

Nonunions and fracture healing

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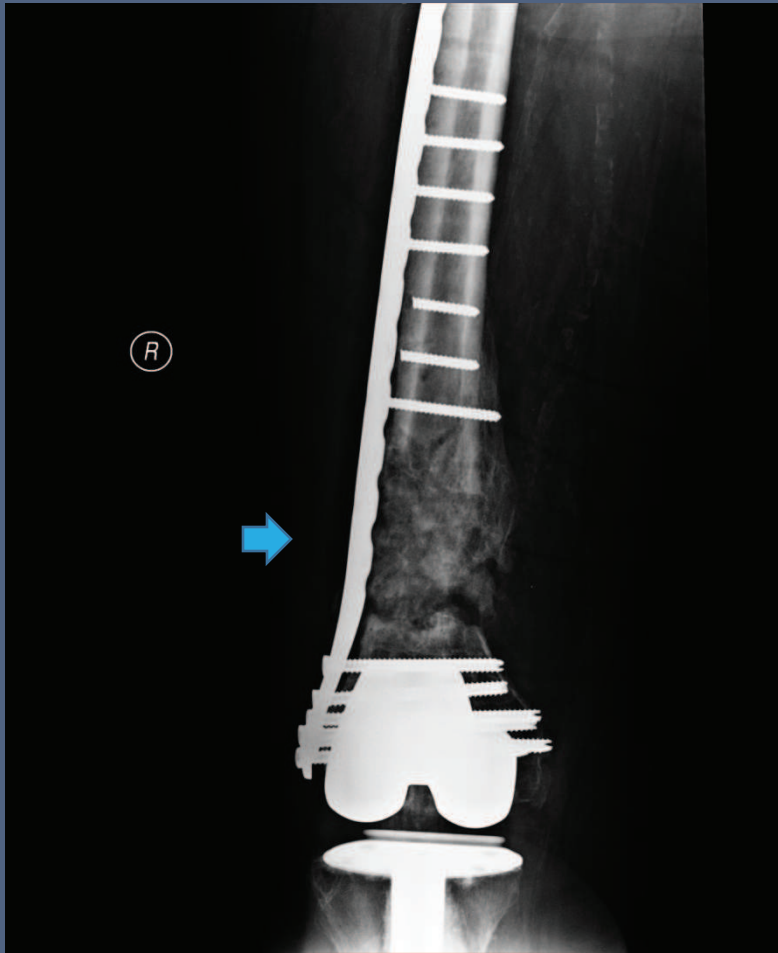
Bone regeneration possible through a lifetime

- One of the few tissues constantly regenerated and repaired
 - Bone remodeling
 - Fracture healing
- Complex, well orchestrated process
- Heals without scar
 - Indistinguishable histologically from adjacent bone
 - Restoration of mechanical properties
 - Restoration of architecture
- Regenerative process can be compromised
 - **Trauma**
 - **Infection**
 - **Physical state** : Old age, Cachexia/malnutrition, Obesity Burns/Radiation
 - **Medications/Habits**: Steroids, NSAIDs?, Opioids?, chemotherapy agents, Cigarette Smoking

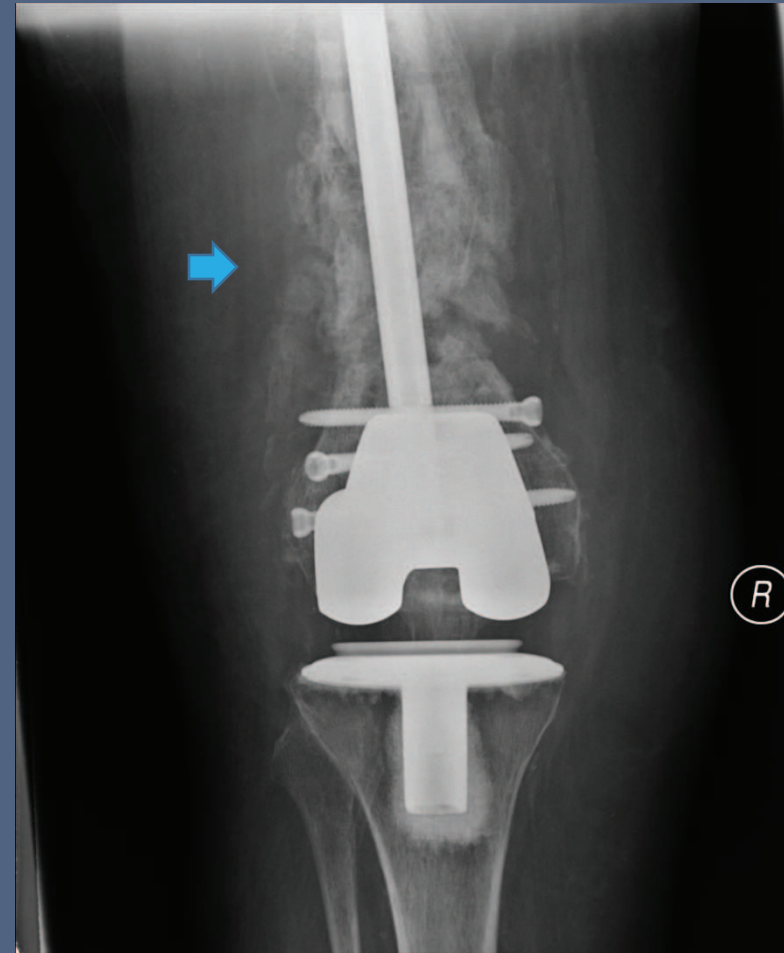
Addressing the bone loss challenges

- Osteoporosis
- Non-union/delayed union
- Avascular necrosis
- Large segment bone loss with trauma
- Tumor resection bone loss

Periprosthetic fracture in 82 yo female

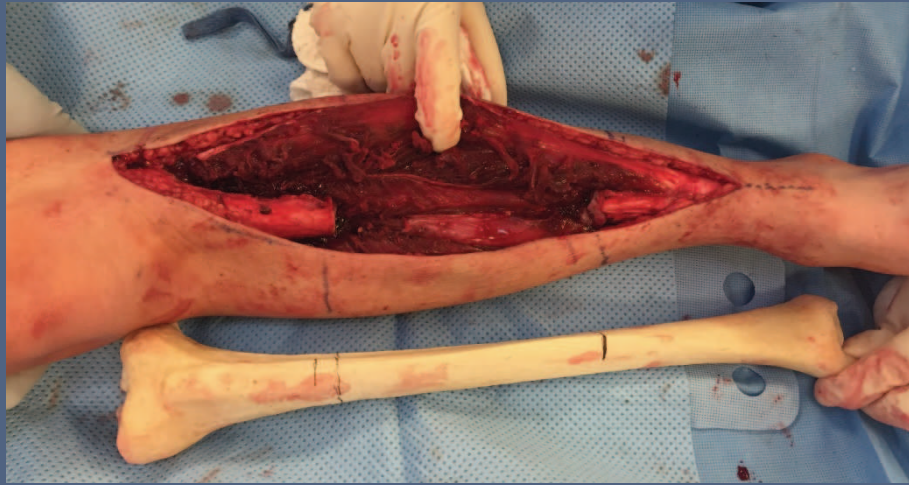


4 months after revision surgery



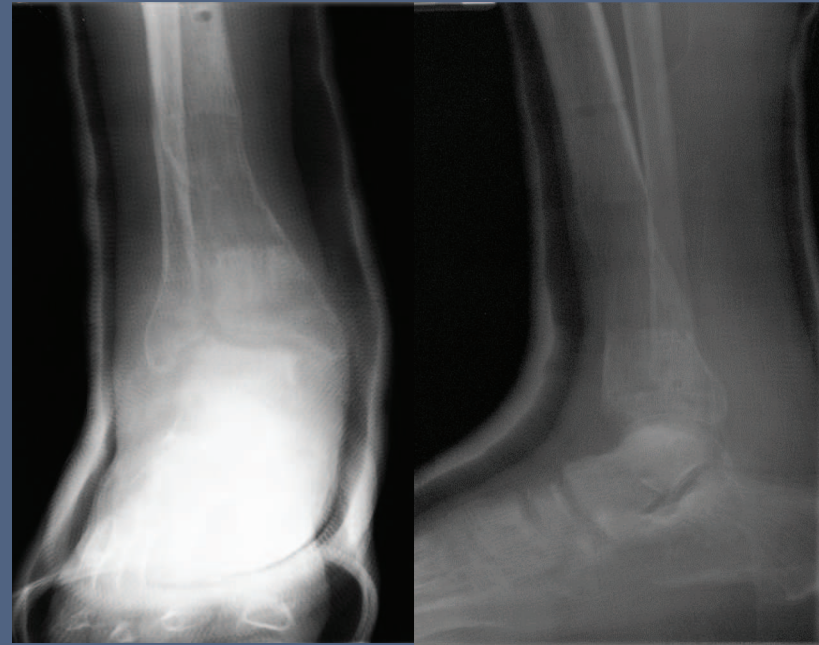
After 12 weeks PTH revised to IM nail

Allograft for large tumor defect



Bone transport/distraction osteogenesis

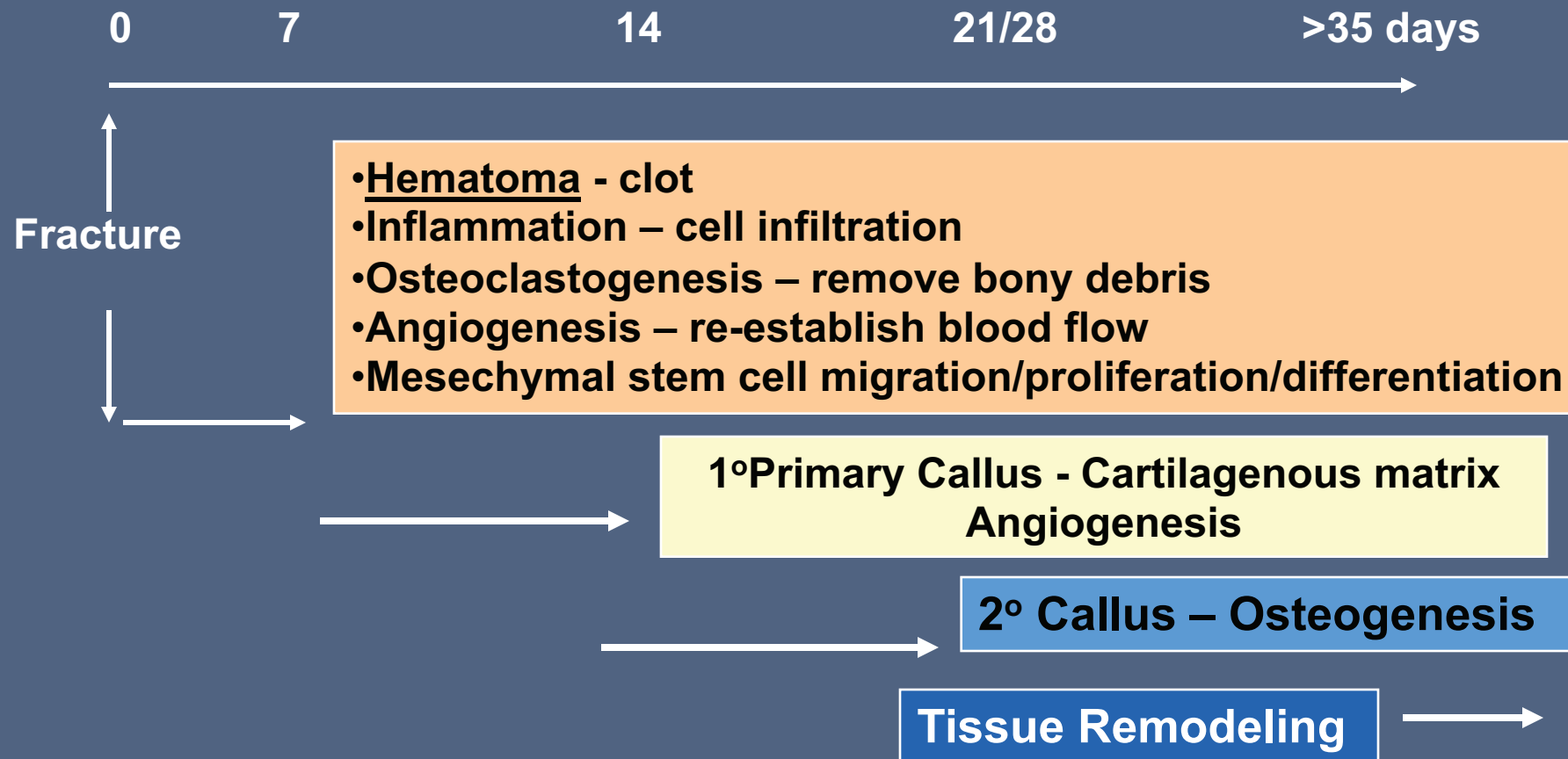
- Use of frames/hardware to create bone
- Slow process (1mm/day)
- Slow consolidation (2x length of distraction phase)
- Newer technique makes membrane and then adds autograft (Masquelet)



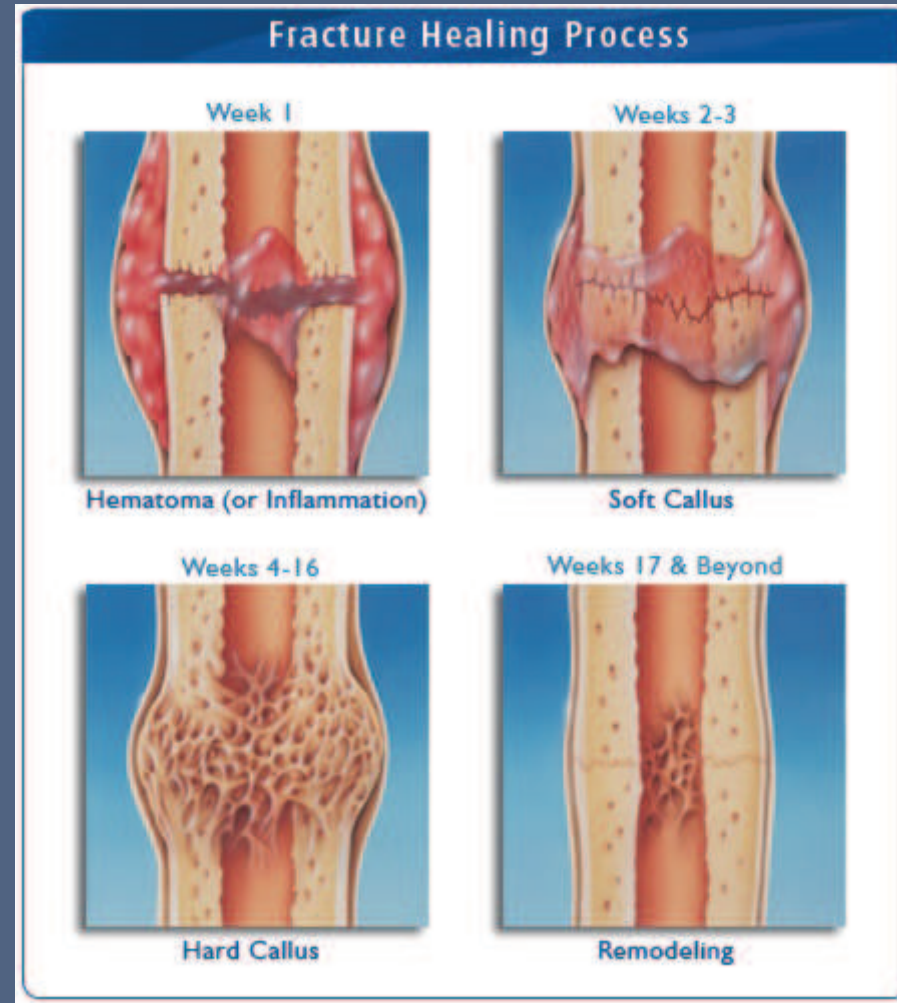
What really happens with fracture healing?

- Follows the fetal development pathways for bone formation after initial injury
 - Intramembranous and endochondral
- Fracture healing sequence
 - Bleeding at the injury site
 - Release of growth factors and prostaglandins
 - Recruitment of stem cells to injury site
 - “Knitting” together of the fracture site
 - Mineralization/ossification of the repair
 - Remodeling

Time Course of Bone Healing

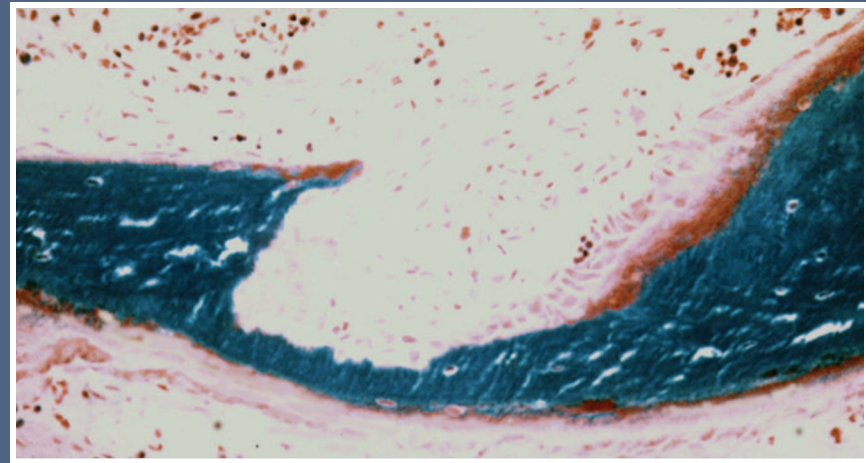


Fracture healing



Primary bone healing more like remodeling

- Healing seen with stress fractures
- Cutting cones from osteoclasts cross the fracture site directly
- Known delays with things that delay remodeling



Nonunion and Delayed Union

- 6 million fractures annually in the US
- 10% of all fractures progress to nonunion (but not 10% at all sites)
 - 300,000 to 600,000 nonunions annually
 - Location
 - Diaphyseal fractures at higher risk
 - Tibia, ulna, femur, humerus, 5th metatarsal (Jones fracture)
 - Patient factors
 - Injury factors
 - Iatrogenic factors

The Nonunions



Injury based factors for problems

- High-energy Impact
- Vascular Injury
- Free bone fragments
- Periosteal Stripping



Patient Factors for Non-union

- Old age
- Cachexia/malnutrition
- Systemic disease
- Steroids
- NSAIDs?
- Burns/Radiation
- Cigarette Smoking
- Obesity
- Medications?



Nonunion and Delayed Union

- Exact time for healing of a fracture not defined
 - Part of the problem with the definition of what is healed?
- Considered delayed if rate of healing for a specific site/type of fracture is slower than expected
 - Generally if still not “healed” after 3-6 months

Nonunion and Delayed Union

- Definition of Nonunion
 - Based on time for a specific fracture location and type
 - Generally > 6 months from time of injury
 - FDA defines as 9 months with no radiographic progression for 3 months
 - Stall in the progression of healing for a period of time
 - Variable opinions on the timetable definition
 - Site, radiographic definition, functional definition, or both?

Traditional Care

- Hardware revision
- Iliac Crest Bone Grafting
 - Osteoinductive and osteoconductive
 - Significant morbidity at harvest site
 - Pain
 - Infection
 - Wound healing problems
 - Increased blood loss
 - Inadequate volume or quality?

Can we do it better?

- Understanding mechano-biology of fracture healing to improve results
- Making better use of the tools we have now
 - Graft material
 - Biologics
 - Medications
- Future directions -- adjuvant treatments

Complex process

- Multiple cell types
- Multiple intracellular and extracellular molecules
- Biomechanical influence on rate and location
- Temporal and spatial sequence

Bone graft

- Properties needed for success
 - Osteogenesis
 - Cells that will form cartilage and bone
 - Osteoconductive
 - Scaffold
 - Osteoinductive
 - Proteins like BMP, growth factors
- Autograft
 - gold standard
 - Osteoconductive, osteoinductive, osteogenesis
 - Histocompatible, non-immunogenic
 - Issues with harvest sites (pain, blood loss, fracture)

Bone graft

- Allograft
 - Donor bone
 - No live cells with processing and freezing
 - Available in multiple forms
 - Demineralized bone matrix
 - Milled cancellous graft
 - Cortical grafts
 - Bulk allografts
 - Issues: immunogenicity/rejection, infection transmission possible, added cost

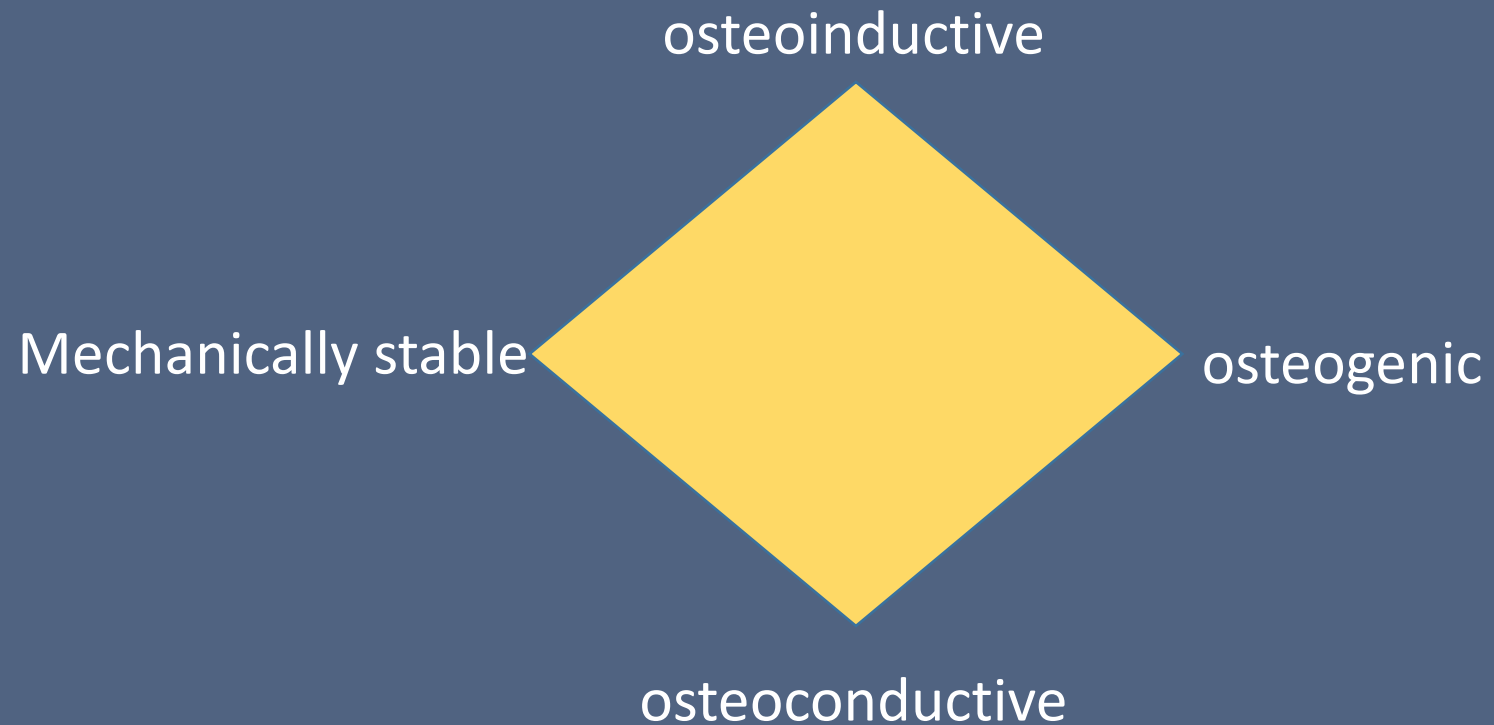
Bone graft substitutes

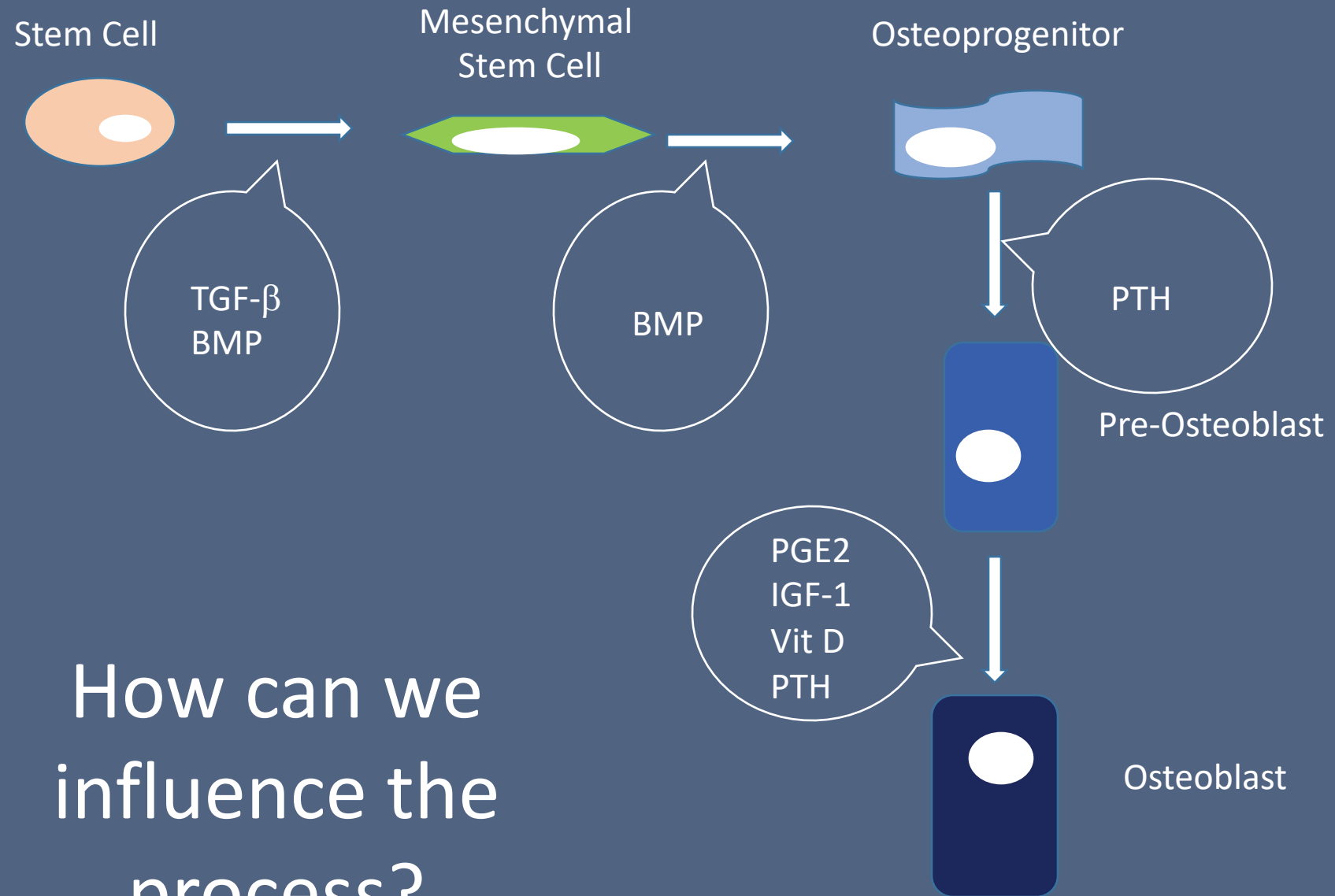
- Scaffolds that promote cell migration/proliferation and bone formation
- Not equivalent biologic or mechanical properties to autograft or allograft
- Wide range biomaterials
 - Collagen
 - Hydroxyapatite
 - β –tricalcium phosphate
 - Glass
 - Ceramics
 - Calcium phosphate
 - coral

Bone graft substitutes

- To get closer to properties of bone
 - Biocompatibility
 - Delivery
 - Combination therapy (tissue engineering)
 - Nanoparticles adherent to scaffolds
 - Allow sequential or timed delivery of growth factors
 - Allow external manipulation of process
 - Magnetic scaffold with external magnetic field that guides collagen crosslinking stimulus from scaffold
- Appropriate porosity
 - Promote cell adhesion, growth, differentiation
 - Allow vascular ingrowth

The healing diamond





How can we
influence the
process?

Growth factors

- BMP
 - Low molecular weight, noncollagenous proteins
 - Members TGF- β superfamily
 - Discovered by Marshall Urist in the 1960's by purifying demineralized bone matrix
 - Now produced using recombinant gene technology
 - Uniform supply of a single BMP

Growth factors

- BMP
 - Potent osteoinductive factors
 - Delivered on a scaffold or carrier
 - Induce proliferation and differentiation of mesenchymal stem cells
 - BMP 2 and BMP 7 used for bone for 15 yrs for nonunion, spine fusion, critical bone defects
 - Supraphysiologic quantities needed for the response
 - Seroma formation around the material
 - Cost
 - Possibility of heterotopic bone formation
 - Needs implantation into the site of concern

Growth factors

- Use for cell proliferation, cell differentiation, cell recruitment, angiogenesis
 - Platelet derived growth factor (PRP)
 - Transforming growth factor β (TGF- β)
 - Insulin-like growth factor -1 (IGF-1)
 - Vascular endothelial factor (VEGF)
 - Fibroblast growth factor (FGF)
- Delivery as combination “cocktails”
- Nanoparticle delivery for longitudinal dosing and multifactor mixes

Bone Morphogenetic Proteins

- Several used in experimental models
 - BMP-2, 4, 6, 7, and 9
- FDA approved forms
 - (rh)BMP-7 (OP-1)
 - Humanitarian device exemption
 - Long bone fractures
 - Posterolateral nonunions
 - (rh)BMP-2 (INFUSE)
 - Within a titanium cage for ALIF
 - Some issues with posterolateral fusion
 - Dose and carrier changes
 - Await approval based upon studies with newer formulation

Bone Morphogenetic Proteins

- Play multiple roles
 - bone formation
 - differentiation stem cells
 - inflammation
- Initiate endochondral bone formation
 - Stimulate local mesenchymal stem cells
 - Enhance bone collagen synthesis
 - Carrier scaffold eventually resorbed

Bone Morphogenetic Proteins

- rh BMP7 (OP-1)
 - Tibial nonunion(122 pts, 124 fractures)
 - IM rod and either rhBMP-7 or autogenous bone graft
 - 24 month follow-up
 - At 9 months 81% rhBMP-7 healed, 85% autograft
 - 20% autograft patients with donor site pain at 2 years
 - Long Bone nonunion(62 patients)
 - Variety of sites
 - 89% success rate in healing aseptic nonunion
 - No adverse events
 - Open tibia fracture (124 pts)
 - IM rod and rhBMP-7 or nothing
 - Lower number of secondary procedures

Bone Morphogenetic Proteins

- rhBMP 2
 - ALIF with titanium cages (279 patients)
 - Fusion rates 99.8% for BMP and 95.6% with iliac crest autograft
 - Open tibial shaft fractures (450 patients)
 - 3 groups with IM nail (nothing, 0.75mg/ml, 1.5 mg/ml)
 - Reduced frequency of secondary interventions 44%
 - Tibial fractures with defects (30 patients)
 - Autogenous graft vs allograft + BMP
 - BMP group 2 failures, autograft 5 failures at 1 year

Bone Morphogenetic Proteins

- Problems with bioavailability
 - Only mcgs/kg of bone
 - Need mgs for effects in humans
 - Disappear quickly
 - Effect may not translate to different anatomic locations
 - Ossification in areas not desirable (spinal canal, adjacent soft tissue)
 - Seroma
 - Inflammatory reaction

Bone Morphogenetic Proteins

- Carriers
 - Slow release
 - osteoconductive
- Heterodimers
 - Combination of BMP elements (BMP-2 and BMP-7)
 - Animal studies with cotransfection of genes
 - Fusion gene for transfection
- Ideally, different BMP's given in sequence
 - Duplicate healing cascade

Mesenchymal Stem Cells

- Adequate supply of osteogenic cells at the appropriate site
- Found natively circulating in young adults after long bone fracture
- Available from periosteum, adjacent muscle, bone marrow
- Can you deliver them locally?
 - Bone marrow aspirate
 - Issues with concentration
 - Issues with quality
 - Issues with aspiration technique and reliability
 - In vitro expansion
 - Issues with contamination
 - Costly
 - Time/second procedure

Mesenchymal stem cells

- Derived from other tissues?
 - Muscle
 - Myotubule cell potential to dedifferentiate after injury
 - Fat
 - Utility debatable
 - Function may be inferior to bone marrow derived cells
- Use of MSC in very early phases of use
 - Can get the cells, but are they really needed at fracture site?
 - Can deliver the cells, but do they stay in the location of delivery?

Engineered tissues

- Generation of “living scaffolds”
 - Combines mesenchymal stem cells with scaffolds
 - Culture expansion of MSCs and optimization of biologic properties of scaffold
 - Animal studies and human studies in early phases
 - So far can get bone formation on scaffold but not bridging to adjacent tissues

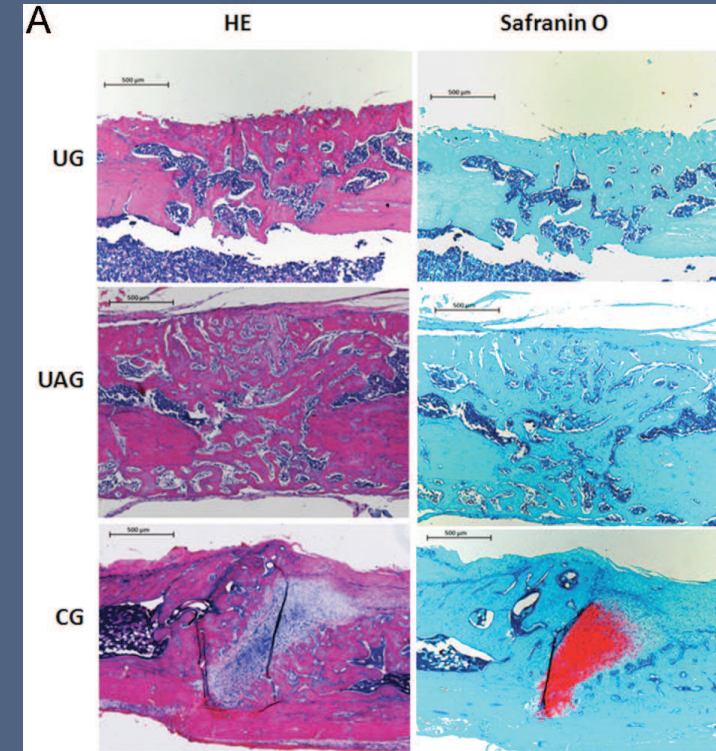
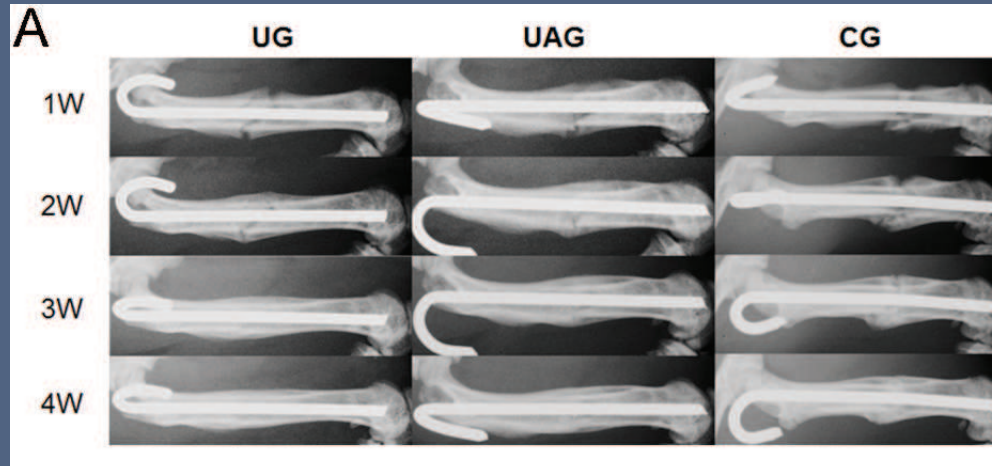
Gene therapy

- Transfer of gene information for growth factors to target cells
- Target cells delivered to host after transfer using current techniques
- Safety concerns
 - Delivery methods
 - Can you screen for aberrant cells before implantation
 - Termination of activity once healing has occurred

LIPUS

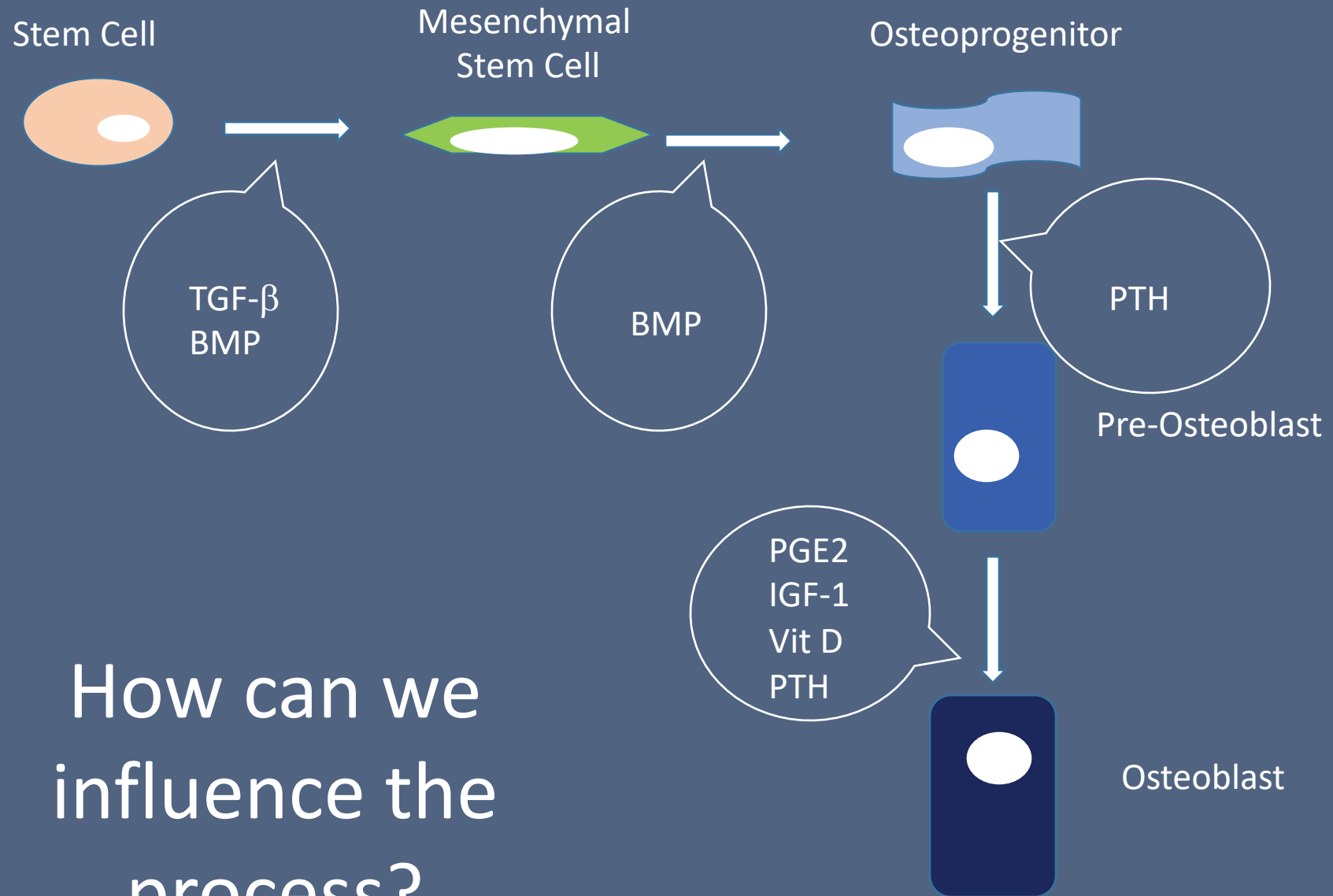
- Low intensity pulsed ultrasound
 - AKA “the bone stimulator”
- Meta-analysis showed some benefit to earlier radiographic union in acute fractures, generally upper extremity
- Often only paid for if delay in fracture healing
- Unclear if benefit or “buying time”
- Recent multicenter randomized trial terminated for futility
 - TRUST

LIPUS



- Appears to stimulate stem cells migration
- Increases content of woven bone in fracture site

Wei FY, et. al. PLoS ONE 2014; 9(9): e106722.



How can we
influence the
process?

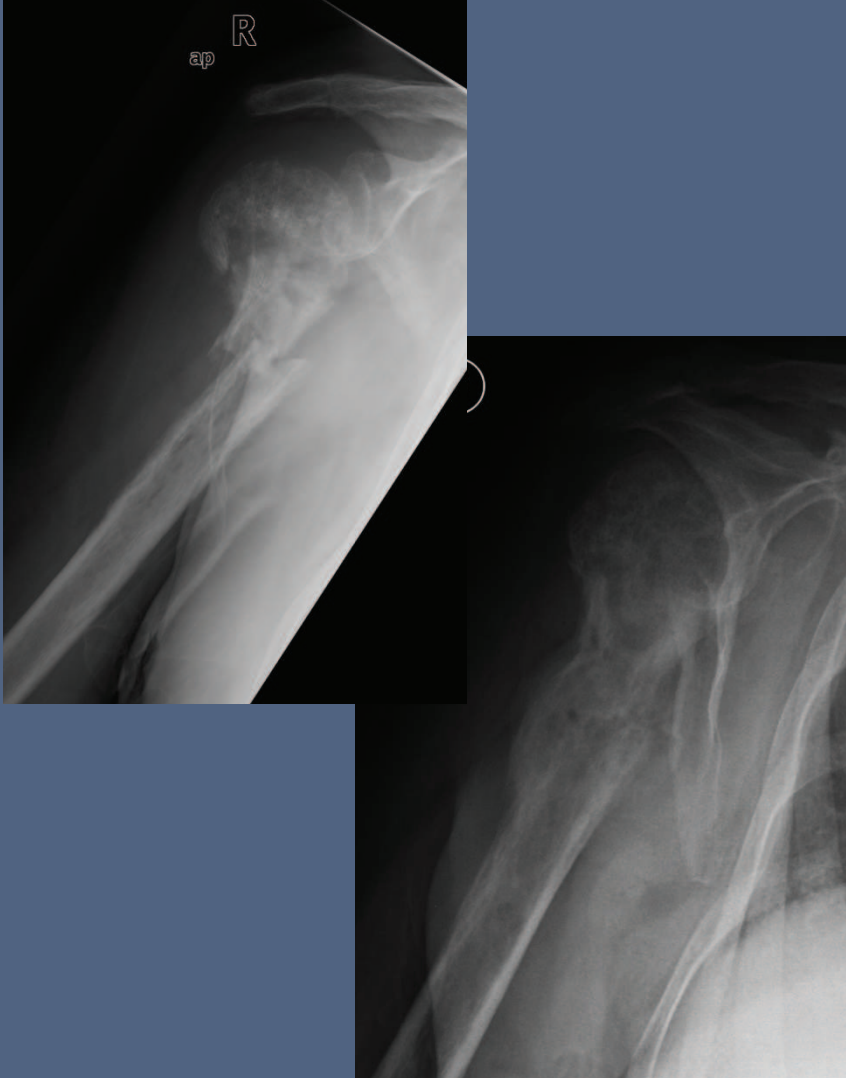
Advantages of Systemic Therapy

- Not all fractures are treated surgically
- BMP cannot be used in all locations, even in patients at high risk for failure
 - Seroma formation in C-spine surgeries
- Risk are involved with surgical intervention
 - Infection
 - Post-operative recovery

Advantages of Systemic Therapy

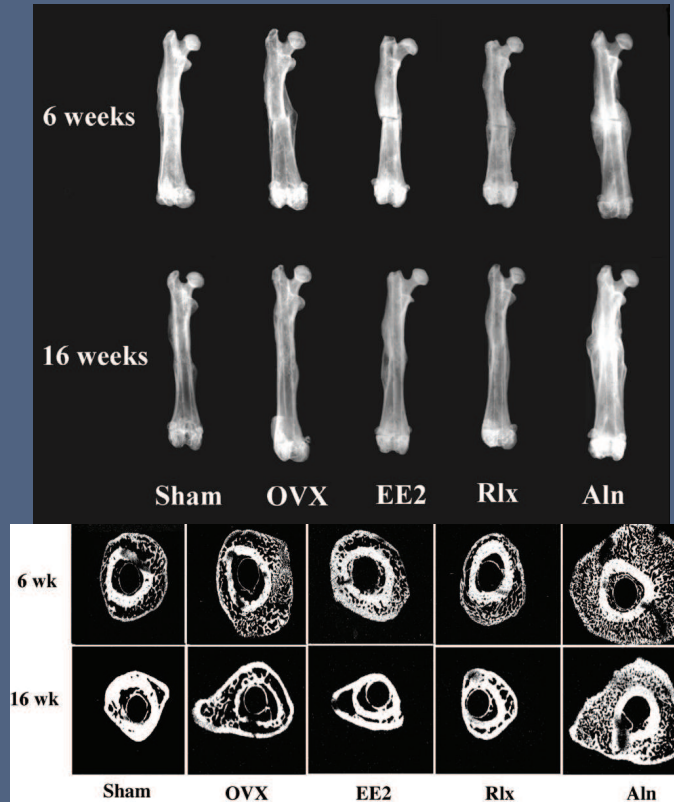
- Potential to add biologic stimulus after surgical fixation has already been done
 - Slower than expected bone formation/healing
 - Patient factors that increase risk of healing problems that cannot be changed
 - Smoking
 - Steroids
 - Age
 - Systemic Diseases

Remember the Importance of Vitamin D



- Required for mineralization of newly formed bone
- Up to 60 % trauma patients Vitamin D deficient
- Treatment with Vitamin D can lead to union in cases of severe deficiency

Callus formation comparisons in rat femur fracture model



They all heal, just the pattern is different

You can start the osteoporosis meds right after the fracture

- wait 6 wks on IV

- wait on stress

fracture

Cao Y, et al., JBMR

2002

17(12): 2237-2246

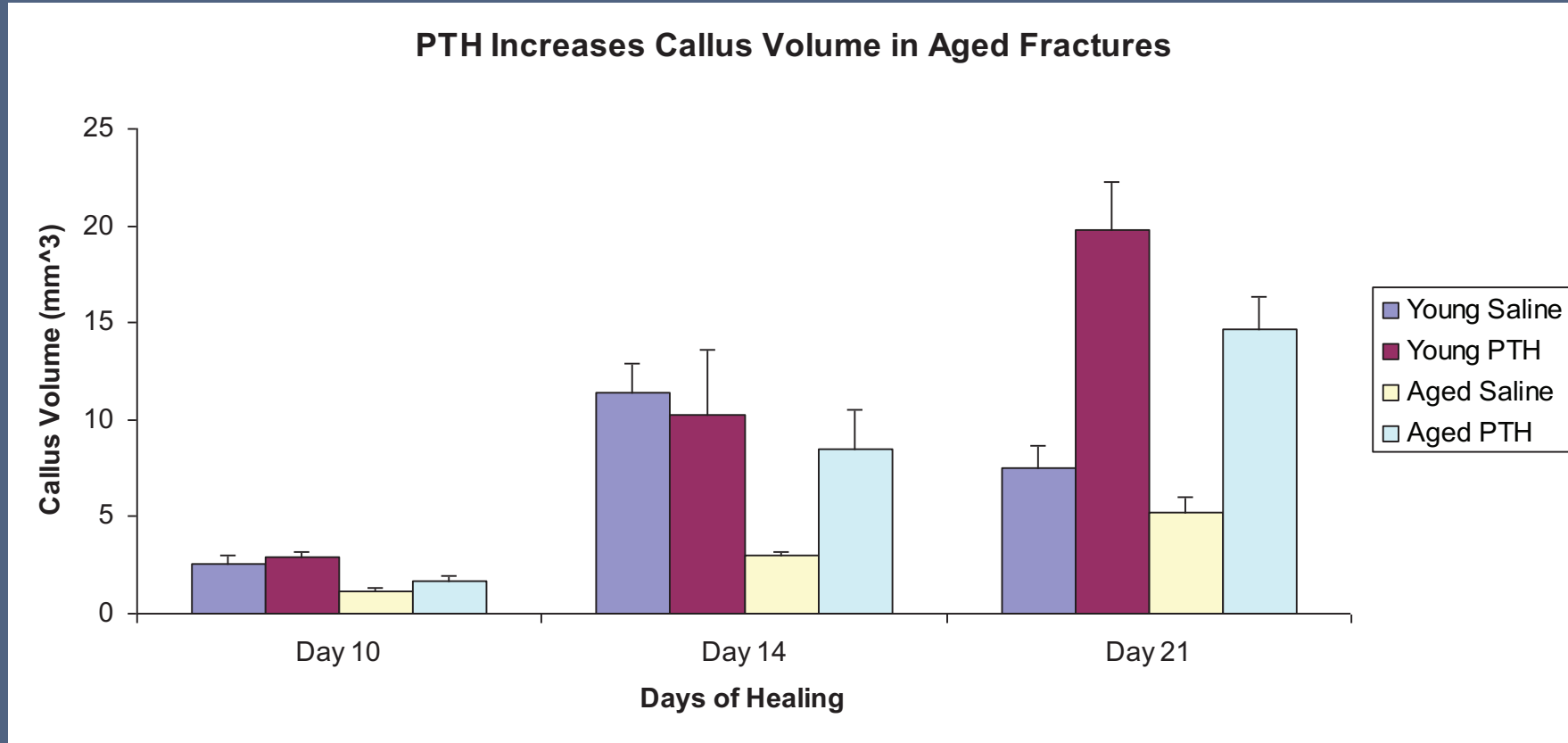
PTH and fracture healing applications?

- Anabolic therapy for osteoporosis
- Stimulates mesenchymal stem cell recruitment and osteoblastic differentiation
- Stimulates VEGF expression
- Works through signals similar to PGE₂

Animal studies for PTH and fracture

- Andreassen et al (Calcif Tissue Int 2004, 74:351-56)
 - Early rat studies with 60-200 mcg/kg/day
 - Enhanced
 - Callus
 - Bone mineral content
 - Bone mineral density
 - Cartilage formation
 - Increased mechanical strength at fracture site

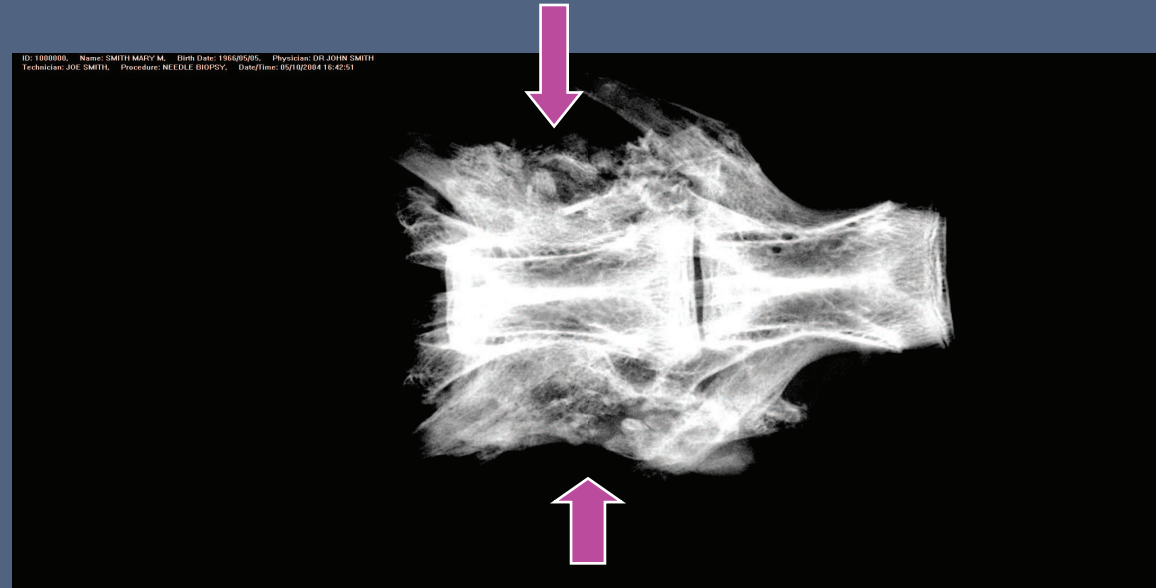
Effect of PTH on Fracture Healing in Aged Mice



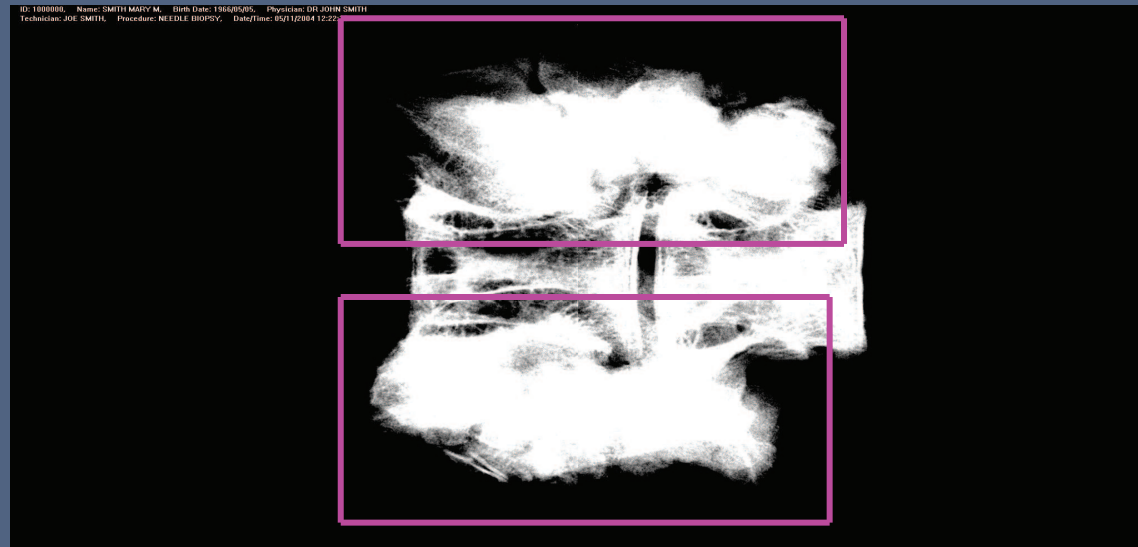
1-34 PTH dose of 10 mcg/kg/day

Control vs. PTH

Control



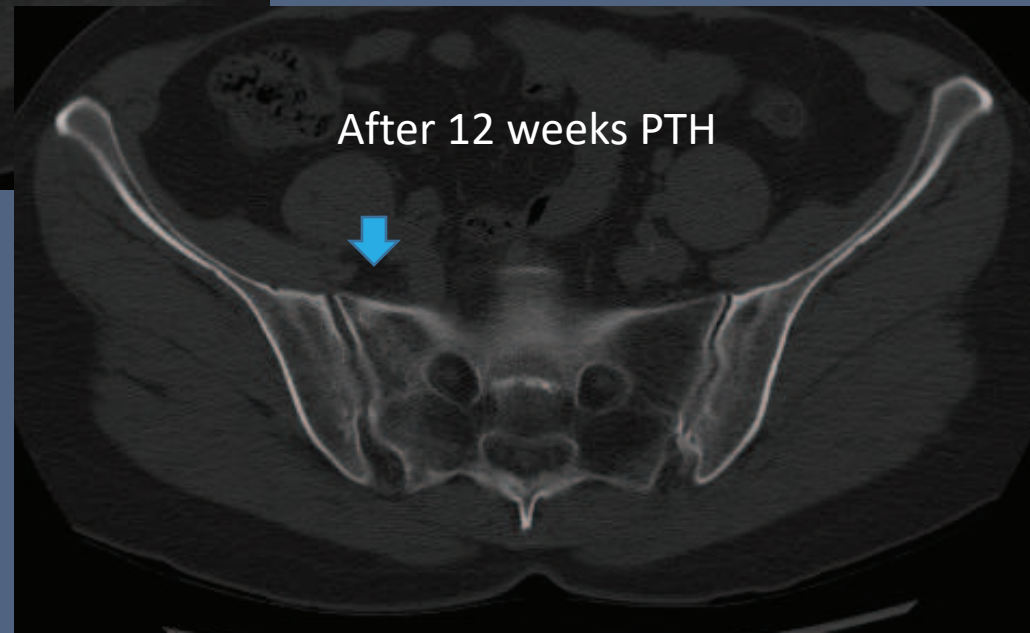
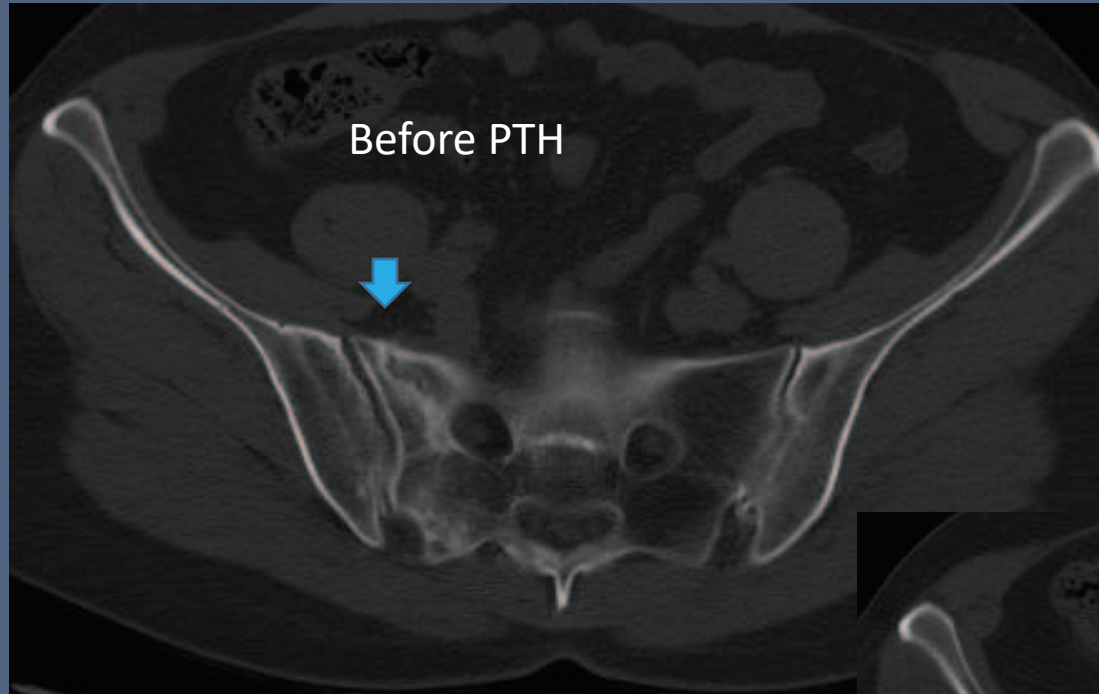
PTH
(10 mcg/kg/day)



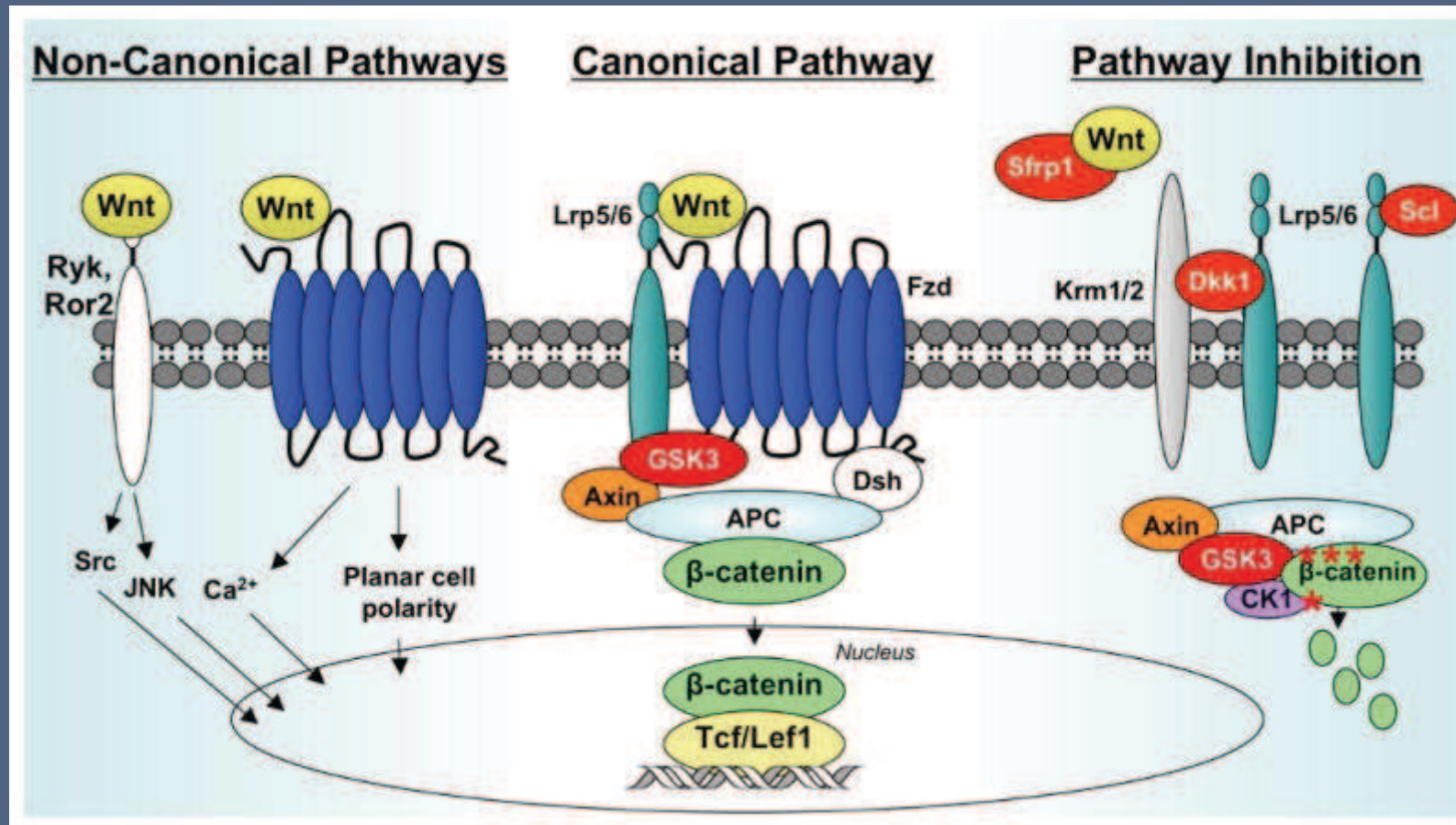
PTH and fracture healing: wrist fractures

- Aspenberg P, et al (JBMR 2010; 25(2))
 - 102 postmenopausal women treated nonoperatively
 - 3 groups (control, 20mcg/day, 40 mcg/day)
 - Placebo controlled, double blinded, randomized
 - Time to bridging 3 or 4 cortices
 - No difference in 40mcg and control group
 - Improved in 20mcg group compared to control ($p=.006$)
 - Study powered for the 40 mcg group
- Aspenberg P, et al (Acta Orthop 2010; 81(2))
 - Early callus formation improved with treatment of distal radius fracture with PTH

9 month old sacral fracture remained painful

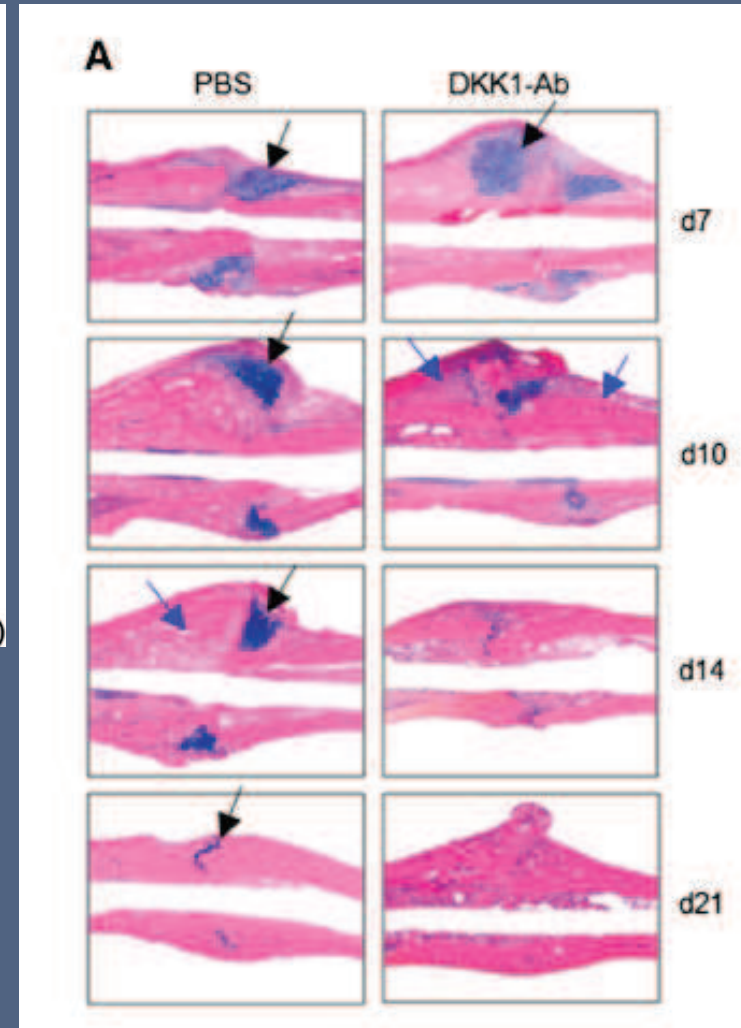
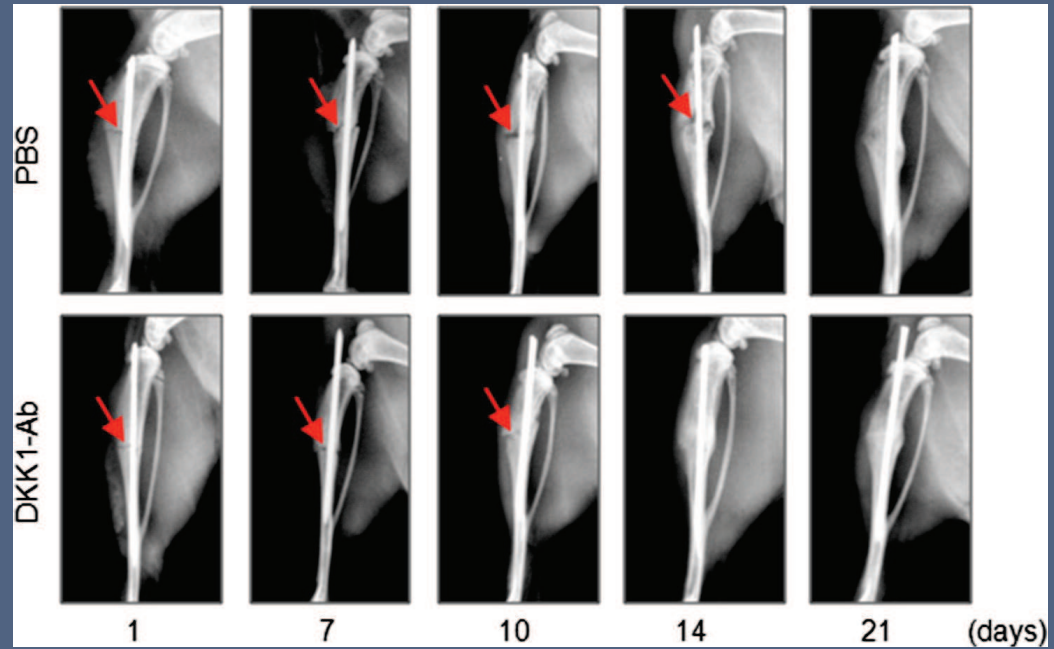


Wnt signaling pathways



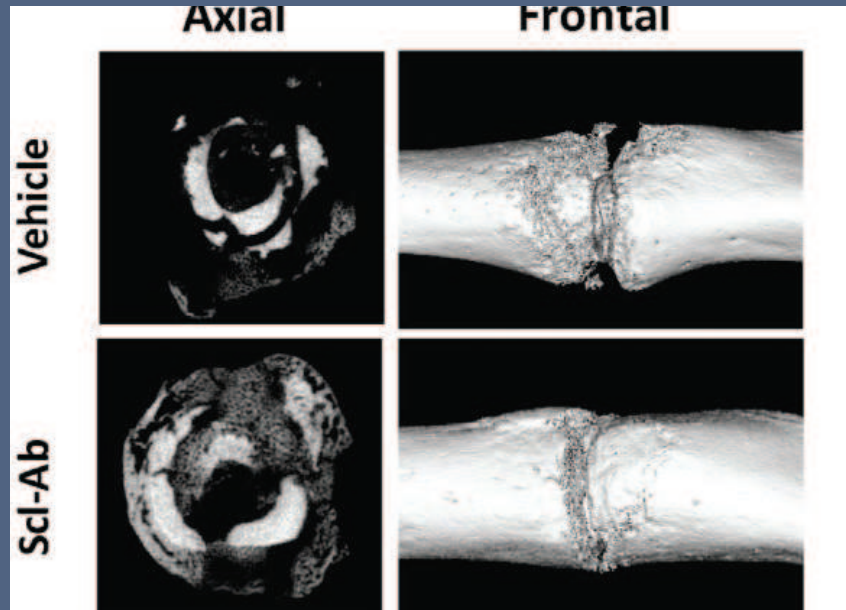
Courtesy of Matthias Bostrom, Hospital for Special Surgery

DKK-1 antibody

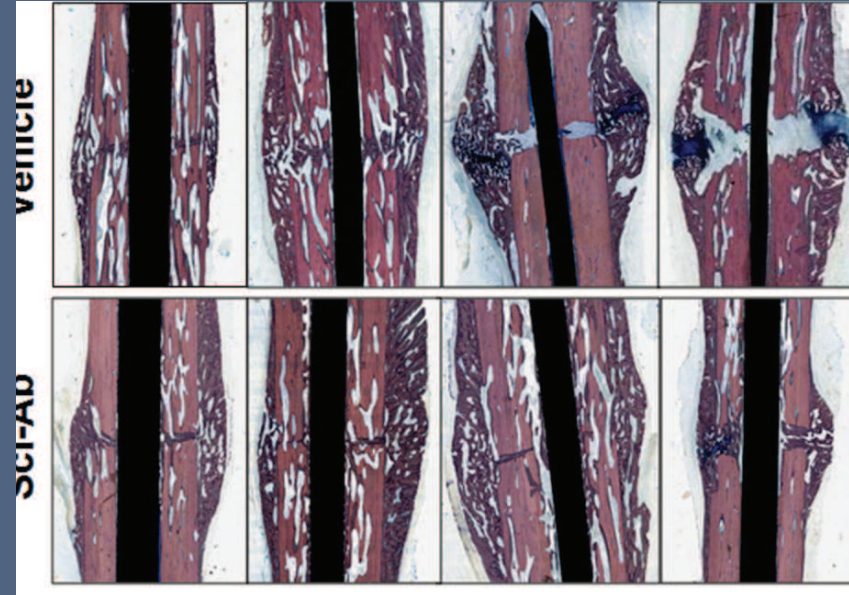


Jin H, et al. Bone 2015; 71: 63-75

Anti-sclerostin antibody



Rat femur fx model



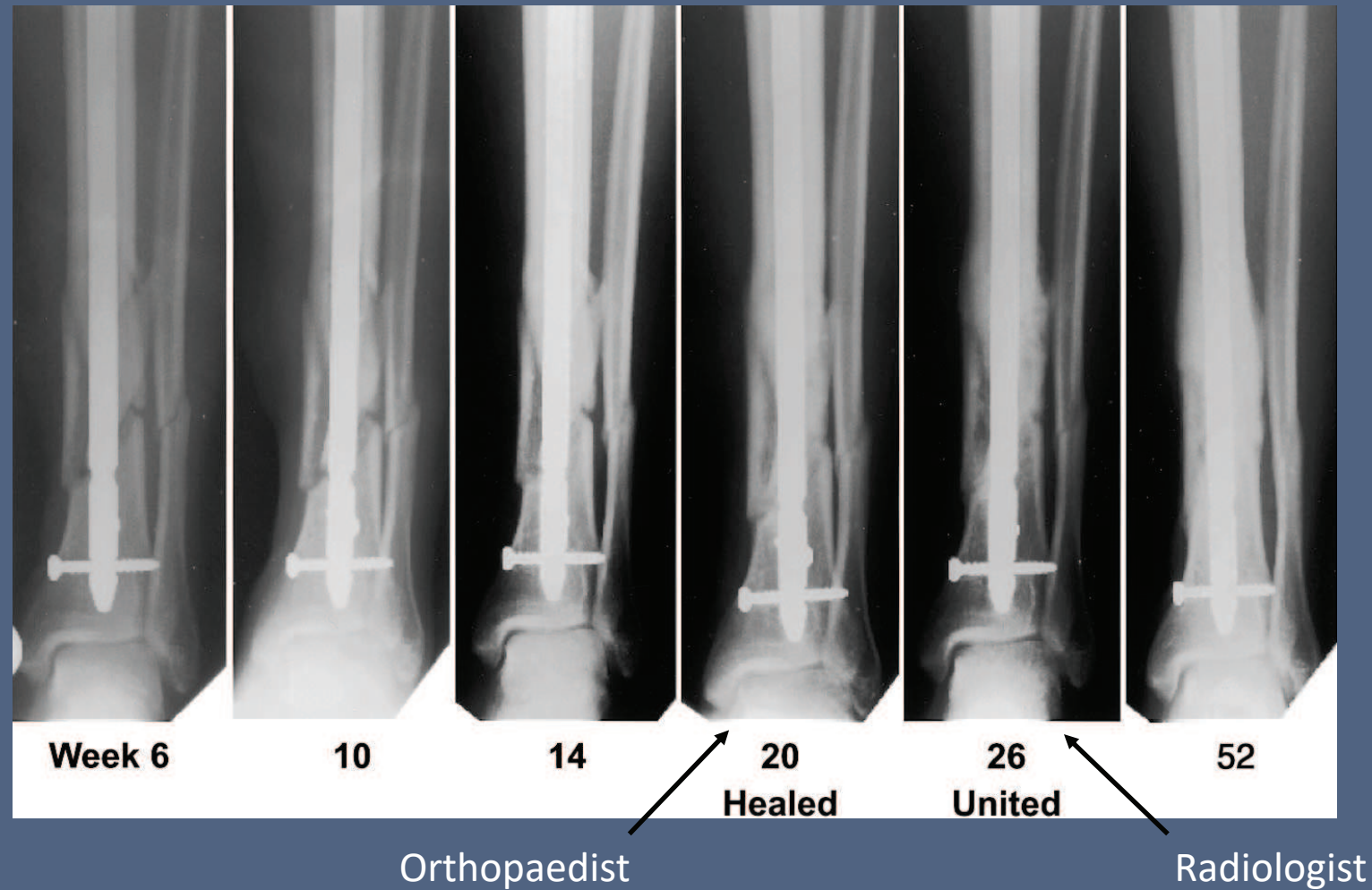
Monkey fibula fracture model

Ominsky MS, et al, JBMR 2011; 26(5): 1012-1021

So what are we looking for as we study clinical fracture healing?

- We do not really know...
 - Pain
 - Function
 - Radiographic evidence of union
 - Reoperation rate

Problems with fracture healing trials



Addressing the issues

- Development and validation of radiographic union scores
- Combined functional and radiographic endpoints for healing
 - 40% of decisions on healing from radiographs changed if clinical notes considered
 - Functional tests for each fracture site?
- Patient reported outcomes
 - Activity level
 - pain

Enhancing the normal or bettering the slow

- Trials with BMP and closed tibia fractures showed no benefit of BMP addition
- Since we do not know the time to heal, difficult to say faster
 - Distal radius fracture study
 - Clinical relevance
 - ?Value added
- Getting slow healers back on track may help us learn what to evaluate

Defining the biology in humans

- Evaluation of RNA expression at various times during normal fracture healing
- Evaluation of RNA expression with nonunions
- Serum or urine markers for problems?
- Genetic predisposition?

Combination Therapy

- Using biologics in sequence to stimulate the right thing at the right time
- Interest in PTH and anti DKK-1 and in anti-sclerostin and denosumab
 - Multiple possibilities of combinations
- Augmenting the effect of BMP or other surgical implants

Bright future

- Better understanding of biology
- Lessons learned from clinical trials of fracture healing
- Recognition of need for changes in how we think about “healed”

NOTHING helps heal a fracture better
than prevention in the first place