Rejuvenation of Your Resident Stem Cells: Therapeutic Strategies on the Horizon

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THE STEADMAN CLINIC AND STEADMAN PHILIPPON RESEARCH INSTITUTE

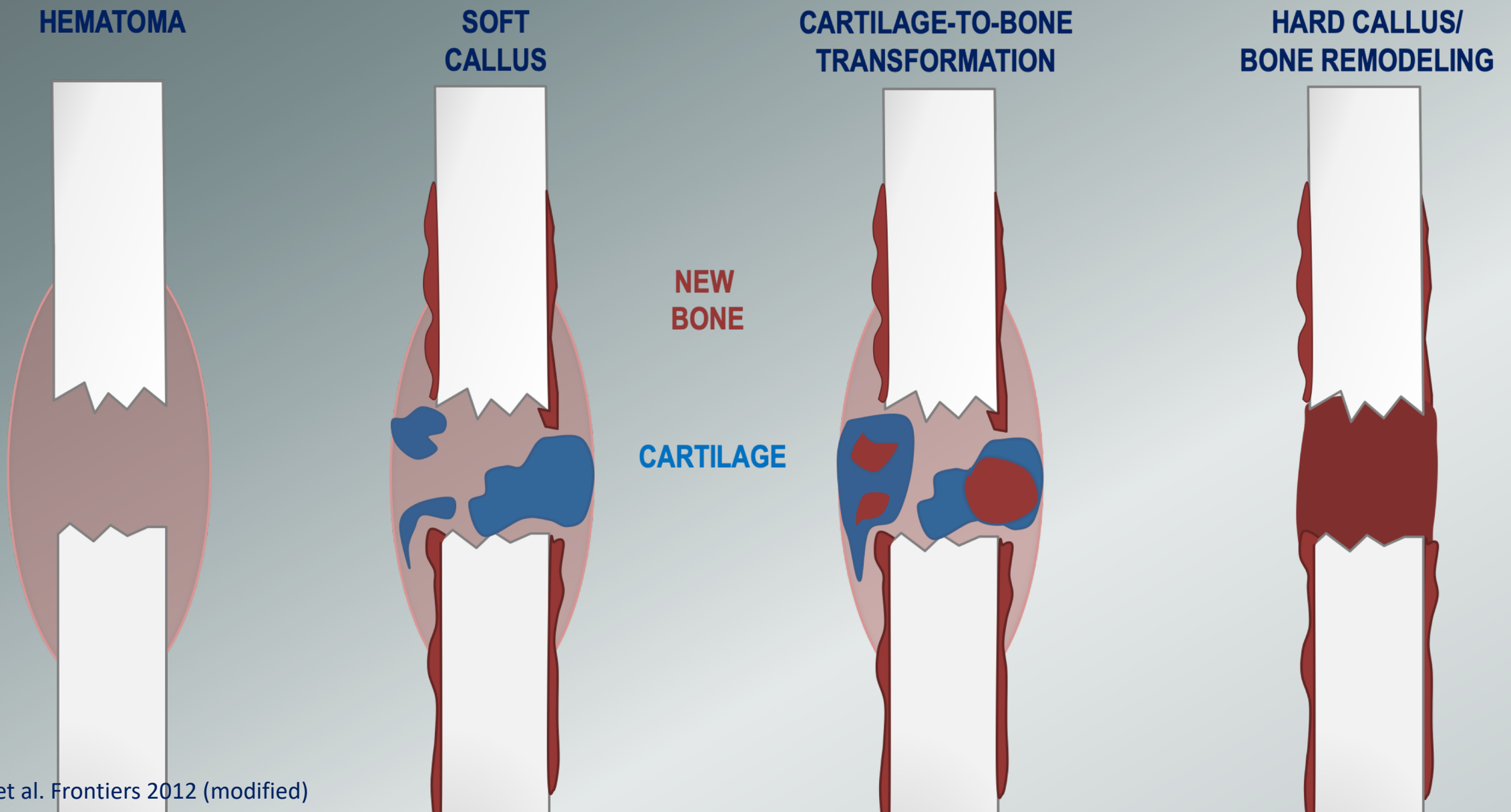
U.S. OLYMPIC NATIONAL MEDICAL CENTER

Broken Bones: One of the Most Common Injuries

Heal Quickly

May Not Heal

Molecular & Cellular Mechanisms of Fracture Repair



Bahney et al. Frontiers 2012 (modified)

Clinical Significance of Fractures

15M fracture injuries/year in the U.S.

WOMEN OVER **50** WILL EXPERIENCE OSTEOPOROTIC FRACTURES. AS WILL MEN. ouch!

10-50% fractures result in delayed or nonunion

$23B cost of hospitalization for fracture injuries

30% mortality and 80% permanent disability @ 1yr

Limitations of Current Methods of Monitoring Healing

CURRENT METHODS

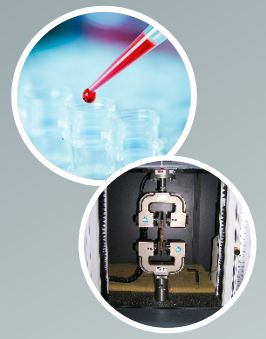
X-ray: late detection

Clinical observation: subjective

Qualitative

CT scan: radiation, expensive

SPRI RESEARCH



Biomarkers correlating to progression of healing have not been identified

Sensors to measure tissue properties

Clinical Need: A method to quantify fracture healing and identify predictive healing patterns

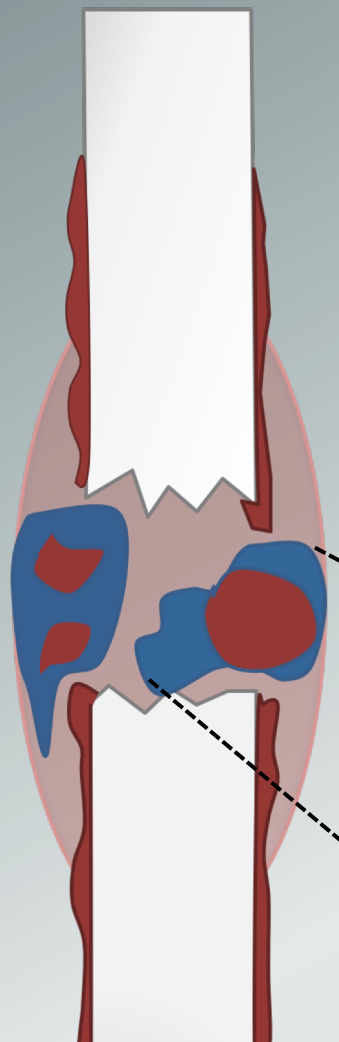
Biomarker of Fracture Healing

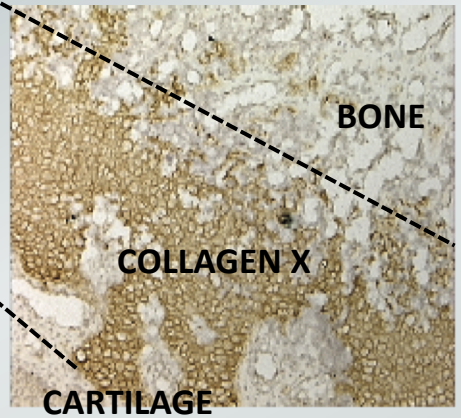
BILL & MELINDA GATES *foundation*

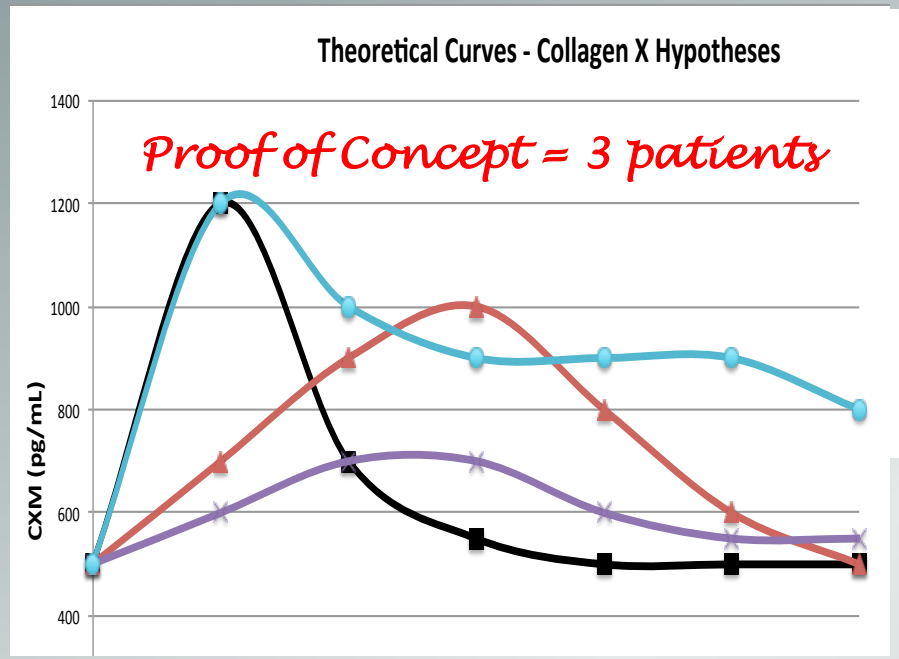
Science Translational Medicine

Coughlan *et al*. Sci Trans Med 2017

CARTILAGE-TO-BONE TRANSFORMATION







5 drops of blood from finger

Leading the Multicenter Clinical Biomarker Validation

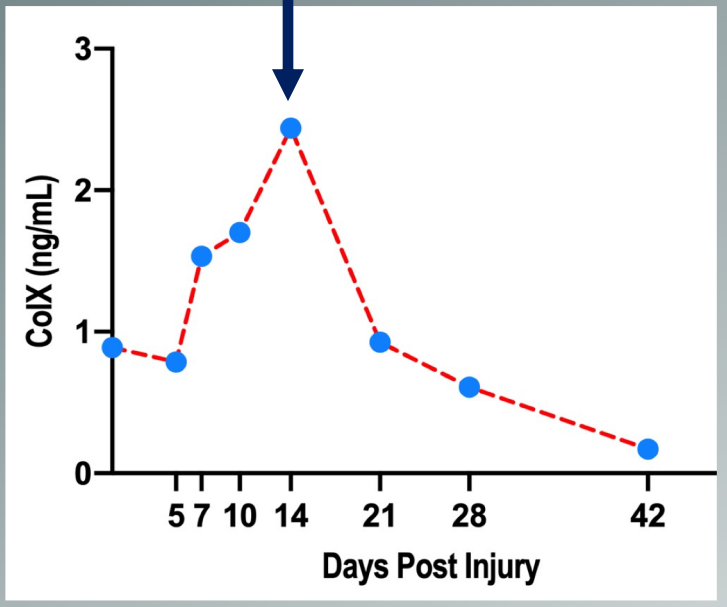
Pre-clinical model shows statistically significant peak at day 14

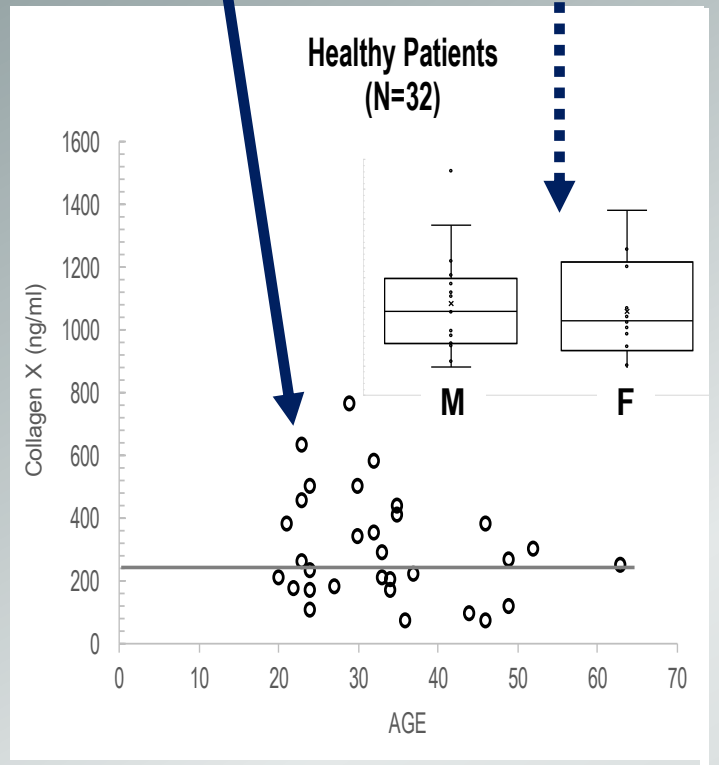
Biomarker baseline is <u>not</u> age dependent

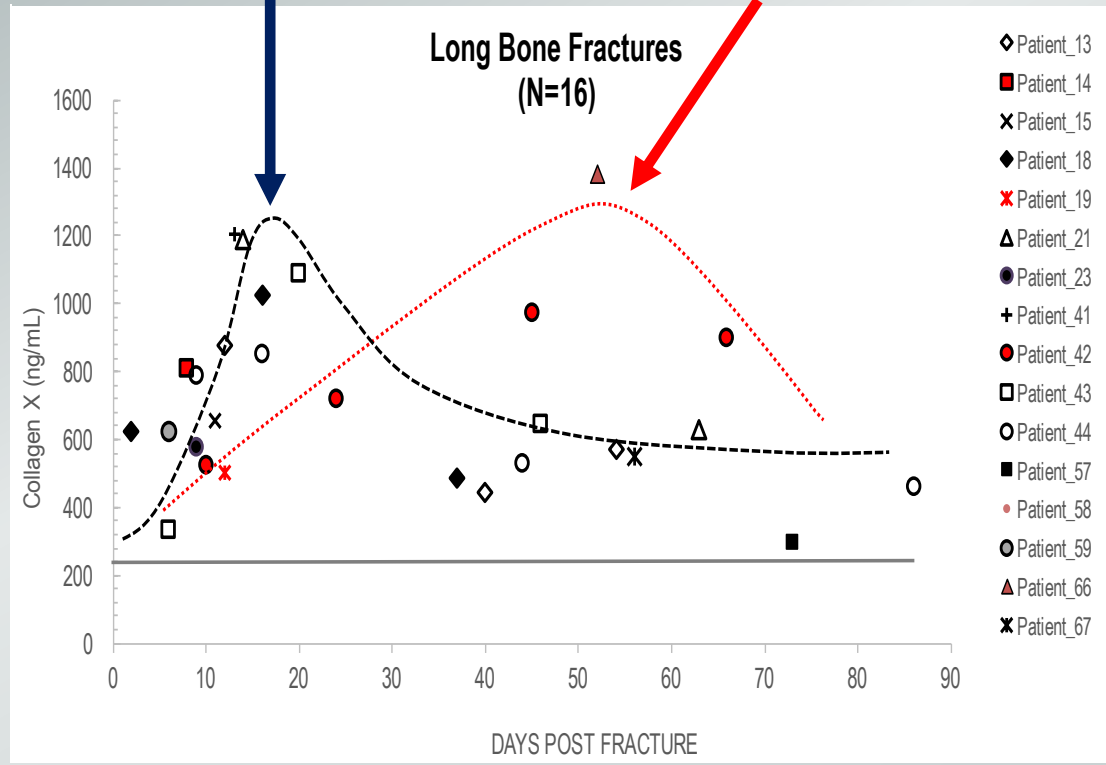
(or sex)

Normal healing peak at day 18

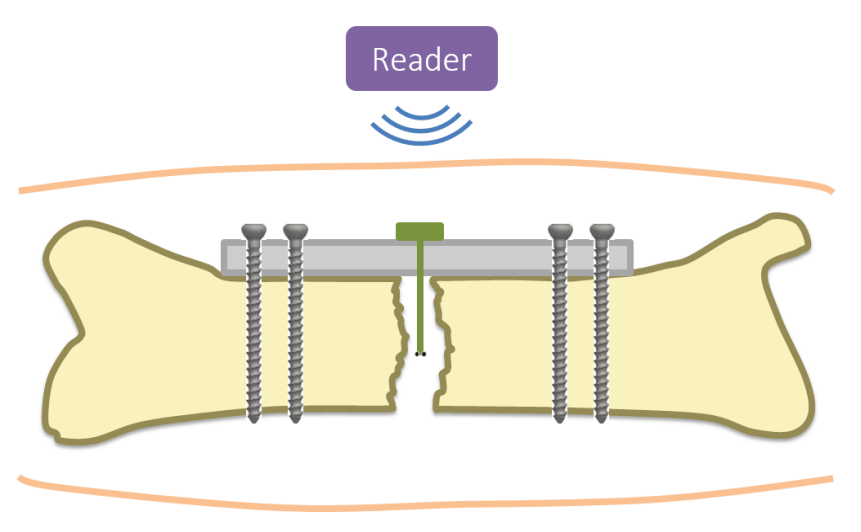
Over 60 → 3⁺ times longer healing



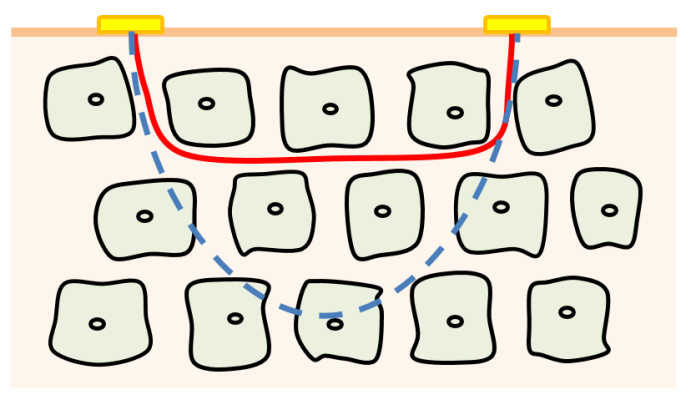




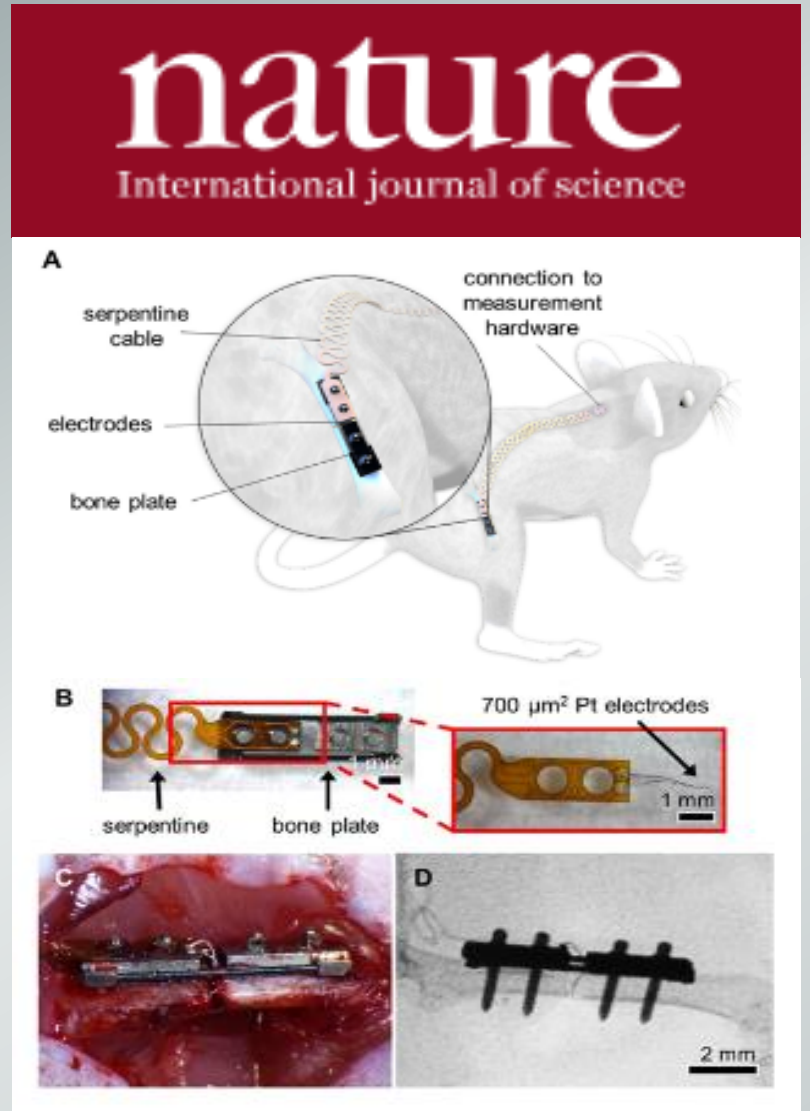
Smart Bone Plates to Monitor Fracture Healing



ELECTRICAL IMPEDANCE



Low Frequency **High Frequency**



- Impedance can distinguish between different types of tissue in fracture callus & correlates to composition
- Measurements differentiates good vs bad healing
- Longitudinal measurements show increasing impedance corresponds with bone mineral density

MC. Lin *et al*. Nature Sci Reports 2019

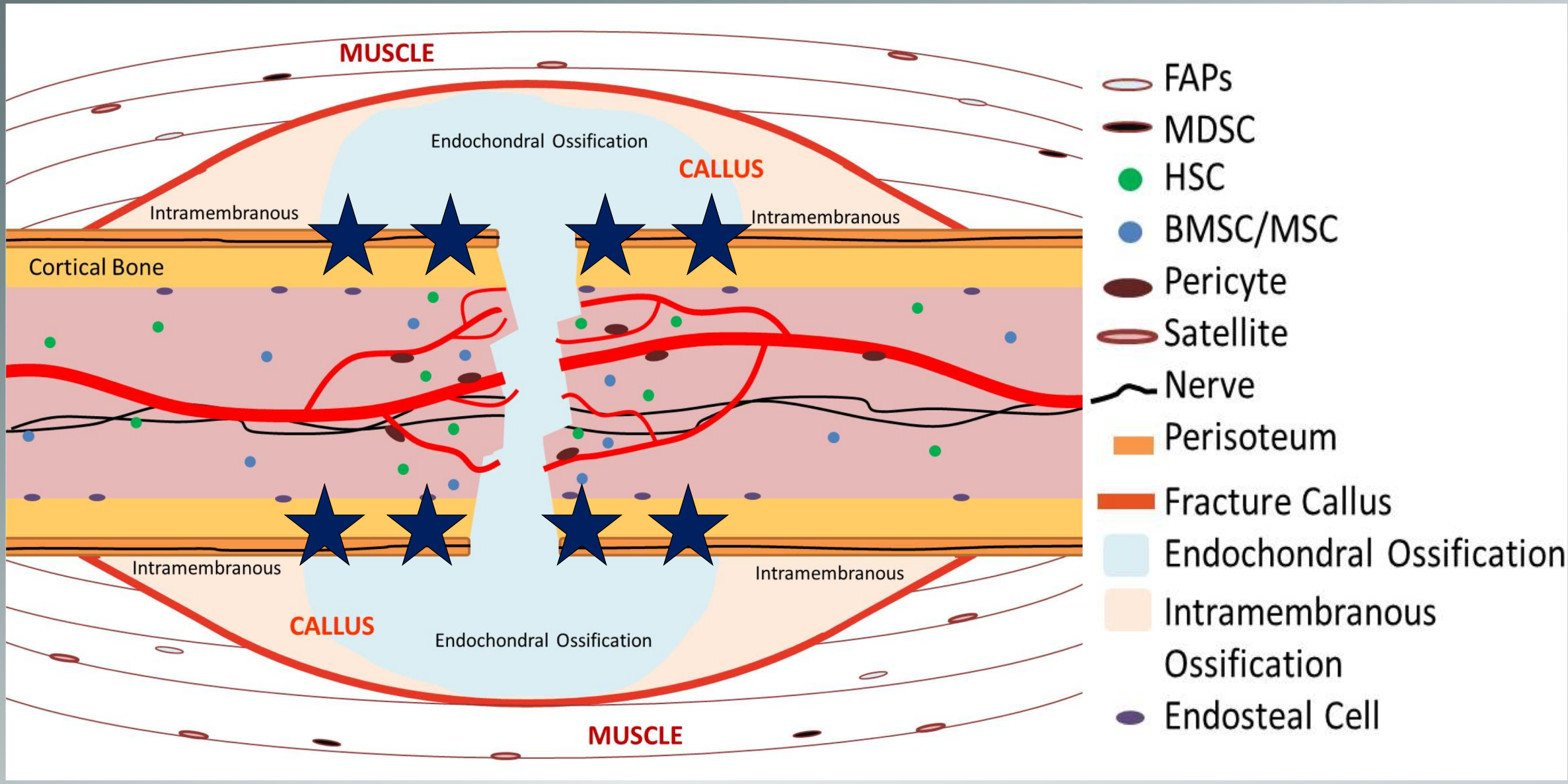
How Can You Accelerate Fracture Repair?

Rejuvenate endogenous stem cells?

Heal Quickly

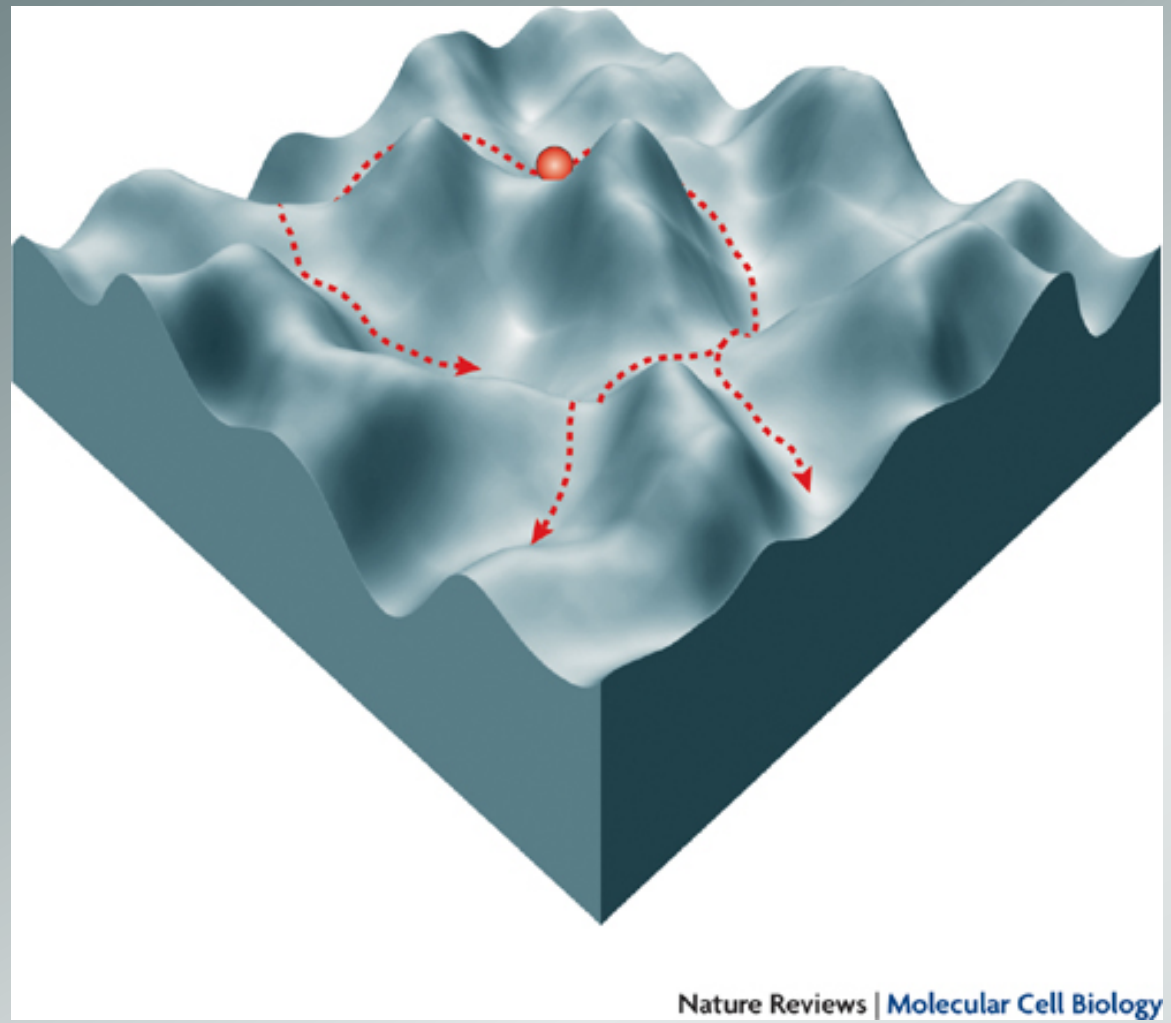
May Not Heal

What are the Stem Cells Involved in Fracture Repair?



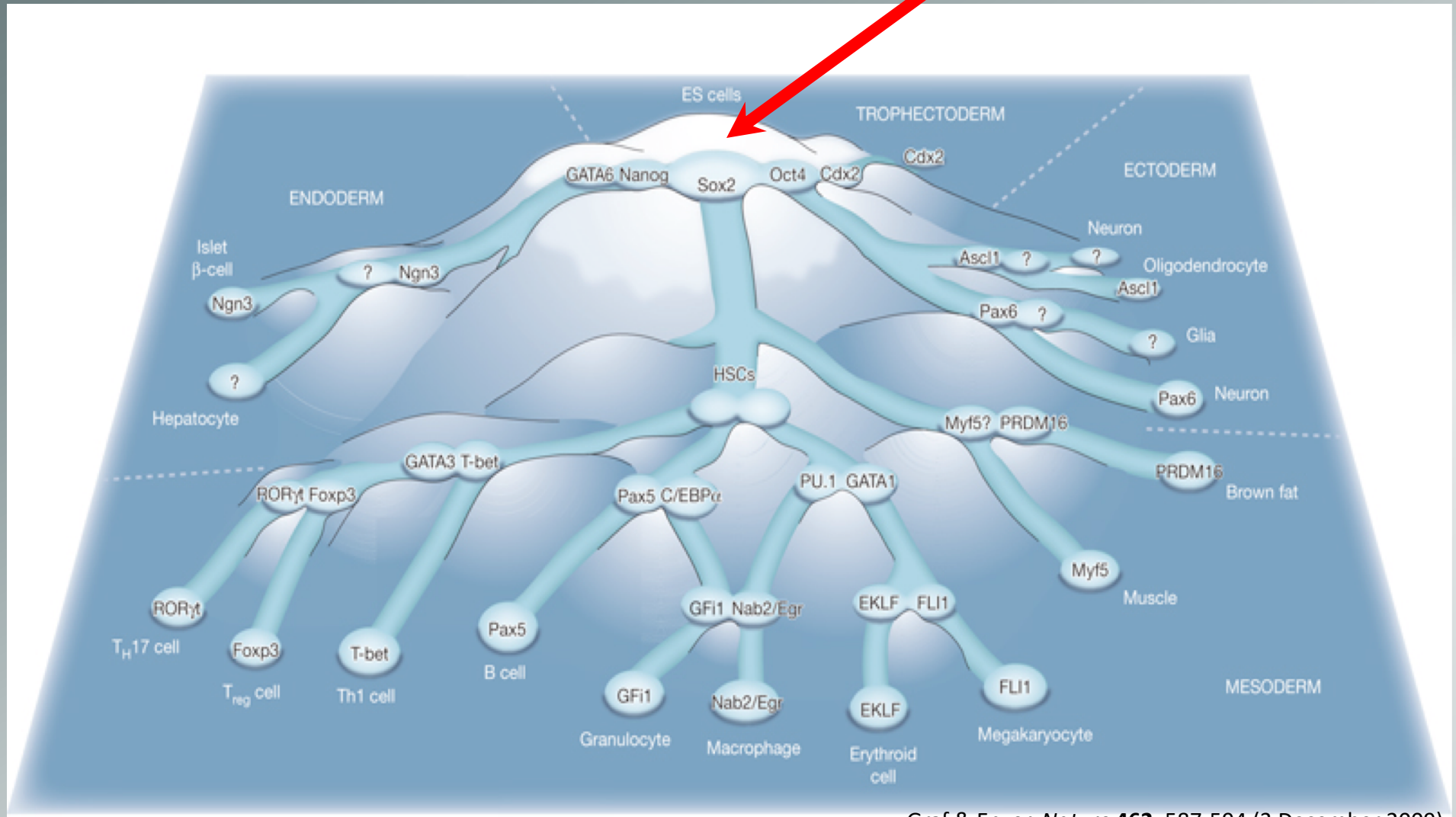
Bragdon & **Bahney**. Current Osteoporosis Reports 2018

Stem Cells Differentiation Landscape



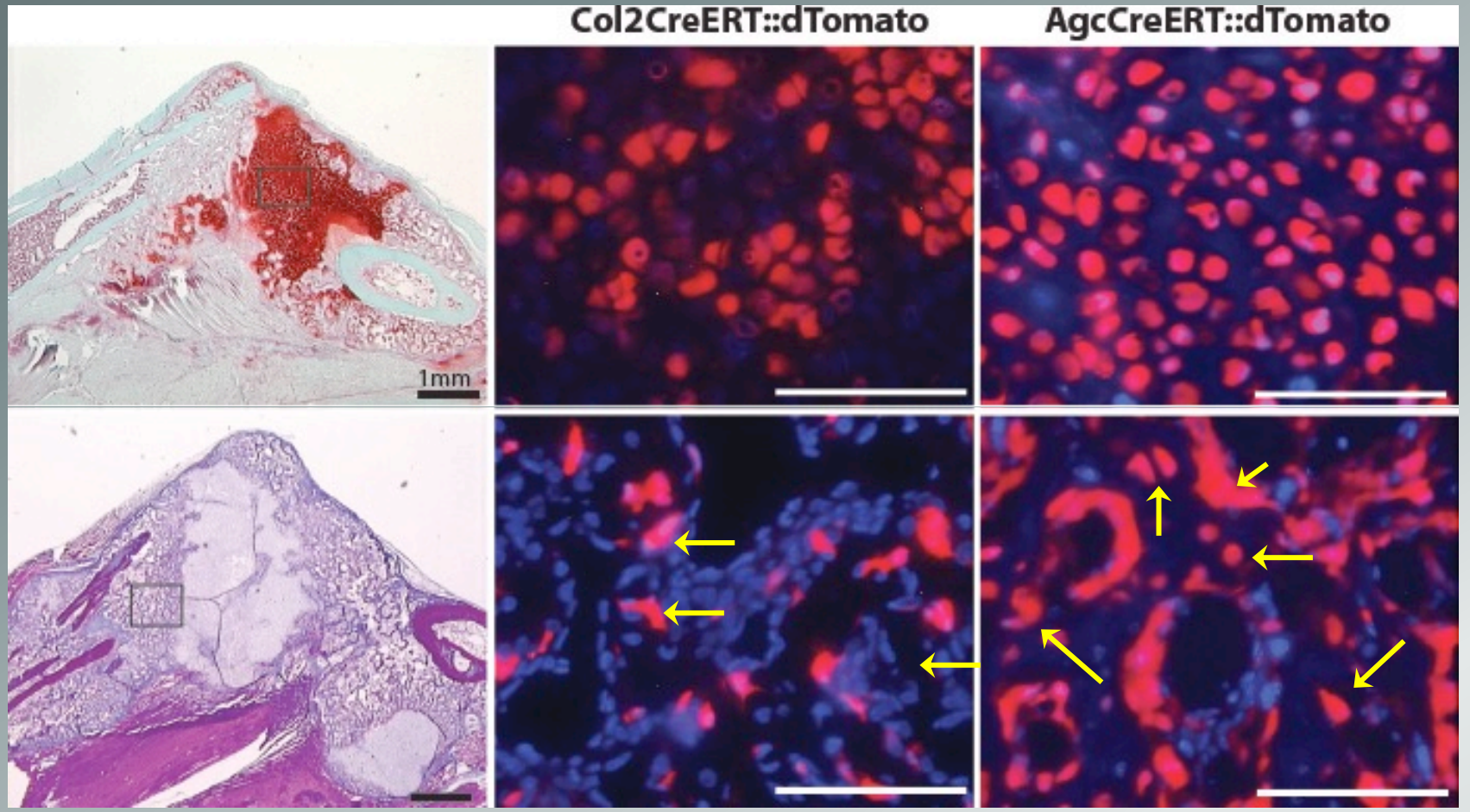
MacArthur BD *et al*. Systems biology of stem cell fate and cellular reprogramming. *Nature Reviews Molecular Cell Biology* **10**, 672-681. (2009)

Gene Regulatory Network – Sox2 is at the top



Graf & Enver. *Nature* **462**, 587-594 (3 December 2009)

Changing Dogma in Fracture Biology



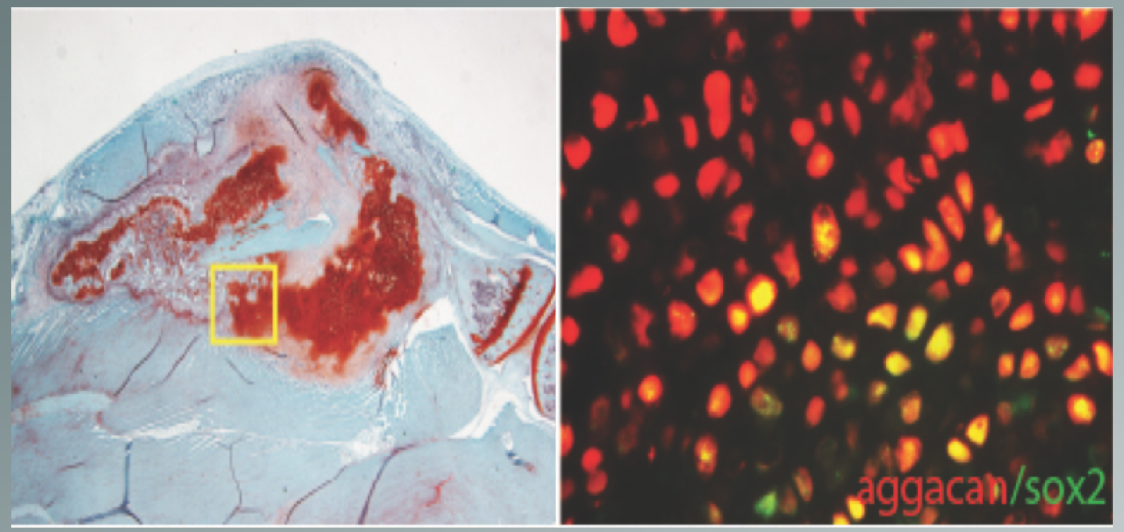
Red Cartilage Cells

Cartilage Becomes Bone

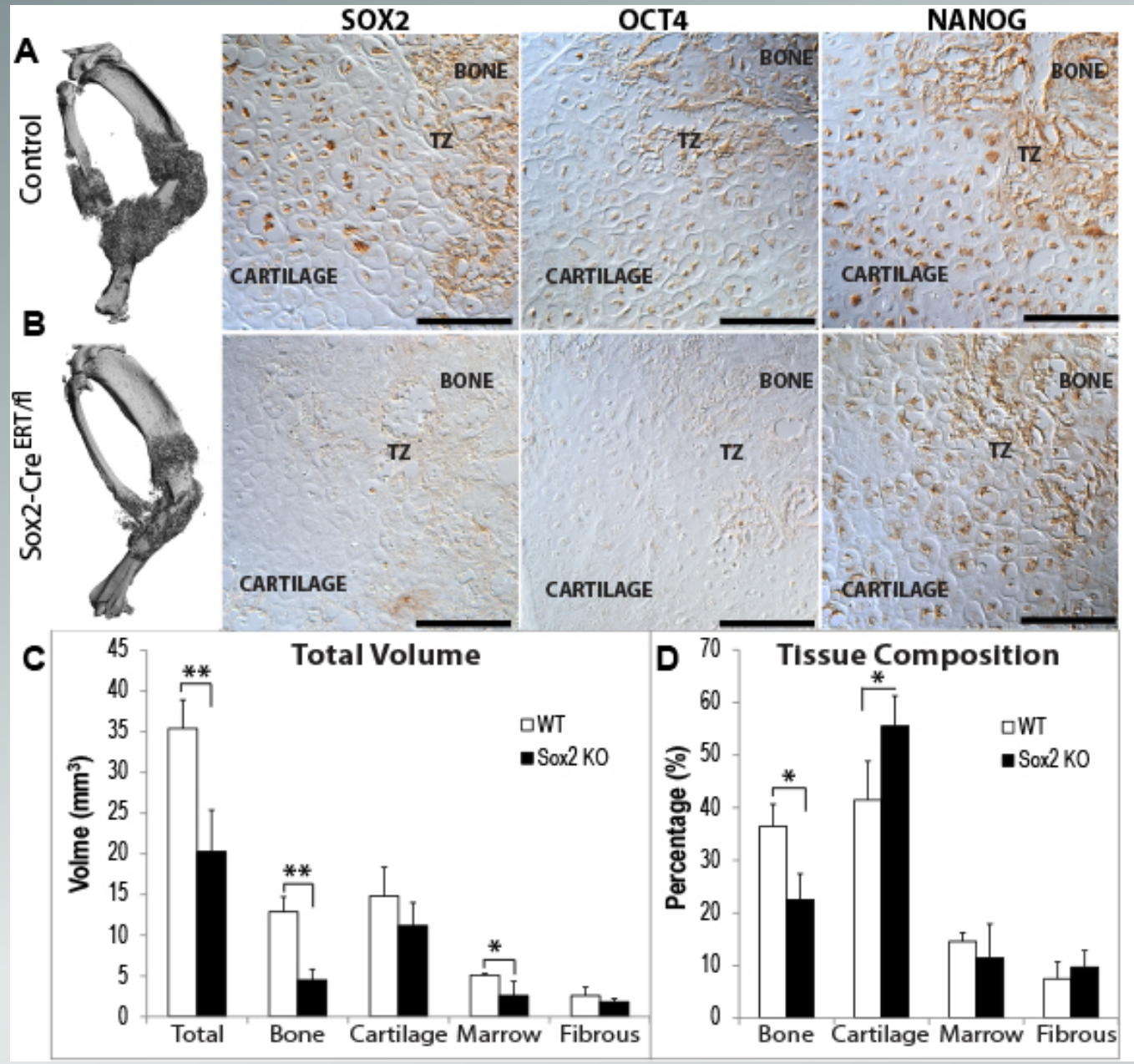
Does cartilage become stem cell-like before becoming bone?

Hu, D *et al*. Development. 2017

Fracture Healing Requires Sox2 Activation



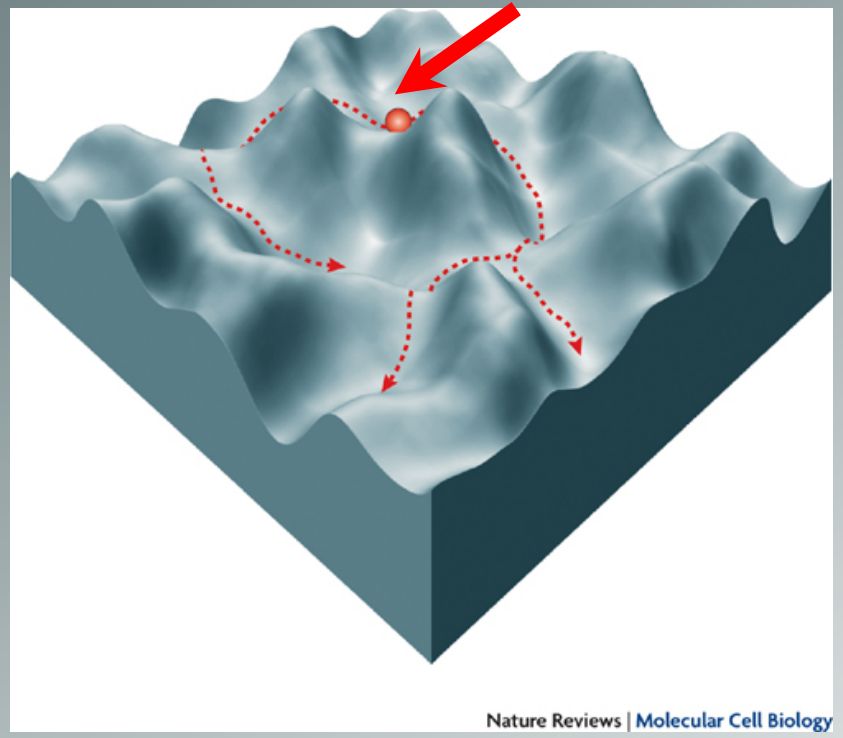
Cartilage turns on Sox2



Hu, D *et al*. Development. 2017

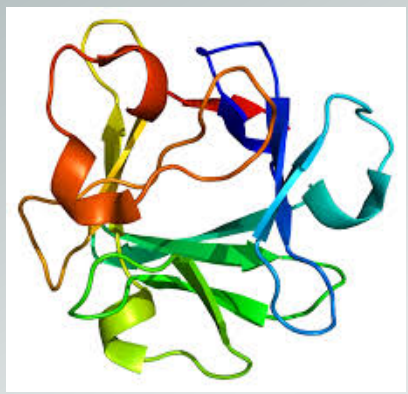
Therapeutics Platforms to Activate Sox2

1) Target stem cell activation
2) Controlled release
3) Local injections

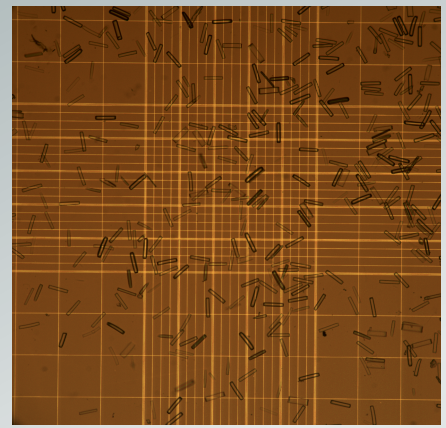


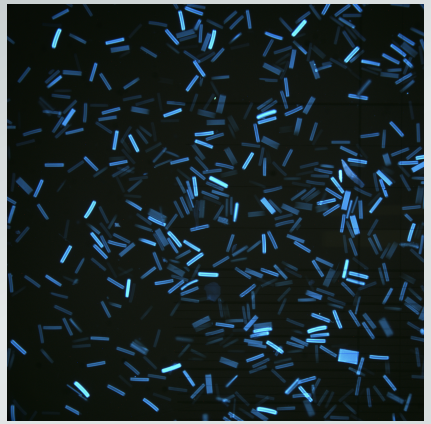
Injectable Hydrogel Microspheres

Biologics



Injectable Microrods





Gene (mRNA)

Rejuvenation of your resident stem cells →
Novel approach to accelerate fracture repair

Inspiration into Regenerative Medicine

(Thank you Dr. Steadman)

Conclusions & Research Directions

- Fracture healing is a significant problem with unmet clinical needs
- Improved diagnostic techniques would help surgeons predict healing
- Novel approaches to stimulating tissue resident stem cells could accelerate fracture repair

NATIONAL INSTITUTES OF HEALTH

MTF Musculoskeletal Transplant Foundation

NSF

FOT

AO Foundation