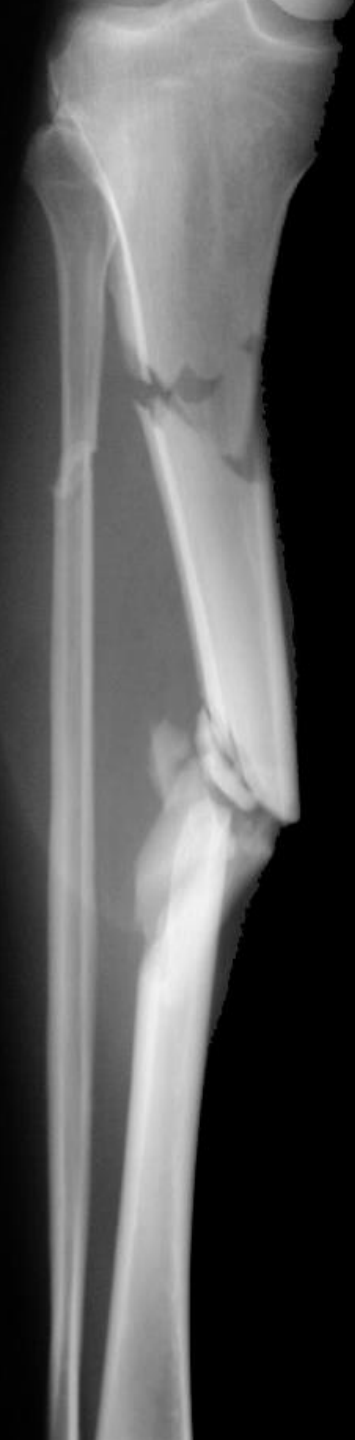


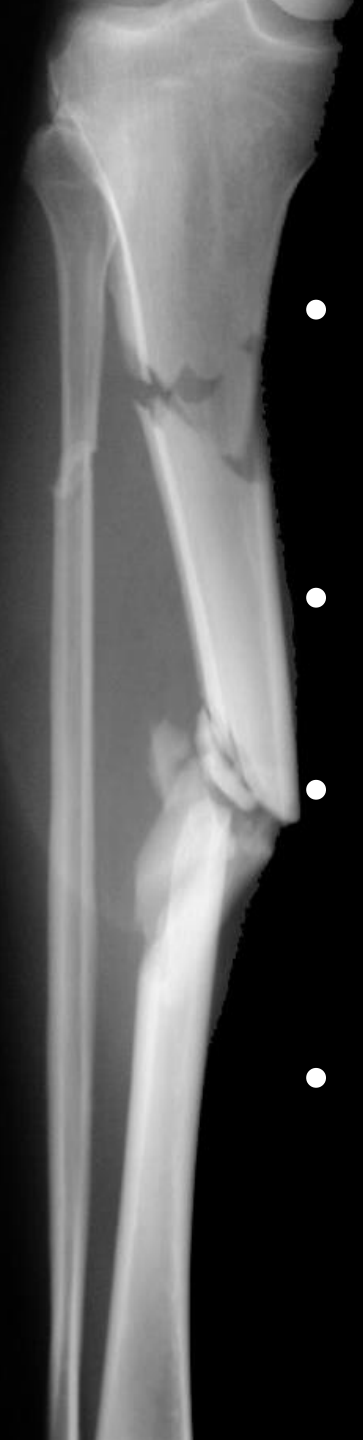
Bone Healing: Are There Any Growth Factors on the Horizon?

Ralph Marcucio, PhD
Orthopaedic Surgery, UCSF

Orthopaedic Trauma Institute
UCSF + SAN FRANCISCO GENERAL HOSPITAL

Disclosures

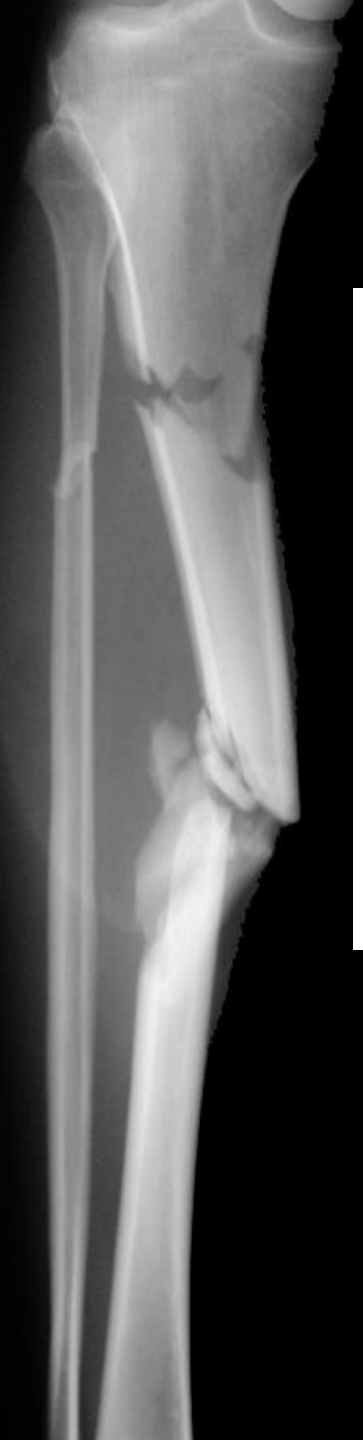
Funding:
Rosies Base



Burden of Fracture is High

- There are approximately 6.5 million fractures in the US each year
- 10-15% fail to heal adequately
- Patient disability is high; 51% fail to return to work in 6 months.
- Developing biological treatments may facilitate healing by promoting faster time to union, reduced non-union rates, and treating established non-unions.

BMPs were not the Magic Bullet



SCIENTIFIC ARTICLES

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]

Author Information

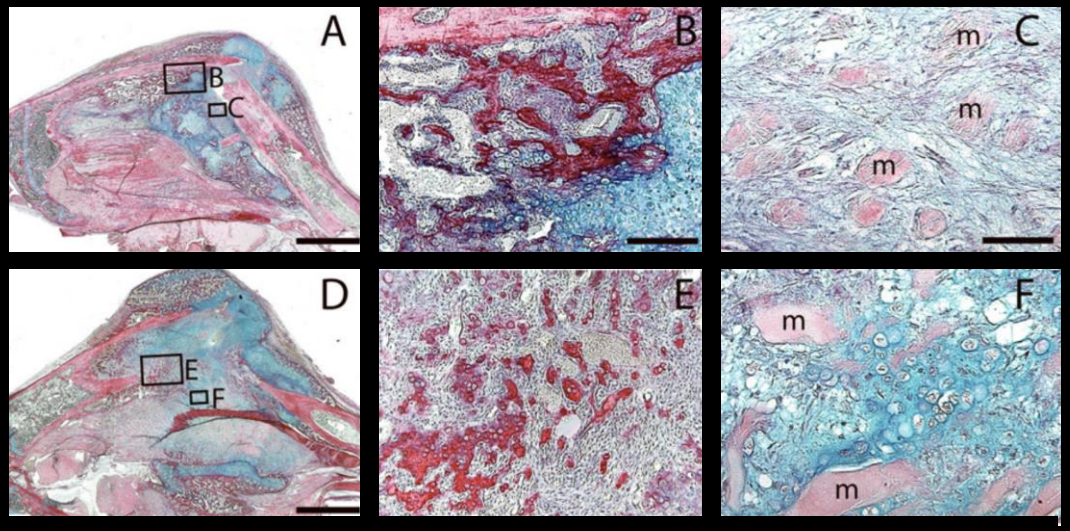
Conclusions:

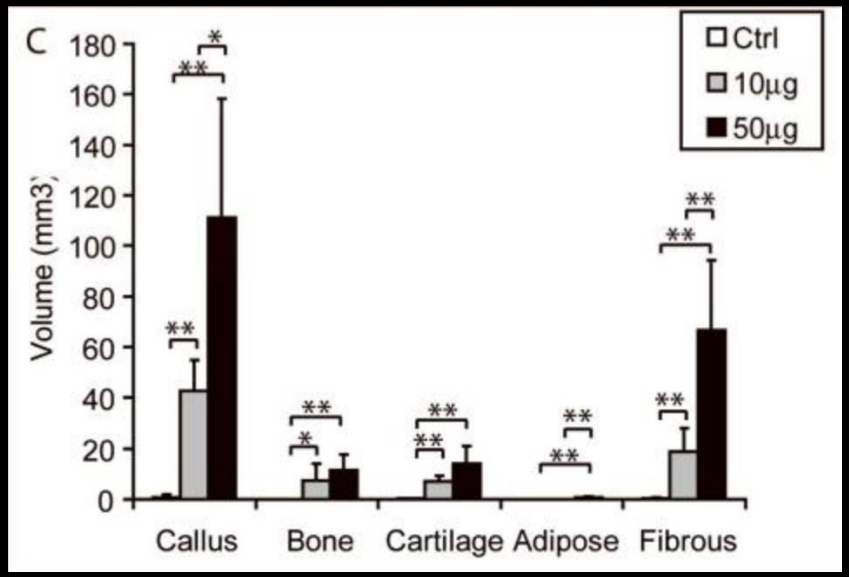
The healing of open tibial fractures treated with reamed intramedullary nail fixation was not significantly accelerated by the addition of an absorbable collagen sponge containing rhBMP-2.

This was Surprising?

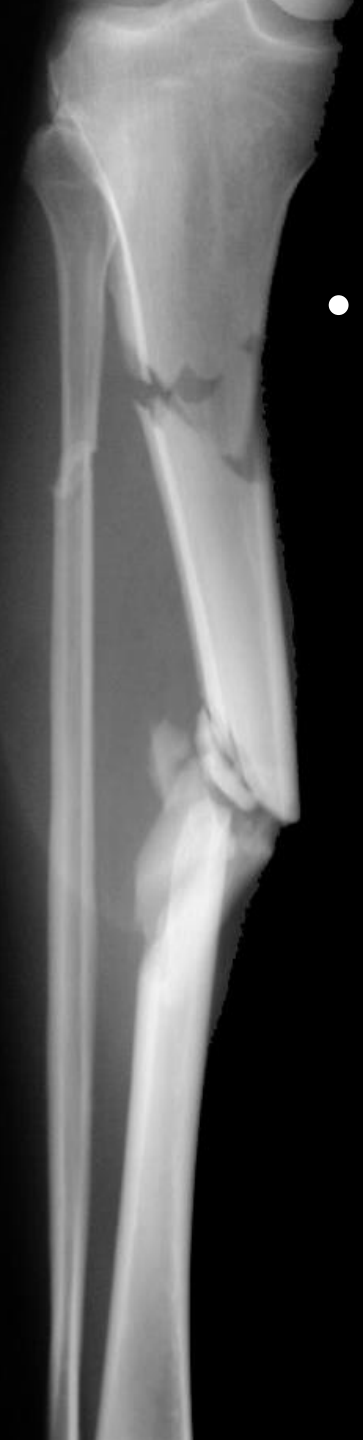
CONTROL

RH-BMP-7





Was the Dosing wrong?
Clearance too rapid?
Timing?



Where do we go from here?

- Back to Biology: Need a better understanding of the processes during healing to develop therapies.

For Example:

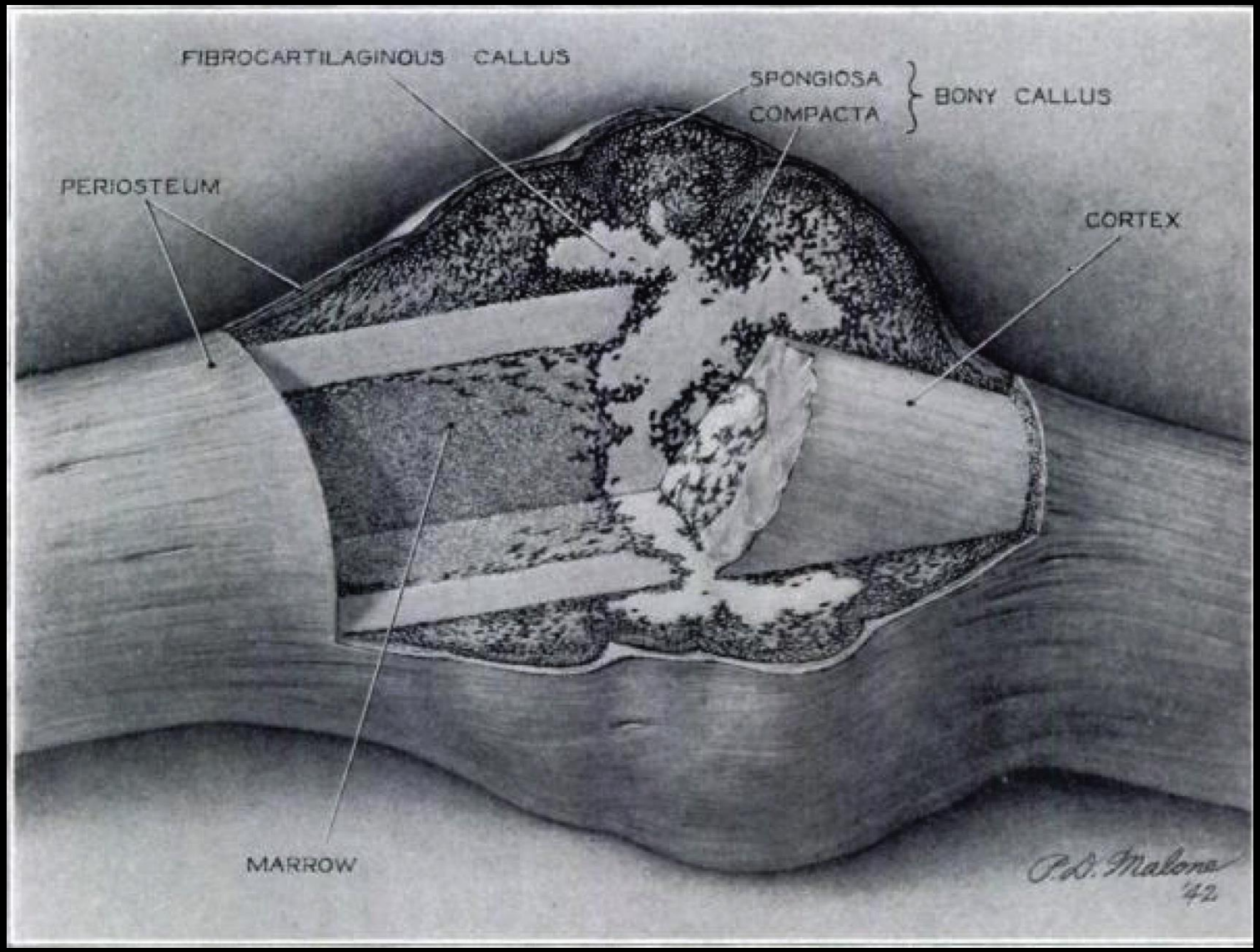
- origin of stem/progenitor cells.

- interactions among cells/tissues.

- conversion of cartilage to bone.

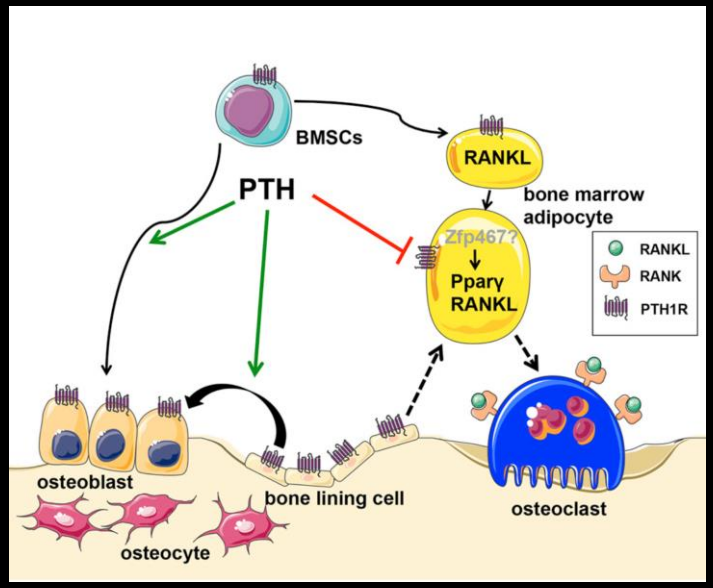
- new technologies for delivery

Fracture Healing is a Complex Set of Interactions



Urist, 1943

Treatments Targeting Progenitors

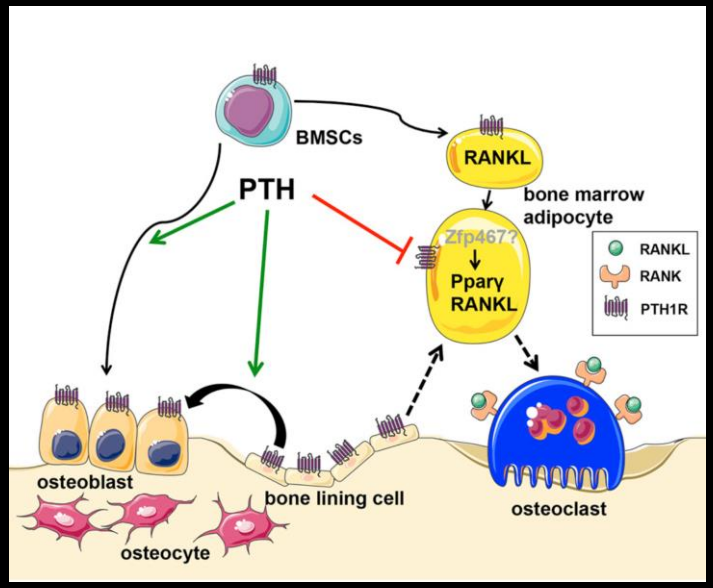


Fan et al, 2017

PTH, PTHrP., Teriparatide (Forteo) , etc:

- All work through the same receptor
- Act on stem cells and osteoblasts

Treatments Targeting Progenitors



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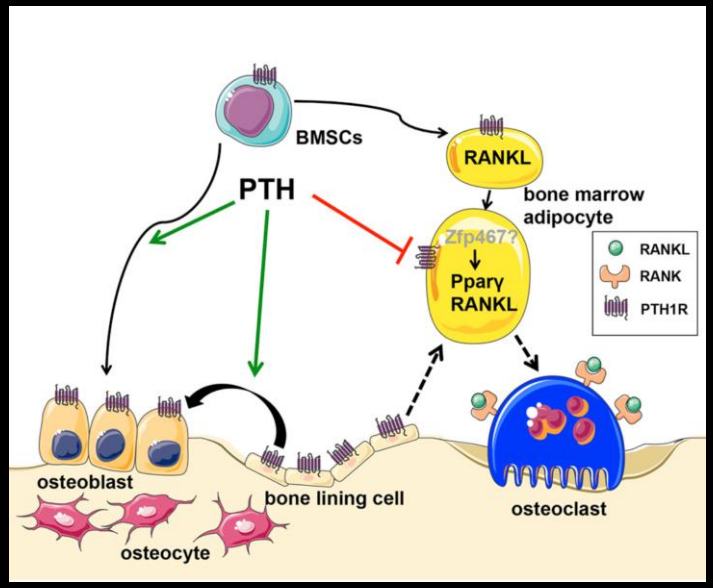
Osteoporosis:

Increases bone mineral density

Reduces fracture risk

Treatments Targeting Progenitors



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PTH, PTHrP., Teriparatide (Forteo) , etc:

All work through the same receptor

Act on stem cells and osteoblasts

Osteoporosis:

Increases bone mineral density

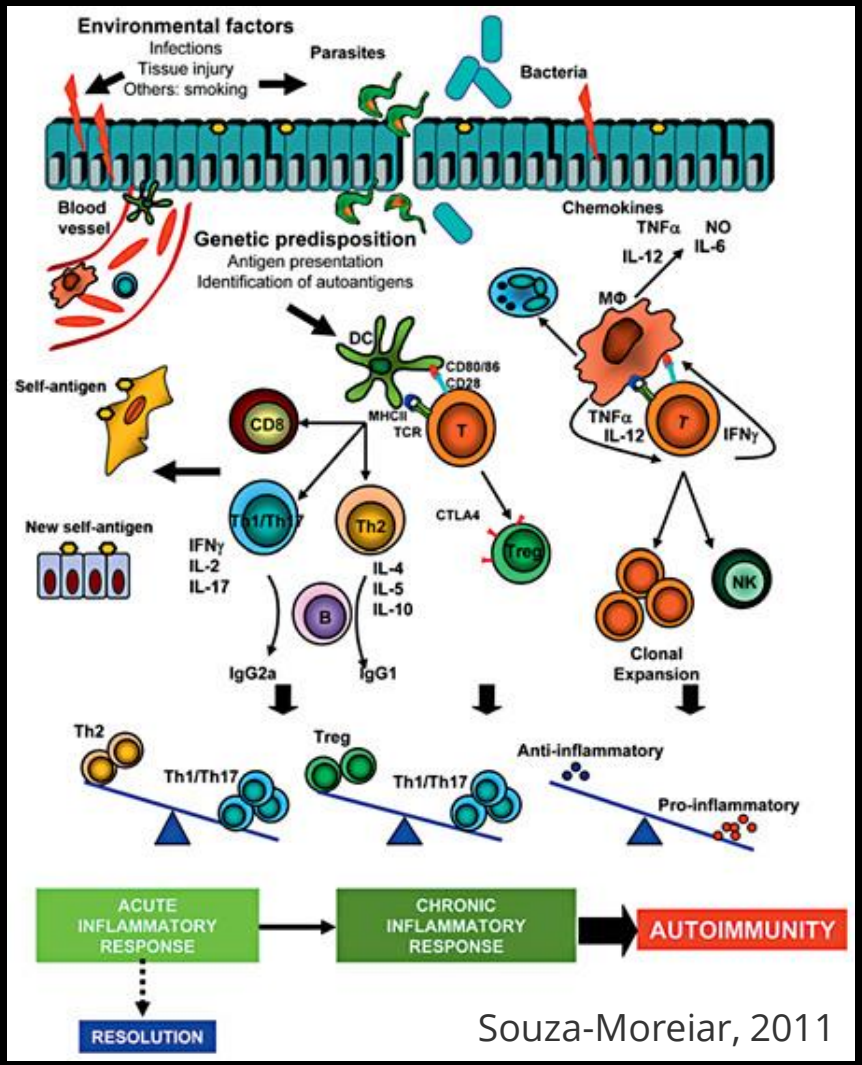
Reduces fracture risk

What about fracture healing?

Works well in small animal and non-human primate models

Clinical data are unclear due to differences dosing, site of injury, age, etc.

Treatments Targeting Tissue Interactions

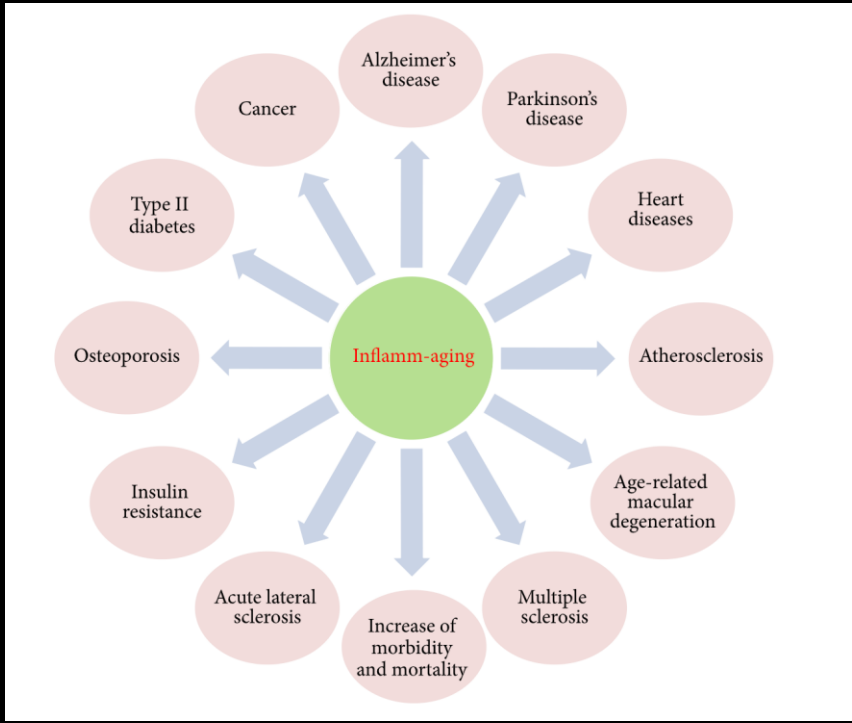


Souza-Moreiar, 2011

-A large influx of all inflammatory cell types after injury that affect healing.

debridement,
cell signaling

Inflammaging



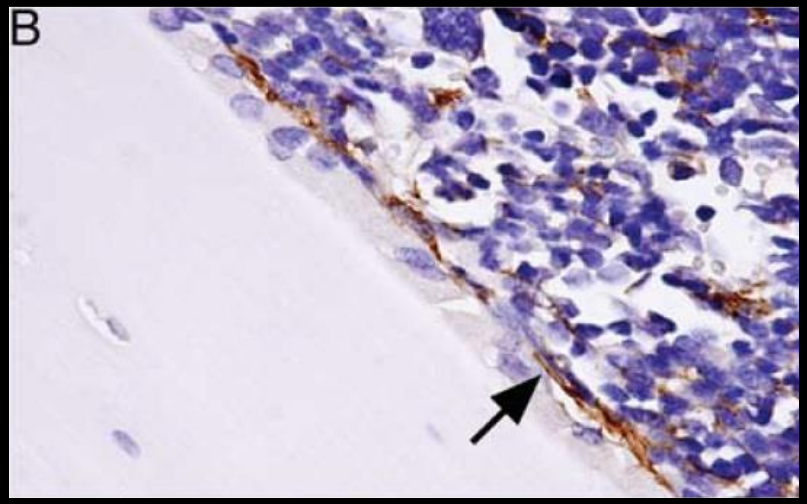
-Aging produces an increasingly pro-inflammatory environment that impairs healing.

Inflammaging = macrophaging

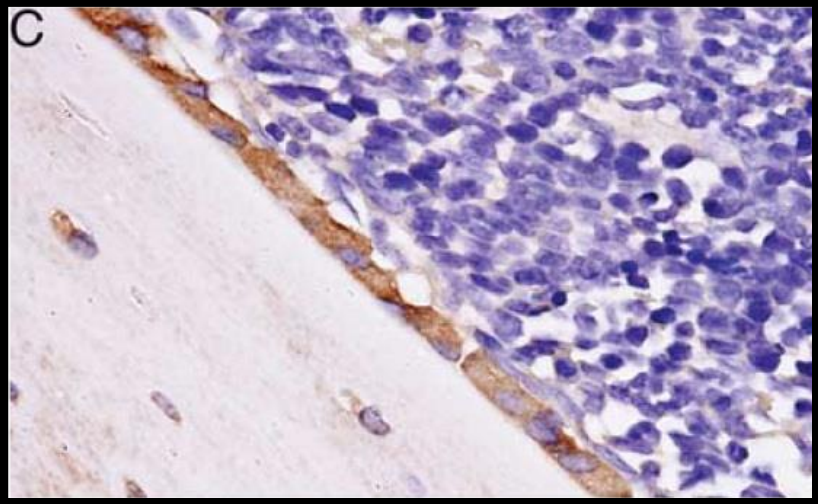
-Can this be targeted therapeutically?

Macrophages are Associated with Bone

Macrophages



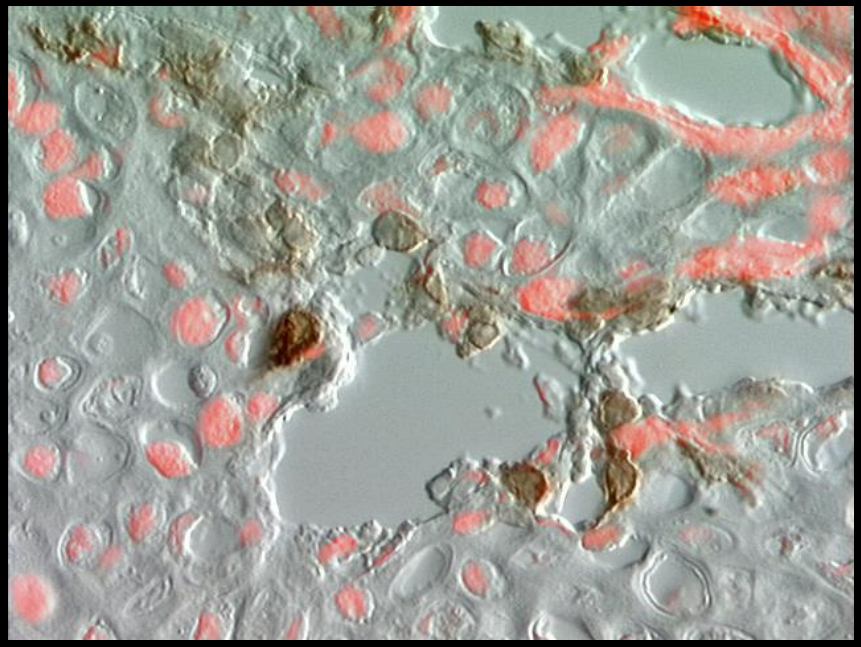
Osteoblasts



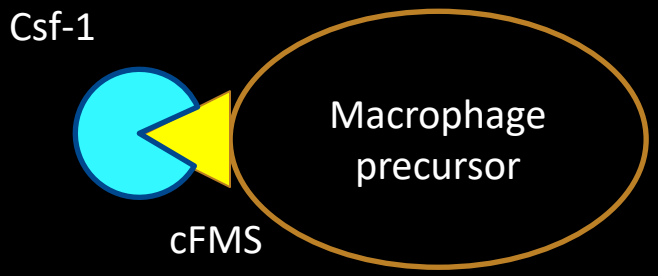
Chang et al, Bone 2008

Macrophages are Associated with Bone Healing

Macrophages and chondrocytes

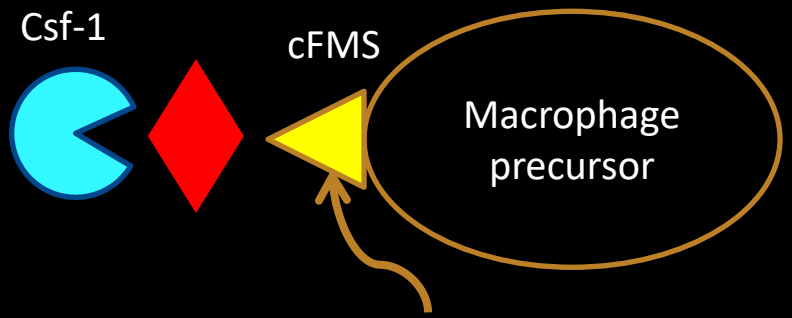


cFms Activation is Required for Differentiation and Function of Macrophages



Csf-1 – cFMS pathway

→ → → → Macrophages

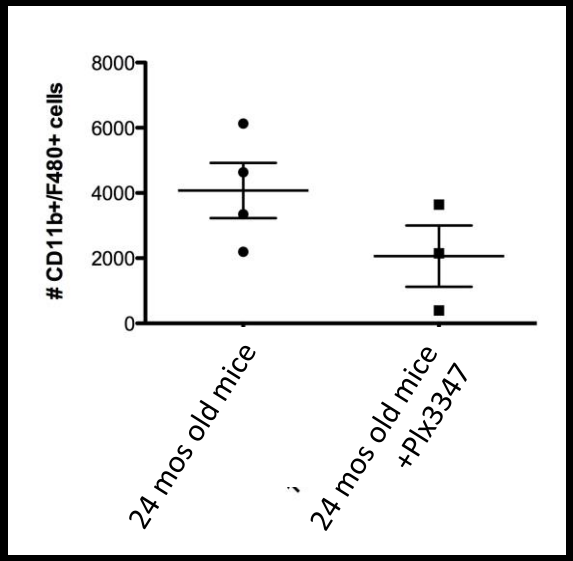


→ Decreased macrophages
In the circulatory system

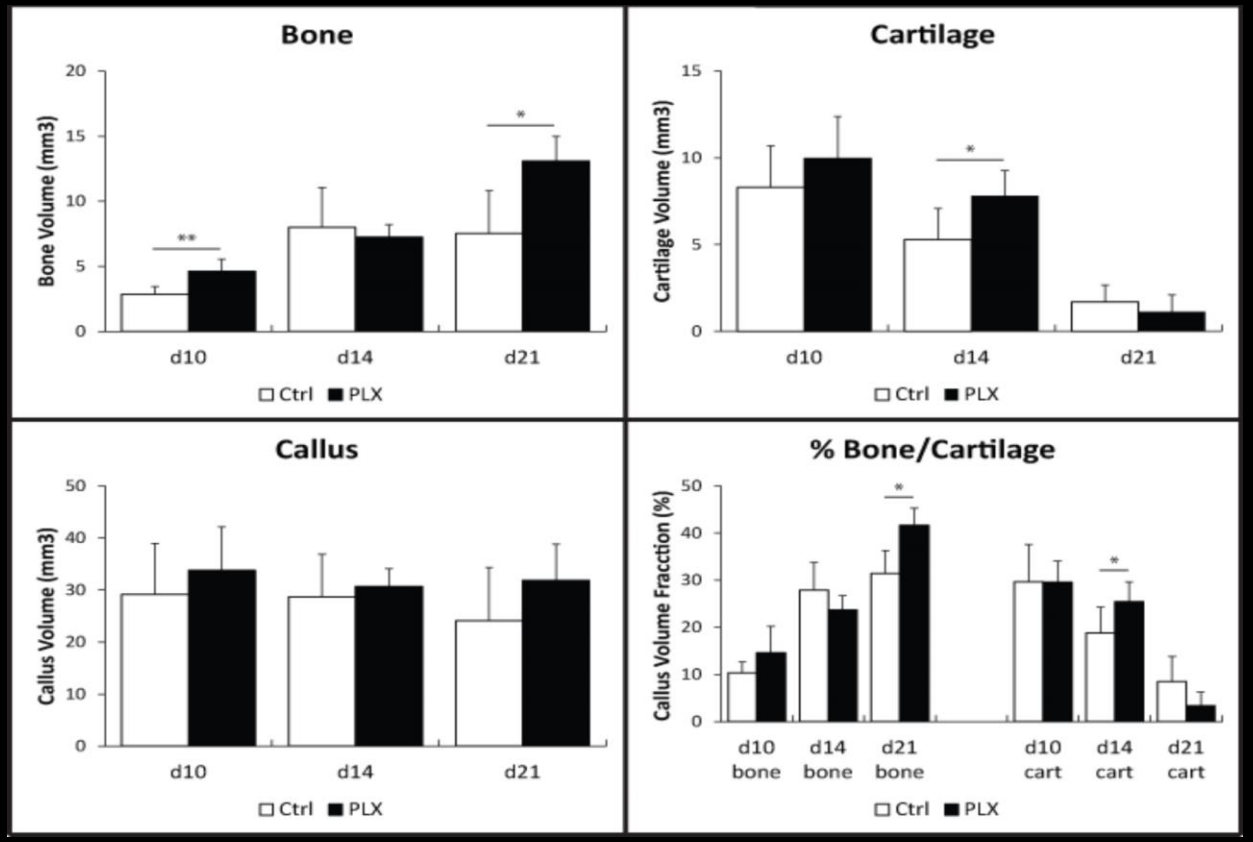
PLX 3397- cFMS inhibitor
(Plexxikon, Berekley, Ca)

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

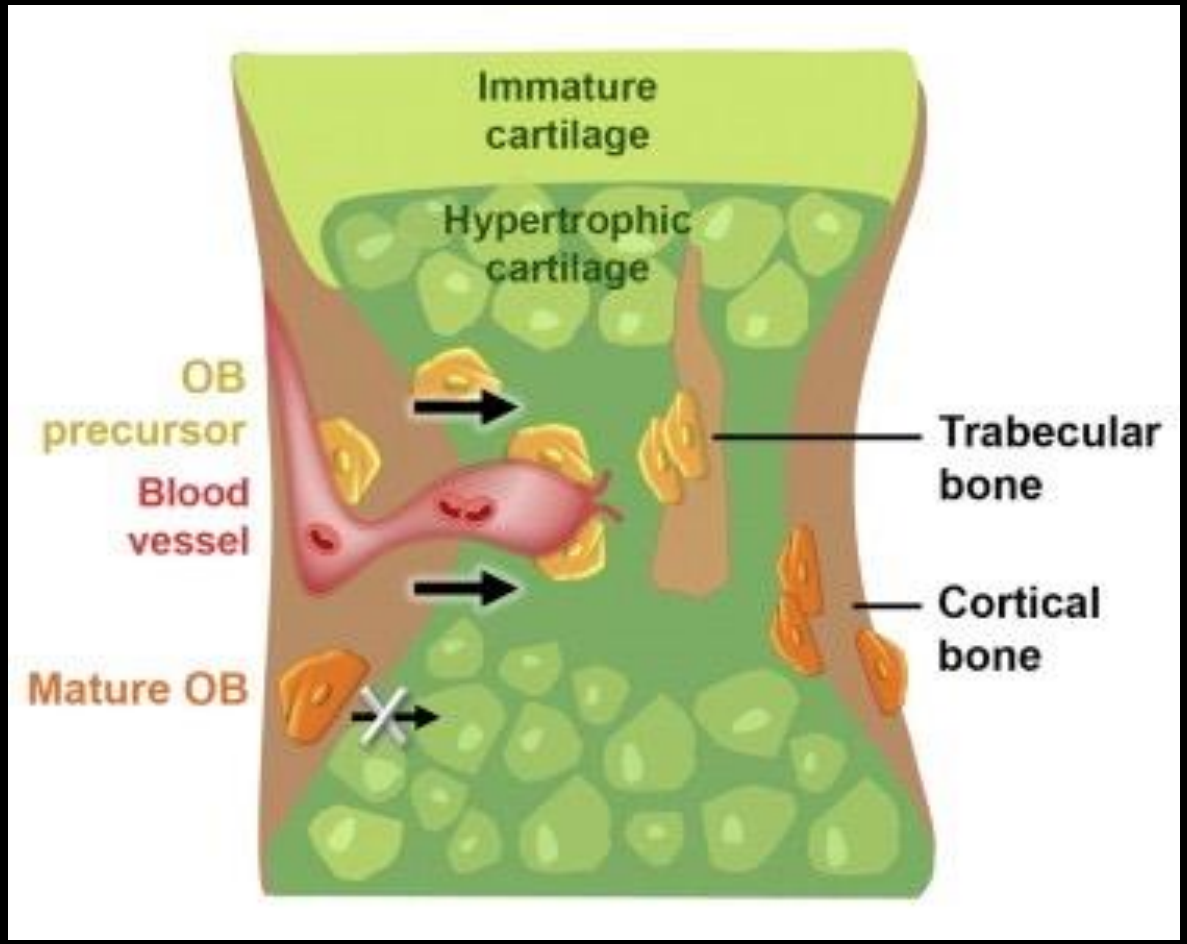
Macrophages



Healing



Endochondral Ossification



Maes et al, 2010

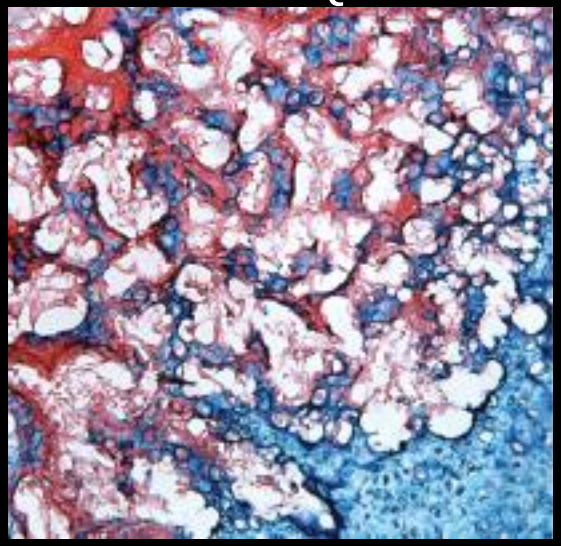
Chondrocytes Give Rise to Osteoblasts During Fracture Healing

Indelibly label chondrocytes genetically.

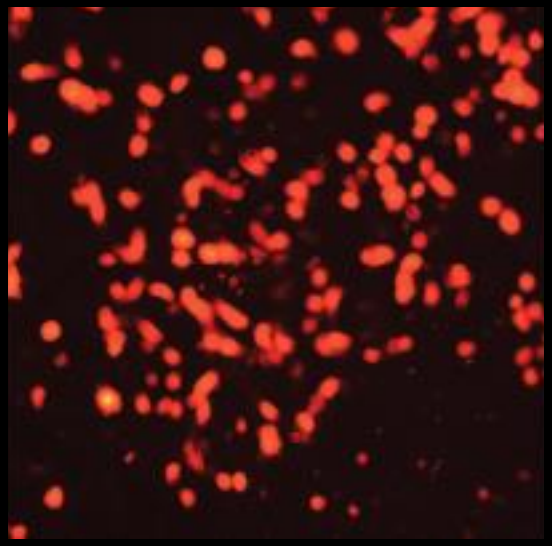
They express a red fluorescent protein.

We can follow their fate.

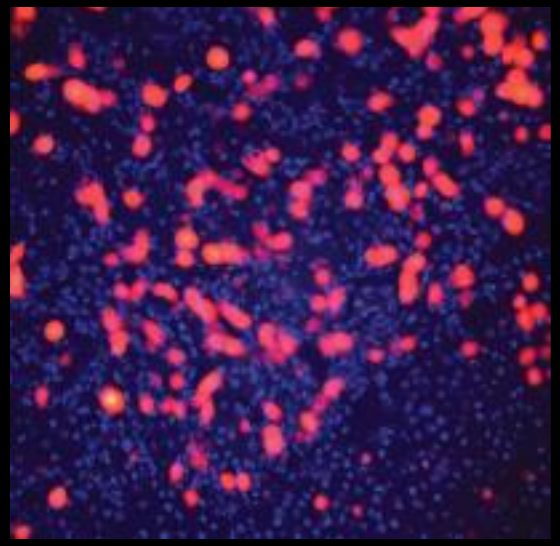
HBQ



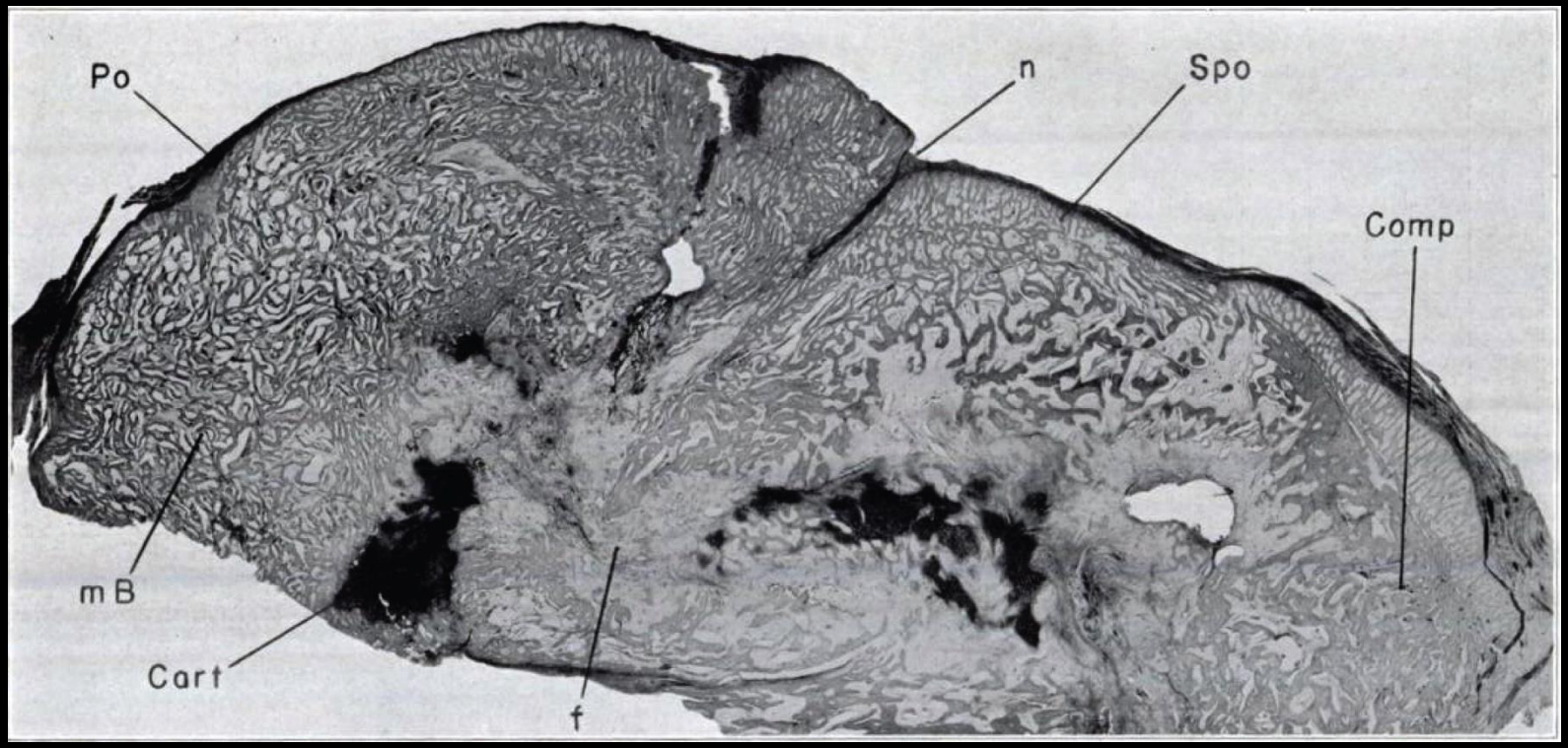
dTom



dTom/Hoescht

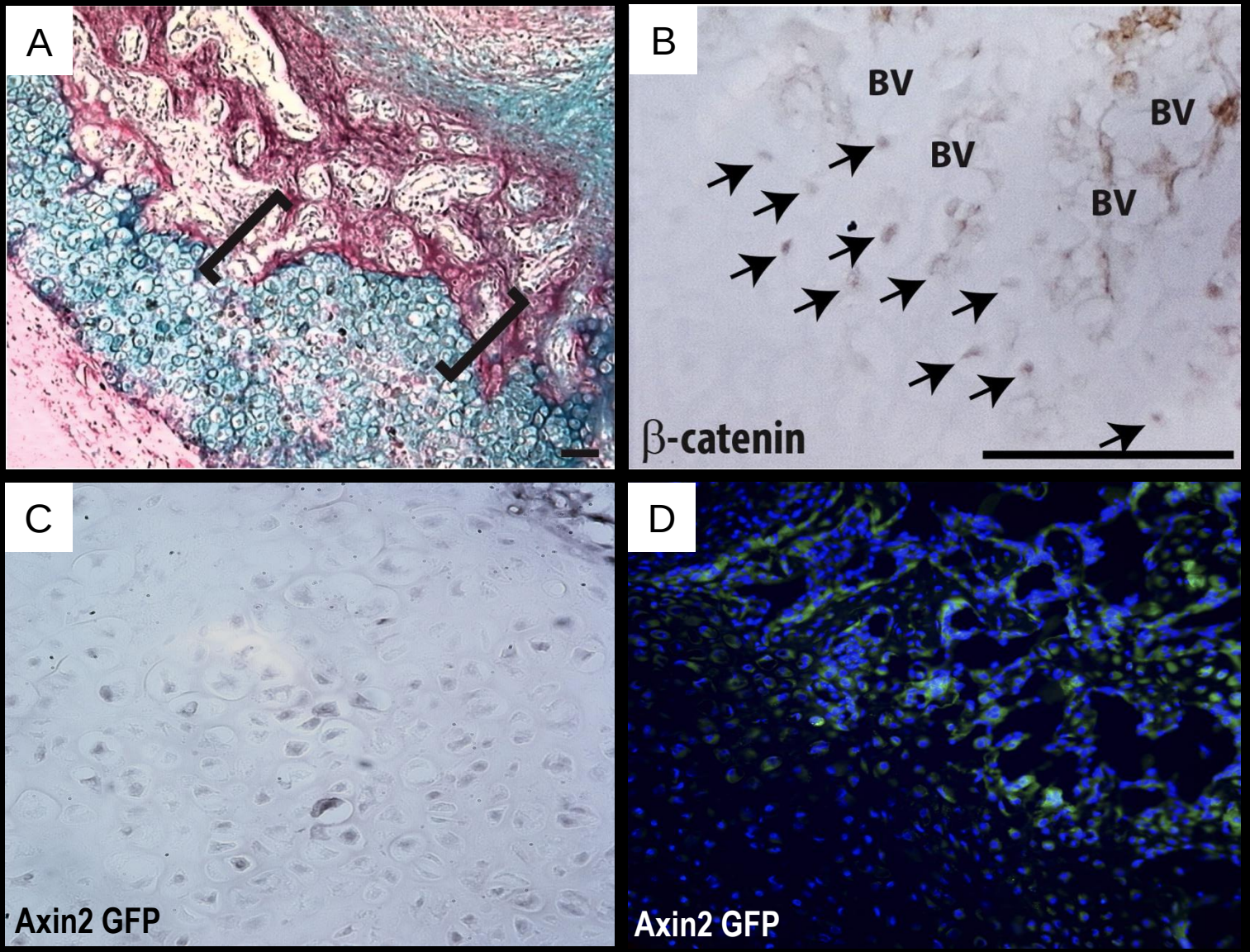


Historical Data Shows the Same Thing



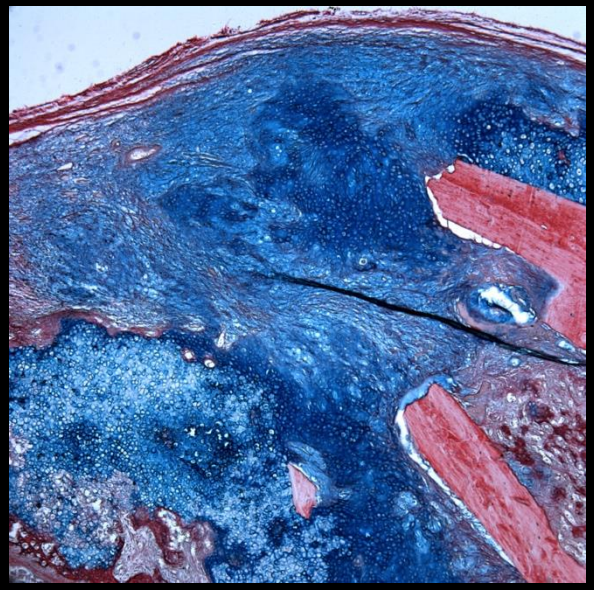
"... *the cartilage appears to lose its basophilic staining and gradually disappears in the osseous tissue as though through transformation of the chondrocytes to the osteocytes. This transformation, regarded by some authors as metaplasia, is a prominent feature of the ossification of the callus…*" Urist, 1943

What are the potential molecular signals?

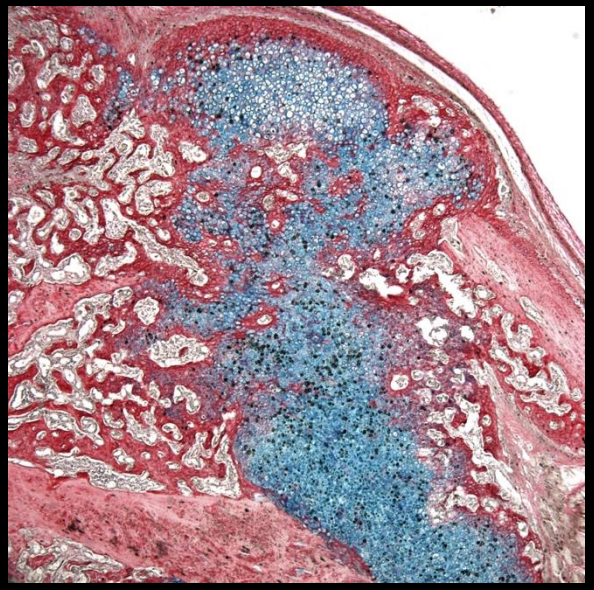


Activating Wnt Accelerates Healing

Control

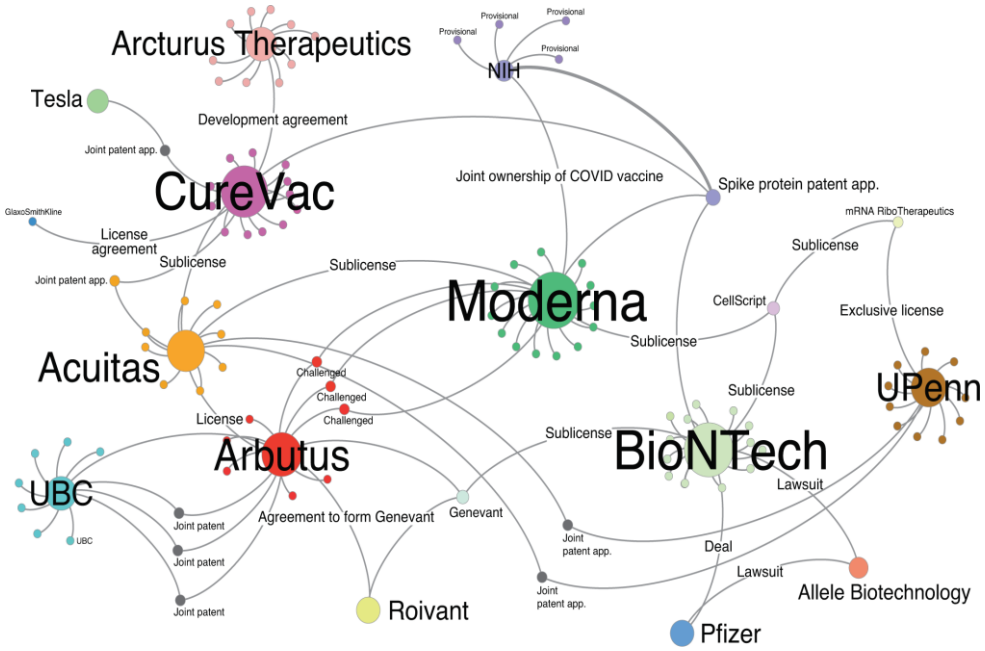


Wnt

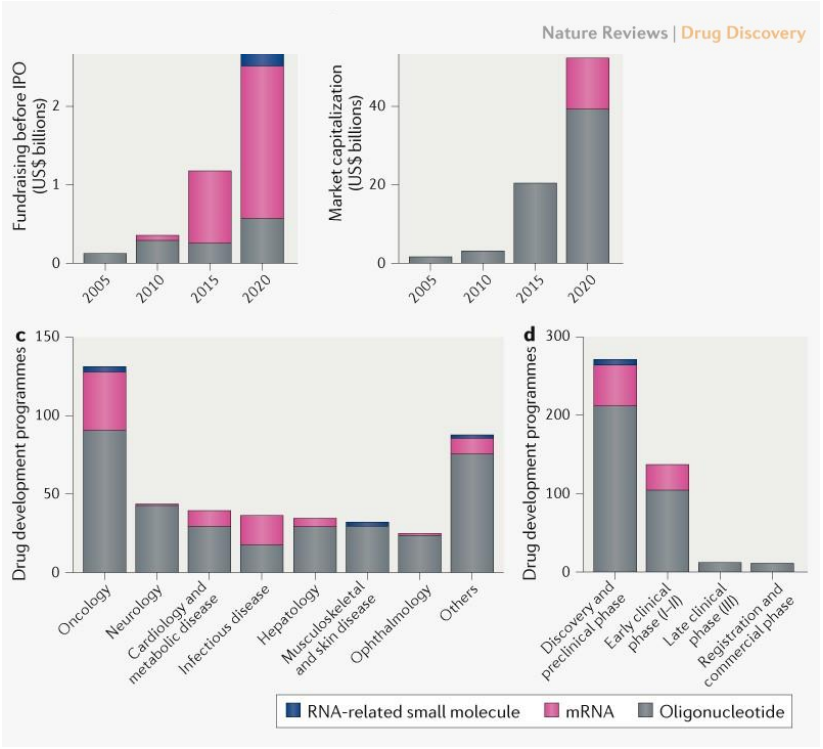


Challenges:
Evenity did not work (Wnt antagonist antagonist
Timing
Dosing
  Wnts are lipid modified
  and not water soluble

Developmental Pipeline of mRNA Therapeutics

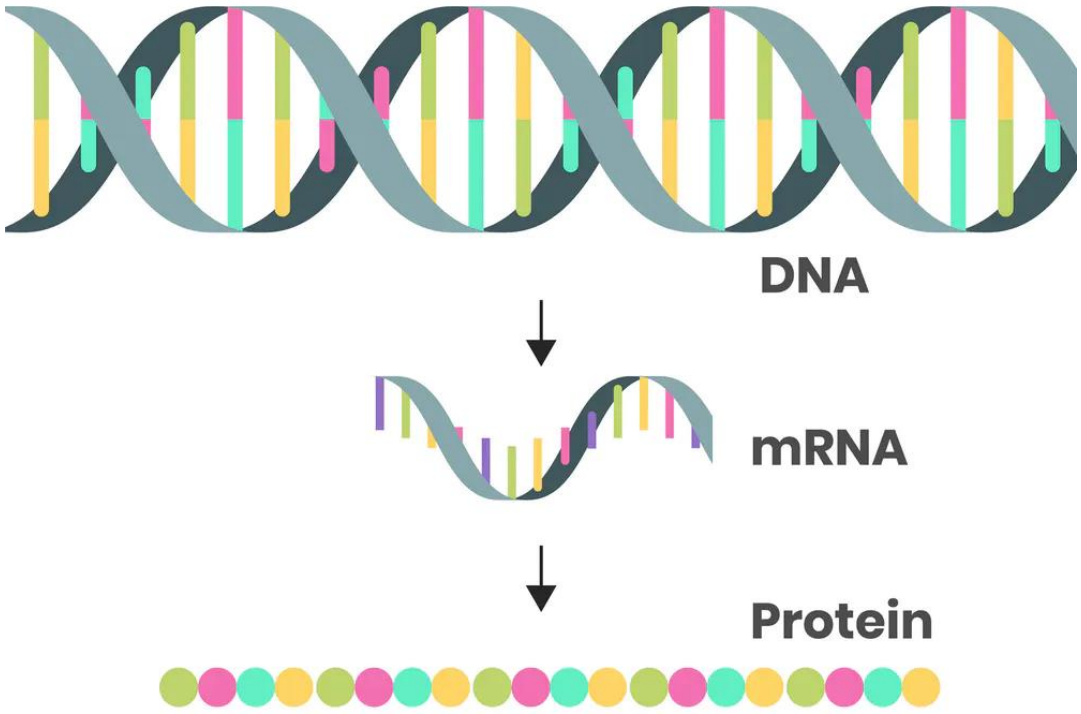


Gavirina and Kilic, Nature Biotechnology 2021.



Wang F, *et al.* Nature Reviews Drug Discovery 2020.

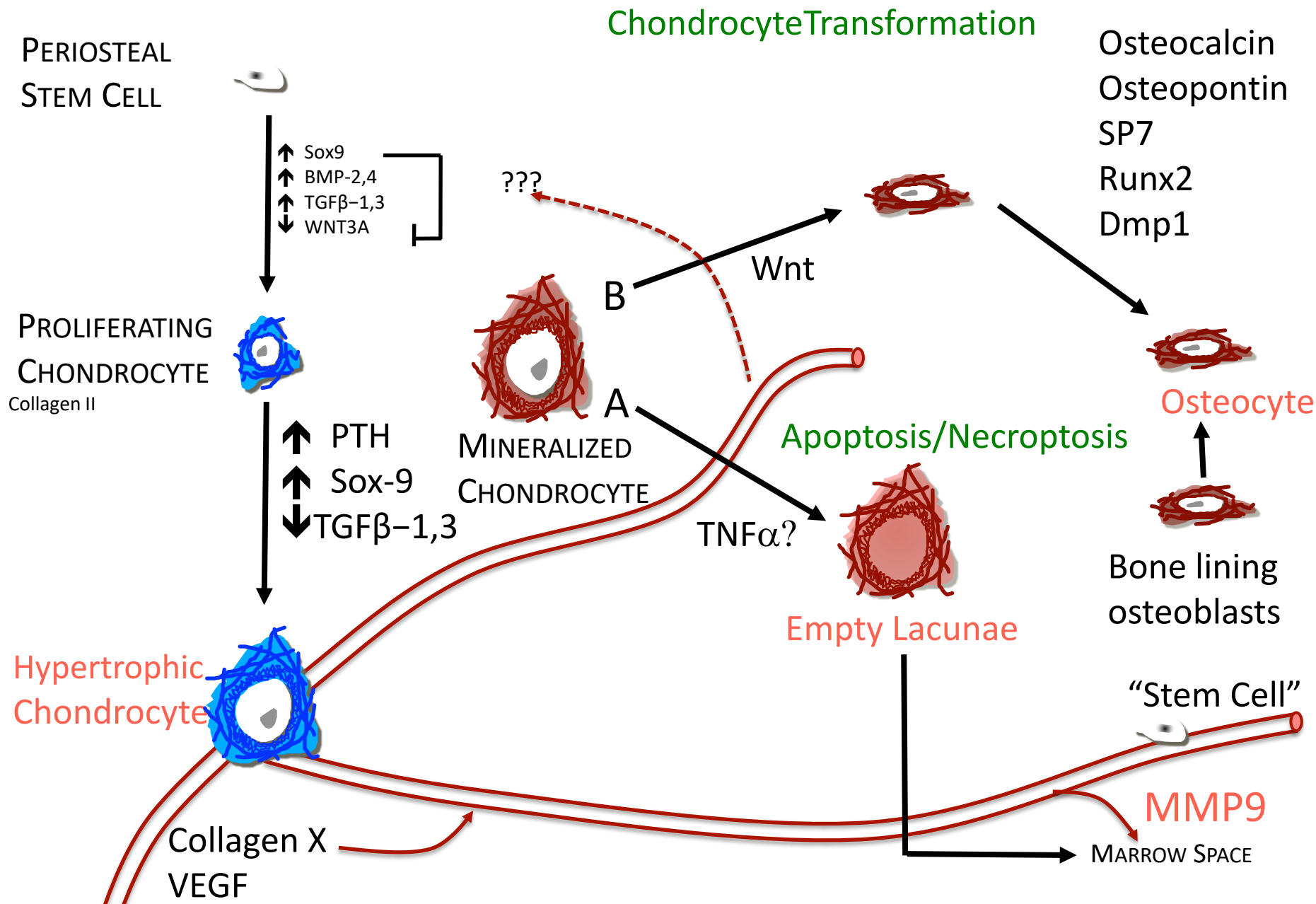
Therapeutic Advantages of mRNA



- Safety concerns (genomic integration)
- Difficult in non-dividing cells

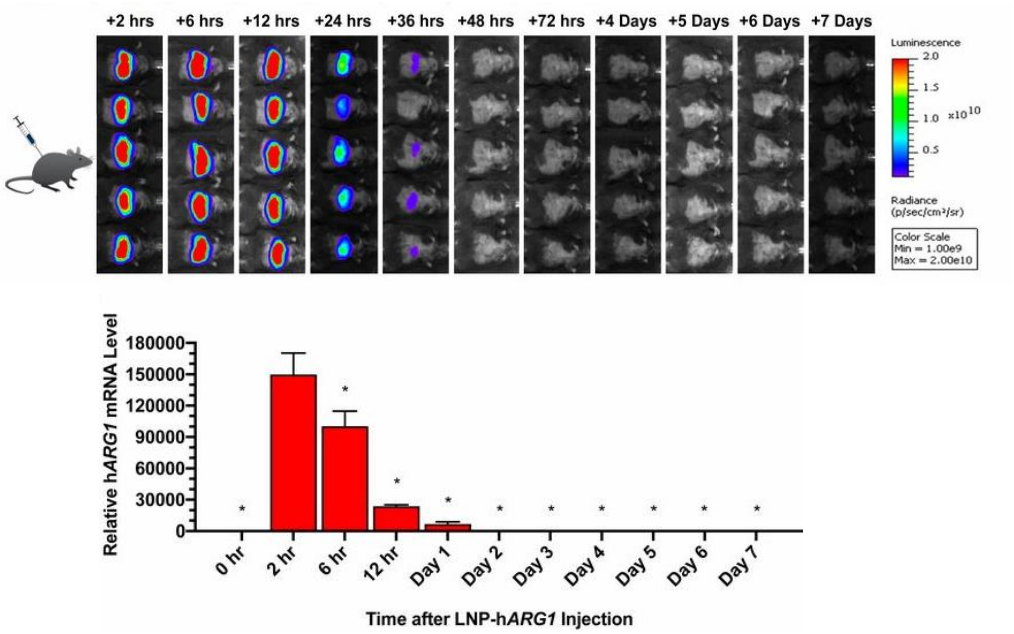
- Short half life
- Limited activity → supraphysiological doses
- Expensive to manufacture

We still need a better understanding of the biology

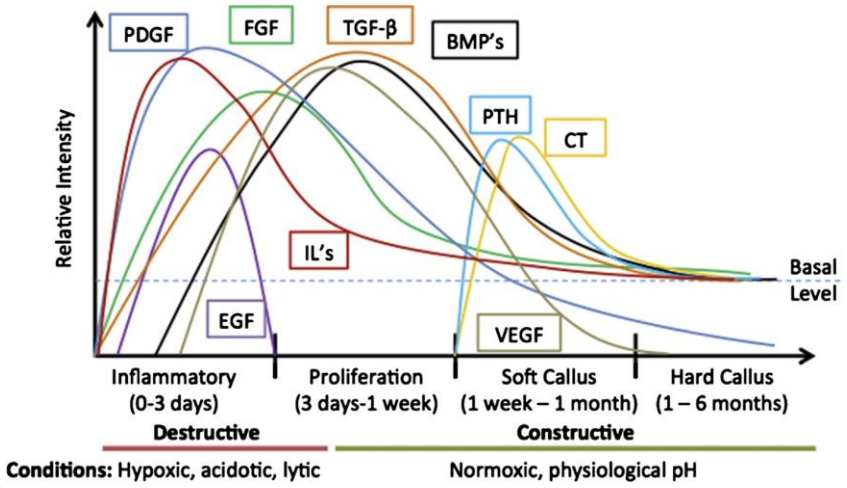


Local and Sustained Delivery of mRNA

- ✓ Bioavailability often on the order of hours.
- ✓ Local delivery may be most effective for repair.

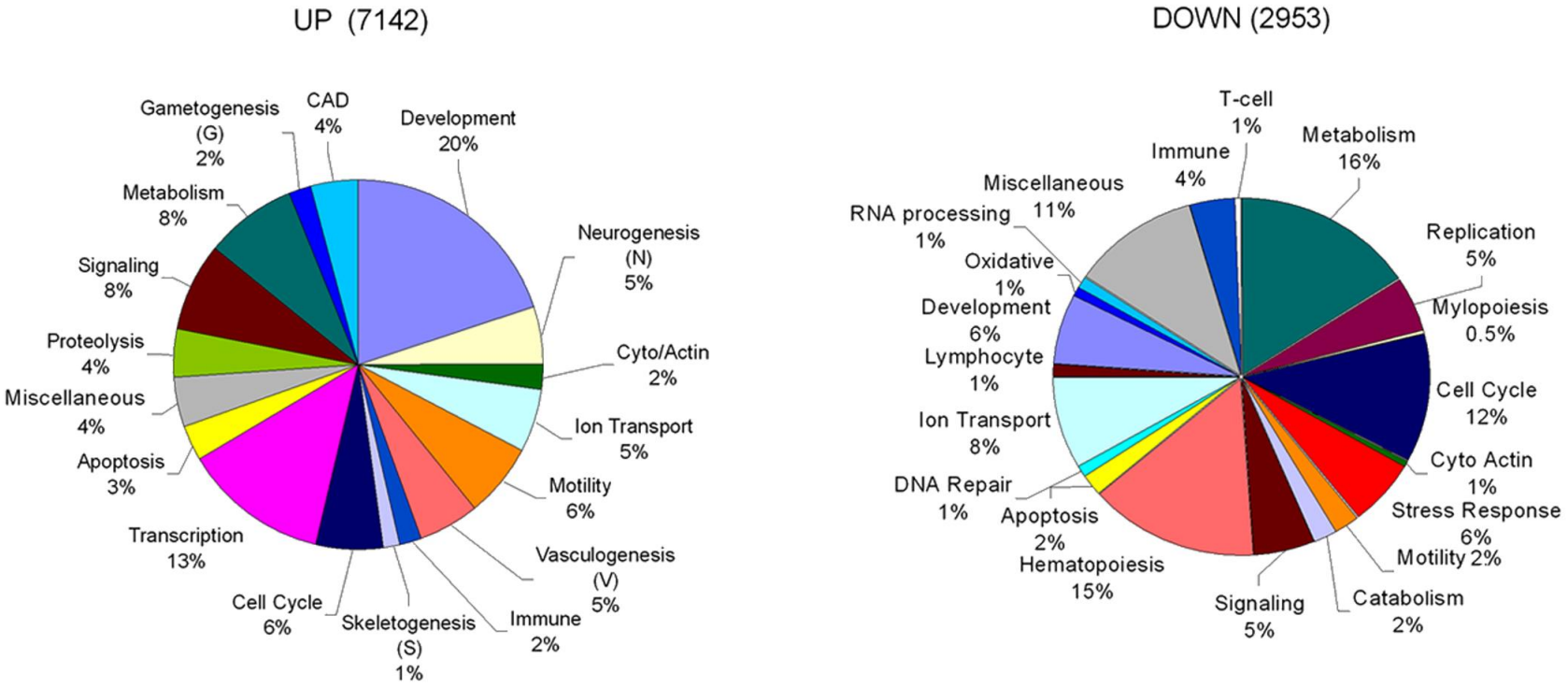


Brian Truong et al. PNAS 2019;116:42:21150-21159



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

Transcriptional Analysis of Fracture Healing: Finding Targets



Bais M, McLean J, Sebastiani P, Young M, Wigner N, et al. (2009) Transcriptional Analysis of Fracture Healing and the Induction of Embryonic Stem Cell–Related Genes. PLOS ONE 4(5): e5393. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0005393