

Cellular Senescence: A Bone Fountain of Youth.

Chelsea S Bahney, PhD

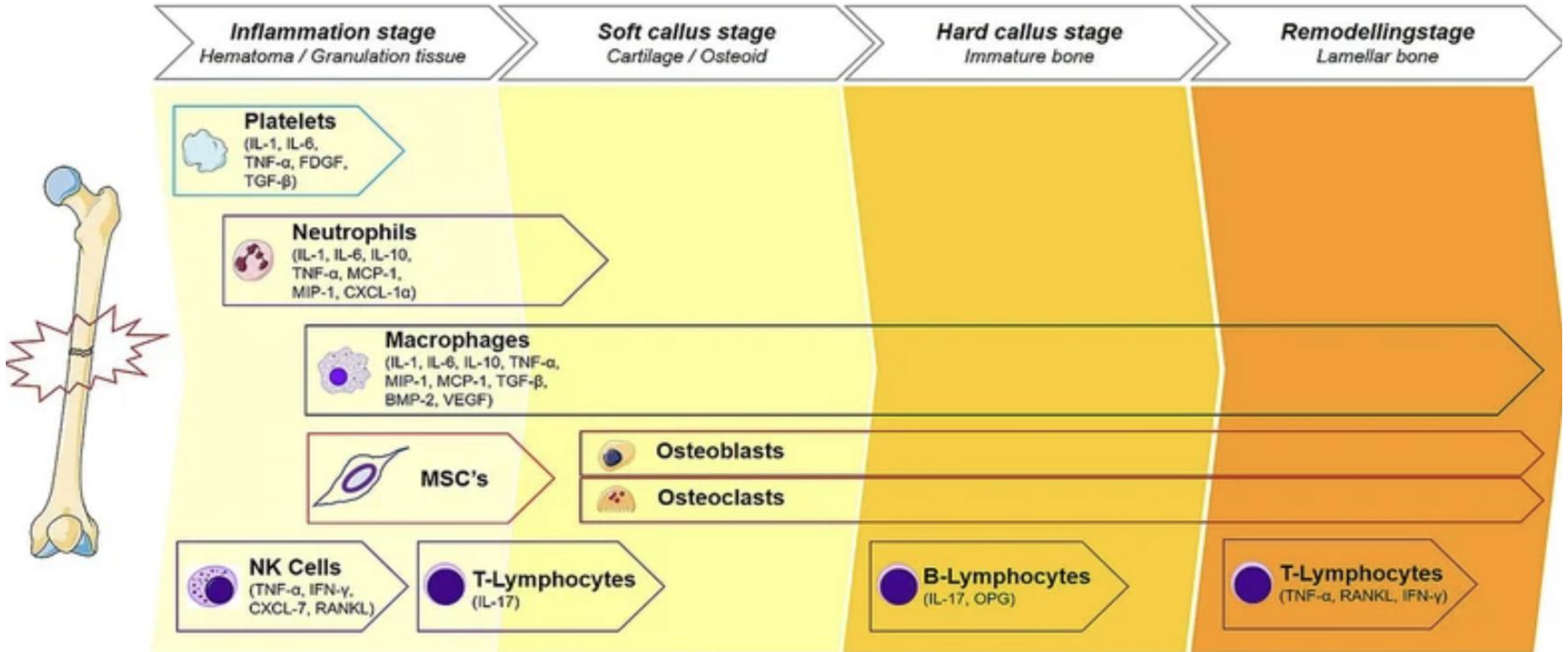
Associate Professor, Orthopaedic Trauma Institute
University of California San Francisco (UCSF)



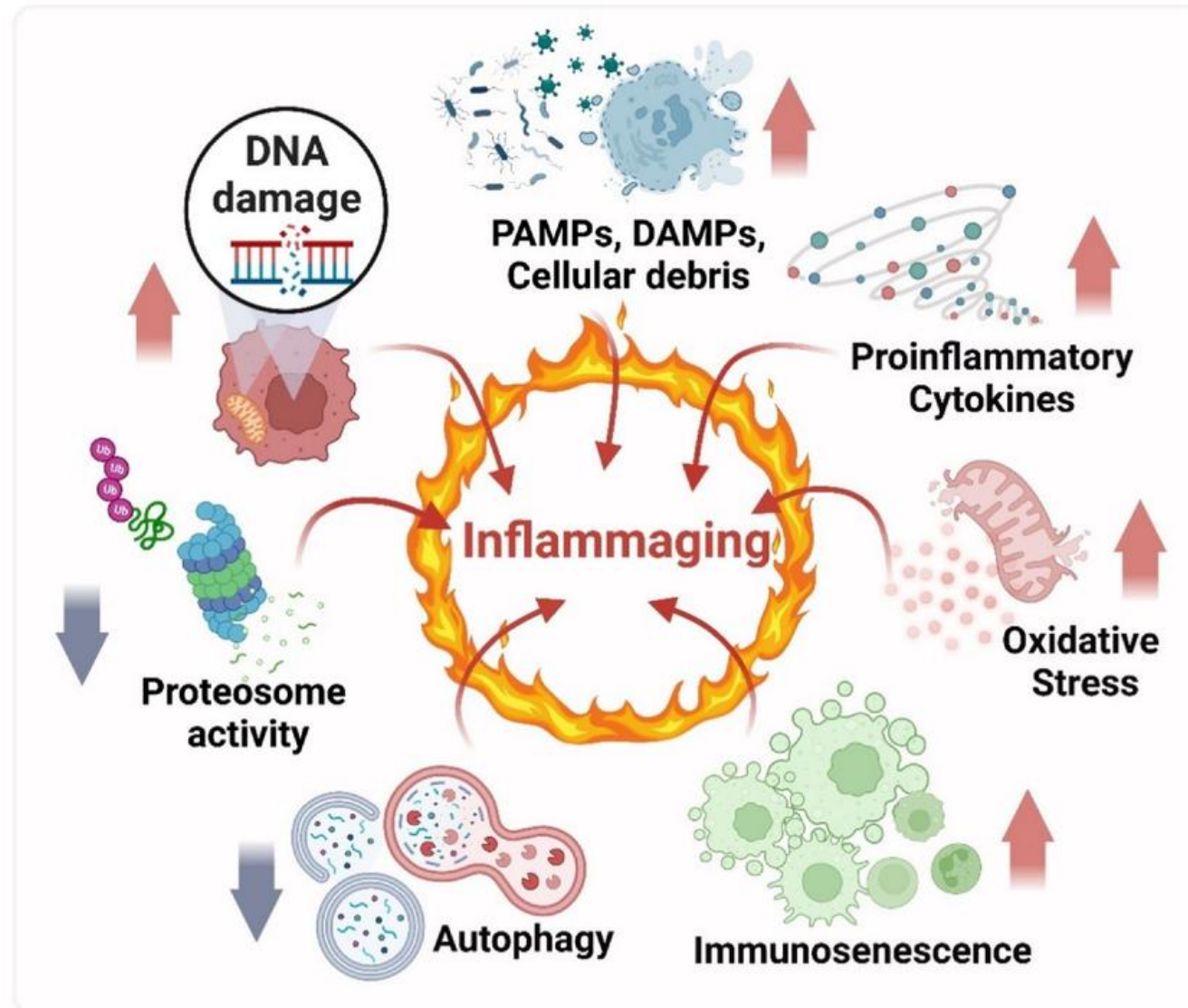
Disclosures

- None

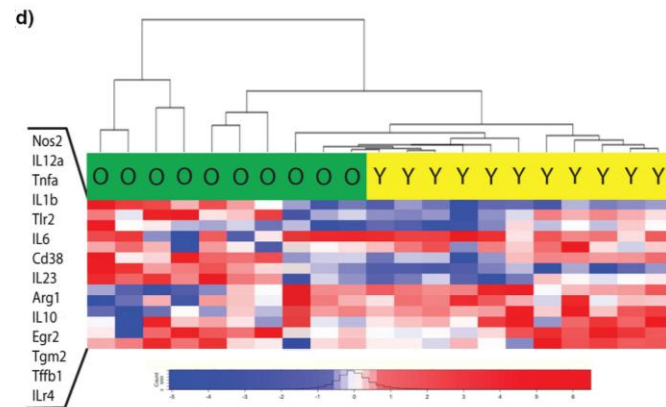
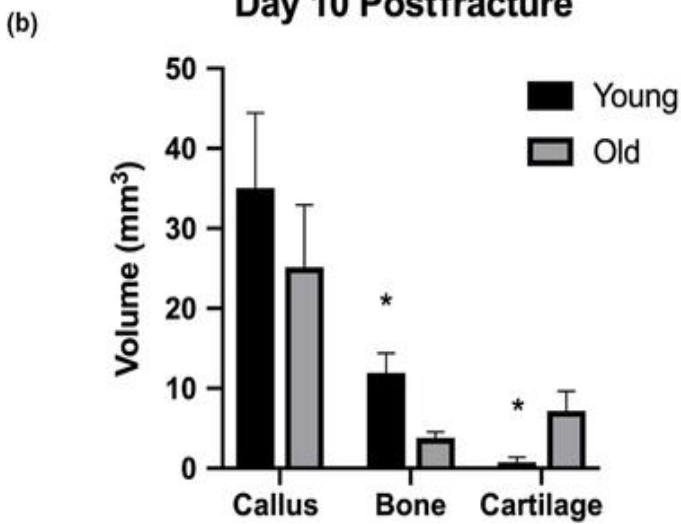
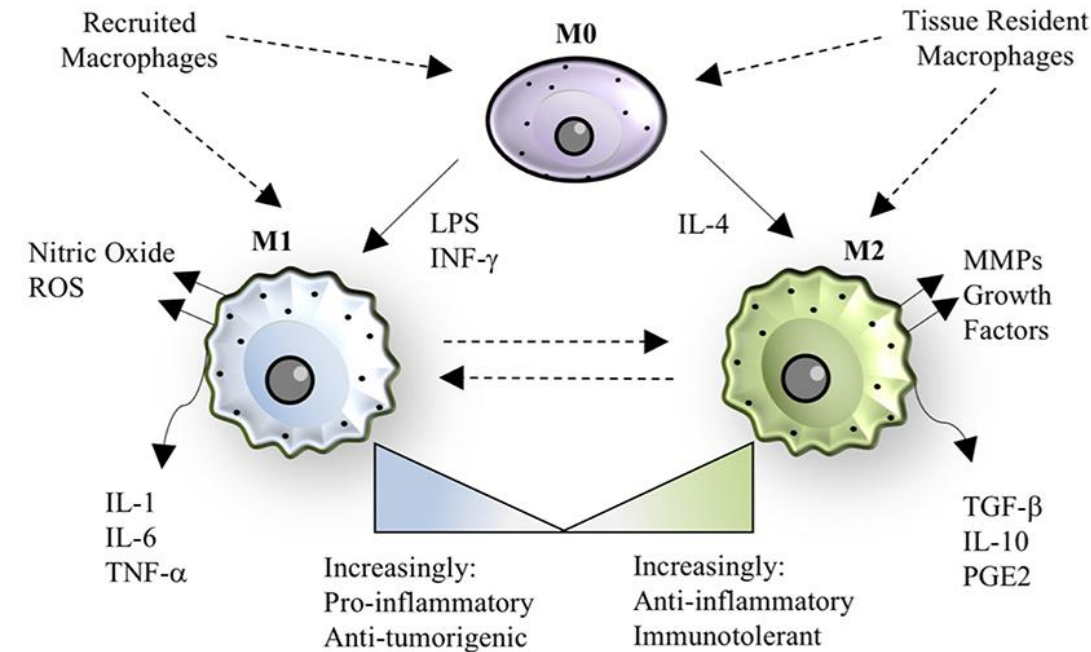
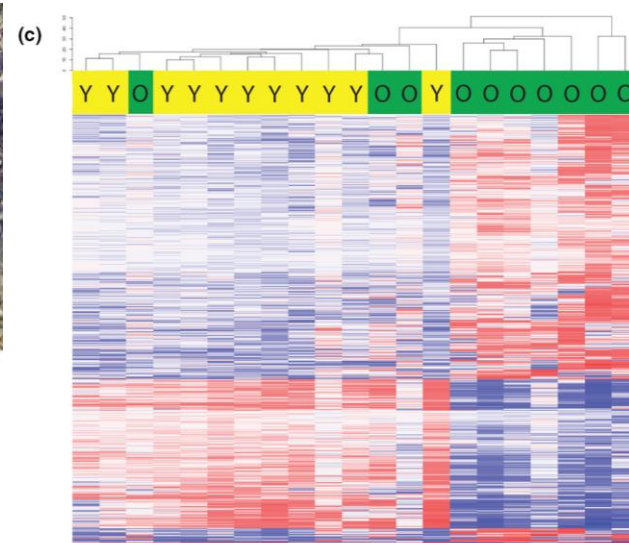
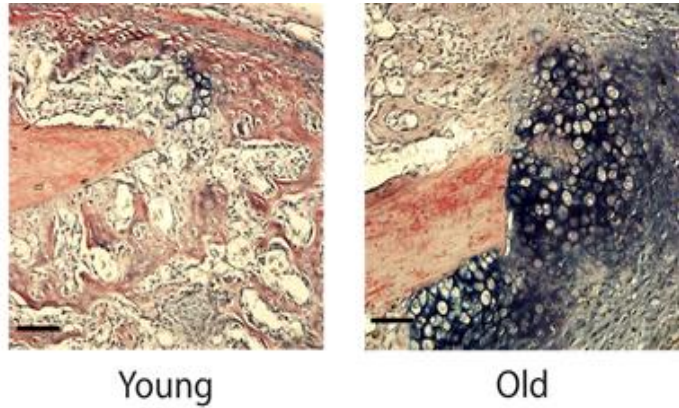
Immune Cell Landscape Following Fracture Repair



Inflammaging: A Root Cause of Delayed Fracture Healing



Macrophage Dysfunction with Aging Delays FX Repair



- Increased pro-inflammatory M1 in elderly
- Defective switch from M1 to M2 in elderly.
- High chronic inflammation prevents sufficient delta in the M1 response

Clark *et al.* Aging Cell 2020.

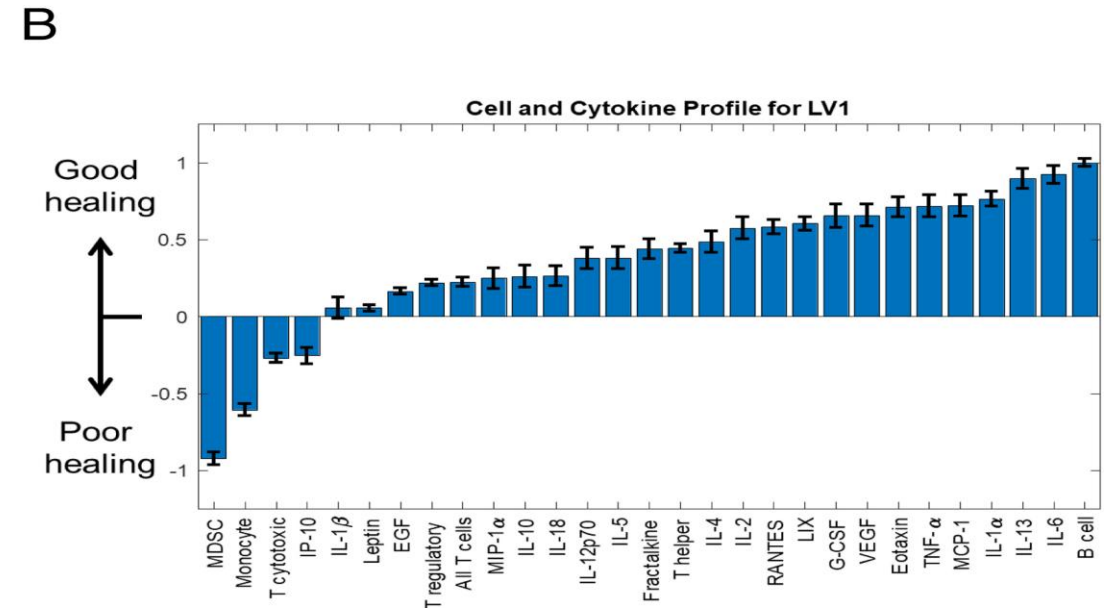
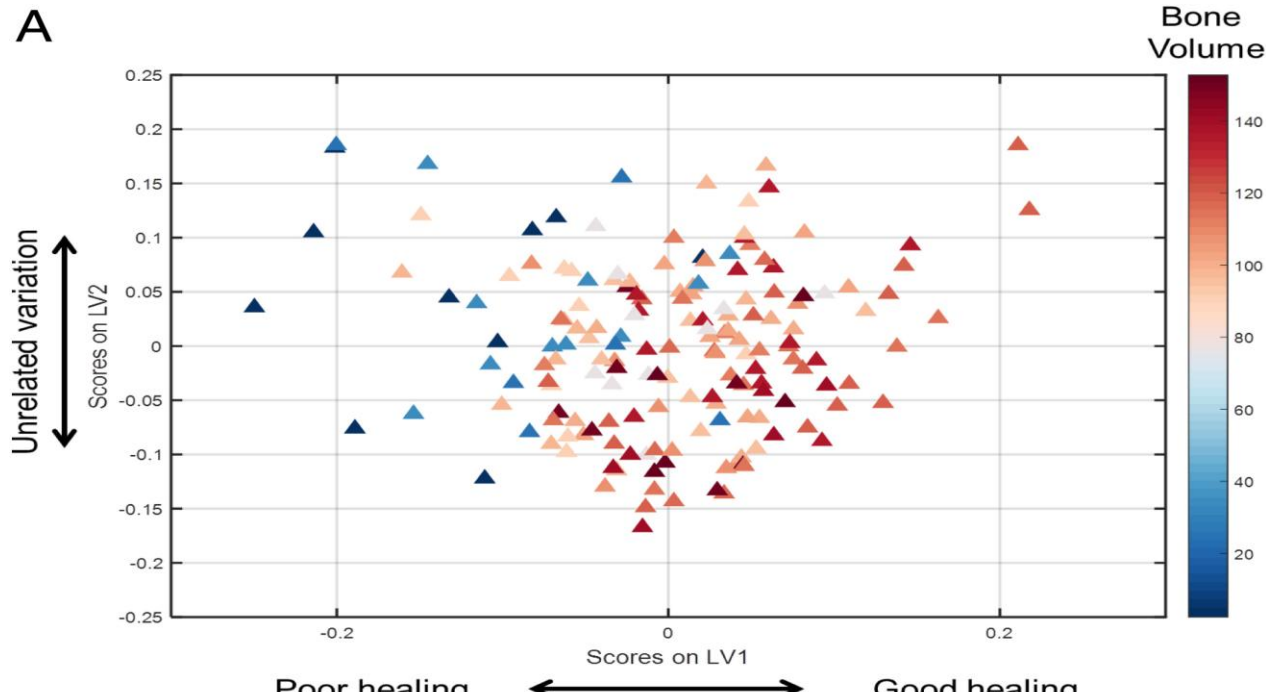
Early Immune Biomarkers of Poor Healing

Myeloid-derived suppressor cells (MDSCs) and the immunosuppressive cytokine interleukin-10 (IL-10) are negatively correlated with functional bone regeneration

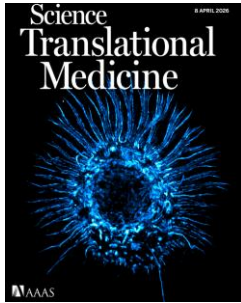


Early systemic immune biomarkers predict bone regeneration after trauma

Albert Cheng^{a,b,1}, Casey E. Vantucci^{b,c,1}, Laxminarayanan Krishnan^b, Marissa A. Ruehle^{b,c}, Theresa Kotanchek^d, Levi B. Wood^{a,b,c}, Krishnendu Roy^{b,c}, and Robert E. Guldberg^{a,b,e,2}



Prognostic Implications of CD8+ T_{EMRA} in Nonunion

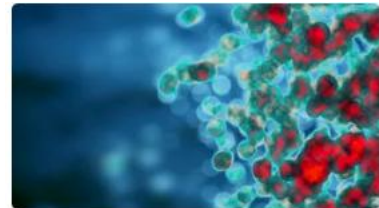


Terminally Differentiated CD8⁺ T Cells Negatively Affect Bone Regeneration in Humans

SIMON REINKE, SVEN GEISSLER, WILLIAM R. TAYLOR, KATHARINA SCHMIDT-BLEEK, KERSTIN JUELKE, VERENA SCHWACHMEYER, MICHAEL DAHNE, TONY HARTWIG,

LEVENT AKYÜZ, [...] AND GEORG N. DUDA [+6 authors](#) [Authors Info & Affiliations](#)

SCIENCE TRANSLATIONAL MEDICINE · 20 Mar 2013 · Vol 5, Issue 177 · p. 177ra36 · DOI: 10.1126/scitranslmed.3004754



ORIGINAL RESEARCH article

Front. Immunol., 22 October 2024

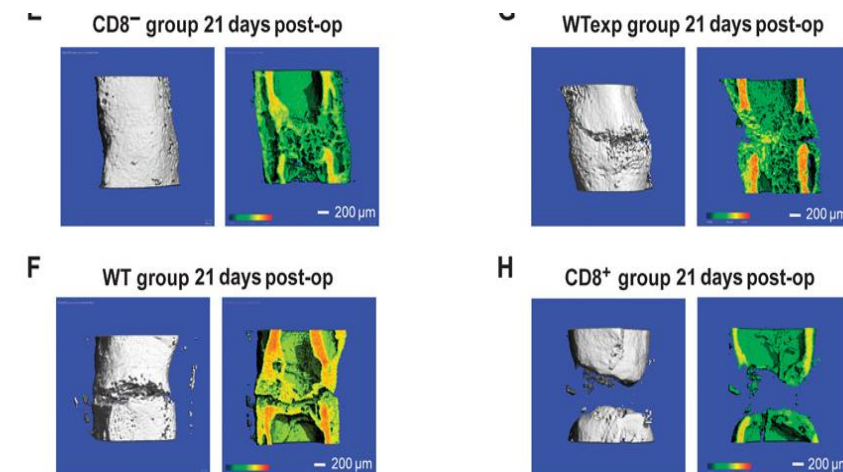
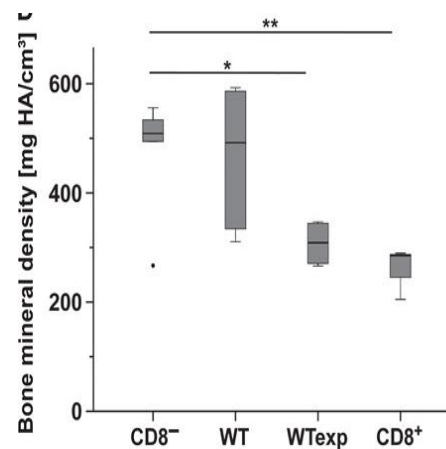
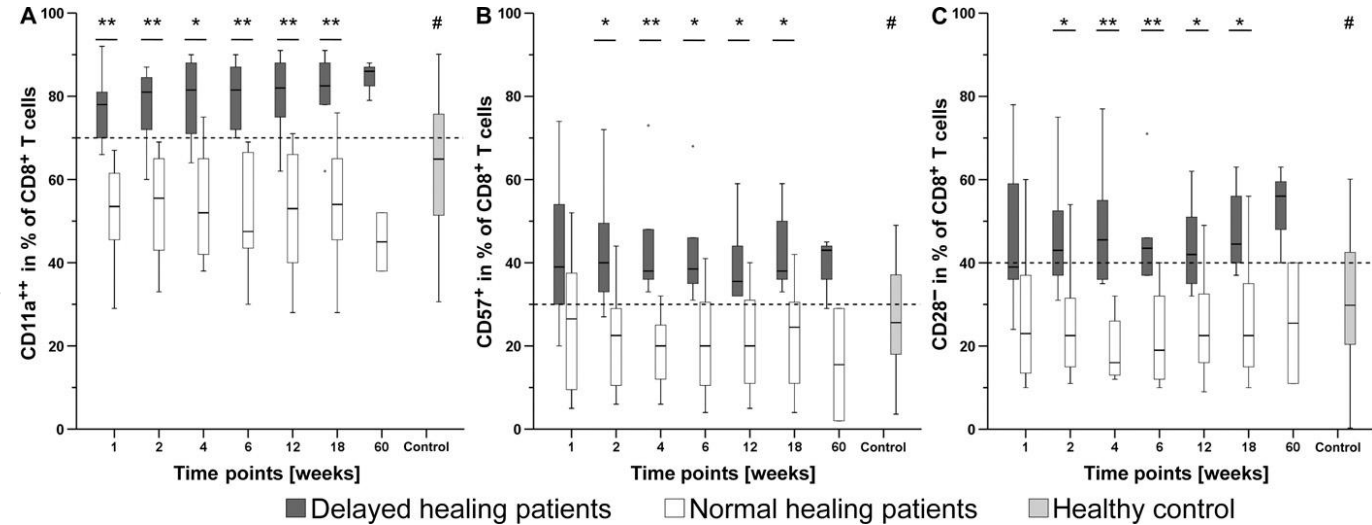
Sec. T Cell Biology

Volume 15 - 2024 | <https://doi.org/10.3389/fimmu.2024.1476009>

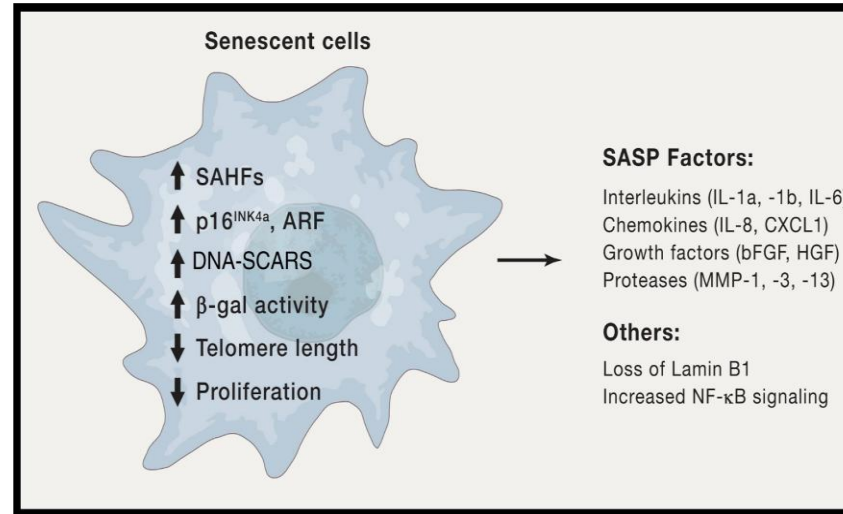
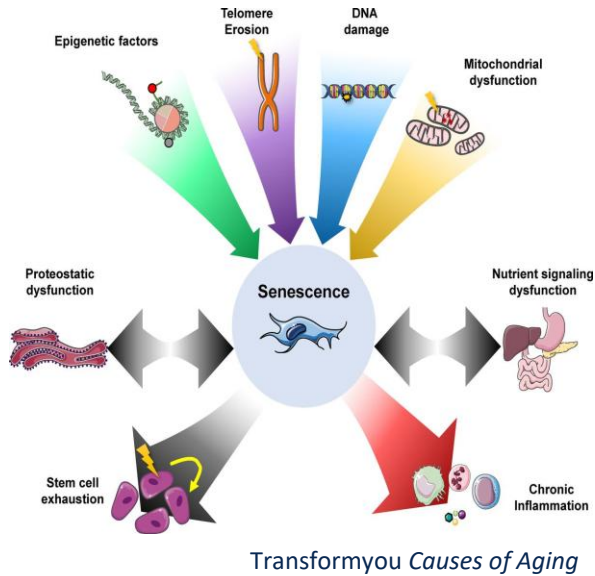
Prognostic implications of a CD8⁺ T_{EMRA} to CD4⁺T_{reg} imbalance in mandibular fracture healing: a prospective analysis of immune profiles

Frontiers in Immunology
T Cell Biology

5.9 impact factor 10.8 citescore



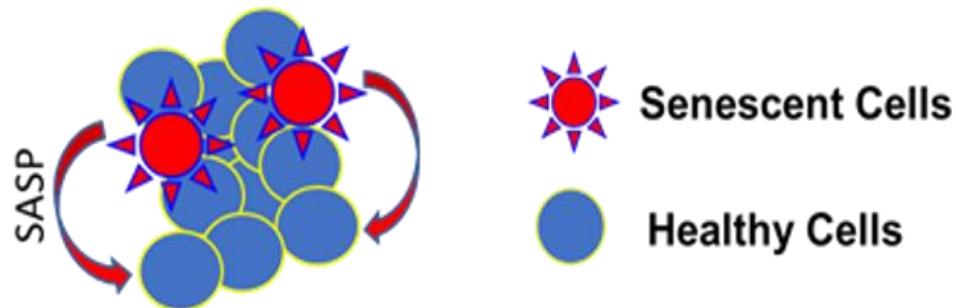
Role for Senescence in Delayed Fracture Healing?



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

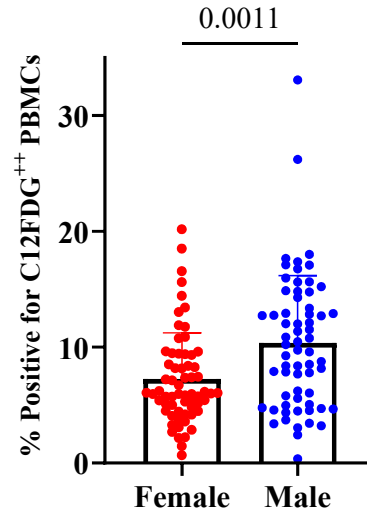
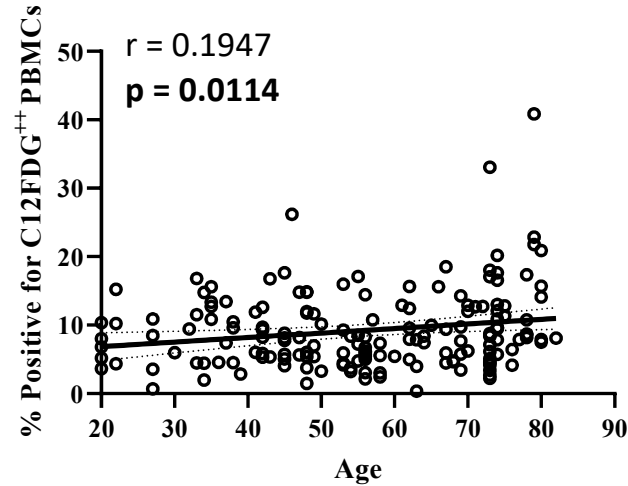
Diseases Associated with Senescence:

- Diabetes/obesity
- Cardiac Dysfunction
- Cancer
- Cognition/Alzheimer's/ALS/Anxiety
- Renal Dysfunction
- Osteoporosis**
- Osteoarthritis**
- Sarcopenia
- Rheumatoid Arthritis**
- and others..

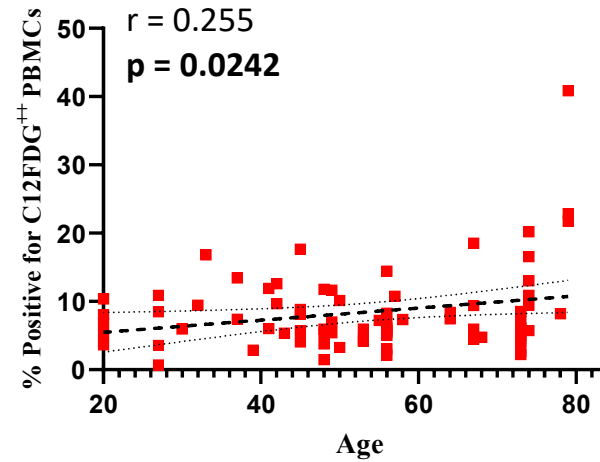


Human Senescence Phenotype Increase with Chronological Age

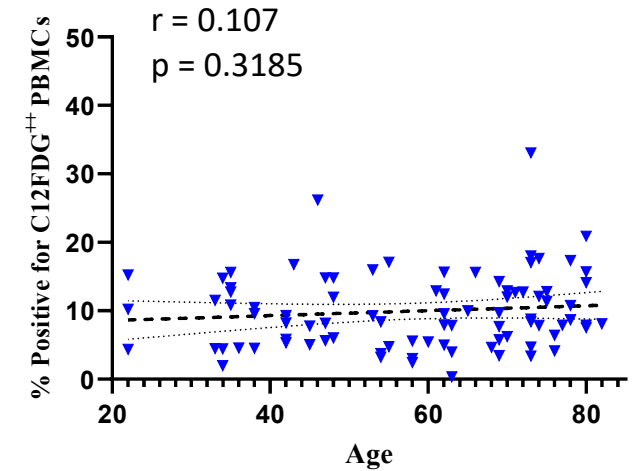
B. Bright PBMCs



C. Bright Female PBMCs



D. Bright Male PBMCs



Accumulation of Senescent Cells Impairs FX Healing

> *Elife*. 2021 Oct 7:10:e69958. doi: 10.7554/eLife.69958.

Modulation of fracture healing by the transient accumulation of senescent cells

Dominik Saul^{1 2 3}, David G Monroe^{1 2 4}, Jennifer L Rowsey^{1 2}, Robyn Laura Kosinsky⁵,
Stephanie J Vos^{1 2}, Madison L Doolittle^{1 2}, Joshua N Farr^{1 2 4}, Sundeep Khosla^{1 2 3 4}

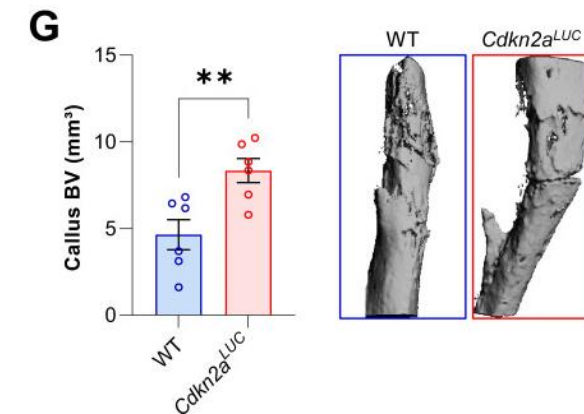
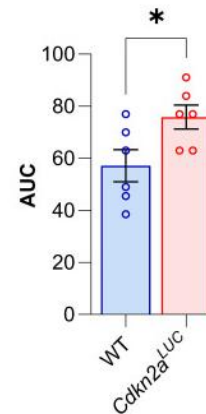
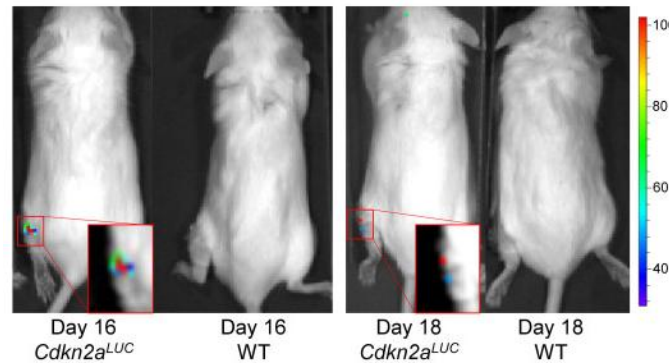
The Journal of Clinical Investigation

RESEARCH ARTICLE

Age-associated callus senescent cells produce TGF- β 1 that inhibits fracture healing in aged mice

Article | [Open access](#) | Published: 25 January 2024

Age-related secretion of grancalcin by macrophages induces skeletal stem/progenitor cell senescence during fracture healing



Why senescence delays fracture repair:

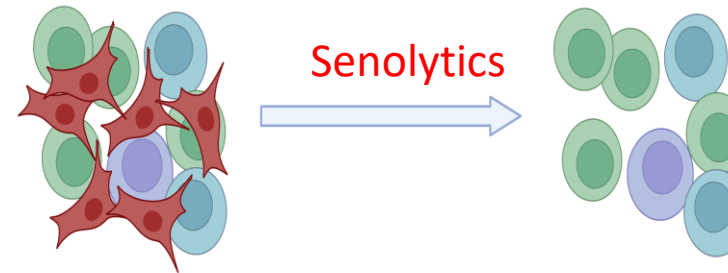
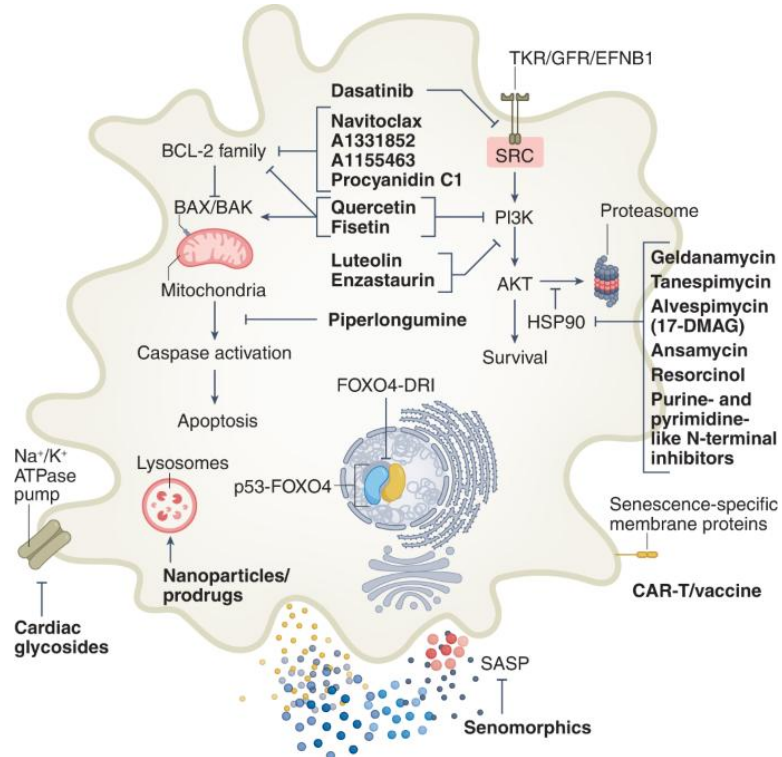
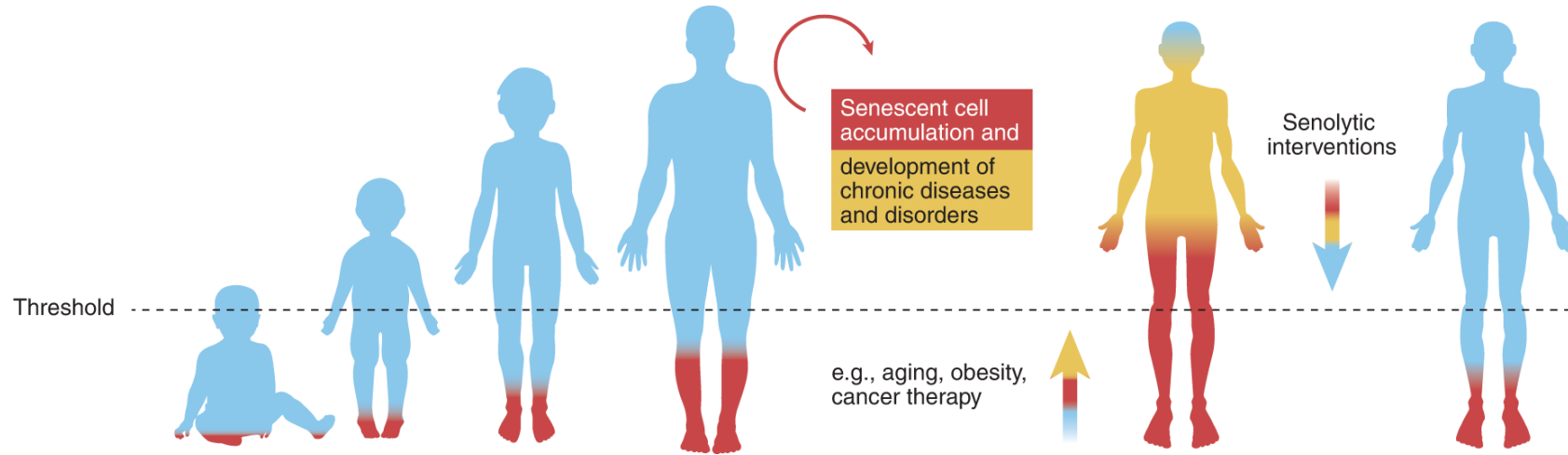
Inflammaging

Loss of Stem Cell Proliferation

Decreased Stem Cell Differentiation

Telomer Shortening

Senolytics: Therapeutics to Reduce Senescence Phenotype



Short-Term Dasatinib + Quercetin may Improve Fracture Repair

Removing “Zombie” Cells With Senolytics Improves Bone Fracture Healing in Young Mice

Mayo Clinic researchers cleared non-proliferating (senescent) cells with senolytic combo to accelerate fracture healing.



Targeting senescent cells to boost bone fracture healing

Lorenz C. Hofbauer,^{1,2} Ulrike Baschant,¹ and Christine Hofbauer^{3,4}

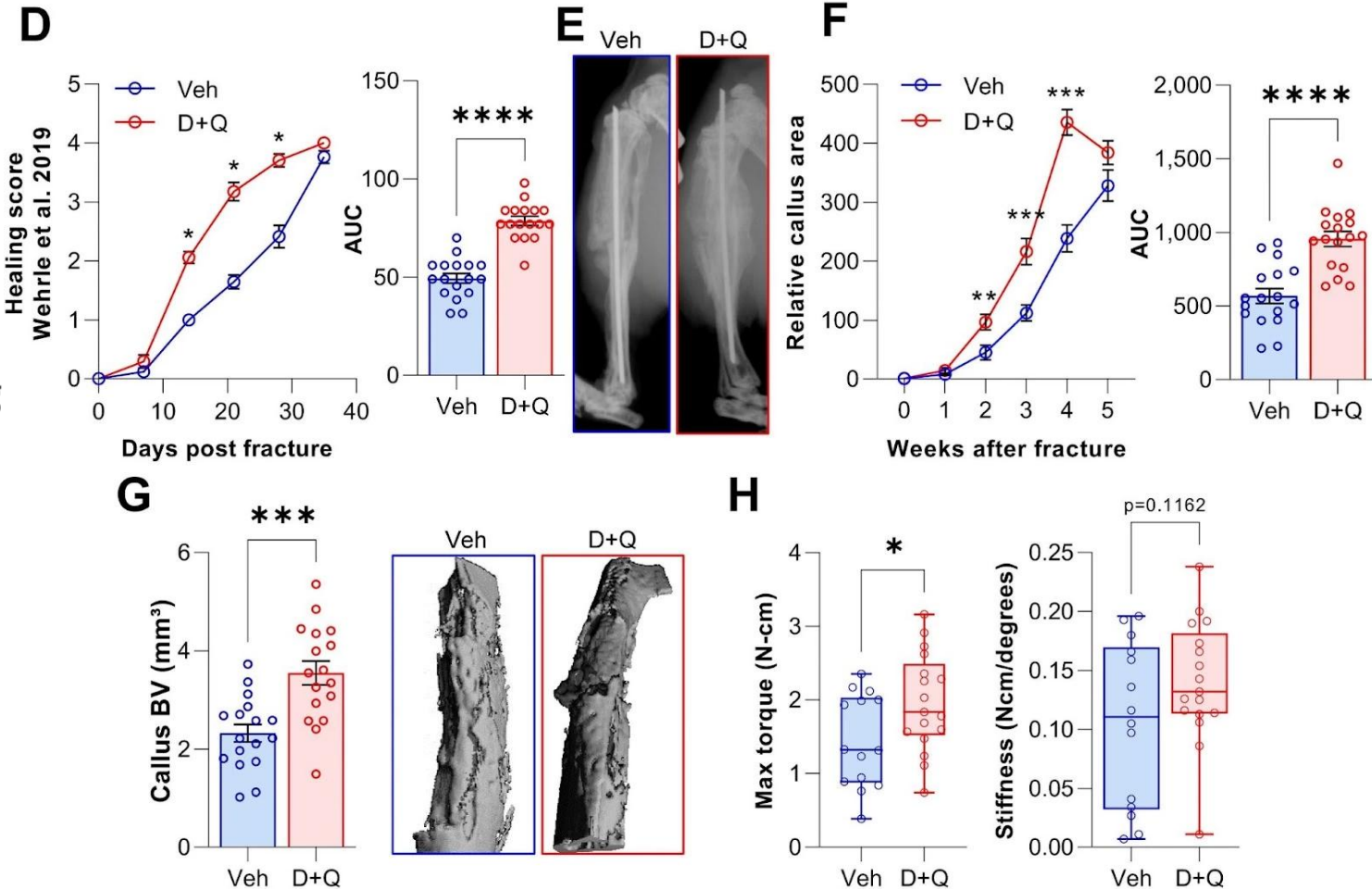


Biomedicine & Pharmacotherapy

Volume 175, June 2024, 116606



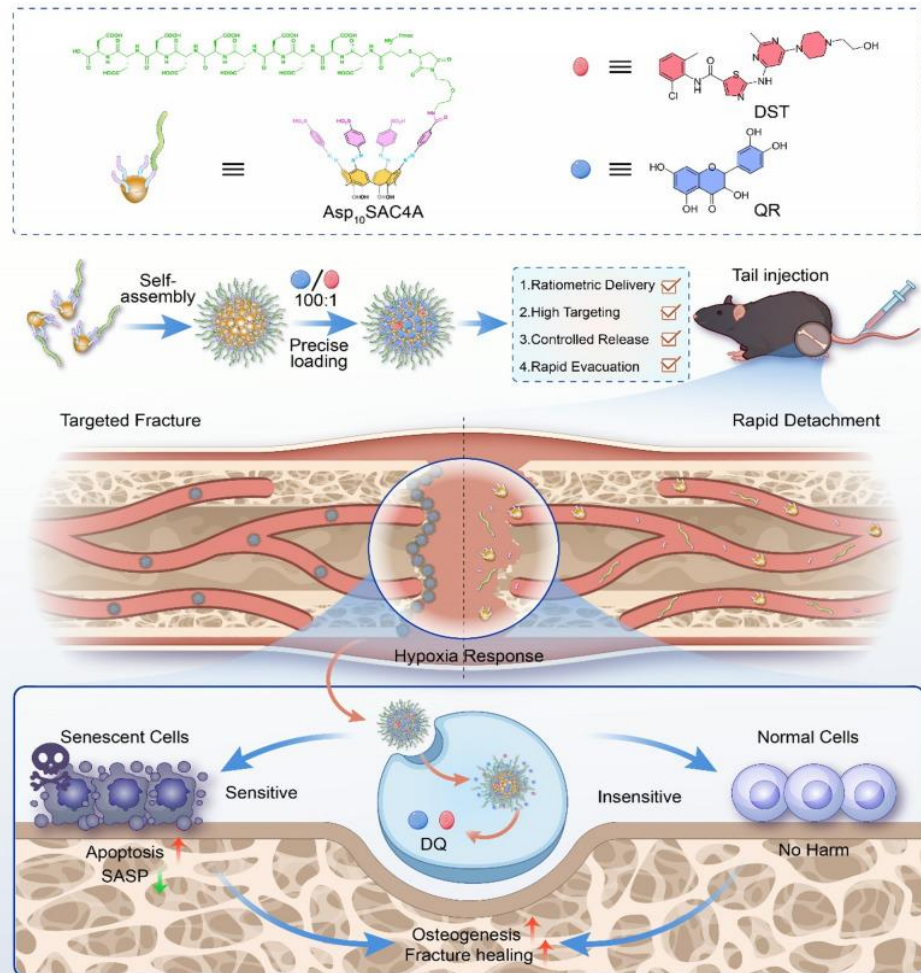
Senolytics ameliorate the failure of bone regeneration through the cell senescence-related inflammatory signalling pathway



Biomaterial Based D&Q Delivery to Reduce Systemic Toxicity

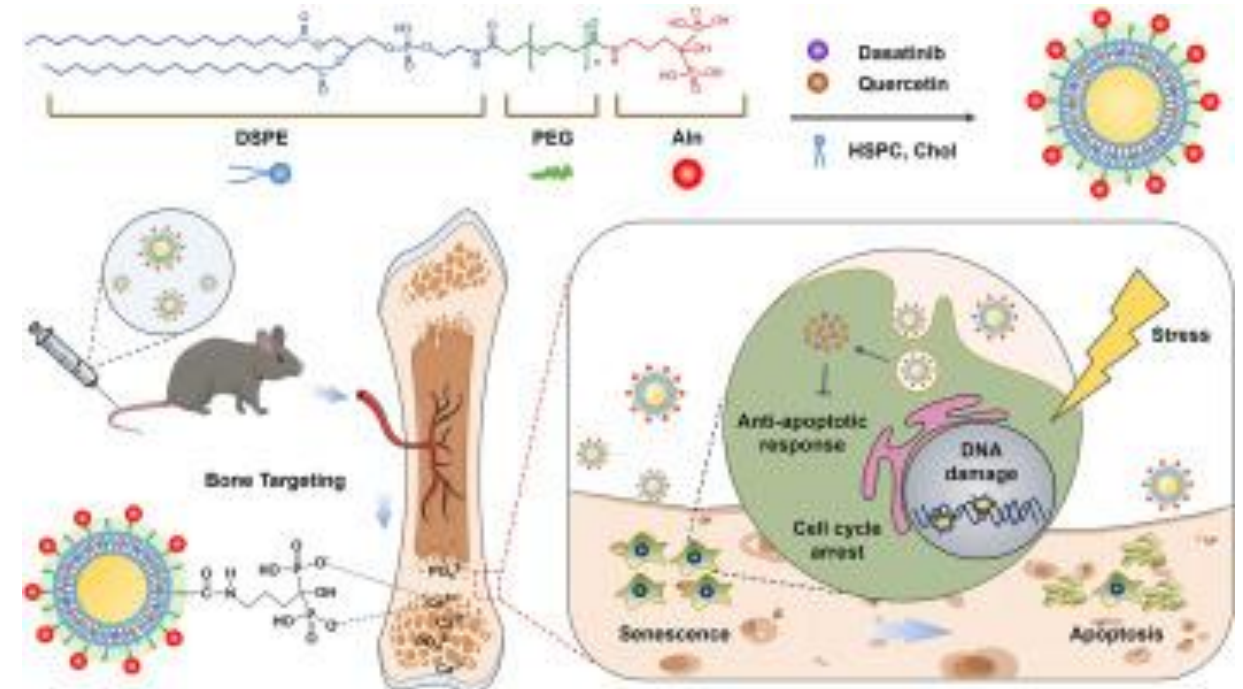
> *J Nanobiotechnology*. 2026 Feb 18;24(1):269. doi: 10.1186/s12951-026-04138-2.

Supramolecular delivery of senolytics enables targeted anti-senescence therapy and accelerated fracture healing

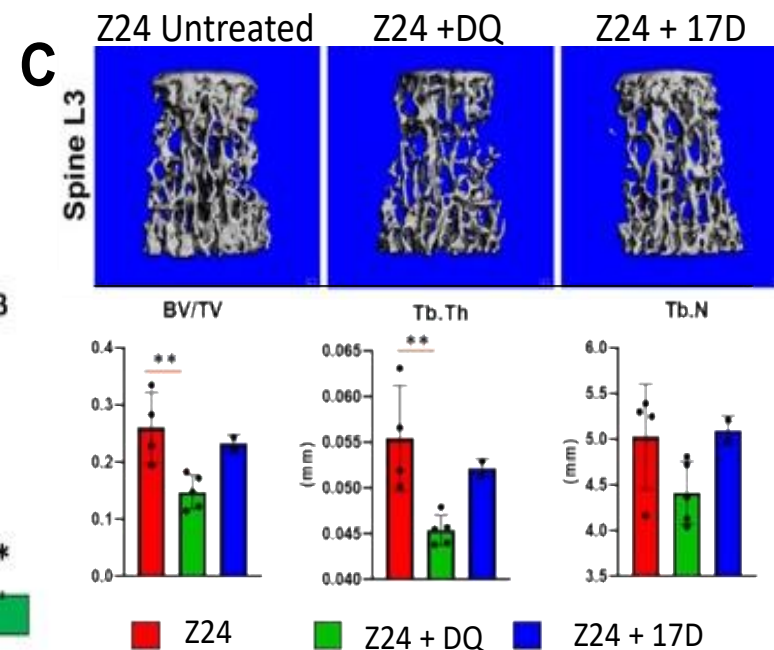
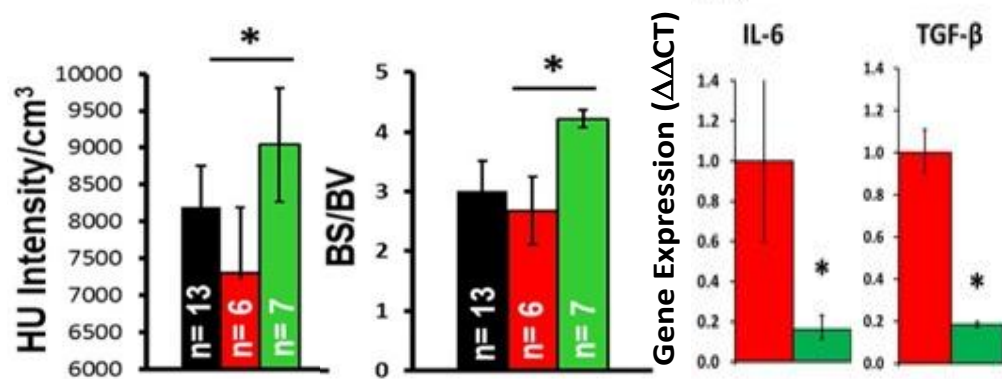
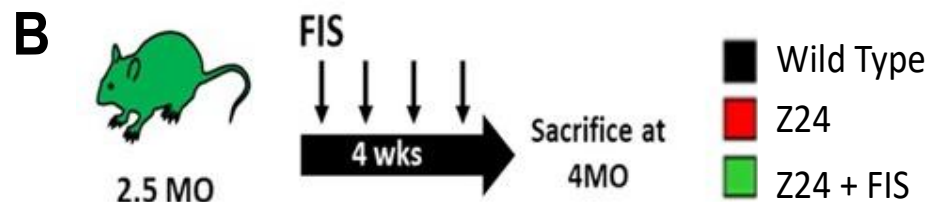
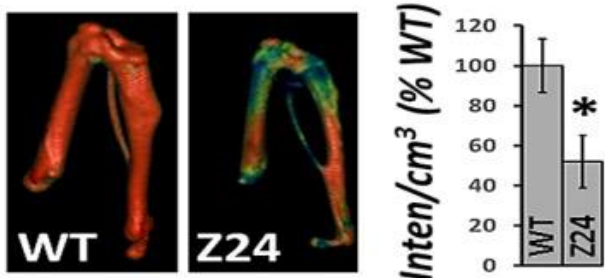


Targeted delivery of liposomal senolytics to alleviate cellular senescence-induced bone loss

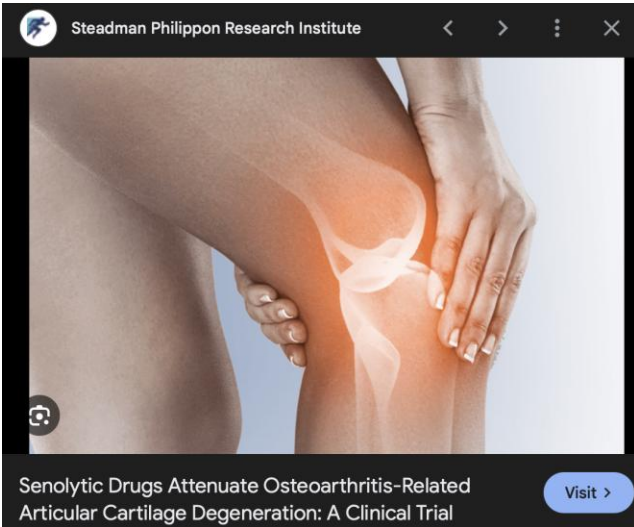
Rong Li^{a,b,1}, Yaohua Wei^{b,1}, Changhao Xiong^b, Jingwei Wang^d, Yixuan Lin^b, Ronghui Deng^b, Hao Qin^b, Yang Chen^b, Nan Li^b, Guyu Zheng^b, Yuanyuan Lv^b, Jian Shi^b, Tingting Yu^d, Yiye Li^{b,c}, Jing Wang^e, Ruifang Zhao^{b,c,*}, Changsheng Liu^{e,*}, Guangjun Nie^{b,c,*}



Safer Senolytics (Fisetin) as a Therapeutic to Increase BMD Loss and Reduce Systemic Inflammation



Fisetin was Safe but not Superior to Placebo in OA



Study Overview

Brief Summary

Phase I/II randomized, double-blind, placebo-controlled clinical trial to test the safety and efficacy of Fisetin for treating mild to moderate osteoarthritis

Detailed Description

This is a Phase I/II randomized, double-blind, placebo-controlled clinical trial that will be conducted at The Steadman Clinic (TSC) and Steadman Philippon Research Institute (SPRI). The purpose of this study is to evaluate the clinical efficacy of Fisetin (FIS), a dietary supplement, in symptomatic knee osteoarthritis (OA) patients. Key aspects of this proposal include the investigator's well-developed methodologies to measure and compare systemic senescence-associated secretory phenotype (SASP) including inflammatory biomarkers and senescent cells, and collect magnetic resonance images, self-reported outcomes, physical performance and other objective clinical data. Given the drug FIS has been empirically demonstrated to reduce senescent cell burden, the main objective(s) are to determine 1) the safety of FIS during dosing and 2) whether FIS reduces senescent cells, pro-inflammatory and cartilage degenerating SASP markers, and reduces OA-symptoms leading to improved joint health and function.

Official Title

Senolytic Drugs Attenuate Osteoarthritis-Related Articular Cartilage Degeneration: A Clinical Trial

Study Start (Actual) ⓘ

2020-01-06

Primary Completion (Actual) ⓘ

2023-01-05

Study Completion (Actual) ⓘ

2023-02-01

Enrollment (Actual) ⓘ

75

Study Type ⓘ

Interventional

Phase ⓘ

Phase 1

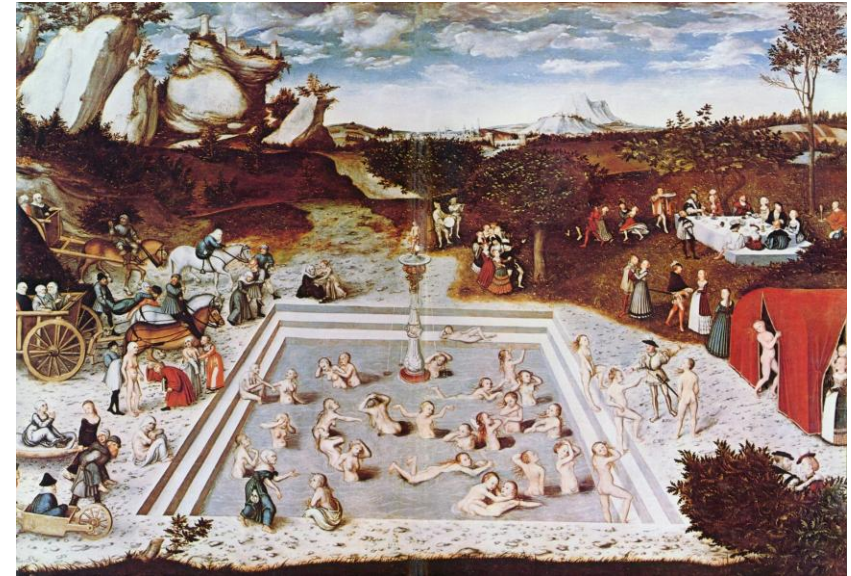
Phase 2

OUTCOMES

- Knee-function and performance measures were very close: TUG 5.93 vs 6.00 seconds, 6-minute walk 22.1 vs 21.7 m/s, stair-climb 8.88 vs 8.66 seconds at month 6, and knee pain scores stayed similarly low and close across weeks 3–12.
- The MRI cartilage measure was also very similar overall: the sum-of-ranks T2 scores were 149.6 vs 150.3 at month 6 and 156.1 vs 144.8 at month 12.

Is there a Bone Fountains of Youth? Key Take Aways

1. Fracture healing in elderly is disrupted due to inflammaging and cellular senescence
2. Immune biomarkers of inflammaging are emerging as potentially novel prognostic tools.
3. Removal of senescent cells improved fracture healing in preclinical models
4. Prospective Phase I/II trial of senolytic in OA found no benefit over placebo





Orthopaedic Trauma Institute

UCSF + SAN FRANCISCO GENERAL HOSPITAL



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