Cellular Senescence: A Bone Fountain of Youth.

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Bench to Bedside (and back)

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Orthopaedic Trauma Institute
UCSF + SAN FRANCISCO GENERAL HOSPITAL

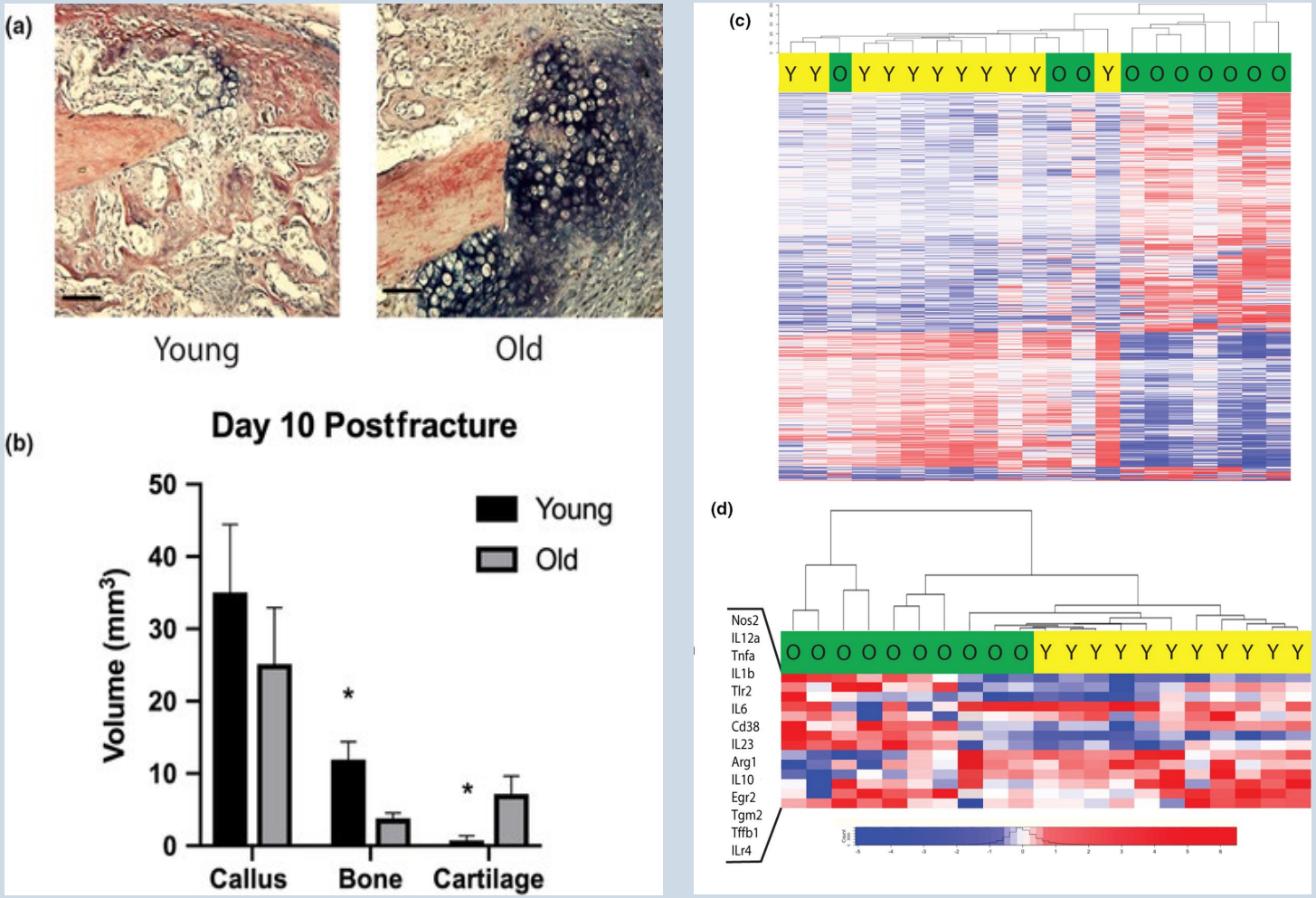
Disclosures

- Royalties Iota Biosiciences: US 041263 **Implants using ultrasonic backscatter for sensing electrical impedance of tissue.** Michel M Maharbiz, Jose M Carmena, Dong Jin Sea, Monica C Lin, Meir Marmor, Safa Herfat, Chelsea S Bahney. Filed 07/07/2017

- Associate Editor Journal of Tissue Engineering and Regenerative Medicine

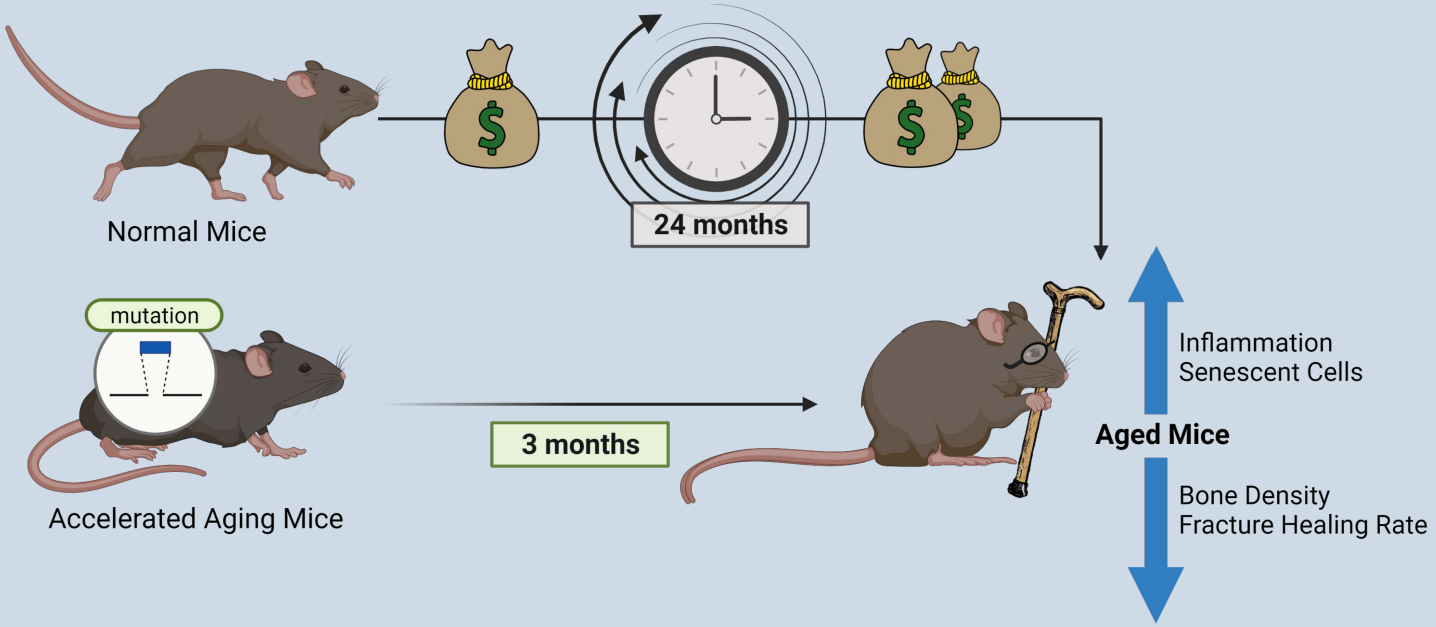
Preclinical Models to Study Mechanism of Action with Aging

Macrophage dysfunction in older mice contributes to delayed fracture healing.

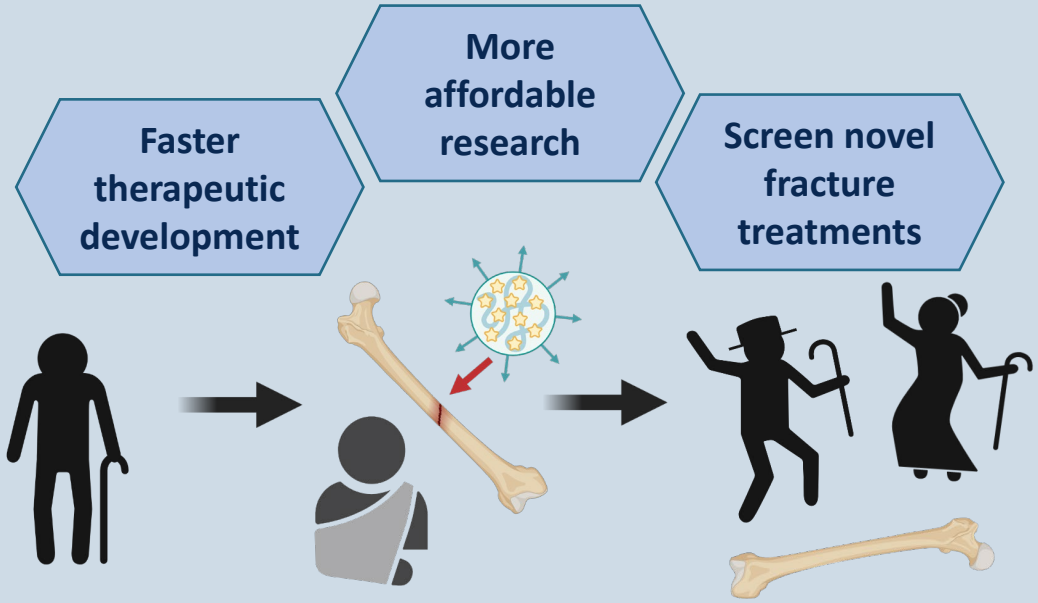


Clark *et al*. Aging Cell 2020.

Need for Better Preclinical Model to Study Aging

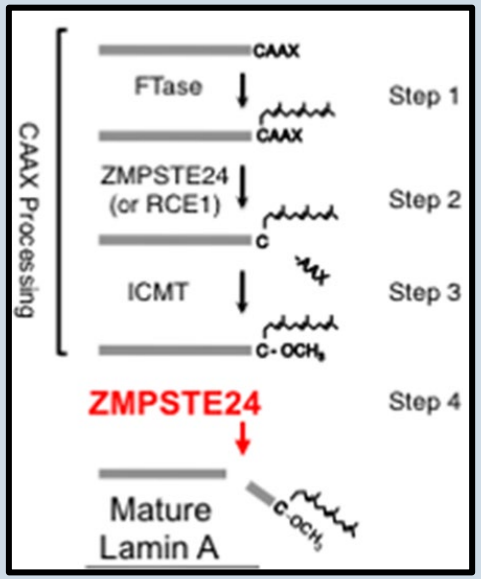


Accelerated Aging Mouse Model

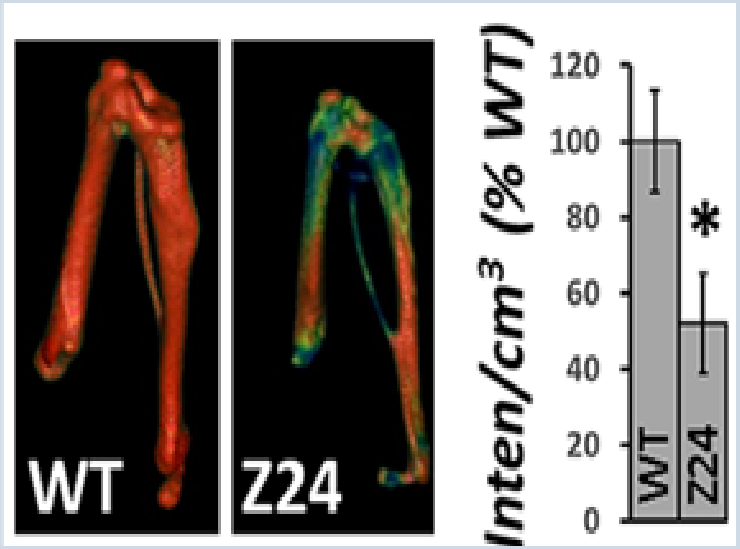


Progeric Mice: Genetic Model of Accelerated Aging in Fracture Research?

Hutchinson-Gilford Progeria Syndrome

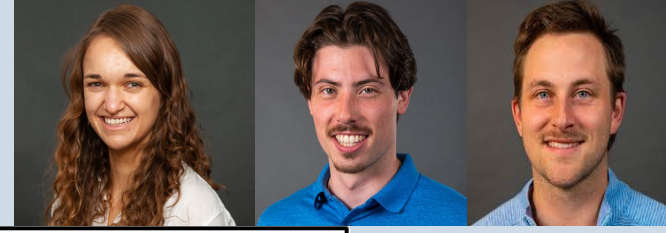


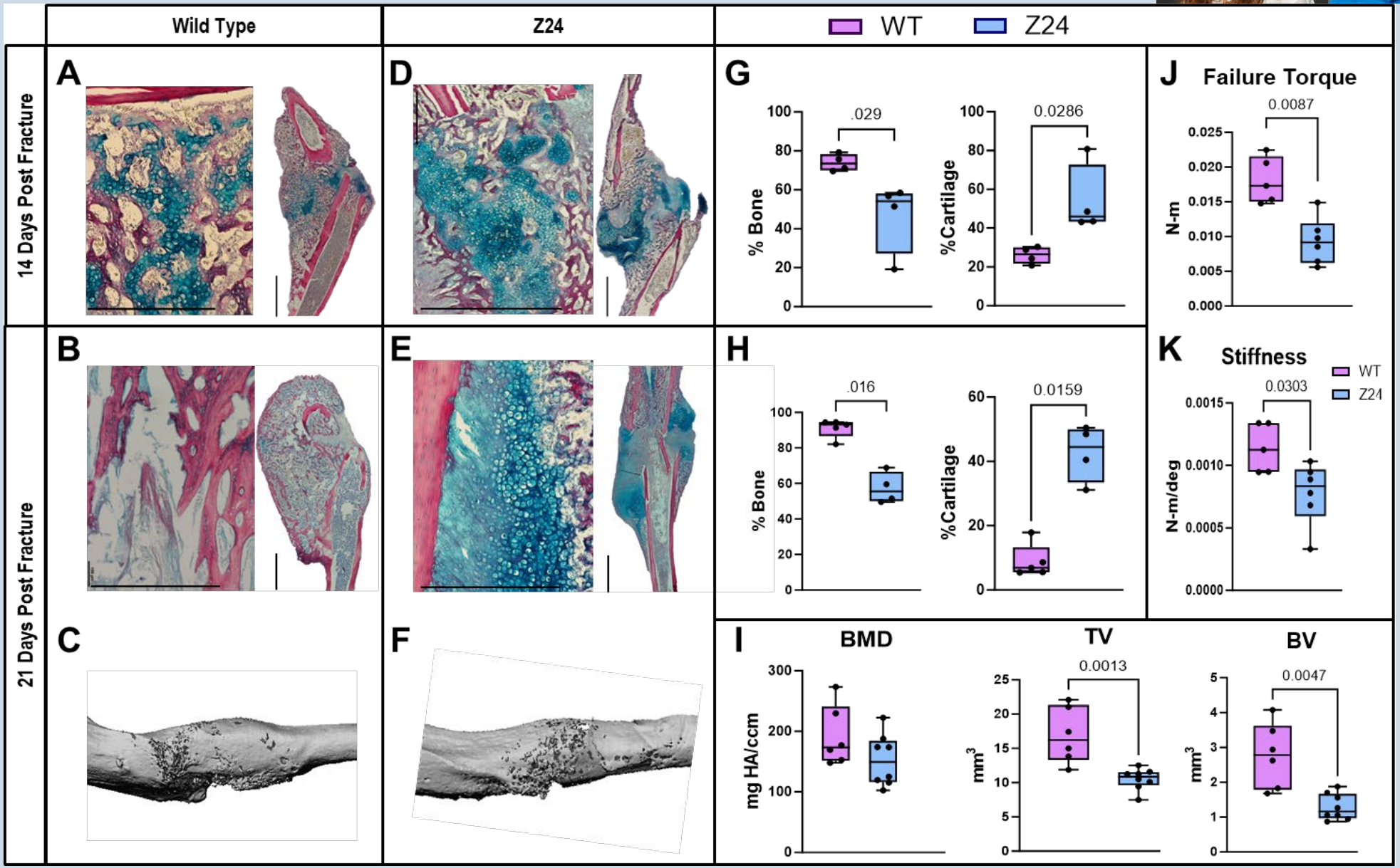
Z24 Progeria Mouse has Skeletal Fragility



Hambright *et al*. Osteoporosis 2022

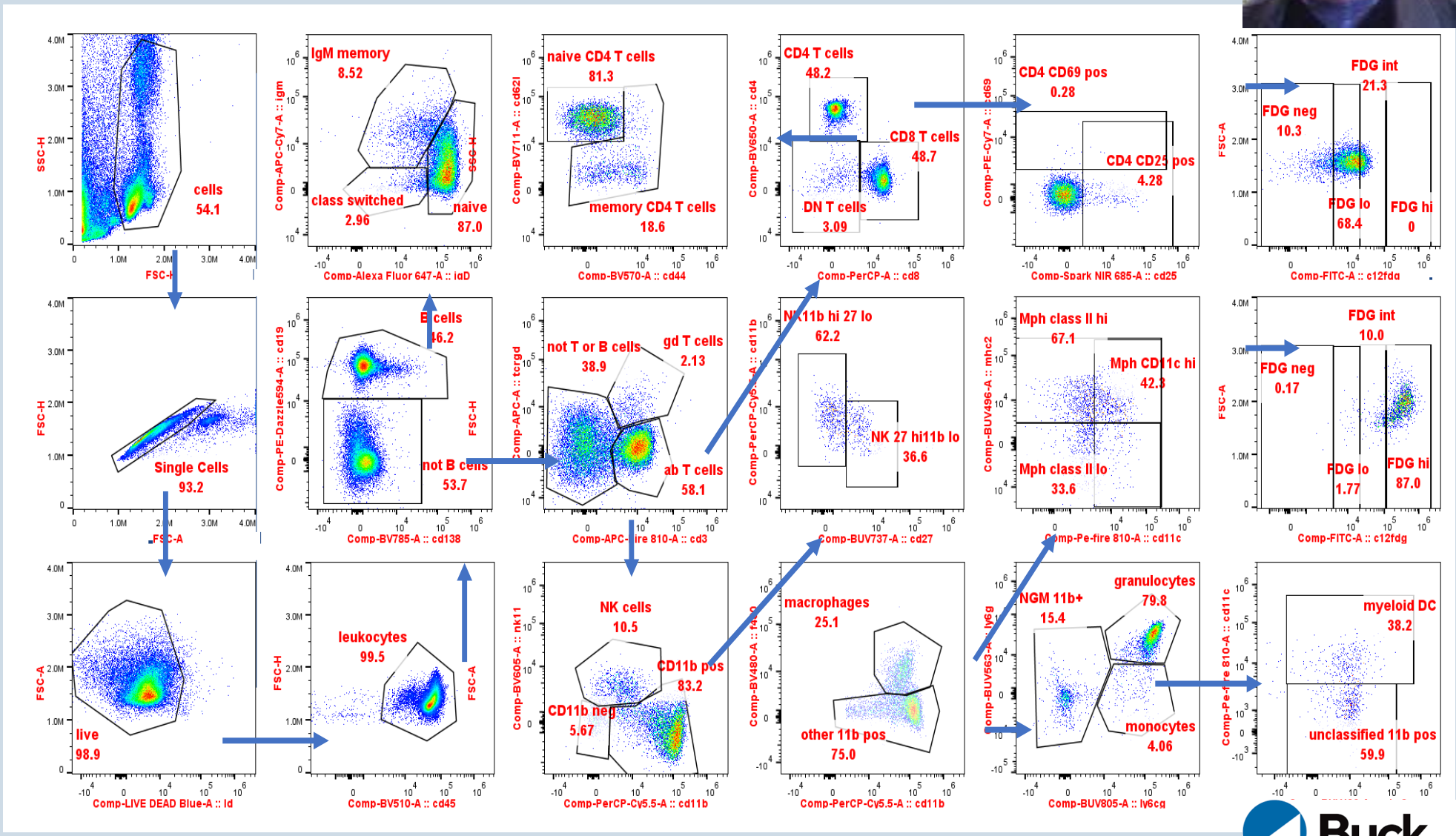
Delayed Fracture Healing in Progeric Mice





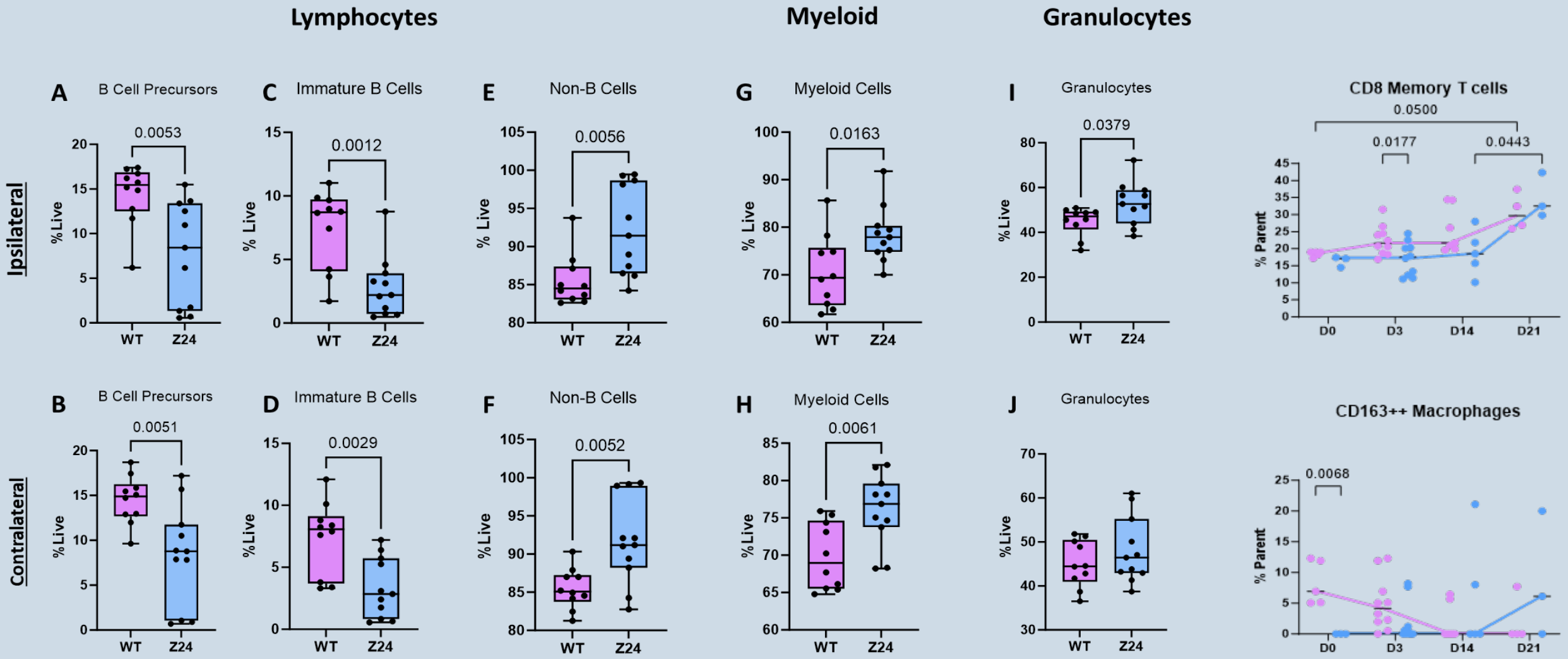
32 Channel Spectral Flow for Immunophenotyping

Target	Fluorochrome	Laser
CD16	BUV395	355
Live/Dead	LIVE/DEAD_Blue	355
Class II	BUV496	355
LY6G	BUV563	355
PD-1	BUV615	355
CD27	BUV737	355
Ly-6C/g	BUV805	355
CD38	Pac Blue	405
F4/80	BV480	405
CD45	BV510	405
CD44	BV570	405
NK1.1	BV605	405
CD4	BV650	405
CD62L	BV711	405
CD138	BV785	405
C12 FDG	FITC	488
CD8	PerCP	488
CD11b	PerCP-Cy5.5	488
CD163	PerCP-eFluor_710	488
CD127	PE	561
CD19	PE-Dazzle_594	561
CD80	PE-Cy5	561
CD206	PE-Fire700	561
CD69	PE-Cy7	561
CD11c	PE-Fire_810	561
tcrgd	APC	640
IgD	Alexa_Fluor_647	640
CD25	Spark_NIR_685	640
CD68	AF700	640
IgM	APC-Cy7	640
CD3	APC-Fire_810	640

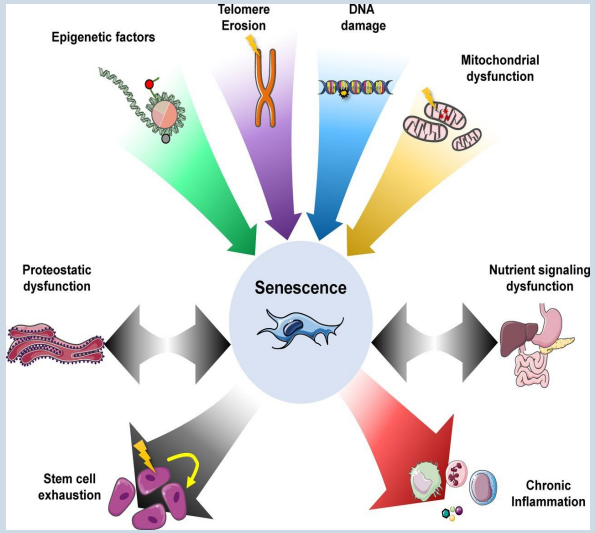


Buck
Live better longer.

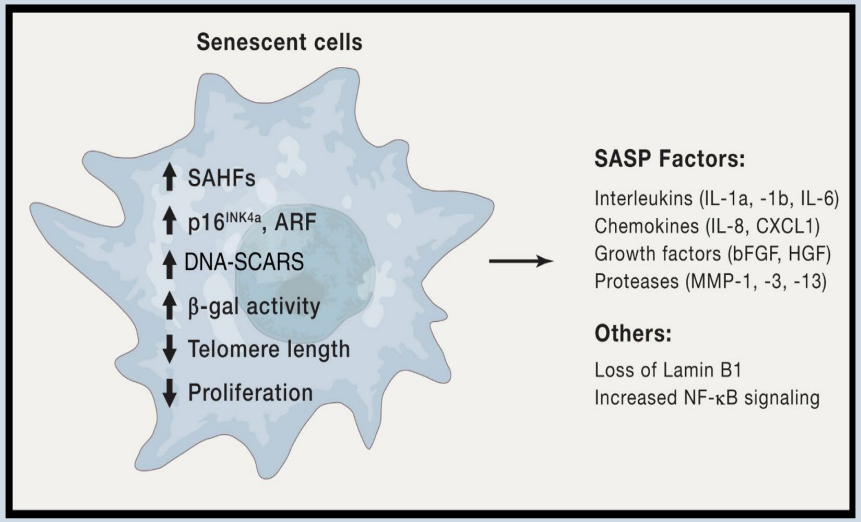
Z24-/- mice have increased myelopoiesis and diminished lymphopoiesis three days following fracture.



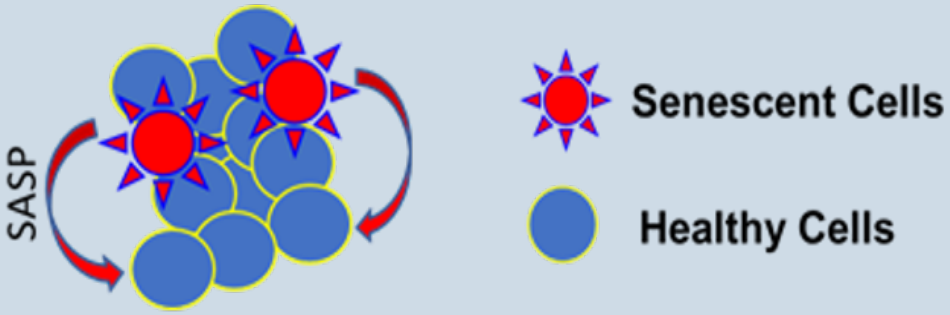
Role for Senescence in Delayed Fracture Healing?



Transformyou *Causes of Aging*



Shenghui He et al. *Senescence in Health and Disease*



Mayo Clinic

Diseases Associated with Senescence:

Diabetes/obesity

Cardiac Dysfunction

Cancer

Cognition/Alzheimer's/ALS/Anxiety

Renal Dysfunction

Osteoporosis

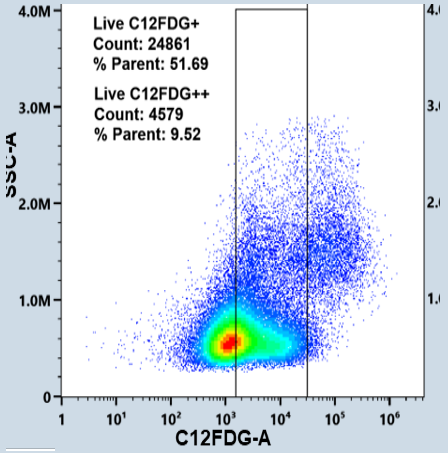
Osteoarthritis

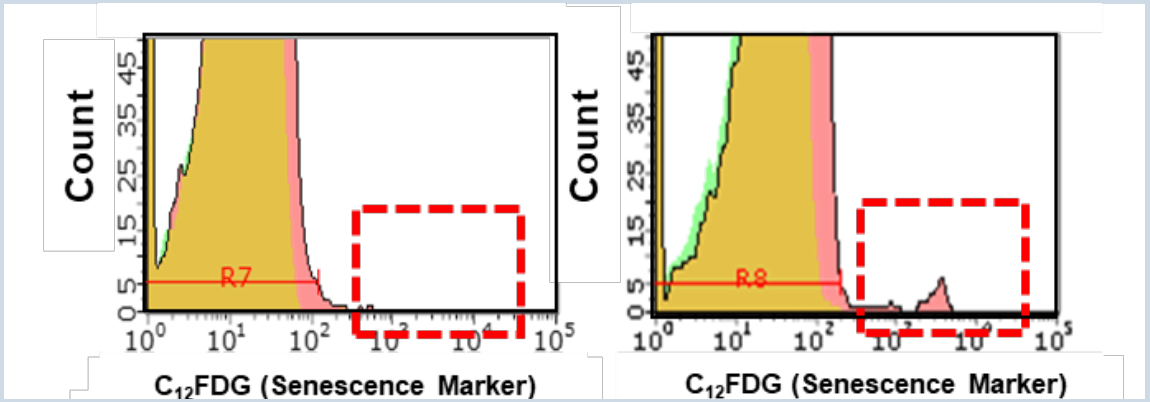
Sarcopenia

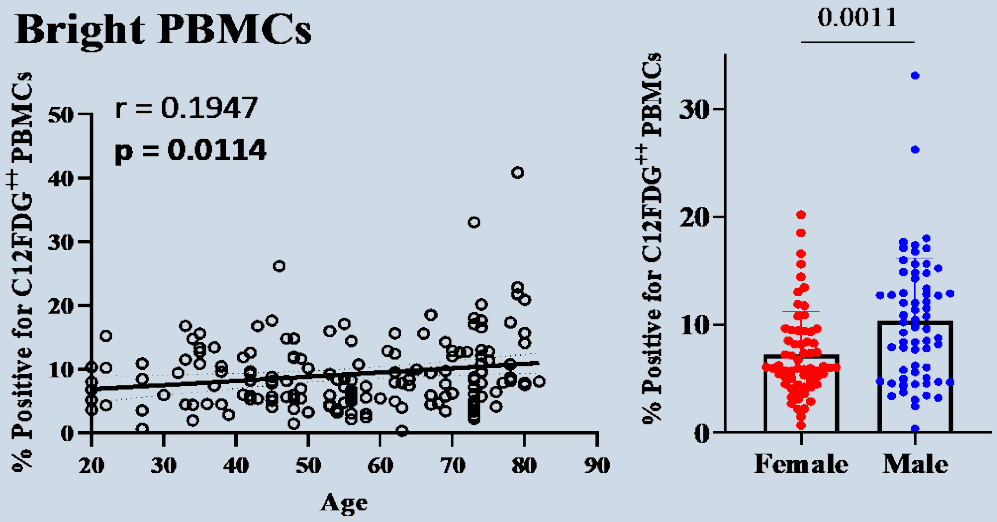
Rheumatoid Arthritis

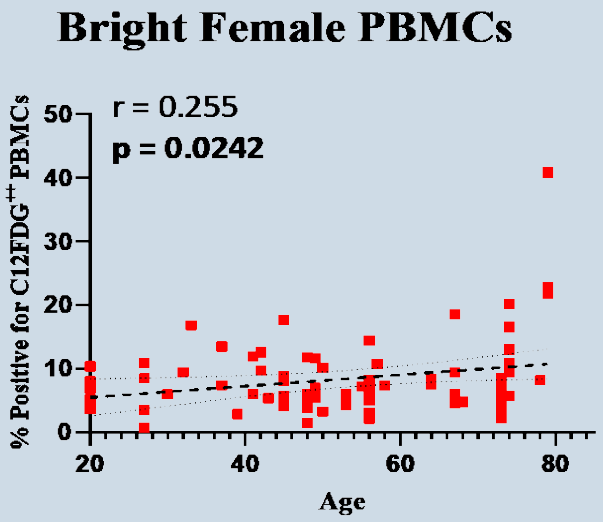
and others..

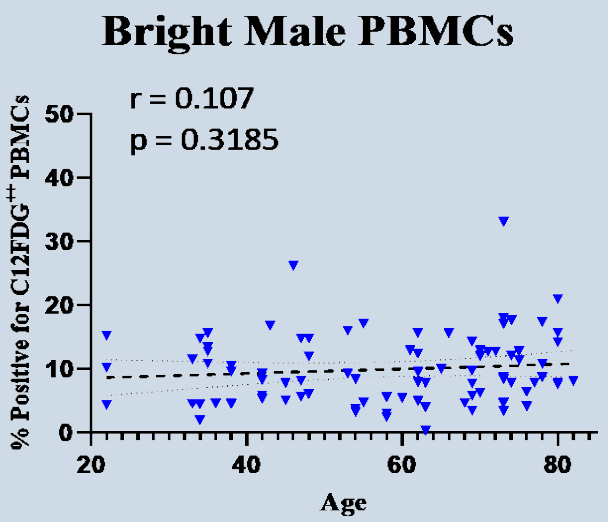
Human Senescence Phenotype Increase with Chronological Age





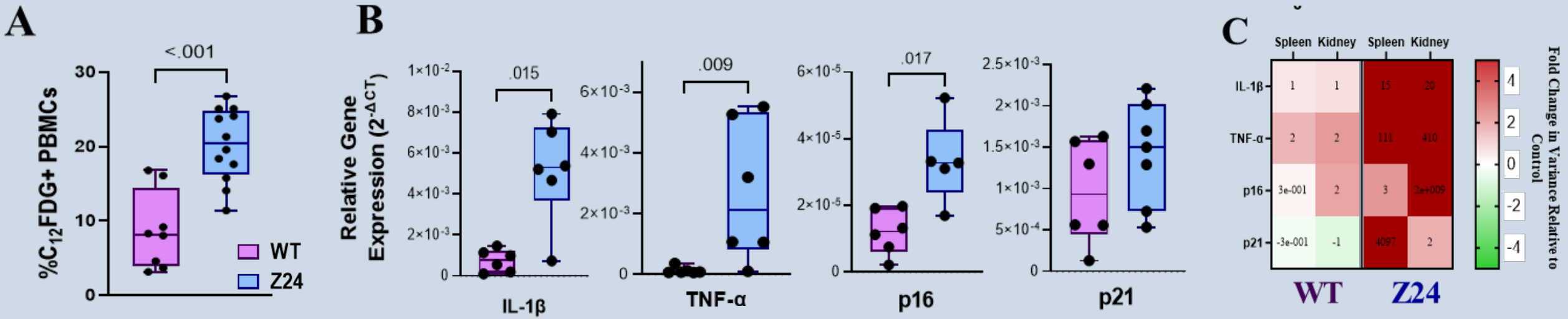




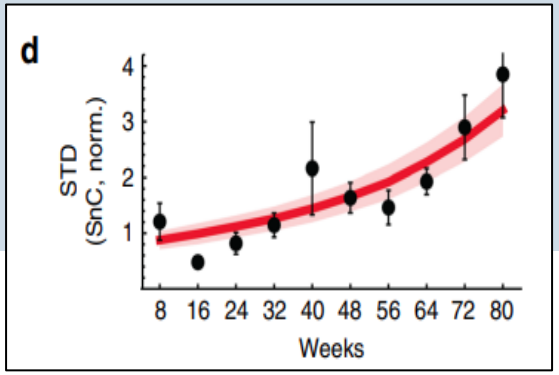


Hambright *et al.* Aging Cell 2024

Progeria Mice Have Increased Senescence and SASP 14-days After Fracture



Karin *et al.* found that the standard deviation of the number of senescent cells increases with age in mouse epithelial cells.



https://www.nature.com/articles/s41467-019-13192-4.pdf

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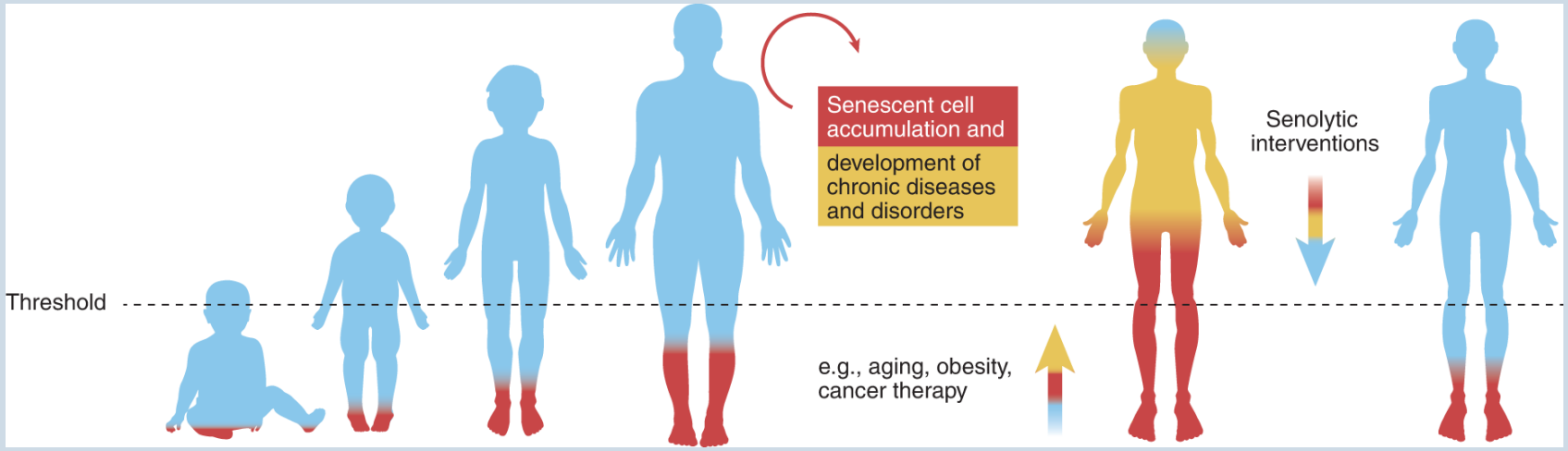
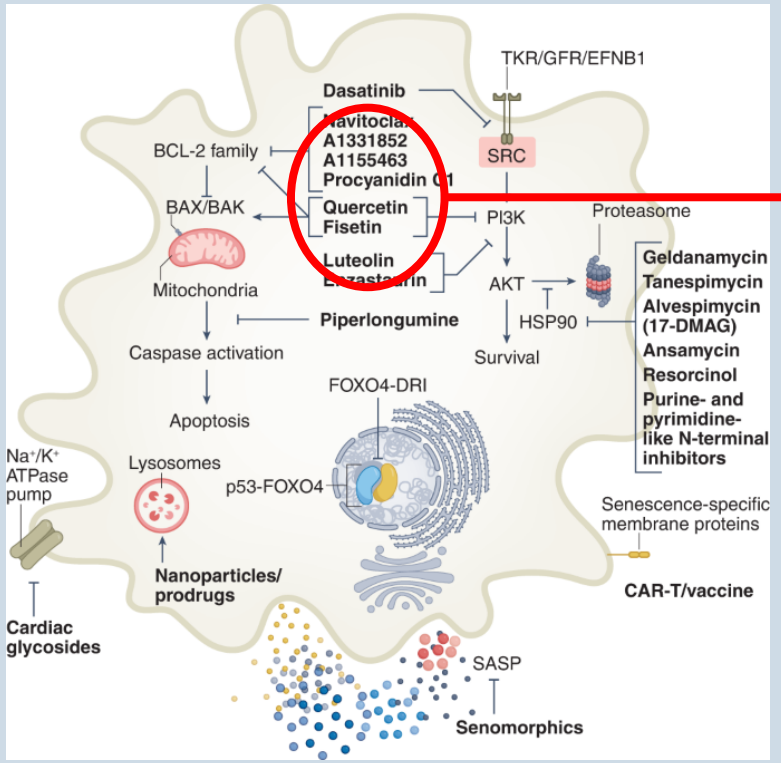
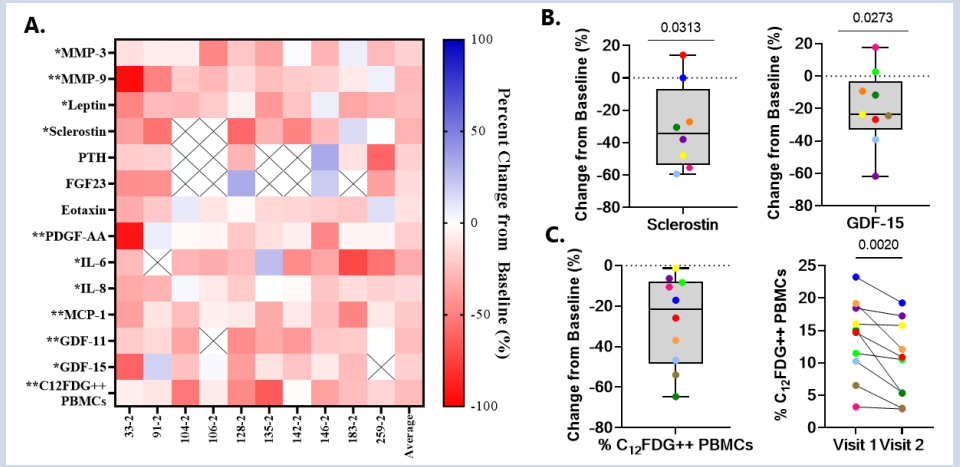
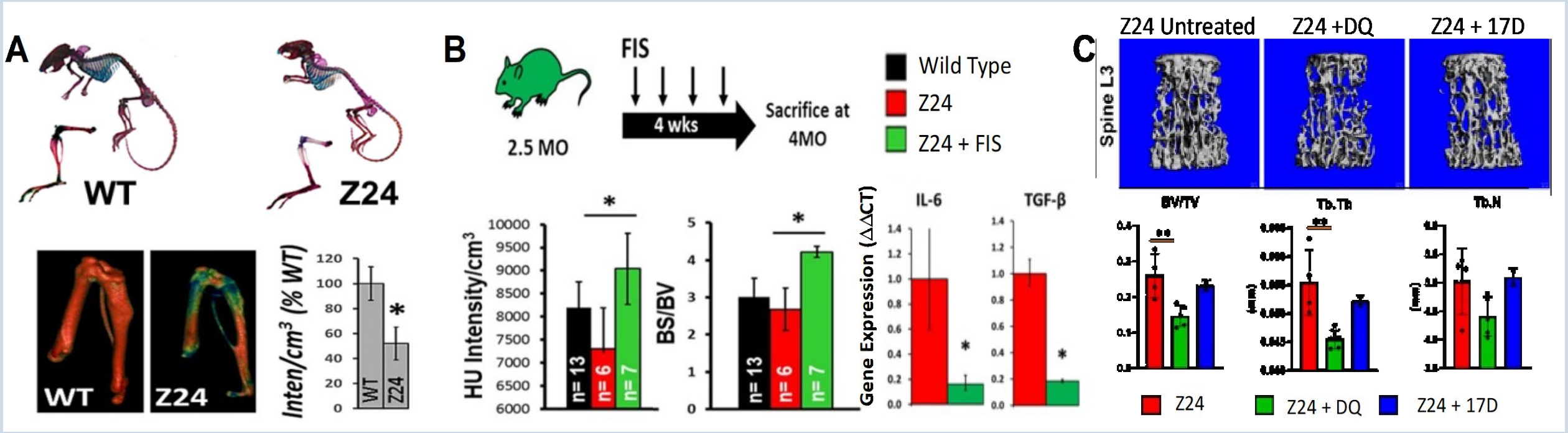
Senolytics: Therapeutics to Reduce Senescence Phenotype





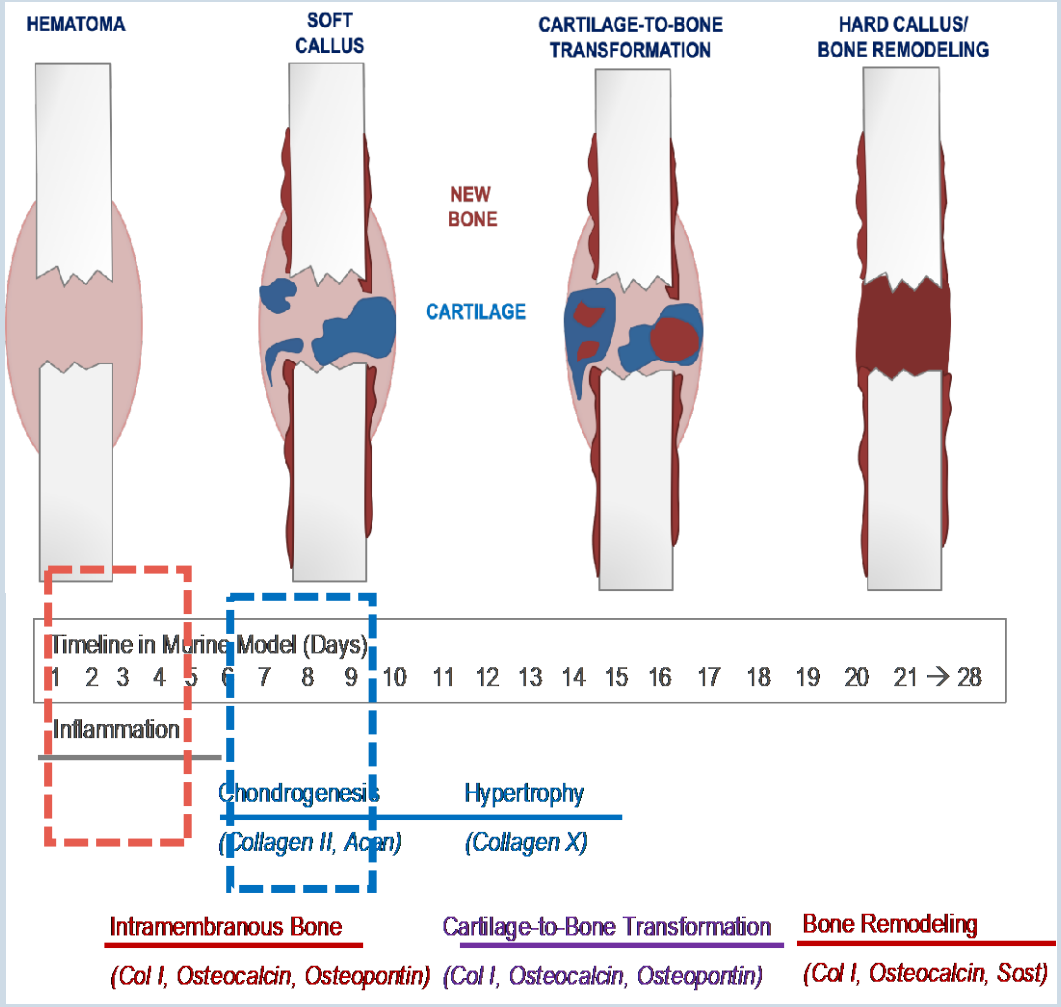


Fisetin Increases BMD Loss and Reduce Systemic Inflammation

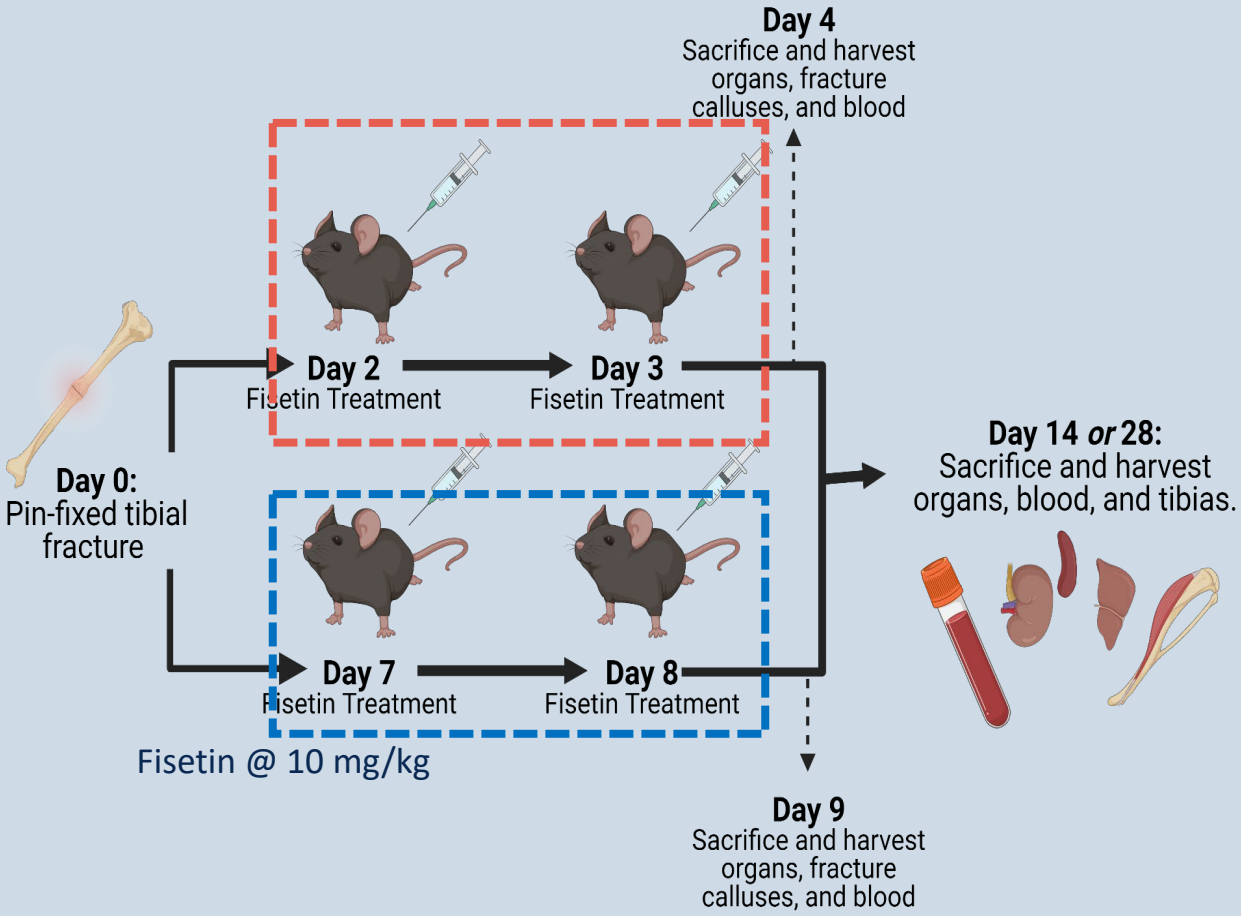


Hambright *et al*. Osteoporosis 2022

Fisetin as a Senotherapeutic for Fracture Repair

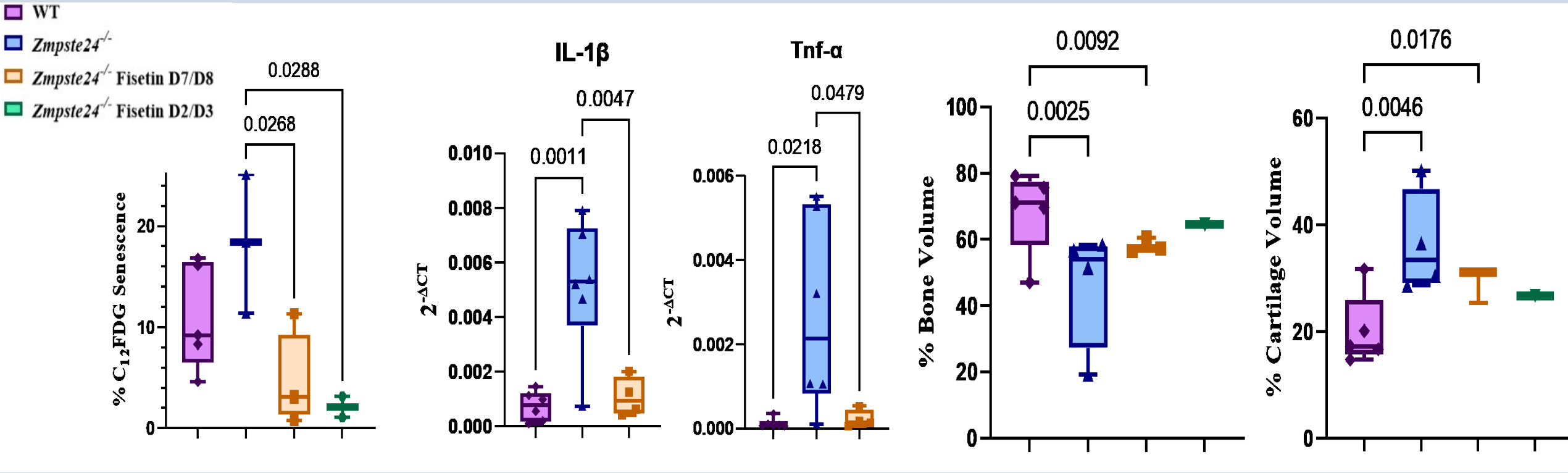


Bahney *et al.* Frontiers Endocrin 2017



***Hypothesis*:** Fisetin treatment during fracture healing will attenuate senescent cell burden and SASP expression in Z24$^{-/-}$ mice to accelerate fracture repair

Fisetin as a Senotherapeutic for Fracture Repair



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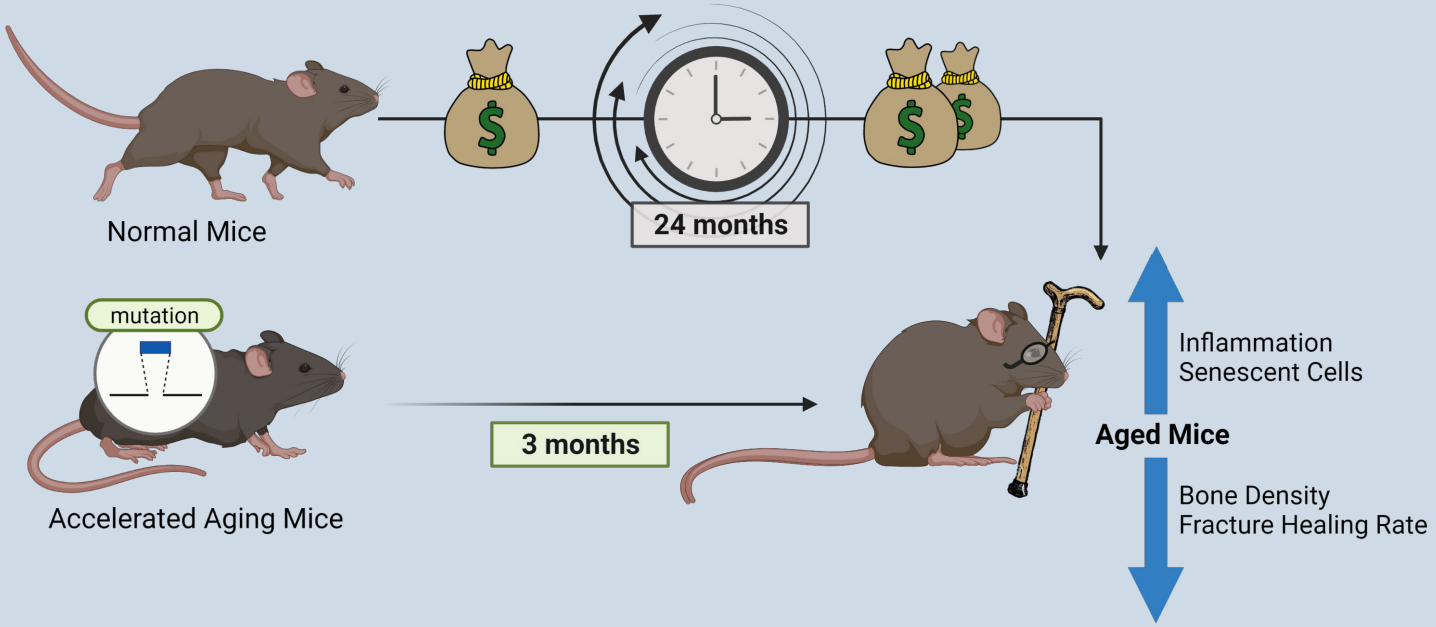
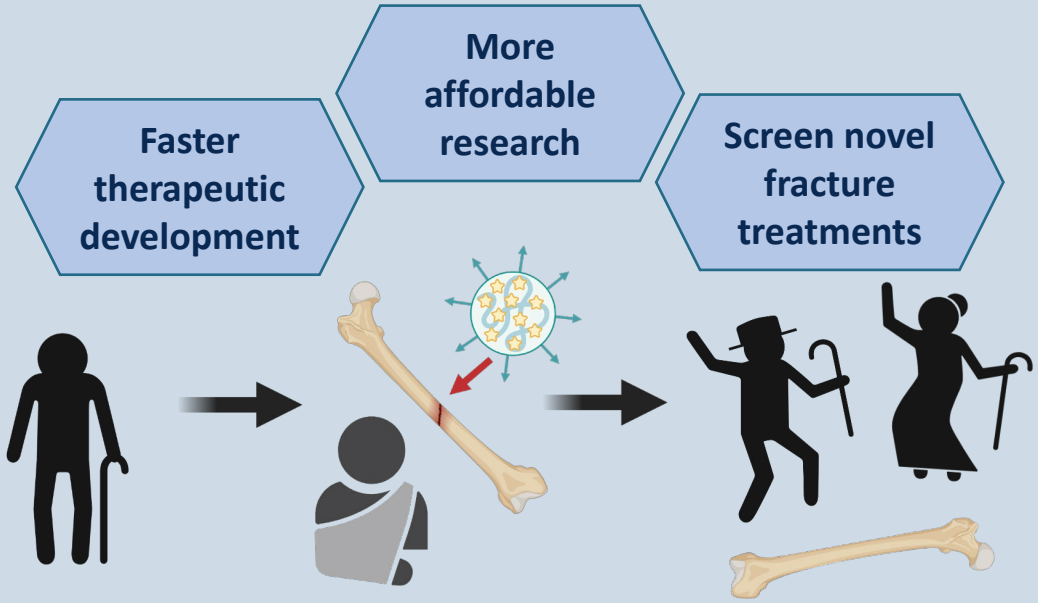
From bench to bedside: Senolytics as a Bone Fountain of Youth??



Accelerated Aging Mouse Model



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