



Injury and Aging: Do Fractures in the Elderly Heal Differently?

WHAT HAS SCIENCE TAUGHT US?

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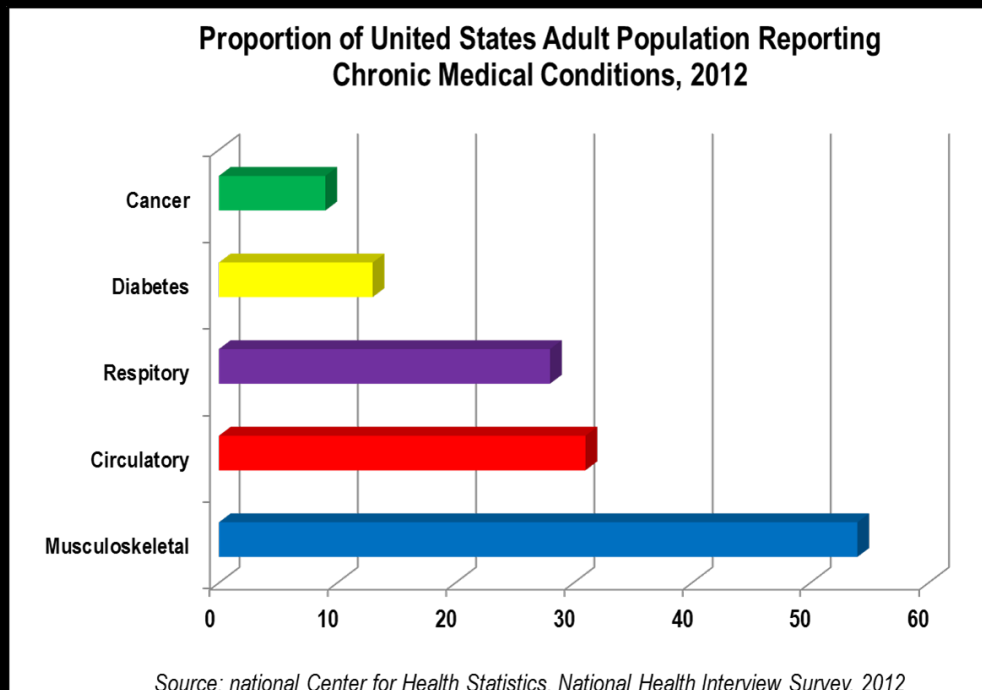


Orthopaedic Trauma Institute
UCSF + SAN FRANCISCO GENERAL HOSPITAL

Why should we study bone healing → burden of disease

Musculoskeletal disability = 2nd largest global burden of disease

- 15 million fractures (\$45B)
- 1.6 million trauma patients
- 2400 primary bone malignancies, 4500 benign bone tumors (~ \$100M)
- Bone is second most commonly transplanted tissue behind blood
- 1 in 4 adults have chronic disability → 3 in 4 people over 65



While most bones heal.....

- 10 - 20 % of fractures don't heal normally
- 46 % of fracture with compromised vasculature don't heal
- 51 % of patients with fractures don't return to work in 6mo
- Aging, diabetes, smoking, infection → delayed healing



Age affects the Orthopaedic Trauma Patient

- Delayed fracture healing is observed in the elderly patients
- Increased morbidity in elderly fracture

Aho, 1966

Cauley et al, 2000

Claes et al, 2002

Research is key to improving outcomes

Goal of Orthopaedic Research

Improve the lives of people living with Musculoskeletal diseases or injuries by understanding the basic and clinical mechanisms and developing novel therapies

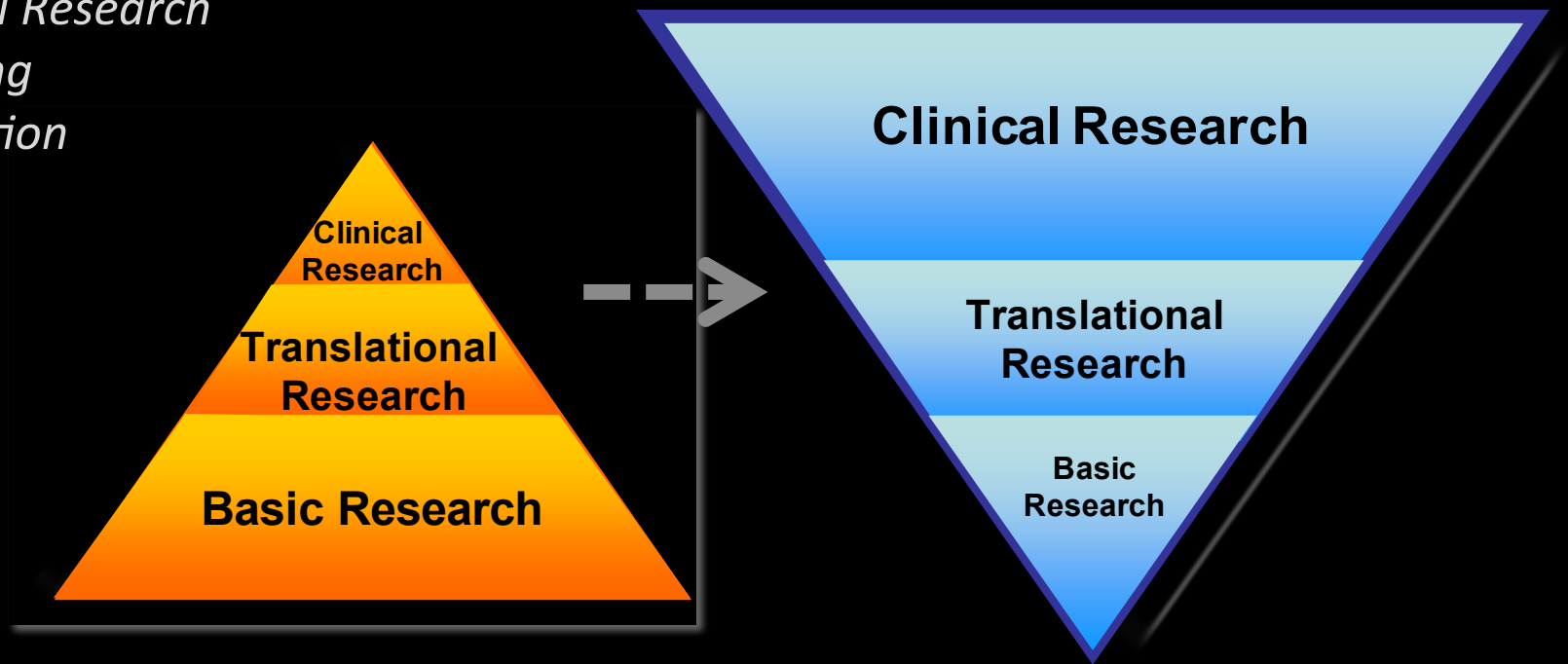
Basic Research

Translational Research

Clinical Research

Training

Education

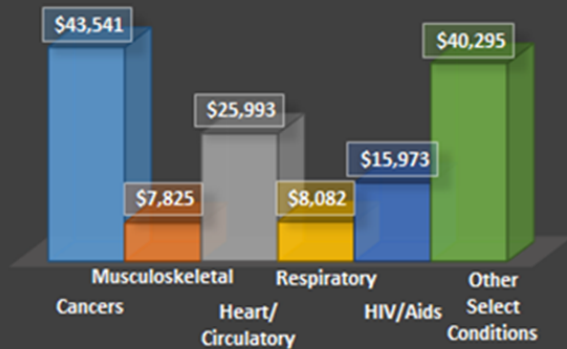


NIH FY 2016 ~ \$32B
(NIAMS ~\$542M)

Industry ~ \$70B

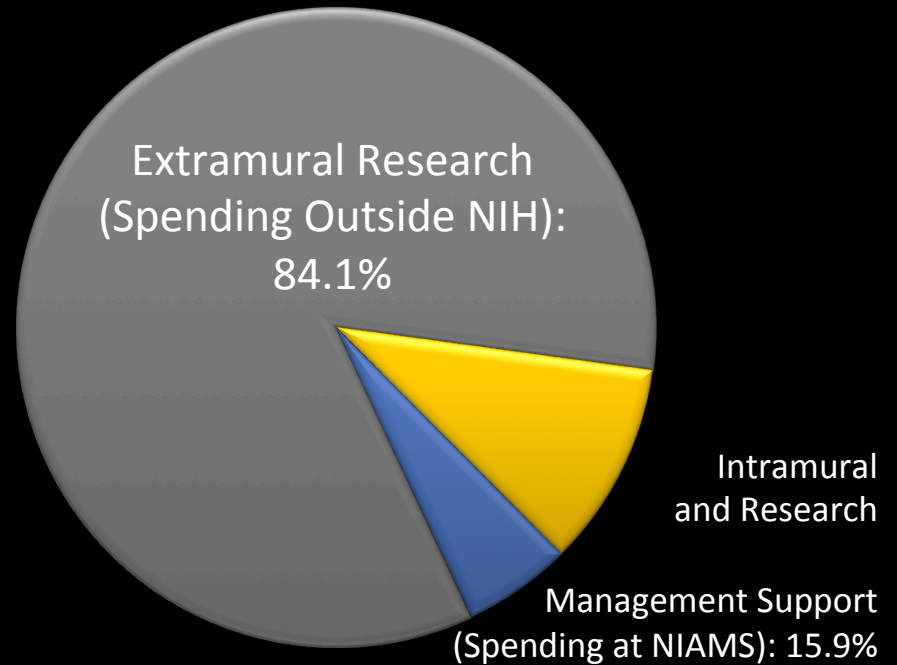
Research is key to improving outcomes

Funding Dollars (in millions) for National Institutes of Health Research by Disease Areas, United States 2009-2013



Source: National Institutes of Health. Estimates of Funding for Various Research, Condition, and Disease Categories. http://report.nih.gov/categorical_spending.aspx
Accessed December 17, 2013.

File: G1A.0.1



- For every \$1 spent on research there is a \$17 ROI

<http://www.nih.gov/about/impact/>

Research is key to improving outcomes by changing clinical practice

Translation

BENCH



BEDSIDE



CLINICAL PRACTICE

Hettrich, Weinstein, & Spindler. *"The role of advocacy in research funding"*. AAOS/RCHD 2016

Extreme CAUTION!

In Vitro

- Cell/matrix
- Genetics
- Cell signaling

\$\$

CLINICAL PRACTICE

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Extreme CAUTION!

Maybe

In Vitro

In Vivo

- Cell/matrix
- Genetics
- Biomechanics

- Animal models
- Biology/healing
- Biomechanics
- Safety

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CLINICAL PRACTICE

Hettrich, Weinstein, & Spindler. "The role of advocacy in research funding". AAOS/RCHD 2016

Extreme CAUTION!

Maybe

Yes! EBM

In Vitro

- Cell/matrix
- Genetics
- Biomechanics

\$\$

In Vivo

- Animal models
- Biology/healing
- Biomechanics
- Safety

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Clinical Trials

- Outcomes
- Complications
- Risk/benefit
- Cost/benefit

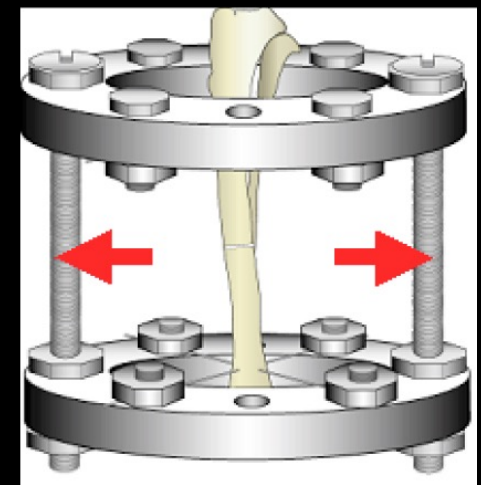
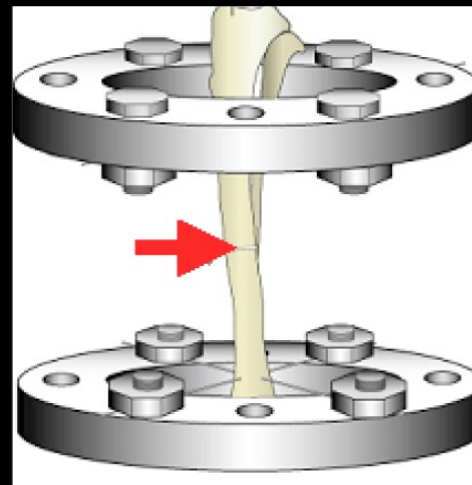
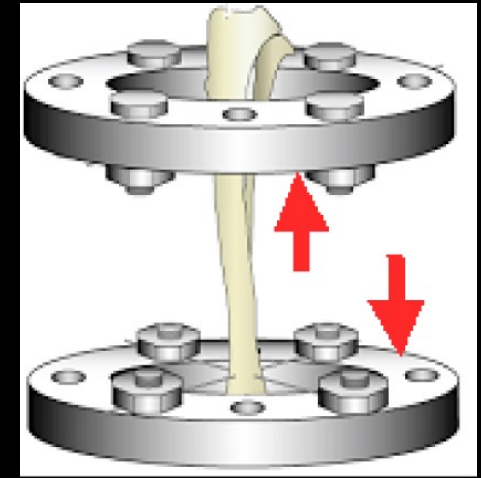
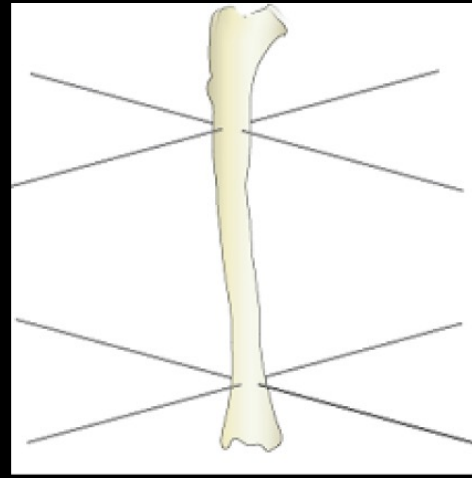
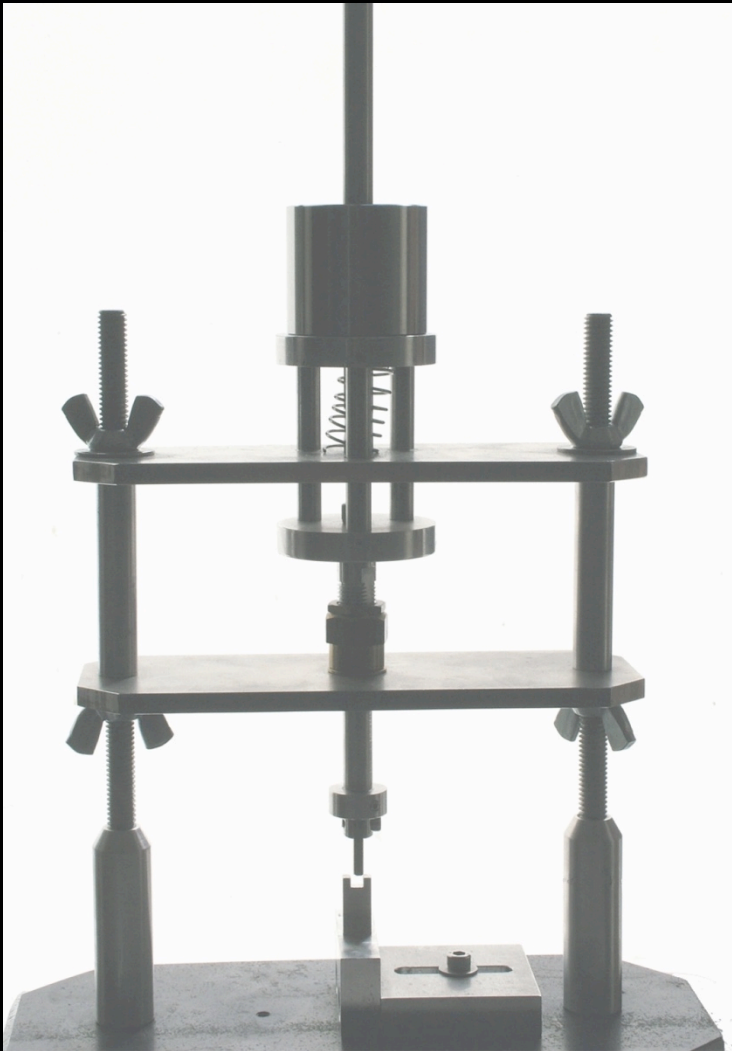
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Overall Goals

- Understand the regulation of bone regeneration
- Develop therapies to improve patient outcomes

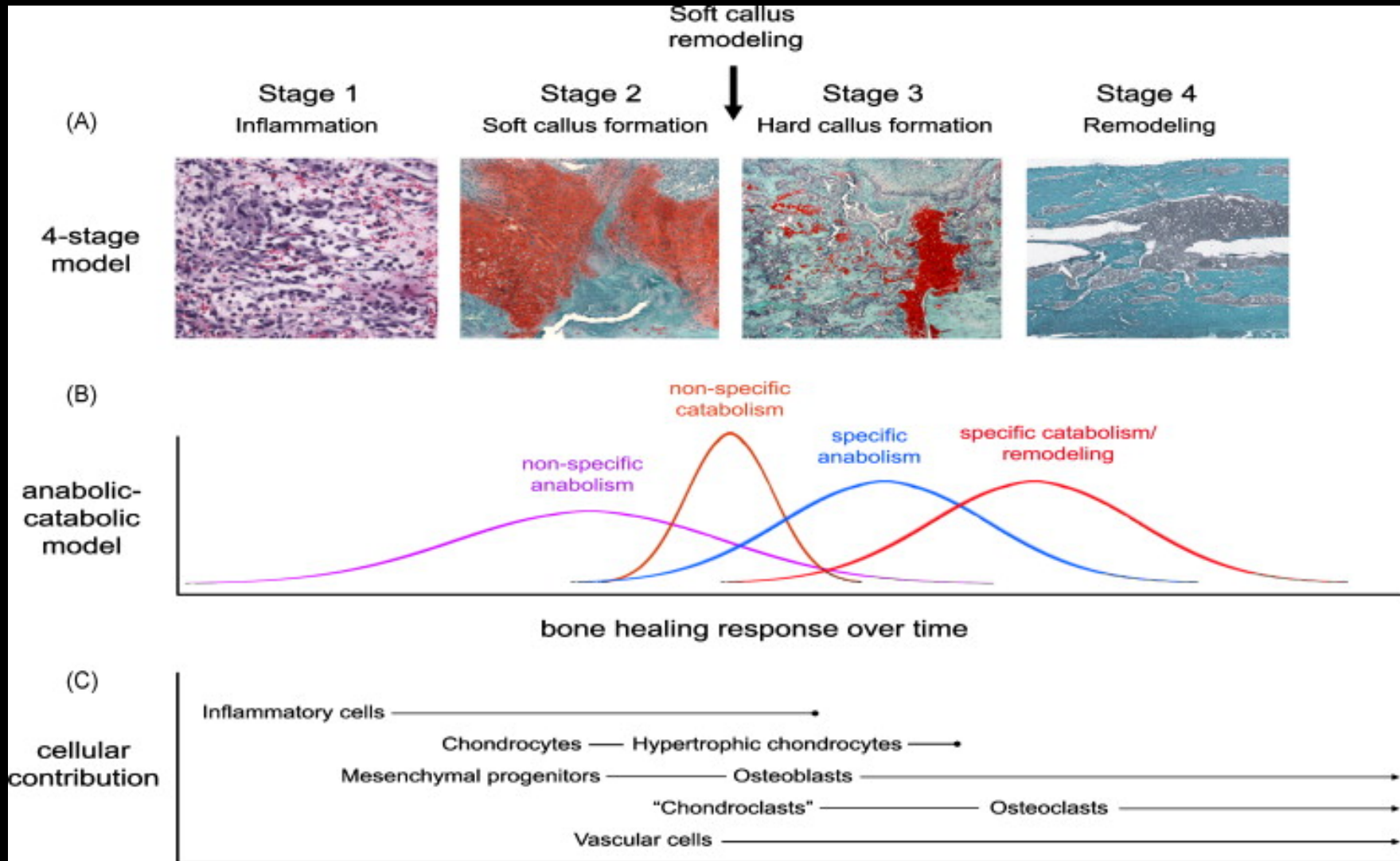


Creating Tibial Fractures in Mice



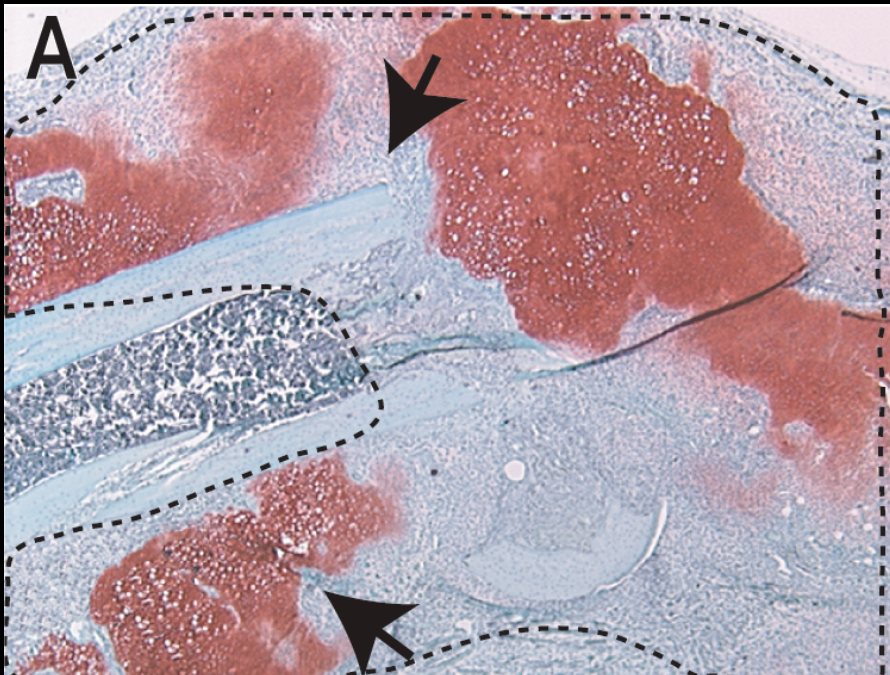
(Thompson et al, JOR, 2002)

Stages of Fracture Healing

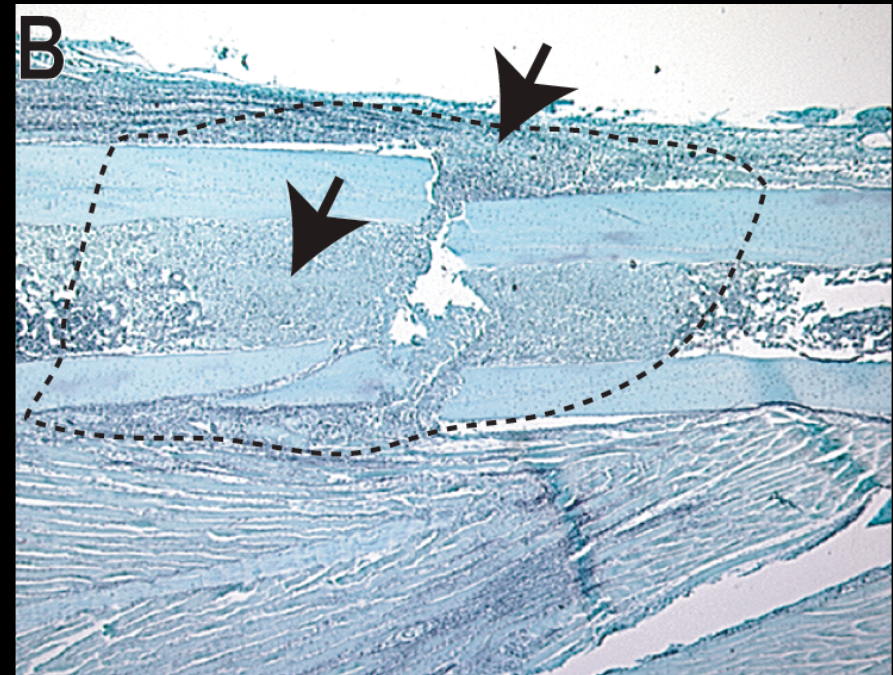


Mechanical stability influences stem cell fate during tibial healing

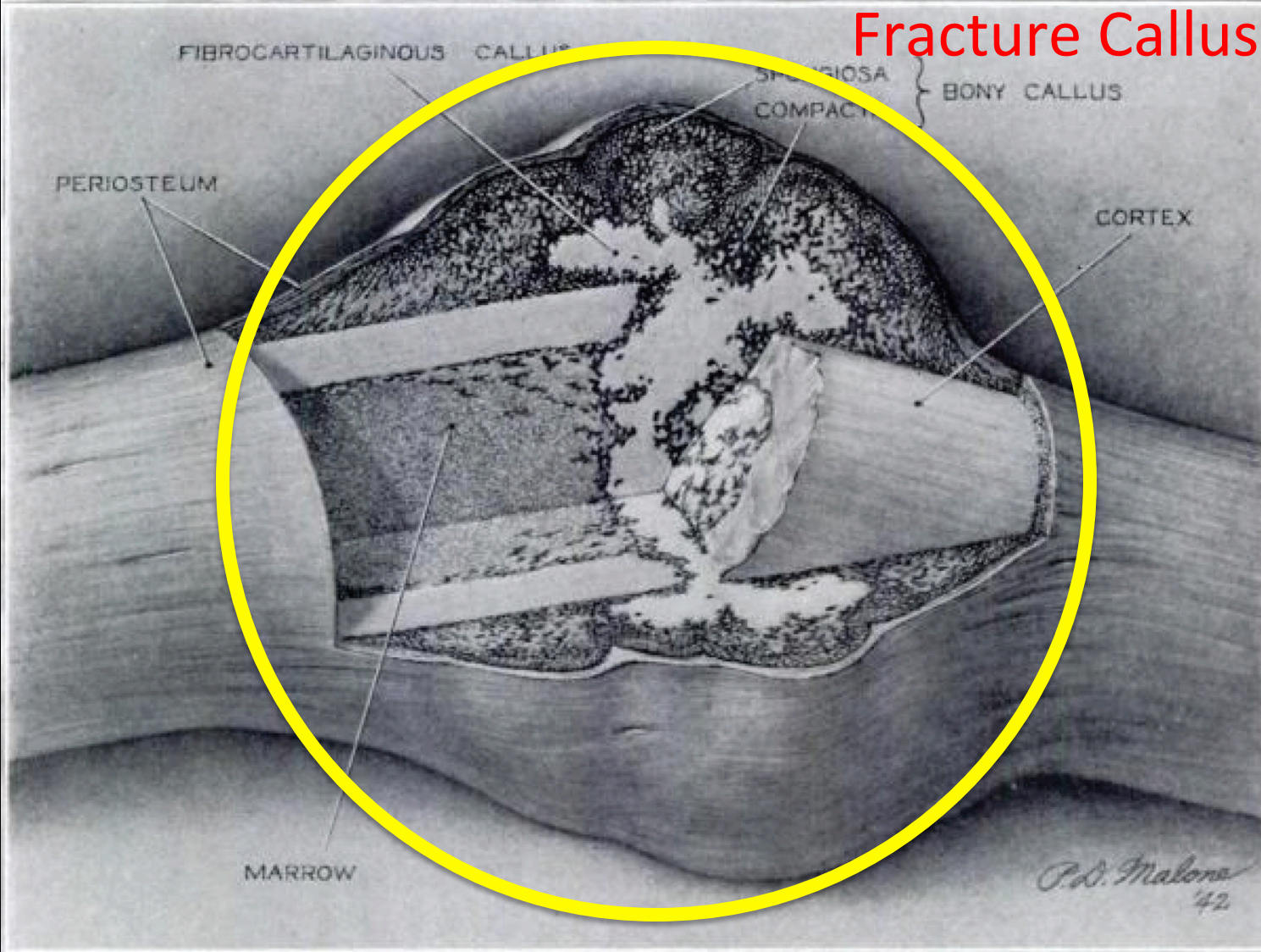
Day 10, Unstable



Day 10, Stable



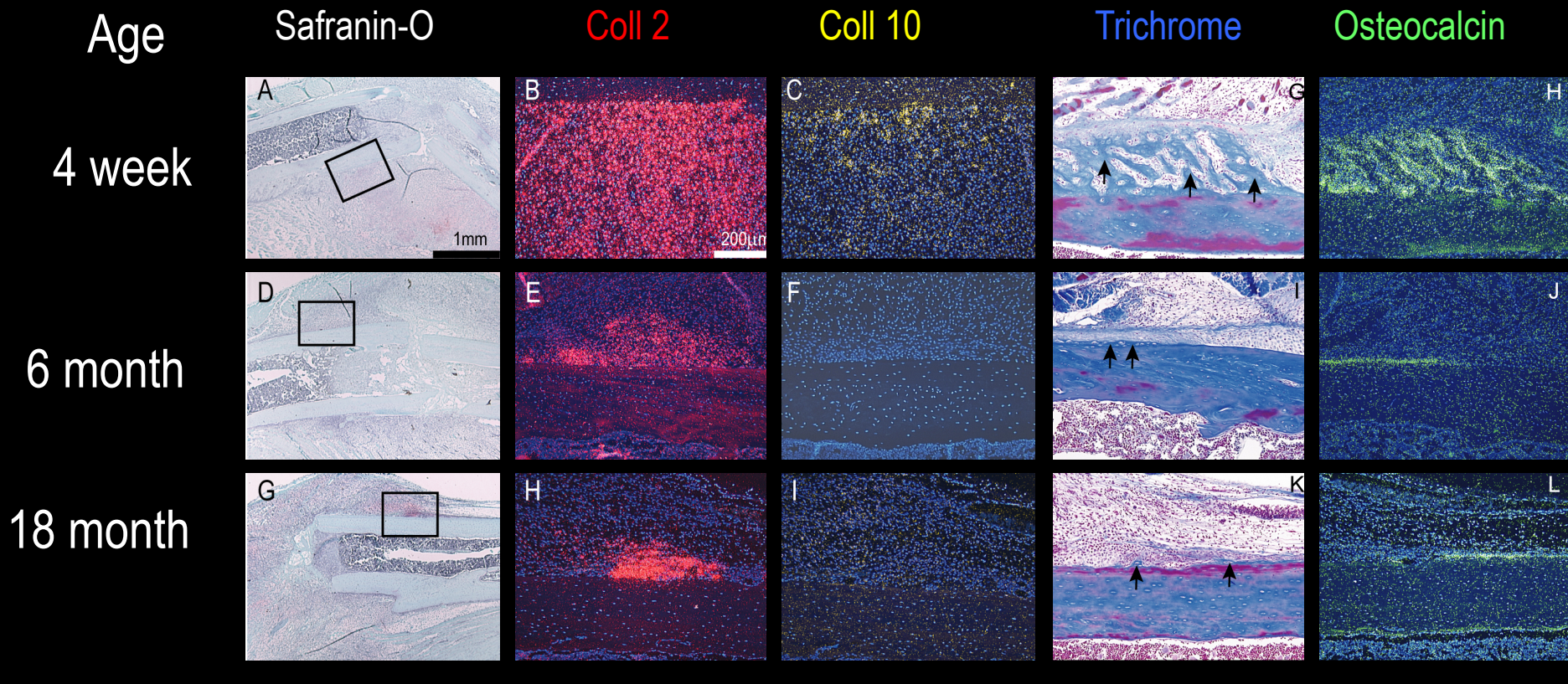
In Patients, Repair Occurs via Cartilage and Bone



Which age-related changes in fracture repair are detectable in our model and can we “correct” them

Aging delays cartilage and bone formation

Day 5 Post-fracture



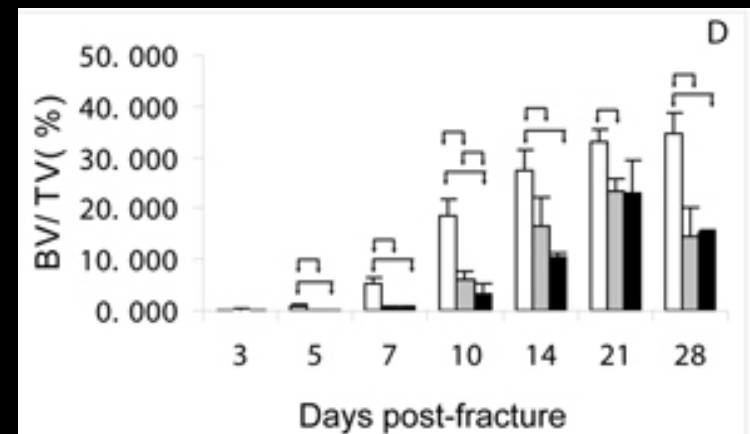
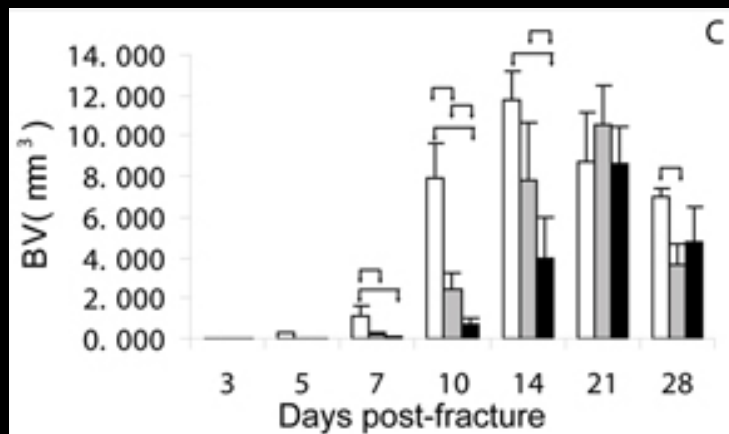
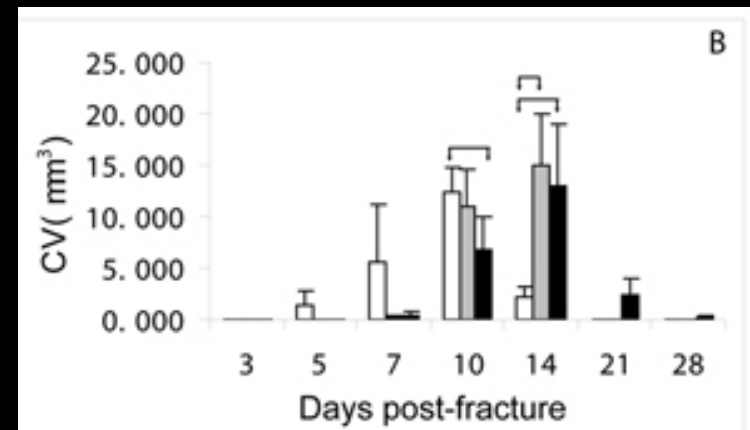
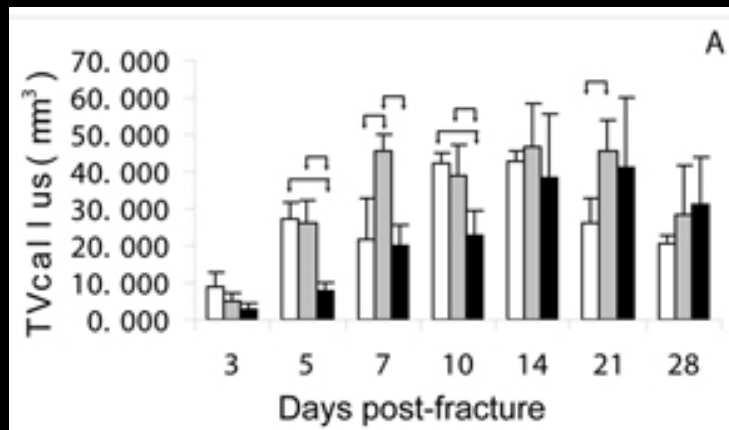
Cartilage

Bone

Rate of fracture healing is age-dependent

Callus

Cartilage



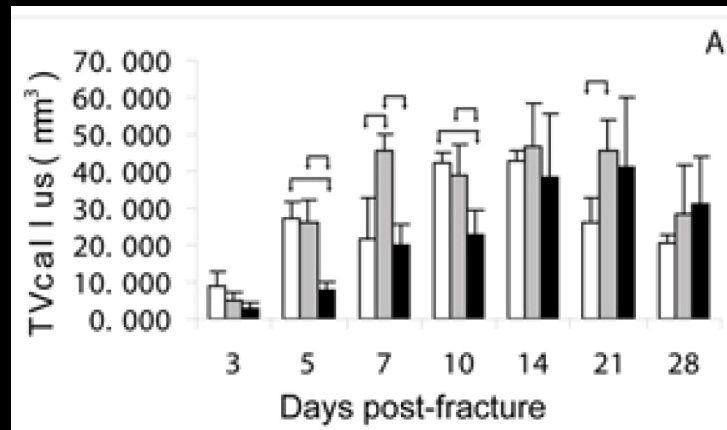
Bone

BV/TV

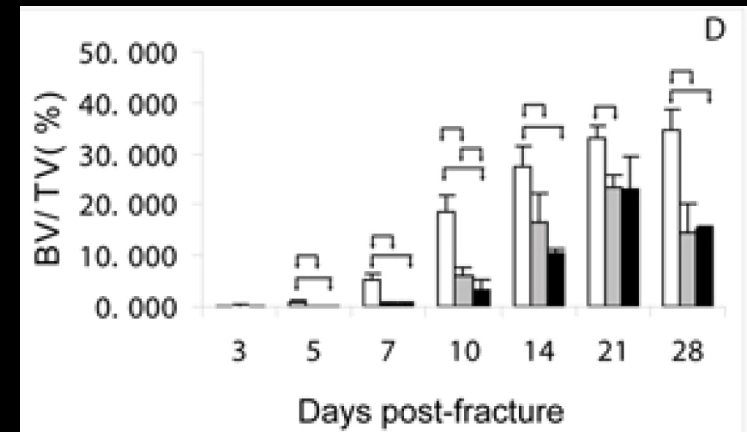
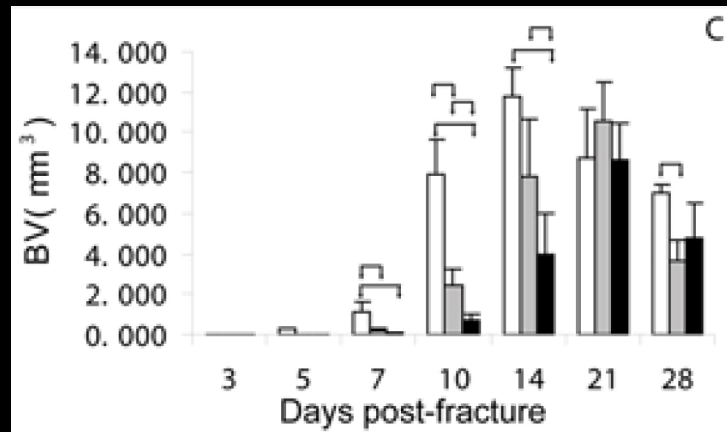
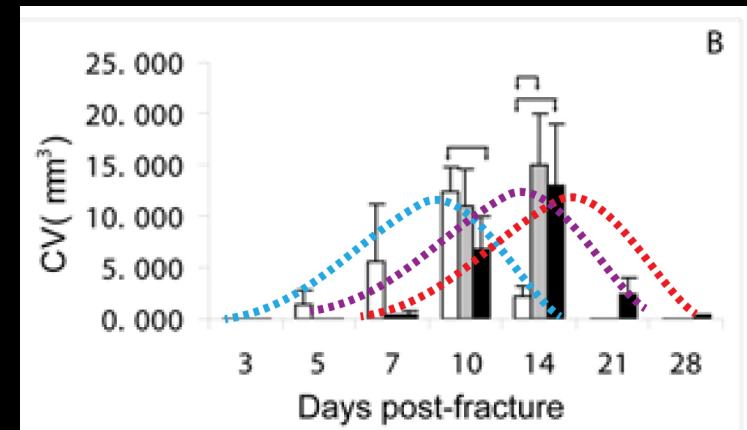
- Juvenile (1 mos)
- Middle-aged (12 mos)
- Elderly (18 mos)

Rate of fracture healing is age-dependent

Callus



Cartilage



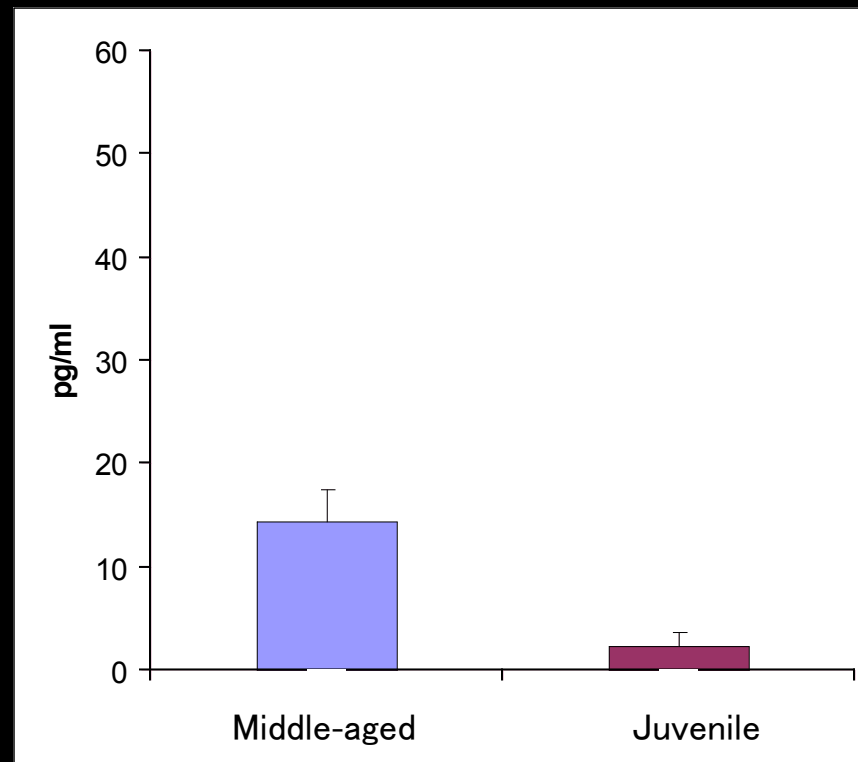
Bone

BV/TV

- Juvenile (1 mos)
- Middle-aged (12 mos)
- Elderly (18 mos)

Systemic inflammatory response is different in old and young animals

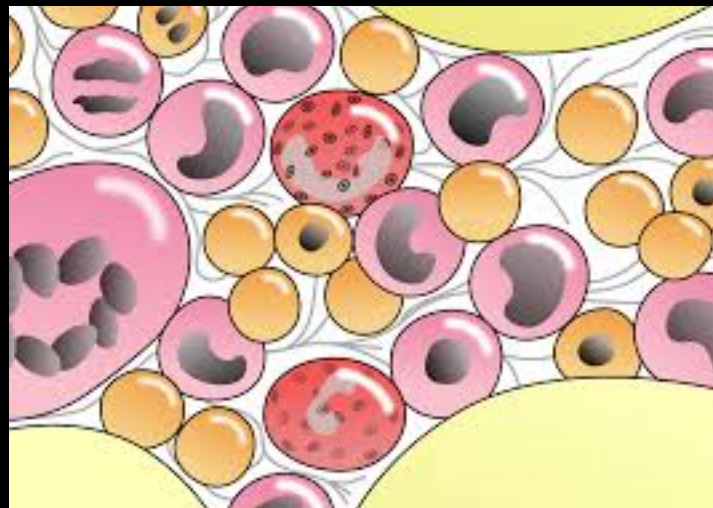
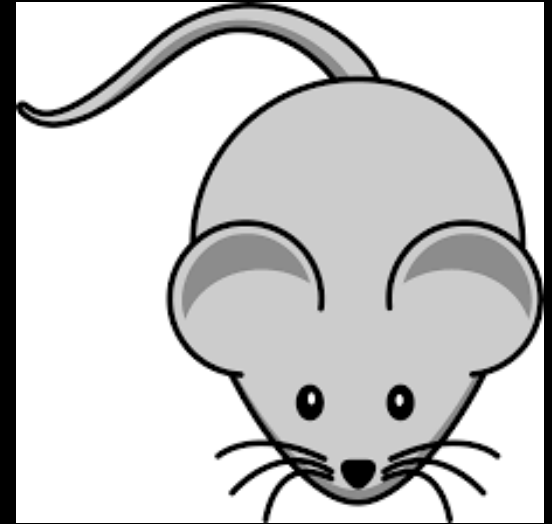
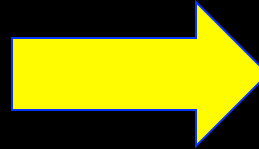
Plasma IL-6 levels, day 7



Hypothesis: Rejuvenating the Immune System can Stimulate Repair in Old Mice



1. Lethal
Irradiation

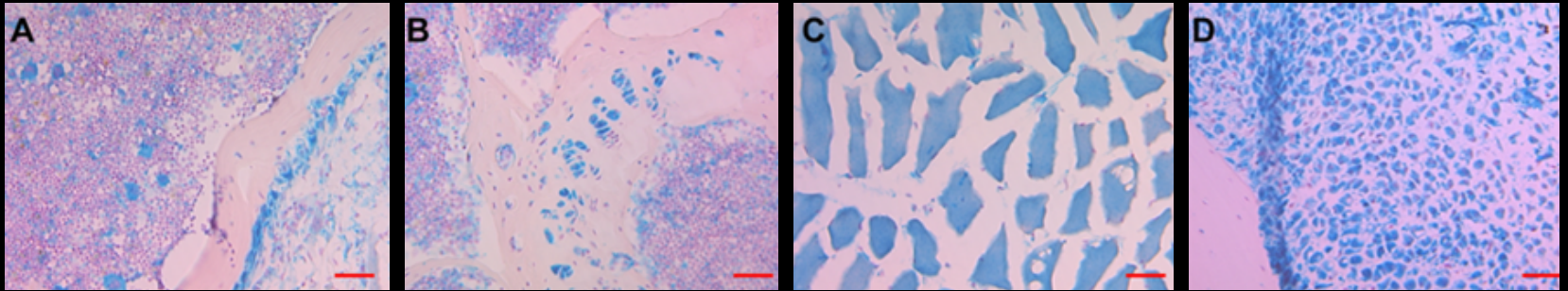


2. Marrow
Transplant

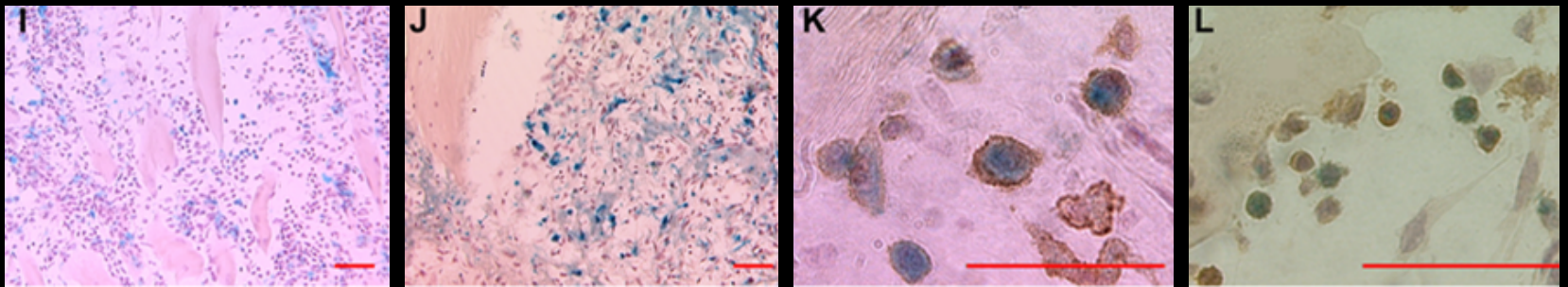
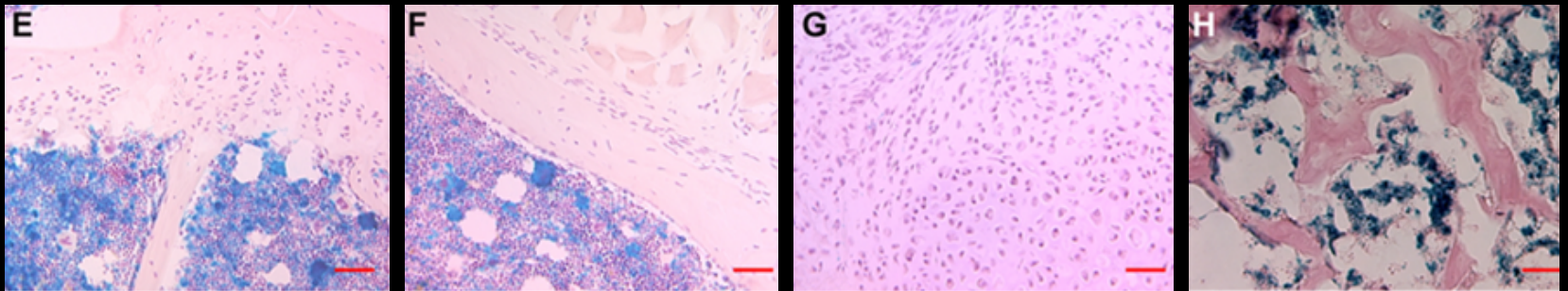


Donor tissue did not form bone or cartilage but did contribute to the callus

ROSA 26



Chimera

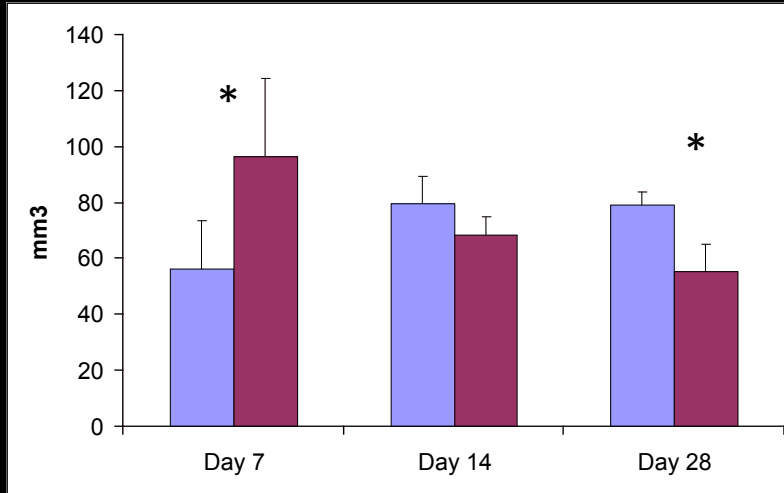


macrophages

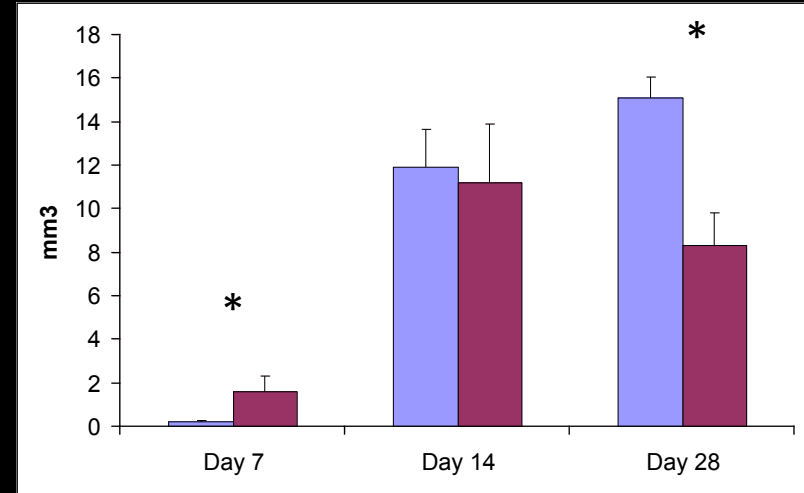
neutrophils

Young bone marrow rejuvenates bone healing

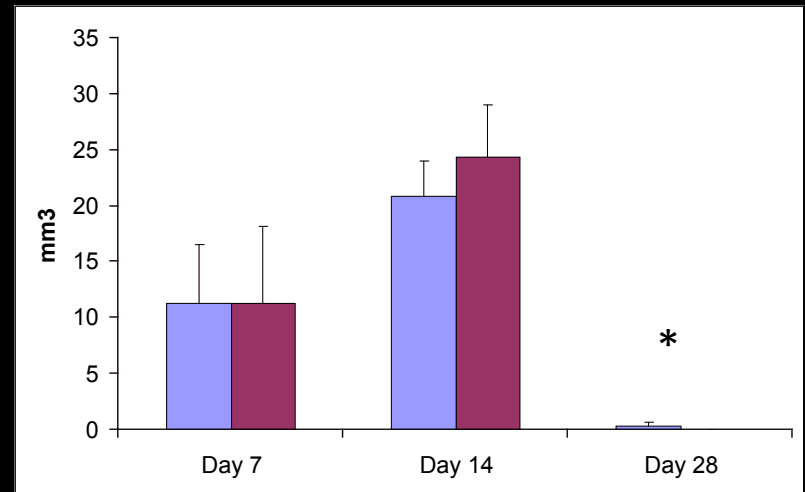
Callus volume



Bone volume



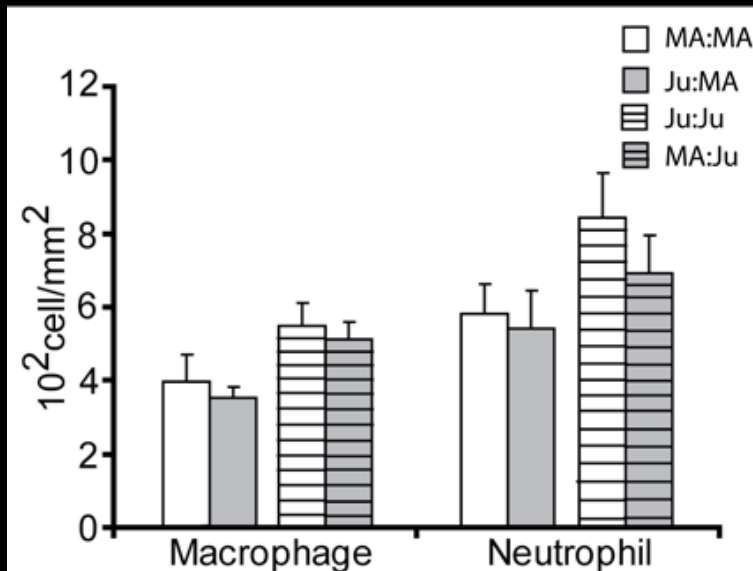
Cartilage volume



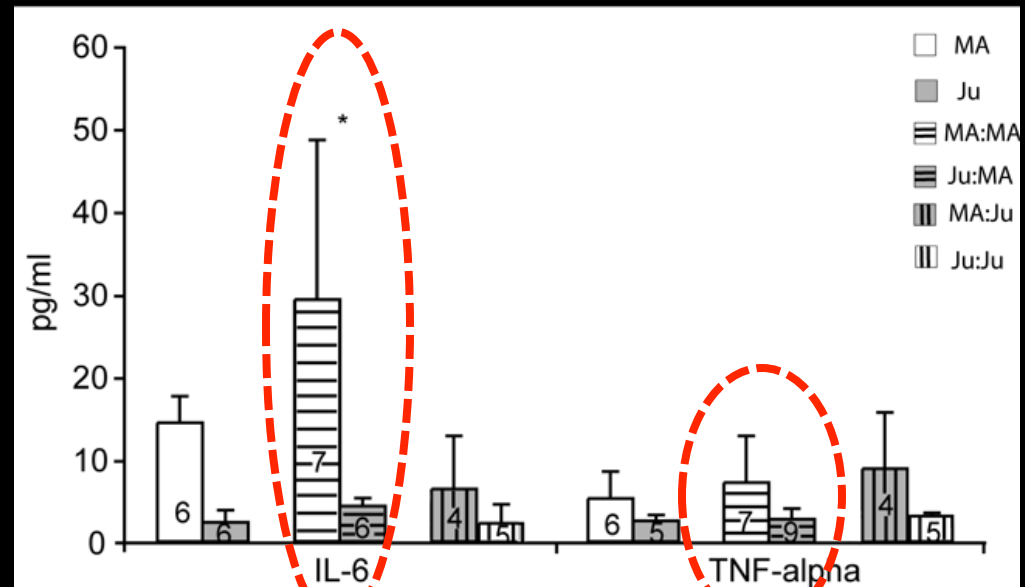
■ Elderly to elderly
■ Juvenile to elderly

Assessing inflammation in the chimeras

Cell recruitment



Systemic inflammation



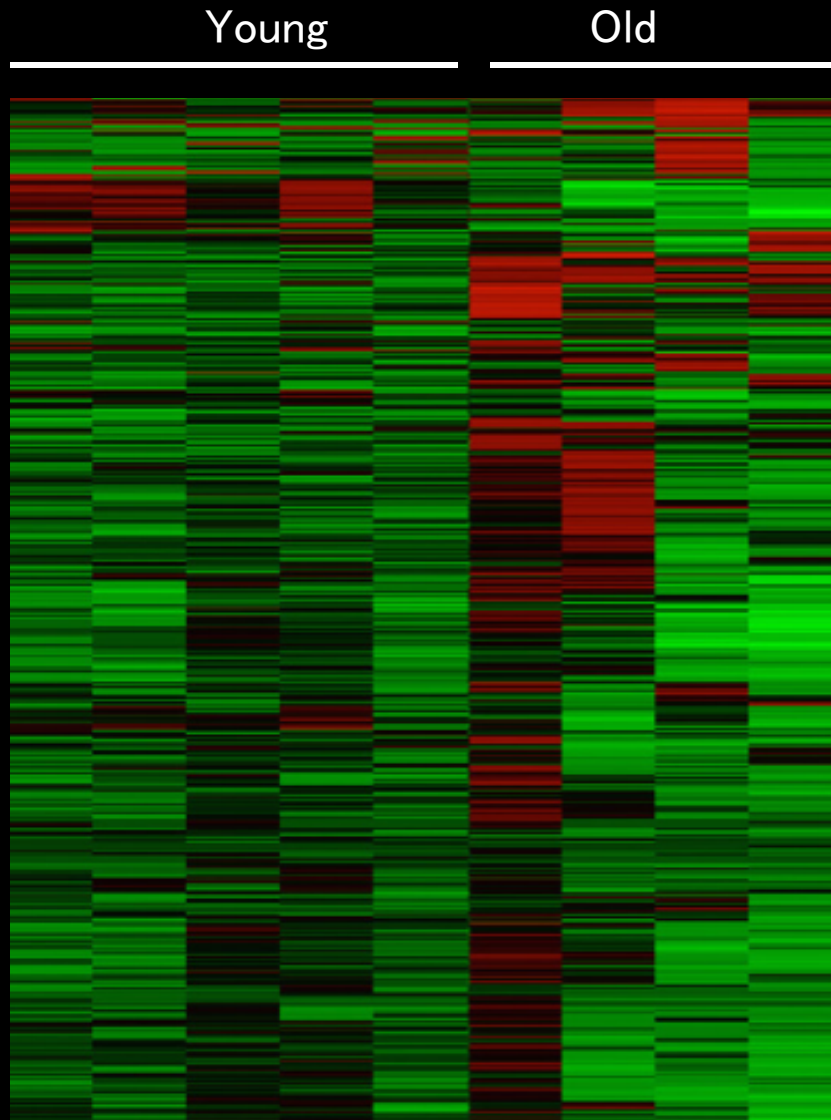
Mature host
Juvenile host

Mature host
Juvenile host

Mature host
Juvenile host

Mature host
Juvenile host

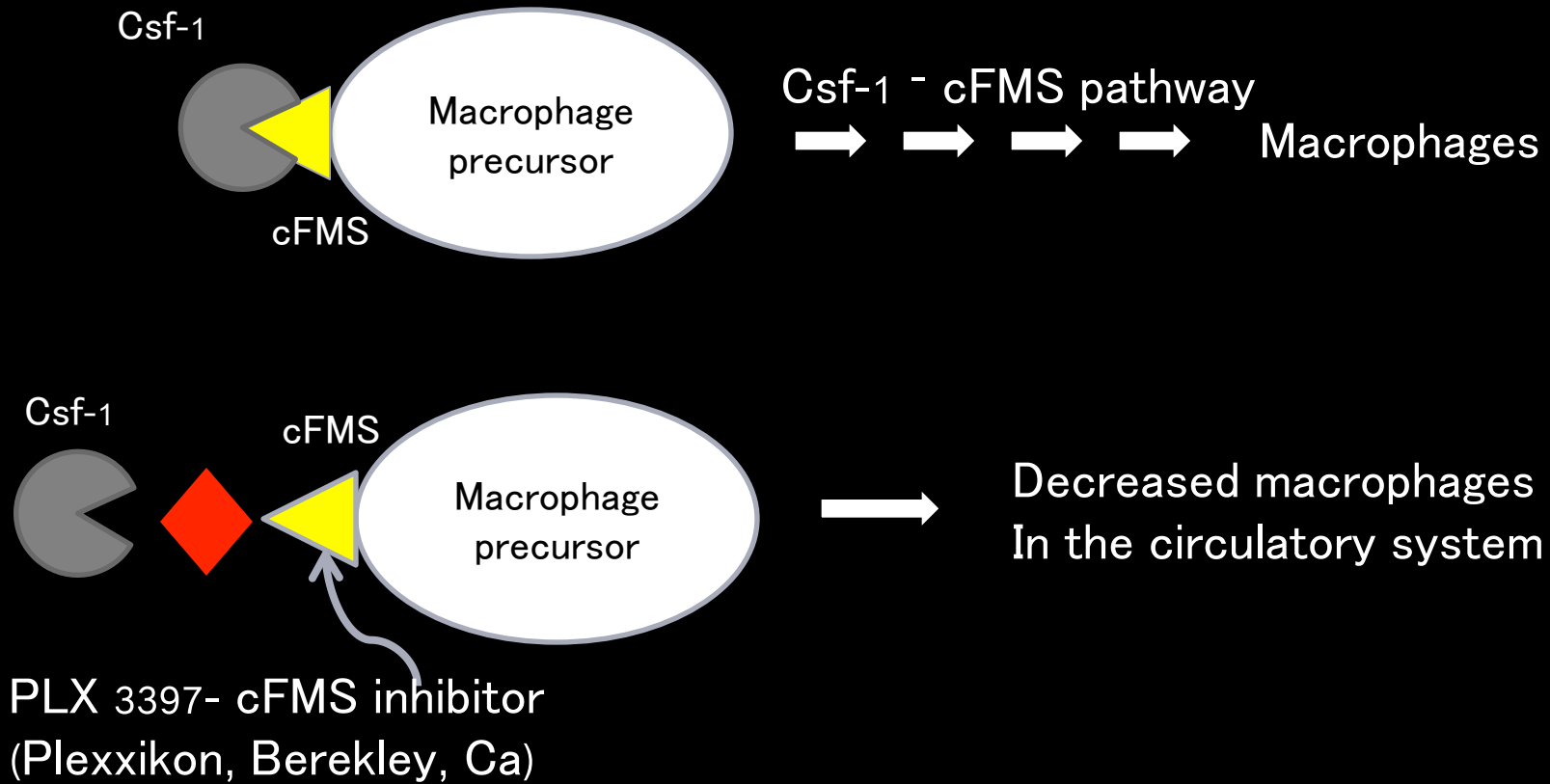
Young (12wk) and old (24m) macrophages exhibit differences in gene expression (day 3)



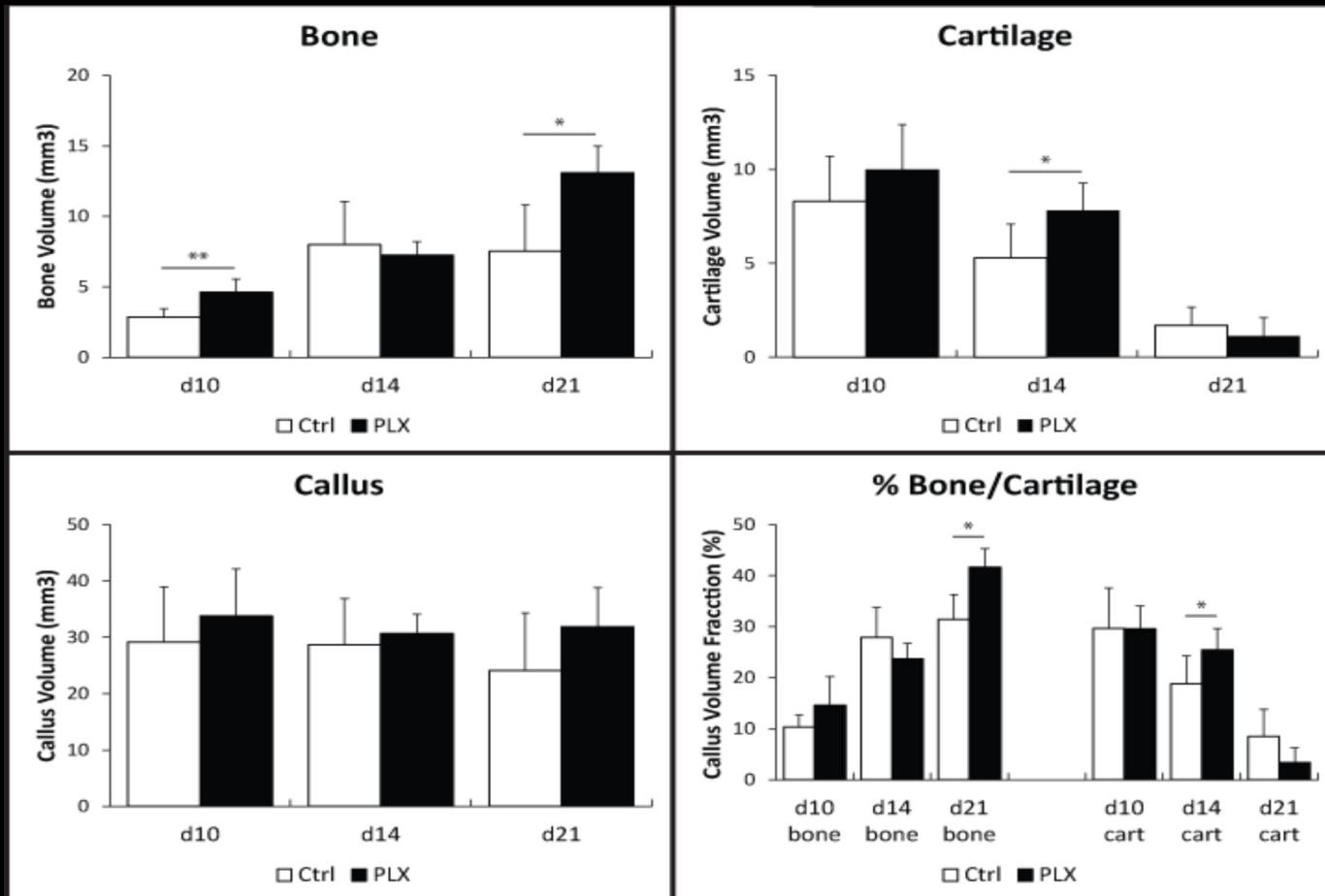
OLD - more *variability* in gene expression changes

-changes do not reflect simple M1/M2 differences

Can We “Target” Macrophages for Therapy?



Feeding PLX3397 to mice stimulates fracture healing





WHAT HAS SCIENCE TAUGHT US?

- Aging impairs fracture healing
- Inflammation may be a therapeutic target