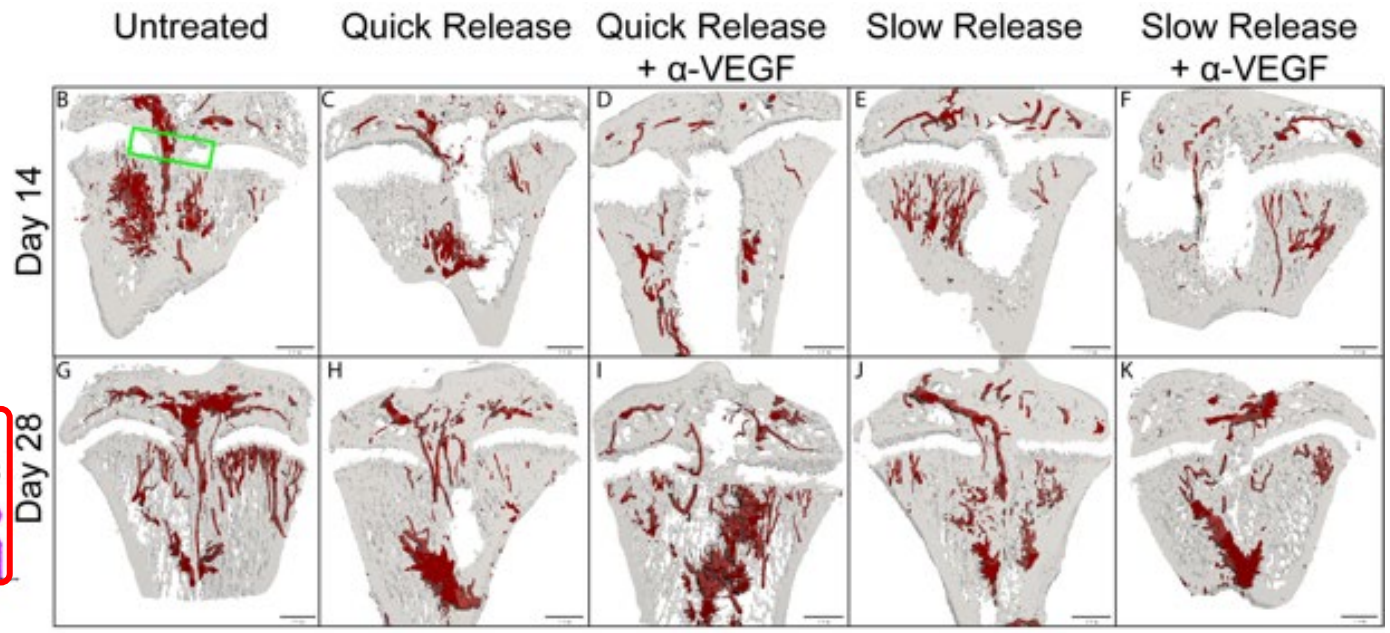


Mean +/- SD, one-way ANOVA, N = 8
*P<0.05 vs. Untreated same time point

Erickson CB. et al. *J Orthop Res.* 2021;39(8):1658-1668

Local delivery of α-VEGF reduces vessel formation

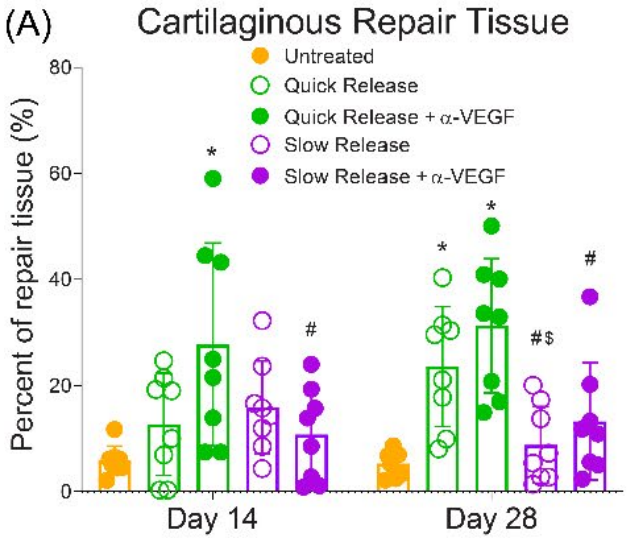




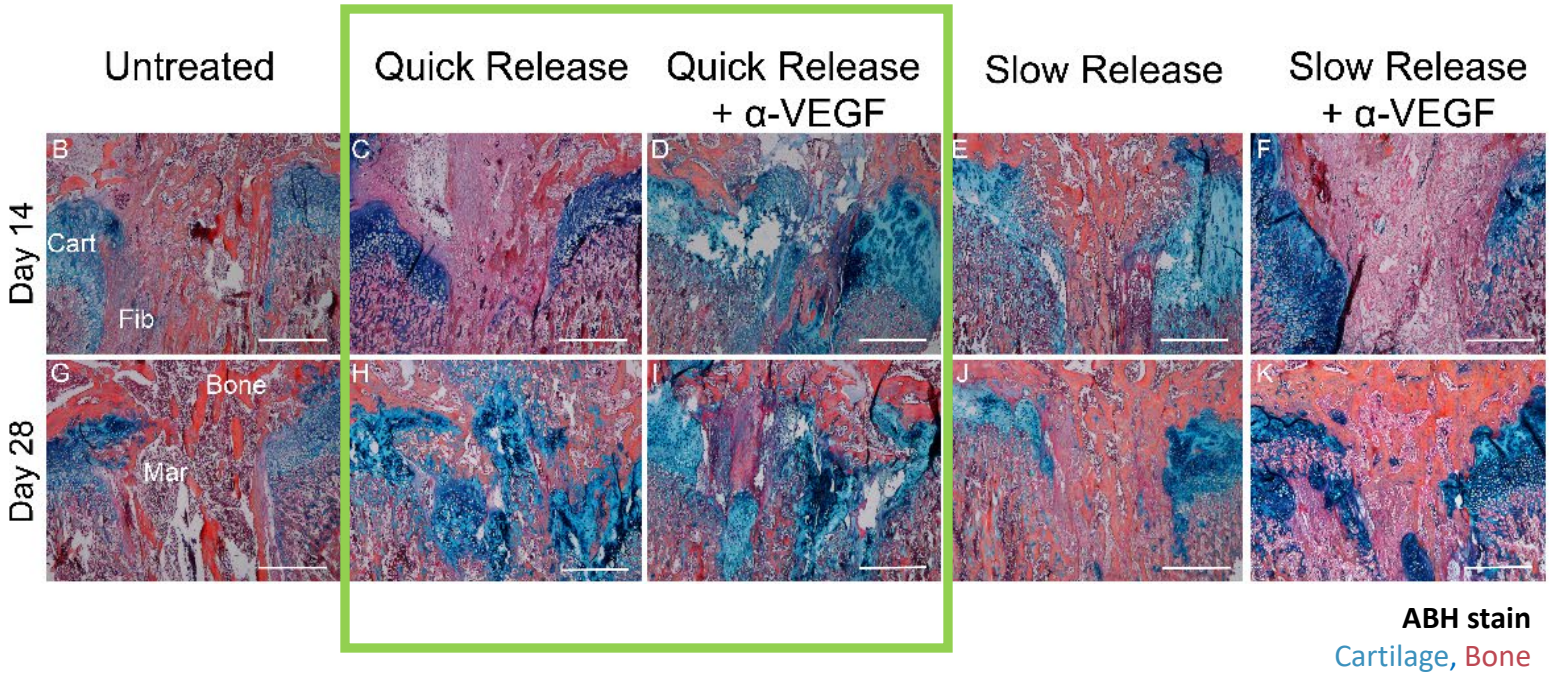
Mean +/- SD, one-way ANOVA, N = 8
*P<0.05 vs. Untreated same time point
$P<0.05 vs. QR same time point

Erickson CB. et al. *J Orthop Res.* 2021;39(8):1658-1668

Quick delivery of α-VEGF increases cartilage repair tissue



Mean +/- SD, one-way ANOVA, N = 8
*P<0.05 vs. Untreated same time point
#P<0.05 vs. QR+aVEGF same time point

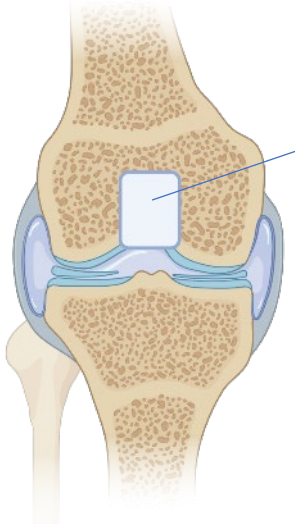


ABH stain
Cartilage, Bone

Could modulation of angiogenesis be a preventative treatment for bony bar formation?

Erickson CB. et al. *J Orthop Res.* 2021;39(8):1658-1668

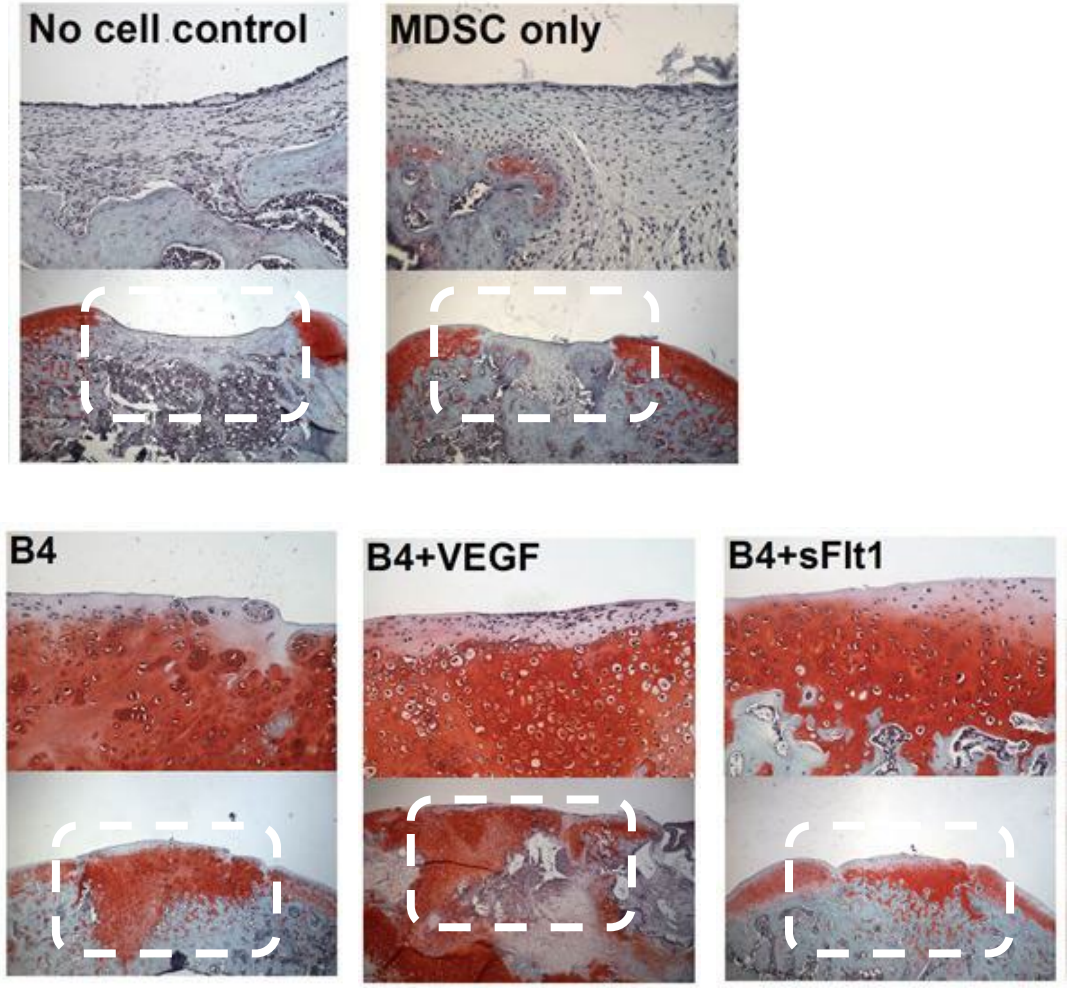
Blocking VEGF improves articular cartilage repair



Rat osteochondral injury

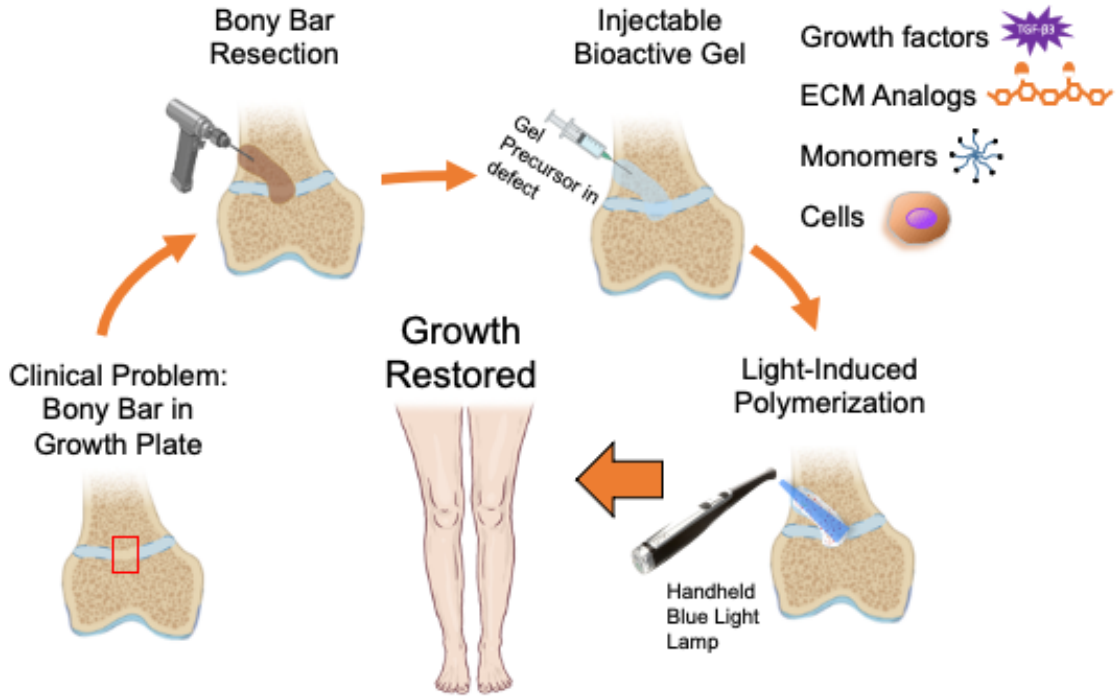
Implant muscle-derived stem cells (MDSCs) transduced to express:

- BMP4 (chondrogenic factor)
- VEGF (angiogenesis)
- sFlt1 (block angiogenesis)



Kubo S, et al. Arthritis Rheum. 2009 Jan;60(1):155-65.

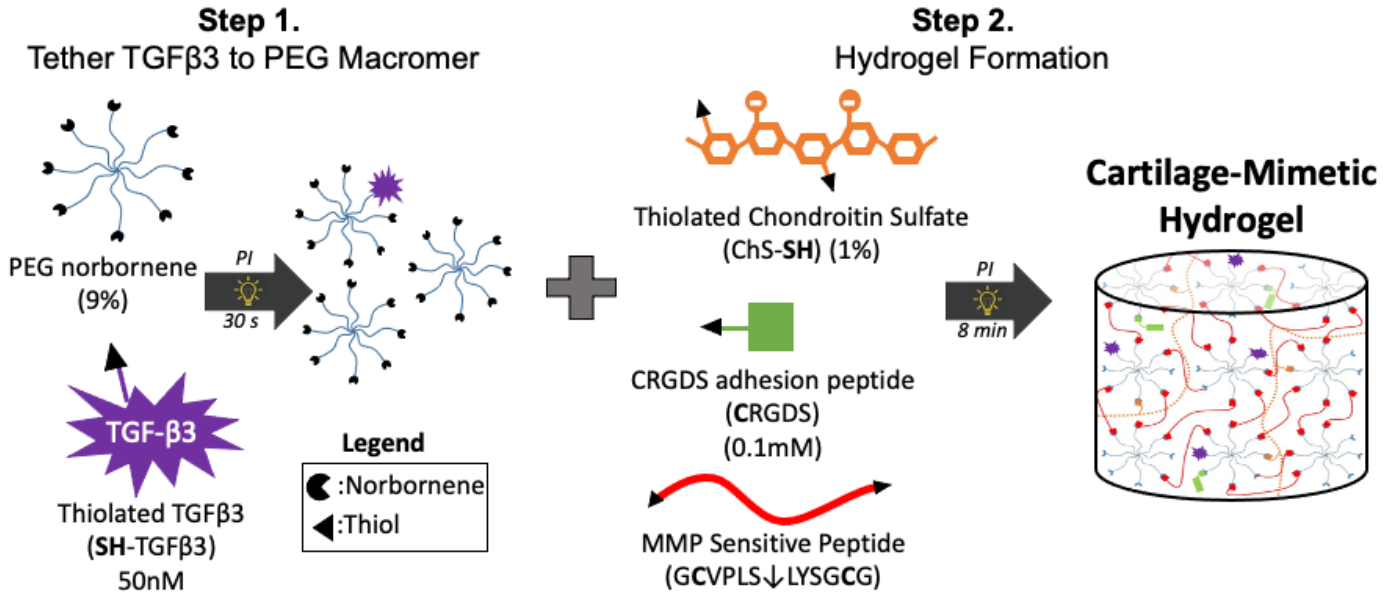
Regenerative Biomaterial to Treat Growth Plate Injuries

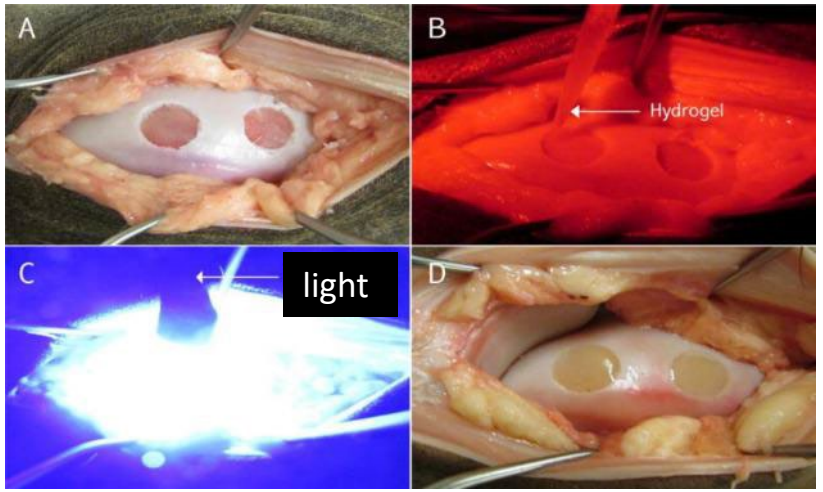


Cartilage-Mimetic Hydrogel

Boulder

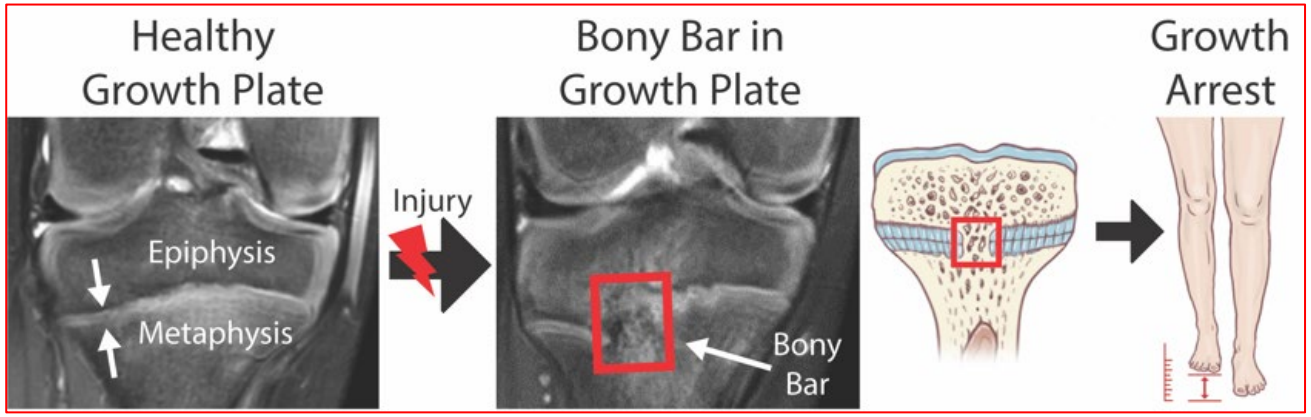
Collaboration with Stephanie Bryant, PhD

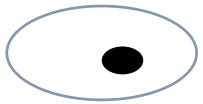




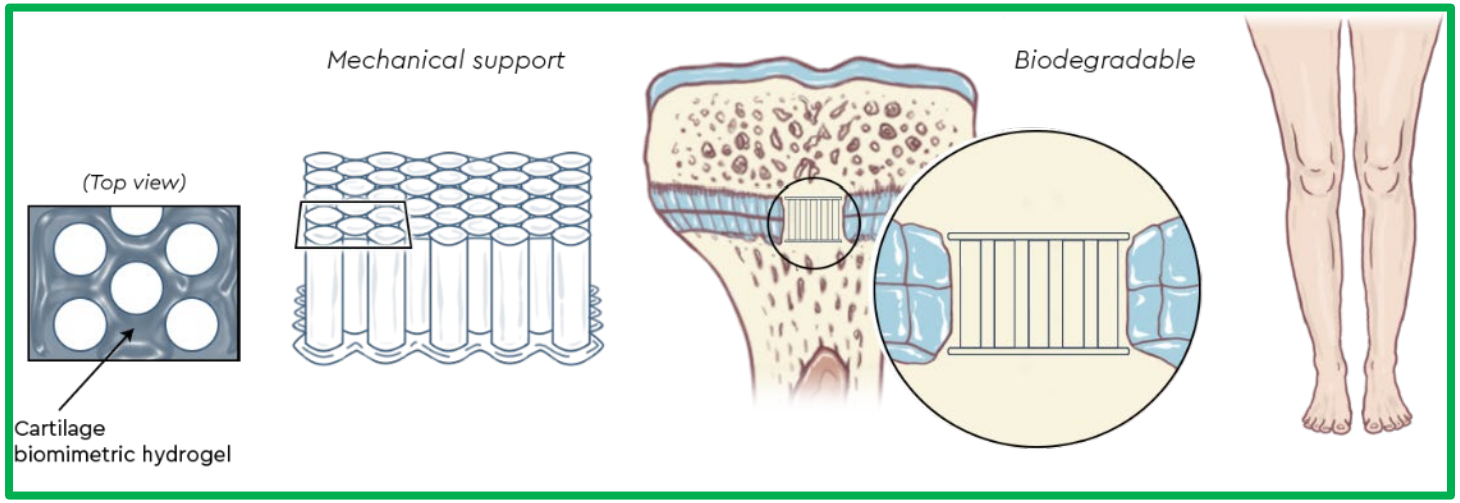
With Laurie Goodrich, DVM, PhD at CSU

Clinical Problem: Growth Plate Injuries

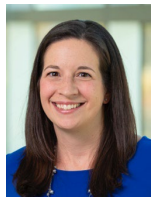


Biochemical cues + Mechanical cues →  cell differentiation
cell synthesizing capabilities

Solution: 3D Printed Growth Plate Mimetic Composite



Multidisciplinary Team

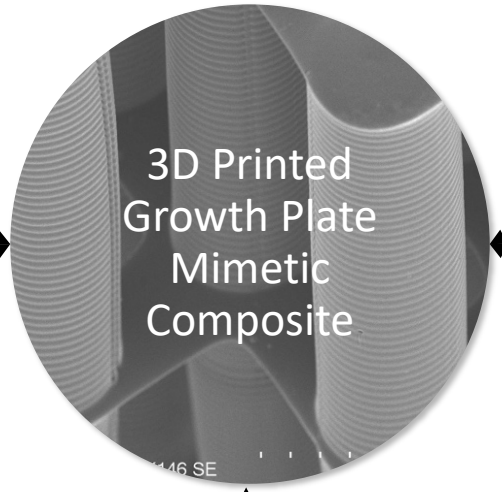


Anschutz

Karin Payne, PhD
- Animal models of growth plate injury
- Chondrogenic differentiation

Children's Hospital Colorado

Nancy Hadley Miller, MD
- Clinical expertise with growth plate injuries



Boulder

Stephanie Bryant, PhD
- Cartilage mimetic hydrogel
- 3D printing
- Cartilage tissue engineering

Boulder

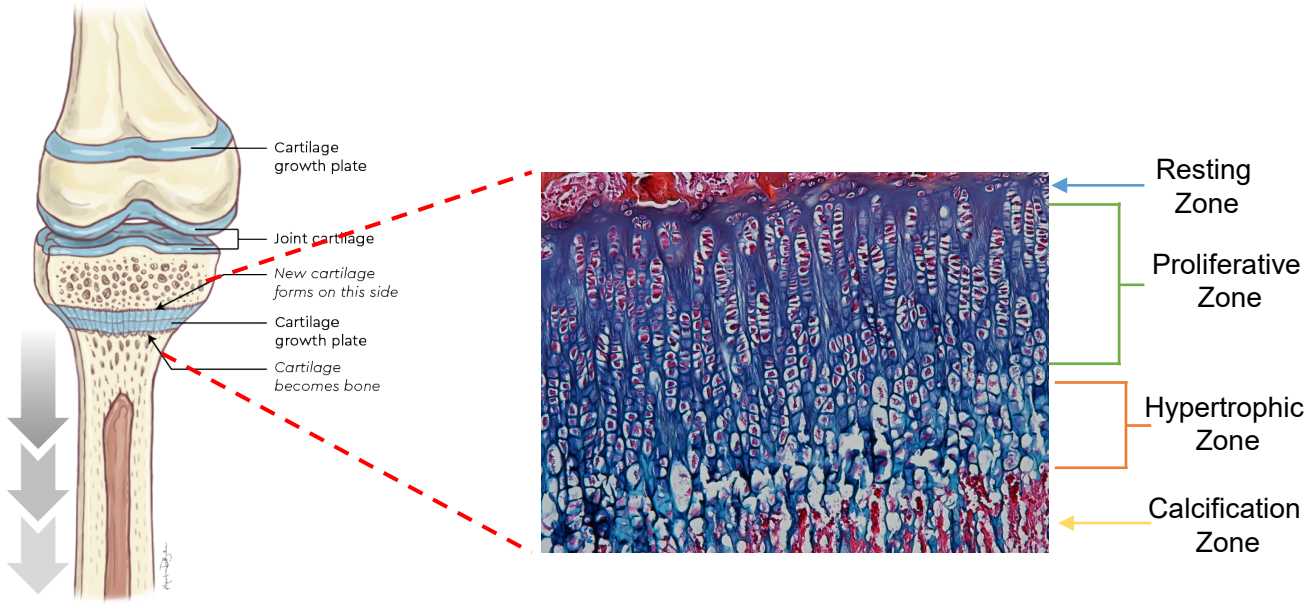
Robert McLeod, PhD
- Additive manufacturing
- Photopolymers

Boulder

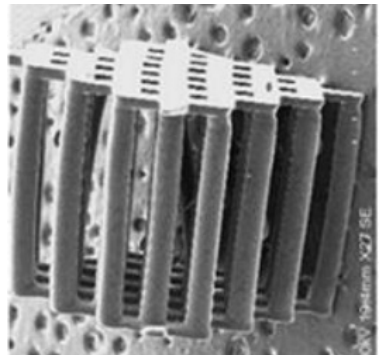
Virginia Ferguson, PhD
- Bone and cartilage tissue characterization
- 3D printing characterization

Designing a 3D printed growth plate mimetic composite

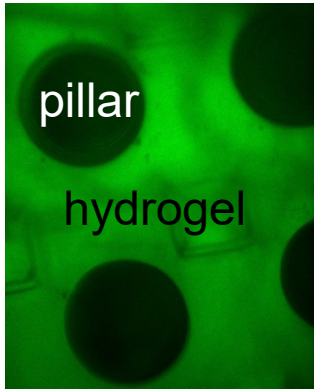
Growth Plate: Area of Bone Growth



Characterize zonal properties and morphology of the rabbit growth plate



3D printed structure is infilled with hydrogel

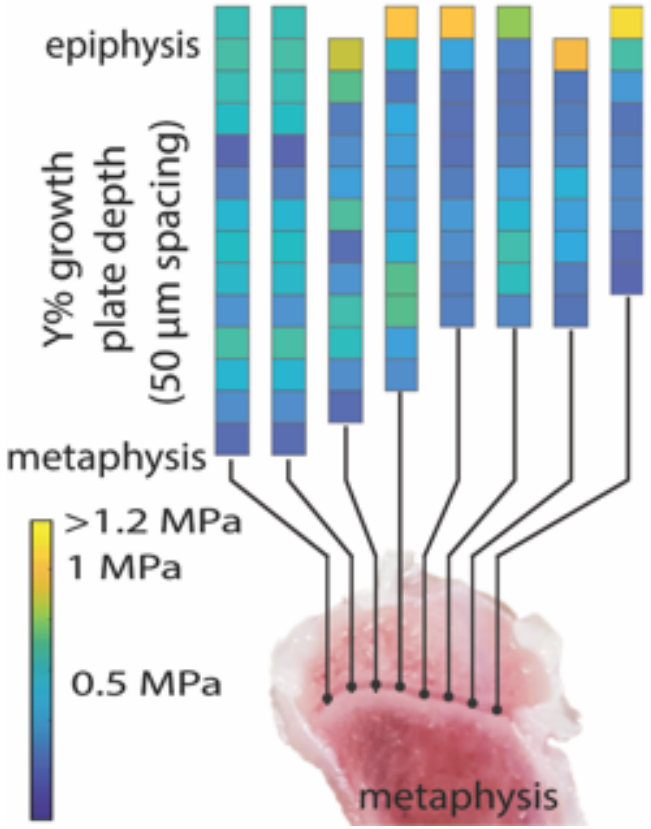


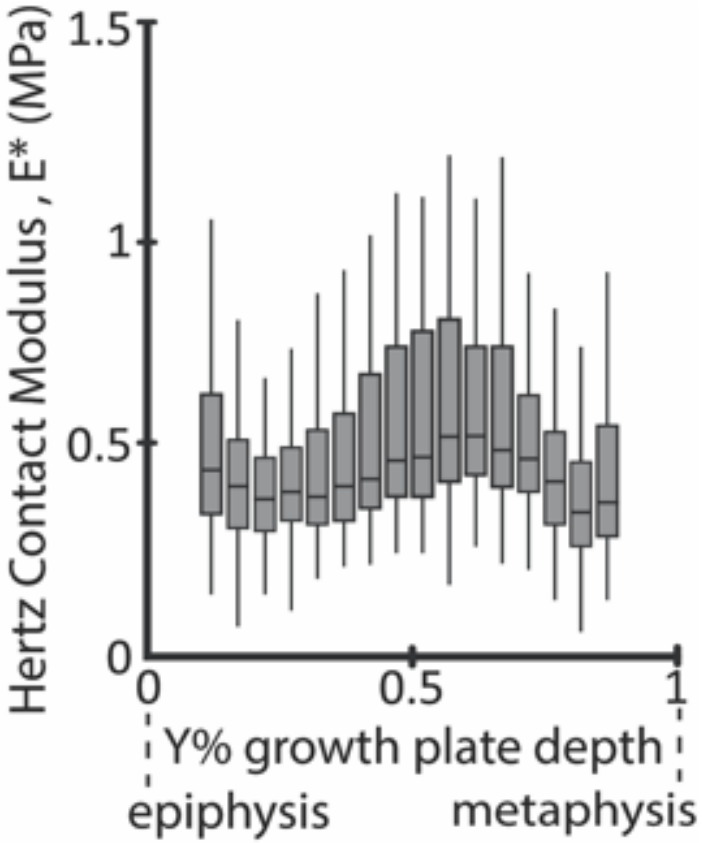
Hydrogel (green) can be injected in between the individual pillars

Mechanical properties vary across the growth plate

Kevin Eckstein, PhD

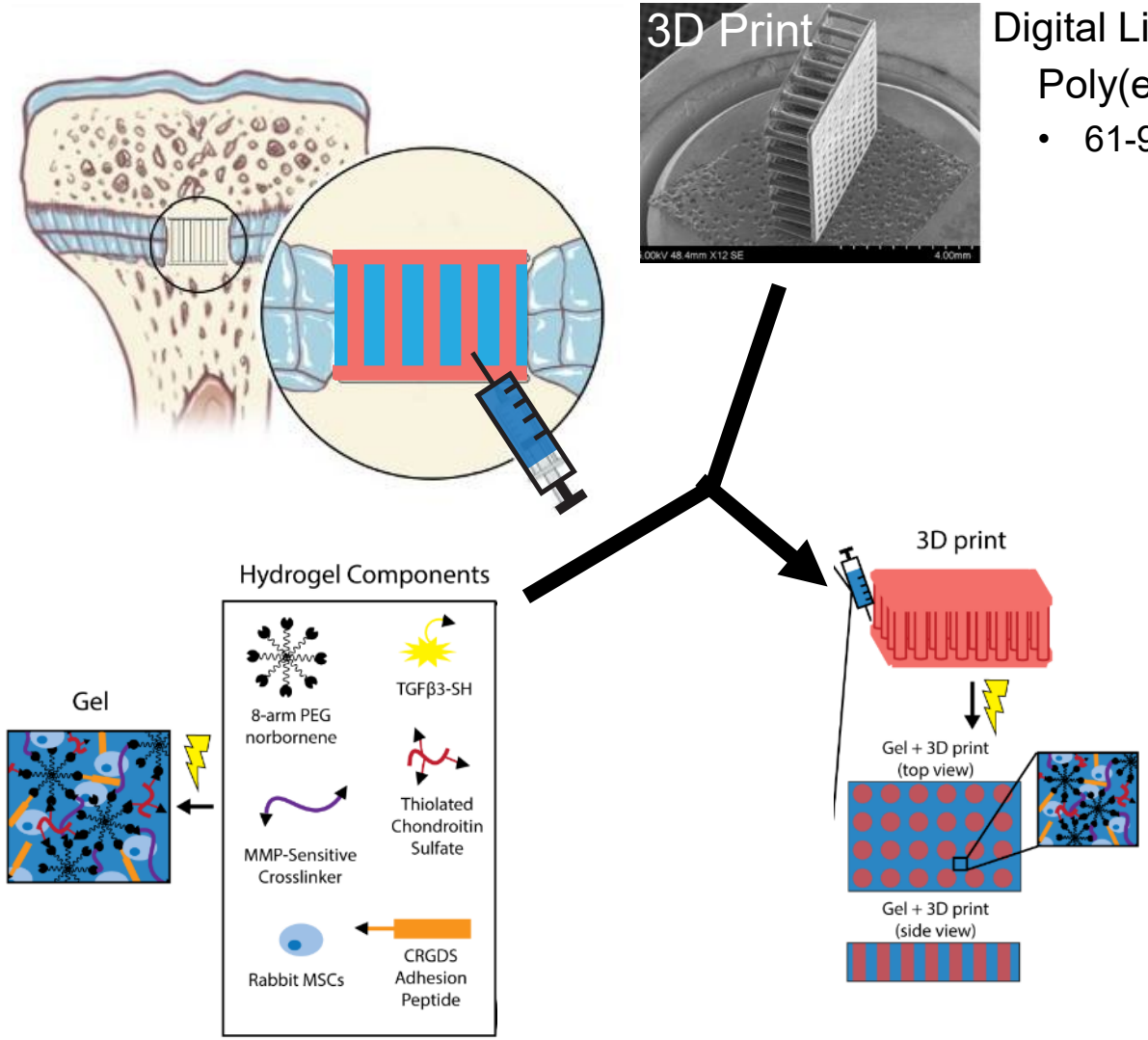
Microindentation maps mechanical properties across the zones of the rabbit growth plate





Eckstein KN et al. *J Mech Behav Biomed Mater*. 2022;128:105102

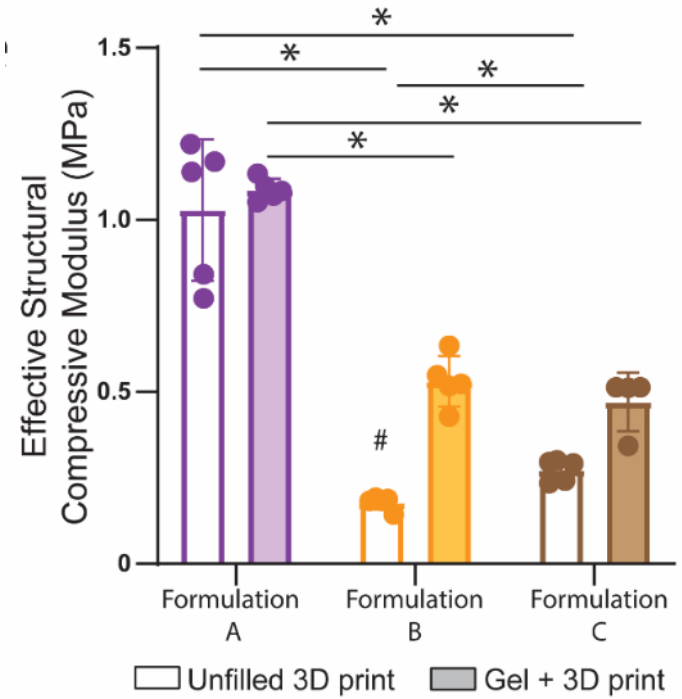
3D printed cartilage mimetic composite



Digital Light Processing

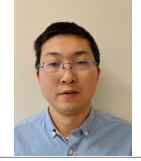
Poly(ethylene glycol) diacrylate (PEGDA)

- 61-98 pillars with lattice on top and bottom layers

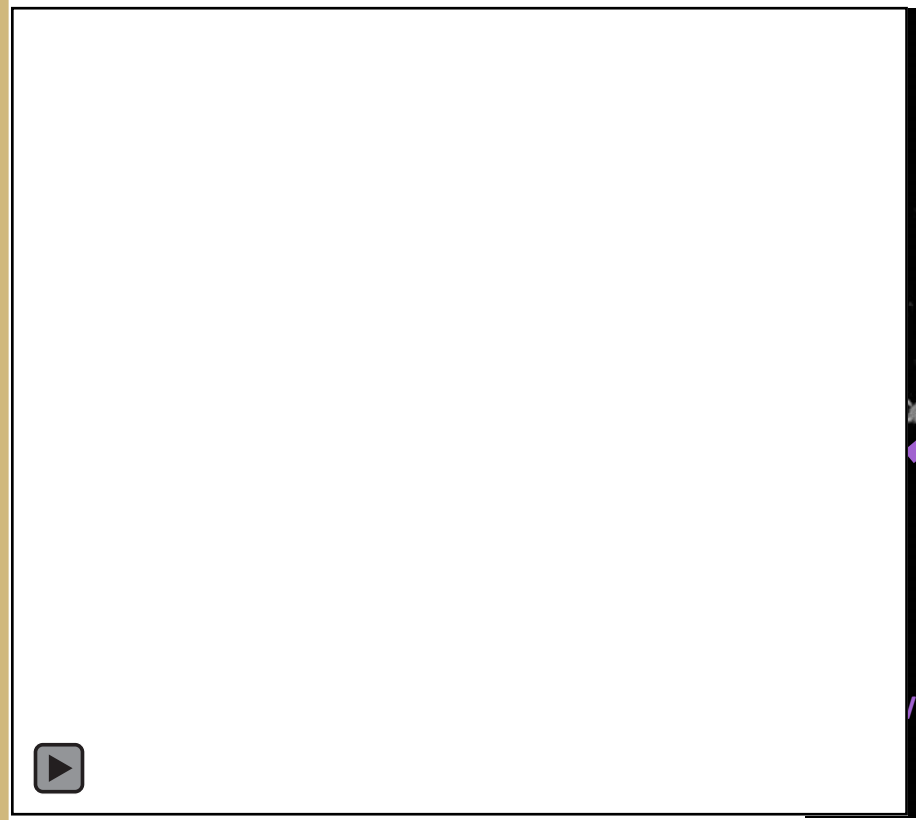


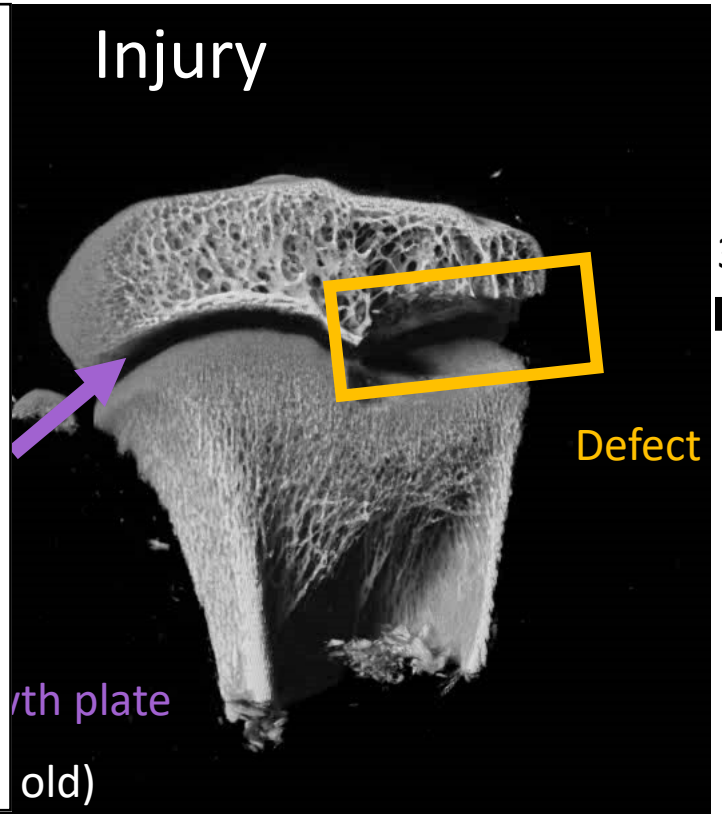
Yu Y., Fischenich KM. et al. npj Regen Med 7, 60 (2022)

Rabbit model of growth plate injury



Yangyi Yu, MD





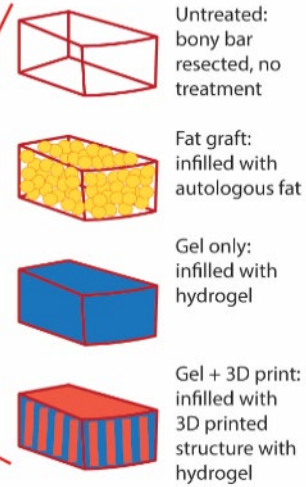
3 weeks

Bony Bar Formation

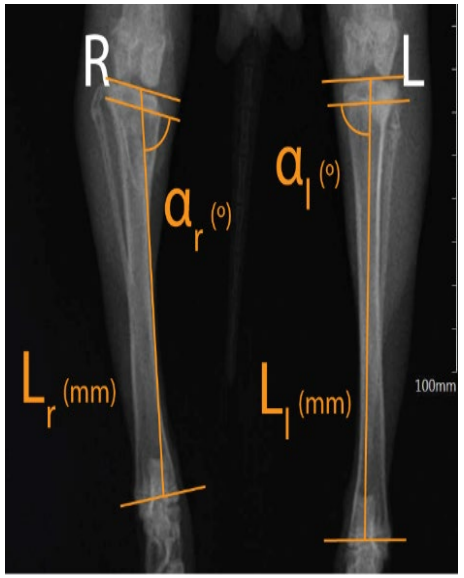
Surgery 2 (9 weeks old)

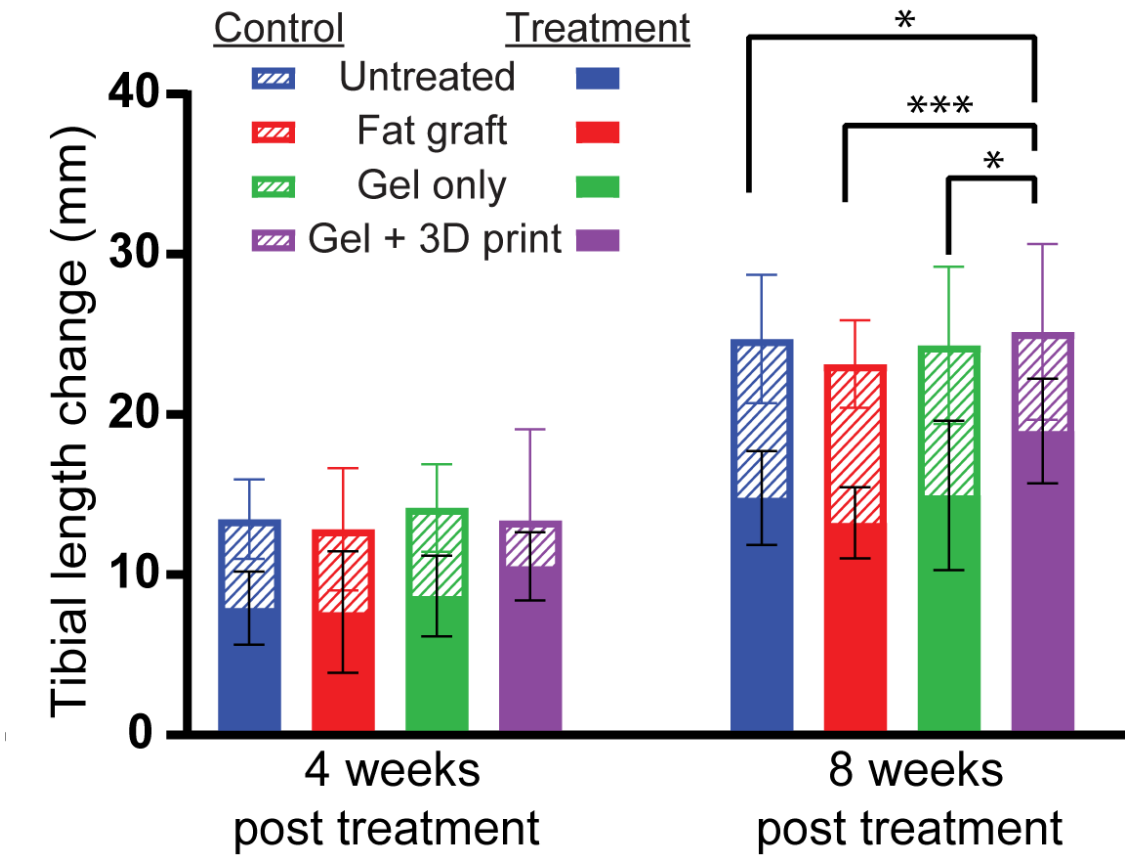
Bony Bar Resection

Treatment



3D printed composite led to increased limb lengthening





*p<0.05 compared to other treatment groups

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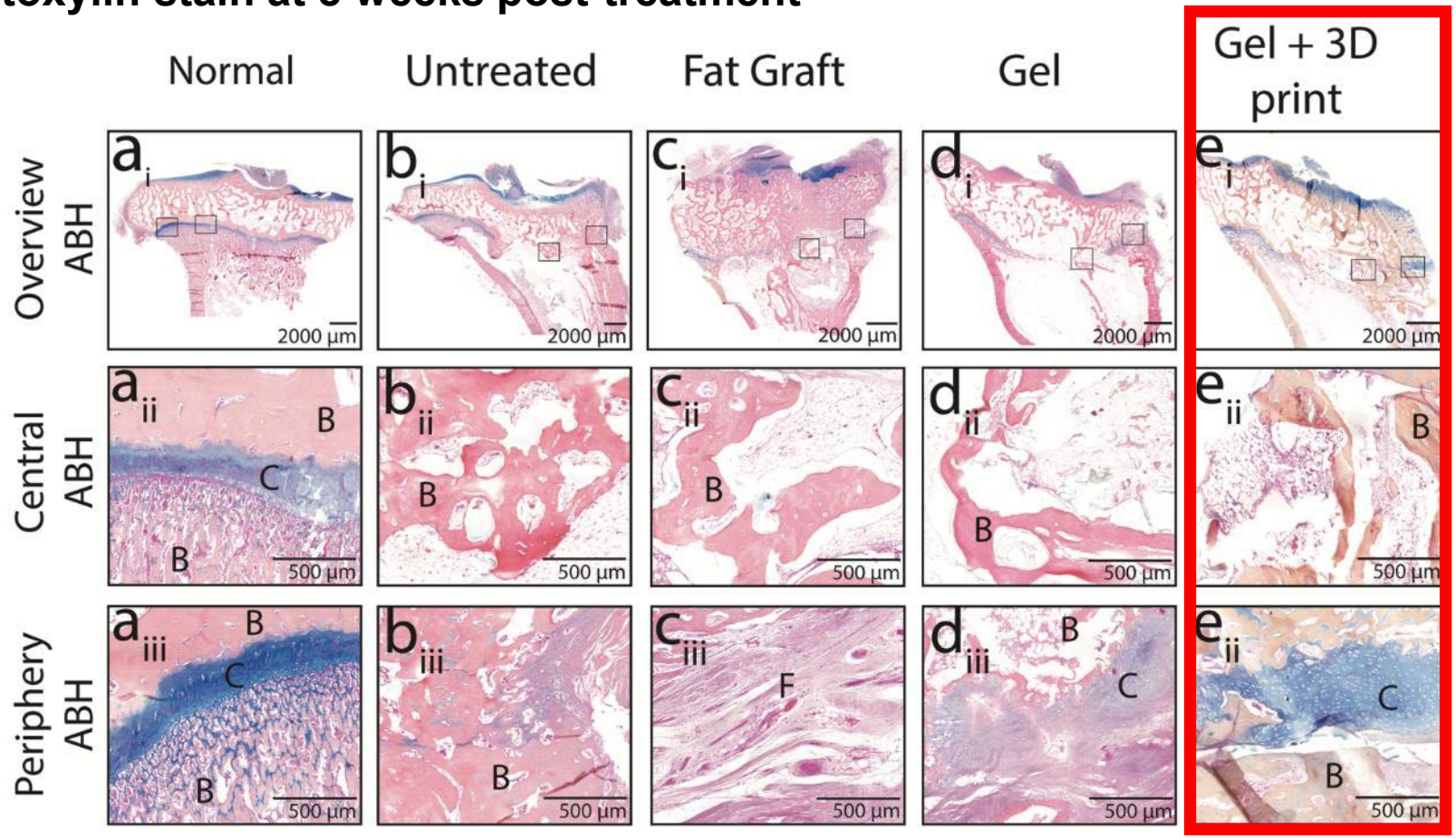
3D composite led to cartilage-like tissue at periphery

Alcian Blue Hematoxylin stain at 8 weeks post-treatment



Cartilage, Bone

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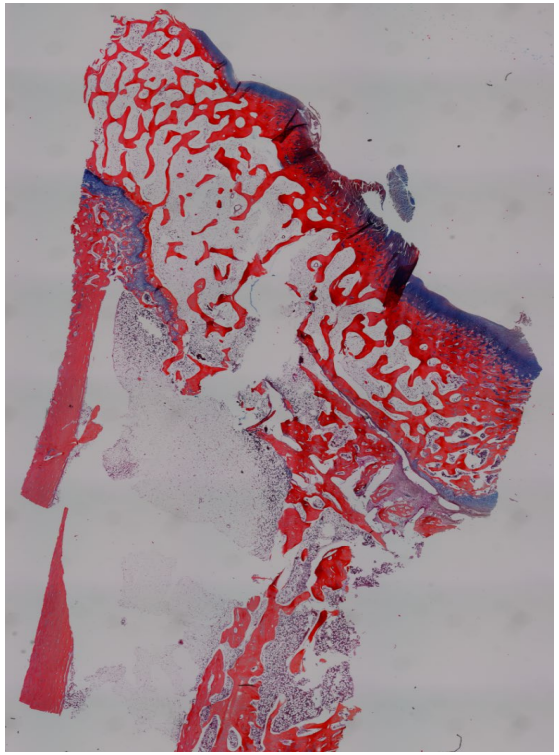
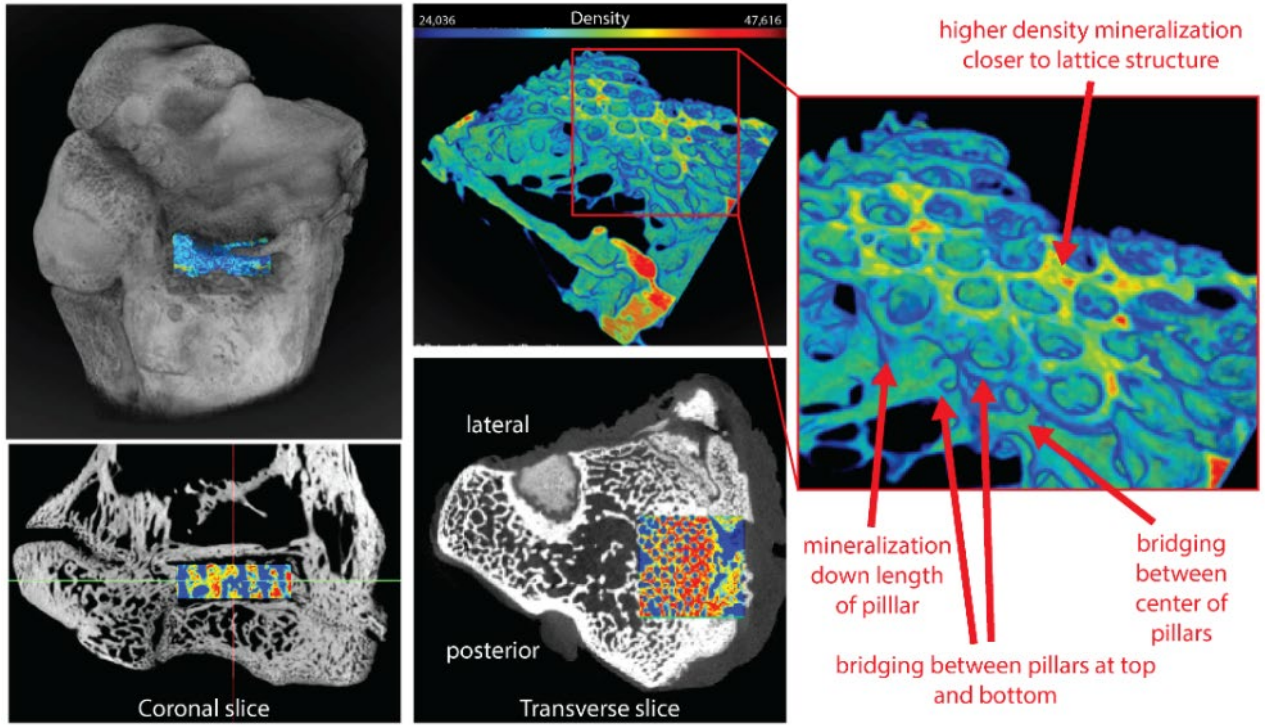
Mineralization within 3D printed composite

Kristine Fischenich, PhD





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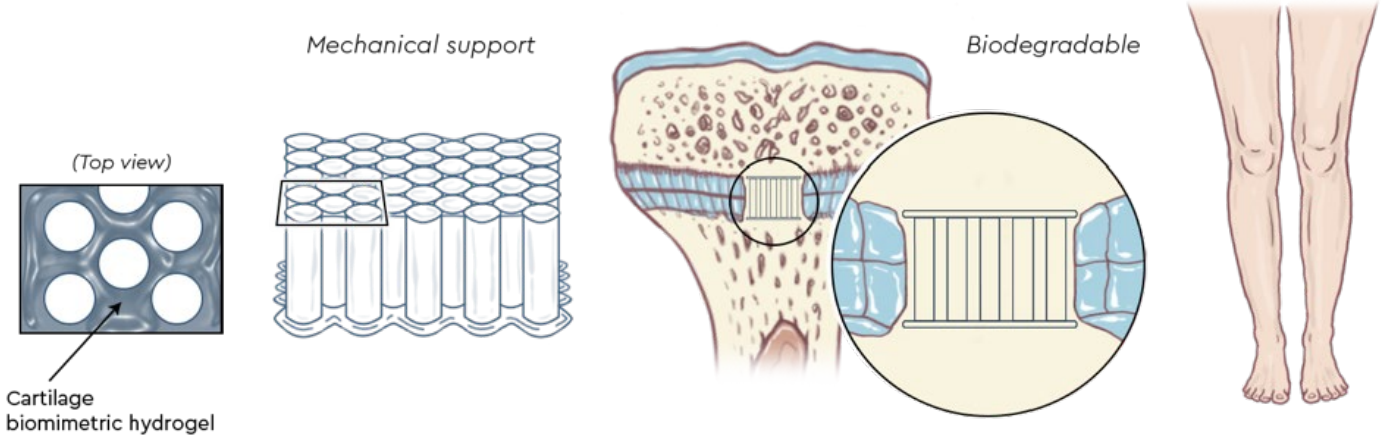
Discussion



- 3D printed structure infilled with cartilage-mimetic hydrogel leads to
  - Increased tibial lengthening – important functional outcome
  - Some cartilage tissue formation
  - Evidence of mineralized tissue around pillars

What happens at early timepoints???

What have we learned?

- Blocking angiogenesis is a potential avenue to prevent bony bar formation and repair articular cartilage.
- 3D printed biomimetic composite postpones the onset of skeletal deformities.
  - Outcomes may be further improved to promote chondrogenesis.
    - Test additional biological factors to recruit MSCs and/or add MSCs.
    - Anchoring mechanisms.
  - Technology can also be used for articular cartilage regeneration due to injury or osteoarthritis.

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Thank You!

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