



Inflammaging: Can It Be Countered?

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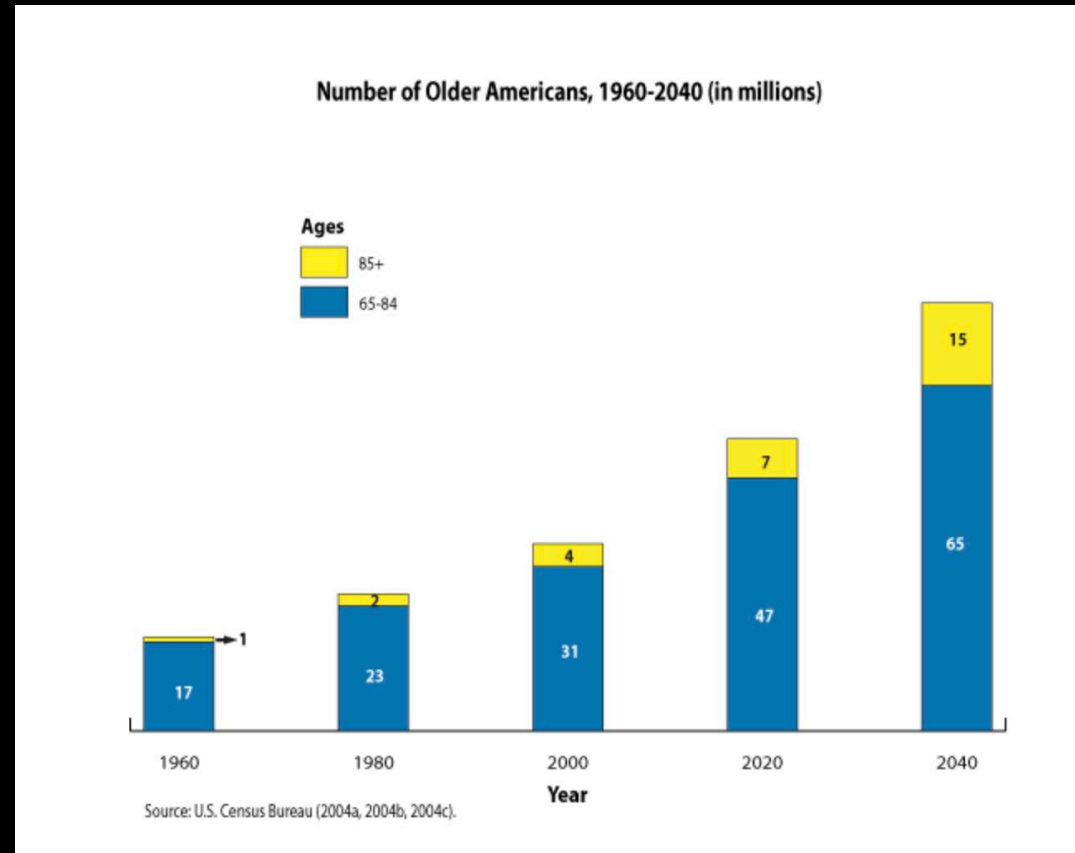
Disclosures

None related to this talk

America's Population is Aging.

The number of Americans ages 65 and older will more than double over the next 40 years, reaching 80 million in 2040.

The number of adults ages 85 and older, the group most often needing help with basic personal care, will nearly quadruple between 2000 and 2040.



Geriatric Fractures will Increase

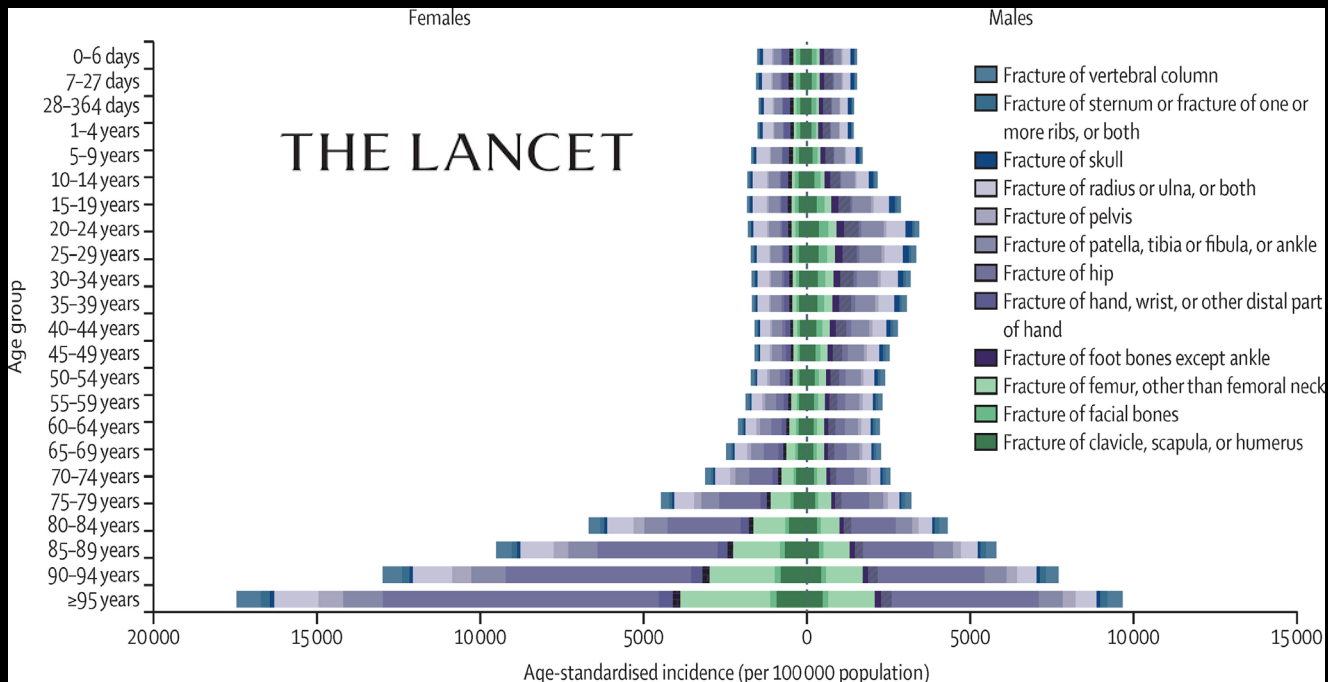
Since 1990

33% increase in global number of new cases of fracture

65% increase in years lived with disability (YLD)

New fragility fracture every 3 seconds

1:3 women; 1:5 males over 65



Age affects the Orthopaedic Trauma Patient

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

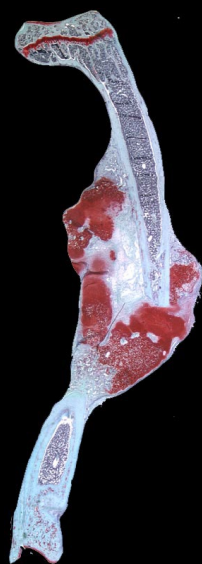
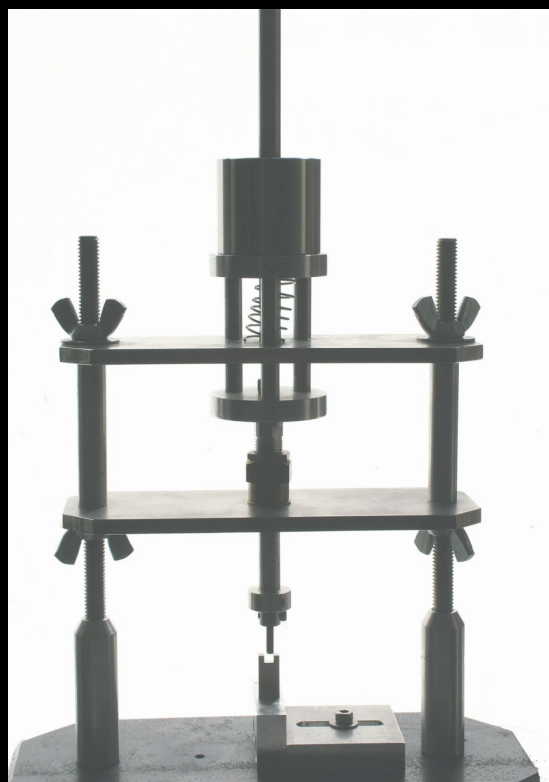
Aho, 1966

Cauley et al, 2000

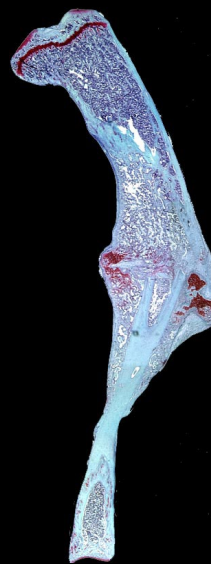
Claes et al, 2002

Can we Develop Treatments for this
Population?

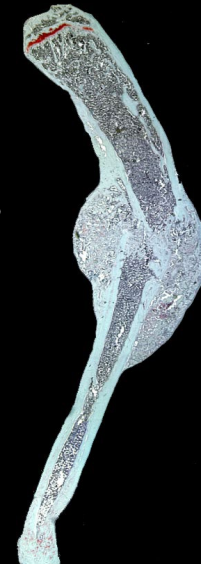
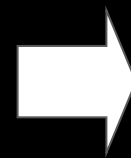
Creating tibial fractures in mice



cartilage



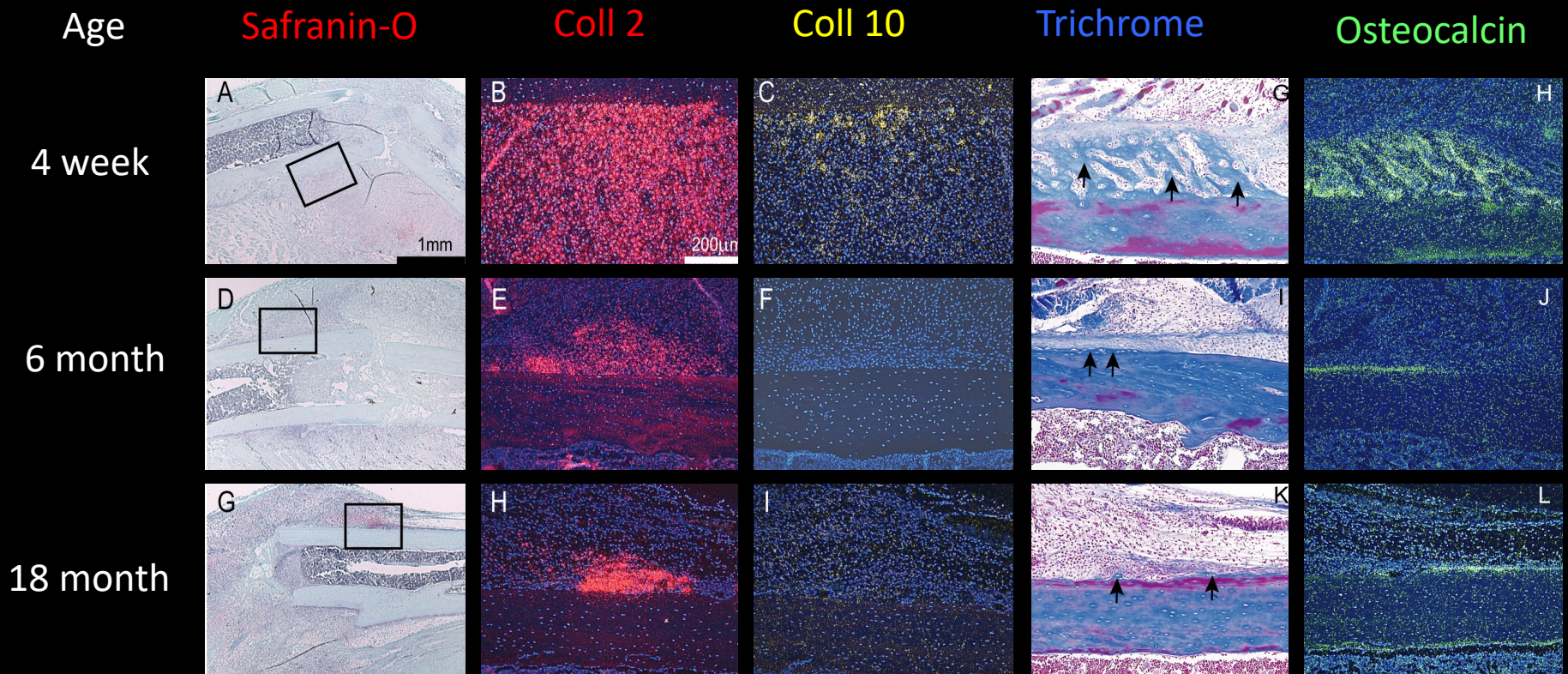
calcified cartilage



bone

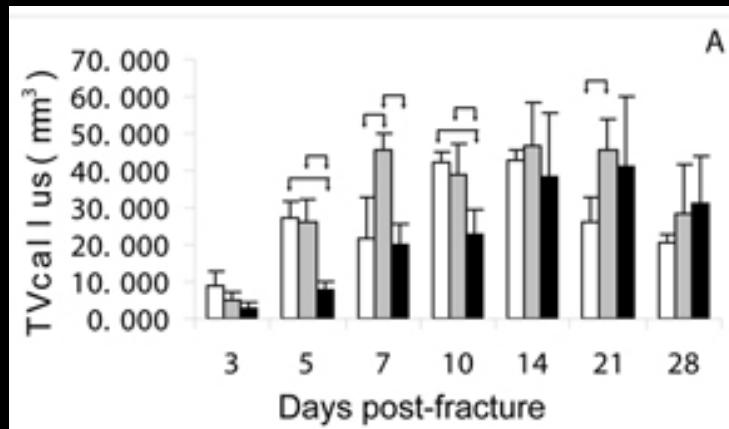
Aging delays cartilage and bone formation

Day 5 Post-fracture

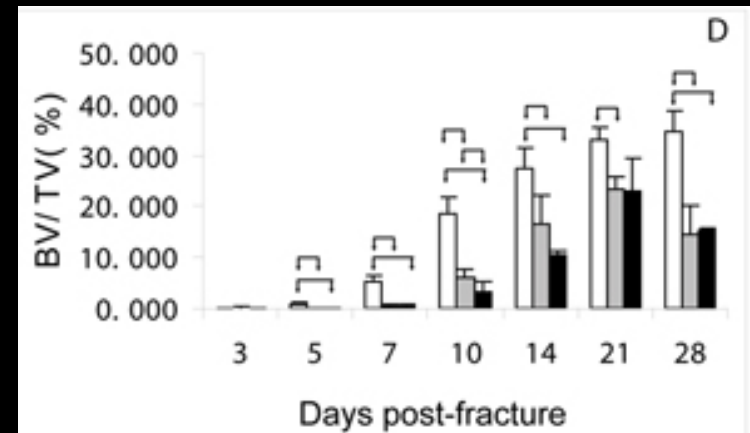
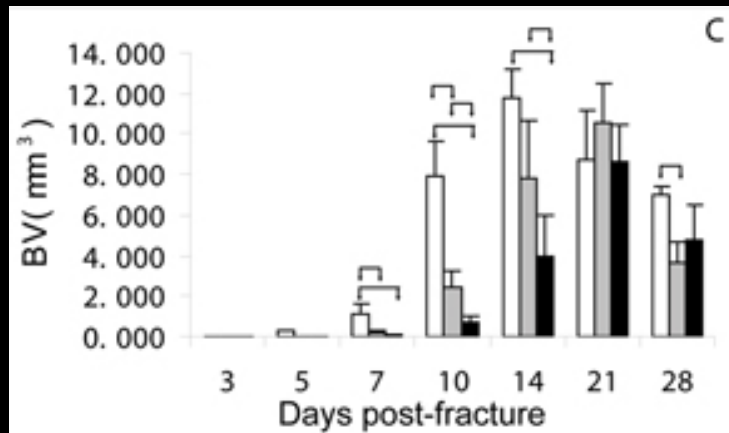
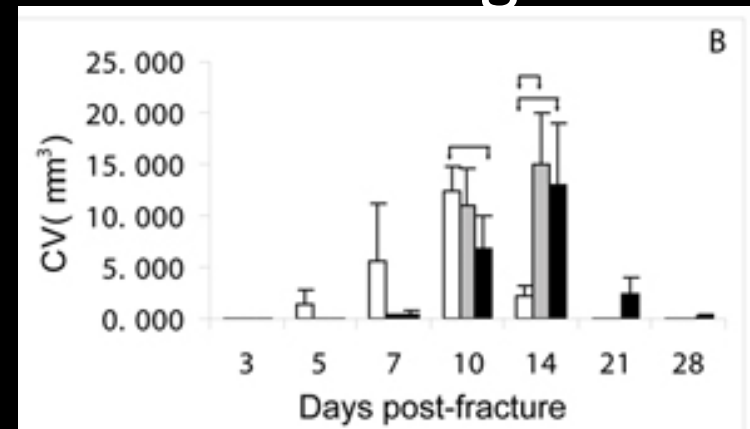


Rate of Fracture Healing is Age-Dependent

Callus



Cartilage



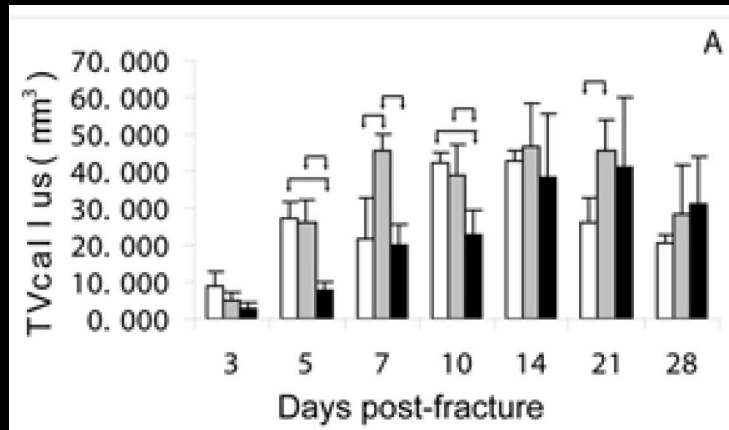
Bone

BV/TV

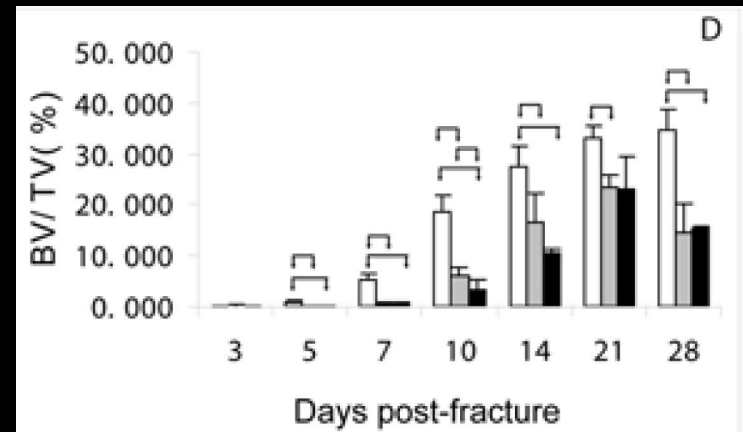
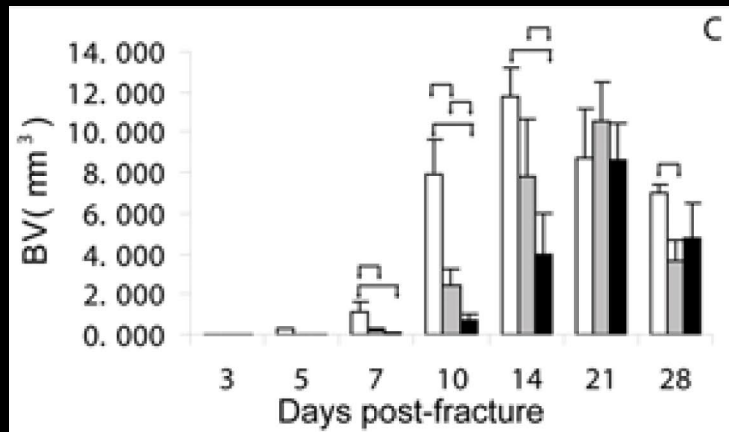
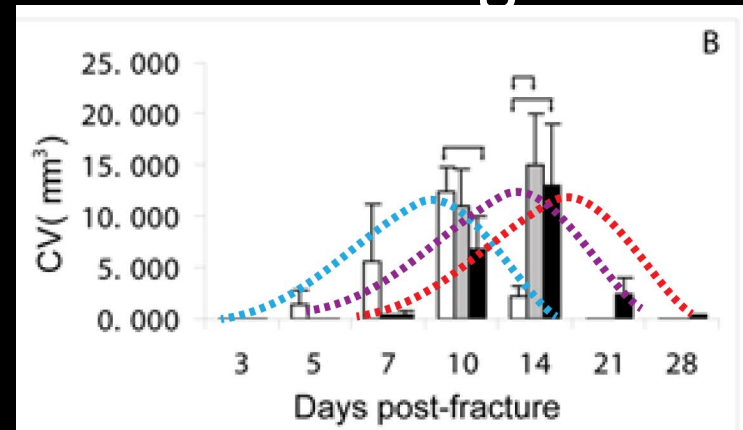
- Juvenile (1 mos)
- Middle-aged (12 mos)
- Elderly (18 mos)

Rate of Fracture Healing is Age-Dependent

Callus



Cartilage



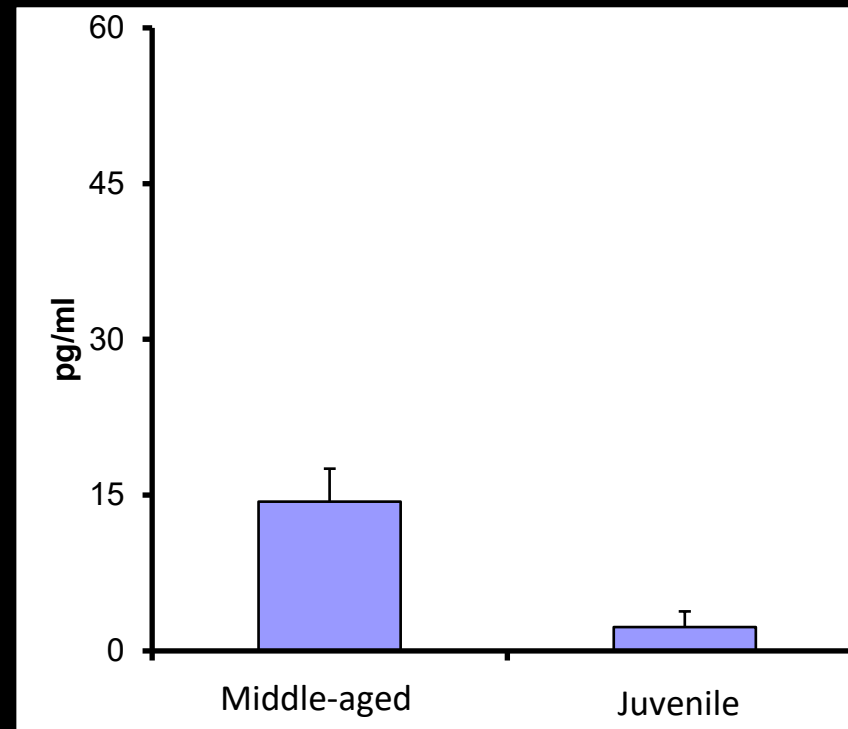
Bone

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



Inflammaging



-Aging produces an increasingly pro-inflammatory environment that impairs healing.

Replace inflammatory system of old animals (12 months) with juvenile (4 week) inflammatory system

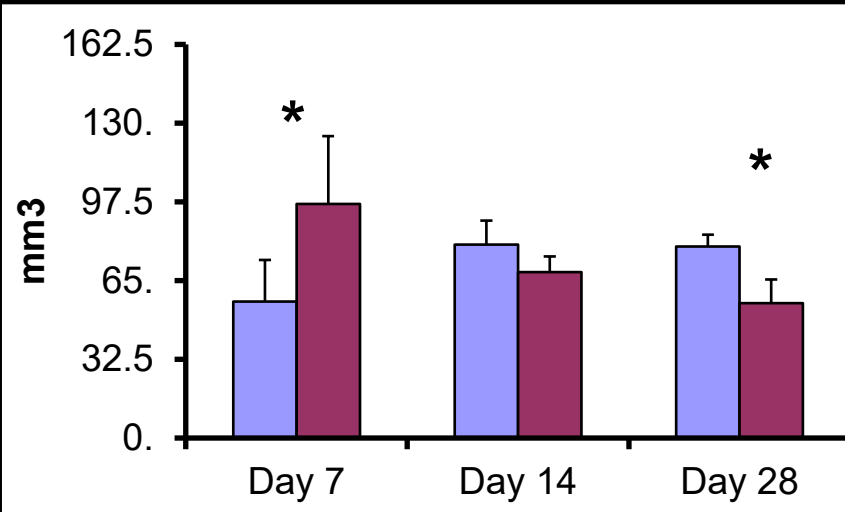
Creation of chimeras

Collect bone marrow from juvenile (4 week old) mice that express b-galactosidase (ROSA26)

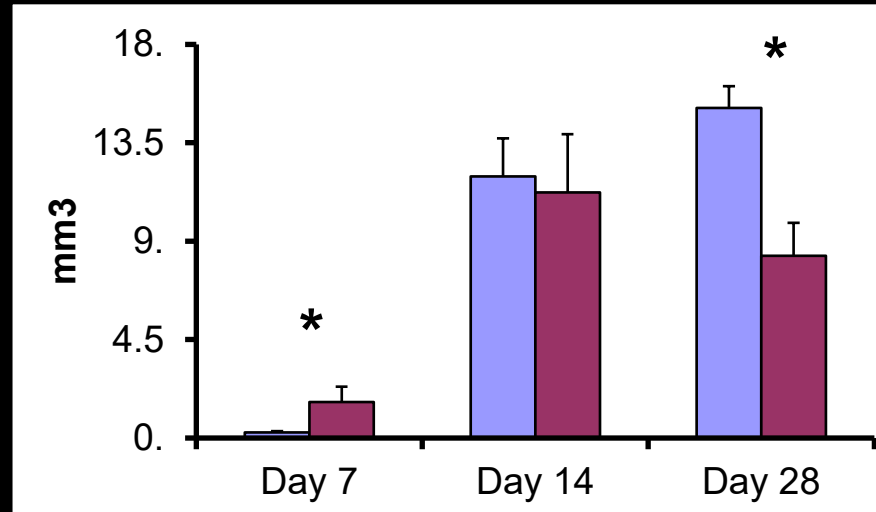
Transplant 10^7 nucleated cells into lethally irradiated (13grey) hosts (12 months old)

Young bone marrow rejuvenates bone healing

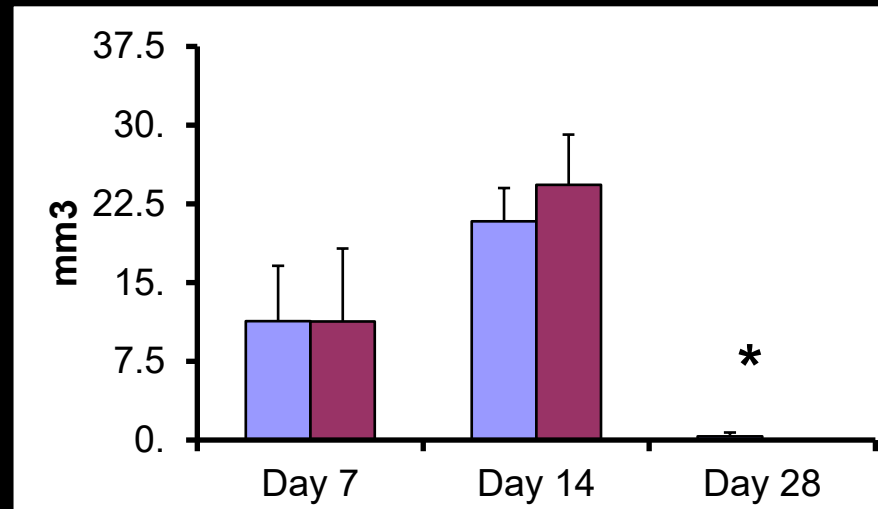
Callus volume



Bone volume



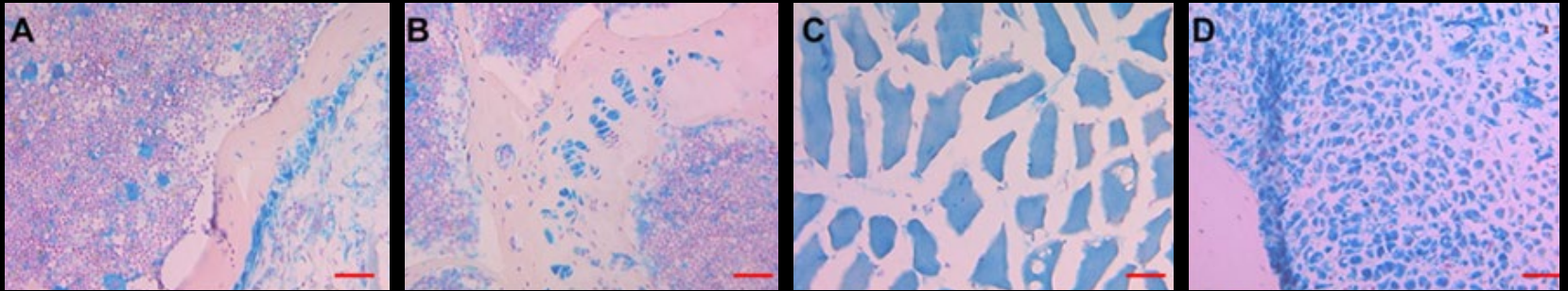
Cartilage volume



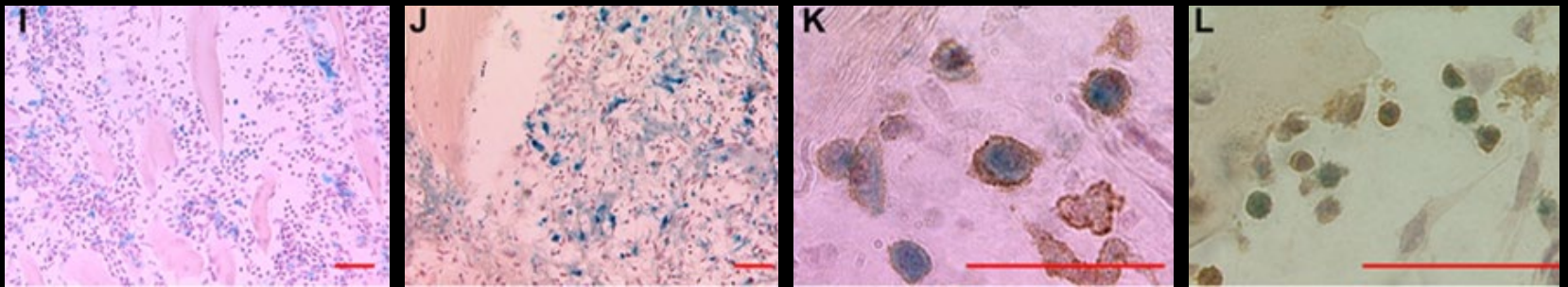
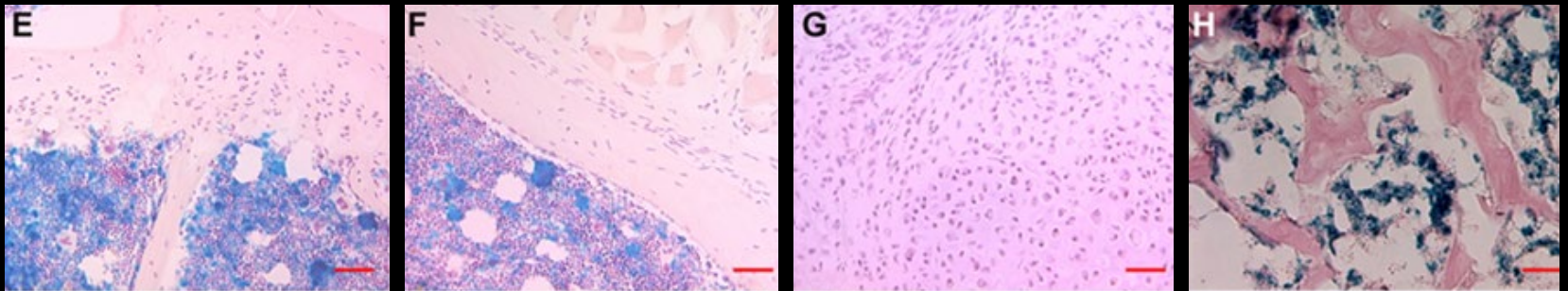
■ Elderly to elderly
■ Juvenile to elderly

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

ROSA 26



Chimera

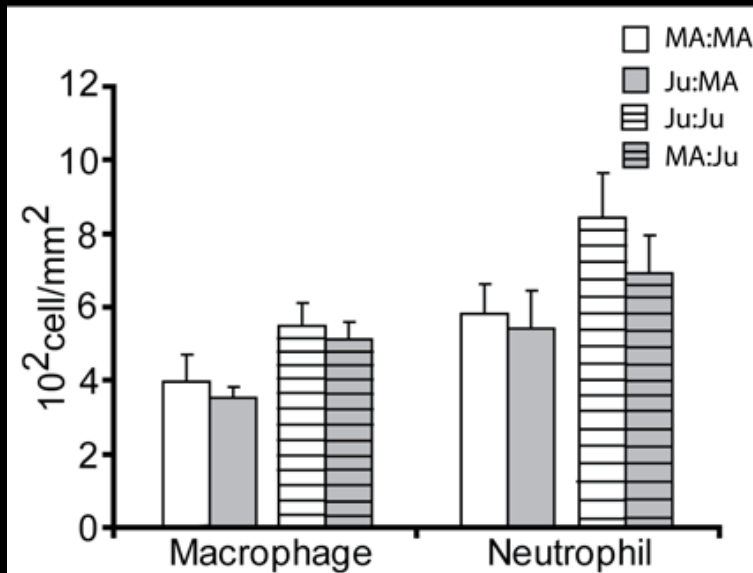


macrophages

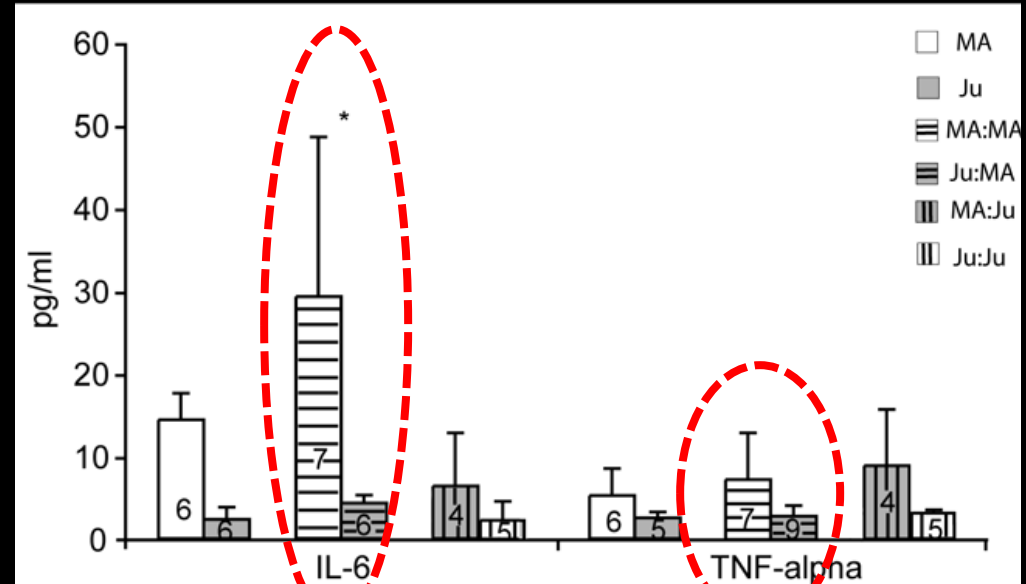
neutrophils

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

Inflammaging



-Aging produces an increasingly pro-inflammatory environment that impairs healing.

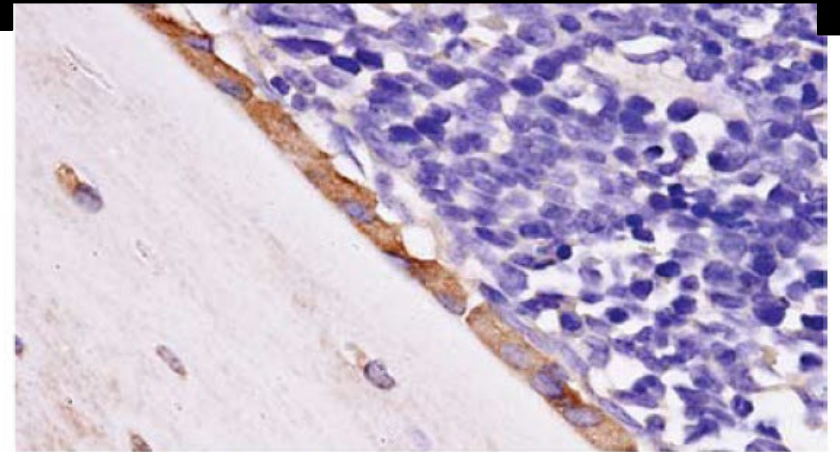
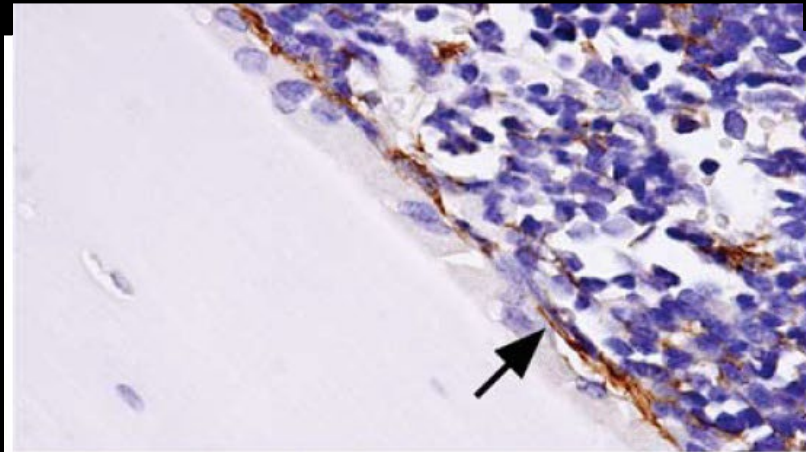
Inflammaging = macrophaging

-Can this be targeted therapeutically?

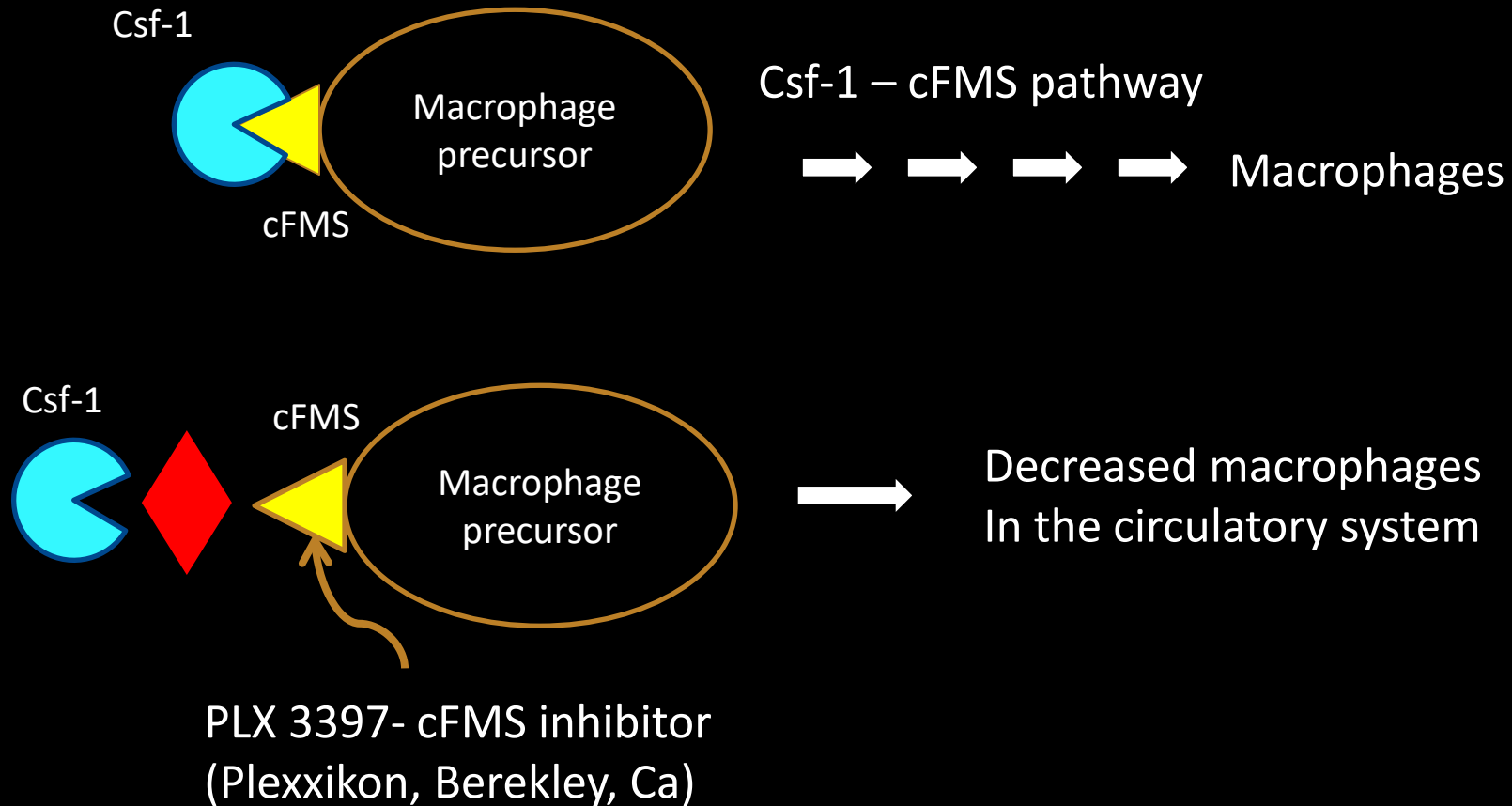
Macrophages are Associated with Bone

Macrophages

Osteoblasts

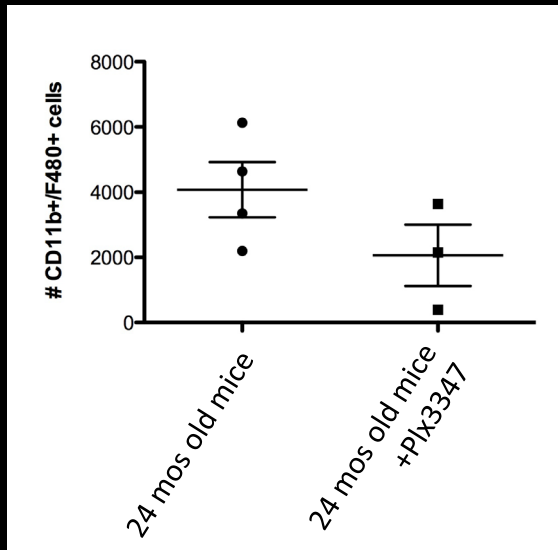


cFms Activation is Required for Differentiation and Function of Macrophages

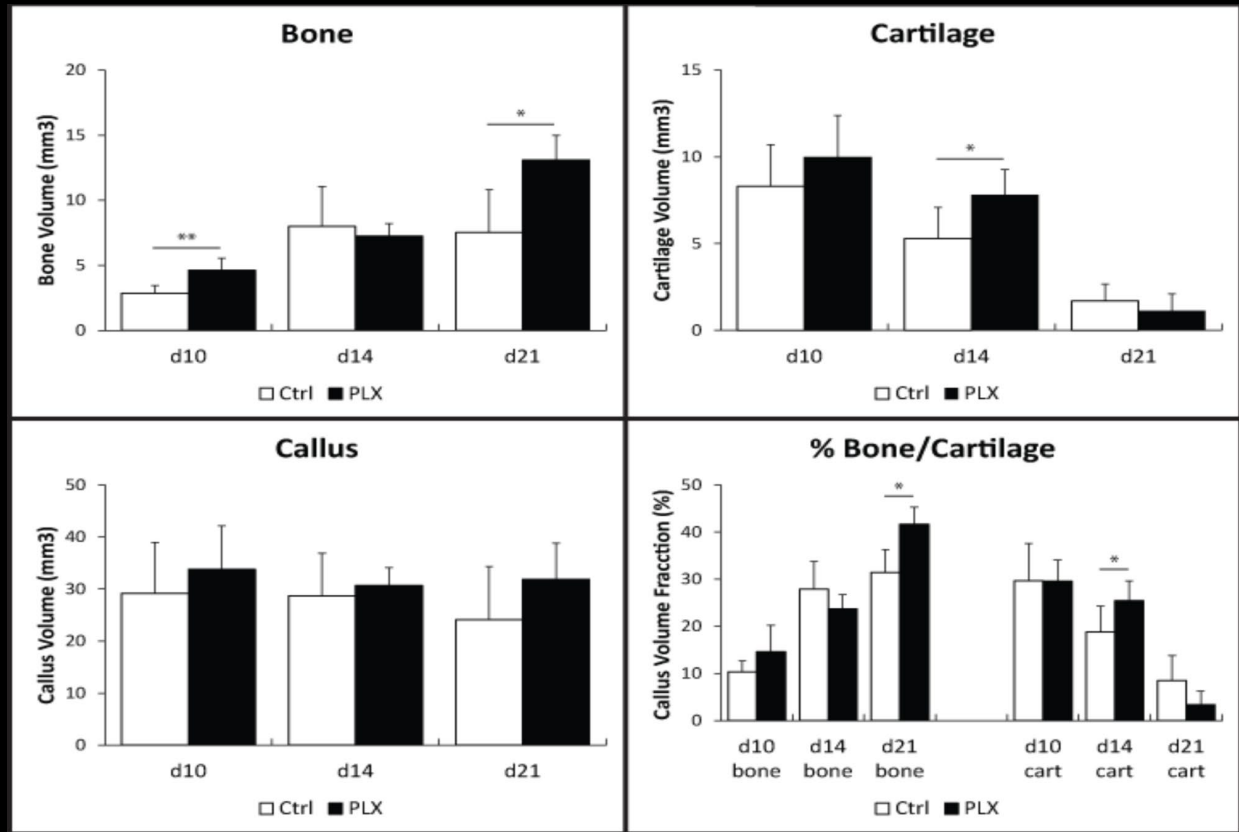


PLX3397 Inhibits Migration of Macrophages and Stimulates Healing in Old Mice

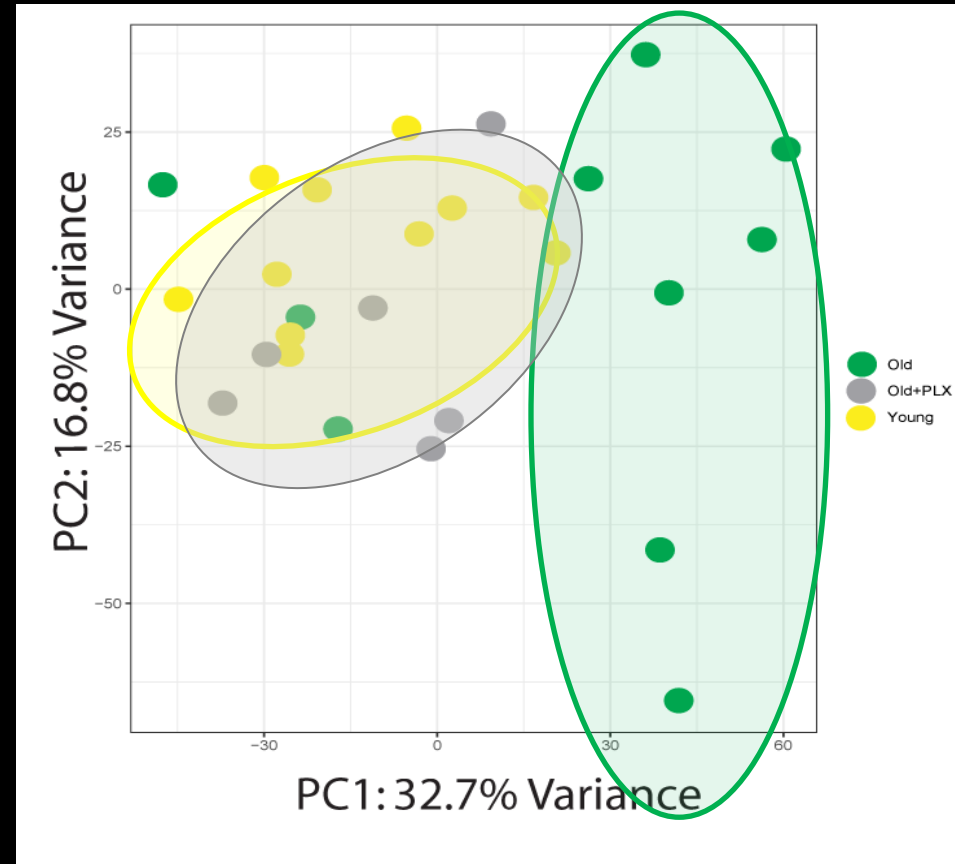
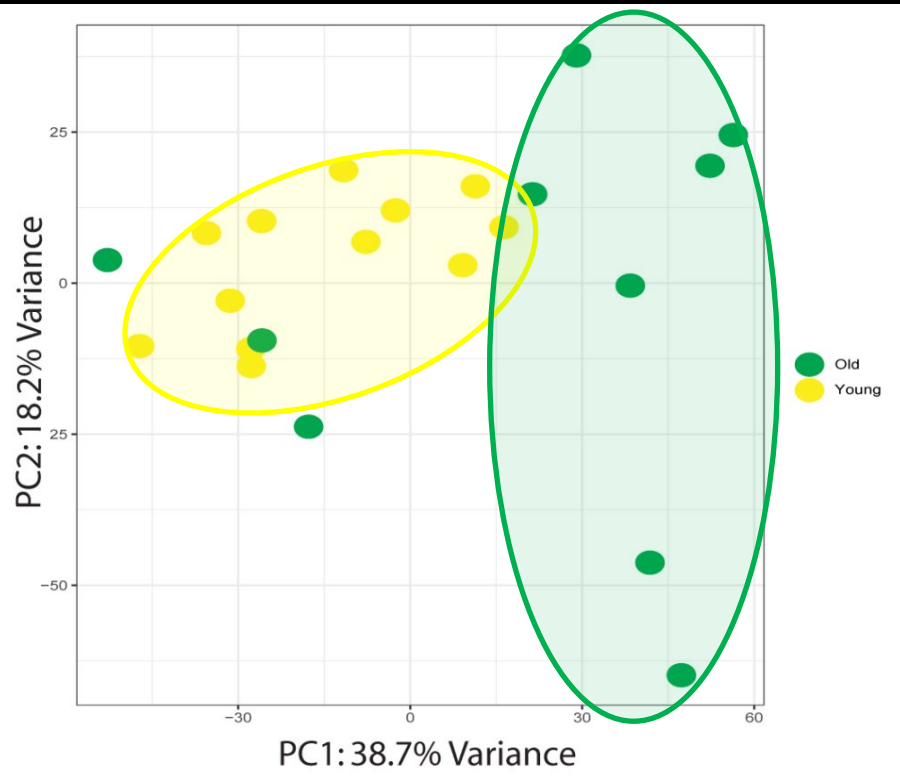
Macrophages



Healing



PLX3397 Rejuvenates the Macrophages



Conclusions

Dysregulation of Macrophages may *contribute* to delayed fracture healing and chronic disease.

Macrophages may be an acute therapeutic target for elderly fracture patients (need to balance infection control with healing).

Why do some people/animals age better than others?