Bone Healing: Are There Any Growth Factors on the Horizon?

TYMLOS® (abaloparatide) injection

FORTEO®

EVENITY® (romosozumab-aqqg) injection 105 mg/1.17 mL

Chelsea S Bahney, PhD

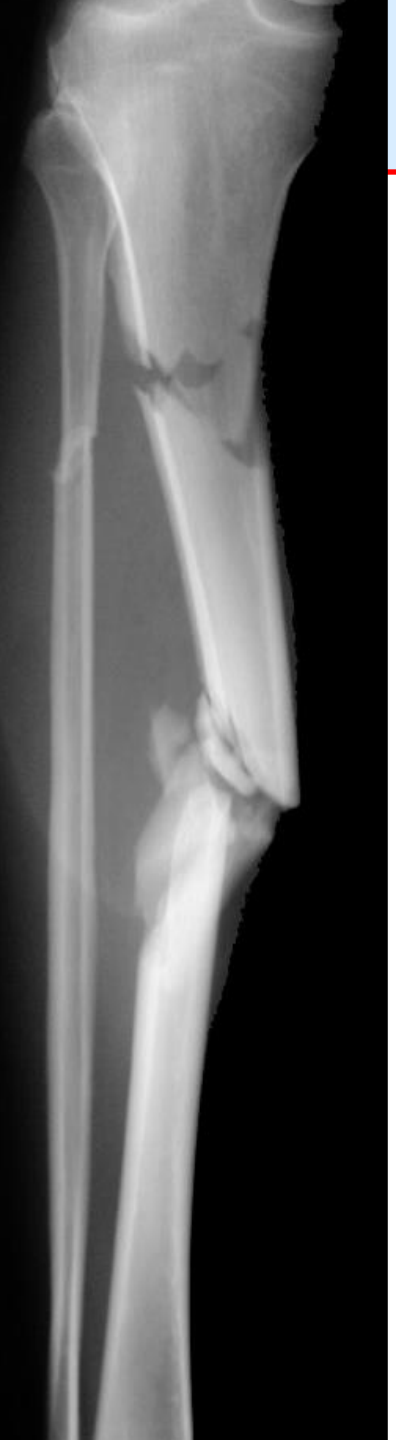
Program Director Bone Repair & Regenerative Therapeutics
Steadman Philippon Research Institute (SPRI), Vail CO
Associate Adjunct Professor, Orthopaedic Trauma Institute
University of California San Francisco (UCSF)

THE STEADMAN CLINIC AND STEADMAN PHILIPPON RESEARCH INSTITUTE

Orthopaedic Trauma Institute
UCSF + SAN FRANCISCO GENERAL HOSPITAL

Disclosures

None related to this talk



Burden of Fracture is High

178M Fracture injuries/year worldwide

THE LANCET

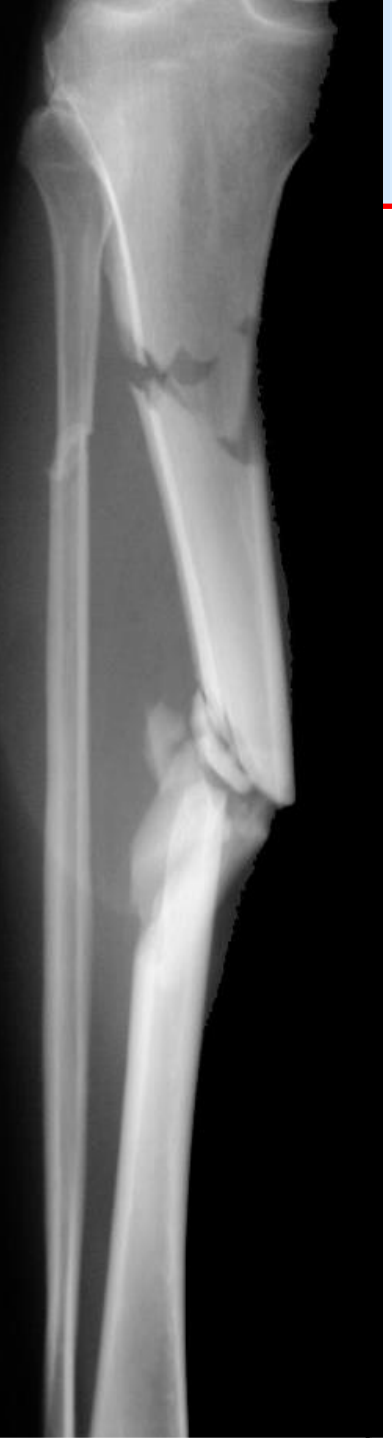
445M Prevalent fracture worldwide

Since 1990:

- 33% increase in global number of new cases of fracture
- 65% increase in years lived with disability (YLD)
- Significantly more prevalent in aging population

Delayed and Non-Union

- 8.1% of fractures were readmitted for healing complications within 2 years post-fracture
- Higher rates in femoral (13.6 %) and tibial (11.7%) shaft



BMPs Were Not the Magic Bullet

Recombinant Human Bone Morphogenetic Protein-2: A Randomized Trial in Open Tibial Fractures Treated with Reamed Nail Fixation

Aro, Hannu T. MD, PhD[1]; Govender, Shunmugam MBBS, MD, FRCS[2]; Patel, Amratlal D. FRCS[3]; Hernigou, Philippe MD[4]; Perera de Gregorio, Arturo MD[5]; Popescu, Gheorghe Ion MD[6]; Golden, Jane Davis MHP[7]; Christensen, Jared PhD[7]; Valentin, Alexandre MD[7]

The Journal of Bone & Joint Surgery 93(9):p 801-808, May 4, 2011. | *DOI:* 10.2106/JBJS.I.01763

Efficacy and Safety of Recombinant Human Bone Morphogenetic Protein-2/Calcium Phosphate Matrix for Closed Tibial Diaphyseal Fracture

A Double-Blind, Randomized, Controlled Phase-II/III Trial

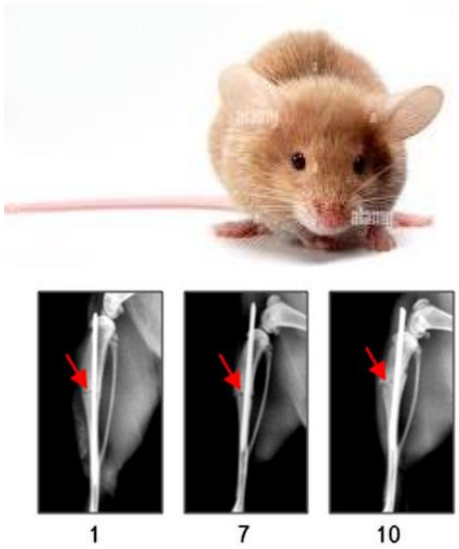
Lyon, Thomas MD[1]; Scheele, Wim MD[2]; Bhandari, Mohit MD, PhD, FRCSC[3]; Koval, Kenneth J. MD[4]; Sanchez, Eduardo Gomez MD[5]; Christensen, Jared PhD[2]; Valentin, Alexandre MD[6]; Huard, Francois MSc, MBA[7]

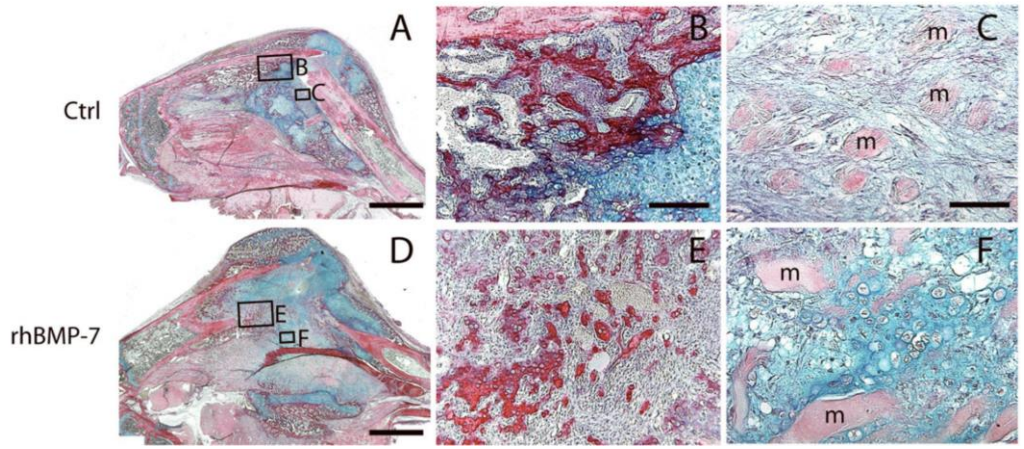
The Journal of Bone & Joint Surgery 95(23):p 2088-2096, December 4, 2013. | *DOI:* 10.2106/JBJS.L.01545

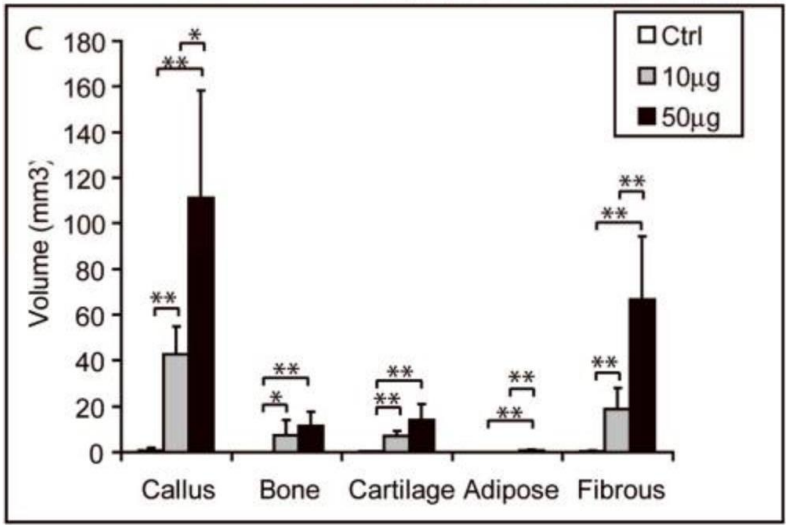
Conclusion

The time to fracture union and pain-free full weight-bearing were not significantly reduced by rhBMP-2/CPM compared with standard of care alone for open or closed fractures.

This was Surprising!

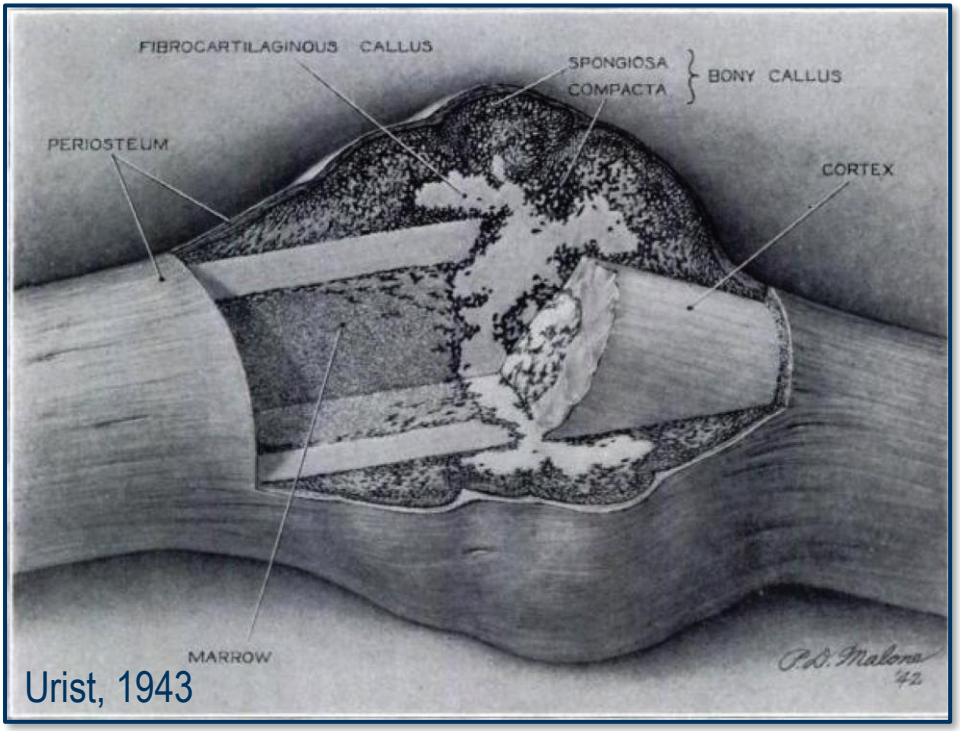




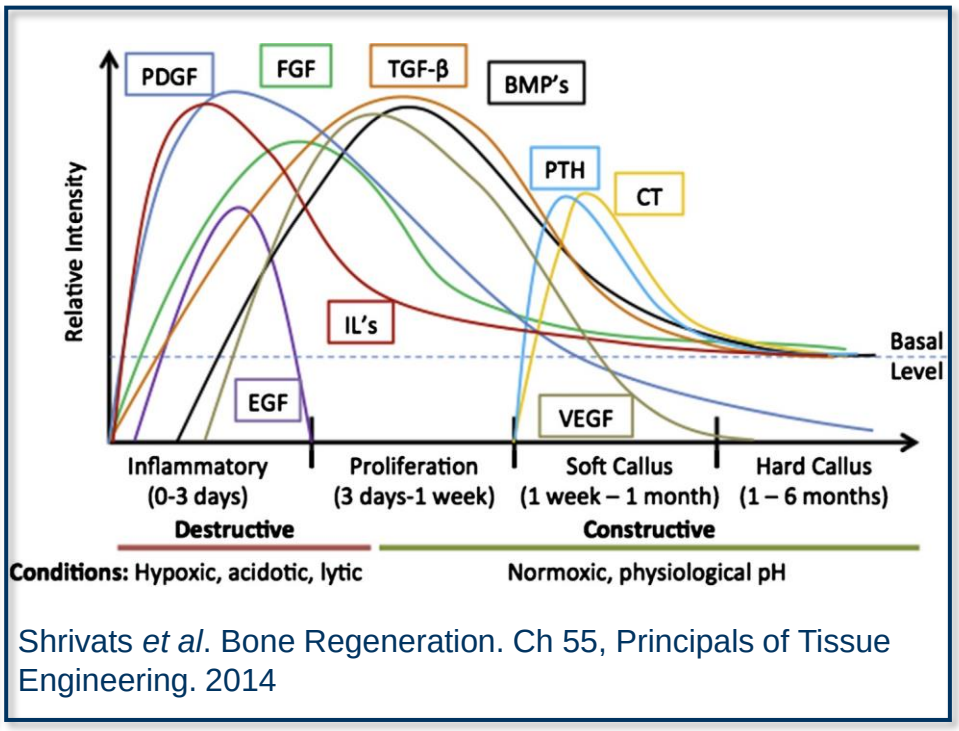


- Was the Dosing wrong?
- Was clearance too rapid?
- Wrong timing?

Fracture Healing is a Complex Set of Interactions

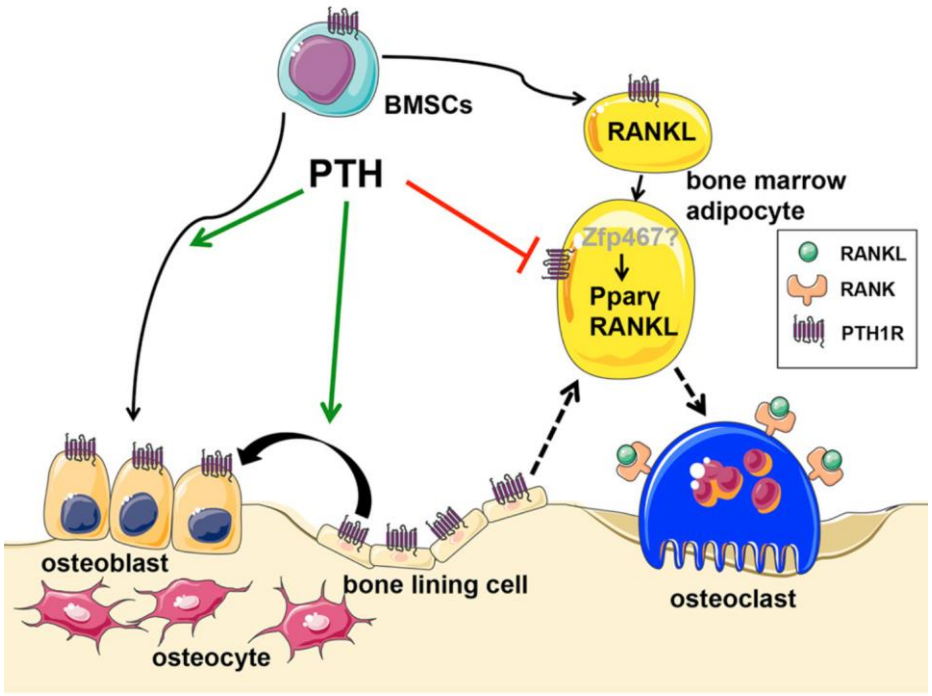


Urist, 1943



Shrivats *et al*. Bone Regeneration. Ch 55, Principals of Tissue Engineering. 2014

Treatments Targeting Bone Remodeling



Bisphosphonates

- Inhibit osteoclasts/anti-resorptive
- Also inhibits osteoblast coupling

Teriparatide (Forteo), Abaloparotide (Tymlos)

- Osteoanabolic
- Act on stem cells and osteoblasts

Osteoporosis:

- Increases bone mineral density
- Reduces fracture risk

Bisphosphonates in Fracture Repair Inhibiting Bone Resorption

TABLE 1

Common Bisphosponates and Their Usesline

BISPHOSPHONATE	USE
TILUDRONATE	
Skelid® (Sanofi-Aventis US LLC, Bridgewater, NJ)	Paget's Disease
ETIDRONATE	
Didronel® (Procter & Gamble Pharmaceuticals, Cincinnati, OH)	Paget's Disease
RISEDRONATE	
Actonel® (Sanofi-Aventis US LLC)	Osteoporosis
ALENDRONATE	
Fosamax® (Merck & Co, Inc, Whitehouse Station, NJ)	Osteoporosis
IBANDRONATE	
Boniva® (Roche Laboratories, Nutley, NJ and GlaxoSmithKline, Research Triangle Park, NC)	Osteoporosis
ZOLEDRONIC ACID	
Zometa® (Novartis Pharmaceuticals Corp, East Hanover, NJ)	Bone Metastases
PAMIDRONATE	
Aredia® (Novartis Pharmaceuticals Corp)	Bone Metastases

- A total of 16 studies involving 5022 patients obtained from selected databases were examined
- No significant effect on fracture healing time
- Significantly increase BMD and prevent osteoporosis
- Inhibits both bone resorption and bone formation markers, resulting in low bone turnover state

frontiers in Endocrinology

Front Endocrinol (Lausanne). 2021; 12: 688269.
Published online 2021 Aug 30. doi: 10.3389/fendo.2021.688269
PMCID: PMC8435630
PMID: 34526966

The Effect of Bisphosphonates on Fracture Healing Time and Changes in Bone Mass Density: A Meta-Analysis

Teriparatide (PTH) in Osteoporosis Targets Bone Formation without Resorption

- **Teriparatide is a daily subcutaneous injection**
  - $2,998 daily
  - $35,976 annually
  - Maximum 2 years cumulative use

- **Fracture Prevention Trial: Large RCT of Teriparatide vs. Placebo for 18 months**
  - 53% risk reduction for vertebral and non-vertebral fractures
  - Approved for men and women
  - Efficacy in osteoporosis and glucocorticoid-induced osteoporosis

Teriparatide (PTH) in Fracture Repair Targets Bone Formation without Resorption

FORTEO®
teriparatide injection

Dosing, optimal duration, sample size???

- No evidence that PTH treatment caused harm or impeded fracture healing.
- Meta-analysis of published data supports the use of PTH improves functional outcomes but not fracture healing rate or pain for different fracture types.
- Did not decrease the complications, need for reoperation, mortality, rate of deformity after fracture healing, or subsequent fracture.

Effectiveness of parathyroid hormone (PTH) analogues on fracture healing: a meta-analysis

K. Eastman, M. Gerlach, I. Piec, J. Greeves & W. Fraser

Osteoporosis International **32**, 1531–1546 (2021) | Cite this article

The Efficacy of Teriparatide in Improving Fracture Healing in Hip Fractures: A Systematic Review and Meta-Analysis

Shuang Han,[1] Shi-Ming Wen,[1] Qin-Peng Zhao,[2] Hai Huang,[1] Hu Wang,[1] Yu-Xuan Cong,[1] Kun Shang,[1] Chao Ke,[1] **Yan Zhuang**,[1] and **Bin-Fei Zhang**[1]

Abaloparatide (PTHrP) Targets Bone Formation without Resorption

Abaloparatide, a PTH Receptor Agonist With Homology to PTHrP, Enhances Callus Bridging and Biomechanical Properties in Rats With Femoral Fracture

Beate Lanske,[1] Heidi Chandler,[1] Allen Pierce,[1] Jeffery Brown,[1] Michael Ominsky,[1] Paul Kostenuik,[2] Gary Hattersley[1]

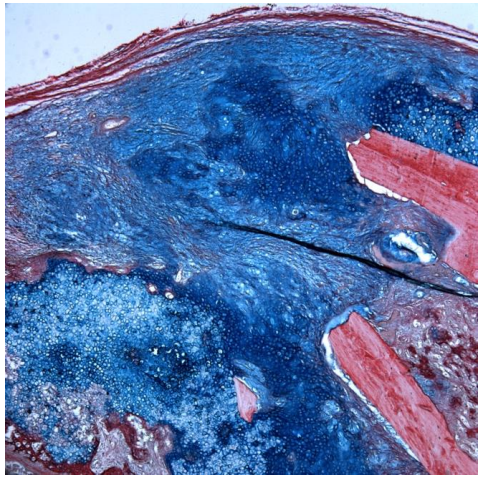
[1]Radius Health Inc., 950 Winter Street, Waltham, Massachusetts, [2]University of Michigan School of Dentistry, Phylon Pharma Services, Newbury Park, California

Received 7 September 2018; accepted 29 January 2019
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jor.24254

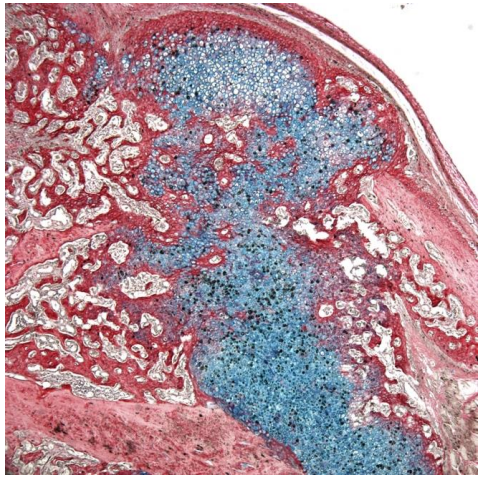
- Newer to the market: approved in 2017 vs 2002 for Forteo
- Phase III efficacy in the treatment of osteoporosis shown in the ACTIVE trial
- Currently only approved for women, clinical trial completed in men
- Numerous preclinical studies showing enhanced fracture healing
- Recruiting NCT04249232 Prospective Trial: Abaloparatide and Pelvic Fracture Healing
- Lower risk of hypercalcemia and greater BMD in hip/femoral neck compared to teriparatide

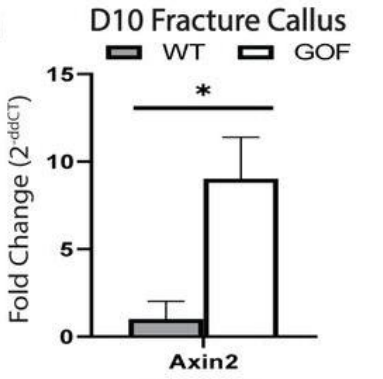
Wnt Signaling as a New Therapeutic Target

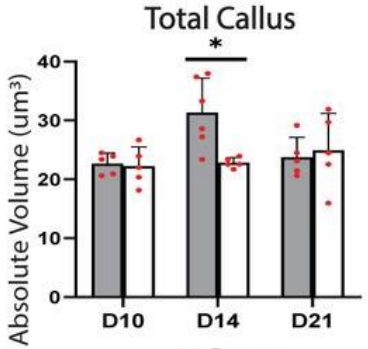
Control

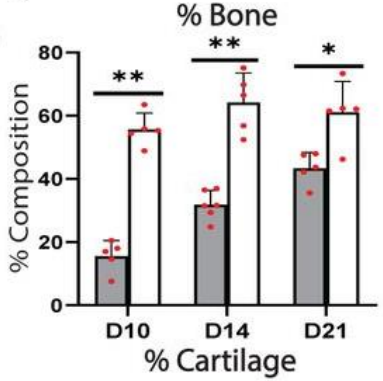


Wnt









- Peak Wnt expression in soft callus
- Important in cartilage to bone conversion
- Preclinical studies very promising in small to large animal models

Animal model	Bone	Bone injury model	Dosage, frequency	Major findings
Mouse	Tibia	Osteotomy	100 mg/kg, 1/wk	BV/TV↑, strength↑
Rat	Femur	Fracture	25 mg/kg, 2/wk	Callus↑, BMC↑, BV/TV↑, strength↑
Cynomolgus monkey	Fibula	Osteotomy	30 mg/kg, 1/2 wk	Callus↑, BMC↑, strength↑
Rat	Femur	Ablation	25 mg/kg, 2/wk	Fixation strength↑, cortical thickness↑, BV/TV↑
Rat	Femur	Fracture	25 mg/kg, 2/wk	BMD↑, BV/TV↑, strength↑, MS/BS↑, BFR/BS↑
Rat	Femur	Osteotomy	25 mg/kg, 2/wk	Callus↑, BMD↑, BV/TV↑, strength↑, bone area↑, cartilage↓
Mouse	Femur	Fracture	25 mg/kg, 2/wk	BV/TV↑, BMC↑
T1DM mouse	Femur	Fracture	25 mg/kg, 2/wk	BV/TV↑, BMC↑
Rat	Femur	Osteotomy	25 mg/kg, 2/wk	Mature callus↑, BMC↑, BMD↑, strength↑
Rat	Tibia	Metaphyseal screw	25 mg/kg, 2/wk	Pull-out strength↑, bone volume surrounding screw↑
Rat	Femur	Distraction osteogenesis	25 mg/kg, 2/wk	Union rate→, (united bones) strength↑, bone volume↑
Rat	Femur	Critical defect	25 mg/kg, 2/wk	Union rate↑, bone formation markers↑
Mouse	Femur	Osteotomy rigid fix	25 mg/kg, 2/wk	Periosteal and/or intracortical bridging→, endosteal bridging↑

Romosozumab (Anti-Scelerostin) Targets Bone Formation

Sclerostin

- Produced by osteocytes
- Inhibits bone formation and bone resorption

FDA Approval April 2019

Romosozumab (Evenity) monthly SC Injection

- Humanized monoclonal antibody that targets sclerostin
- Inhibits Sclerostin to **ACTIVATE WNT** pathway

FRAME Trial: Large (7180) RCT of Romosozumab (210 mg) or placebo for 12 months

- Additional 12 months of denosumab
- 75% risk reduction for vertebral fractures

Romosozumab (Anti-Scelerostin) Targets Bone formation without Resorption

Romosozumab in Skeletally Mature Adults with a Fresh Unilateral Tibial Diaphyseal Fracture

A Randomized Phase-2 Study

Mohit Bhandari, MD, PhD, Emil H. Schemitsch, MD, FRCS(C), Theofilos Karachalios, MD, Parag Sancheti, FRCS(Ed), MS(Orth), DNB(Orth), MCh(UK), PhD(Dundee, UK), Rudolf W. Poolman, MD, PhD, John Caminis, MD, Nadia Daizadeh, PhD, Ricardo E. Dent-Acosta, MD, Ogo Egbuna, MD, MSc, Arkadi Chines, MD, and Theodore Miclau, MD

- Prospective, double-blind phase-2 RCT (N=402)
- 1 of 9 Romosozumab groups or placebo for 3 months
- Primary outcome: radiographic fracture healing at 6 months
- Romosozumab did not accelerate tibial fracture-healing

Romosozumab (Anti-Scelerostin) Targets Bone formation without Resorption

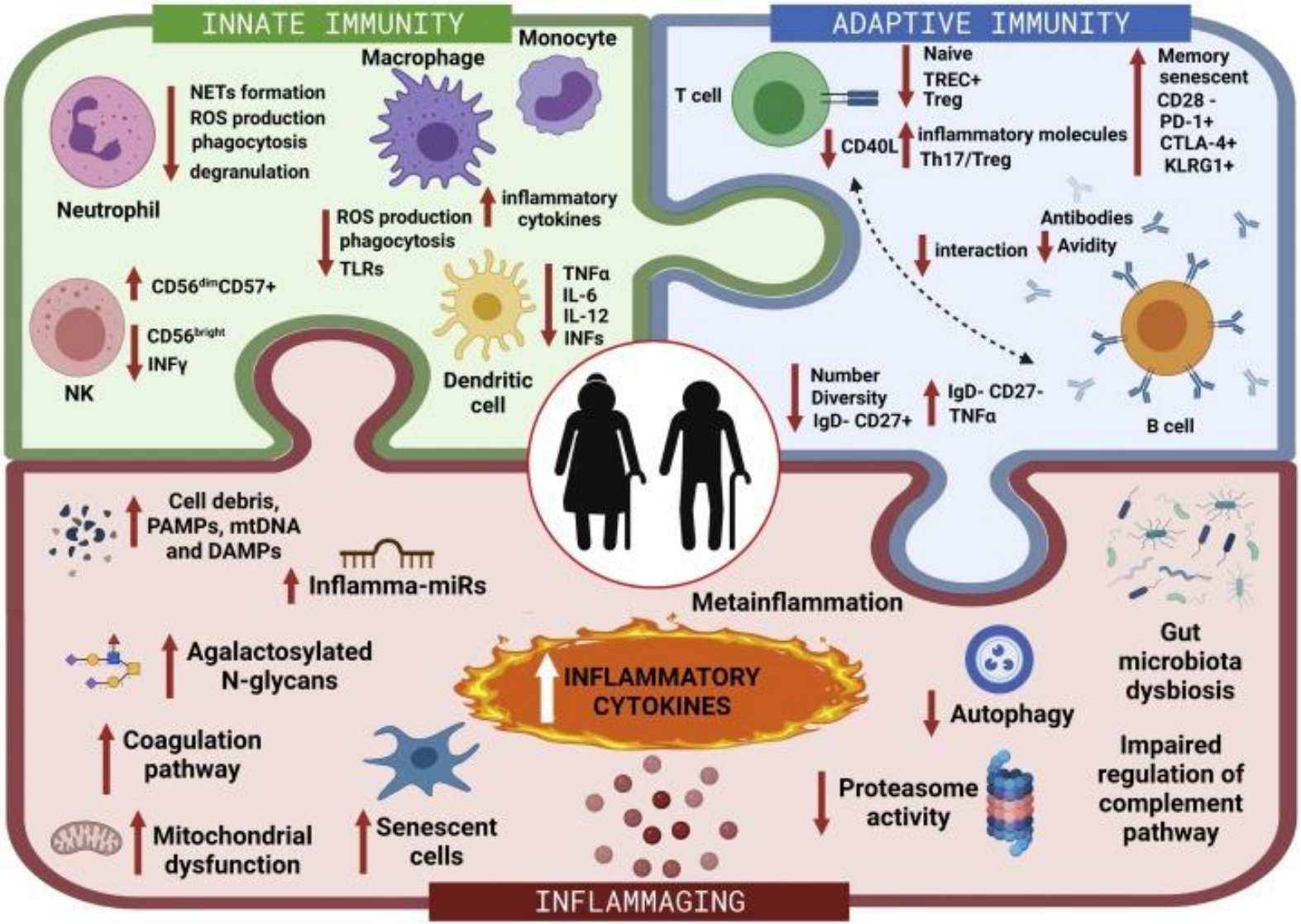
A Randomized, Placebo-Controlled Study of Romosozumab for the Treatment of Hip Fractures

Timing, drug target, systemic delivery

Andreas Grauer, MD, and Mohit Bhandari, MD, PhD

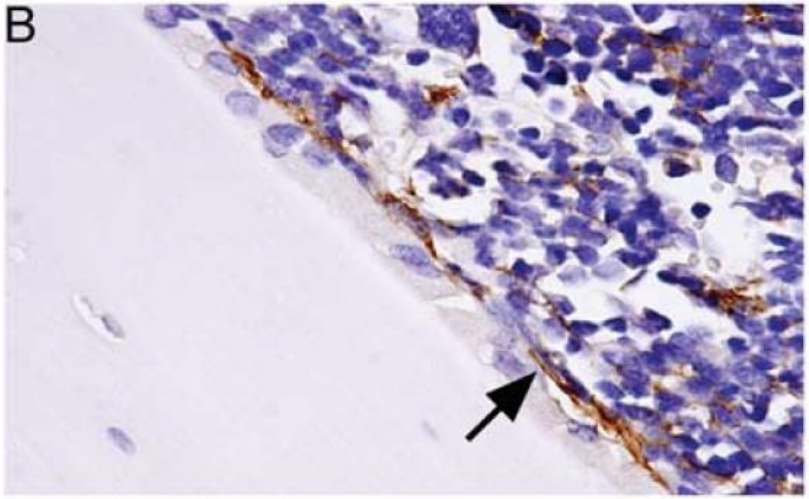
- Prospective, double-blind phase-2 RCT (N = 332; over age 55)
- Romosozumab (70, 140, or 210 mg) or a placebo until 3 months
- Outcomes: mean timed "Up & Go" score and radiographic fracture healing
- Romosozumab did not accelerate clinical or radiographic hip fracture-healing

Treatments Targeting Immunosenescence & Inflammaging

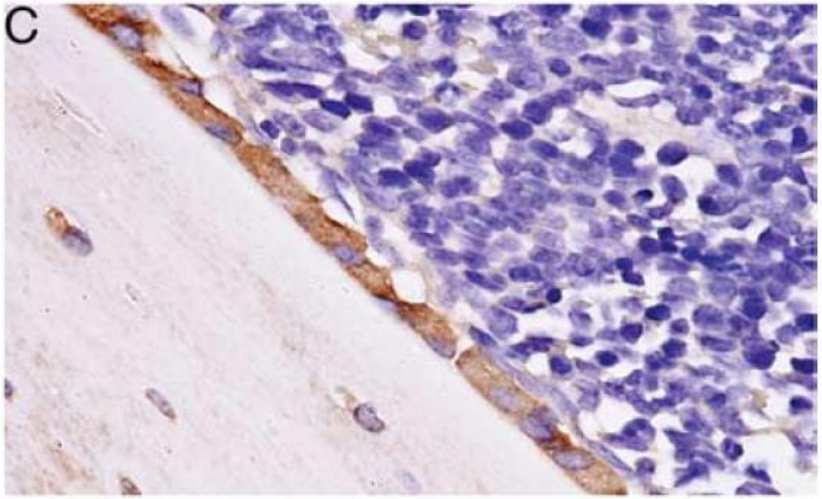


Increased Inflammation and Senescence with Aging

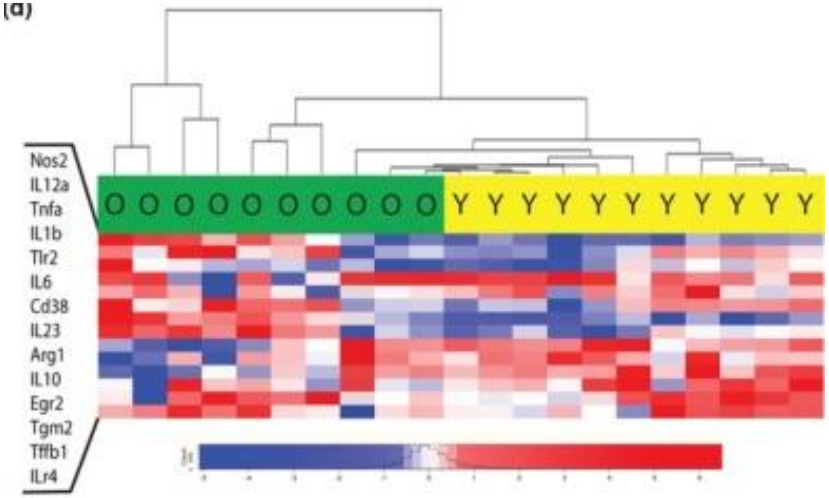
Macrophages



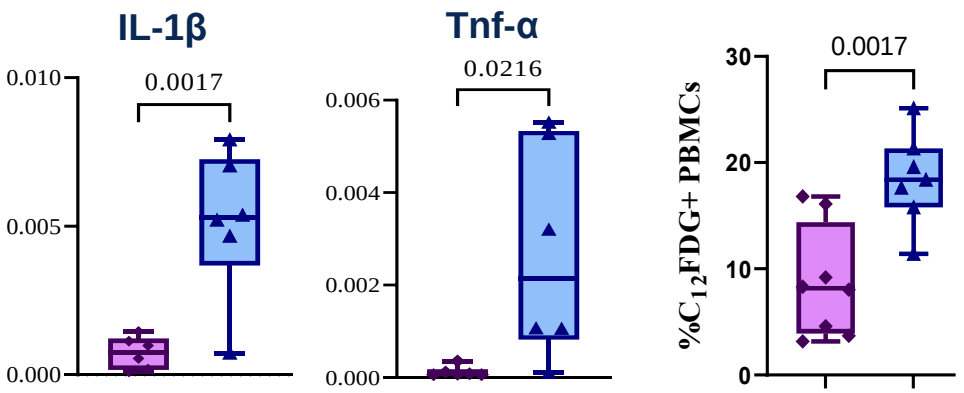
Osteoblasts



Chang et al, Bone 2008

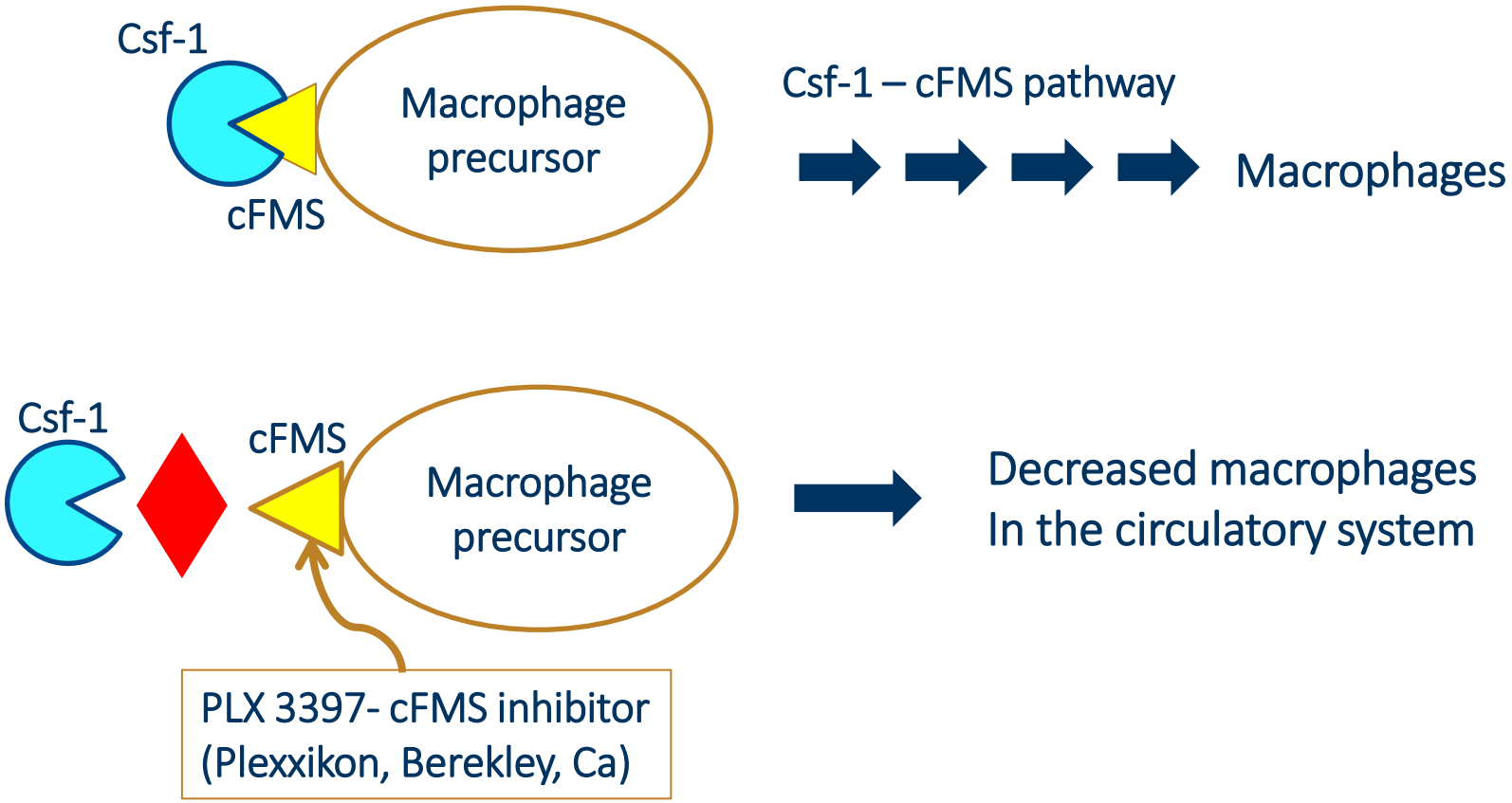


D Clark, Aging Cell 2020



Philippon, Duke et al. Unpublished

cFms Activation Required for Differentiation & Function of Macrophages

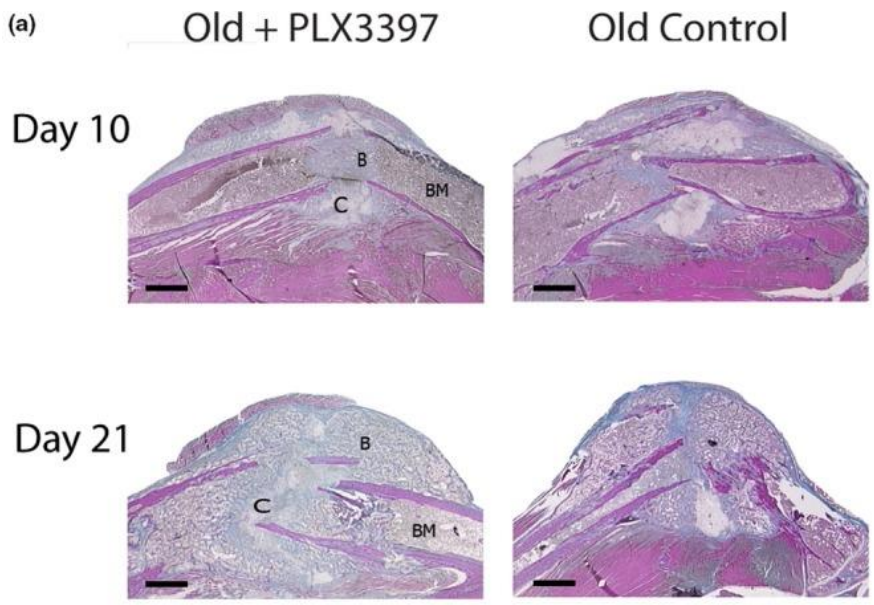


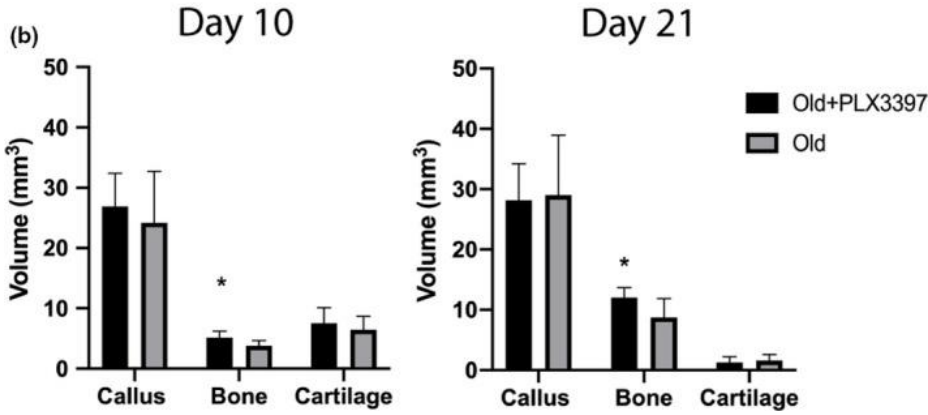
PLX3397 to Mice Inhibits Migration of Macrophages and Stimulates Healing in Old Mice

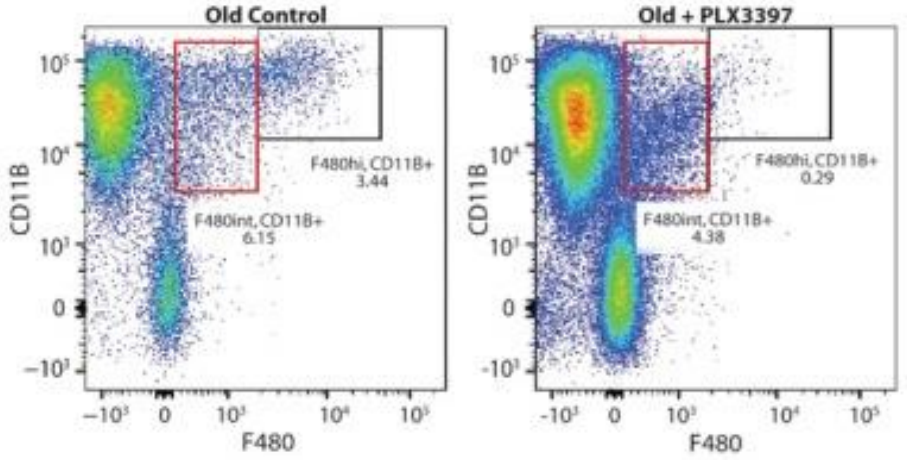
Aging Cell Open Access ANATOMICAL SOCIETY

Aging Cell. 2020 Mar; 19(3): e13112. PMCID: PMC7059136
Published online 2020 Feb 25. doi: 10.1111/acel.13112 PMID: 32096907

Age-related changes to macrophages are detrimental to fracture healing in mice







Clearance of Senescent Cells Improves Fracture Healing

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 Kosinsky[5], Stephanie J Vos[1,2], Madison L Doolittle[1,2], Joshua N Farr[1,2,4]*, Sundeep Khosla[1,2,3,4]*

[1]Division of Endocrinology, Mayo Clinic, Rochester, United States; [2]Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, United States; [3]Department of Trauma, Orthopedics and Reconstructive Surgery, Georg-August-University of Goettingen, Goettingen, Germany; [4]Division of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, United States; [5]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, United States

gation

COMMENTARY

enolytic treatment: a paradigm to
ure repair during aging

, and Rafael de Cabo

te on Aging (NIA), NIH, Baltimore, Maryland, USA.

changes, and
capacity for
d to changes
f senescent
res. In this
olytic drug
one fracture
e at fracture
should provide

for treatments tailored to older individuals. During aging, a therapeutic window may exist, in which short-term senolytic treatments could boost the organism's bone repair potential. However, if senescent cells are present at the site of repair, regardless of the age of the individual, defining the window of treatment opportunity is important to maximize therapeutic benefit. Experiments should evaluate the effects of senolytic or senomorphic (SASP-modulating) treatments at various ages to identify the limits of therapeutic benefit and determine whether the dura-

The Journal of Clinical Investigation

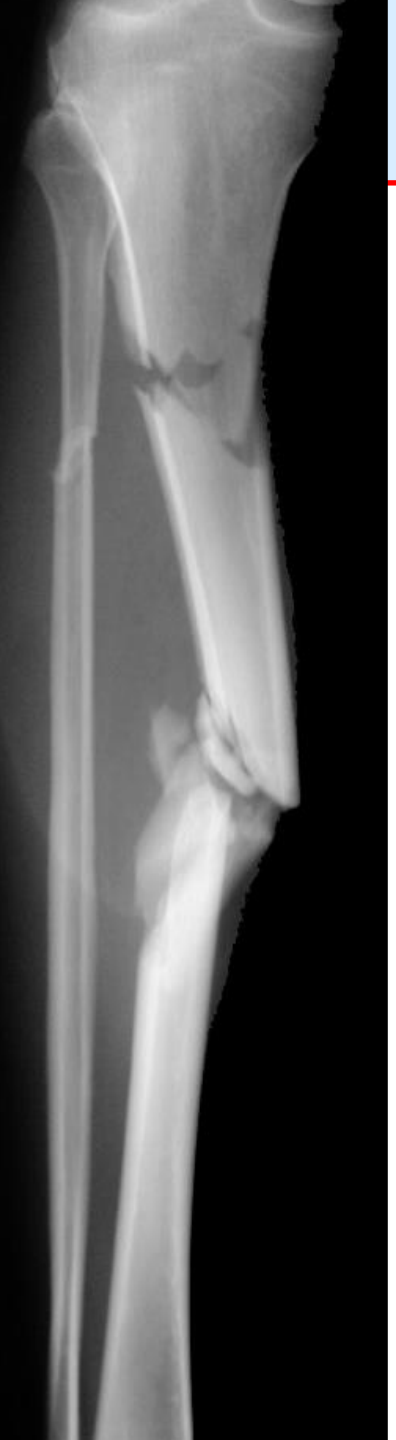
RESEARCH ARTICLE

Age-associated callus senescent cells produce TGF-β1 that inhibits fracture healing in aged mice

Jiatong Liu,[1] Jun Zhang,[2,3] Xi Lin,[1] Brendan F. Boyce,[1] Hengwei Zhang,[1] and Lianping Xing[1]

[1]Department of Pathology and Laboratory Medicine, Center for Musculoskeletal Research, University of Rochester Medical Center, Rochester, New York, USA. [2]Plastic Surgery Center, Department of Orthopedics, Zhejiang Provincial People's Hospital, Hangzhou, Zhejiang, China. [3]Suzhou Institute of Systems Medicine, Suzhou, China.

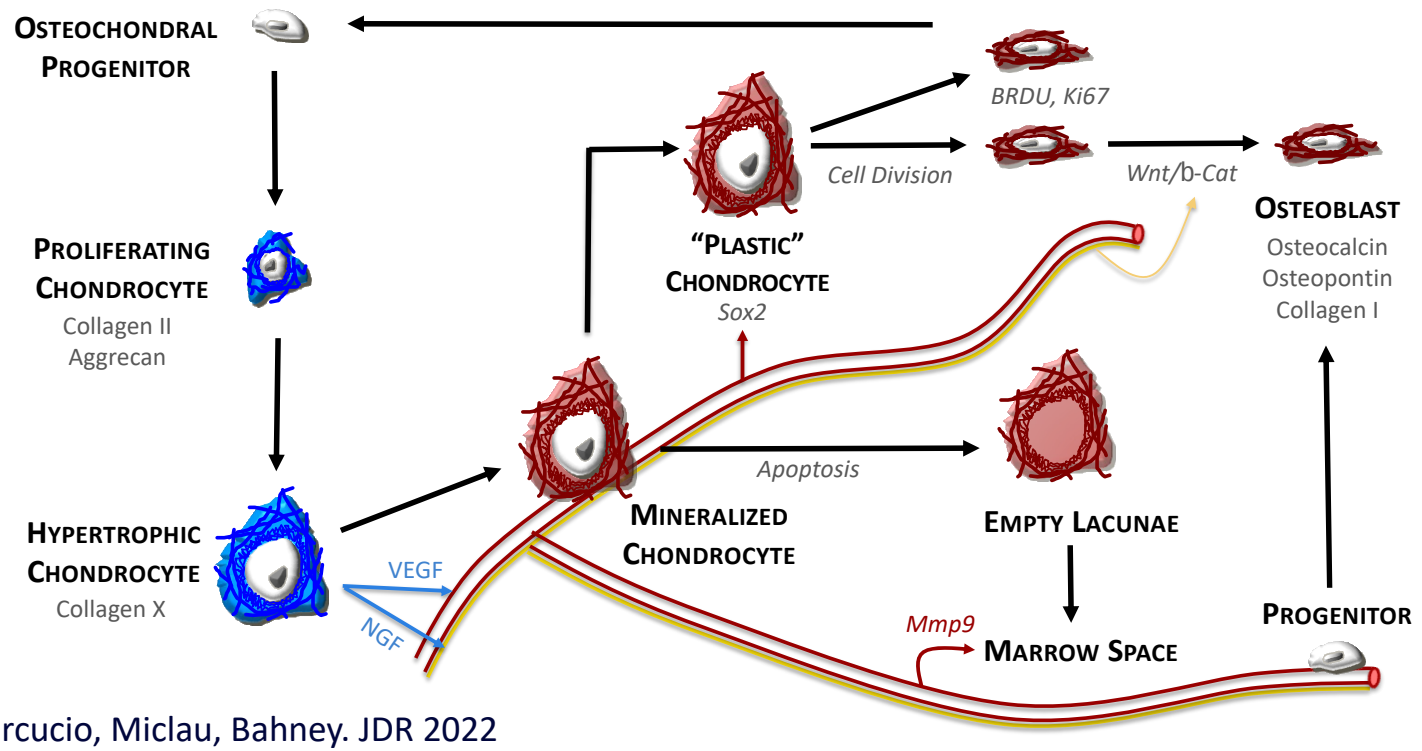
Cellular senescence plays an important role in human diseases, including osteoporosis and osteoarthritis. Senescent cells (SCs) produce the senescence-associated secretory phenotype to affect the function of neighboring cells and SCs themselves. Delayed fracture healing is common in the elderly and is accompanied by reduced mesenchymal progenitor cells (MPCs). However, the contribution of cellular senescence to fracture healing in the aged has not to our knowledge been studied. Here, we used C57BL/6J 4-month-old young and 20-month-old aged mice and demonstrated a rapid increase in SCs in the fracture callus of aged mice. The senolytic drugs dasatinib plus quercetin enhanced fracture healing in aged mice. Aged callus SCs inhibited the growth and proliferation of callus-derived MPCs (CaMPCs) and expressed high levels of TGF-β1. TGF-β–neutralizing Ab prevented the inhibitory effects of aged callus SCs on CaMPCs and promoted fracture healing in aged mice, which was associated with increased CaMPCs and proliferating cells. Thus, fracture triggered a significant cellular senescence in the callus cells of aged mice, which inhibited MPCs by expressing TGF-β1. Short-term administration of dasatinib plus quercetin depleted callus SCs and accelerated fracture healing in aged mice. Senolytic drugs represent a promising therapy, while TGF-β1 signaling is a molecular mechanism for fractures in the elderly via SCs.



Back to Biology for New Candidates

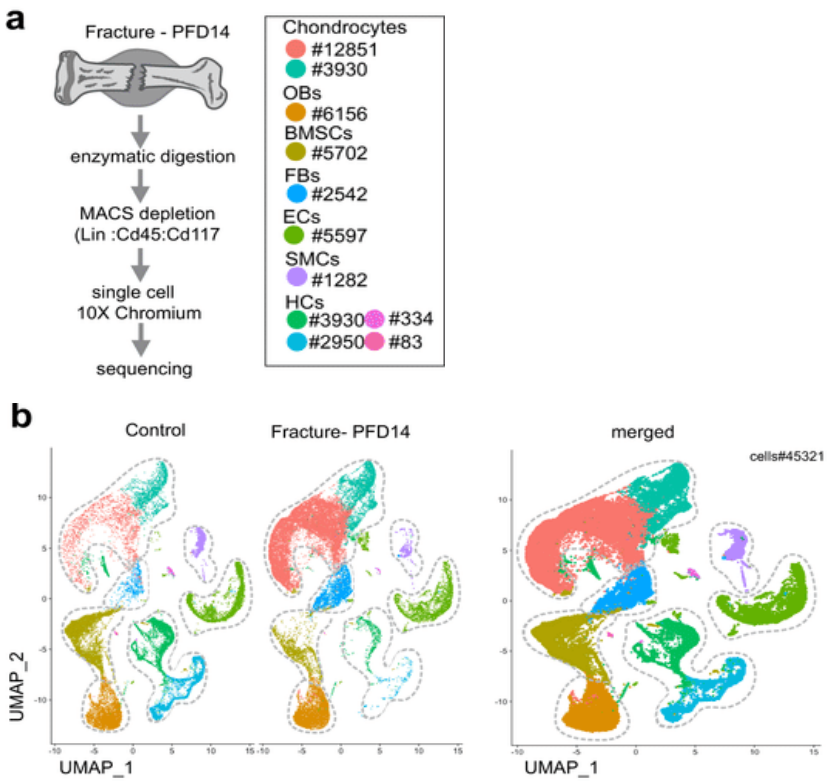
Need a better understanding of the processes during healing to develop therapies.

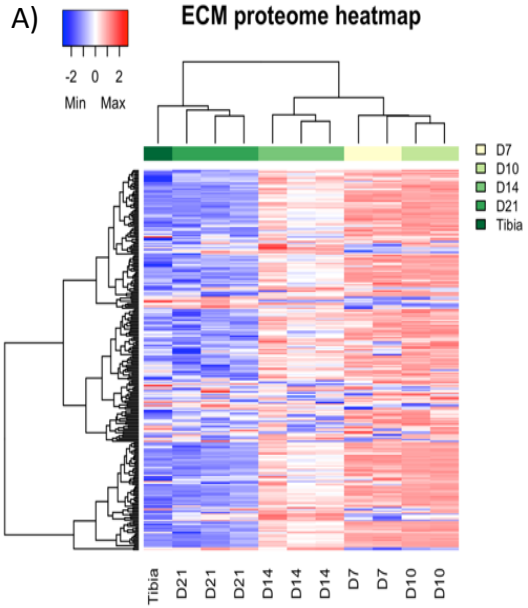
- ✓ Origin of stem/progenitor cells
- ✓ Optimized timing for growth factor delivery
- ✓ Conversion of cartilage to bone

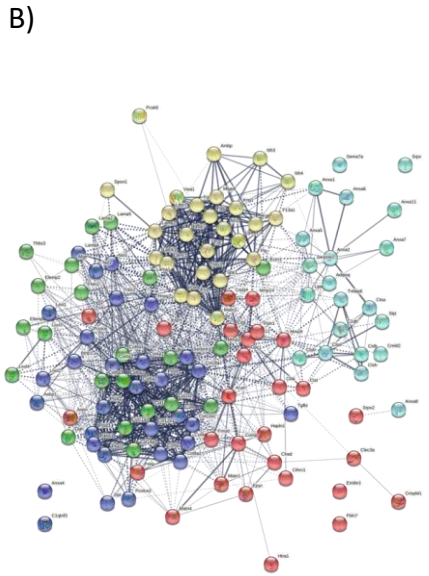


Marcucio, Miclau, Bahney. JDR 2022

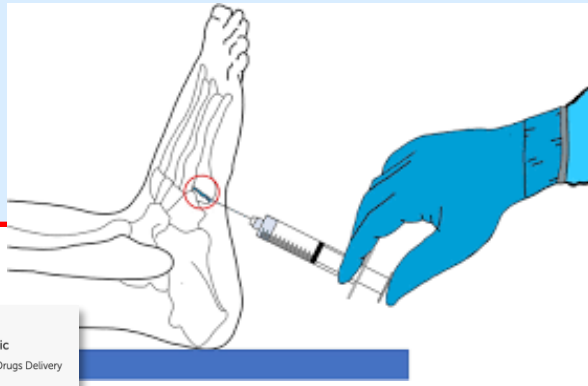
Big Data and Bioinformatics of Fracture Healing: Finding New Targets

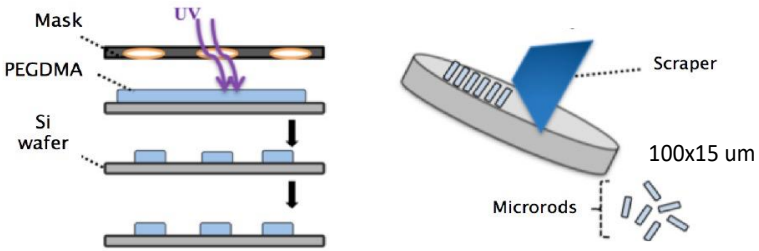






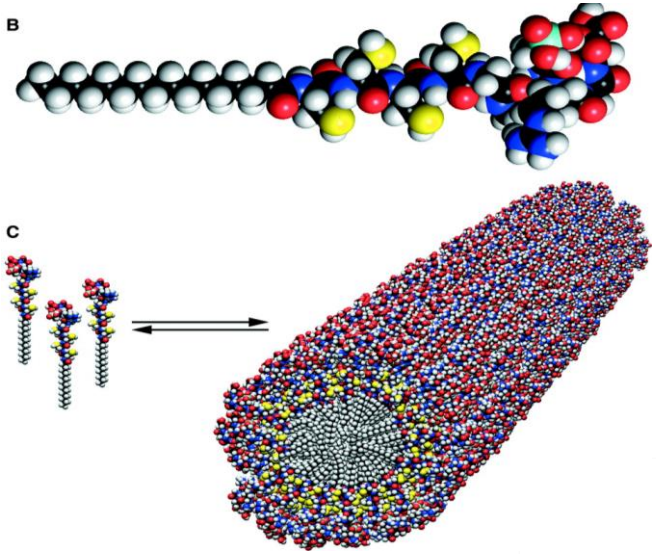
Biomaterials for Controlled & Sustained Local Delivery





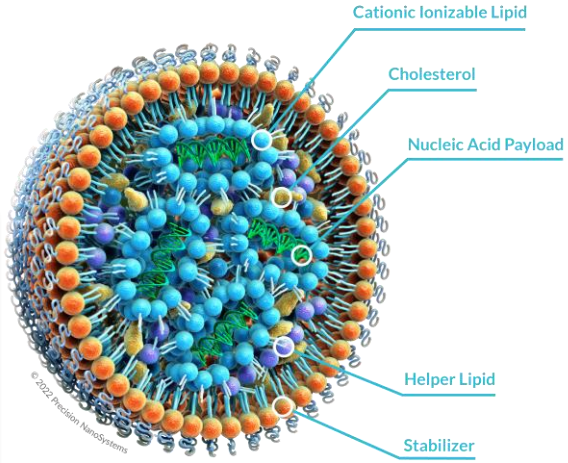
ORIGINAL RESEARCH article
Front. Bioeng. Biotechnol., 22 May 2023
Sec. Biomaterials
Volume 11 - 2023 |
https://doi.org/10.3389/fbioe.2023.1190371
This article is part of the Research Topic
Advanced Nanomaterials and Hydrogels for Drugs Delivery and Controlled Release
View all Articles >

Encapsulation of β-NGF in injectable microrods for localized delivery accelerates endochondral fracture repair



ADVANCED HEALTHCARE MATERIALS
Full Paper

Gel Scaffolds of BMP-2-Binding Peptide Amphiphile Nanofibers for Spinal Arthrodesis



WILEY Journal of Tissue Engineering and Regenerative Medicine
This Article | For Authors | Learn More | Submit
J Tissue Eng Regen Med. 2022 Nov; 16(11): 961–976.
Published online 2022 Sep 16. doi: 10.1002/term.3349
PMCID: PMC9826348
PMID: 36112528

Therapeutic approaches to activate the canonical Wnt pathway for bone regeneration

Anna Laura Nelson, [1,2] GianLuca Fontana, [3] Elizabeth Miclau, [1] Mallory Rongstad, [3] William Murphy, [3,4] Johnny Huard, [1,5] Nicole Ehrhart, [2,5] and Chelsea Bahney [1,2,5,6]