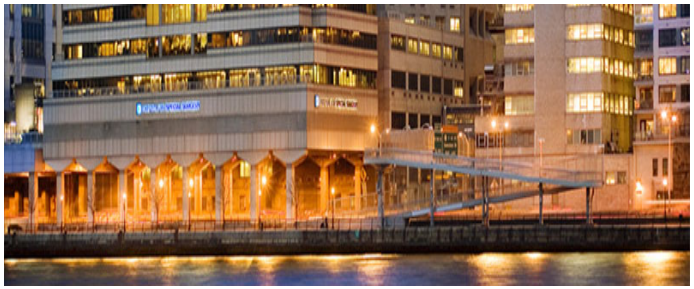
Mechanisms of bone damage in RA

Steven R. Goldring, M.D.

Chief Scientific Officer Emeritus, Hospital for Special Surgery, Professor of Medicine,
Weill Cornell Medical College,
New York, NY

Disclosures

- *Consultant: Bone Therapeutics, Jannsen Pharmaceutical, Novartis, Roche*
- *Research Grant: Boehringer Ingelheim*



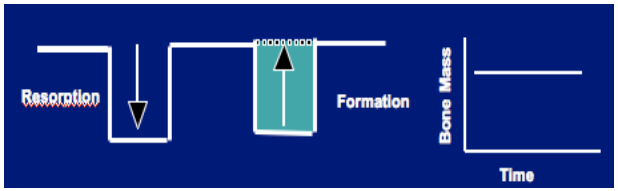
HOSPITAL FOR SPECIAL SURGERY

Outline

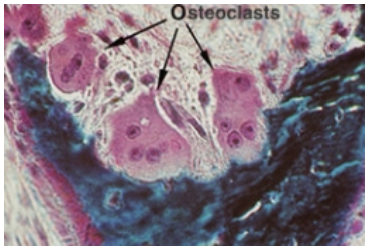
- **General principles of physiological bone remodeling**
- **Mechanisms of "coupling" of bone resorption and formation**
- **Mechanism of de-regulated bone remodeling in rheumatoid arthritis**
- **Therapeutic implications/opportunities**

Physiologic Bone Remodeling

- Adapt shape and structural organization to alterations in biomechanical forces
- Maintain structural integrity
  - Repair microdamage
- Maintain mineral ion homeostasis

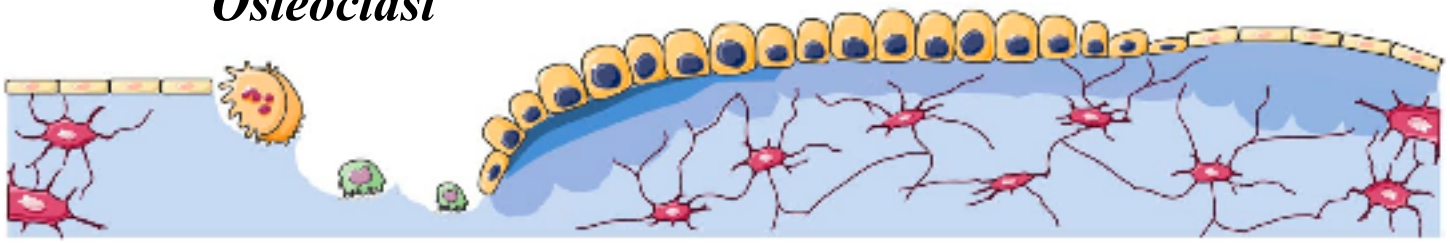


Resorption=Formation
"Coupled"



Osteoclasts are required for bone resorption

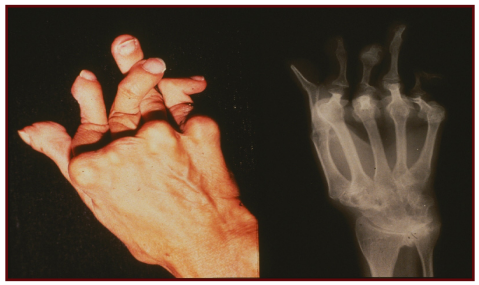
Osteoclast ***Osteoblast***



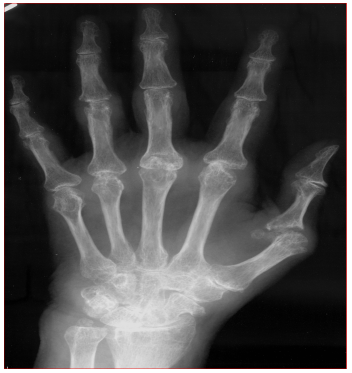
Resorption **Formation**

Temporal sequence

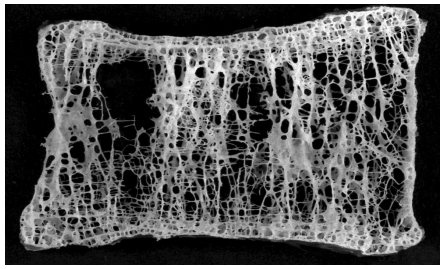
Rheumatoid Arthritis: a paradigm of pathologic bone remodeling



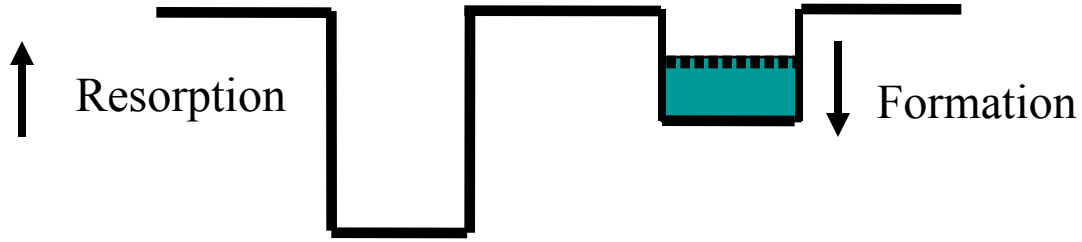
ARTICULAR EROSIONS



PERIARTICULAR OSTEOPENIA



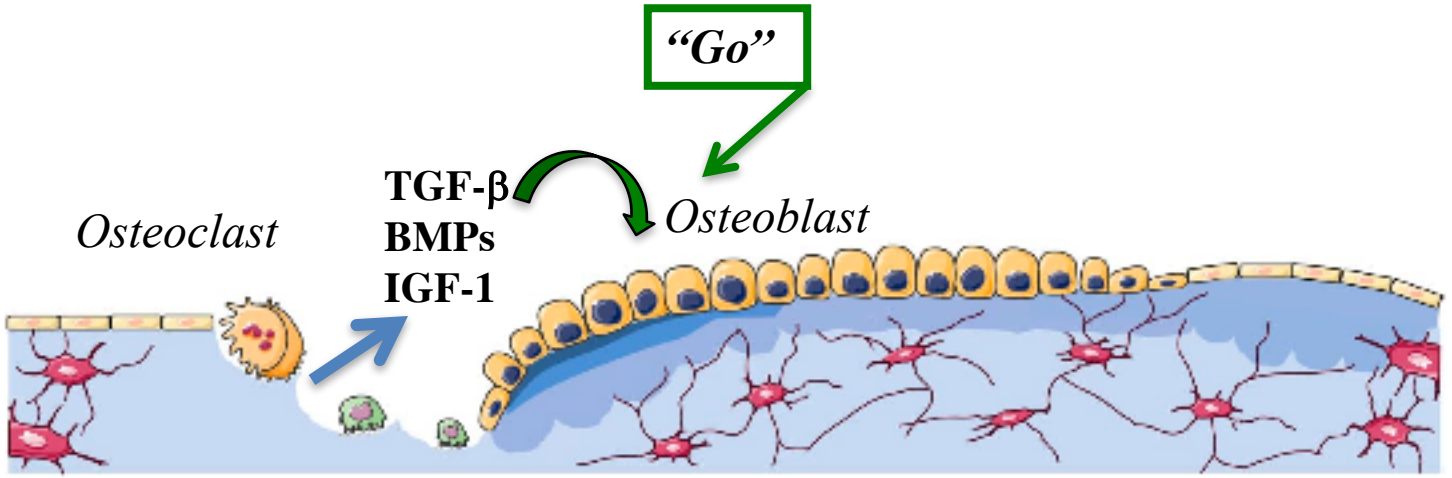
SYSTEMIC OSTEOPOROSIS



- **Bone resorption and formation are uncoupled**
- **What are the underlying mechanisms?**
- **Are there therapeutic options to restore homeostasis?**

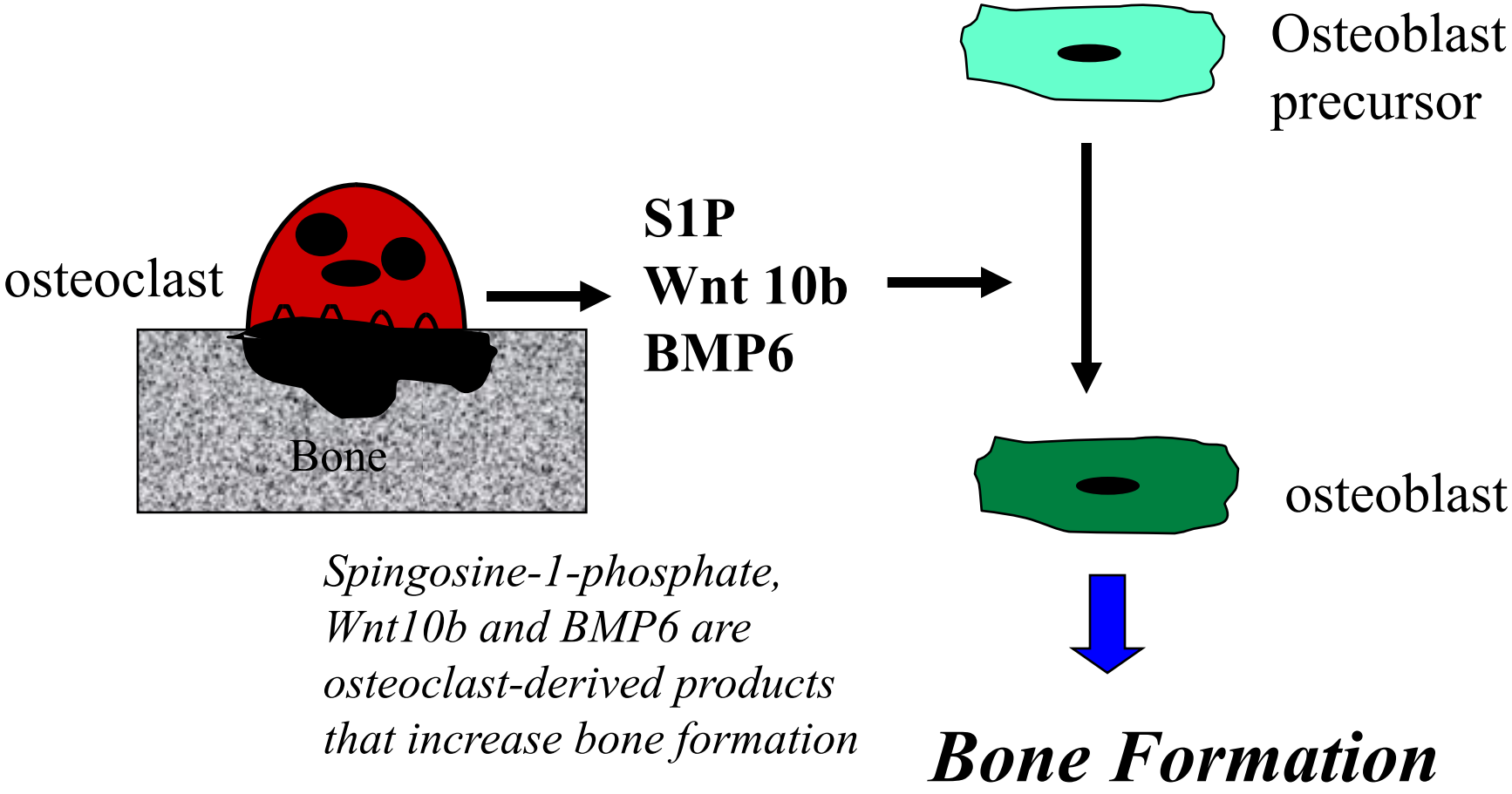
Physiological Bone Remodeling

Question: What are the mechanisms of *coupling* of bone resorption/formation?



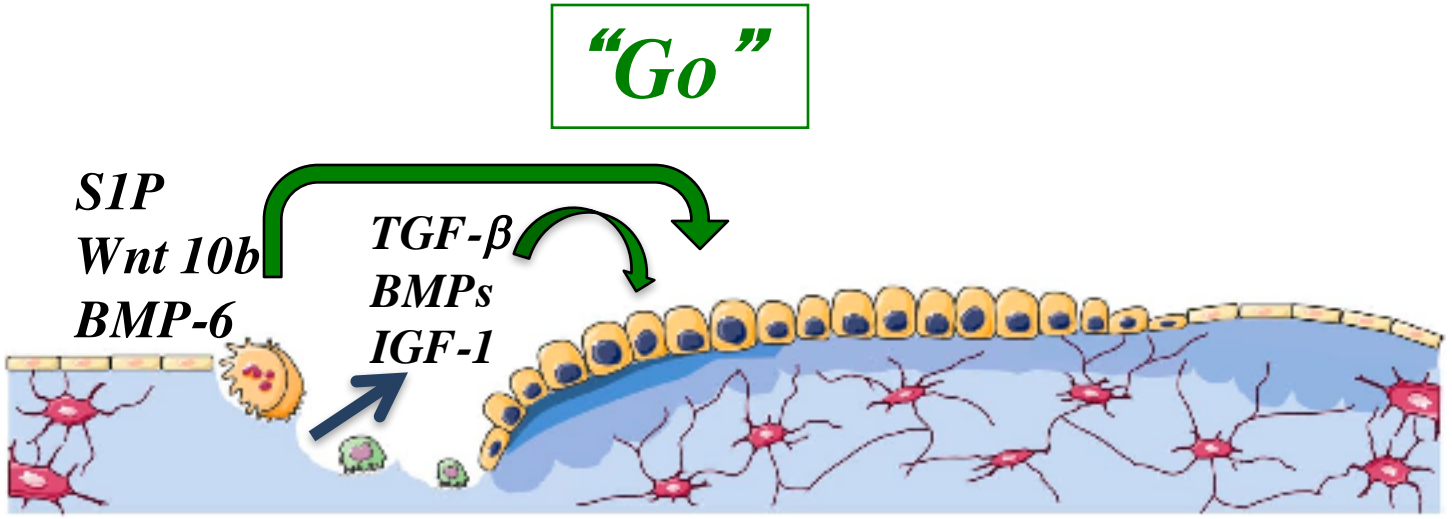
Products released from the bone matrix activate osteoblast-mediated bone formation

Osteoclasts produce factors that stimulate bone formation



Pederson L et al. PNAS 2009; 105:20764-20769
Masuzaki E et al. Bone 2013; 55:315-24
Purdue PE, Goldring SR, McHugh KP. Sci Rep. 2014 Dec 23;4:7595

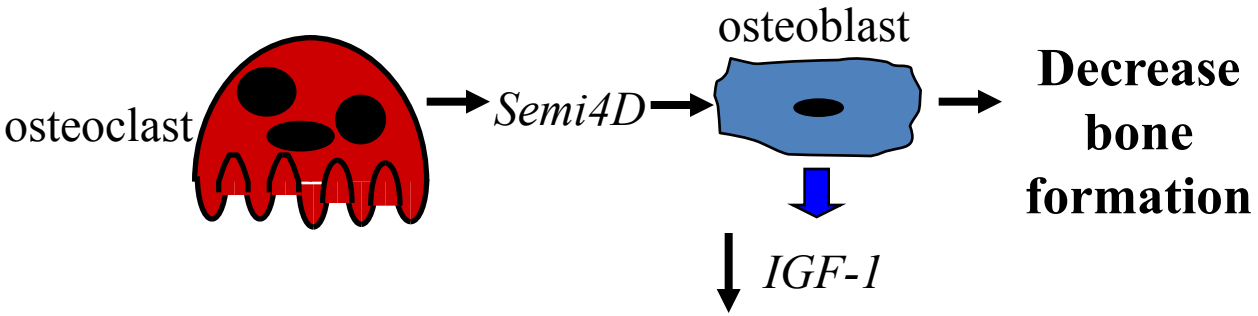
Mechanisms of coupling of bone resorption/formation

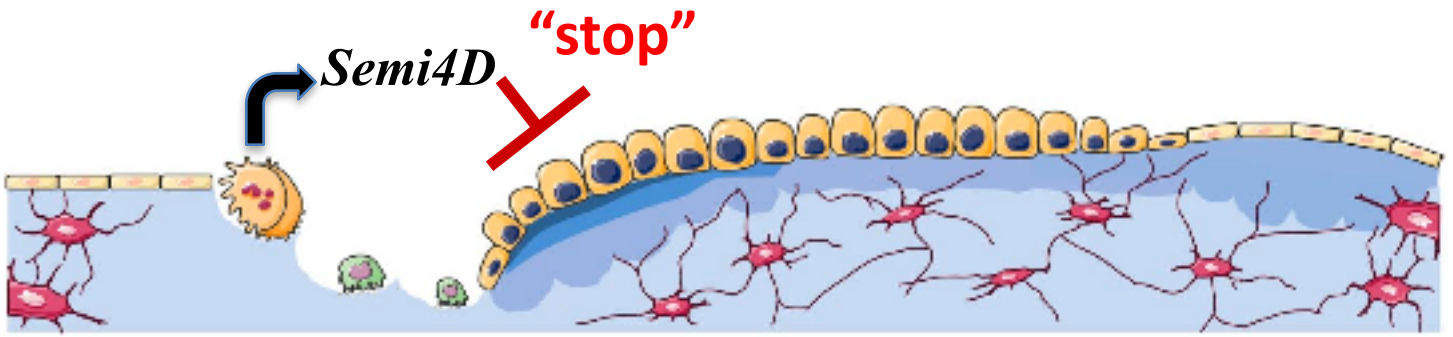


Osteoclast-derived products contribute to coupling of bone resorption and formation

What are the mechanisms involved in termination of bone formation in a bone remodeling unit, *e.g. the "stop" signal?*

- *Osteoclast–derived products provide "stop" signals*





Negishi-Koga T et al. Nat Med 2011; 17:1473-81

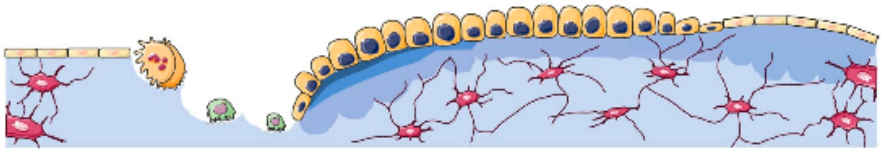
Factors that regulate coupling of bone remodeling

- Bone matrix –derived products
- Osteoclast–derived products
- ***Local biomechanical factors*** **play a major role in the termination (and initiation) of the bone remodeling cycle**

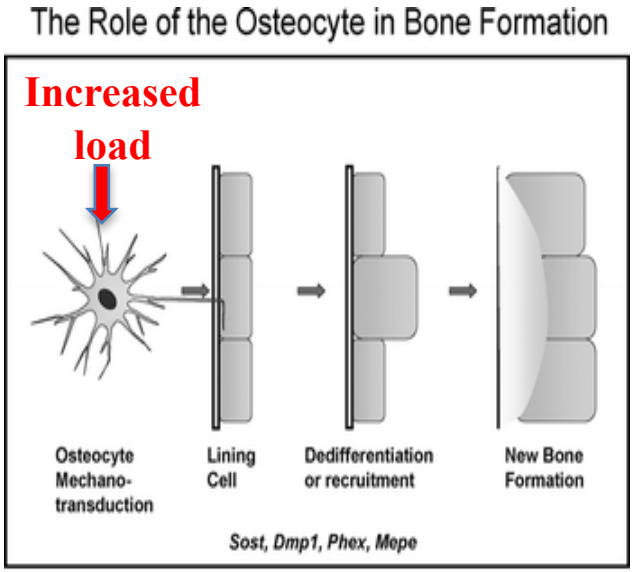
<u>Question</u>: How does bone sense its biomechanical environment and contribute to regulation of bone remodeling ?

Mechanism of bone adaptation to local mechanical influences

The *osteocyte* is mechano-sensor of bone

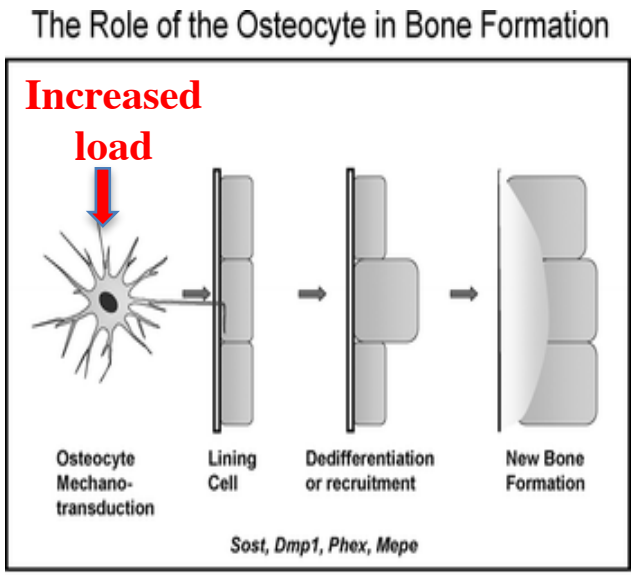


- The osteocytes form a syncytium within bone
- Their interconnected network is in contact within the cells on the bone surface and with each other
- Osteocytes regulate bone remodeling and modeling via interaction with osteoblast and osteoclasts (and their precursors)
- Osteocyte regulate bone resorption and formation via direct cell-cell communication and by the release of soluble mediators

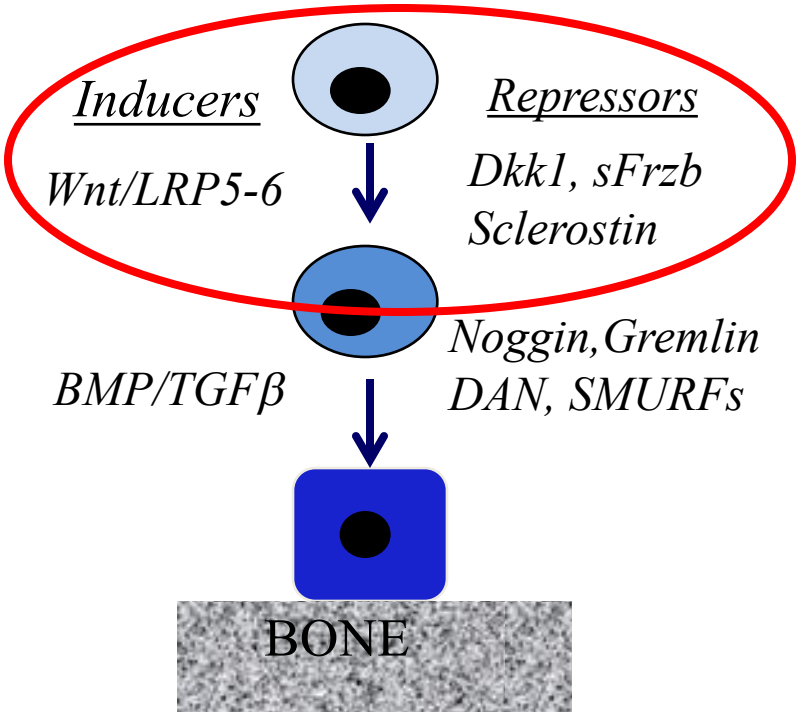


From the *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th Edition*. www.asbmrprimer.org

What are the mechanisms responsible for load-induced increases in bone formation?



Regulators of osteoblast-mediated bone formation

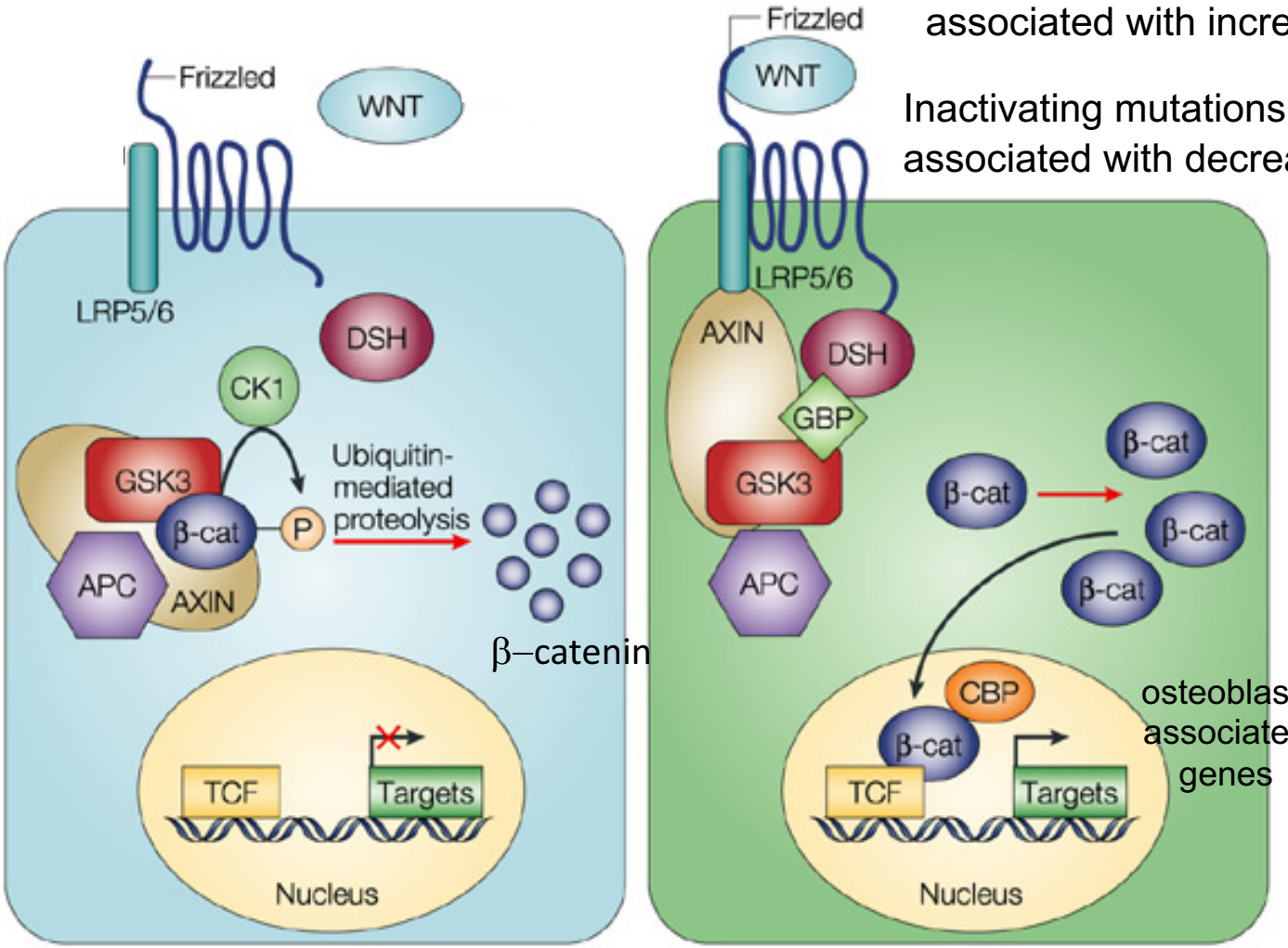


Osteocytes regulate bone formation by production of molecules that control osteoblast differentiation and activity

Canonical Wnt/β-Catenin signaling pathway

Activating mutations of LRP-5 associated with increased bone mass

Inactivating mutations of LRP-5 associated with decreased bone mass



Moon RT et al. 2004; 5:689-99

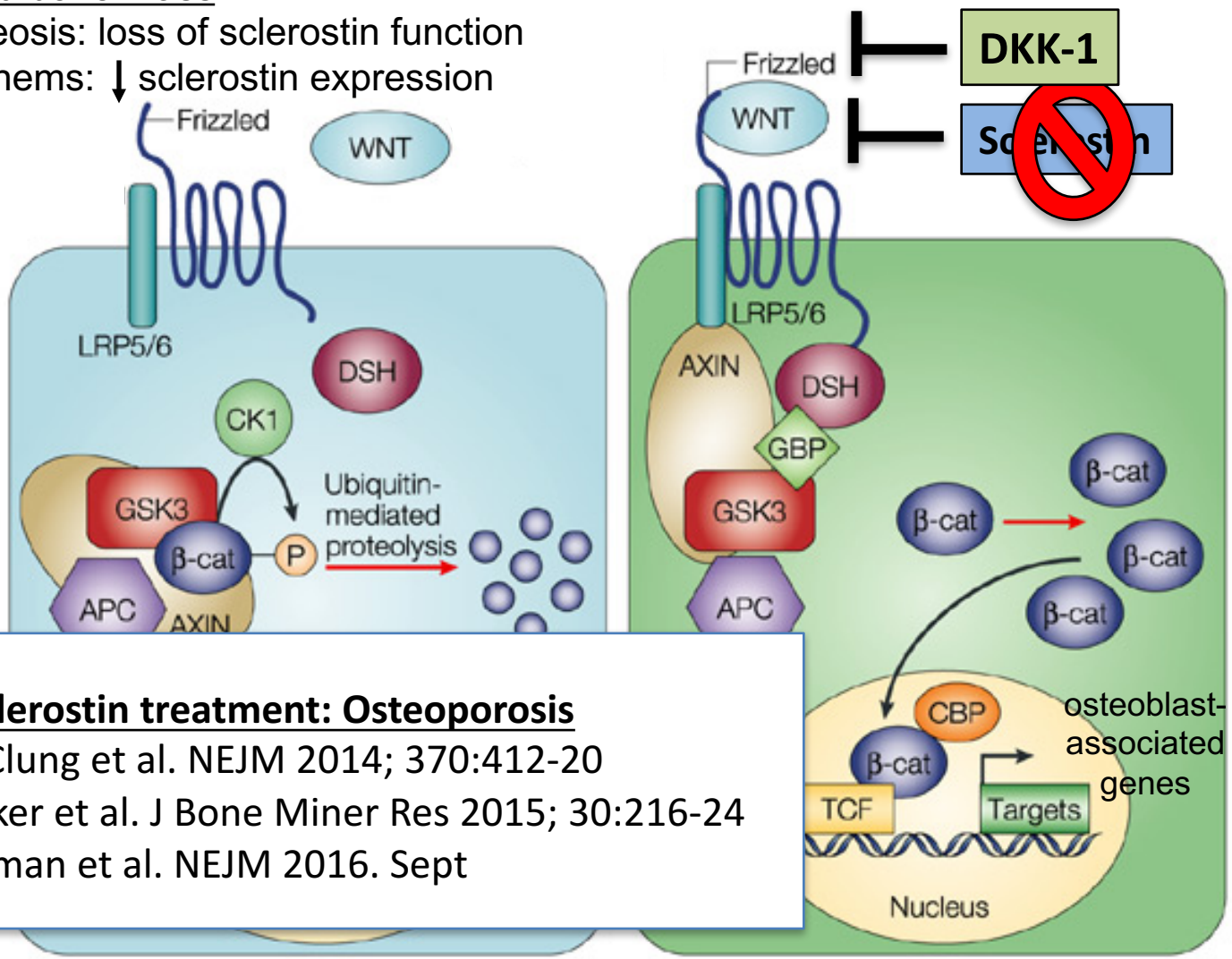
Nature Reviews | Genetics

Canonical Wnt/β-Catenin signaling pathway

Increased bone mass

Sclerosteosis: loss of sclerostin function

Van Buchems: ↓ sclerostin expression



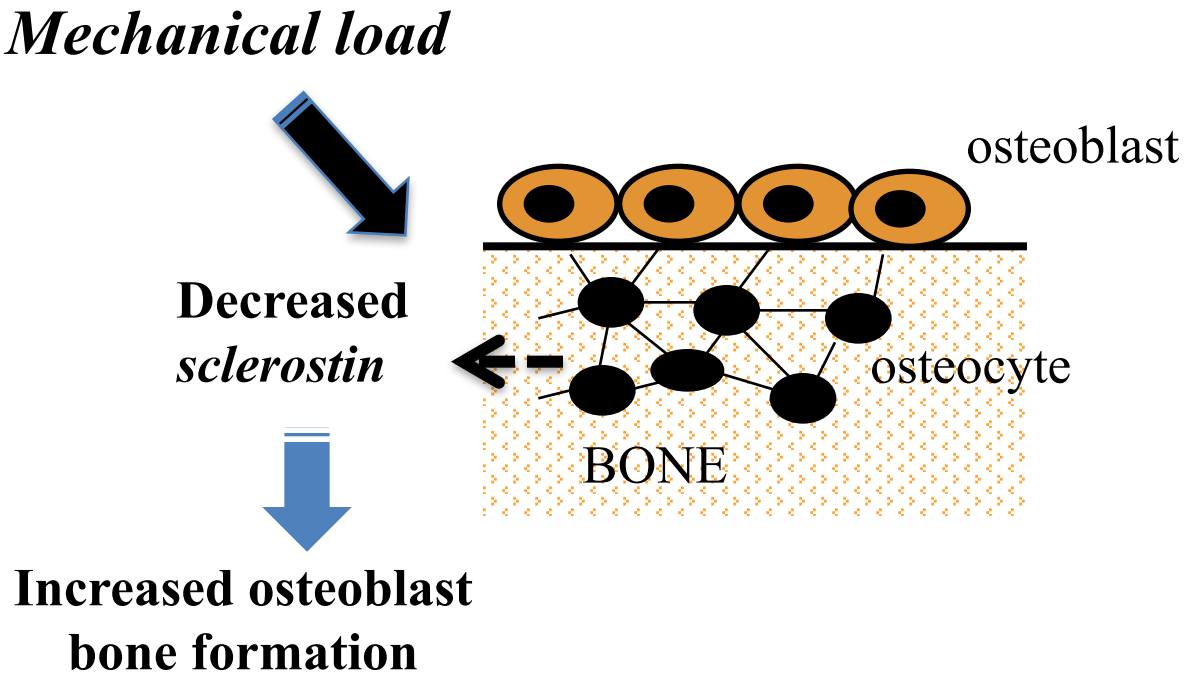
Anti-sclerostin treatment: Osteoporosis

- McClung et al. NEJM 2014; 370:412-20
- Recker et al. J Bone Miner Res 2015; 30:216-24
- Cosman et al. NEJM 2016. Sept

Moon RT et al. 2004; 5:689-99

Nature Reviews | Genetics

Osteocyte-derived sclerostin modulates bone formation

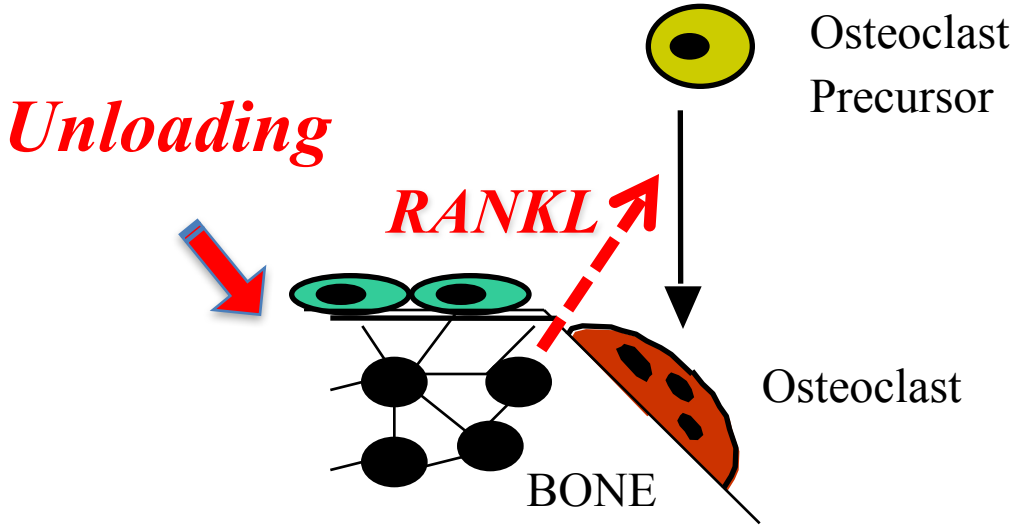


- **The effects on bone formation are mediated by osteocyte-derived sclerostin (Wnt pathway inhibitor)**

- **Inhibiting sclerostin increases bone formation**

Bellido T et al Endocrinology. 2005; 146:4577-83
Robling AG et al. JBC; 2008;283:586-75

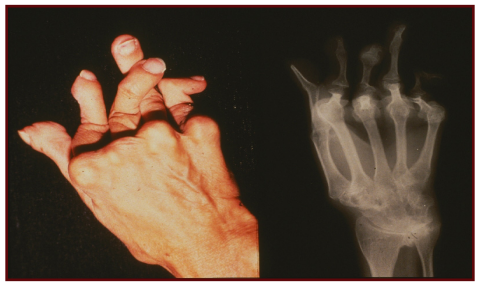
Role of osteocytes in regulation of osteoclast-mediated bone resorption



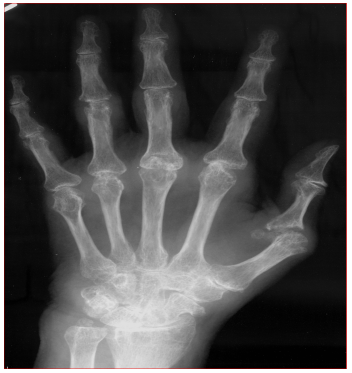
- **Osteocytes up-regulate RANKL in response to unloading**
- **Osteocytes via *RANKL* or *sclerostin* production regulate adaptation of bone to mechanical (and hormonal) signals**

-Xiong et al. Nat Med 2011; 17:1235-41
-Nakashima et al. Nat Med 2011; 17:1231-34

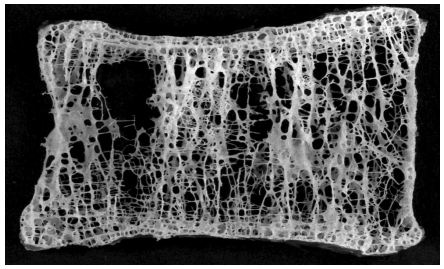
Rheumatoid Arthritis: a paradigm of pathologic bone remodeling



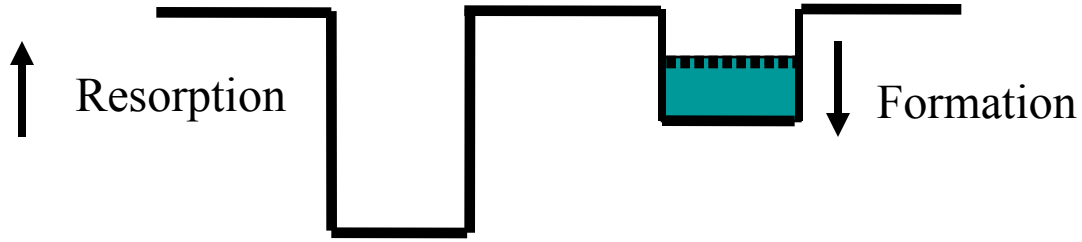
ARTICULAR EROSIONS



PERIARTICULAR OSTEOPENIA

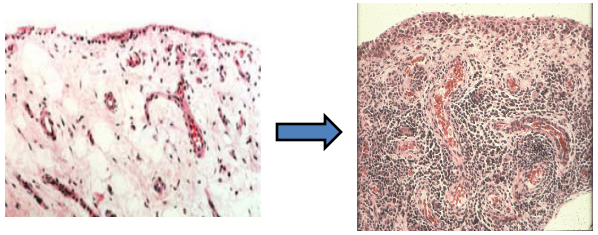


SYSTEMIC OSTEOPOROSIS

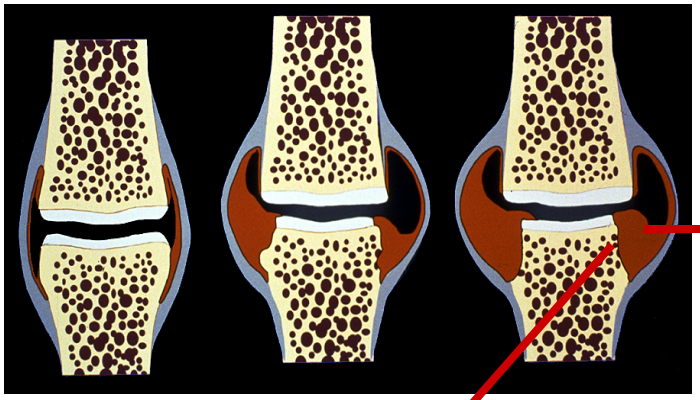


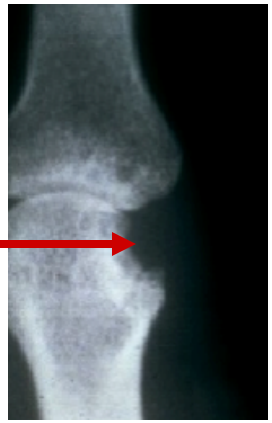
- **Bone resorption and formation are uncoupled**
- **What accounts for increased bone resorption?**

Marginal Joint Erosions in RA

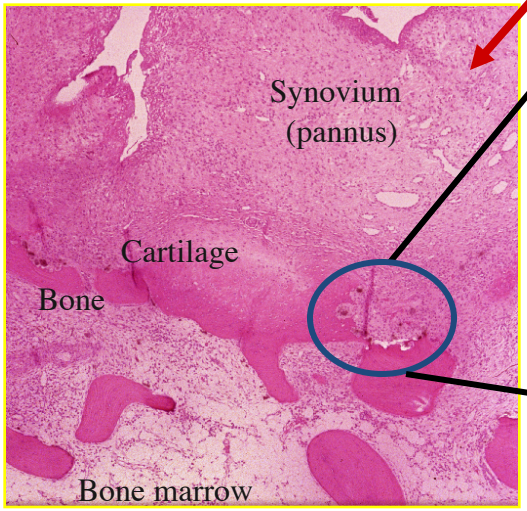


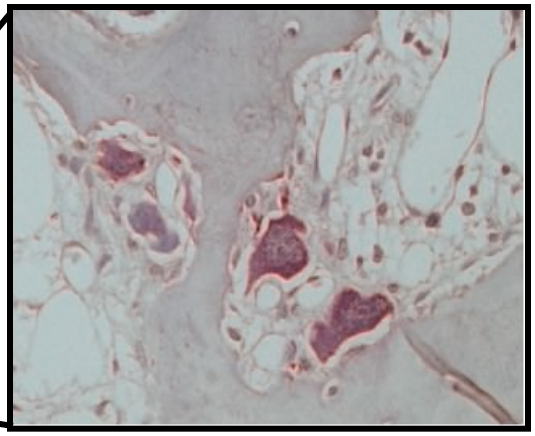
- *Synovial fibroblast hyperplasia*
- *Neovascularization*
- *Inflammation: T cells, B cells, macrophages, dendritic cells*





Inflamed synovium contains osteoclast precursors





Cells with phenotypic features of osteoclasts are present in resorption lacunae at the bone synovial interface.

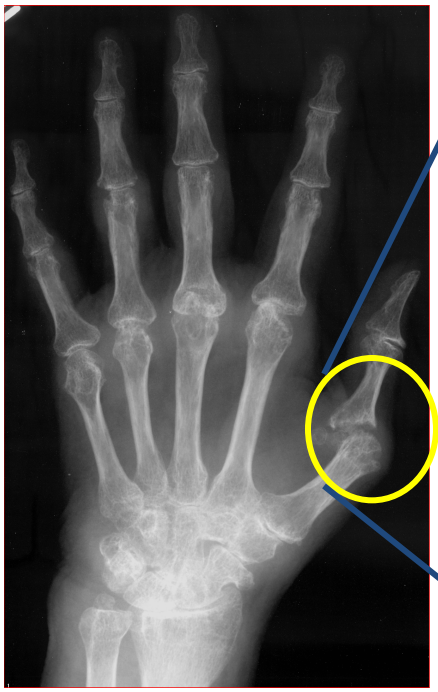
Gravallese, Goldring et al. Am J Pathol, 1998; 152:943-951

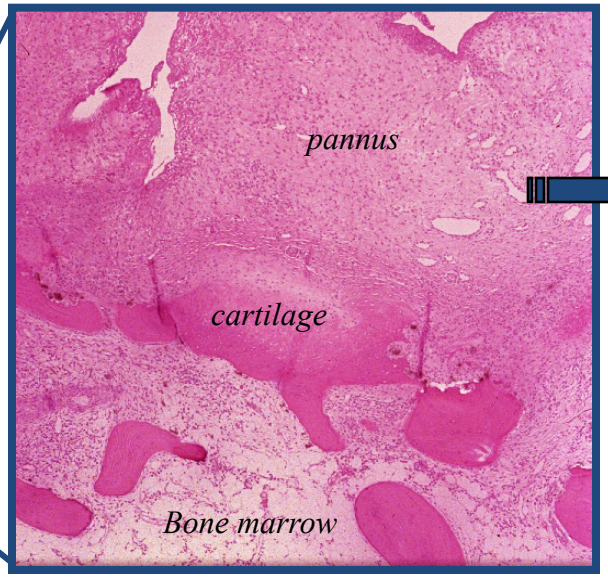
Takayanagi et al A&R 2000; 43: 259-69
Itonaga I et al J Pathol 2000;192:97-104
Haynes DR Rheumatology 2001; 40:623-30
Suzuki Y Rheumatology 2001; 40:673-82
Lubberts E Arthritis Rheum 2002; 46:3055-64

Genetic ablation of RANKL in a model of RA prevented bone erosions. *Osteoclasts are required for bone erosions*

Pettit, Goldring, Gravallese g et al. Am J Pathol 2001; 159:1689-1699

Immunomodulatory and proinflammatory factors produced by RA synovium with osteoclastogenic activity



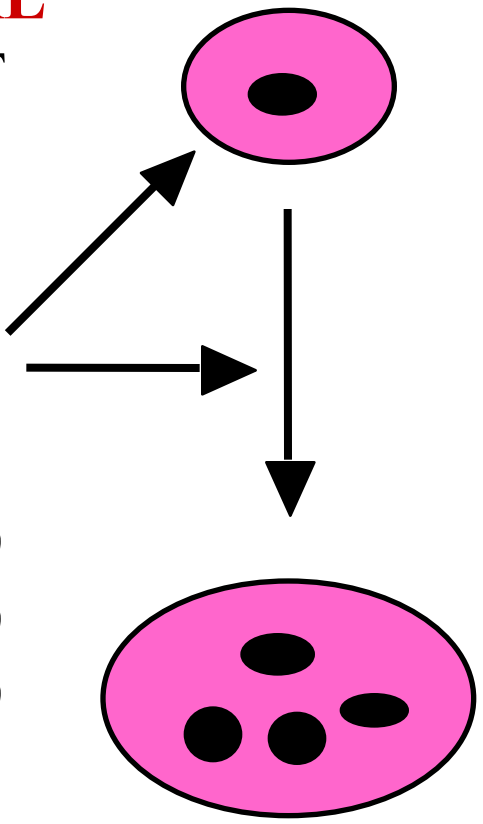


Inflamed synovium contains osteoclast precursors

Takayanagi et al A&R 2000; 43: 259-69
Itonaga I et al J Pathol 2000;192:97-104
Haynes DR Rheumatology 2001; 40:623-30
Suzuki Y Rheumatology 2001; 40:673-82
Lubberts E Arthritis Rheum 2002; 46:3055-64

Macrophage lineage cell

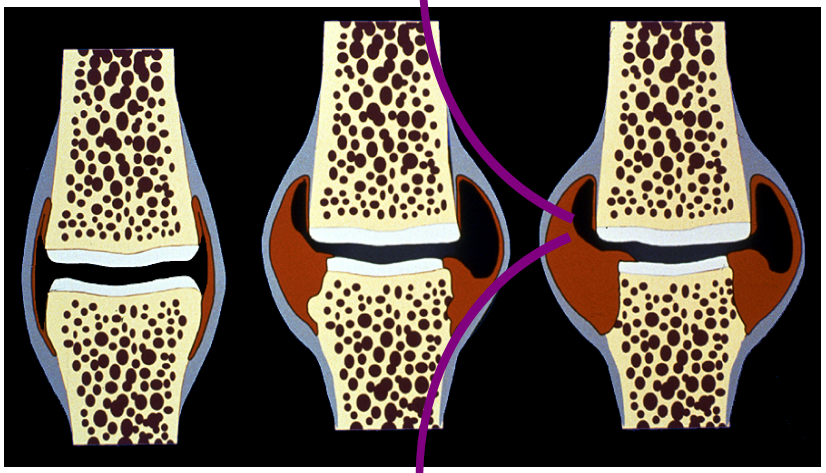
RANKL
M-CSF
TNF-a
IL-1
IL-6
IL-11
OSM
(IL-15)
(IL-17)
(IL-23)



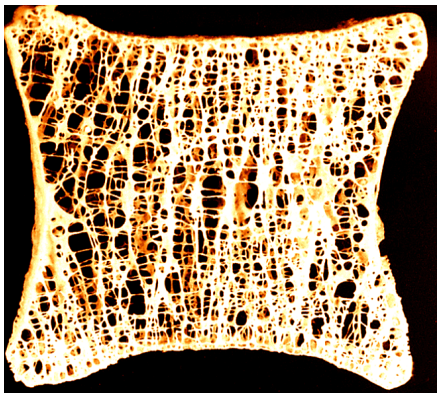
Osteoclast

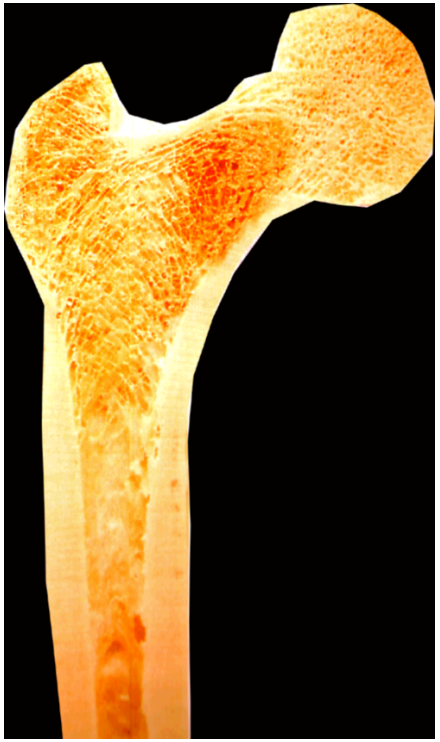
Proposed mechanism of systemic bone loss in RA

RANKL
TNF-a
IL-1
IL-6
DKK-1



RANKL
TNF-a
IL-1
IL-6
DKK-1





Resorption

Formation

SYSTEMIC
BONE LOSS

OSTEOPOROSIS

Summary of factors responsible for enhanced osteoclastogenesis in RA

- Recruitment of osteoclast precursors to the inflamed synovium (e.g. chemokines)
- Production of osteoclastgenic factors by the inflamed synovium (e.g. RANKL,TNF-α)
- Absence of inhibitors of osteoclastogenesis (e.g. soluble factors (e.g. interferon-γ), cells (e.g.Tregs)
- Production of osteoclastogenic immunoglobulins (e.g. anti-CCP abs)

Denosumab treatment effects on structural damage, bone mineral density and bone turnover in RA

A 12 month, multicenter, randomized, double-blind, placebo-controlled phase II clinical trial

-Decrease in progression of MRI erosions

-Decrease in progression of Sharp erosion scores

-Sustained suppression of bone turnover markers

-Positive effect BMD

-No effect JSN

-No effect disease activity

-No difference in adverse events

Conclusion: *RANKL* blockade inhibits osteoclastic bone resorption and inhibits the development of bone erosions

Cohen et al. Arthritis Rheum 2008; 58:1299-1309

Denosumab-mediated increase in hand bone mineral density associated with decreased progression of bone erosion in rheumatoid arthritis patients

- Patients receiving methotrexate for erosive RA were randomized in to receive subcutaneous placebo, denosumab 60 mg, or denosumab 180 mg at 0 and 6 months

Conclusion: In patients with RA, denosumab provided protection against erosion, and not only prevented bone loss but increased hand BMD as measured by DXA

Deodhar et al. Arthritis Care Res (Hoboken). 2010 Apr;62(4):569-74

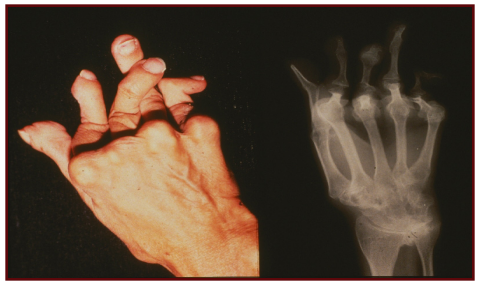
Effect of denosumab on Japanese patients with rheumatoid arthritis: a dose-response study of AMG 162 (Denosumab) in patients with rheumatoid arthritis on methotrexate to validate inhibitory effect on bone erosion

- Multicentre, randomised, double-blind, placebo-controlled, phase II clinical trial
- Denosumab significantly inhibited the progression of bone erosion at 12 months
- No obvious evidence of an effect on joint space narrowing for denosumab
- No apparent difference was observed in the safety profiles of denosumab and placebo

Conclusion: Addition of denosumab to methotrexate has potential as a therapeutic option for patients with RA with risk factors of joint destruction.

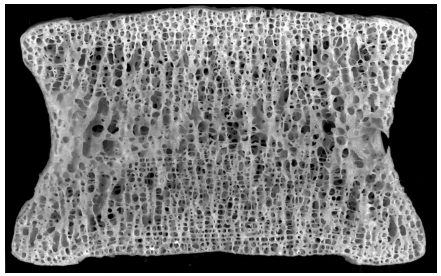
Takeuchi et al. Ann Rheum Dis. 2016 Jun;75(6):983-90

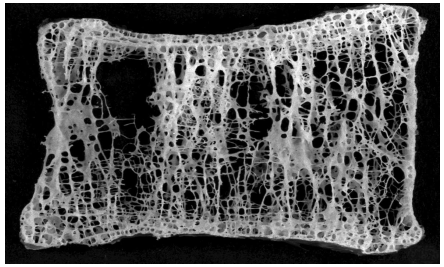
Rheumatoid Arthritis: a paradigm of pathologic bone remodeling



ARTICULAR

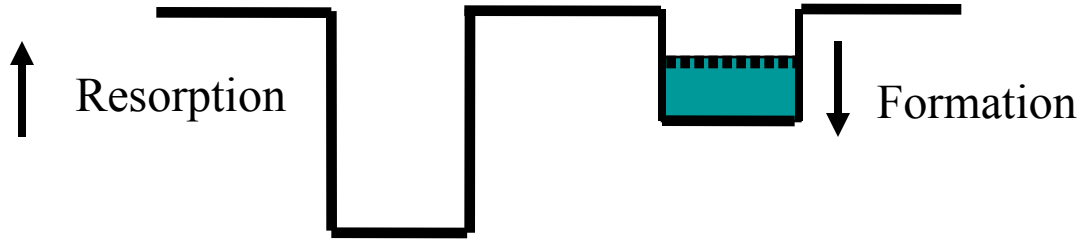
Normal vertebral body





Osteoporotic

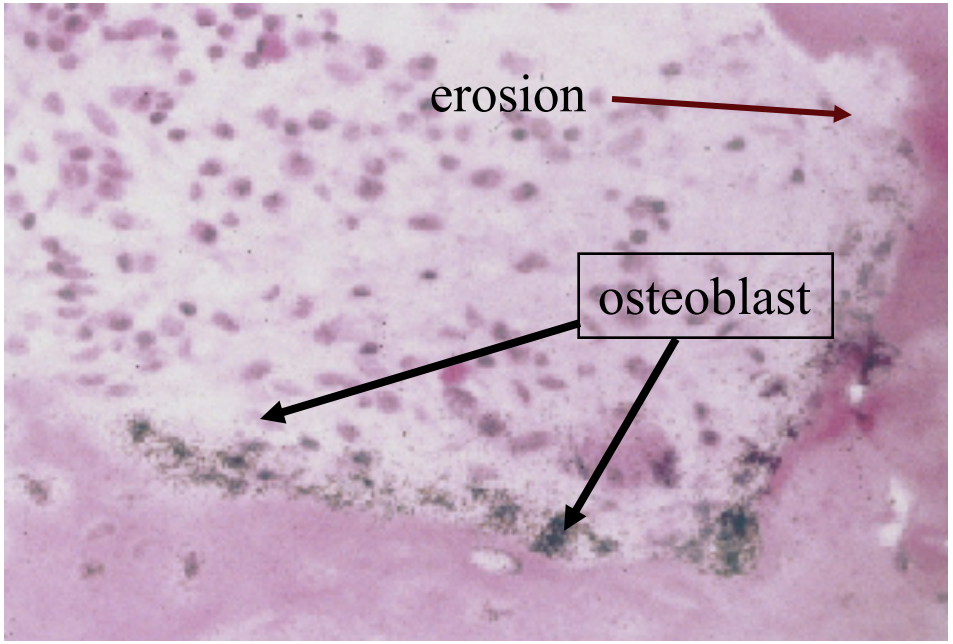
SYSTEMIC



Bone resorption and formation are uncoupled

What accounts for the bone formation defect?

Osteoblast-like cells at sites of bone erosions express PTH receptors

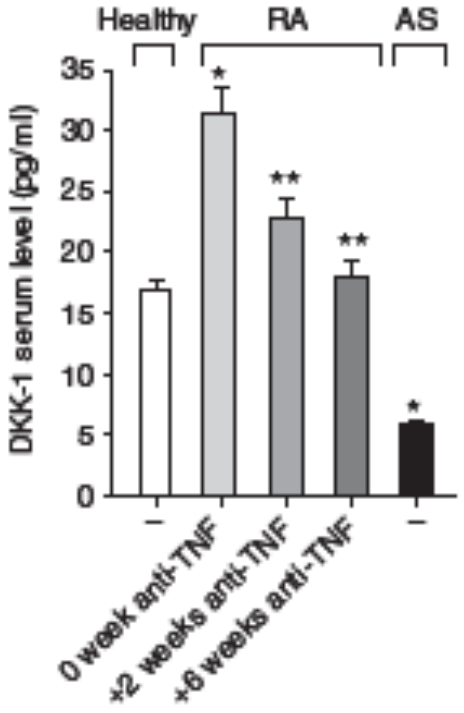


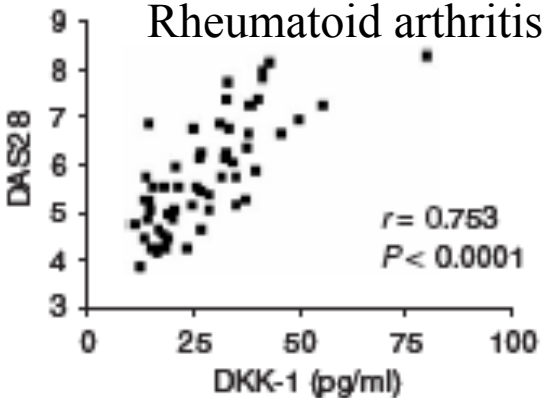
Despite the presence of osteoblasts in regions of focal bone erosions, there is defective bone formation.

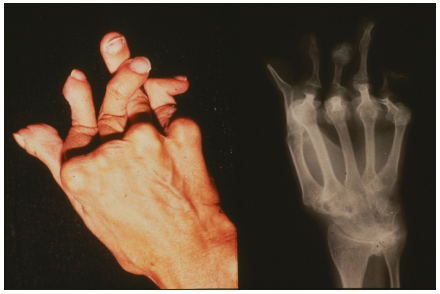
-Gravallese EM, Goldring SR et al. Am J Pathol, 1998; 152: 943-951

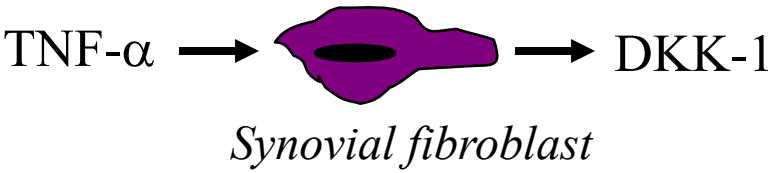
-Walsh N, Burr DB, Gravallese et al. JBMR, 2009;24:1572-85

Role of DKK-1 in suppression of bone formation in inflammatory arthritis



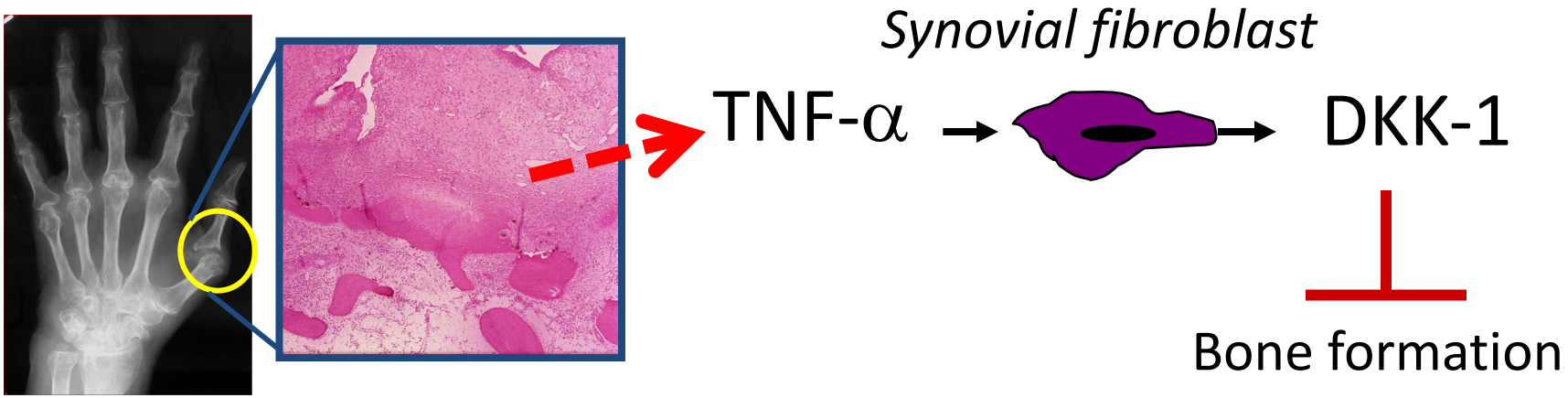






Diarra et al. Nat Med 2007; 13:156

TNF-α induces DKK-1 in RA synovial fibroblasts



- **Monocyte- and T cell-derived TNF–α induces DKK-1 by synovial fibroblast**
- **DKK-1 inhibits bone formation**

Diarra et al. Nat Med 2007; 13:156

Role of DKK-1 in supression of bone formation in inflammatory arthritis

- **DKK-1 levels elevated in serum and synovial tissue from RA patients**

- **TNF induces DKK-1 in synovial fibroblasts**

- **Treatment of animals with inflammatory arthritis (TNF-transgenic, collagen-induced arthritis or serum transfer arthritis) with a DKK-1 blocking antibody preserved bone formation.**

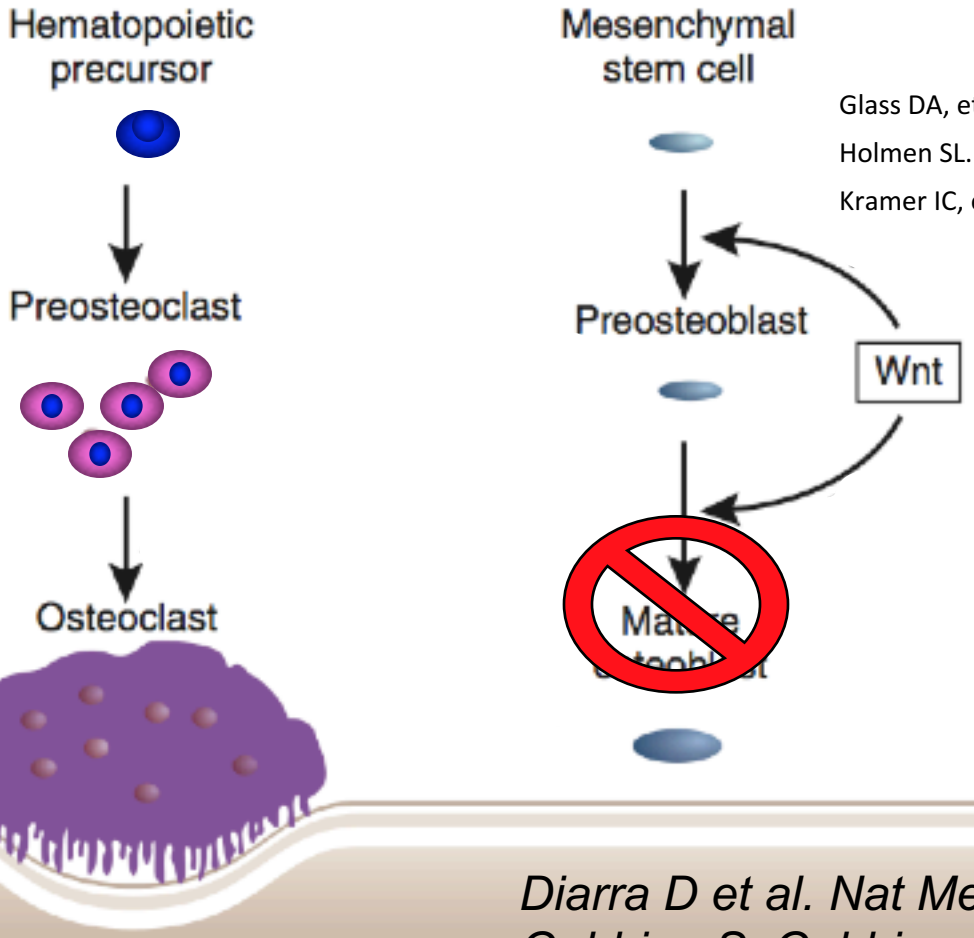
Diarra et al. Nat Med 2007; 13:156

-DKK-1 inhibits bone formation in inflammatory arthritis

-DKK-1 enhances bone resorption in inflammatory arthritis

-Inhibition of DKK-1 restores bone formation

-Inhibition of DKK-1 increases OPG and decreases bone erosion



Glass DA, et al. Dev. Cell. 8:751-764. 2005

Holmen SL. JBC 280: 21162-21168. 2005

Kramer IC, et al. Mol. Cell. Biol. 30: 3071-3085. 2010

Diarra D et al. Nat Med 2007; 13:156-163

Goldring S, Goldring M.. Nat Med 2007; 13:133-

Sclerostin inhibition reverses systemic, periarticular and local bone loss in arthritis

Chen, Schett et al. Ann Rheum Dis. 2013 Oct;72(10):1732-6

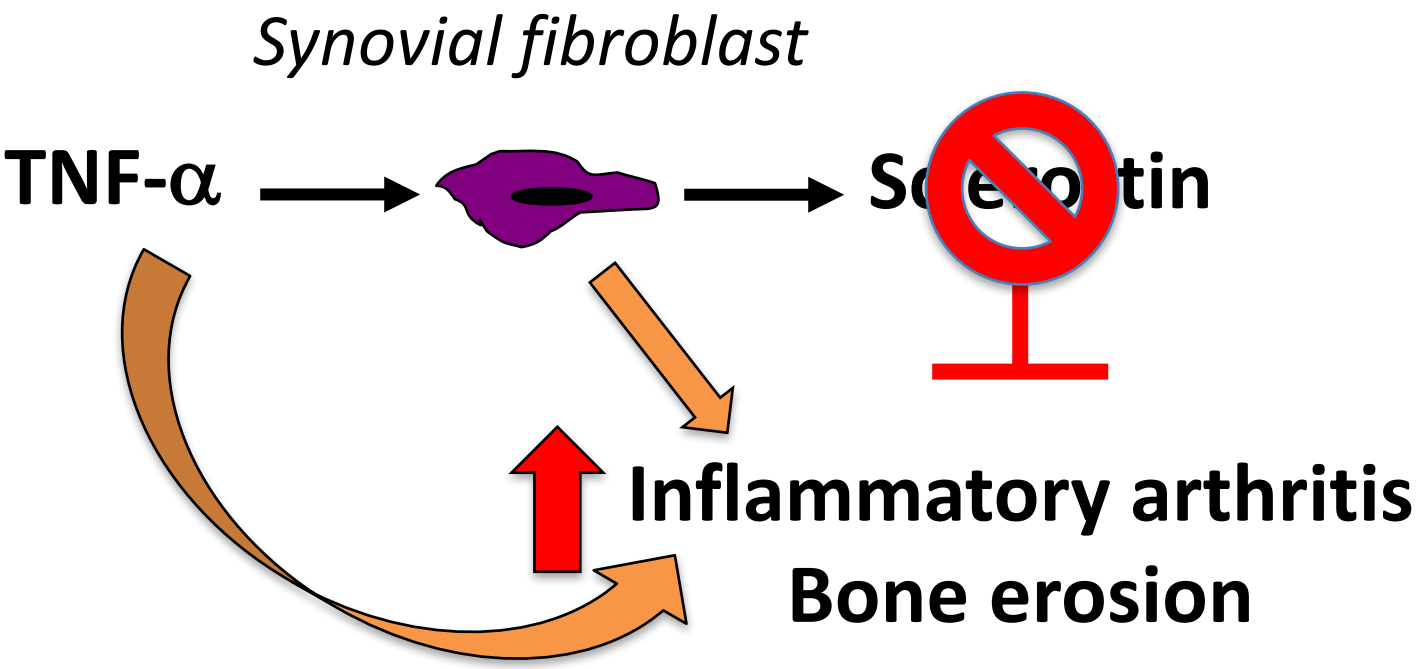
- Scl-Ab did not affect joint swelling or synovitis in hTNFtg mice
-
- Systemic bone loss in the spine and periarticular bone loss in the proximal tibia were completely blocked and partially reversed by inhibition of sclerostin but not by inhibition of TNF.

- Scl-Ab completely arrested the progression of bone erosion in hTNFtg mice and in combination with TNF inhibition even led to significant regression of cortical bone erosions.

- Protective effects of Scl-Ab were also observed for the articular cartilage.

***Wehmeyer** et al. Sci Transl Med. 2016 Mar 16;8(330):330ra35*

(RA-like disease in human TNFα transgenic (hTNFtg) mice)



Removing sclerostin or blocking its activity enhances joint inflammation and bone erosion in the hTNFtg mouse model of RA

Sclerostin inhibition promotes TNF-dependent inflammatory joint destruction

Wehmeyer et al. Sci Transl Med. 2016 Mar 16;8(330):330ra35

- TNF−α induces sclerostin in synovial fibroblasts
- Lack of sclerostin or its antibody enhanced RA-like disease in human TNFα transgenic (hTNFtg) mice
- In contrast, inhibition of sclerostin ameliorated disease severity in K/BxN serum transfer-induced arthritis mouse model, which is independent of TNF receptor signaling, suggesting a specific role for sclerostin in TNFα signaling
- Sclerostin effectively blocked TNFα- but not interleukin-1-induced activation of p38, pointing to a protective role of sclerostin in TNF-mediated chronic inflammation

Conclusion: *Caution should be taken when considering anti-sclerostin therapy for inflammatory bone loss in RA and when using anti-sclerostin antibodies in patients with TNFα-dependent comorbidities*

Summary

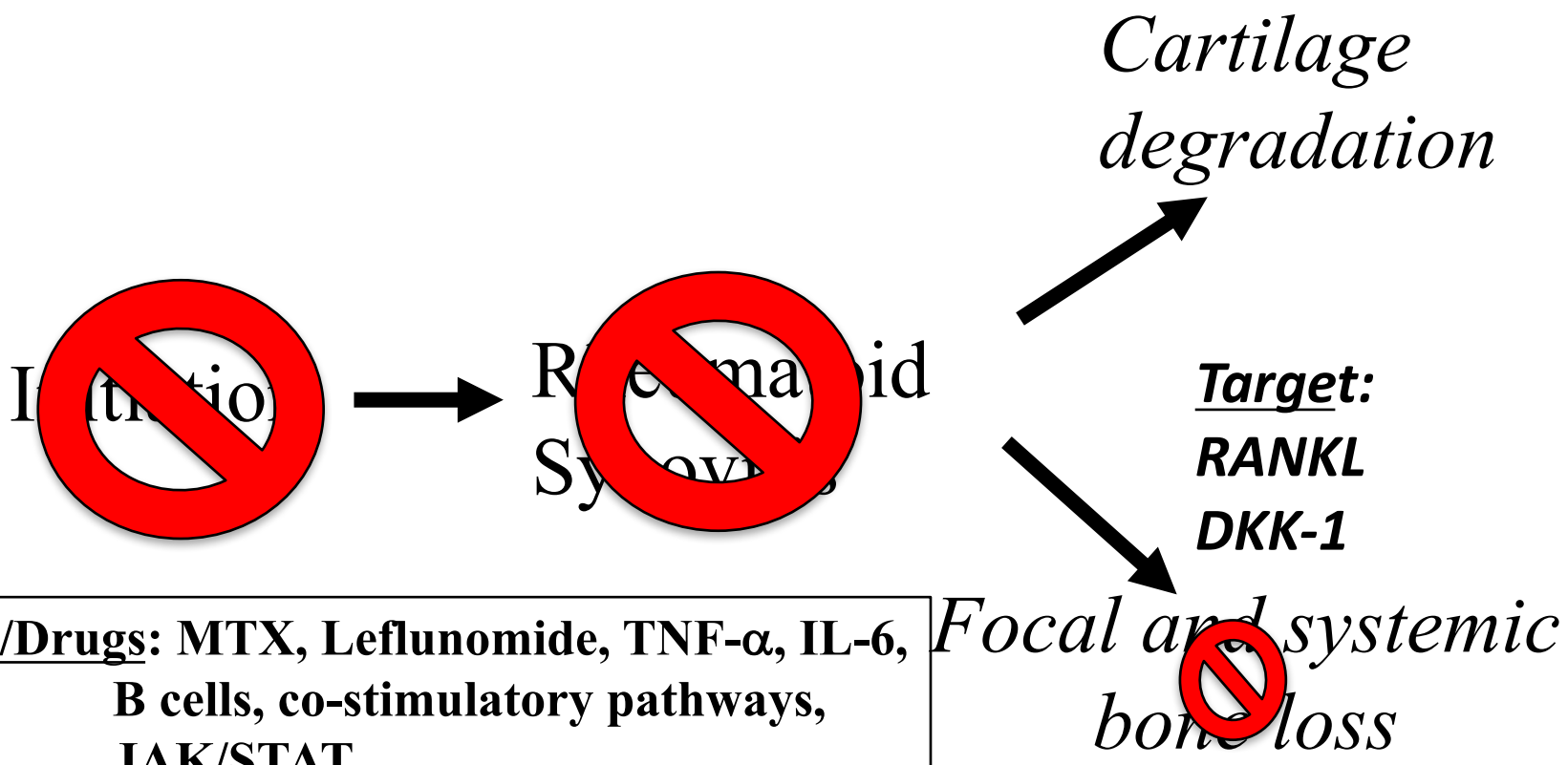
- **Rheumatoid arthritis is associated with de-regulated bone remodeling (increased resorption/suppressed bone formation**

- **Products generated by the inflammatory process deregulate the activity and function of bone resorbing osteoclasts and bone forming osteoblasts**

- **Targeting RANKL, which enhances osteoclast-mediated bone loss, or DKK-1 (or sclerostin?) which suppresses bone formation represent rationale approaches to preventing bone pathology in RA**

- **An understanding of the cellular and molecular mechanisms involved in the de-regulated bone remodeling provides a unique opportunity to develop novel and improved therapies for treatment of inflammatory arthritis**

Prevention of joint bone and cartilage destruction in RA



Targets/Drugs: MTX, Leflunomide, TNF-α, IL-6, B cells, co-stimulatory pathways, JAK/STAT

Goal: Prevention of initiation and/or progression of synovial inflammation

Acknowledgements

- **Kevin McHugh**
- **Tania Crotti**
- **Zhenxin Shen**
- **Merrilee Flannery**
- **Robert Fajardo**
- **Nicole Walsh**
- **Regina O'Sullivan**
- **Y. Harada**
- **H Lin**
- **A Gorn**

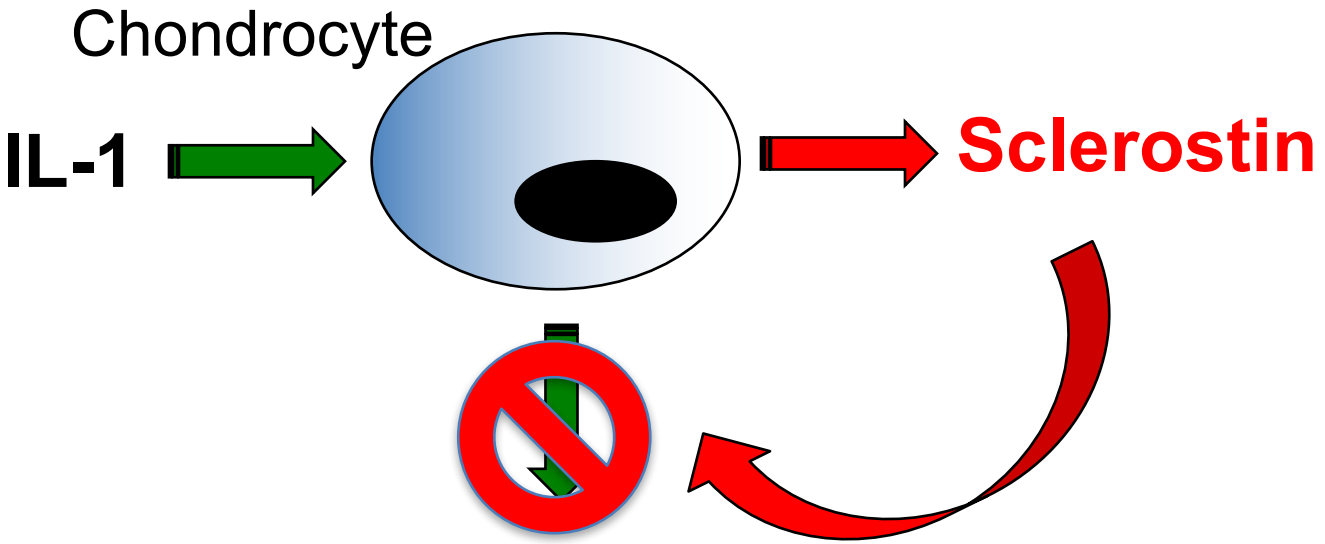
- **Ellen Gravallese**
- **Allison Pettit**
- **Cathy Manning**

- **Ed Purdue**
- **N Binder**

- **Stephen Krane**

N.I.H., Arthritis Foundation, ACR-REF, New England Baptist Bone and Joint Institute, Hospital for Special Surgery

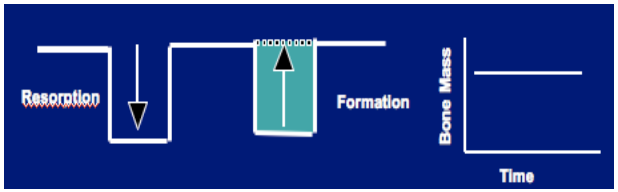
- IL-1 (but not TNF-α) induces sclerostin expression in chondrocytes
- Sclerostin inhibits IL-1-induced aggrecanases and MMPs
- Chondrocyte-derived sclerostin inhibits cartilage degradation

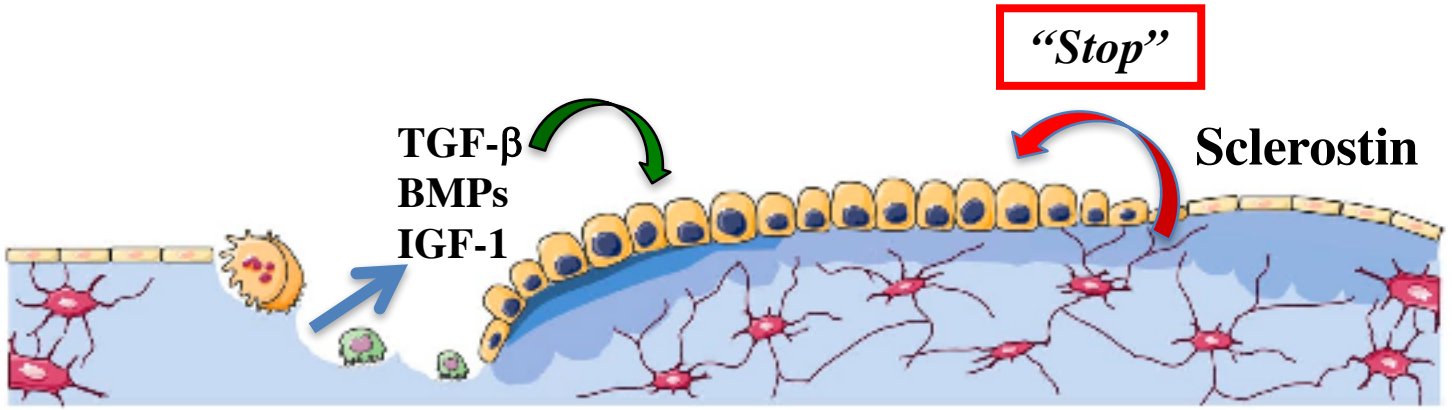


Chan et al. OA&C 2011; 19:874-885

Physiologic Bone Remodeling

- Adapt shape and structural organization to alterations in biomechanical forces
- Maintain structural integrity
  - Repair microdamage
- Maintain mineral ion homeostasis





Osteocyte-derived sclerostin provides a "stop" signal for terminating bone formation in a bone remodeling unit