National Aeronautics and Space Administration

Ames

Discovery Innovations Solutions

So you want to go to Mars: bones and matters of the heart

Candice Tahimic, PhD
Globus Lab

March 8, 2017

The Big Goal

Long duration, human habitation in space -
stay healthy during and after

Presentation outline

1. Challenges of the space environment
2. Why bones and hearts matter in space
3. Relevance to human health on earth
4. Our hypothesis and research aims
5. The toolbox: Earth-based models for spaceflight
6. Findings on the skeletal system
    - Responses to radiation and simulated weightlessness
    - Mechanisms and mitigation strategies
7. Summary
8. Some current projects
9. Concluding remarks
10. Q&A

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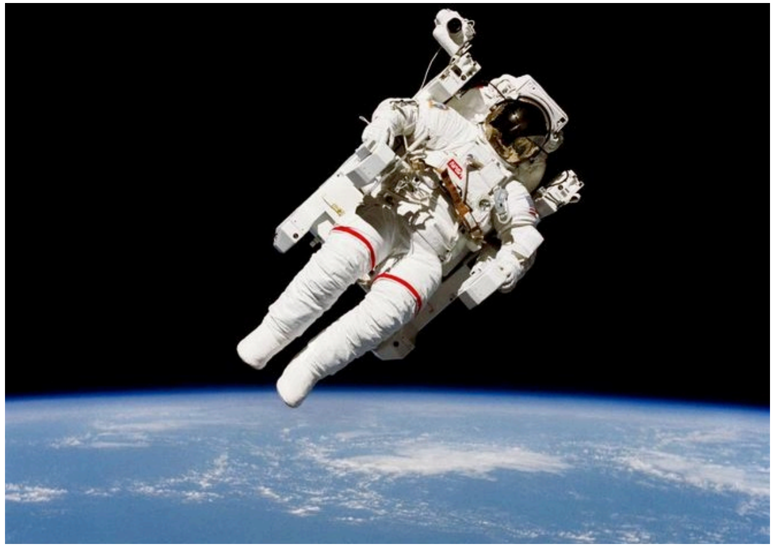
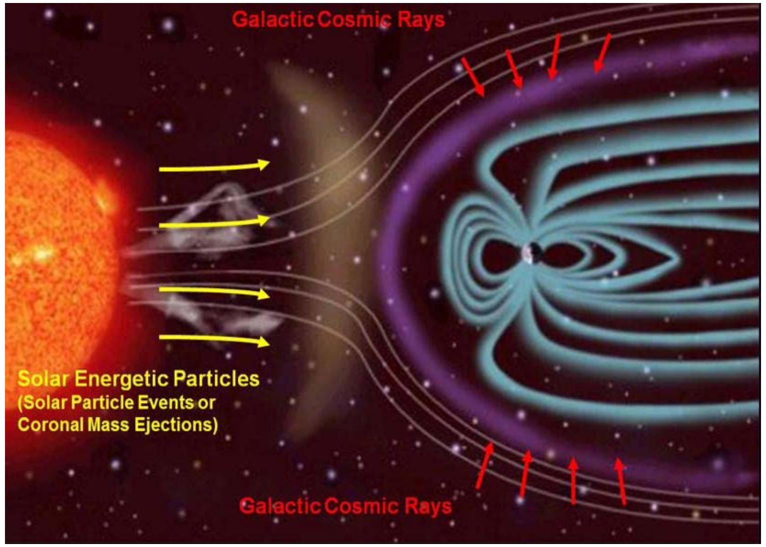
Challenges of living in space

Weightlessness



Space radiation



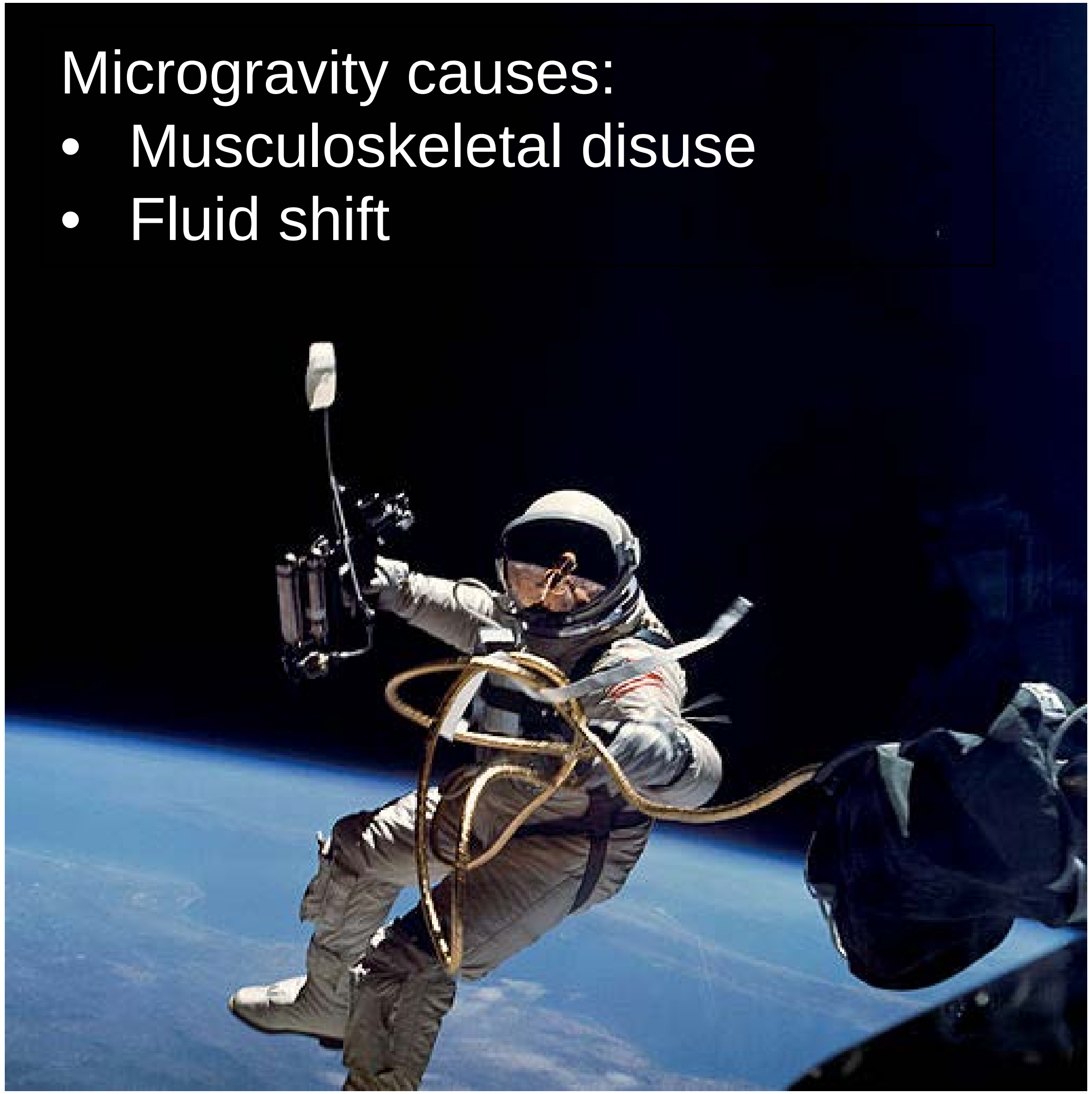
Sources
- Galactic cosmic radiation
- Solar particle events

Ionizing radiation
- Predominantly protons
- High-Z, high-energy (HZE particles)
- Secondary (primarily gamma)

- Demanding workload
- Sleep disruption
- Confined environment
- Elevated CO_2
- Nutrition

Spaceflight affects most organ systems

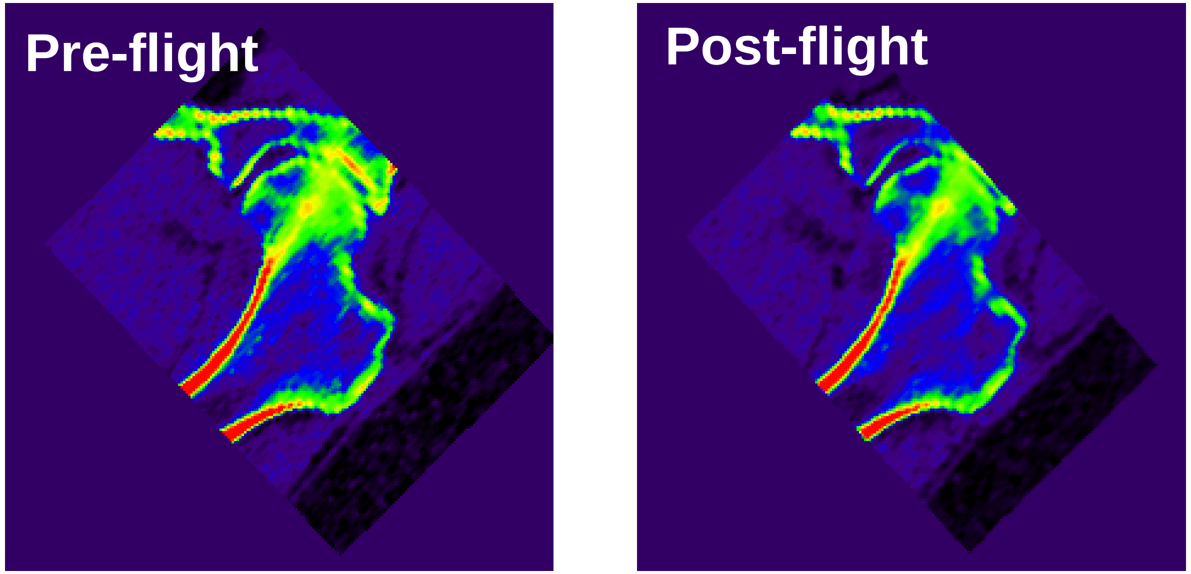
Bone
Muscle
Cardiovascular
Vestibular system
Sensory
Blood
Immune
Vision



Microgravity causes:
- Musculoskeletal disuse
- Fluid shift

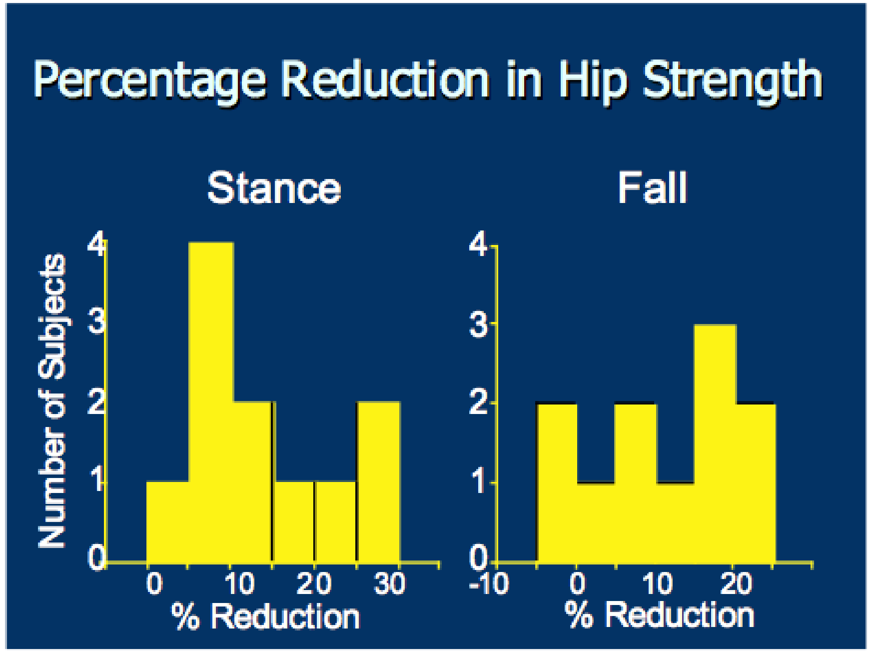
Long duration spaceflight leads to bone loss and greater fracture risk in astronauts

Loss of mineralized tissue



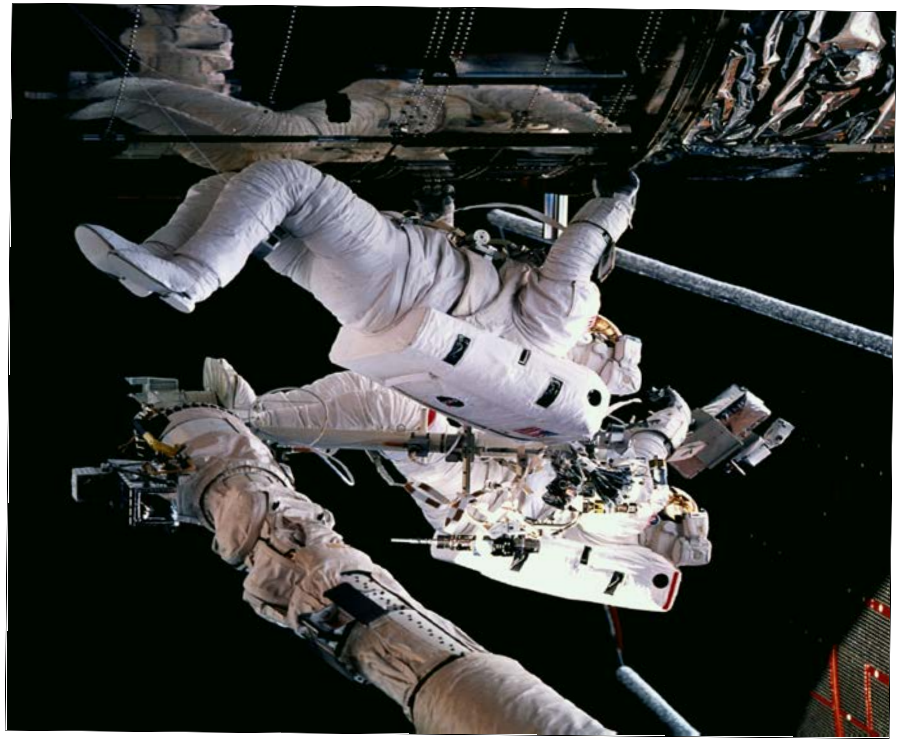
Loss of BMD in trabecular compartment, thinning of cortex at the femoral neck during flight (Lang et al. 2004 and 2006)

Reduced Strength



Up to two long-duration astronauts display 20-30% decrease in hip strength based on finite element analysis (Keyak et al. 2009)

Musculoskeletal disuse and skeletal health: relevance on earth



Osteoporosis

- Osteoporotic fracture incidence: 1 in 3 women and 1 in 5 men over 50 (Melton et al. 1992 and 1998)
- Overall mortality: ~20% in first 12 months after hip fracture; higher mortality in men (Center et al. 1999)

Radiation and skeletal health: relevance on Earth

High doses (>2 Gy) ionizing radiation and bone health: established relevance to human therapies and disease

Beneficial uses: Radiotherapy for cancers

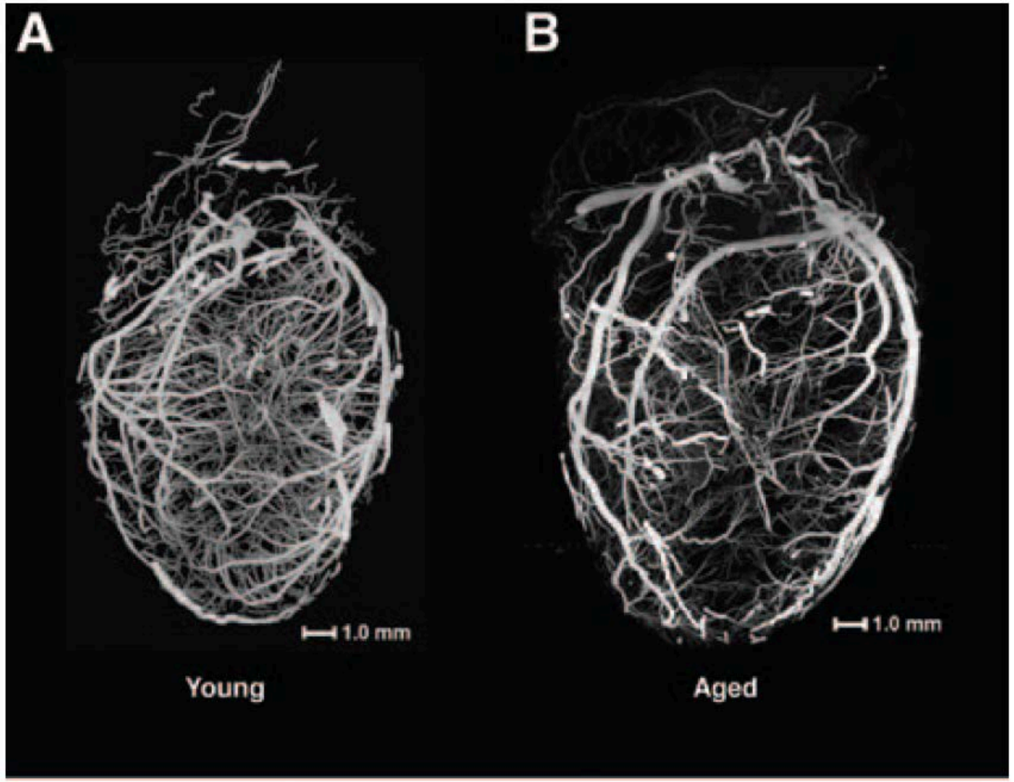
- Comes with a cost: increased fracture risk post-treatment
- Hip fractures: ⬆76% in men and ⬆65%– 216% in women (Elliott et al. 2011; Baxter et al. 2005)

Occupational/environmental exposures, low doses

- Astronauts, On earth: radiation workers, miners
- Relevance to skeletal and cardiac health less understood

Cardiovascular responses to spaceflight

- Increased post-flight carotid artery stiffness (Hughson et al 2016)
- Altered baroreflex responses; increased arterial pressure (Eckberg et al 2010)
- Resemble some features of cardiovascular aging on earth
- Impact of long duration exposure to spaceflight less understood



Sangaralingham et al. 2011

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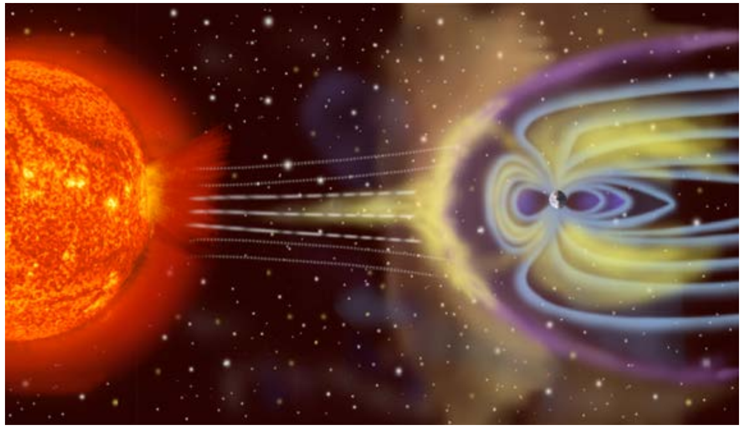
Staff:
Candice Tahimic, PhD; Senior Scientist, Lab Manager
Ann-Sofie Schreurs, PhD; Staff Scientist
Masahiro Terada, PhD; Postdoctoral fellow
Sonette Steczina; Research Intern
Samantha Torres; Research Intern

"We aim to understand the responses of mammalian tissue to spaceflight with the long-term goal of developing effective strategies to maintain crew health during and after missions."



Our Hypothesis

Reactive Oxygen Species **(ROS)** in excess
e.g. O_2^-, OH^-, H_2O_2

Oxidative damage
DNA, proteins, lipids

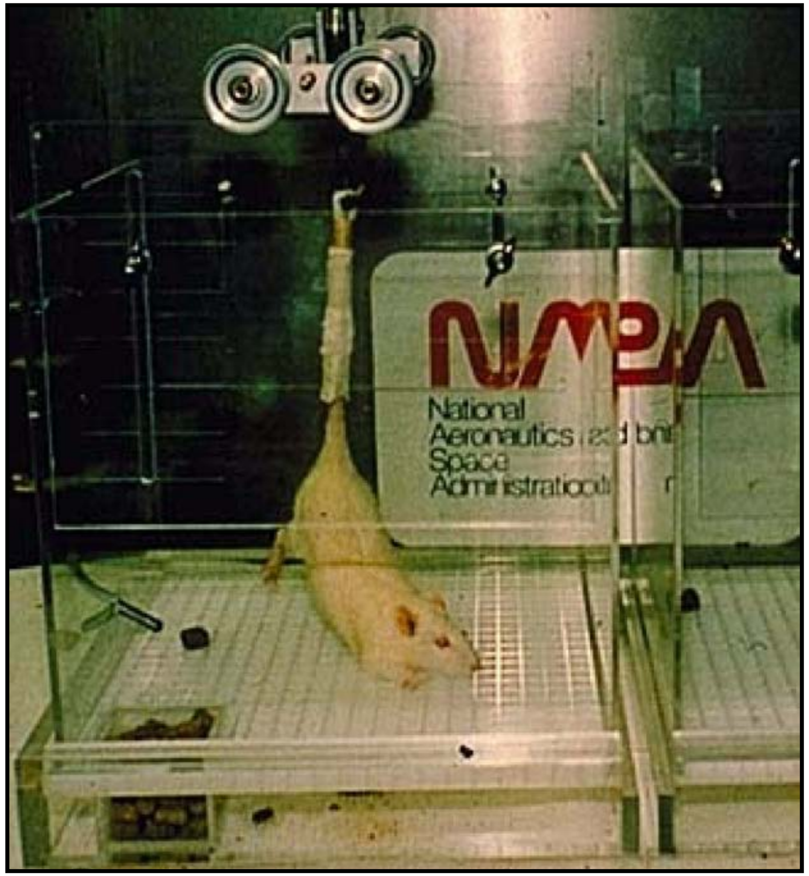
Tissue degeneration
Inflammation

Disrupt cell-cell and intracellular signaling

Accelerated aging of tissues?
Cardiovascular
Nervous System (CNS)
Skeletal tissue

Our toolbox: simulated spaceflight using Earth-based analogs

Hindlimb unloading (HU)

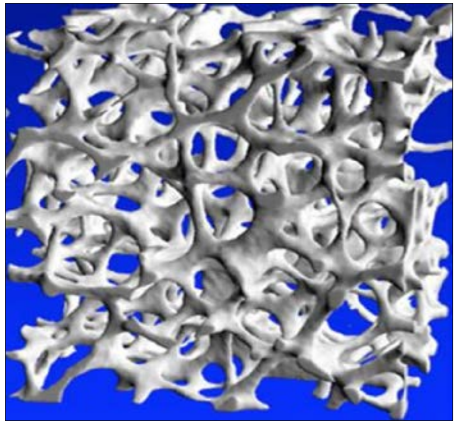


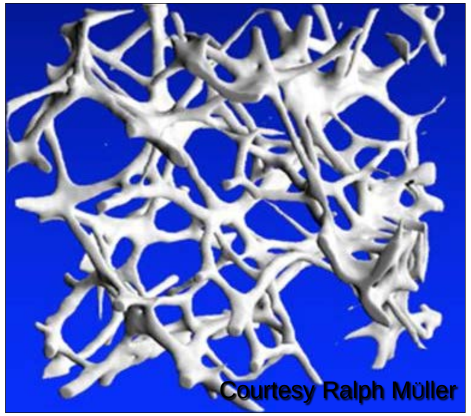
Space radiation simulations: NASA Space Radiation Lab or gamma/x-ray

Combined HU and radiation: custom rack

Mouse as a model for tissue degeneration in response to simulated spaceflight

Comparing rates of bone loss (osteoporosis) in humans and rodents

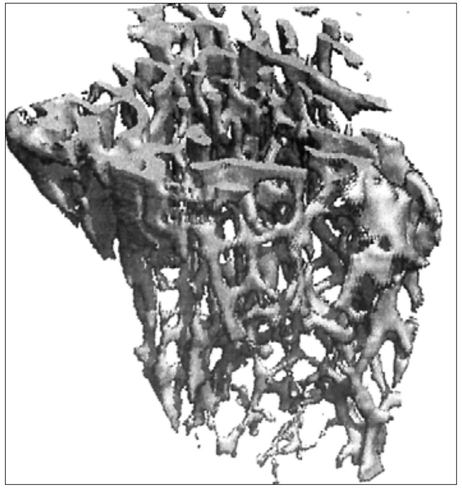




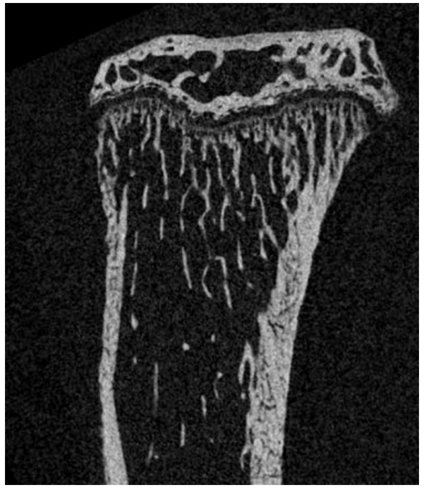
HUMANS:
Months - Decades

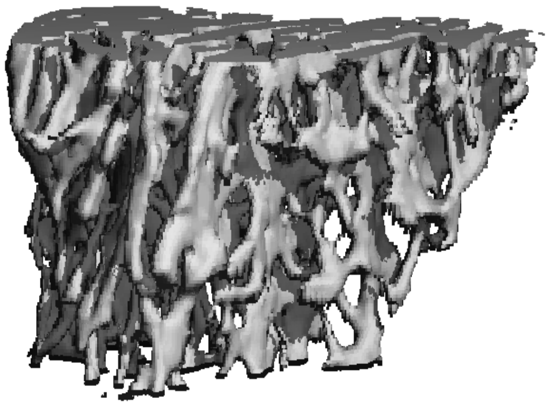
Aging, radiation and disuse

RODENTS:
Weeks - Months



Radiation exposure vs HU: Rapid cancellous bone loss, different microarchitectural deficits





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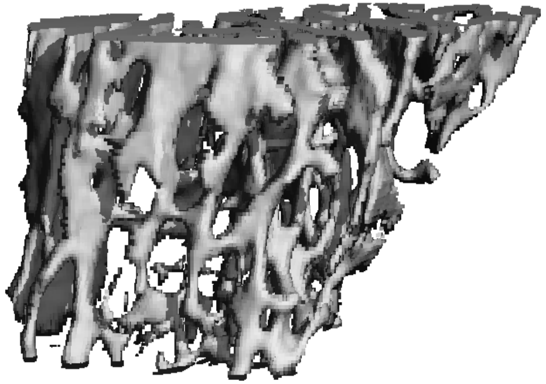
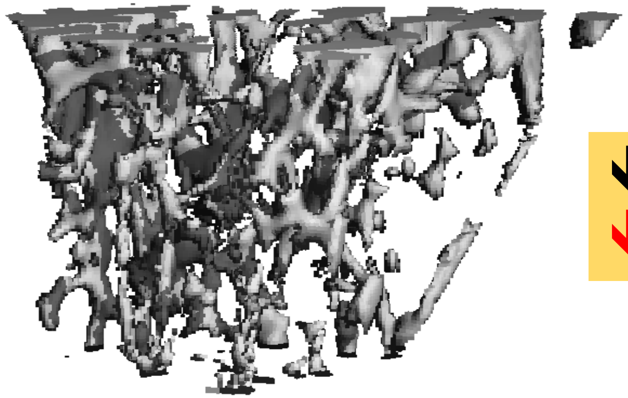


↓ Bone Volume/Total Volume
↓ Trabecular thickness

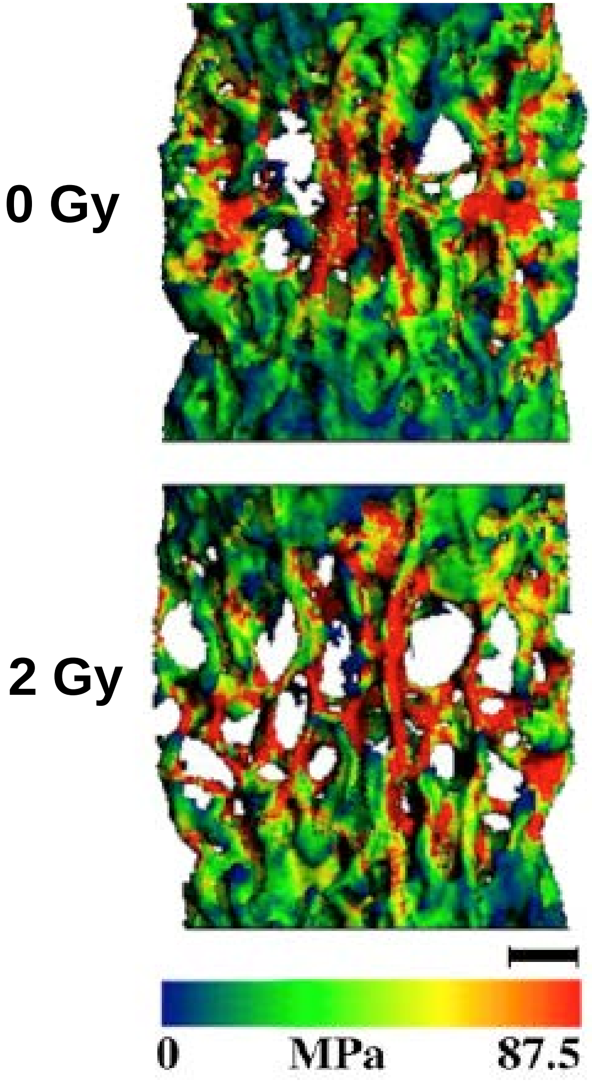
Radiation
HZE, ^{56}Fe at 0.5-2 Gy
Gamma, ^{137}Cs at 1-2 Gy



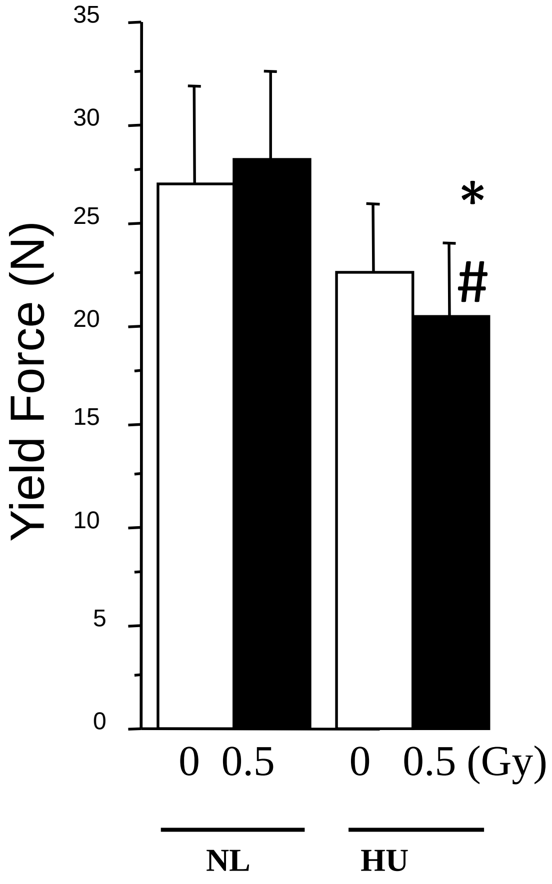
↓ Bone Volume/Total Volume
↓ Trabecular number

Radiation exposure and HU can impair bone mechanical properties

Finite Element Modeling



Compression testing



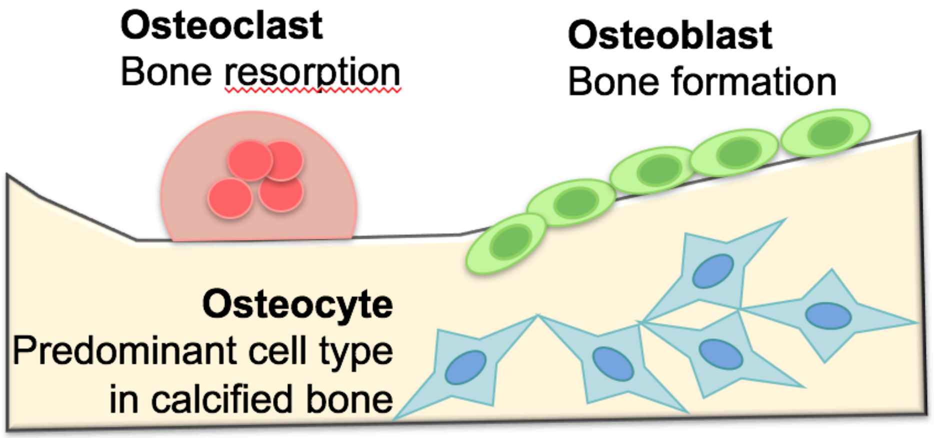
Lumbar vertebra (4th)
HU: 2 weeks
IR: ^{56}Fe, 0.5Gy, 1GeV/n

*p<0.05 vs NL 0 Gy Control
#p<0.05 vs NL/0.5 Gy

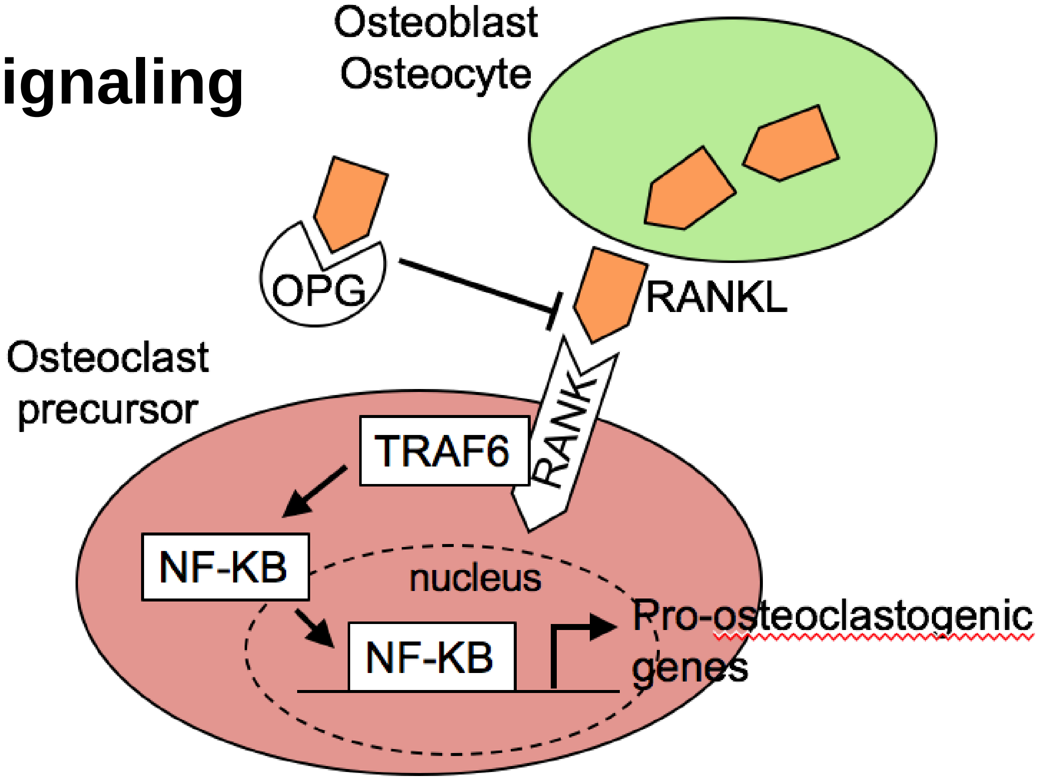
Alwood et al. 2010

Cellular and molecular mechanisms of bone loss

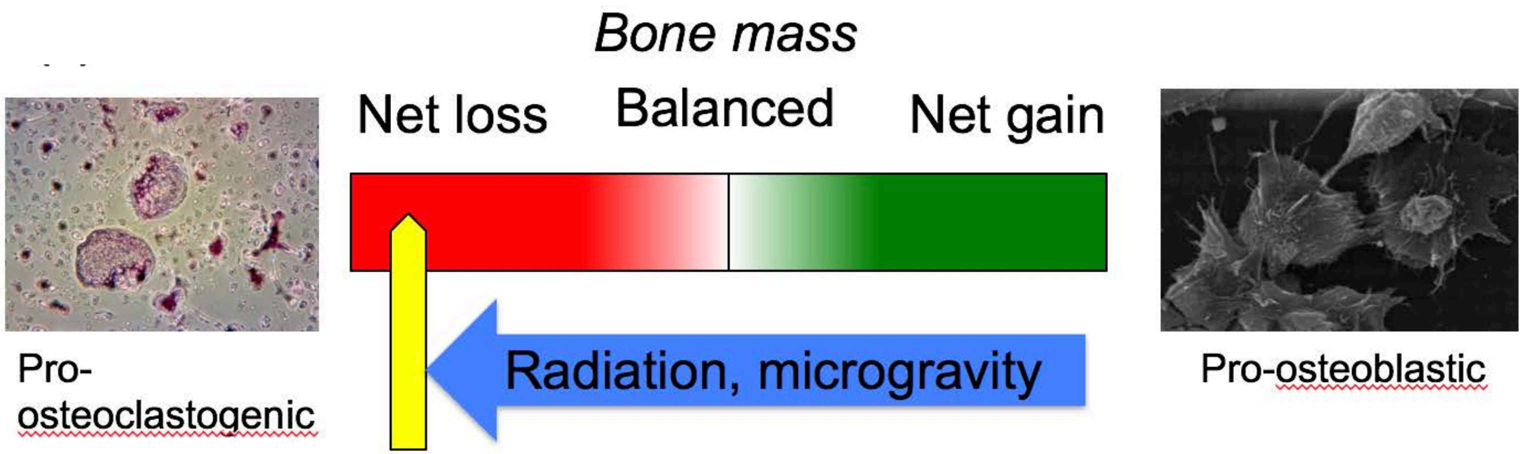
Major cell types involved



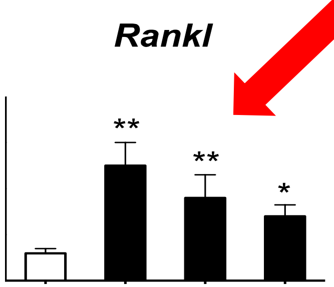
RANKL signaling



Bone homeostasis

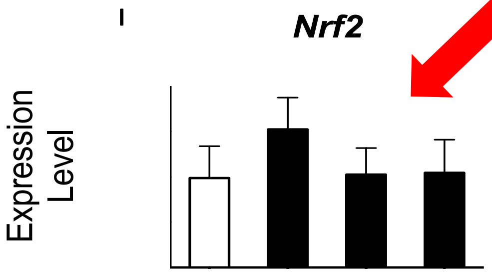


Temporal radiation-induced changes in expression of genes related to osteoclastogenesis and antioxidant defense



In bone marrow, at one day post-irradiation

Expression Level

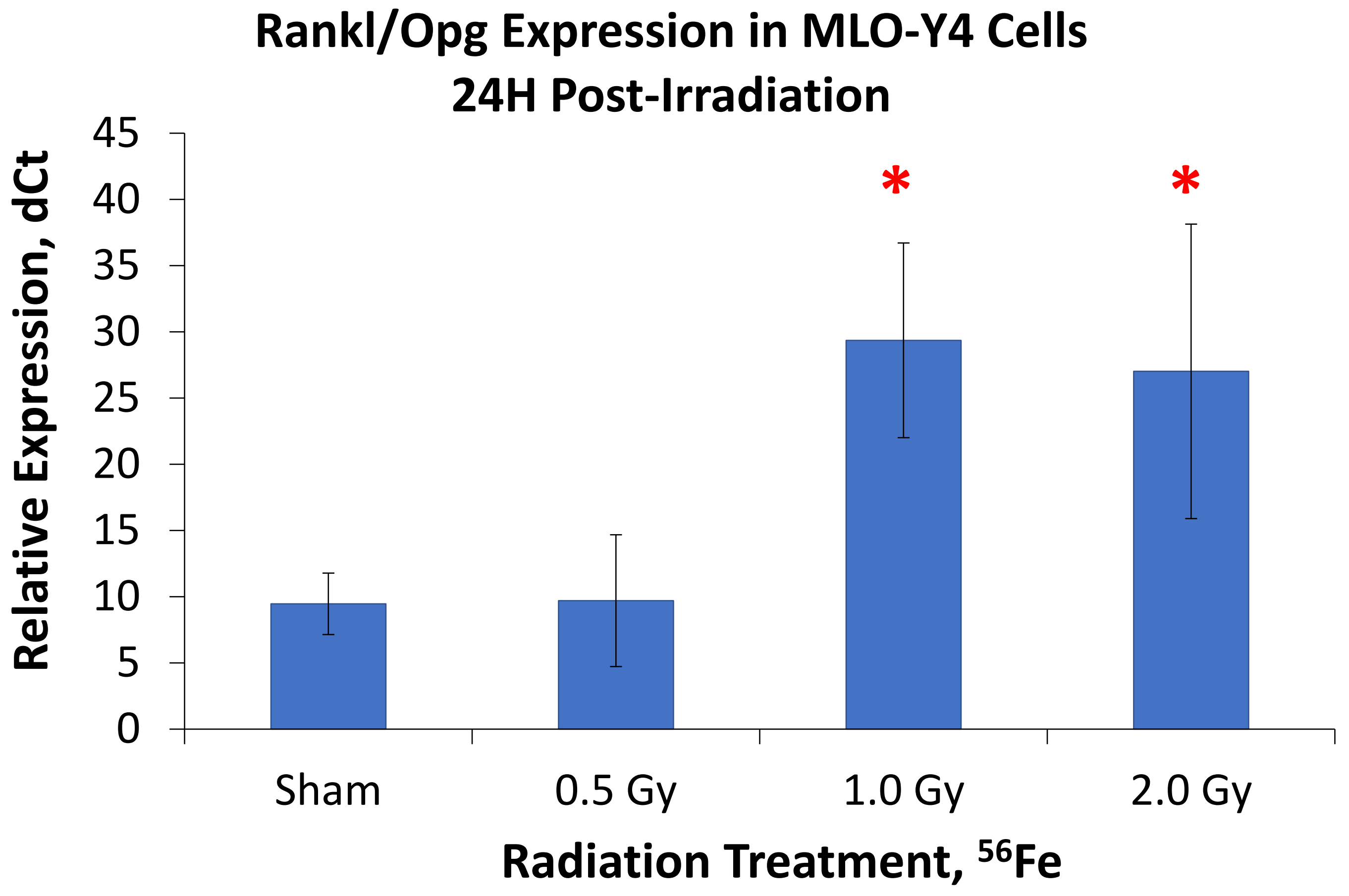


adiation (days)

)

Alwood et al. 2015

Spaceflight-like radiation promotes pro-osteoclastogenic signals in osteocyte-like cells

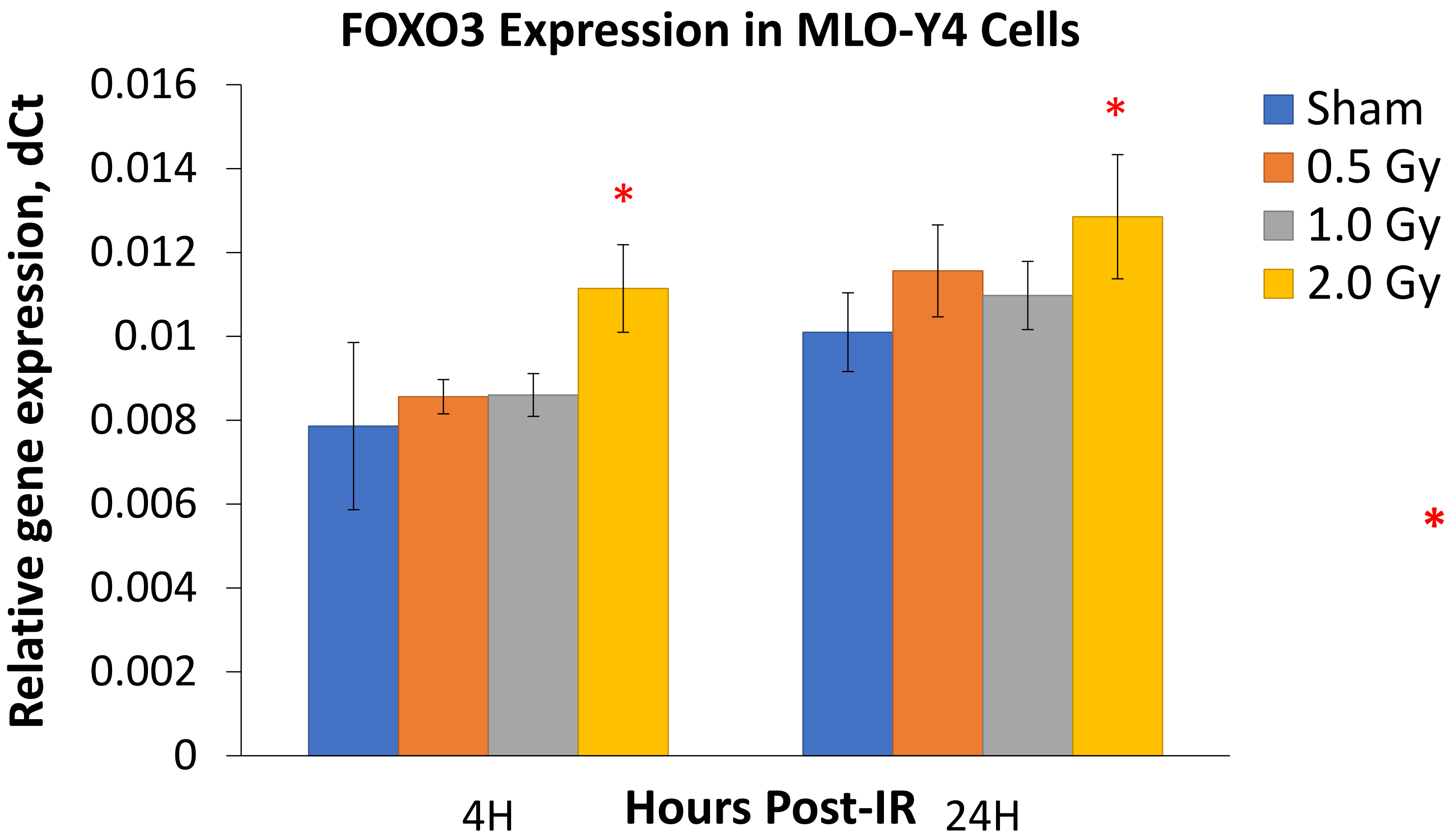


* $p < 0.05$ vs 0 Gy (Sham)

Tahimic et al, unpublished

Spaceflight-like radiation invokes rapid and persistent increase in FoxO3 expression

FoxO3: Encodes a transcription factor responsible for activating other antioxidant genes (protects against oxidative stress)



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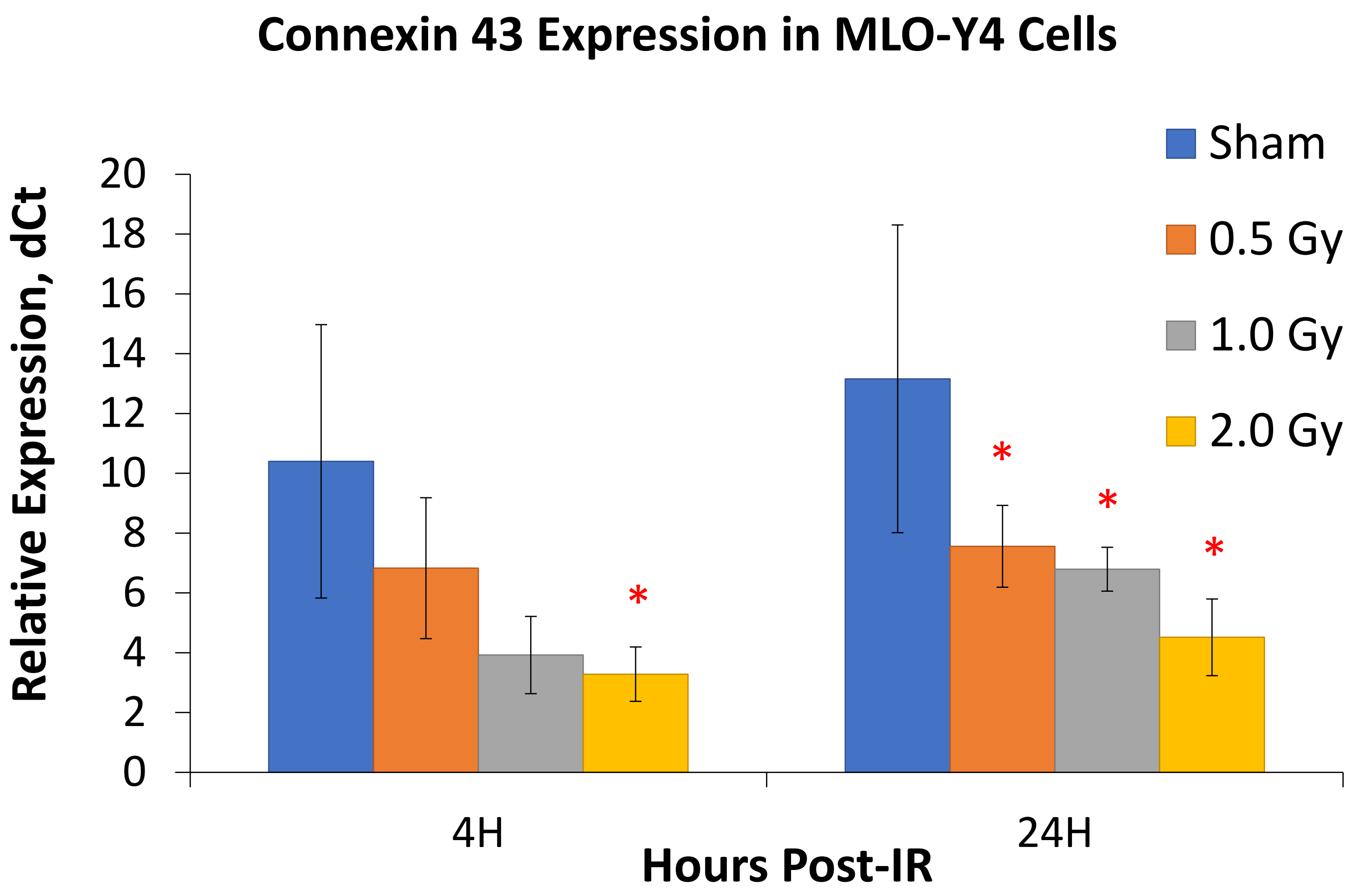
Tahimic et al, unpublished

Spaceflight-like radiation decreases Connexin 43 expression in osteocyte-like cells

Connexin 43:

- Gap junction protein that mediates osteocyte communication
- Inhibition exacerbates H_2O_2-induced cell death (Kar et al 2013)
- Osteocyte knock-in mutant: increased apoptosis and osteoclast number (Xu et al. 2015)



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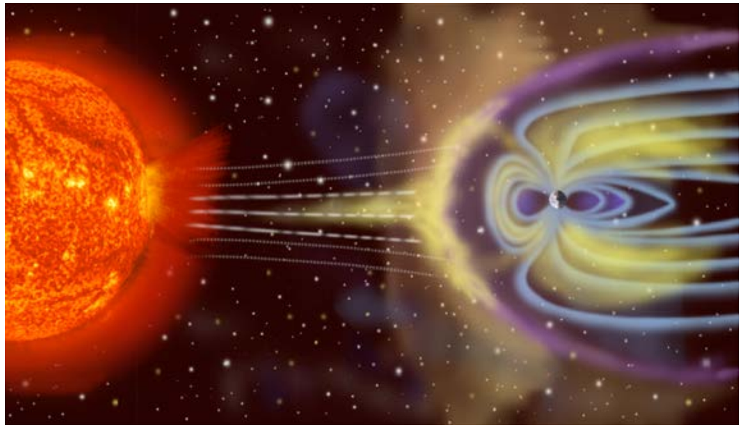

Testing our hypothesis, Part 2

Reactive Oxygen Species **(ROS)** in excess
e.g. O_2^-, OH^-, H_2O_2

Oxidative damage
DNA, proteins, lipids

Tissue degeneration
Inflammation

Disrupt cell-cell and intracellular signaling

Accelerated aging of tissues?
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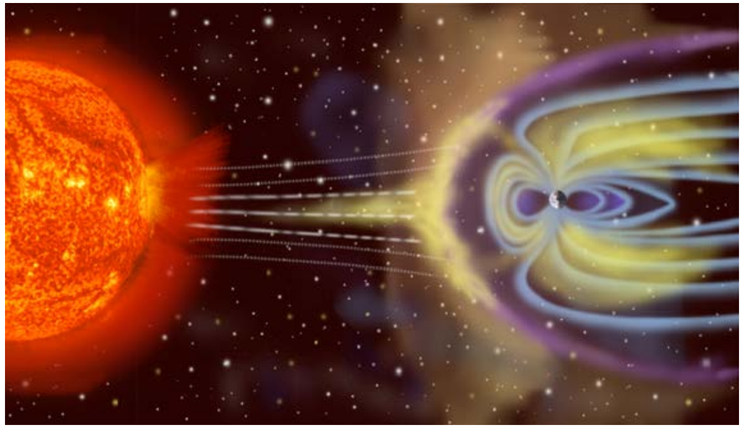

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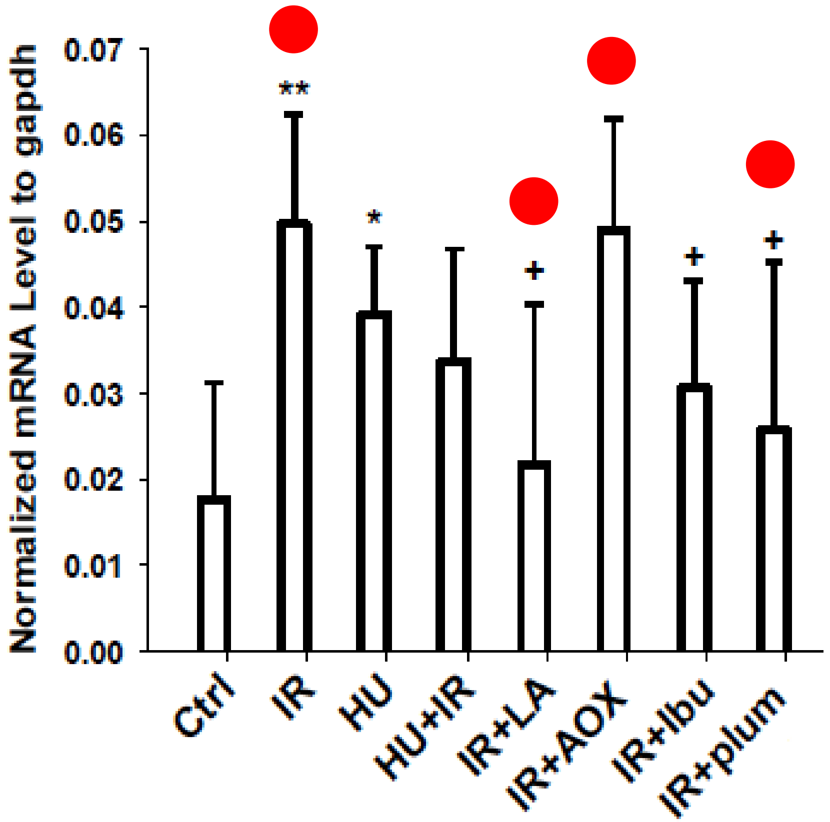
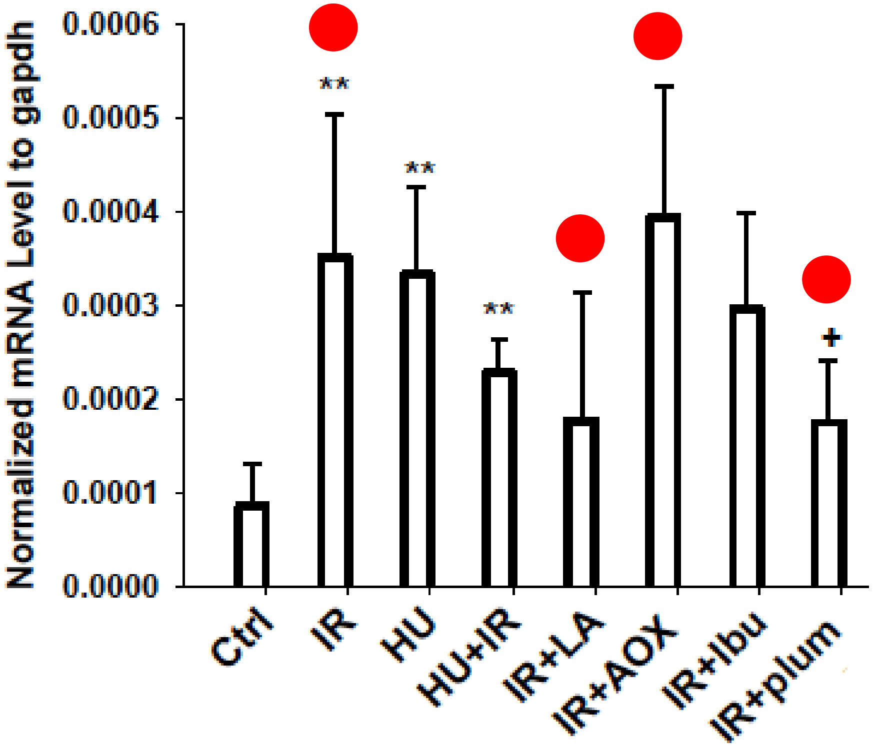
Emerging from mechanistic studies: candidate anti-bone loss agents

Bone marrow, 1 day post-irradiation with ^{137}Cs (2Gy)

Nrf2



Rankl

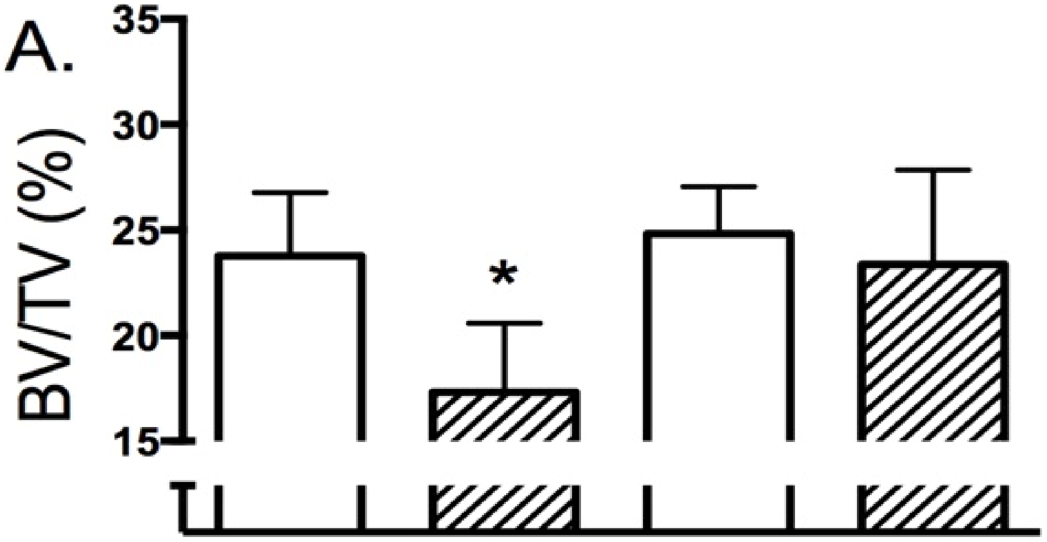


Some antioxidants are effective in blunting pro-osteoclastogenic signals, some are not

LA: lipoic acid (IP: 25 mg/kg X2 daily)
AOX: Dietary anti-oxidant cocktail

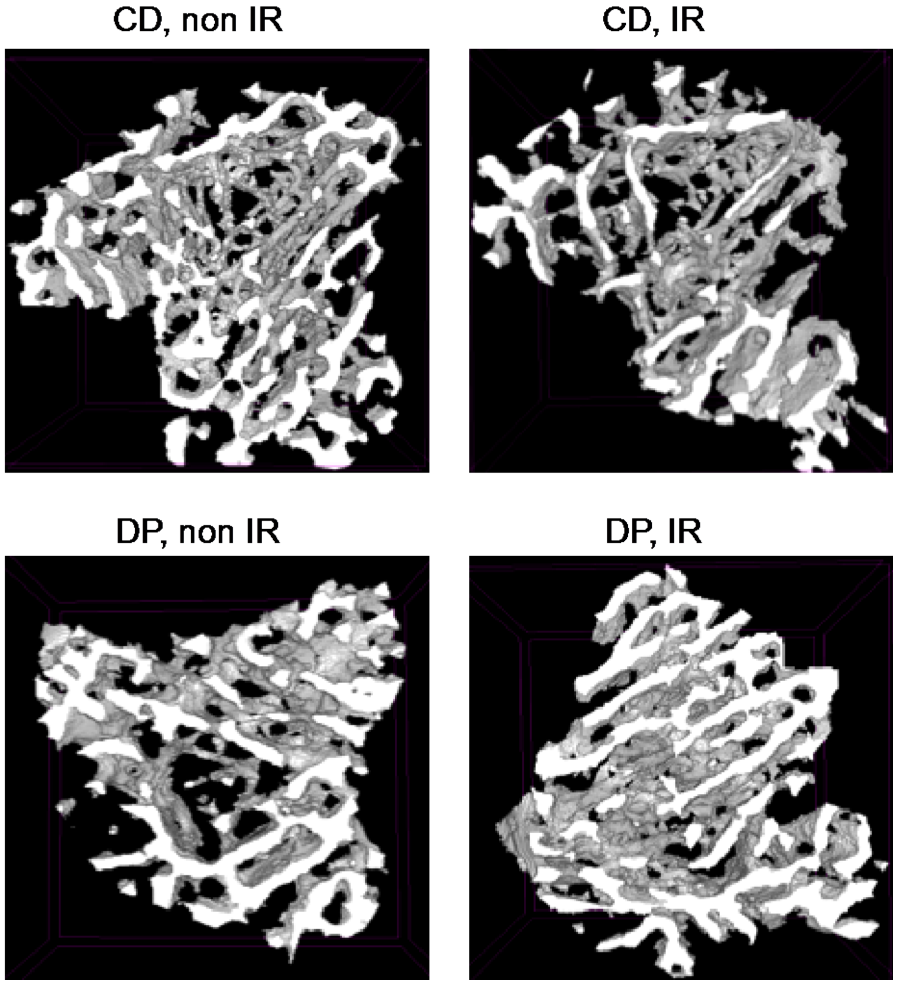
Ibu: Ibuprofen (IP: 10mg/kg X2 daily)
Plum: Dietary dried plum (20%)

Dried plum diet protects from bone loss caused by ionizing radiation



Tx:	CD3	CD3	DP	DP
IR:	-	+	-	+

Tx: $p < 0.01$; IR: $p < 0.01$; Tx*IR: $p < 0.05$



Schreurs et al. Scientific Reports 2015

Summary and new questions

- Spaceflight environment poses challenges to human health
- Some tissue responses to spaceflight resemble features of human disease on earth
- Radiation and simulated weightlessness cause cancellous bone loss;

Impairment can be worse if factors combined

- Radiation and simulated weightlessness activate pathways related to anti-oxidant defense and osteoclastogenesis
- Antioxidants have varying abilities to protect from radiation-induced bone loss, a diet rich in polyphenols (DP) looks promising
- Will quenching ROS production in mitochondria protect from tissue deficits induced by simulated weightlessness?
- Long-term effects of simulated weightlessness on other tissues (e.g.heart)?

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Acknowledgements

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