Femoral Head Bone Loss Following Short and Long-Duration Spaceflight

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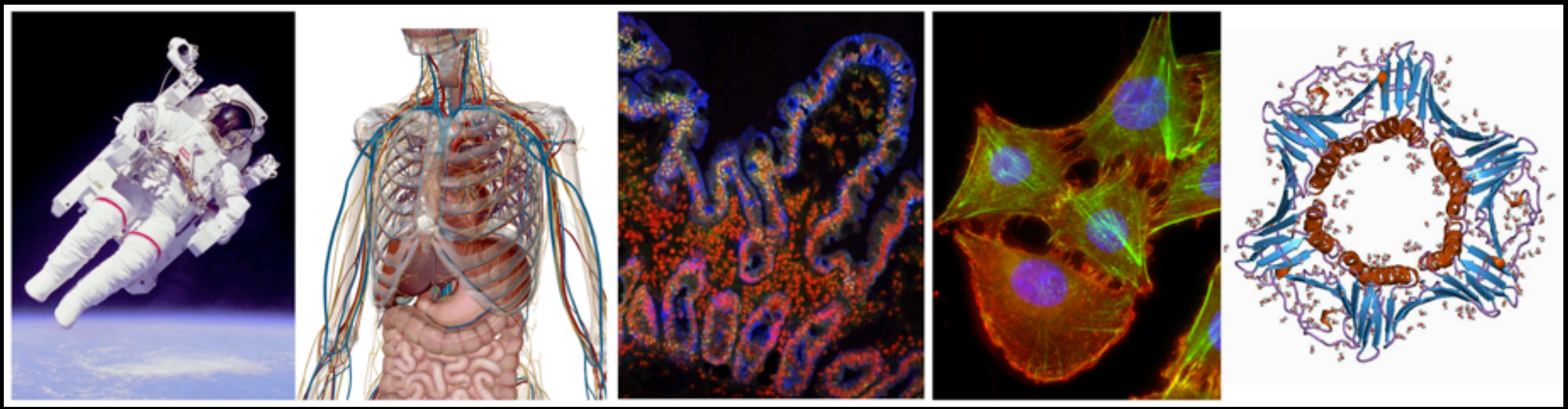
Spaceflight mechanically unloads the body and causes physiological effects at all levels of biological organization

Organism | Systems | Tissues | Cells | Molecules



Nausea, Vestibular Effects

Cardiovascular Deconditioning, Calcium Imbalance, Reduced Immunity

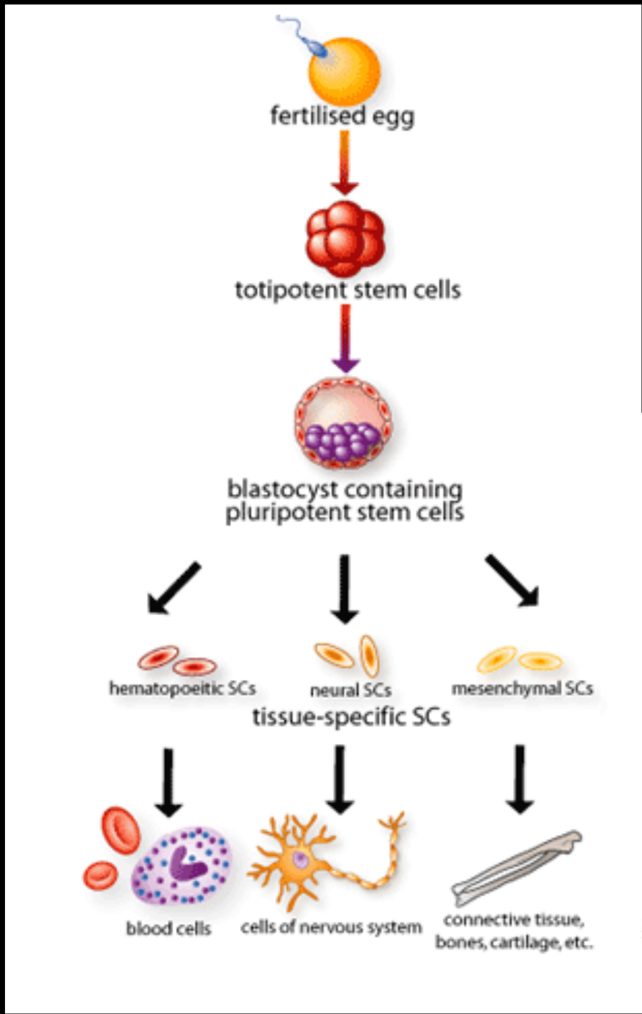
Bone and Muscle Tissue Loss, Anemia, Poor Healing

Proliferation, Differentiation, Migration

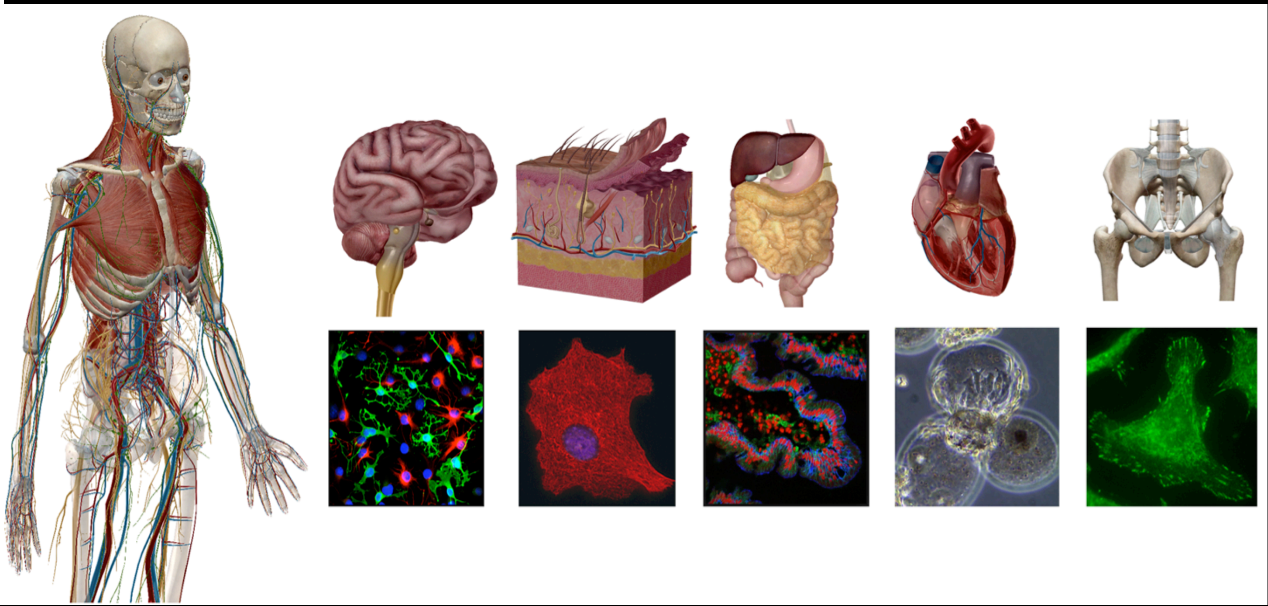
p21/CDKN1a, p53

CAN SOME OF THESE EFFECTS BE EXPLAINED BY MICROGRAVITY EFFECTS ON STEM CELLS?

Stem cell proliferation and differentiation occurs during growth and development resulting in the formation of functional adult tissues



A portion of these stem cells remain partially differentiated (multipotent) in specific tissues during adult life to enable the process of tissue regeneration, repair and maintenance to occur. This process is thought to be dependent on mechanical load



Gravity Tissue Regeneration Hypothesis:

Mechanical unloading in microgravity may inhibit the proliferation and/or differentiation of somatic/adult stem cell required for normal tissue repair and regeneration

Normal tissue health requires constant tissue regeneration and repair by tissue-specific somatic stem cells

Mechanical stimulation promotes bone, muscle, and immune tissue repair and regeneration mediated by somatic stem cell proliferation and differentiation

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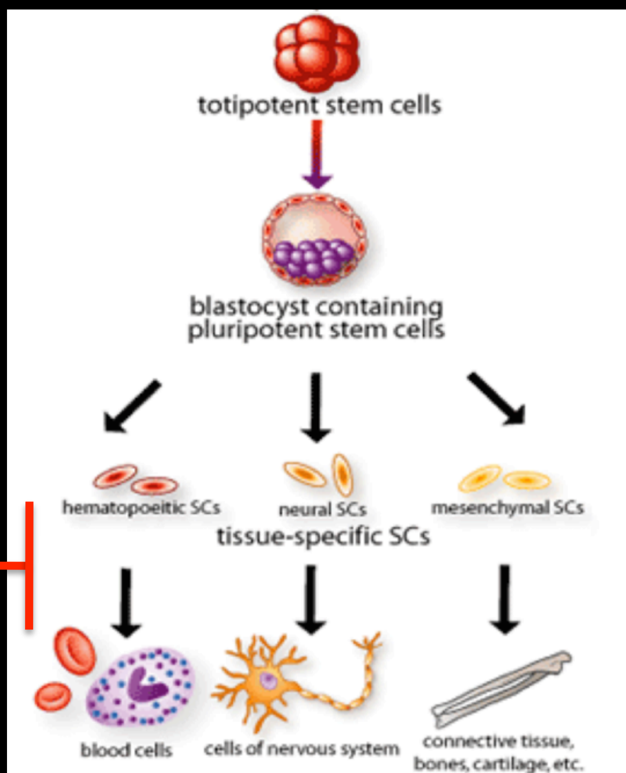
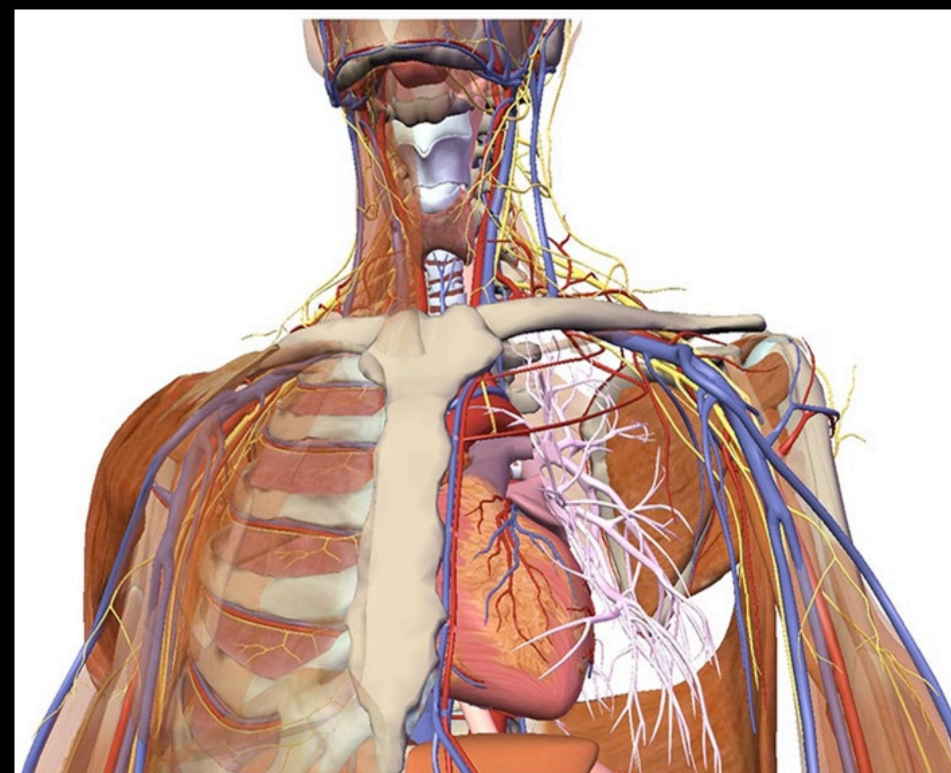
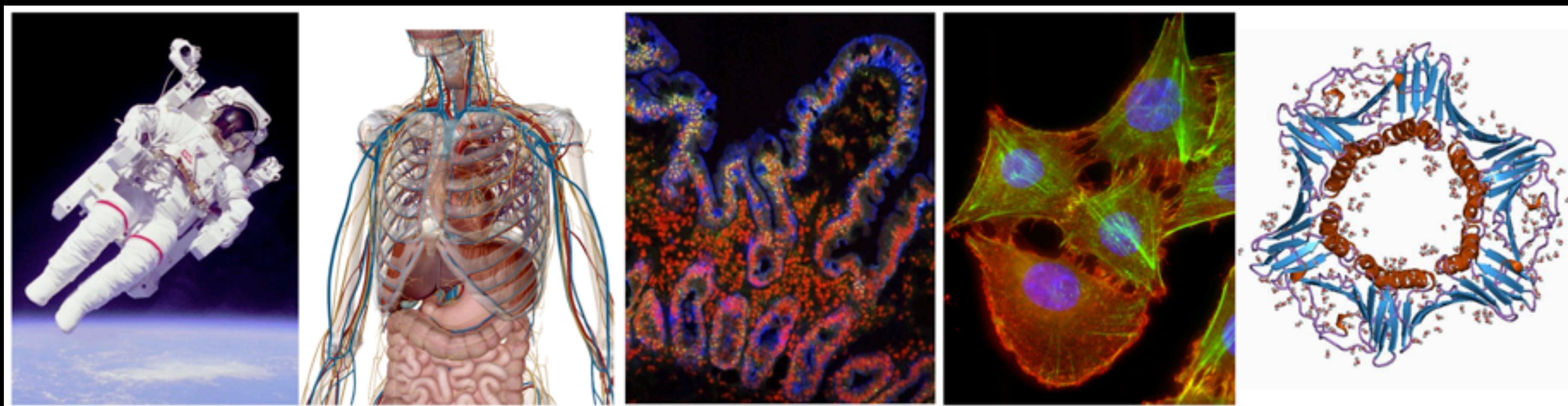




Can some of the tissue, cell and molecular effects of microgravity be linked to stem cell-based tissue regenerative processes?

Organism | Systems | Tissues | Cells | Molecules



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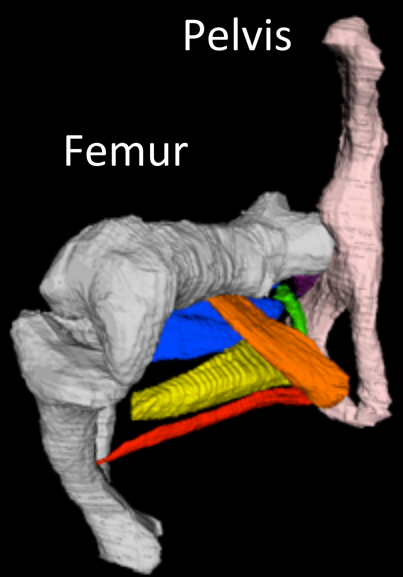
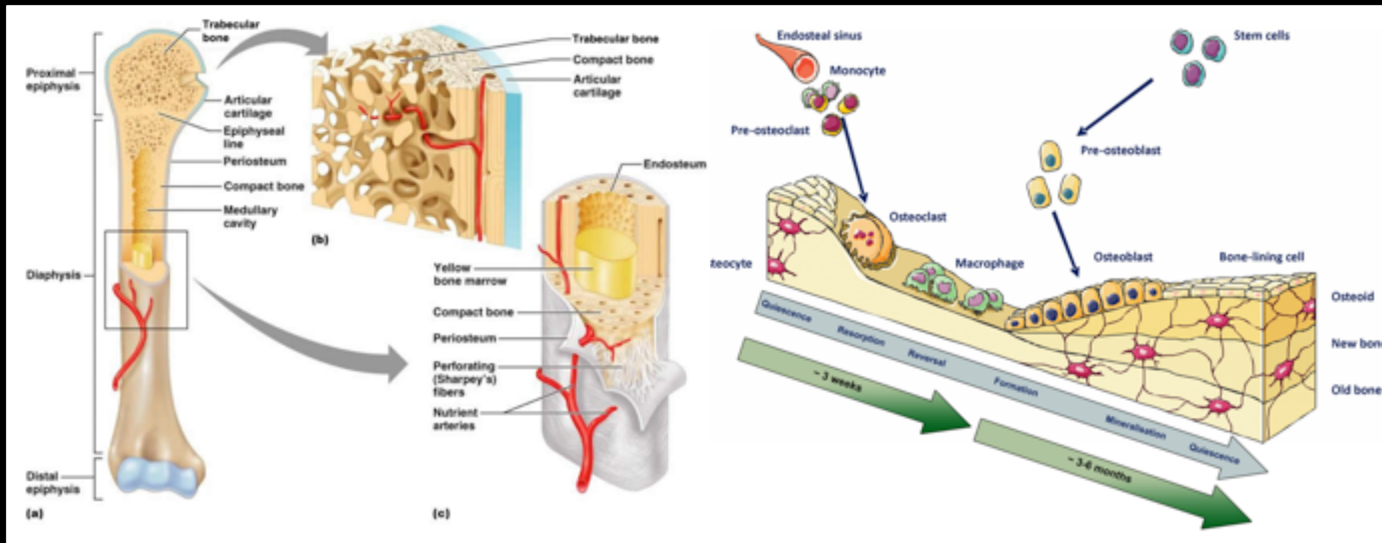
Bone as a model of tissue regeneration

The mouse hindlimb musculoskeletal system is used as an in-vivo model to study tissue degeneration in conditions of mechanical unloading in microgravity, and disuse on earth



Mouse hindlimb – pelvis, femur and tibia



Bone tissue = cortical and trabecular bone + bone marrow

Homeostasis: Osteoblast = Osteoclast
Bone loss: Osteoclast > Osteoblast
Bone gain: Osteoblast > Osteoclast

Bone loss is mediated by active osteoclast-mediated degeneration as well as osteoprogenitor regenerative deficits

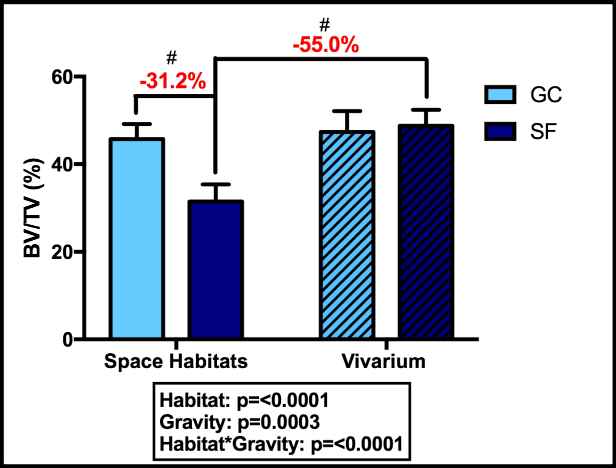
BionM1 and RR1 provided unique opportunities to study long-duration spaceflight

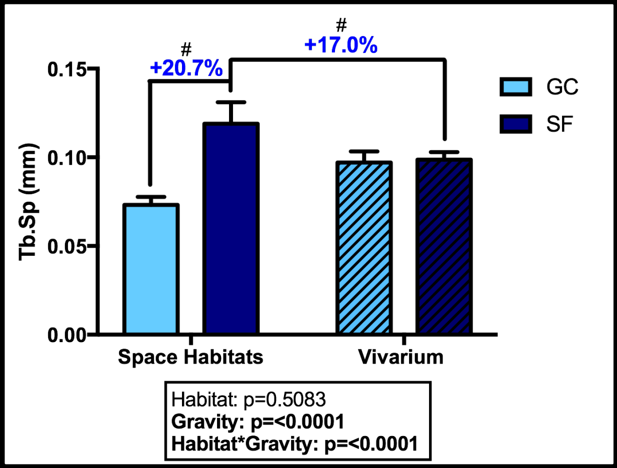
We hypothesized that the bone loss and inhibition of stem cell based tissue regeneration observed during short-0duration shuttle missions would continue during long-duration spaceflight and result in significant alterations in tissue structure

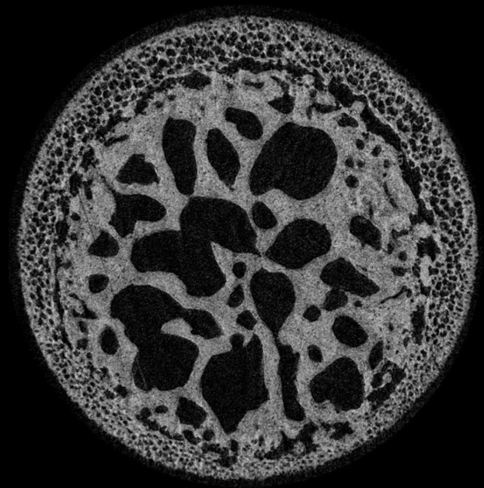
BionM1 vs. RR1

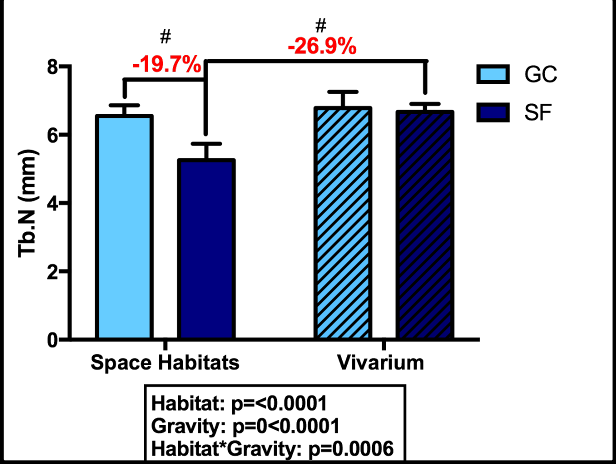
	БИОН	Rodent Research 1
Age	16 weeks old	16 weeks old
Gender	Male	Female
Flight period	30 days	37 days
Ground control	Asynchronous (3 months)	Asynchronous (3 days)
Live animal return	Yes (12 h delay)	No
Dissection	Biospecimen Sharing Program	Frozen Carcass
Tissues collected	Pelvis, proximal femur, bone marrow cells	Pelvis, femur, tibia
Analysis Methods	MicroCT, histology, gene expression analysis, stem cell proliferation and differentiation, motility/migration assays	MicroCT, histology, mecahnical strength testing, gene expression analysis

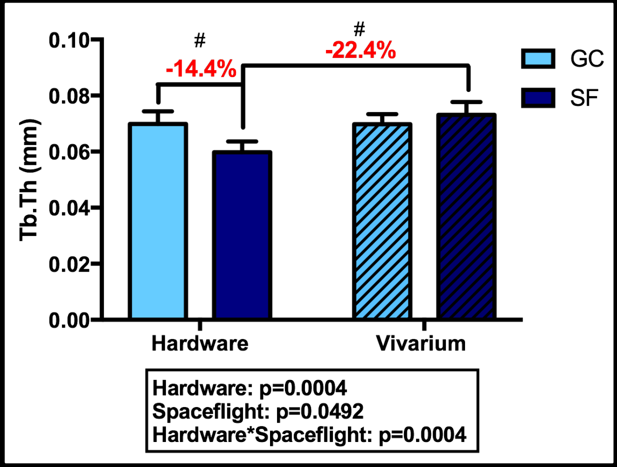
Male mice exhibit significant bone loss during 30 days of spaceflight

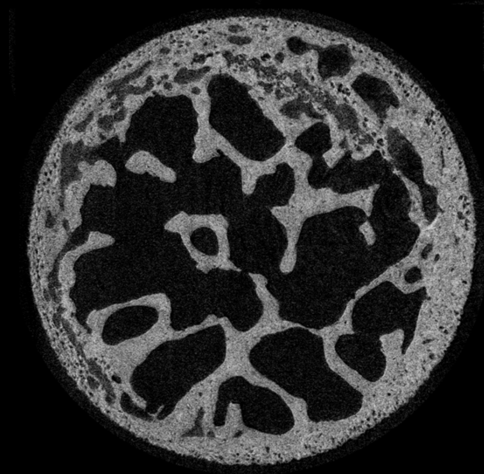




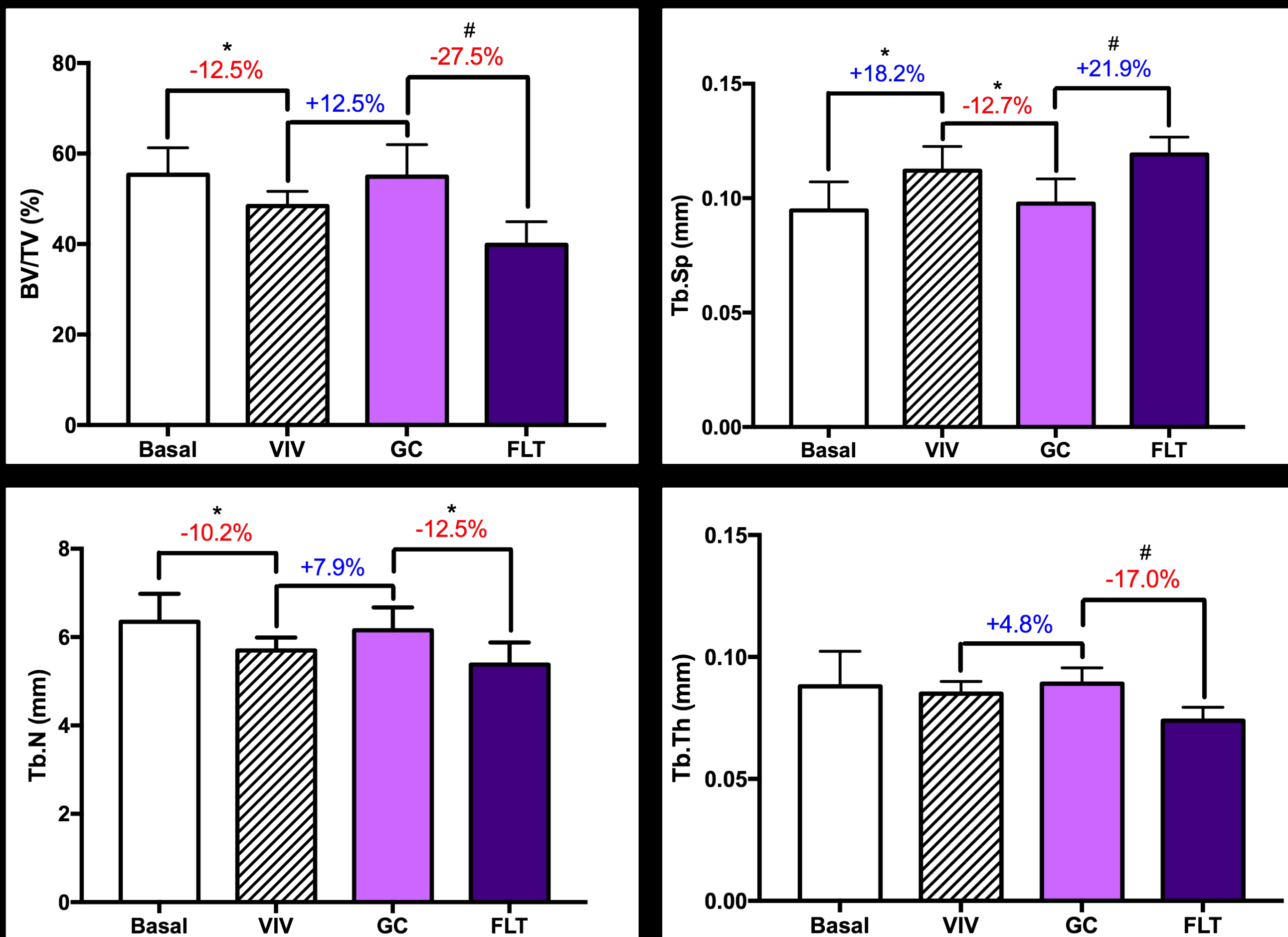


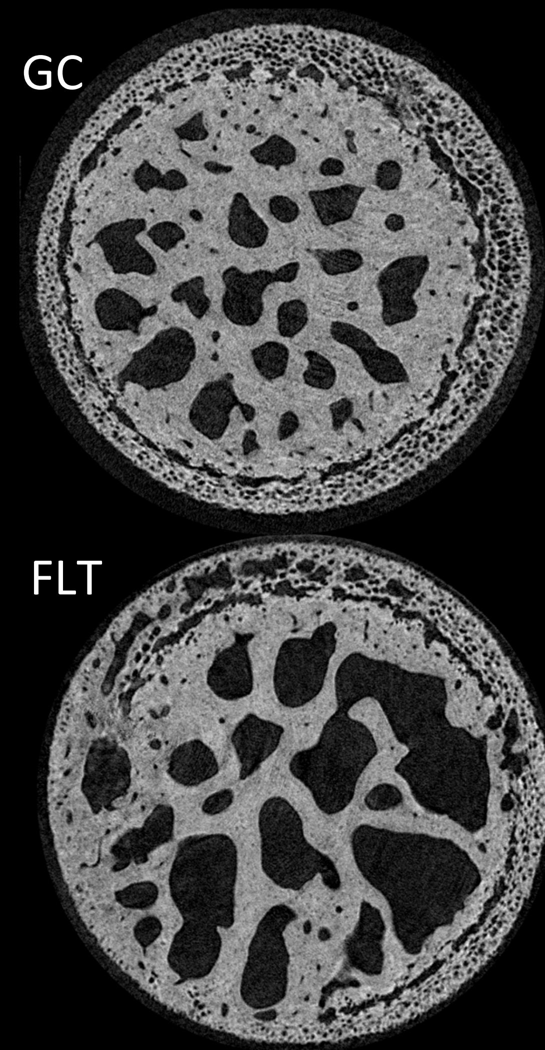




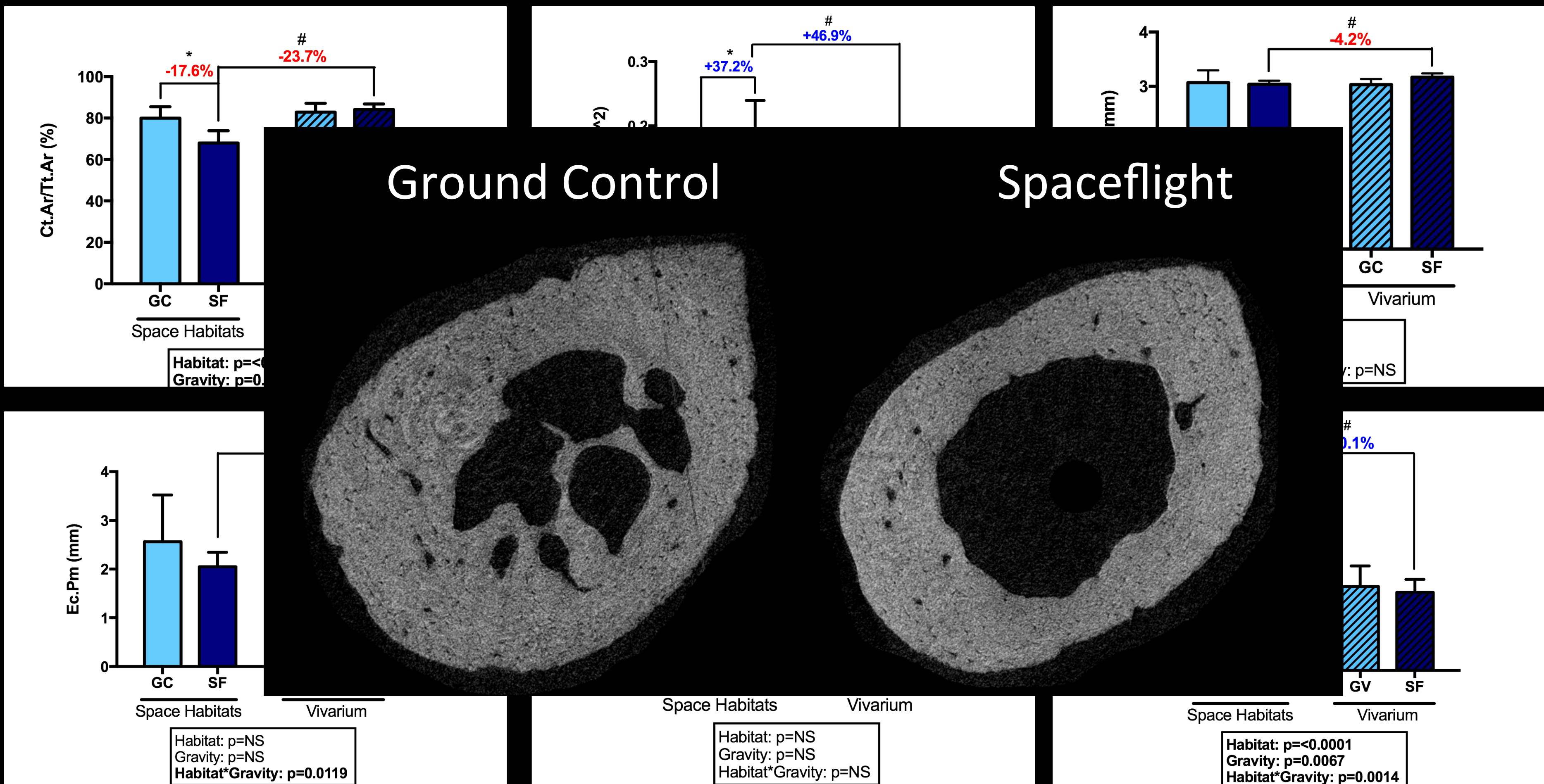


Female mice also exhibit significant bone loss during spaceflight, albeit to a lesser extent

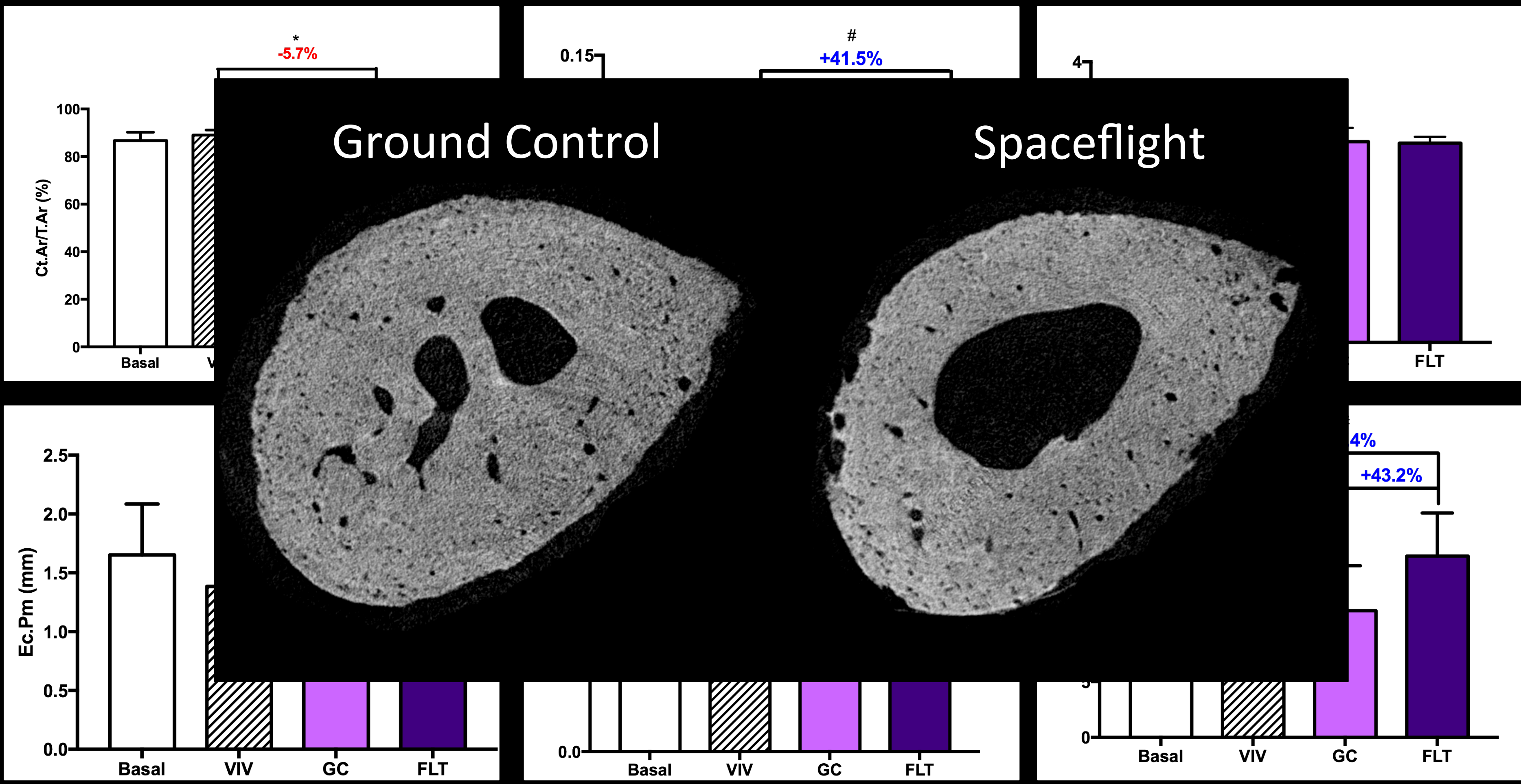




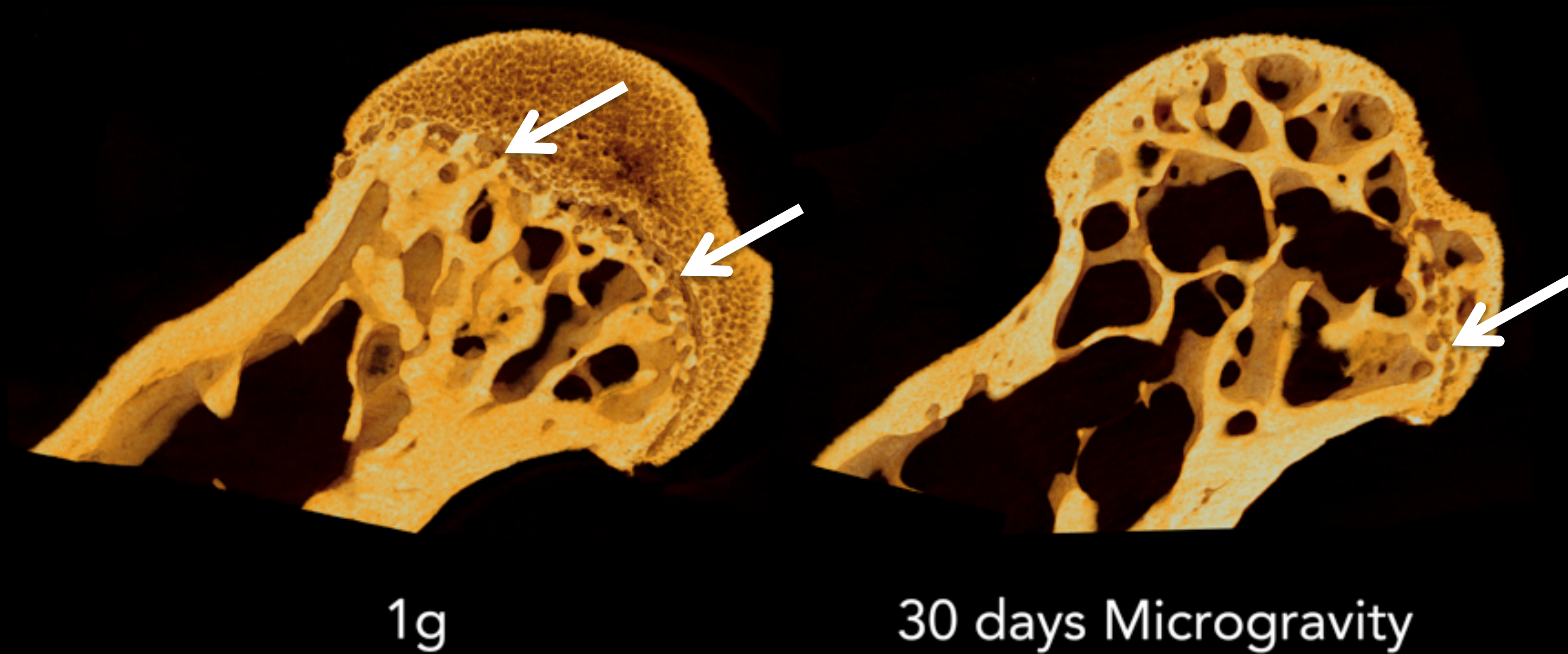
Cortical bone loss in the femoral neck of male mice



Cortical bone loss in the femoral neck of female mice



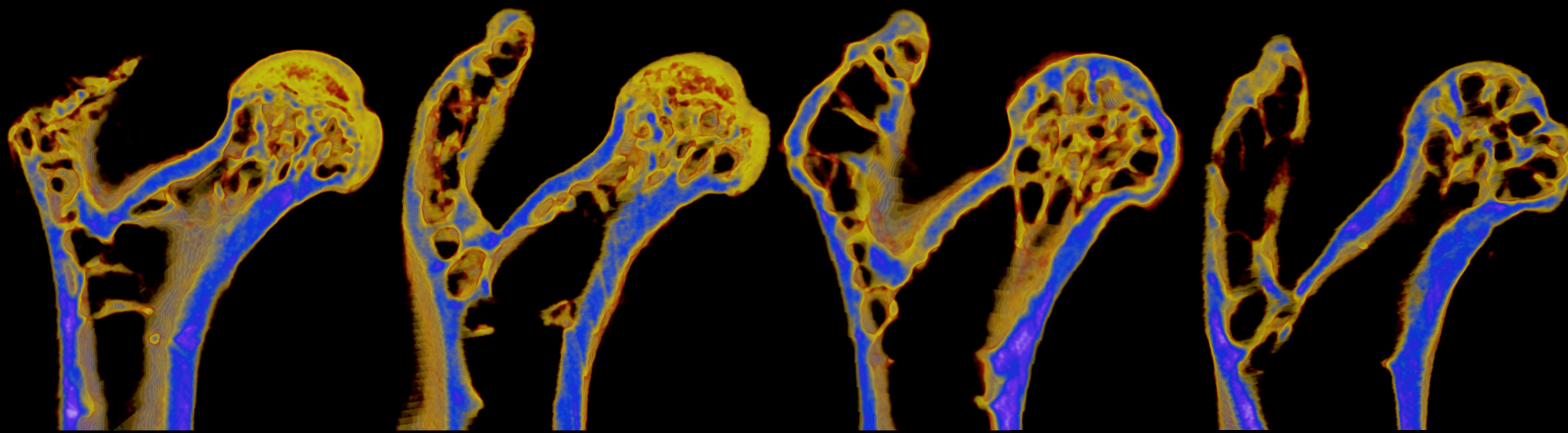
In addition to bone loss, BionM1 mice exhibit significant alterations in the tissue structure of the femoral head



600 nm resolution microcomputed tomography images of the femoral head from BionM1

Spaceflight phenotype resembles that of aging but how accelerated is this?

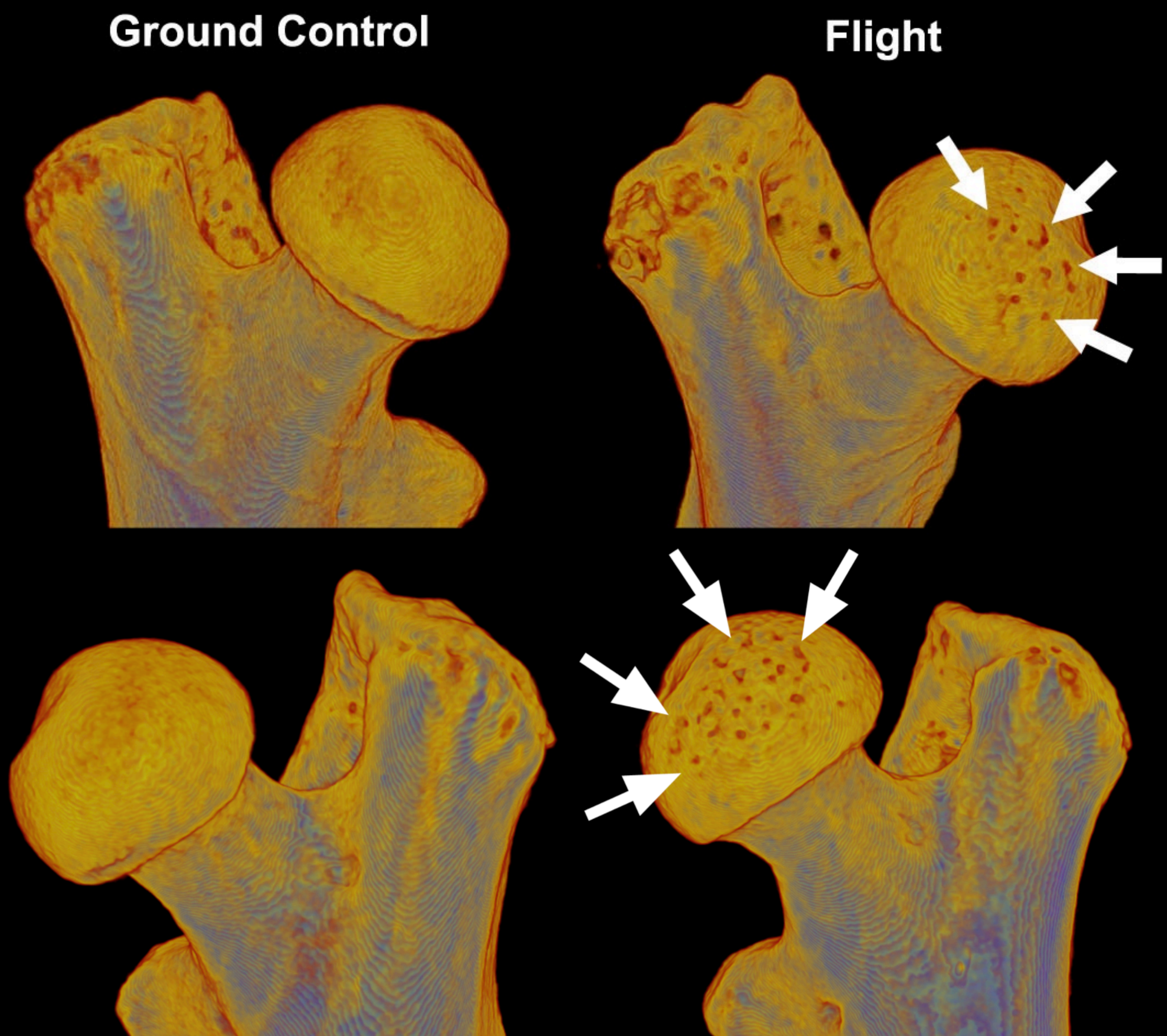
Bone loss in male mice during normal ageing



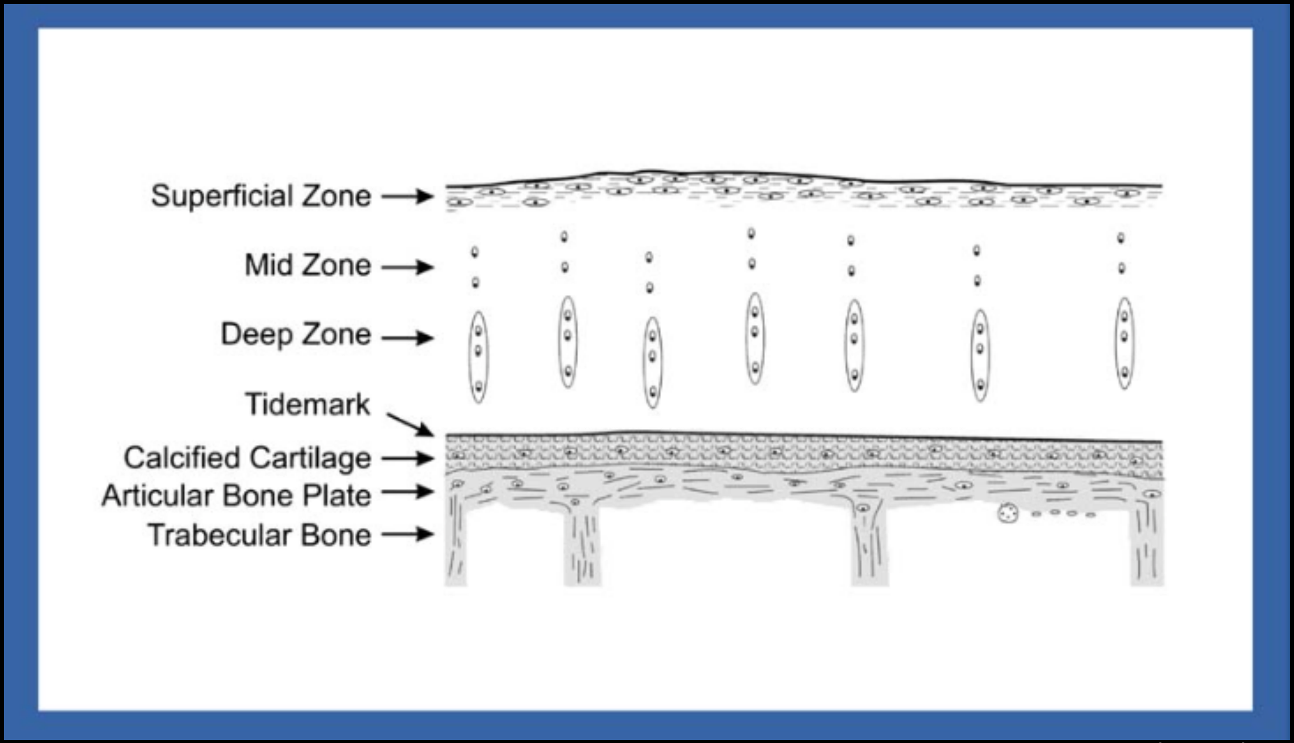
15 weeks | 19 weeks | 40 weeks | BionM1 19 weeks

30 days of spaceflight causes more drastic bone loss than what normally occurs during 5 months of aging with normal ambulation

In addition to accelerated aging, fissures on the surface of the femoral head resemble that which occurs during the development of osteoarthritis

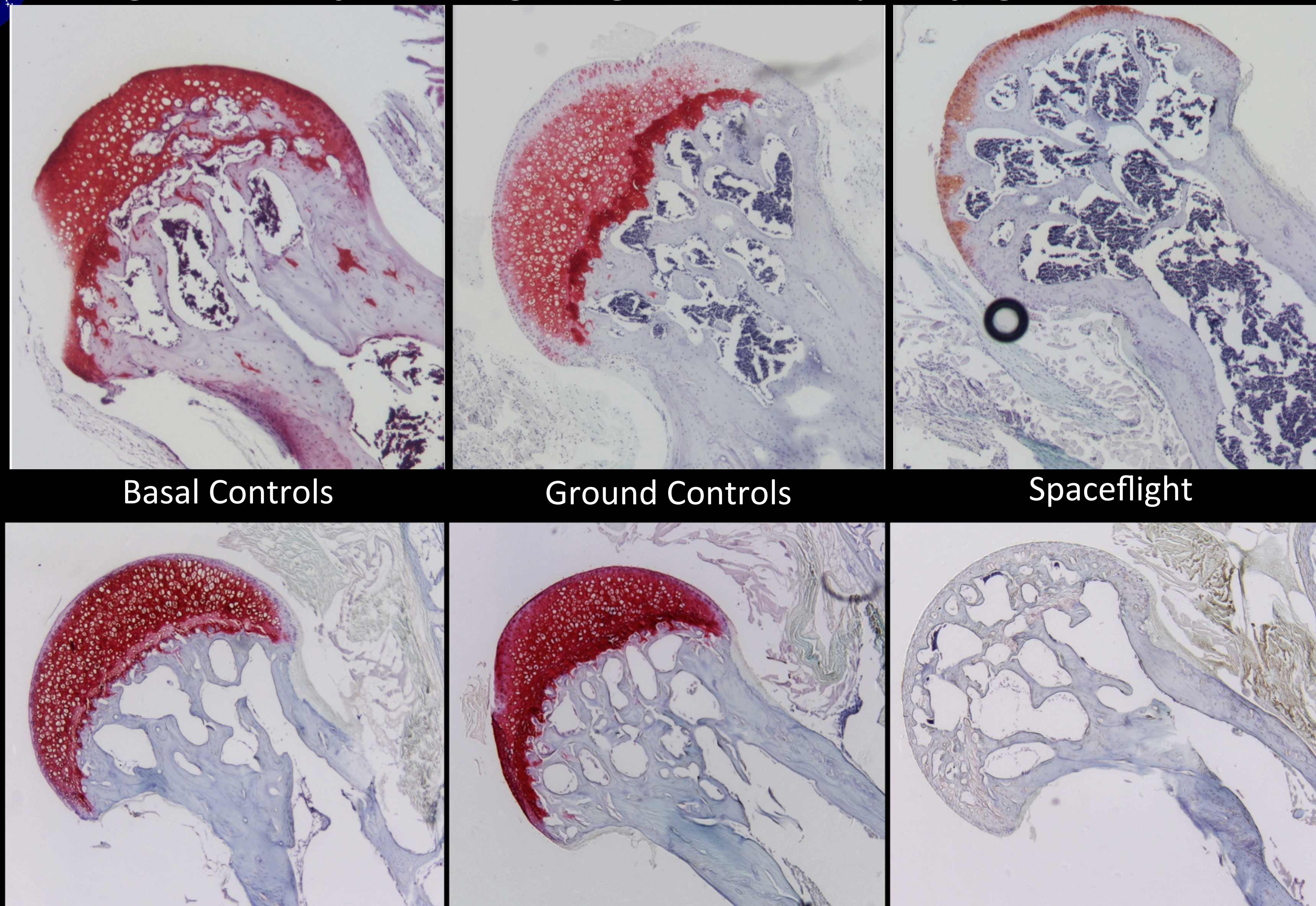


Osteo-chondro matrix – Saffranin-O staining



Pritzker et al. (2006) OsteoArthritis and Cartilage, 14, p. 13-29

Saffranin-O staining shows the extent of cartilage degradation following long-duration spaceflight

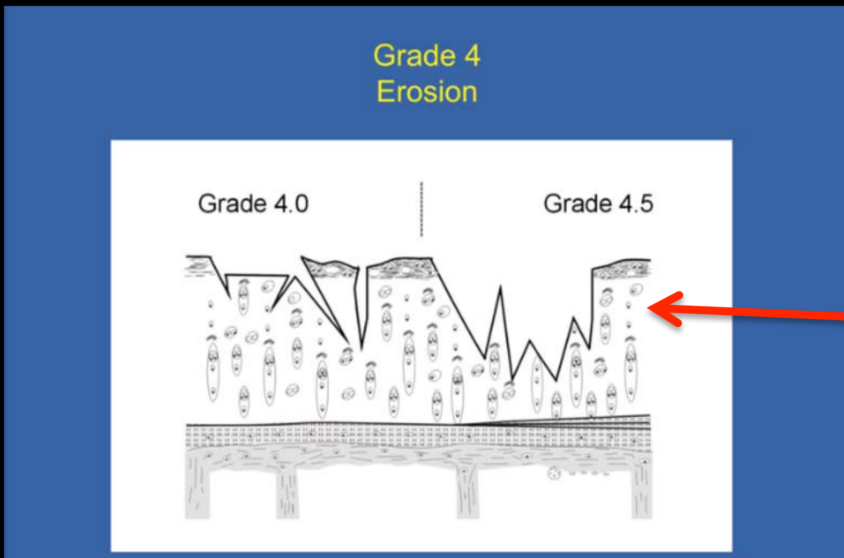


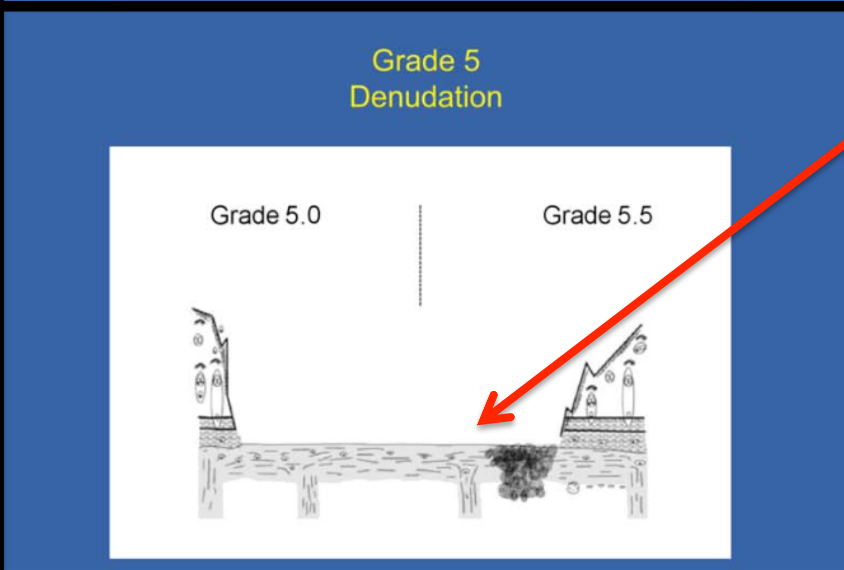
BionM1

Basal Controls | Ground Controls | Spaceflight

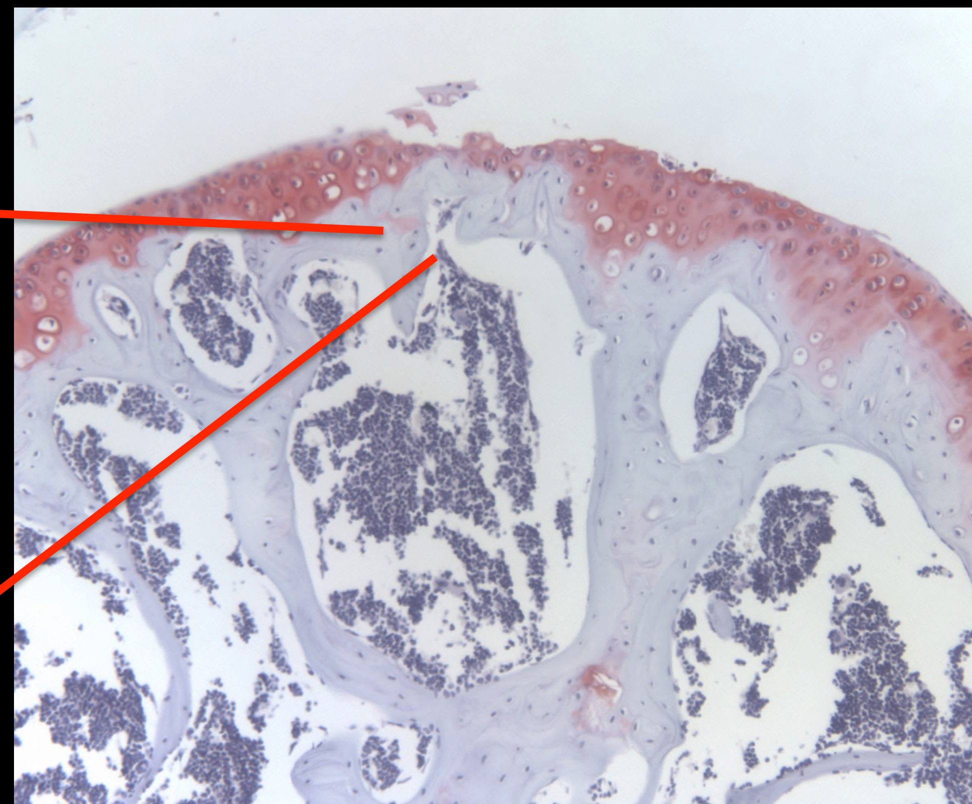
RR1

Flight samples appear to exhibit similar characteristics to stage4/5 osteoarthritis





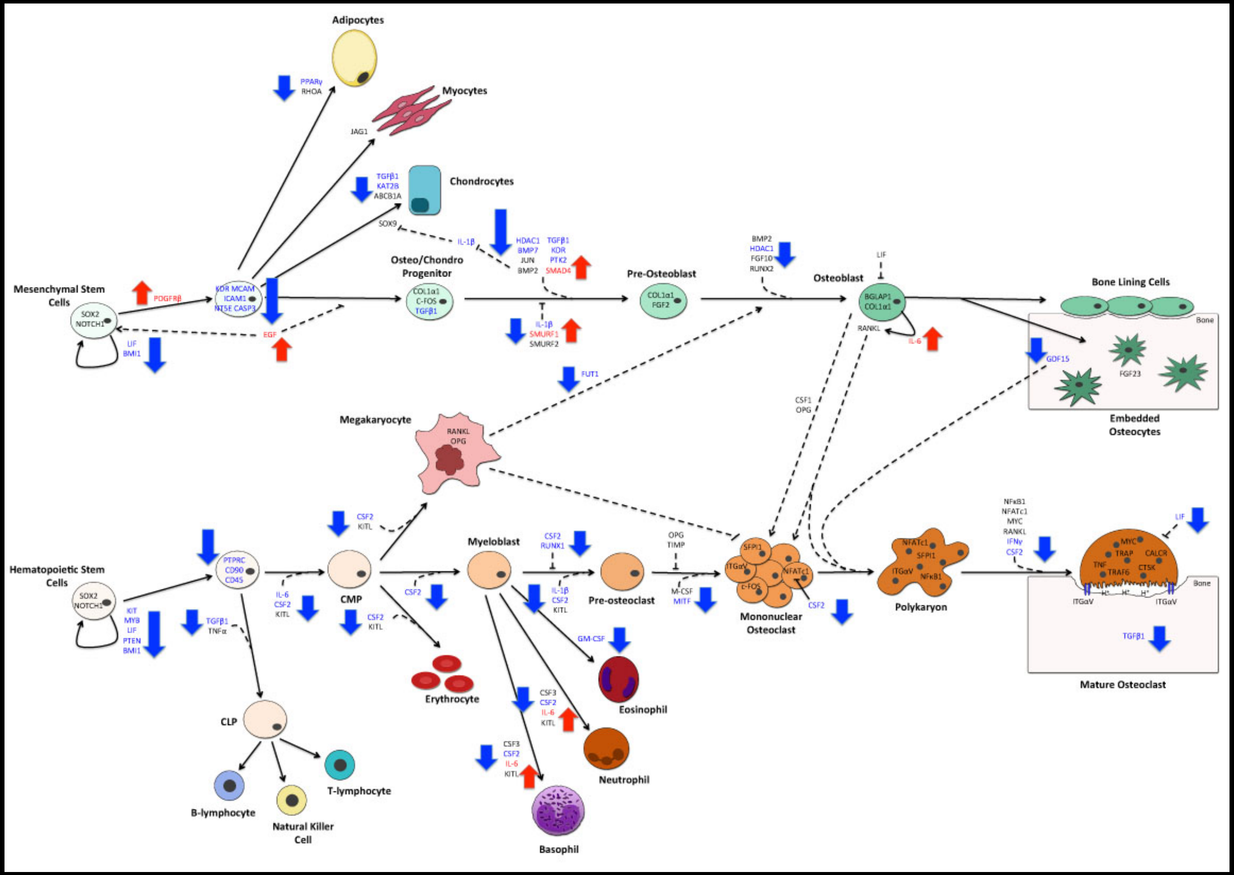
BionM1 and RR1 spaceflight samples appear similar to Stage 4/5 osteoarthritis



RR mice also exhibit similar phenotype in the distal femur – see **Meg Cheng-Campbell's poster #248**

OA and spaceflight

Stem cell senescence and inhibition of cell regeneration is thought to be a major contributor of osteoarthritis. Mechanical loading is required for maintenance of stem cell health and tissue regeneration and we have shown that spaceflight results in an inhibition of stem cell based tissue regeneration.



Could mechanical unloading in spaceflight result in early onset OA? Could this help us to elucidate the mechanisms of OA induction on Earth and develop countermeasures?

Conclusions

Spaceflight causes an alteration in tissue regeneration - increased stem cell pluripotency and inhibition of differentiation

Under conditions of reduced mechanical load e.g. physical inactivity, mechanical disuse conditions and spaceflight, differentiation of somatic stem cells may be inhibited, possibly resulting in serious regenerative heath effects

Mice exposed to spaceflight in the BionM1 hardware, exhibit significant bone loss and furthermore exhibit signs of accelerated aging and early onset osteoarthritis

Mice exposed to spaceflight in the Rodent Research hardware also exhibit bone loss - but not to the same extent as BionM1

Although there were differences in these experiments (gender, orbit etc.), it is possible that the mechanical stimulation gained from running on the 3D grid during RR1 partially mitigates the accelerated aging and early onset osteoarthritis phenotype seen in the BionM1 mice

Mechanical unloading during spaceflight could provide critical insight into the mechanisms of OA and potential treatments

Acknowledgements

Dr. Eduardo Almeida
Dr. Ruth Globus
Dr. Brendan Burns
NASA ARC Bone and Signaling Lab

Funding – NASA grants:
NNH08ZTT003N
NNH08ZTT003
NNH14ZTT001N
NJ13ZSA002N-FLAGSHIP