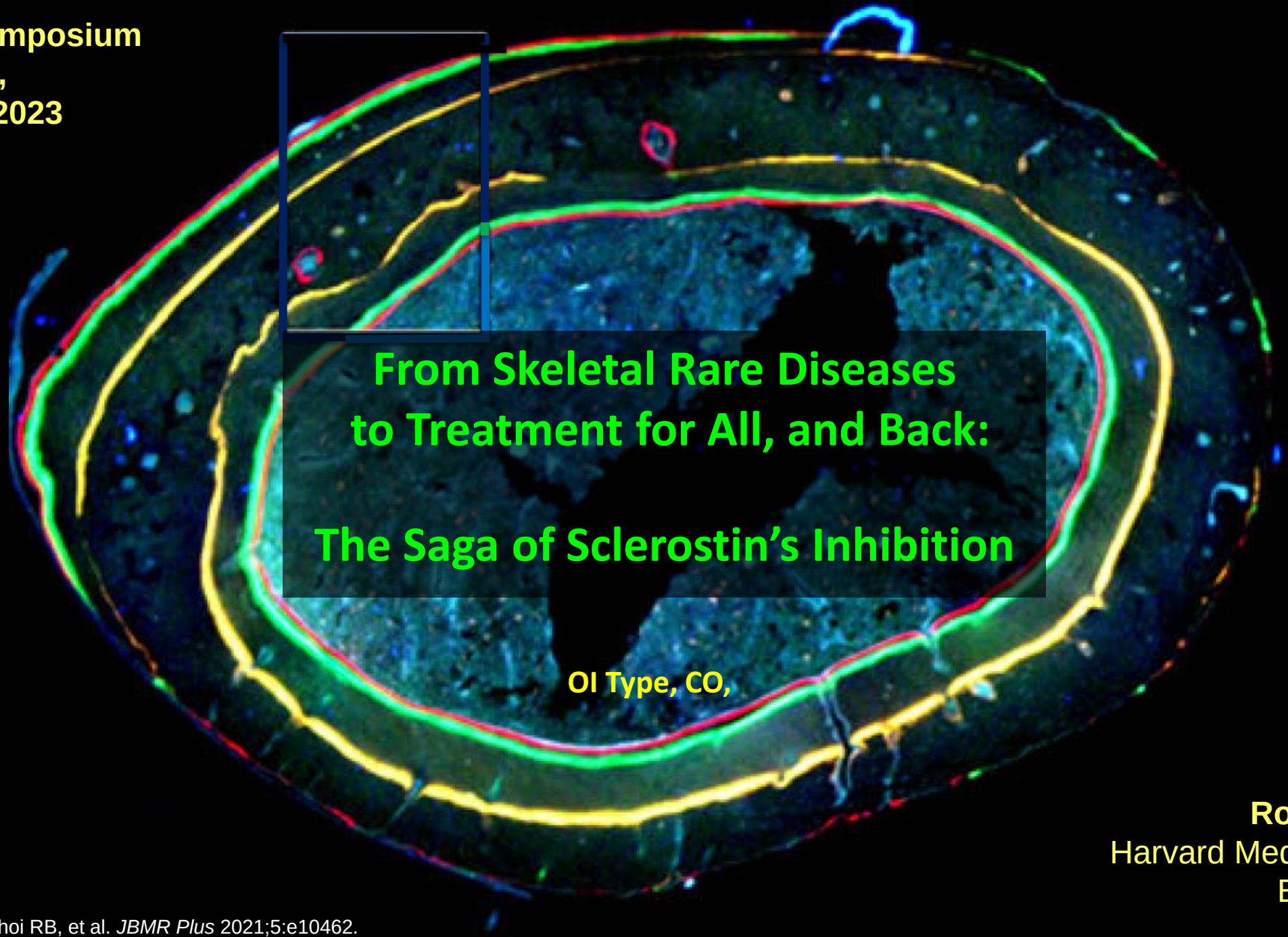
GoldLab Symposium
Boulder CO,
May 18-20, 2023



From Skeletal Rare Diseases to Treatment for All, and Back:

The Saga of Sclerostin's Inhibition

OI Type, CO,

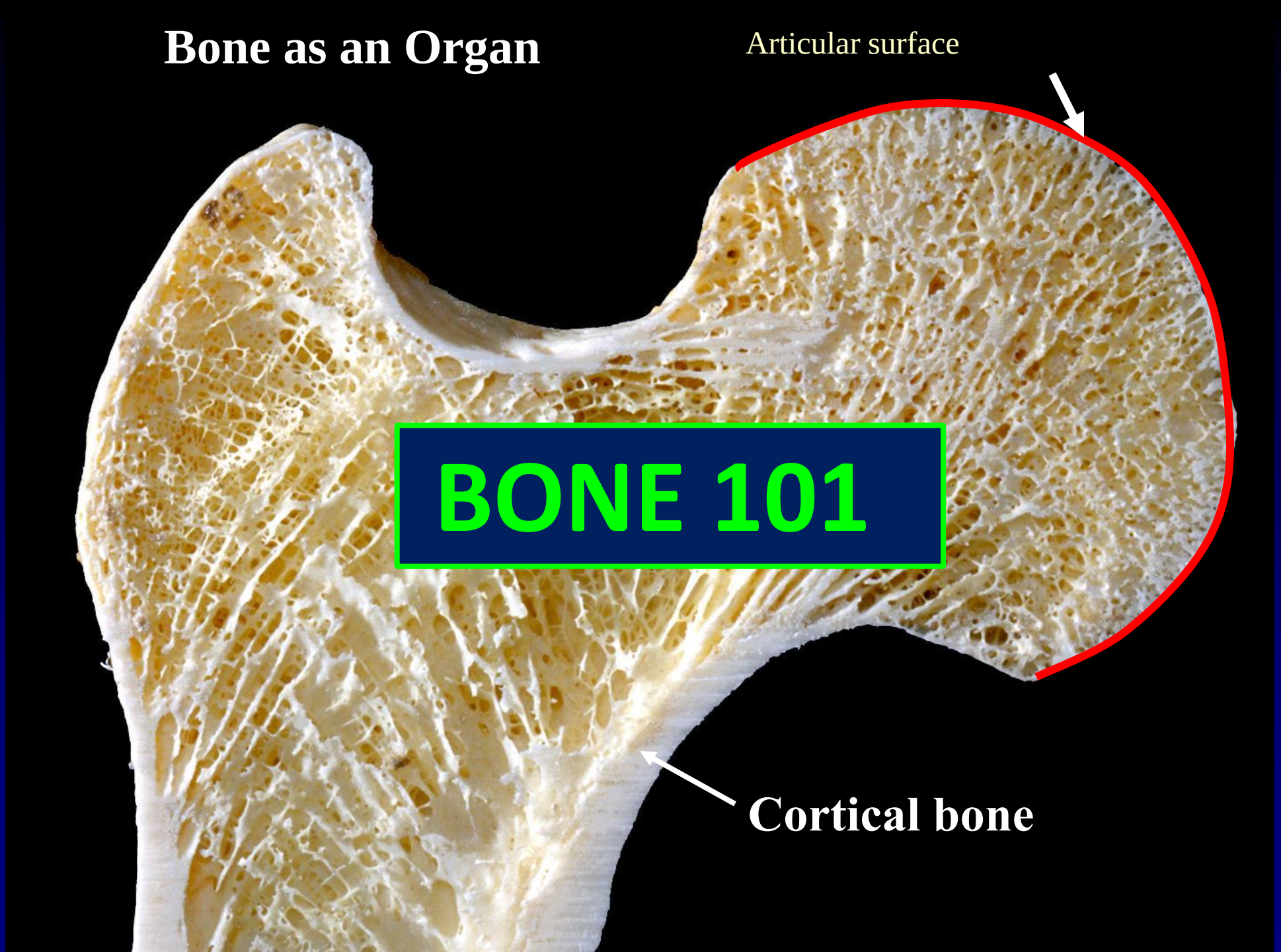
Roland Baron
Harvard Medical School,
Boston, USA

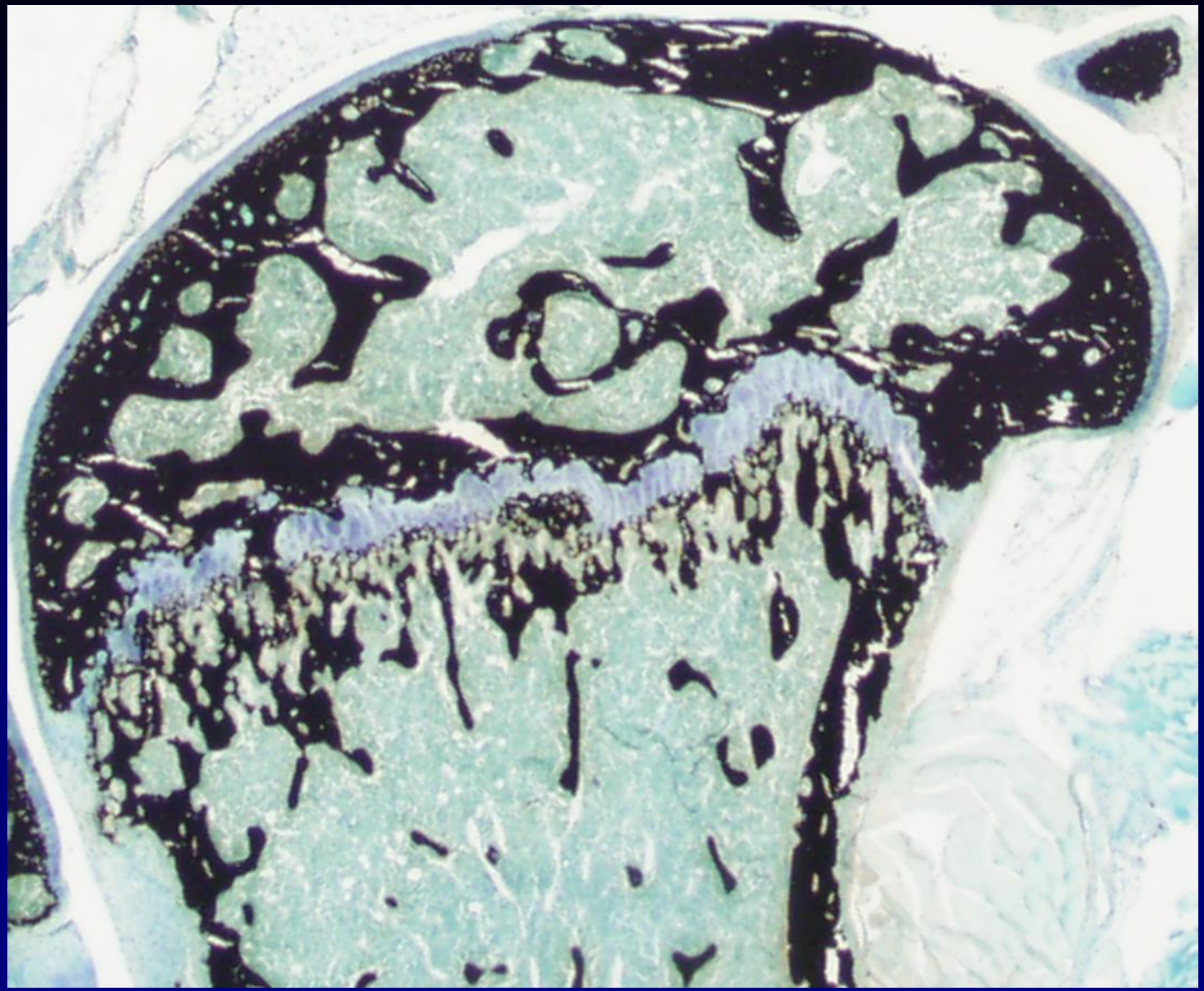
Original image Choi RB, et al. *JBMR Plus* 2021;5:e10462.

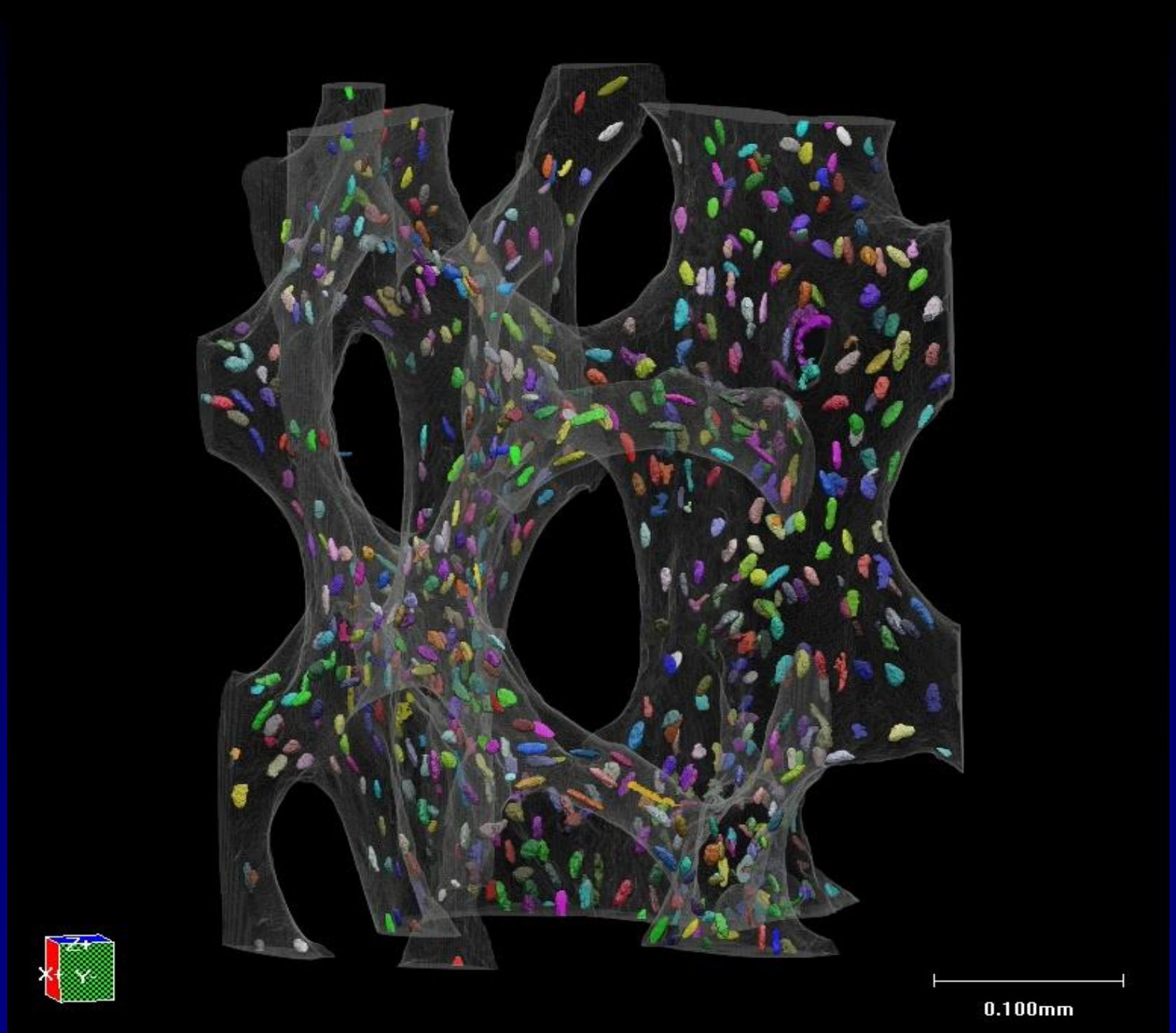
Disclosures

- Advisory Boards: Radius Health, OsteoPharma, Bone-Tech, Mesentech, Beryl Health, Curelab Oncology, XY Therapeutics, Ankasa Regenerative Therapeutics
- Lecturing: Amgen, Astellas, UCB
- Consulting: Flagship 75, Home Biosciences
- Research funding: NIH, Radius Health, Sophie's Neighborhood

Bone as an Organ



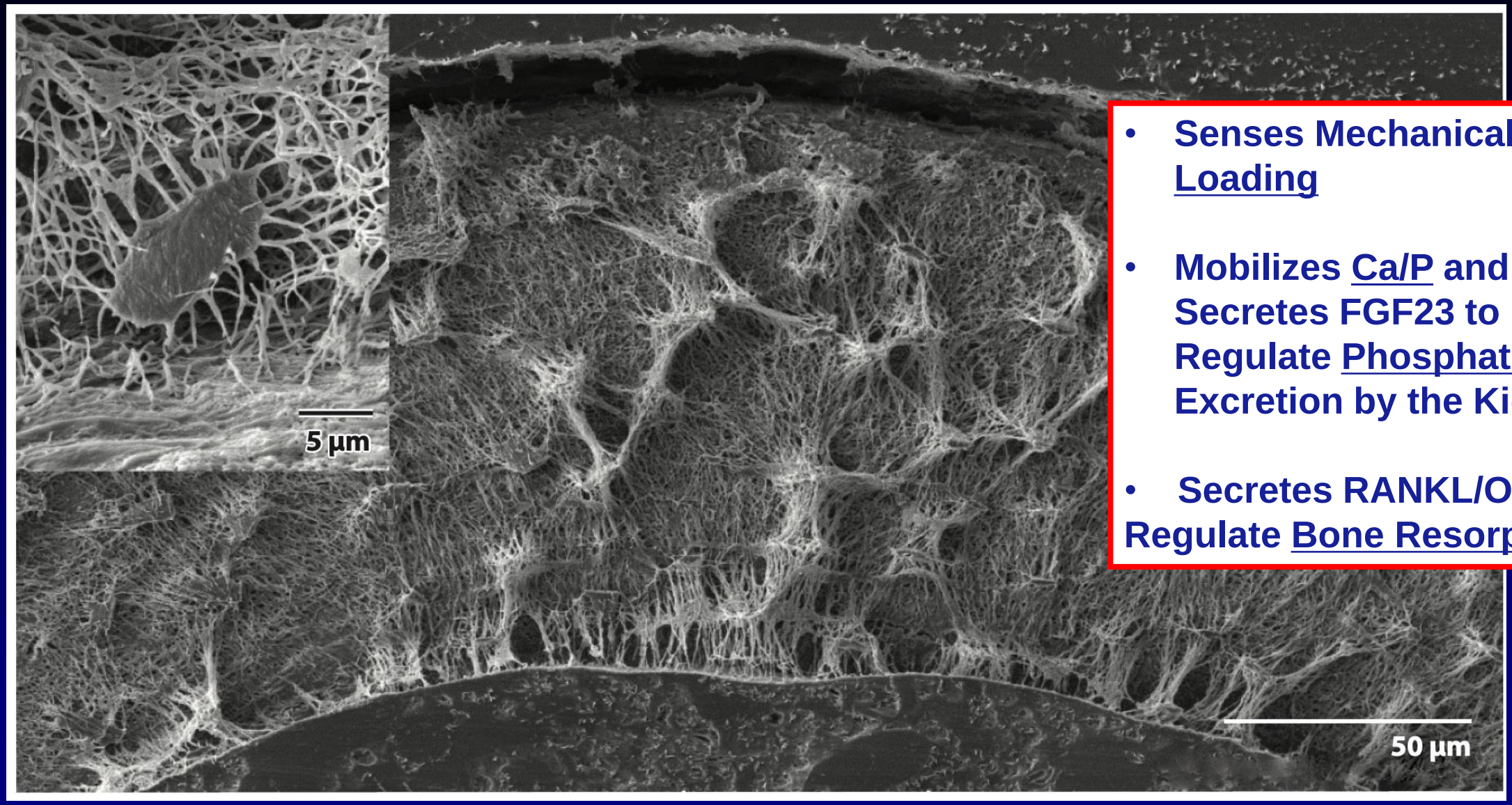




Osteocytes:

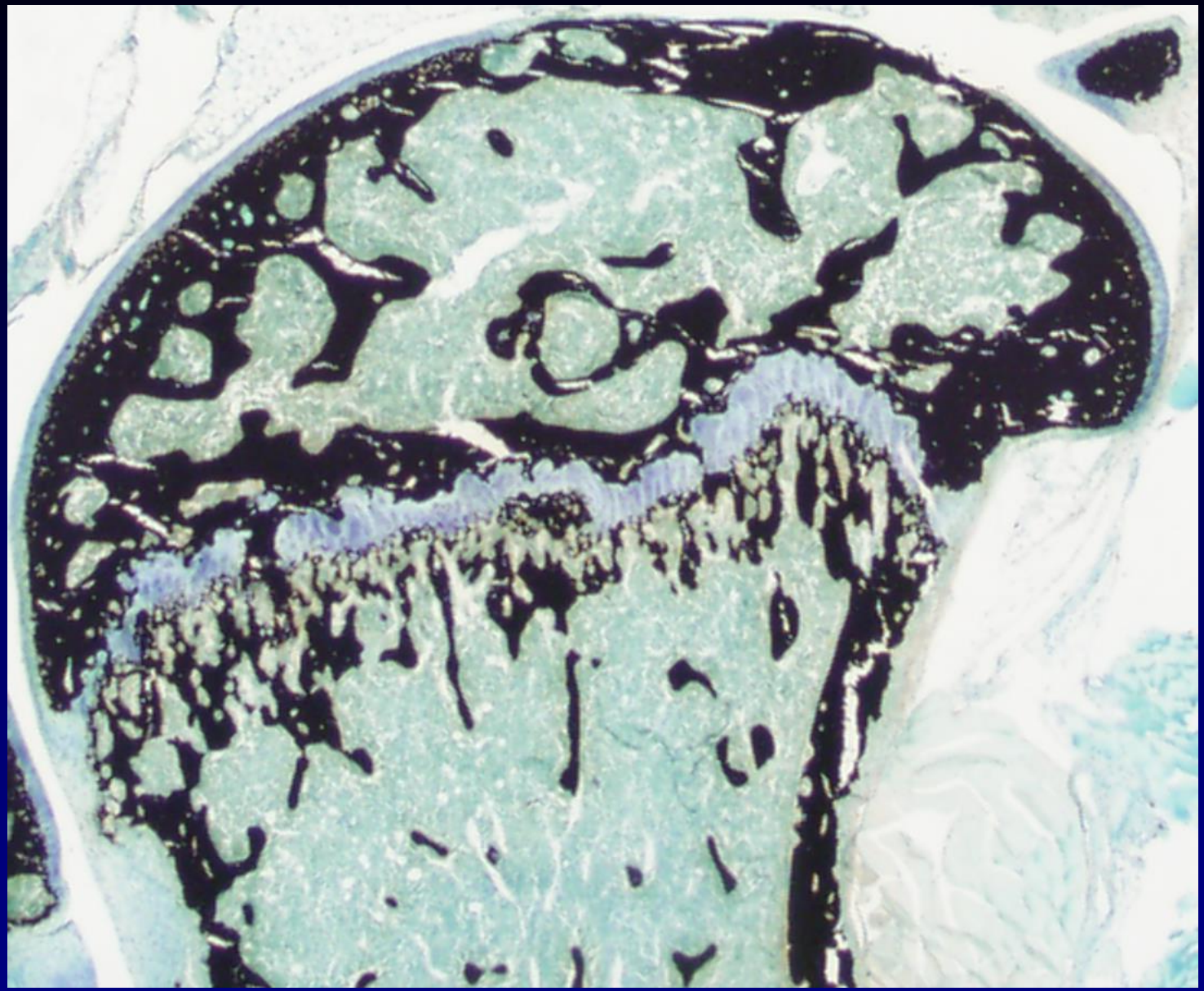
The Most Abundant Cell in One of the Largest Organs in the Body

The Osteocytes

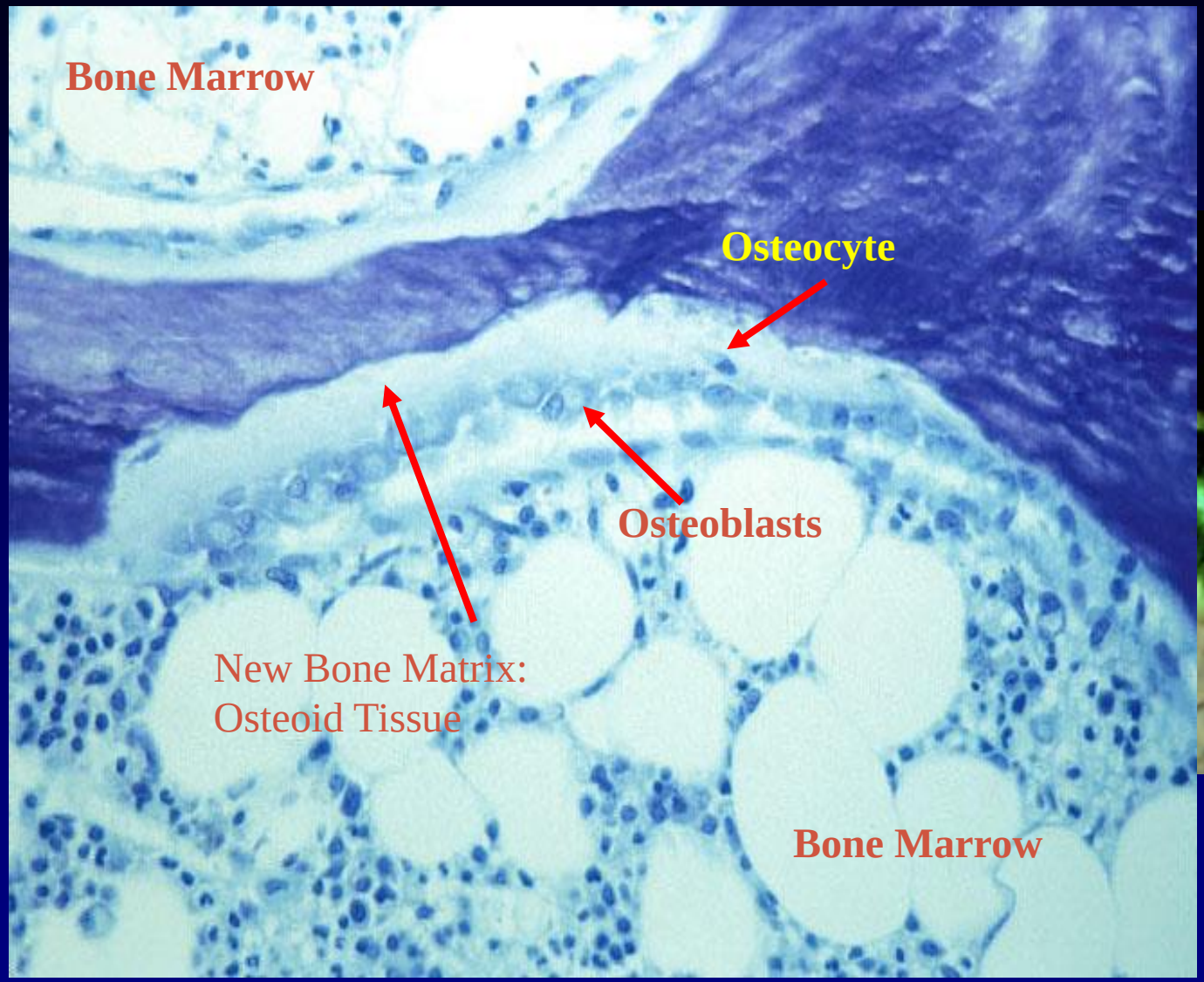


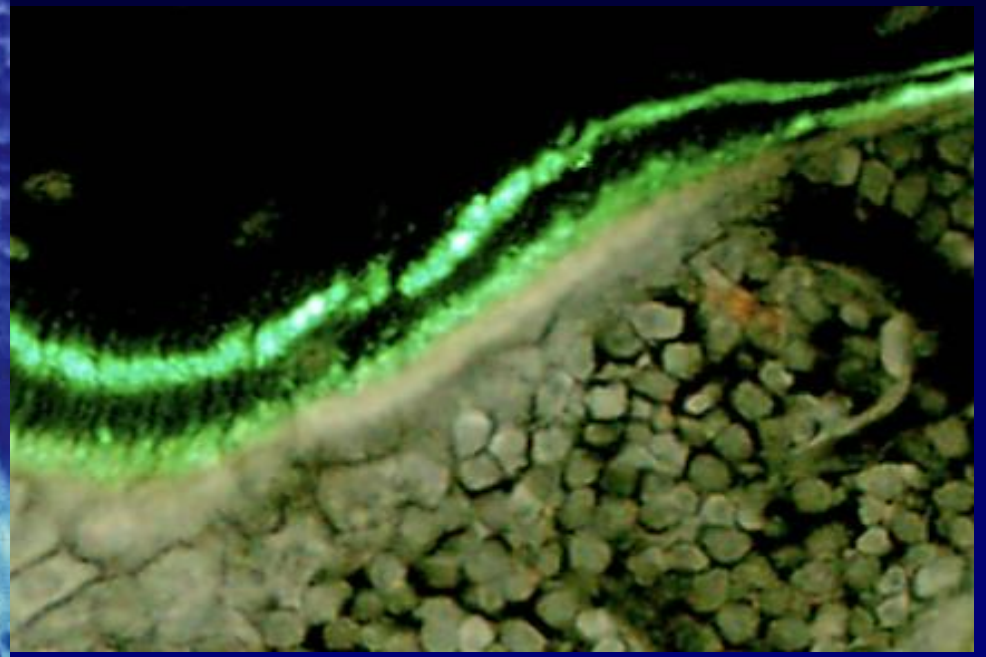
- Senses Mechanical Loading
- Mobilizes Ca/P and Secretes FGF23 to Regulate Phosphate Excretion by the Kidney
- Secretes RANKL/OPG to Regulate Bone Resorption

Robling and Bonewald, Ann Rev Physiol, 2020



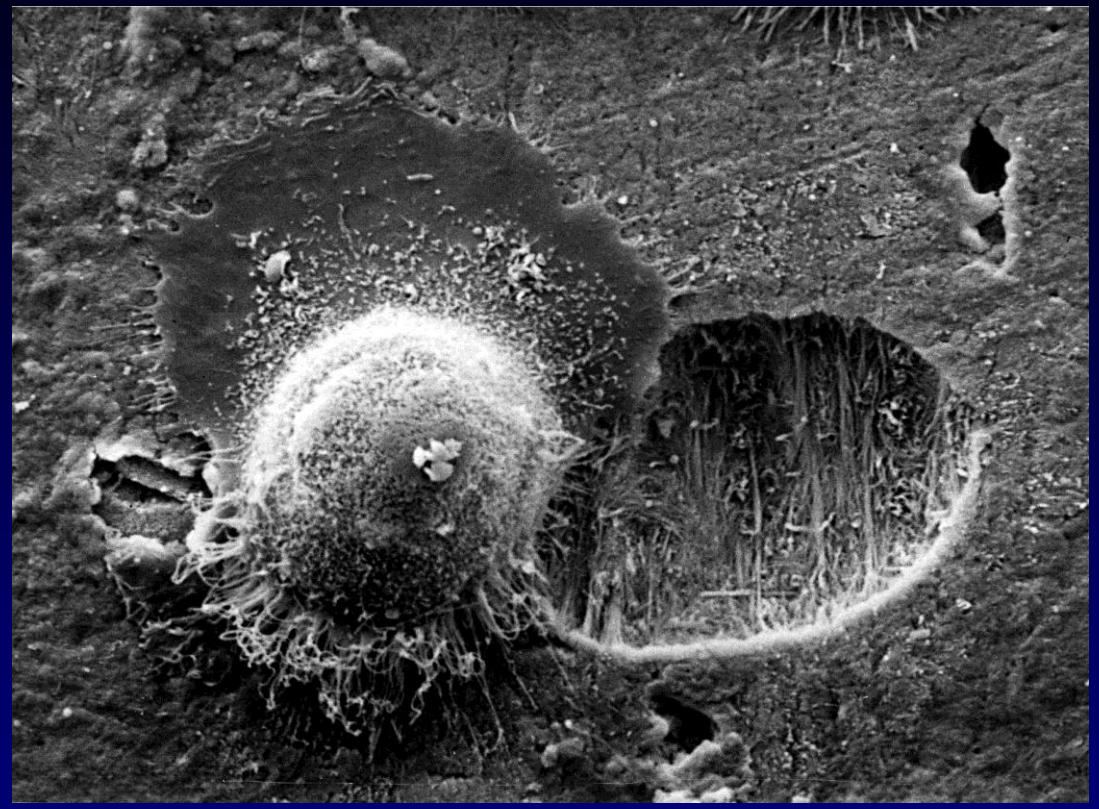
Bone Formation Surface With Osteoblasts

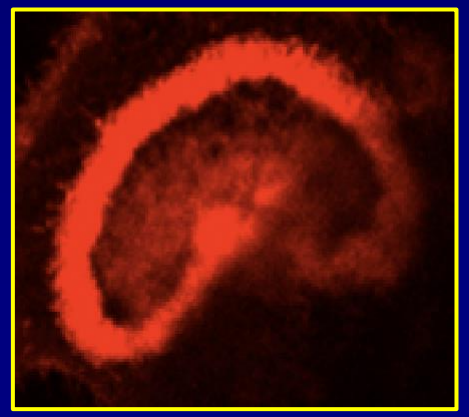


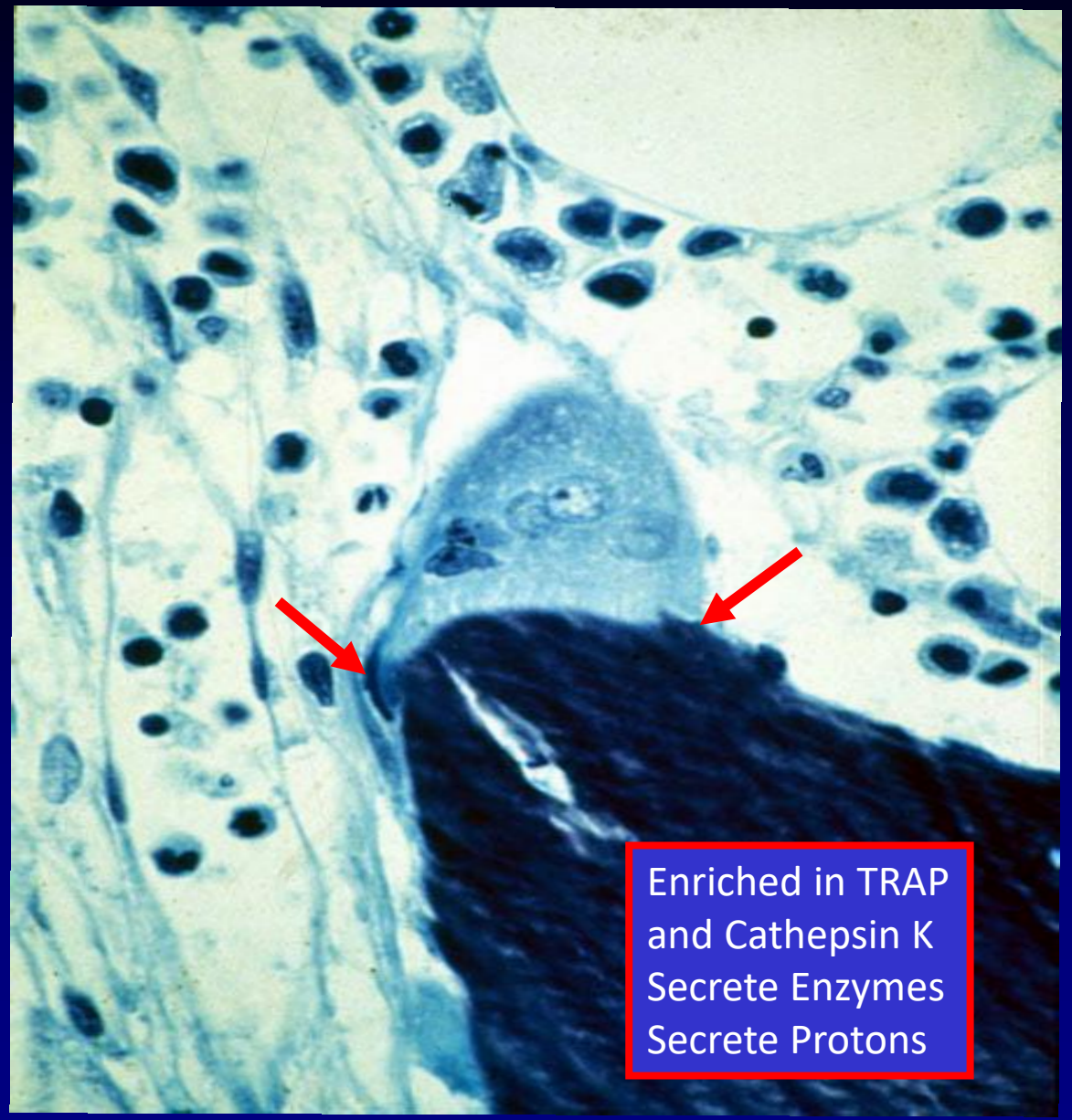


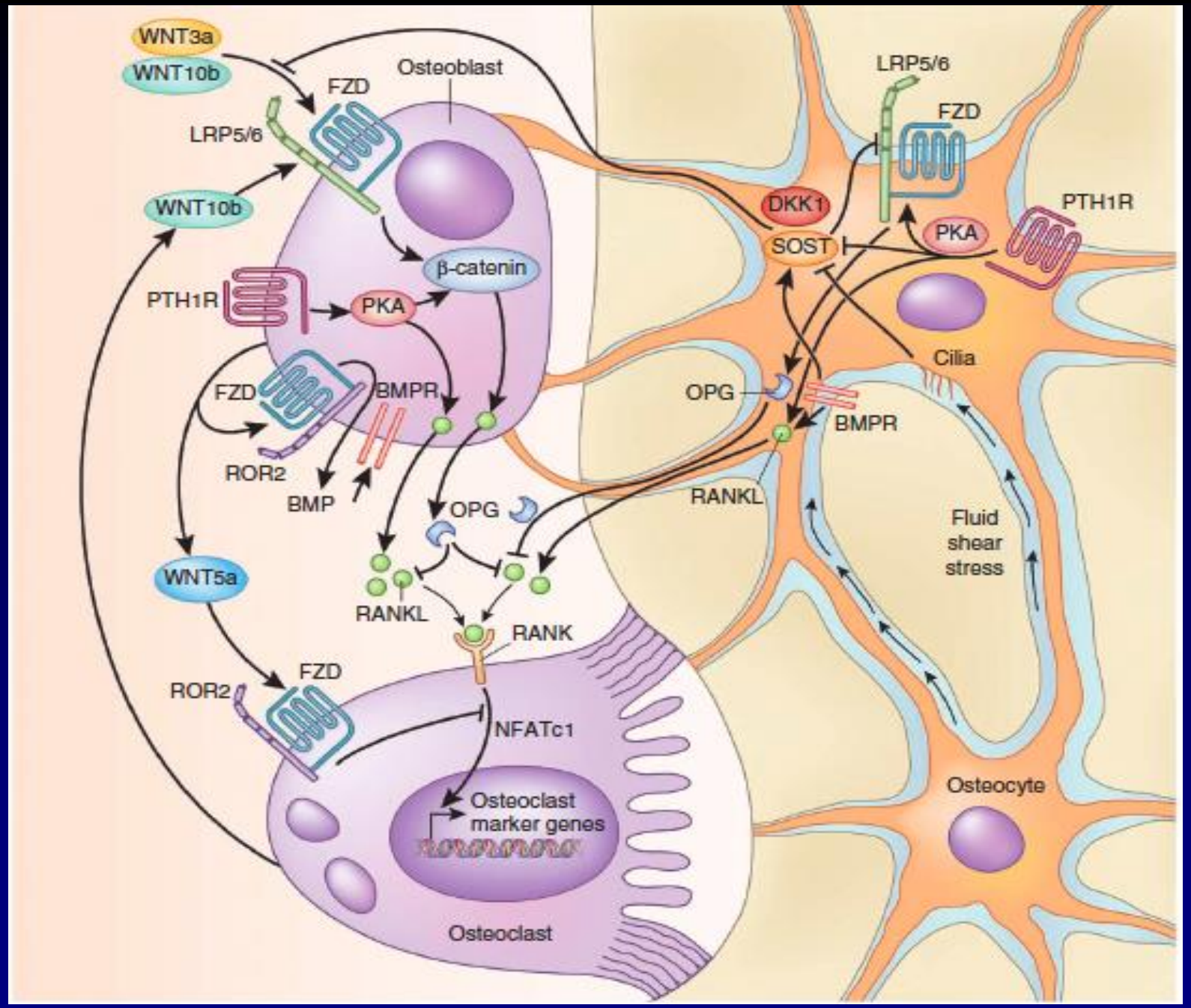
Enriched in Alkaline Phosphatase
Secrete Collagen and Matrix components

Bone Resorbing Surface with Osteoclasts



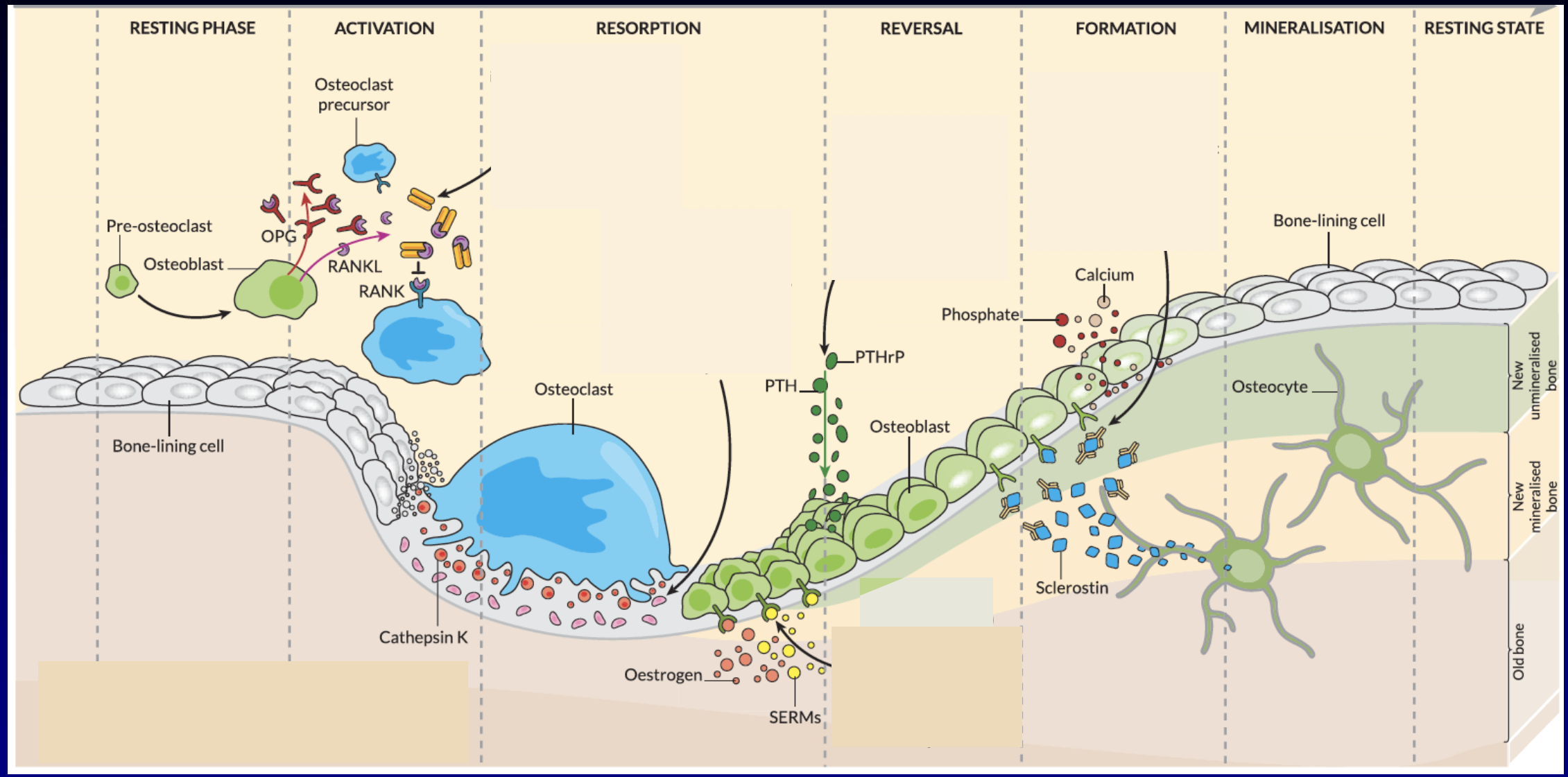






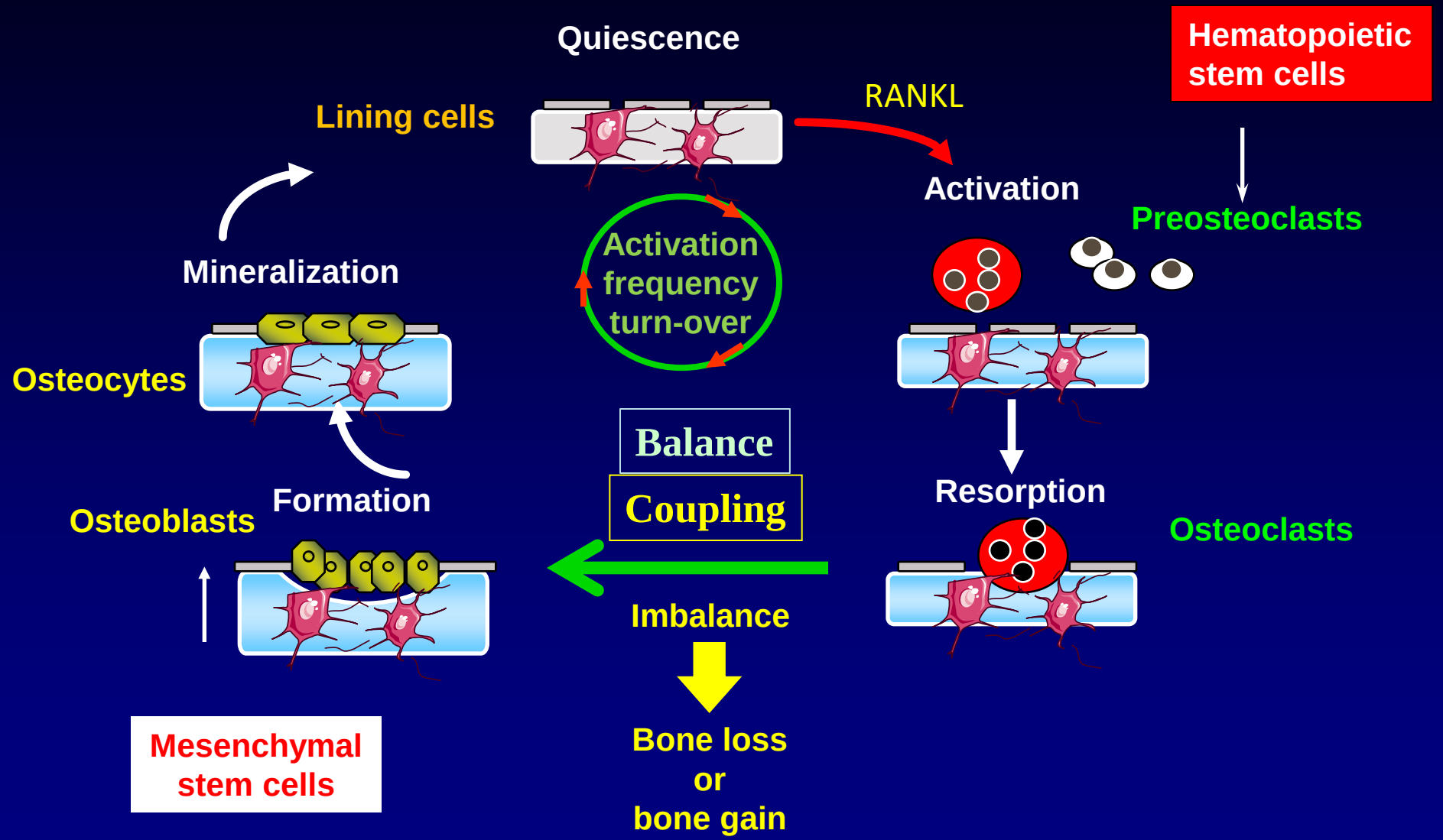
Baron R. and Kneissel M., Nature Medicine, 2013

The Bone Remodeling Sequence



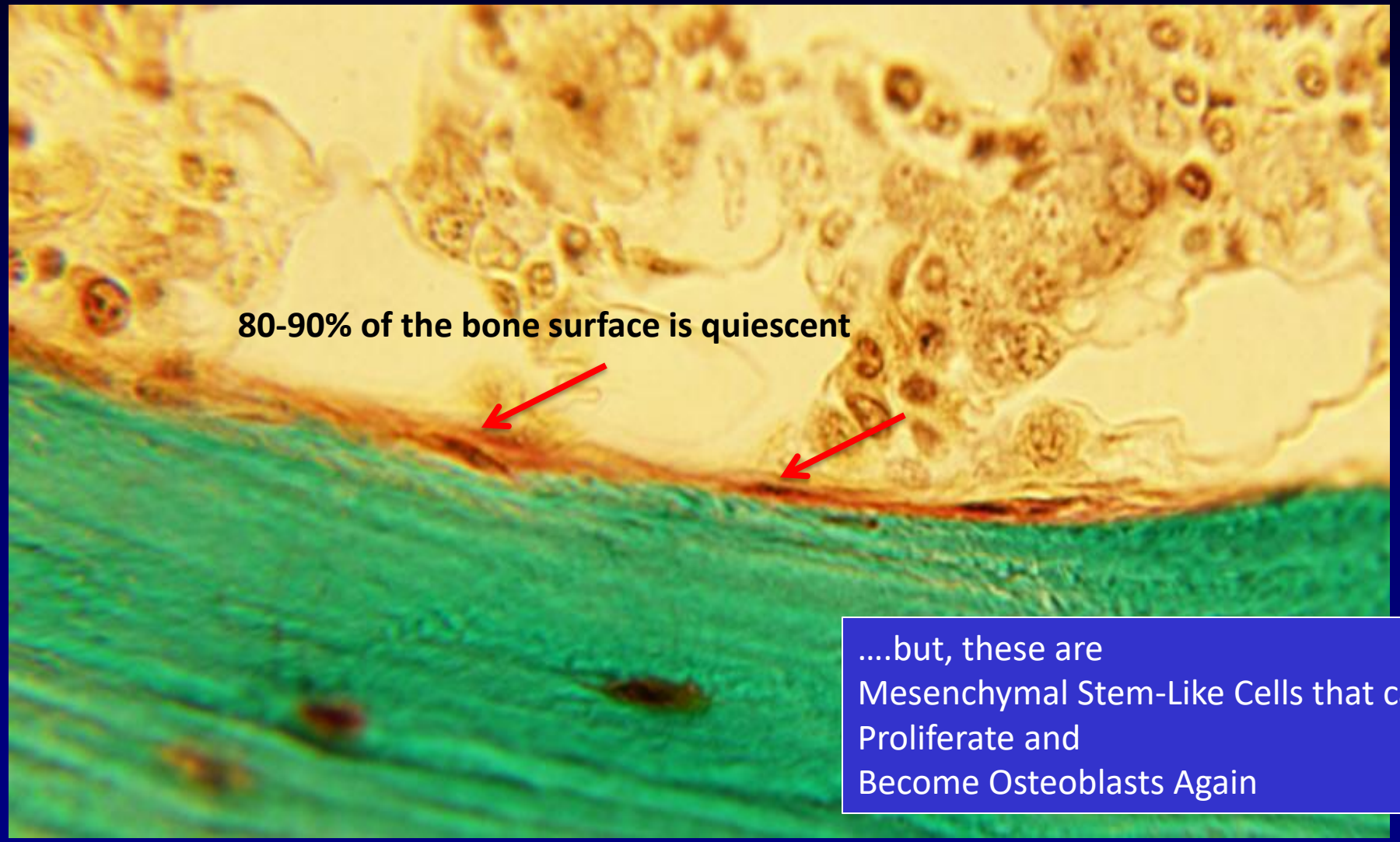
Adapted from Langdahl, Brit. J. Pharmacol. 2020

How is Bone Remodeling Regulating Bone Mass ?



Baron R, unpublished

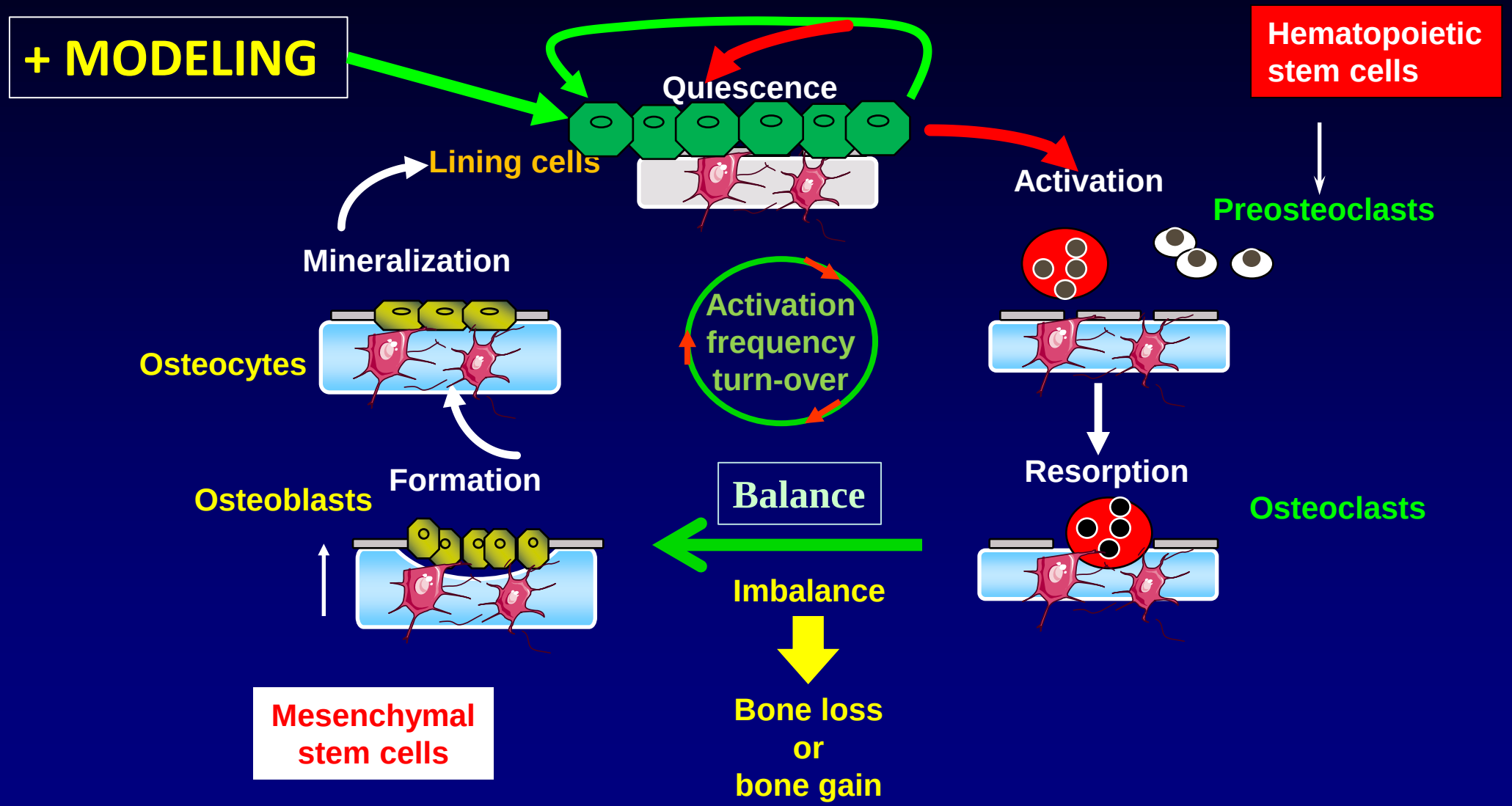
Quiescent Surface with Lining Cells



….but, these are
Mesenchymal Stem-Like Cells that can
Proliferate and
Become Osteoblasts Again

Image courtesy of D. Dempster

Adult Bone Mass is Regulated by Both Remodeling and Modeling

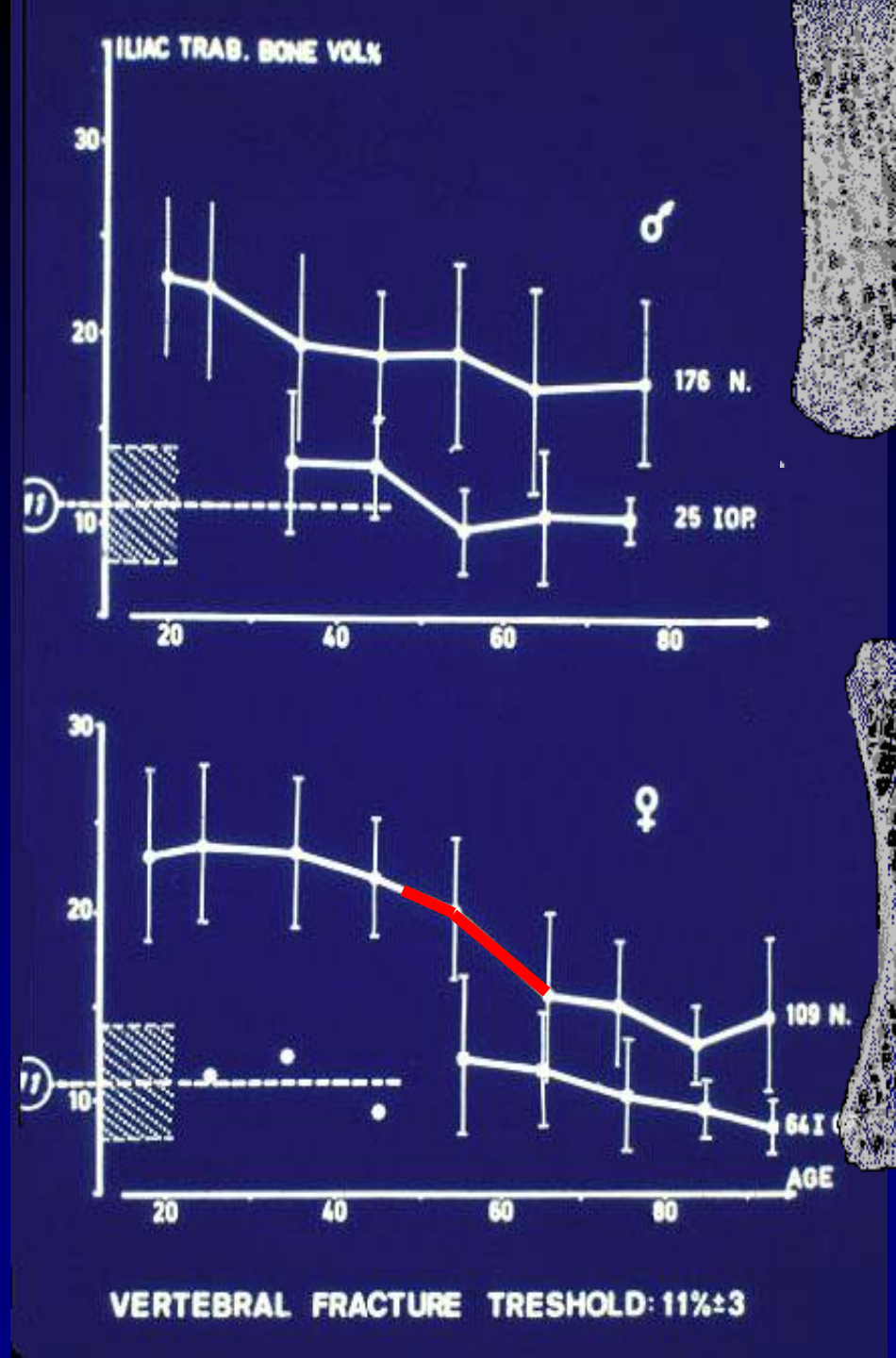


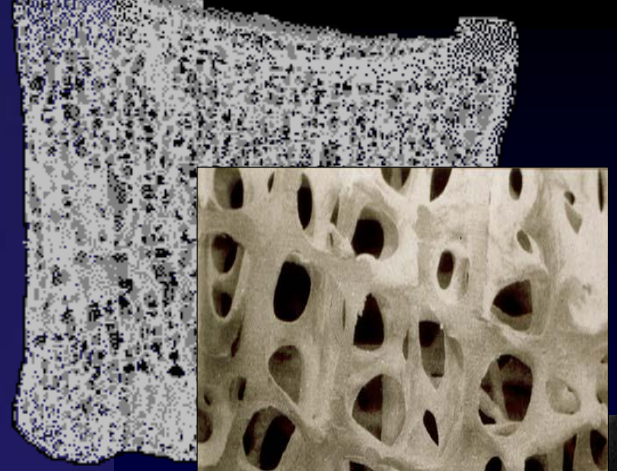
Baron R, unpublished

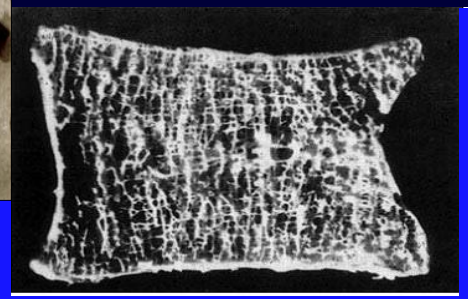
Modeling and Remodeling Are Important

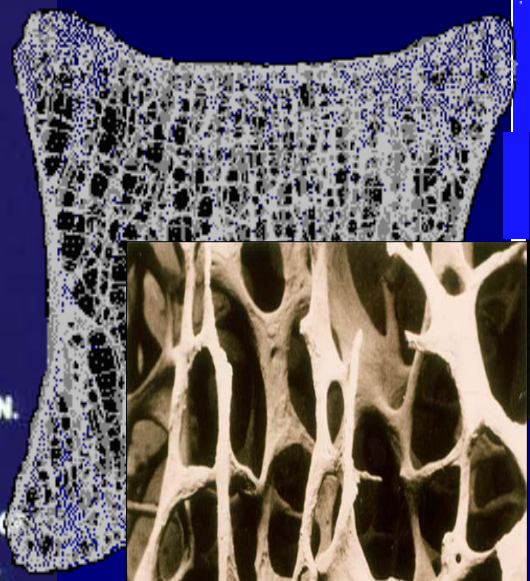
- To allow adaptation to local and systemic changes (increase or decrease BMD, adapt microstructure to load, allow storage/mobilization of calcium and Phosphate)

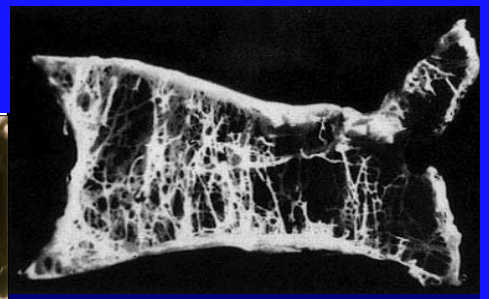
- To renew bone matrix components and osteocytes while maintaining skeletal homeostasis, i.e. bone mass


ILIAC TRAB. BONE VOL%
30
20
10
♂
176 N.
25 IOP
20
40
60
80
30
20
10
♀
109 N.
64 I
AGE
20
40
60
80
VERTEBRAL FRACTURE TRESHOLD: 11%±3









Progression of Osteoporosis – Three Generations

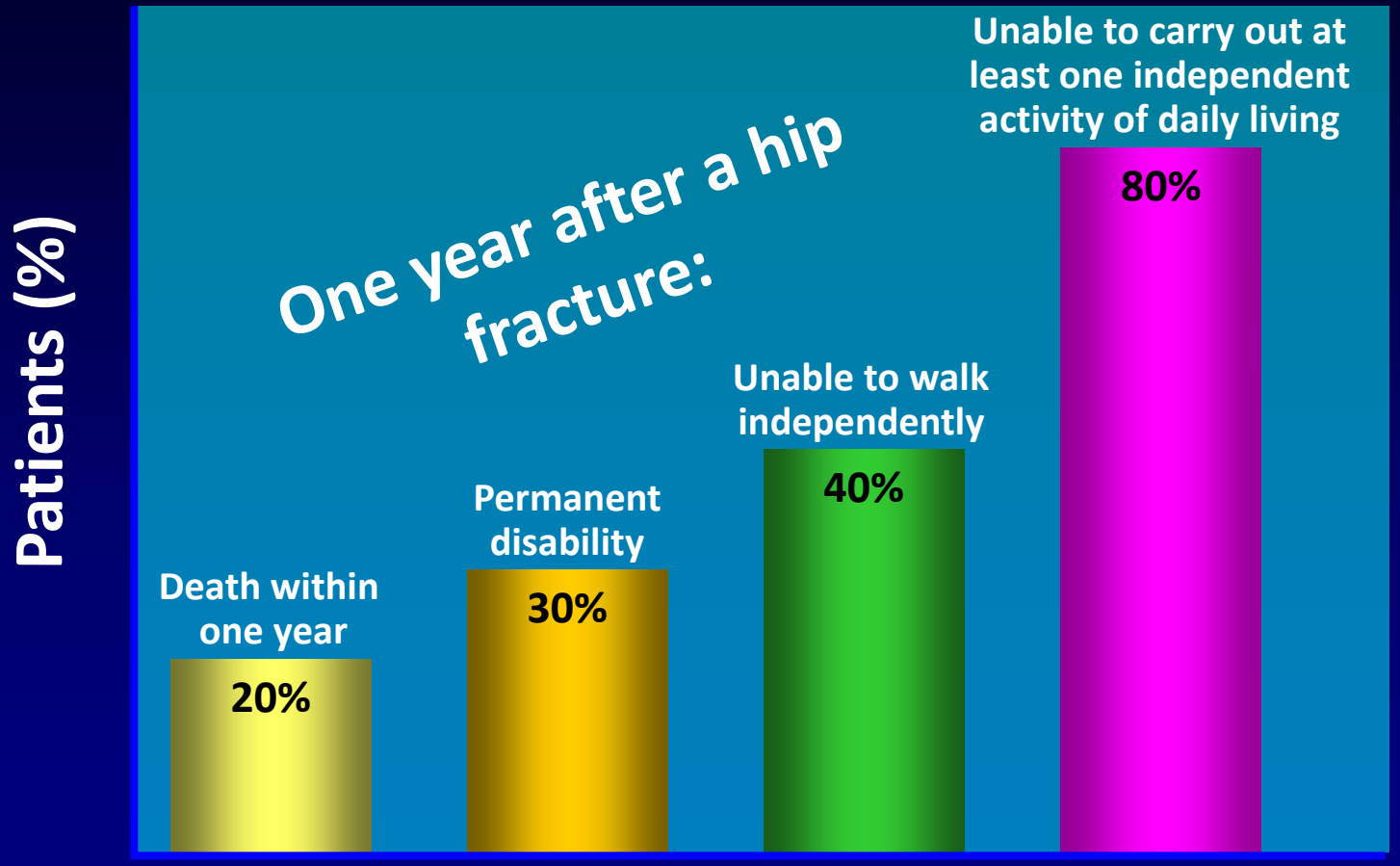
Photo credit: Geoff Higgs, MD, courtesy eMotion pictures – An Exhibition of Orthopedics in Art

Remaining lifetime fracture risk (%) in Caucasian population at the age of 50

Type of Fracture	Men	Women
Forearm	4.6	20.8
Hip	10.7	22.9
Spine	8.3	15.1
Proximal humerus	4.1	12.9
Any	22.4	46.4

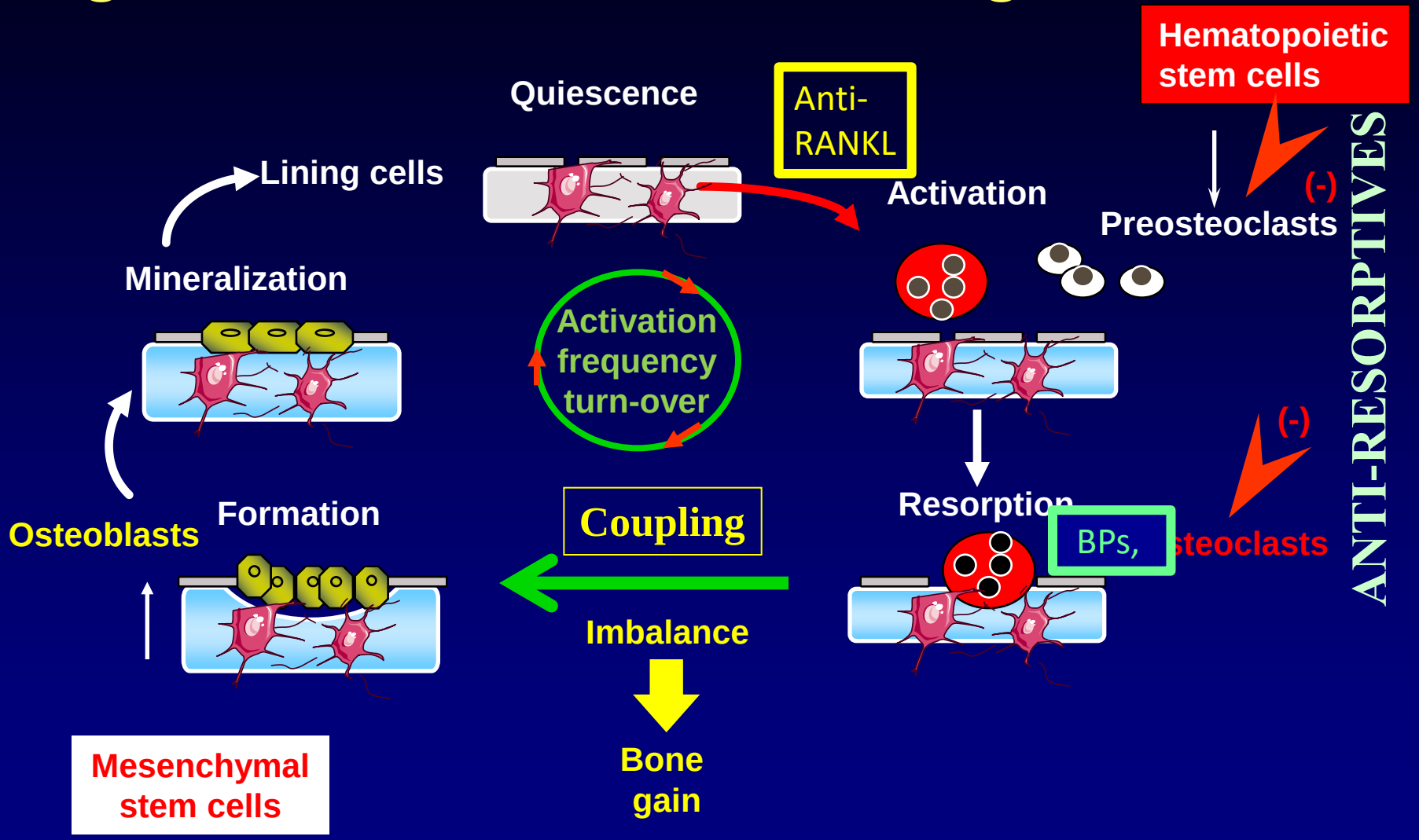
Kanis JA et al, Osteoporos Int, 2000:11:669-674

All fractures are associated with morbidity



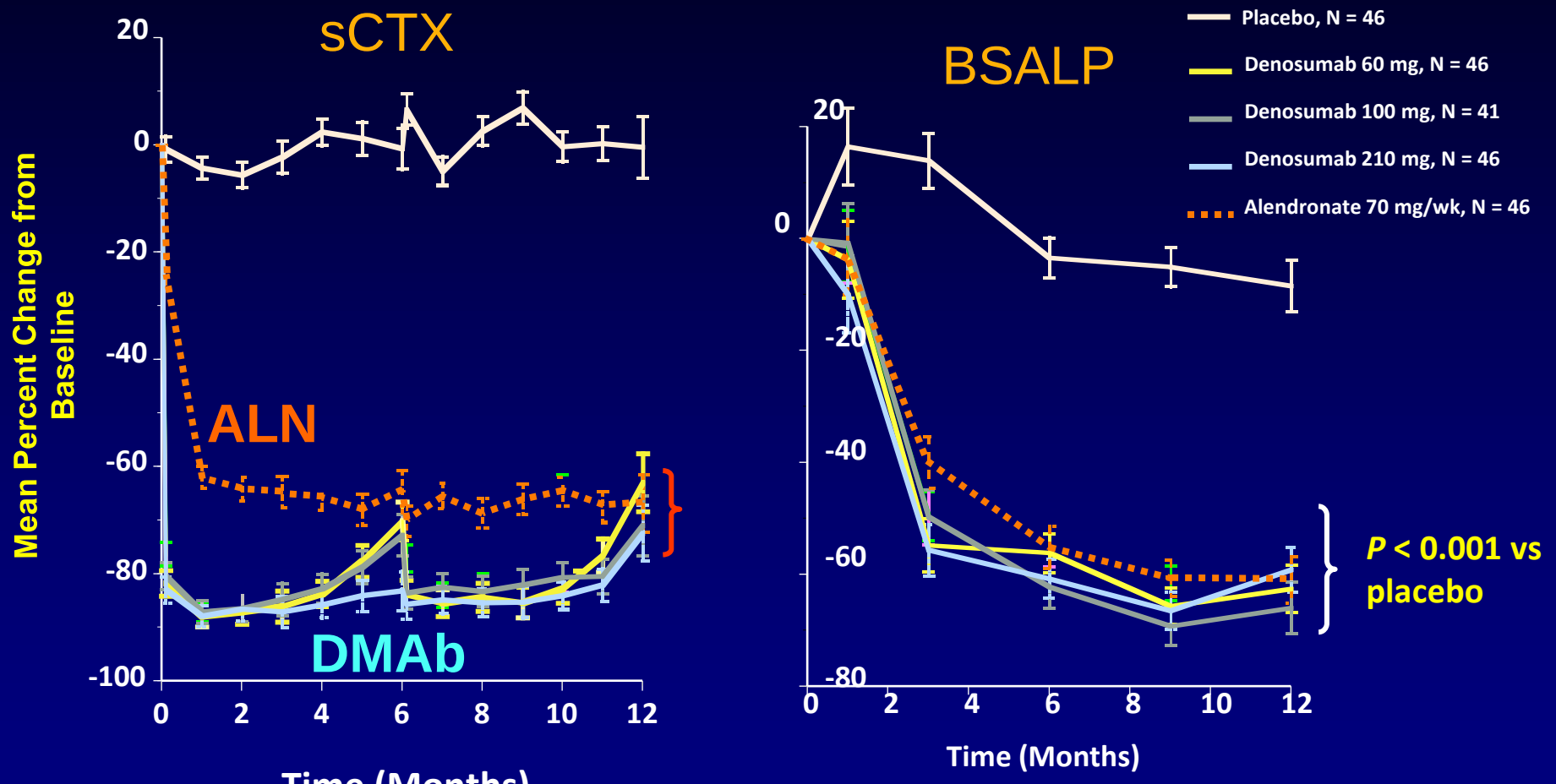
Cooper C, Am J Med, 1997;103(2A):12S-17S

Anti-Resorptives Decrease Resorption and Remodeling-based Bone Formation, Slowing Bone Turnover



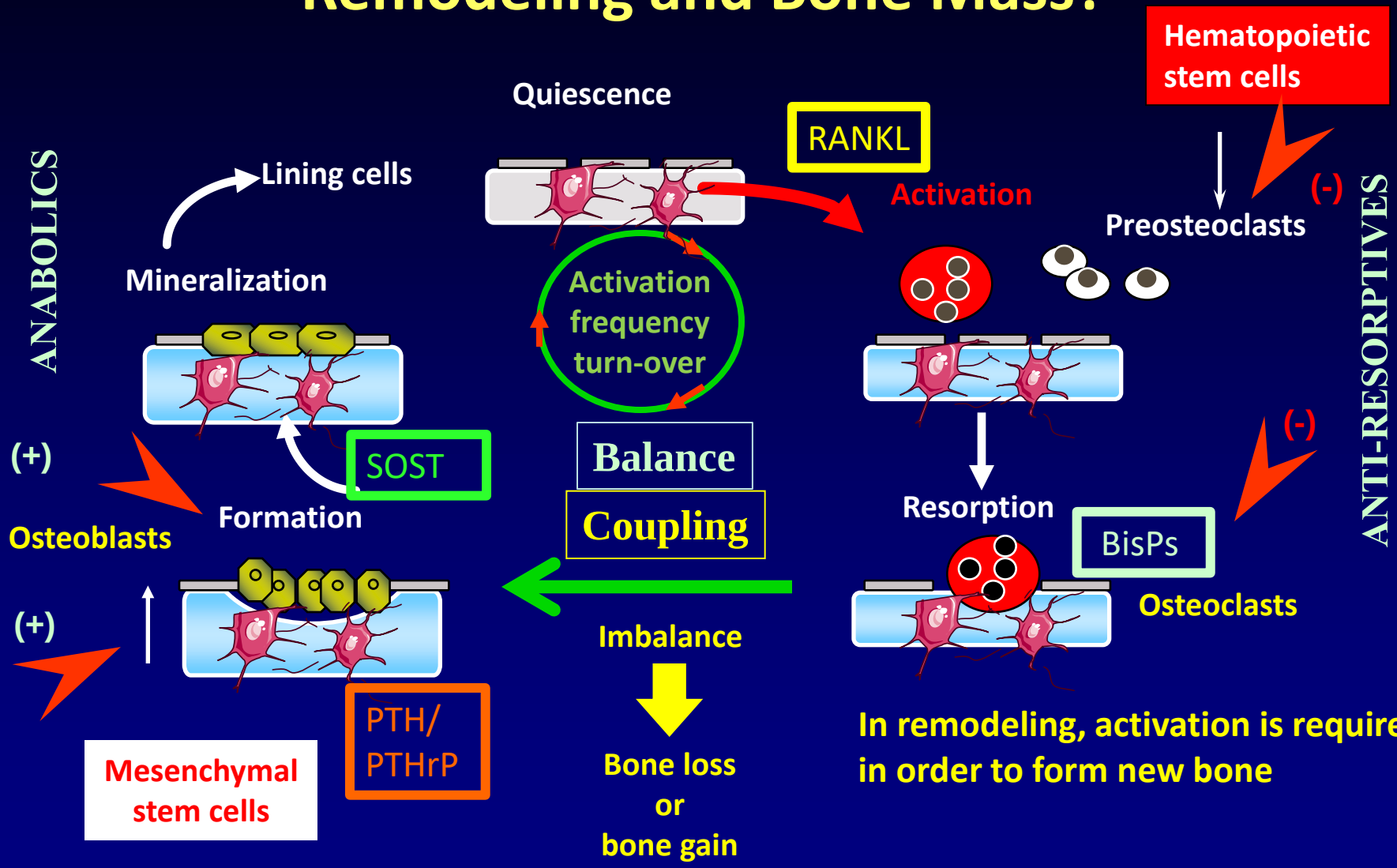
Baron R, unpublished

Bone Turnover Markers for Alendronate or Denosumab Phase 2: Postmenopausal Women with Low BMD

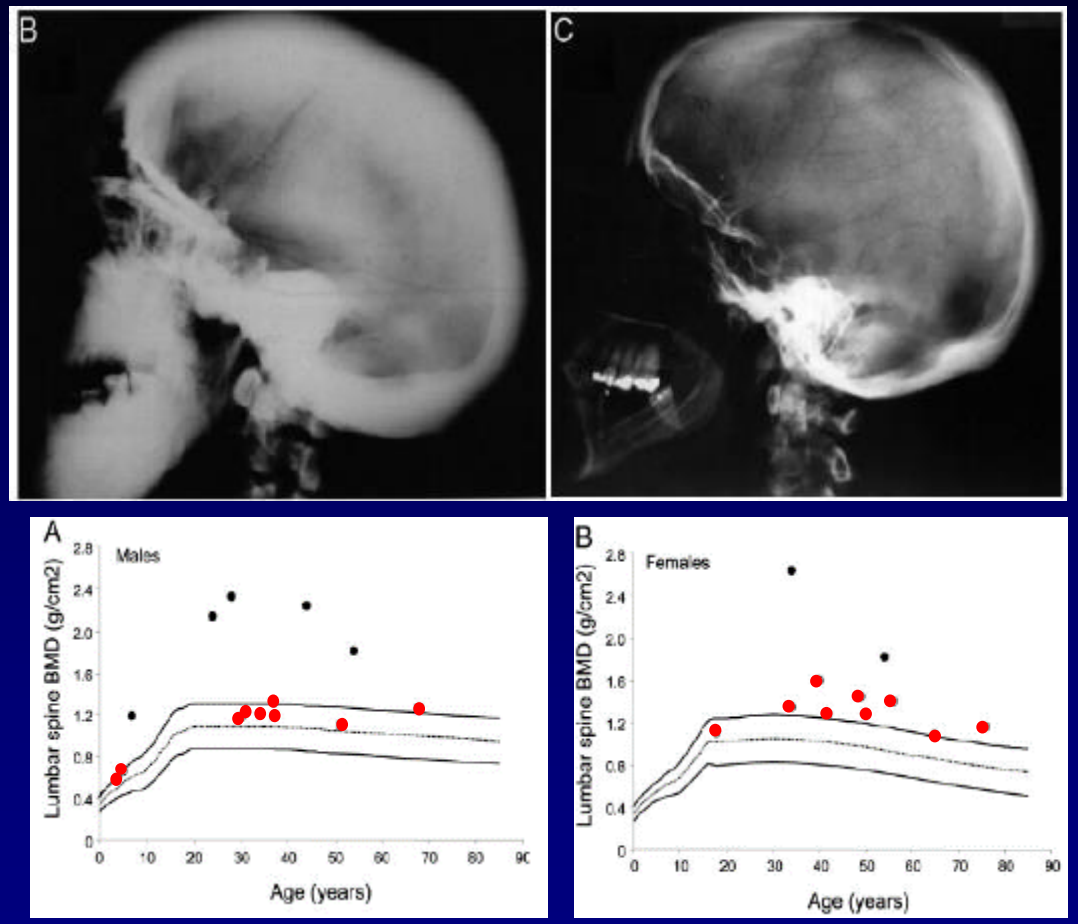


McClung MR, et al. N Eng J Med. 2006;354:821-831.

How Current Treatments Affect Bone Remodeling and Bone Mass?



Absence or Reduction of Sclerostin Lead To High Bone Mass (Sclerosteosis)



Sclerosteosis and Van Buchem Syndrome

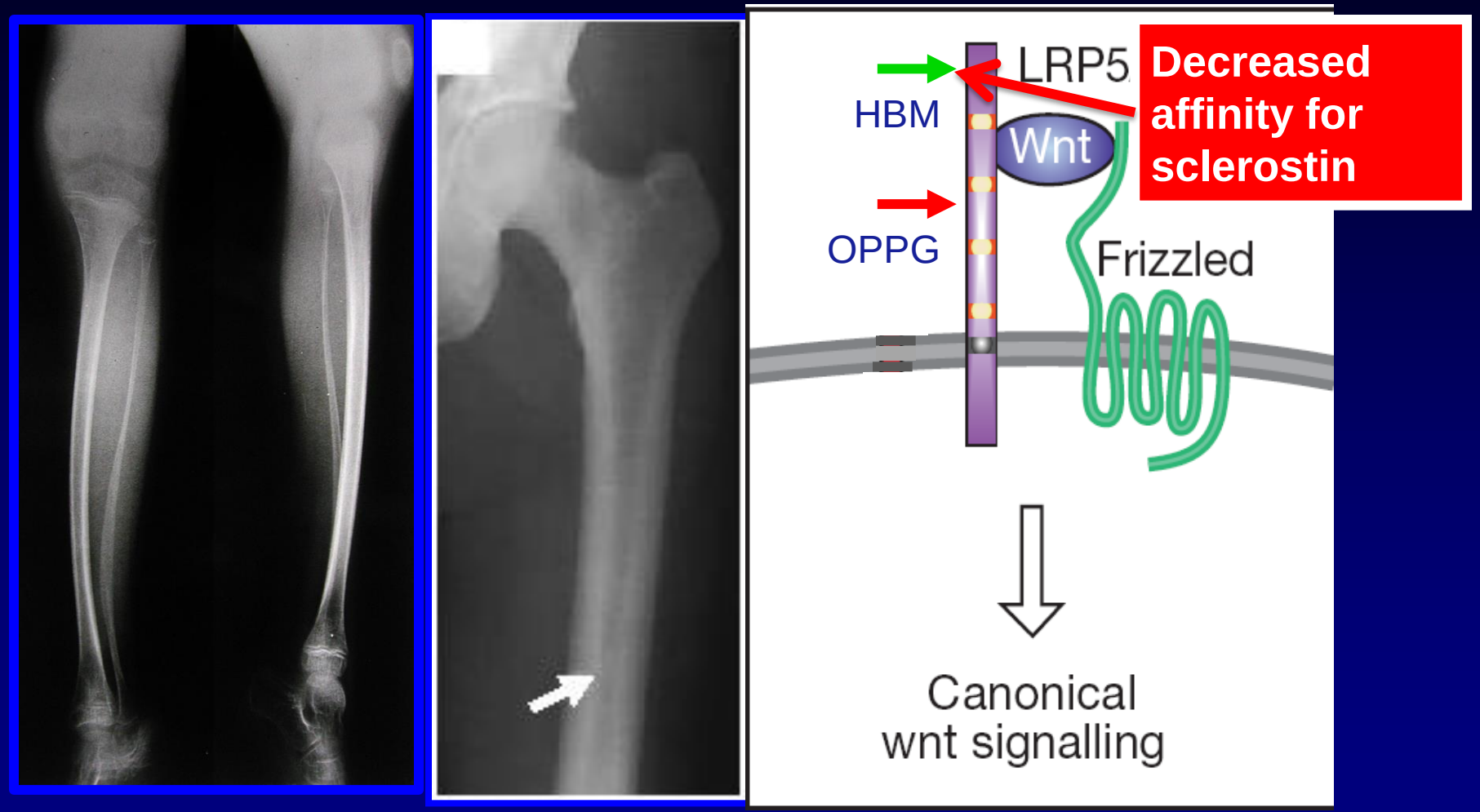
Increased bone density, thick cortices

- Sclerosteosis: **All null mutations in *SOST*, the gene that encodes sclerostin**[1]
- Van Buchem syndrome: **Promoter deletion with decreased sclerostin expression**[2–4]
- **Haplo-insufficient carriers have high bone mass**[5] **and no side effects**[6]

BMD, bone mineral density; SOST, sclerostin.

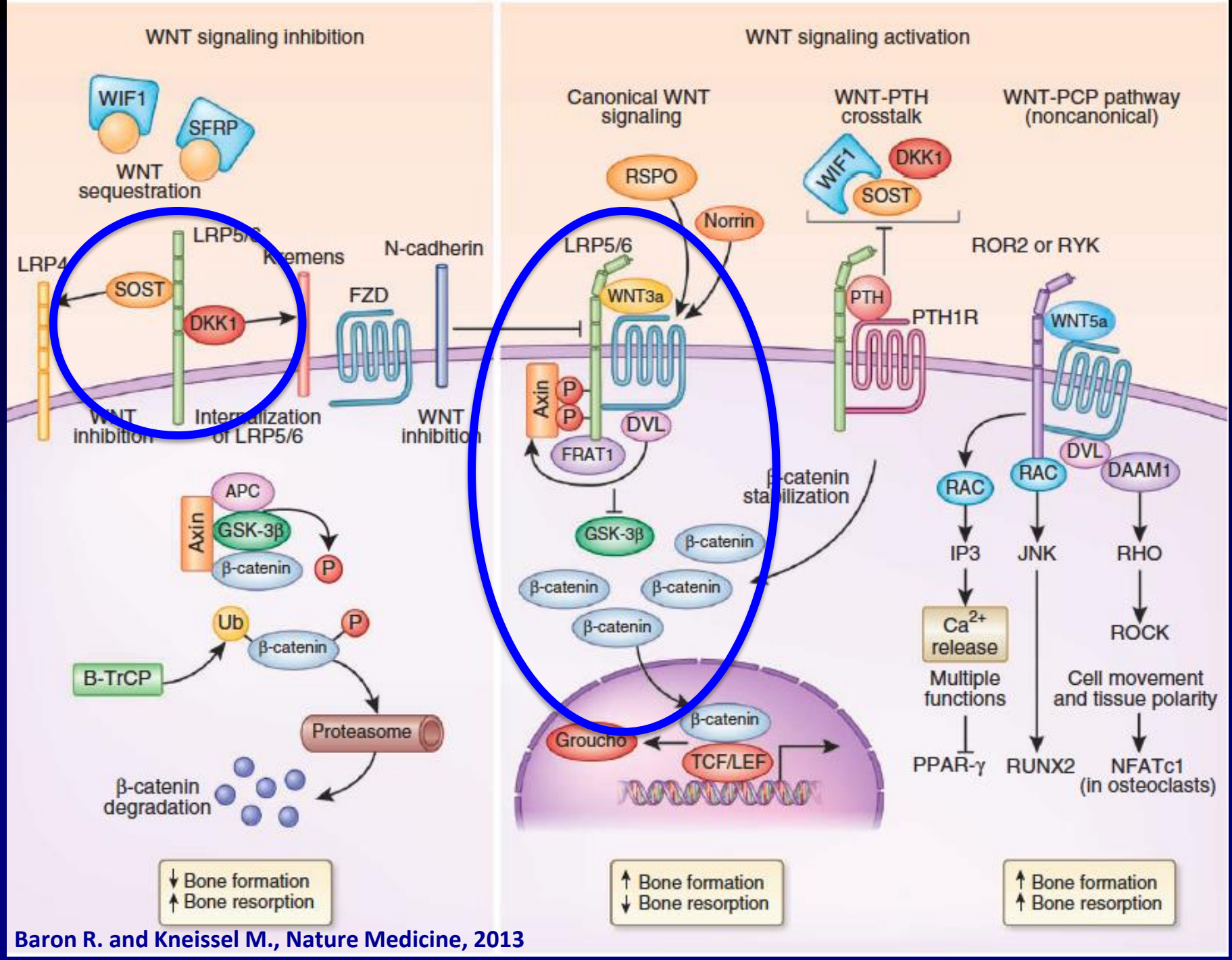
1. Balemans W, et al. *Hum Mol Genet*. 2001;10:537–43.
2. Brunkow ME, et al. *Am J Hum Genet*. 2001;68:577–89.
3. Balemans W, et al. *J Med Genet*. 2002;39:91–7.
4. Loots GG, et al. *Genome Res*. 2005;15:928–35.
5. Gardner MJ, et al. *Arthritis Rheum*. 2006;54:1961–73.
6. Papapoulos S, et al. *J Bone Miner Res*. 2012;27:694–701.

HBM phenotype linked to mutations in LRP5 that decrease sclerostin inhibition on canonical WNT signaling



HBM, high bone mass; LRP5; low-density lipoprotein receptor-related protein 5;
OPPG, osteoporosis-pseudoglioma syndrome; WNT, wingless-related integration site.

Gong Y, et al. *Cell* 2001;107:513-23;
Little RD, et al. *Am J Hum Genet* 2002;70:11-19.

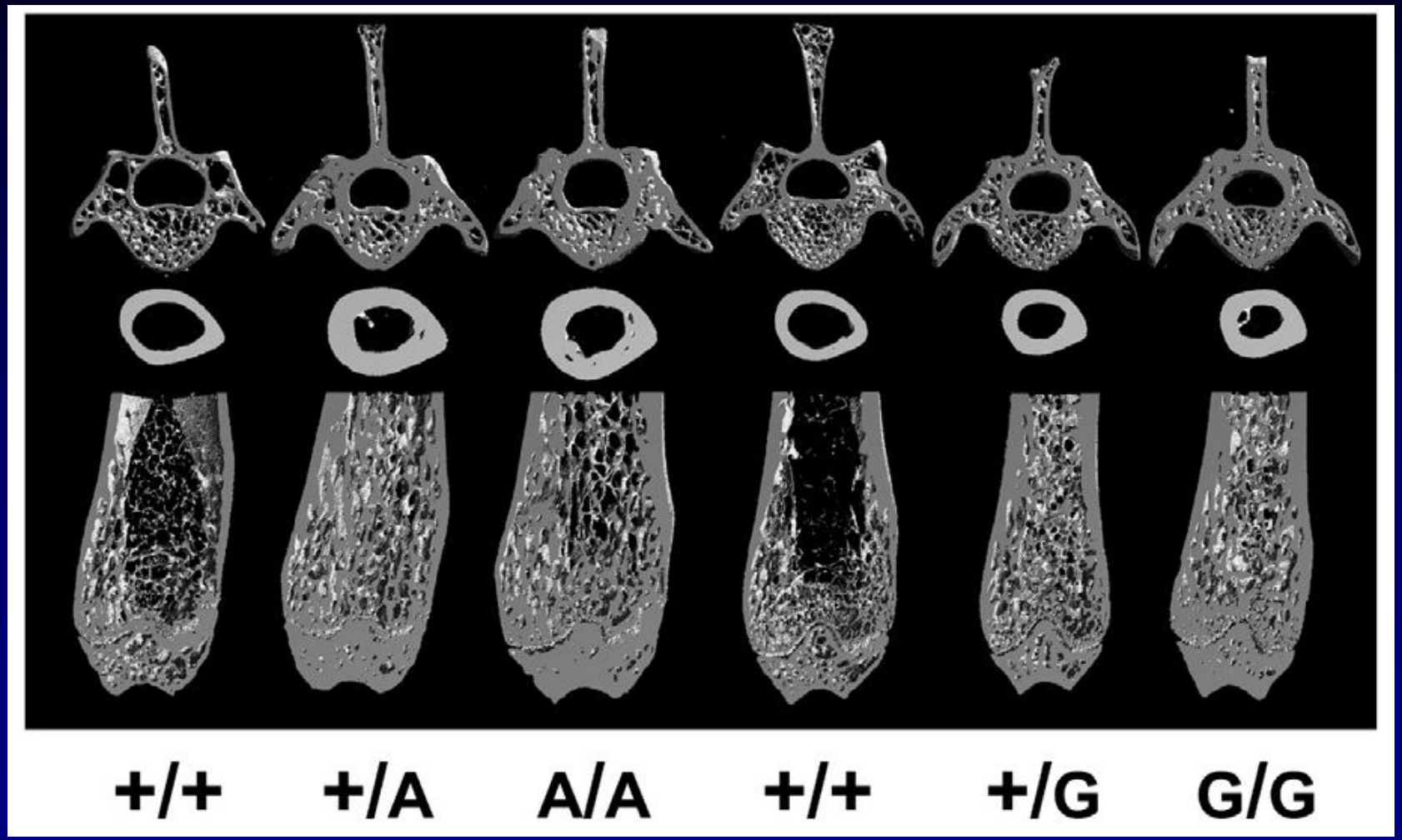


Baron R. and Kneissel M., Nature Medicine, 2013

Source: Sclerostin is predominantly expressed in osteocytes and its dendrites

Poole KE, et al. *FASEB J* 2005;19:1842-44.

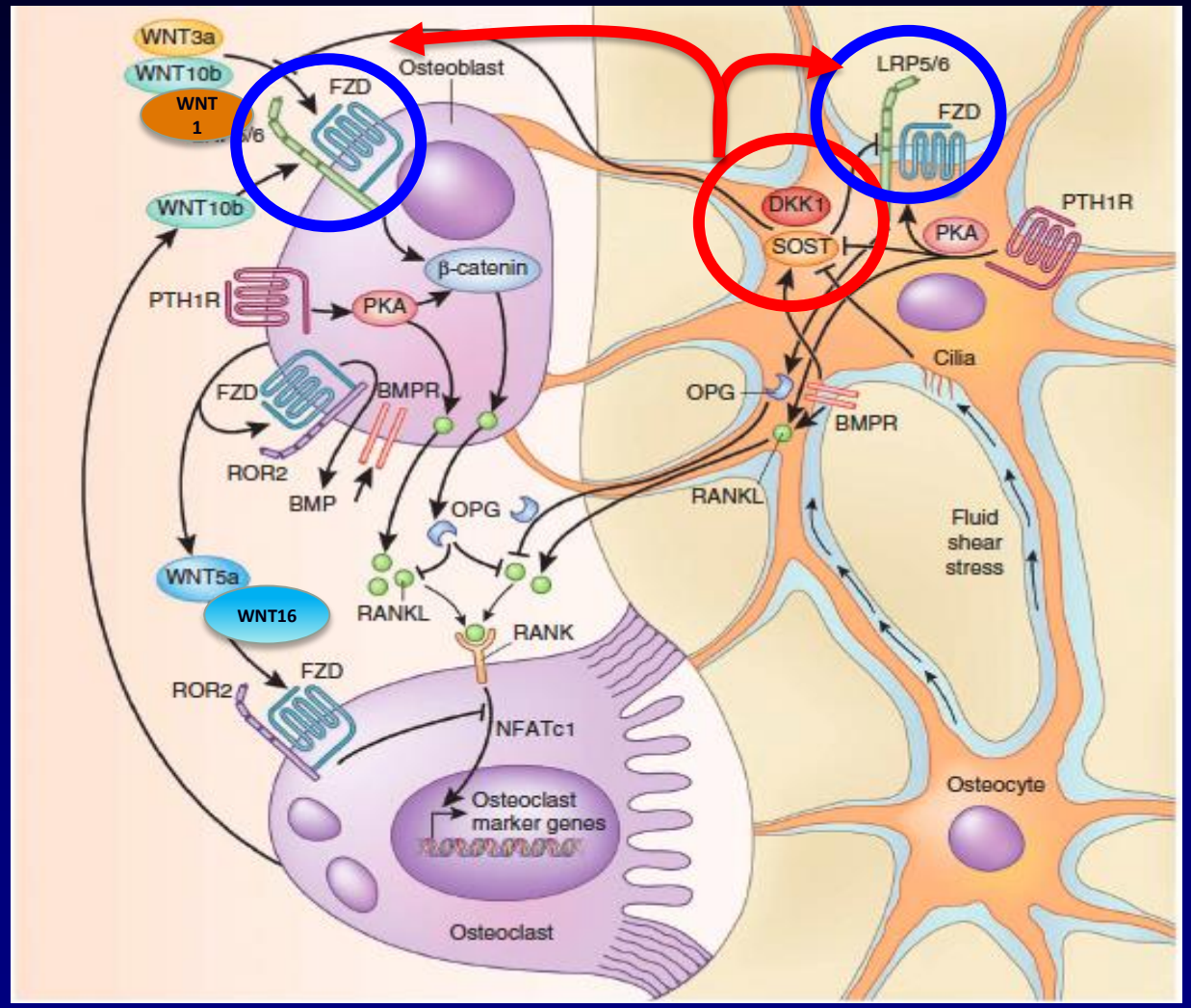
The HBM alleles knocked-in in Osteocytes recapitulate the human HBM phenotype



HBM, high bone mass.

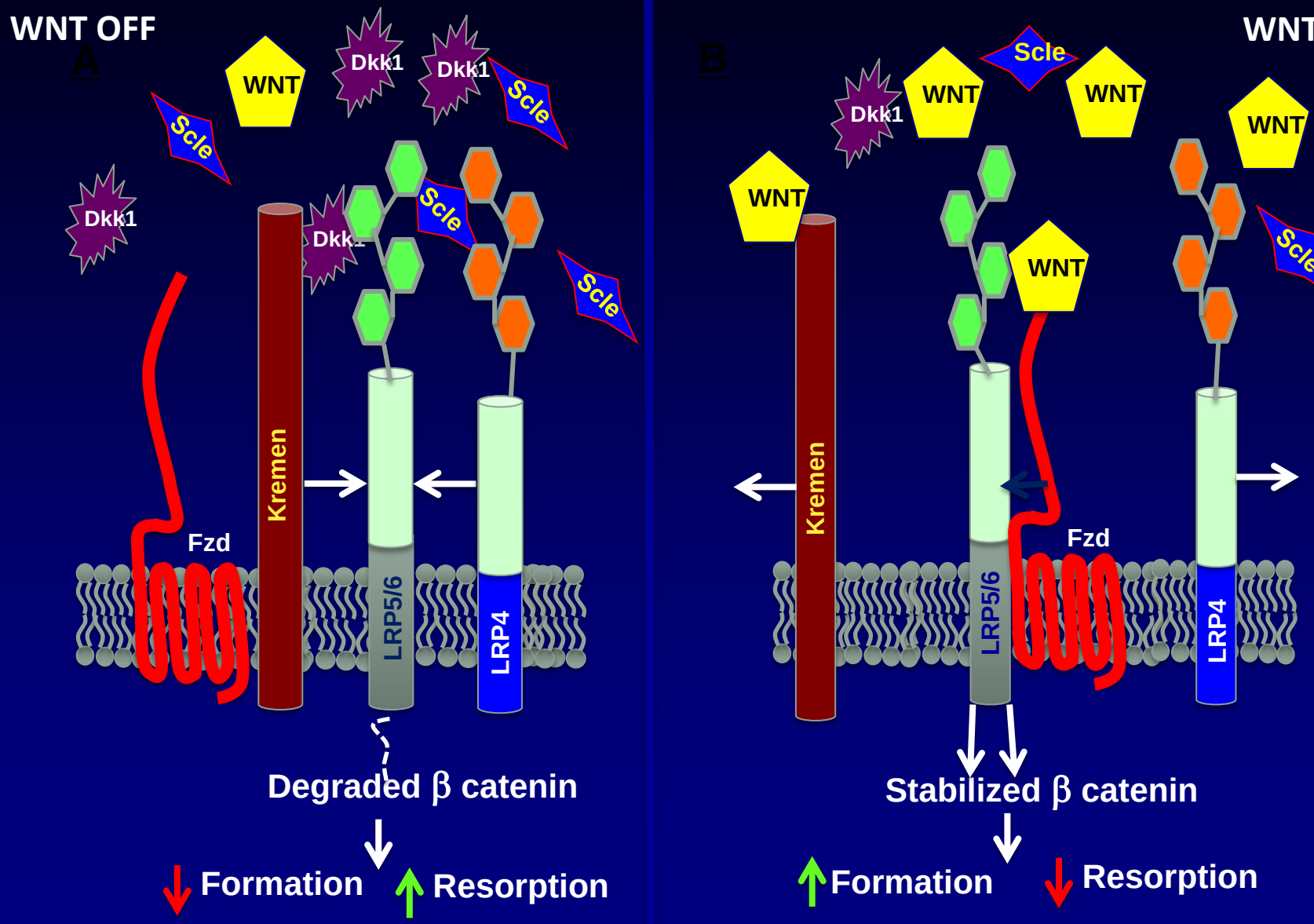
Cui Y, et al. *Nat Med* 2011;17:684-91.

The osteocyte and lining cells are the centerpiece of WNT signaling and sclerostin effects in bone



Adapted from Baron R, and Kneissel M, *Nat Med* 2013;19:179-92.

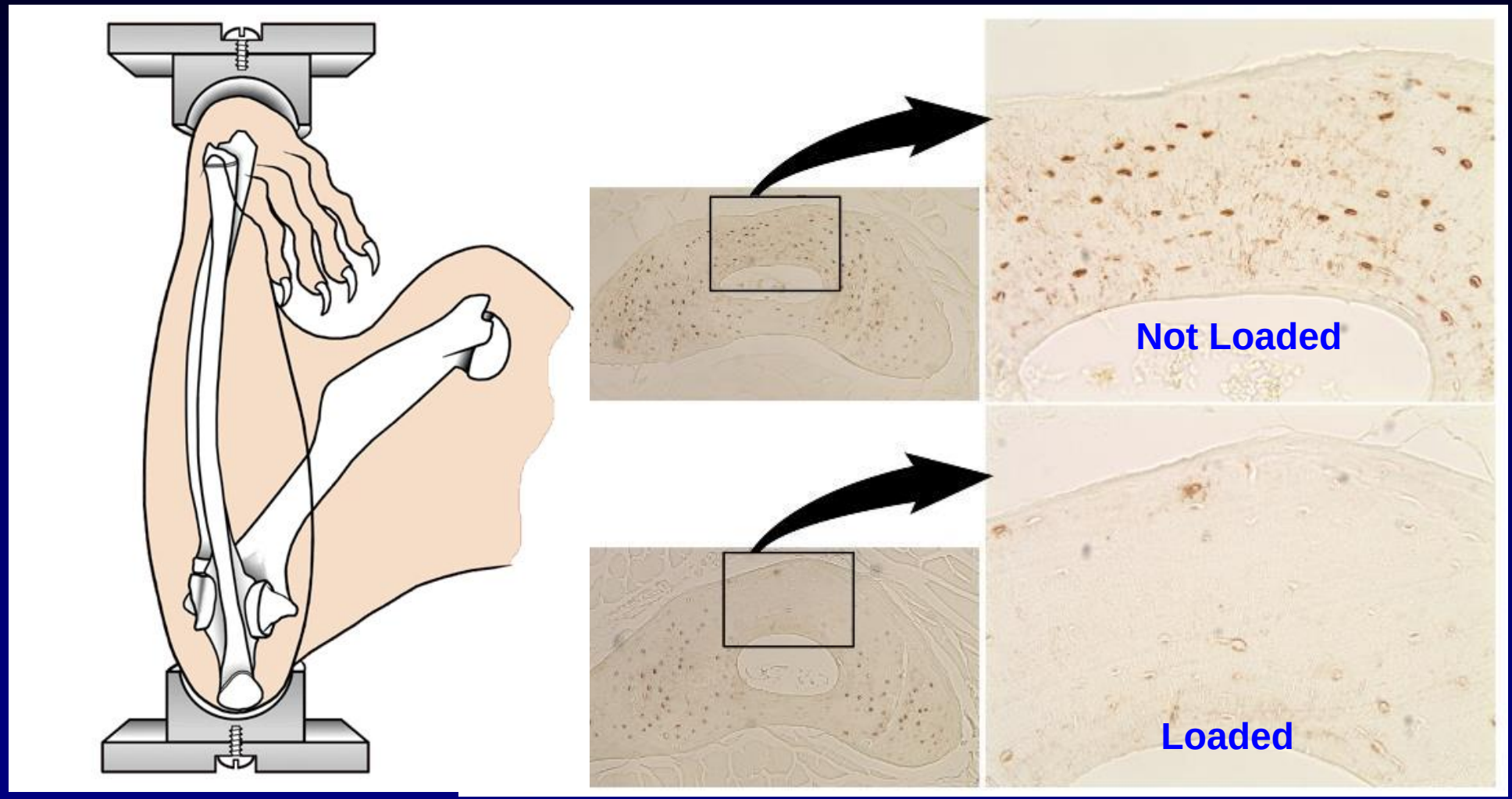
Receptors, Ligands and Inhibitors of WNT signaling



Baron R. and Gori F., Curr Opin in Pharmacology, 2018

How is sclerostin expression regulated?

Mechanical Loading Decreases Sclerostin Protein Levels, Favoring Bone Formation

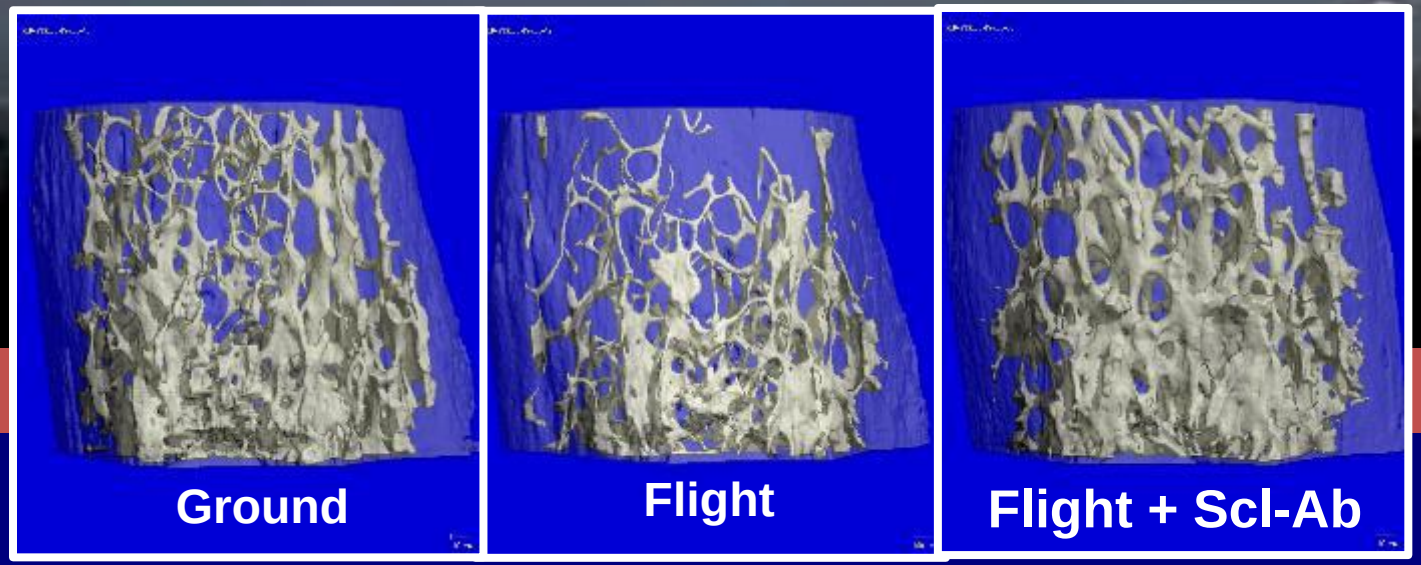


Courtesy of C. Turner.

Effects of Sclerostin Antibody on Spaceflight-Induced Bone Loss

Mary L. Bouxsein, Baron et al.

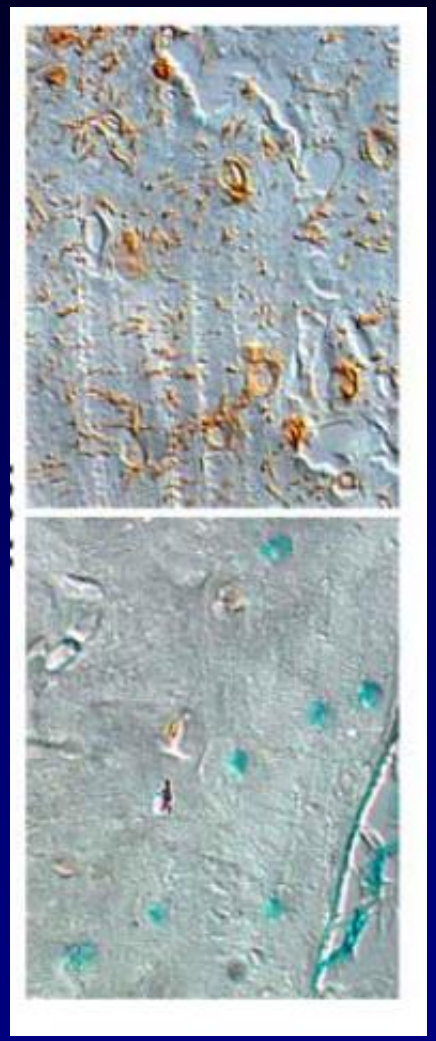
Department of Orthopedic Surgery, BIDMC, Harvard Medical School
Division of Endocrinology, MGH; Bioastronautics Program, MIT-HST

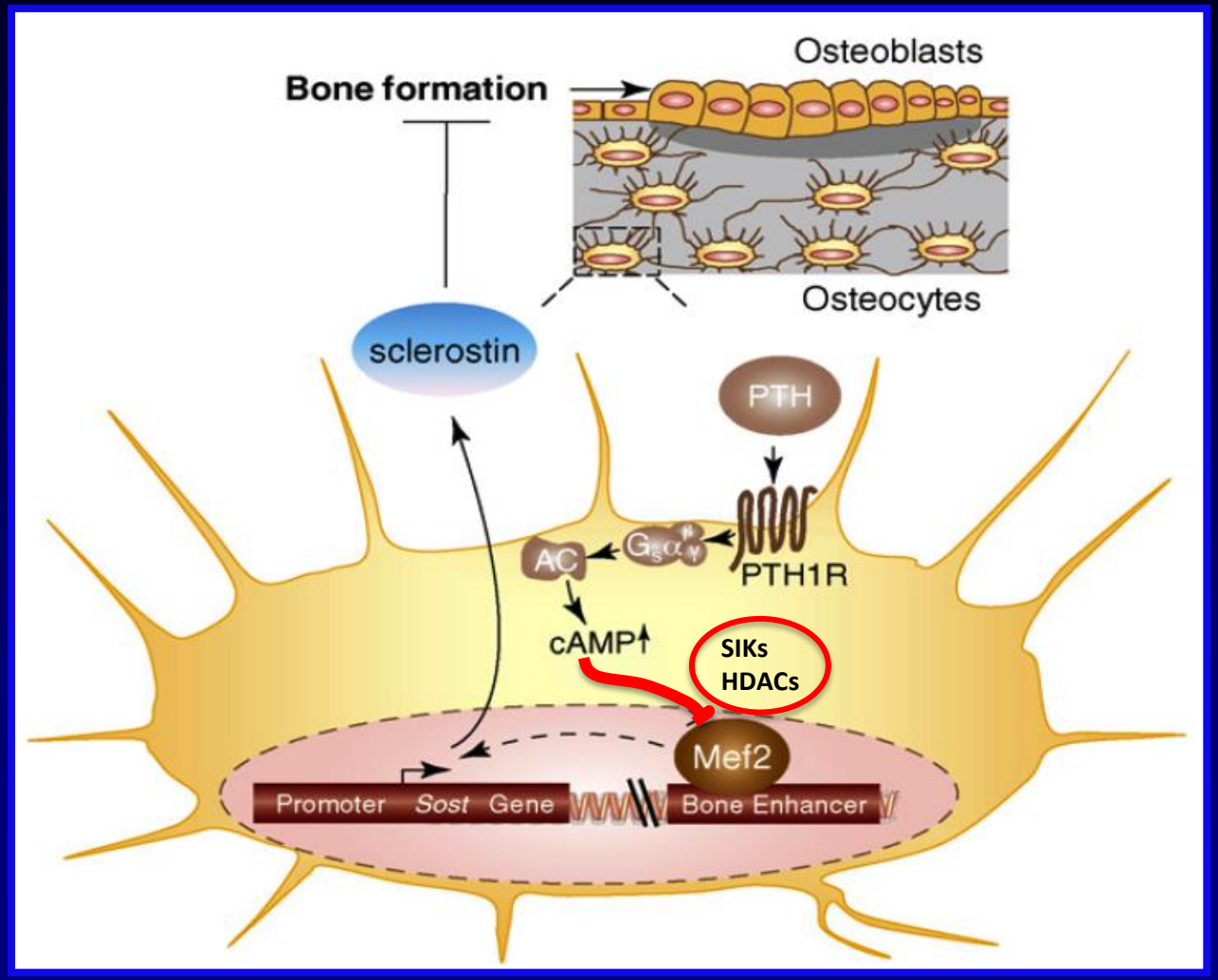


Funded by NASA NNX10AE39G and Amgen/UCB

Bouxsein ML, et al. Unpublished data.

PTH represses sclerostin expression



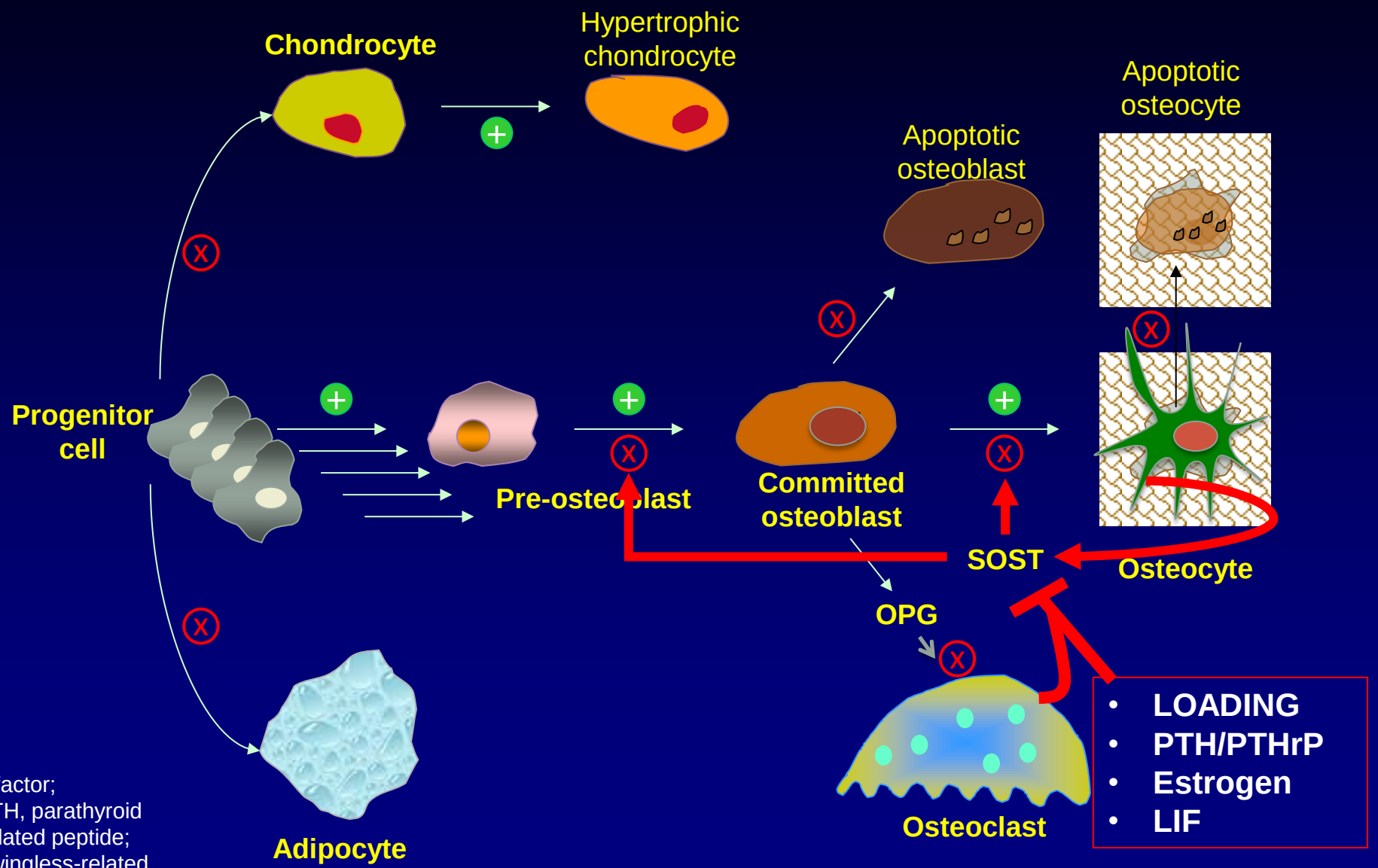


PTH, parathyroid hormone; SOST, sclerostin.

O'Brien EP, et al. *Proc Natl Acad Sci USA* 2008;105:13403-408;
Kramer I, et al. *Trends Endocrinol Metab* 2010;21:237-44;
Wein M, et al. *Nat Commun* 2016;7:13176.

Mechanisms of action of sclerostin inhibition

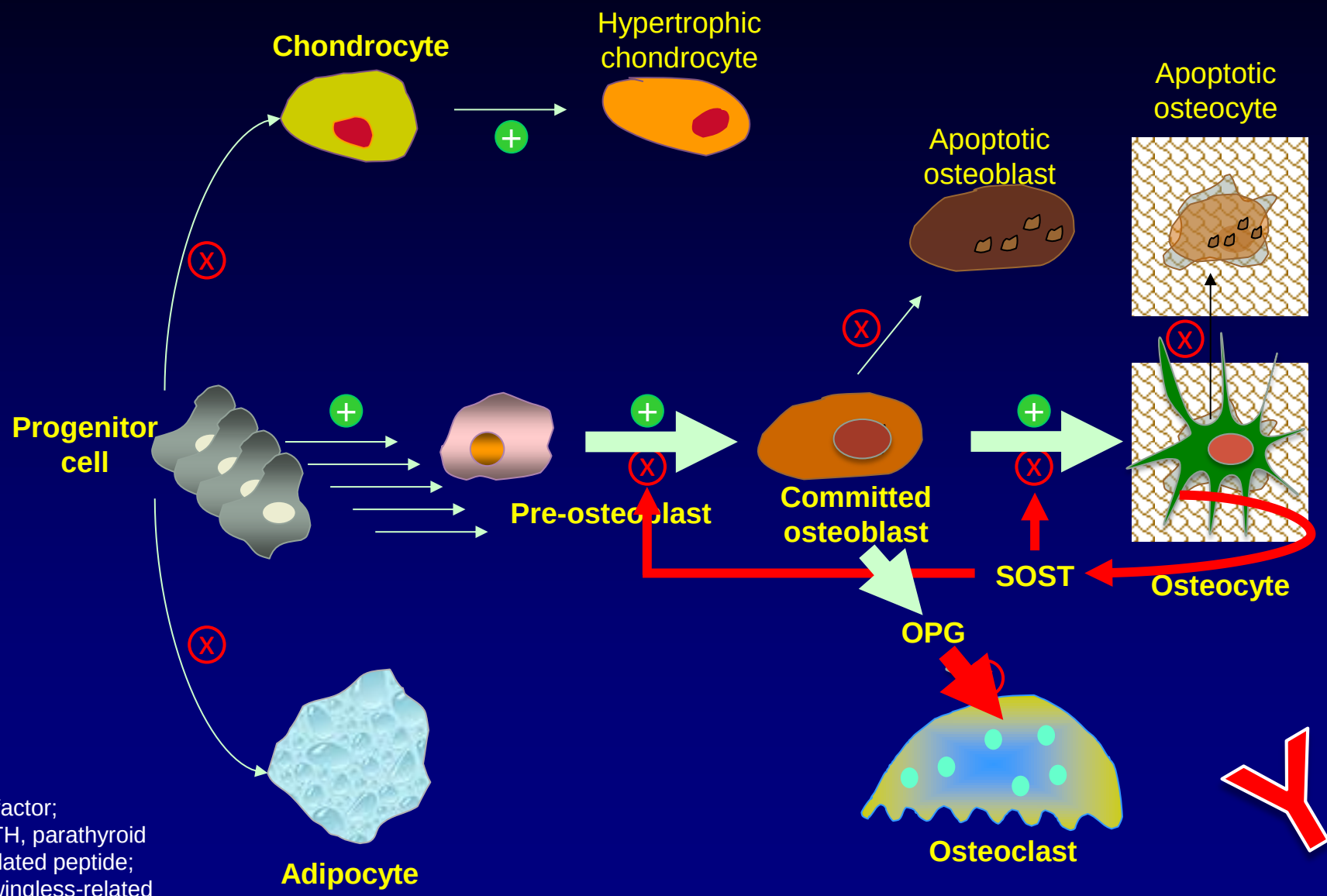
Sclerostin Inhibition Enhances Canonical WNT signaling: Dual action on Bone



LIF, leukaemia inhibitory factor; OPG, osteoprotegerin; PTH, parathyroid hormone; PTHrP, PTH-related peptide; SOST, sclerostin; WNT, wingless-related integration site.

Adapted from Baron R, and Rawadi G. *Endocrinology* 2007;148:2635-43.

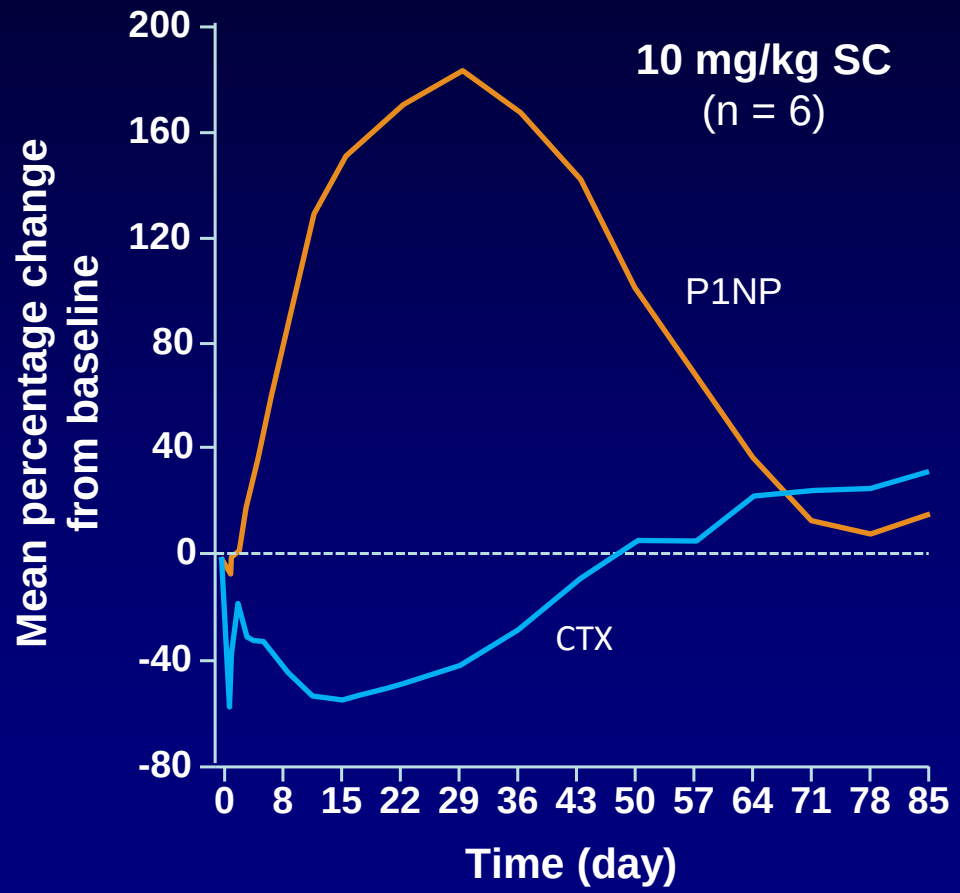
Sclerostin inhibition: Dual action



LIF, leukaemia inhibitory factor; OPG, osteoprotegerin; PTH, parathyroid hormone; PTHrP, PTH-related peptide; SOST, sclerostin; WNT, wingless-related integration site.

Adapted from Baron R, and Rawadi G. *Endocrinology* 2007;148:2635-43.

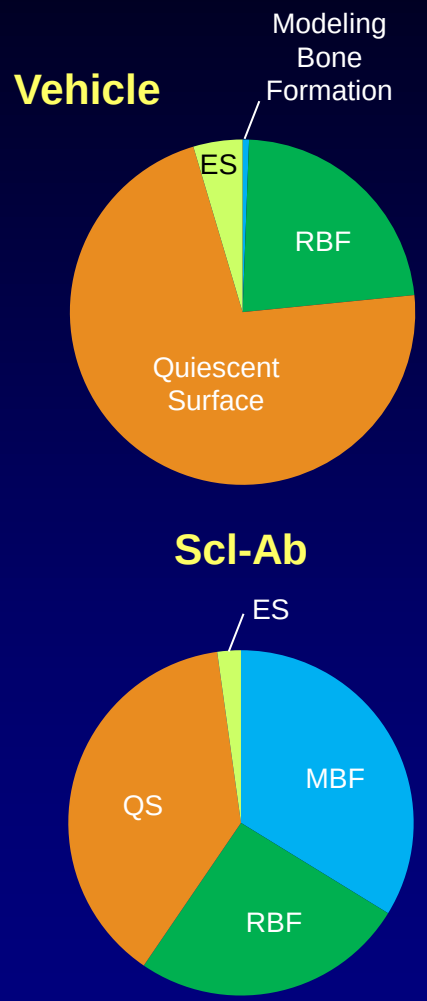
Effect of a single sclerostin antibody injection on bone markers in humans

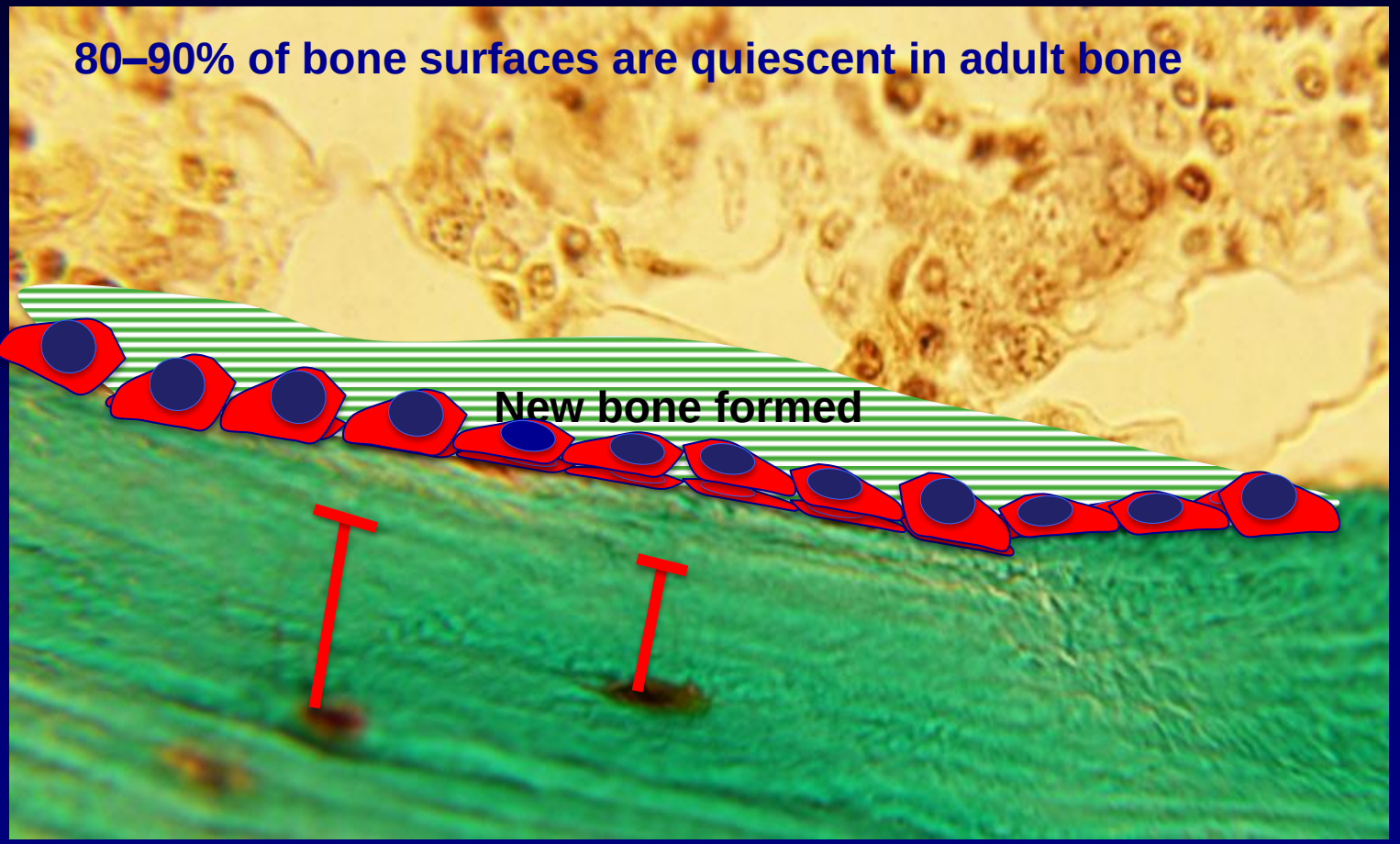


CTX, C-terminal telopeptide of type 1 collagen;
P1NP, procollagen type 1 N-terminal propeptide; SC, subcutaneous.

Padhi D, et al. *J Bone Miner Res* 2010;26:19-26.

Scl-Abs make lining cells along quiescent bone surfaces become active osteoblasts

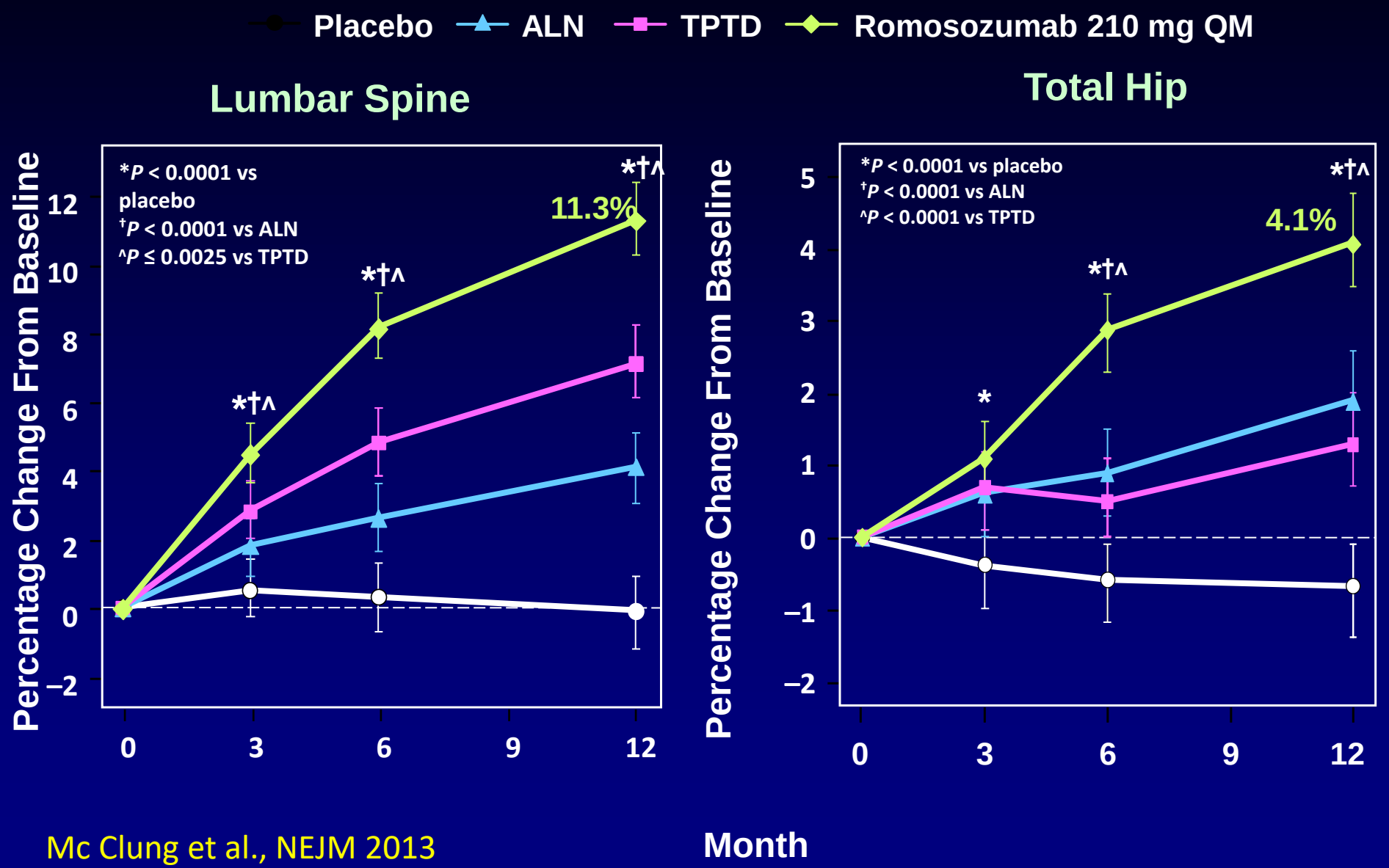




Ominsky MS, et al. *Bone* 2015;81:380-91;
Eda H, et al. *J Bone Miner Res* 2016;31:1225-34;
Matic I, et al. *Stem Cells* 2016;34:2930-42.

Baron R. unpublished

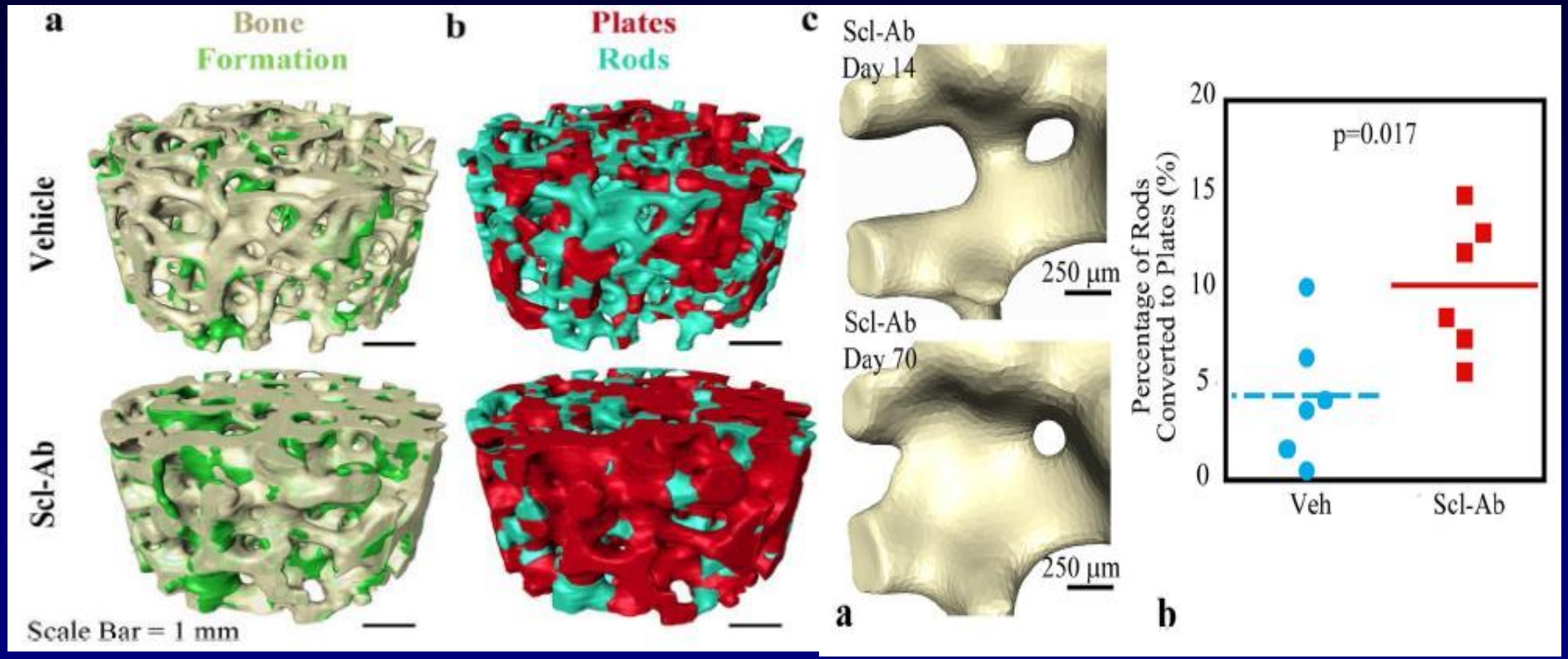
Changes in BMD with Romosozumab



Mc Clung et al., NEJM 2013

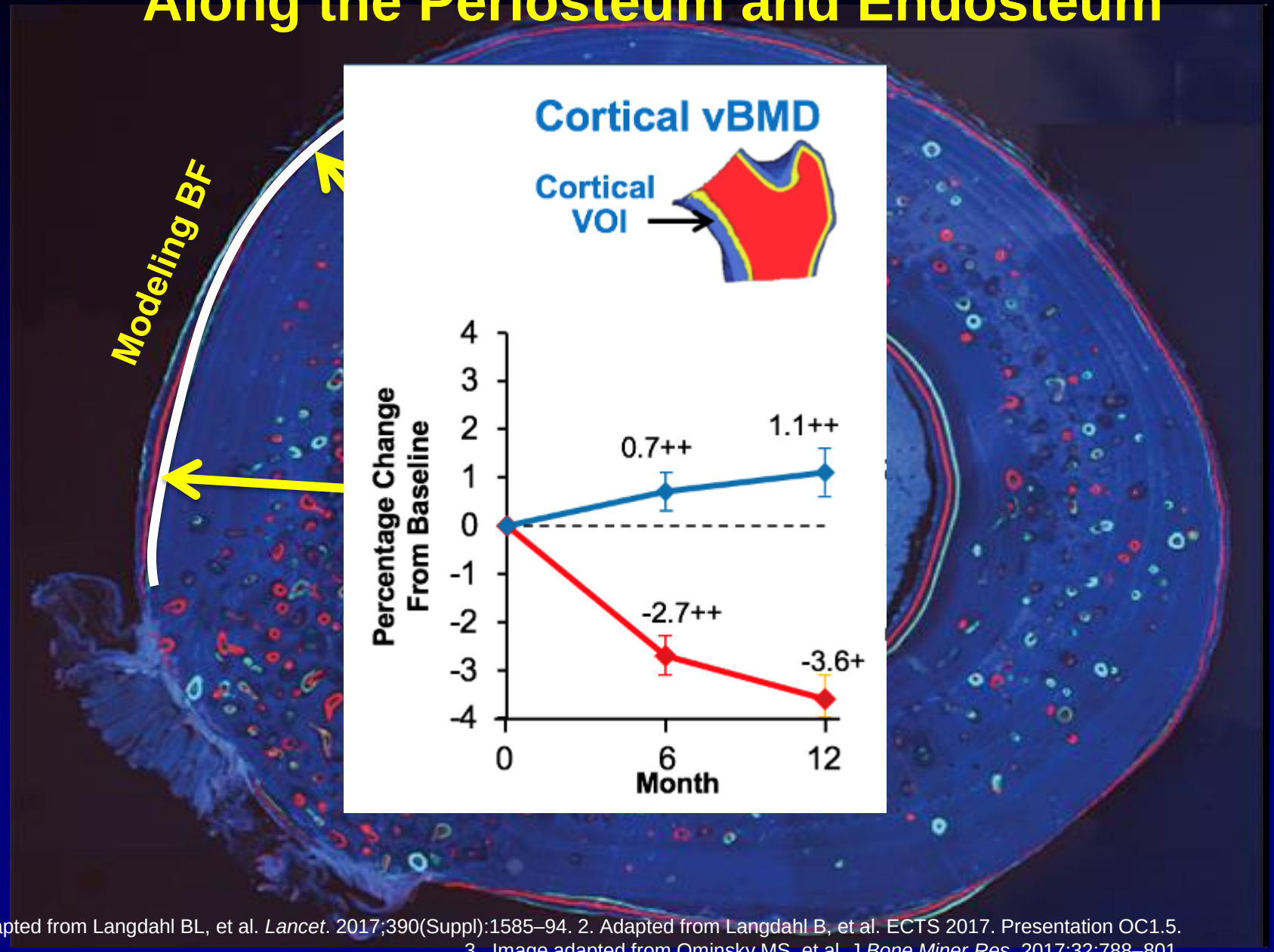
Data are LS means and 95% CIs. *P* values are only shown for the romosozumab 210 mg QM group.

Scl-Abs, Through Modeling, Favor Trabecular Bone Microarchitecture



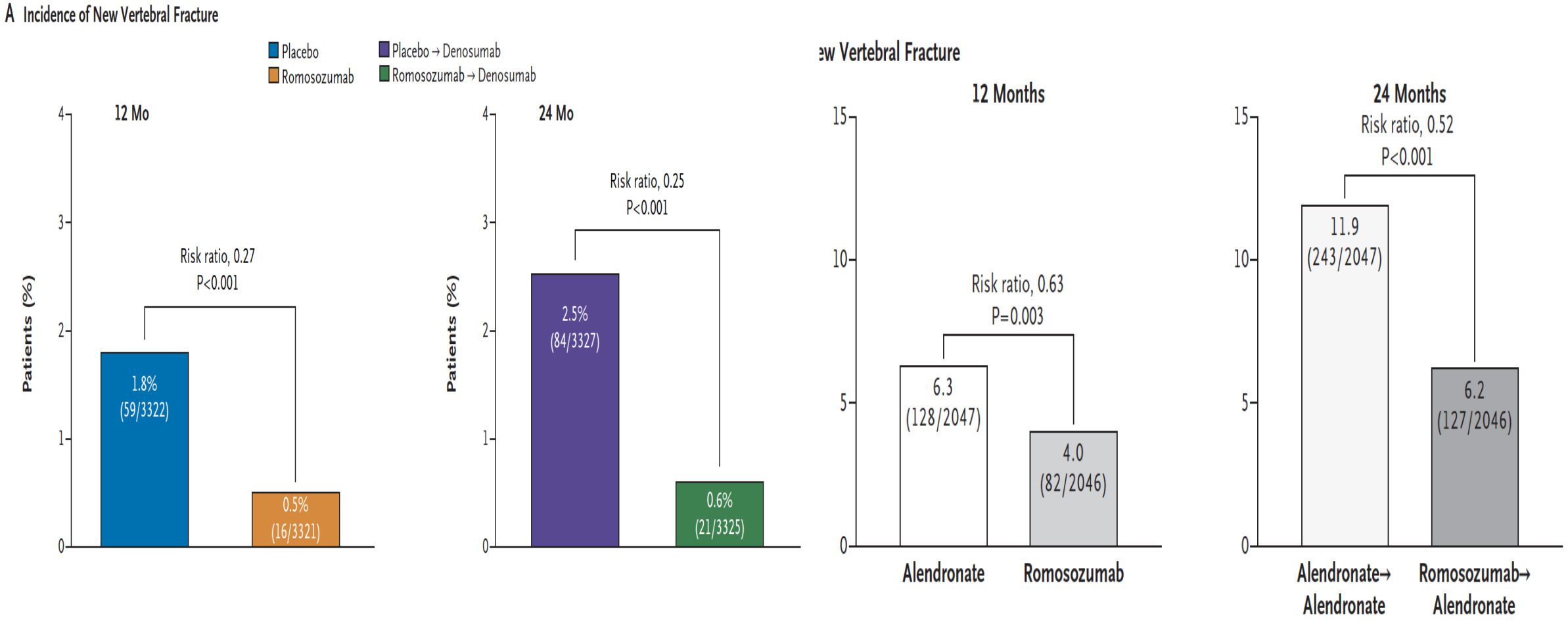
Matheny JB, et al. *Calcif Tissue Int*. 2017;101:82–91.

Romosozumab induces Modeling in the Cortex Along the Periosteum and Endosteum



1. Adapted from Langdahl BL, et al. *Lancet*. 2017;390(Suppl):1585–94. 2. Adapted from Langdahl B, et al. ECTS 2017. Presentation OC1.5.
3. Image adapted from Ominsky MS, et al. J *Bone Miner Res.* 2017;32:788–801.

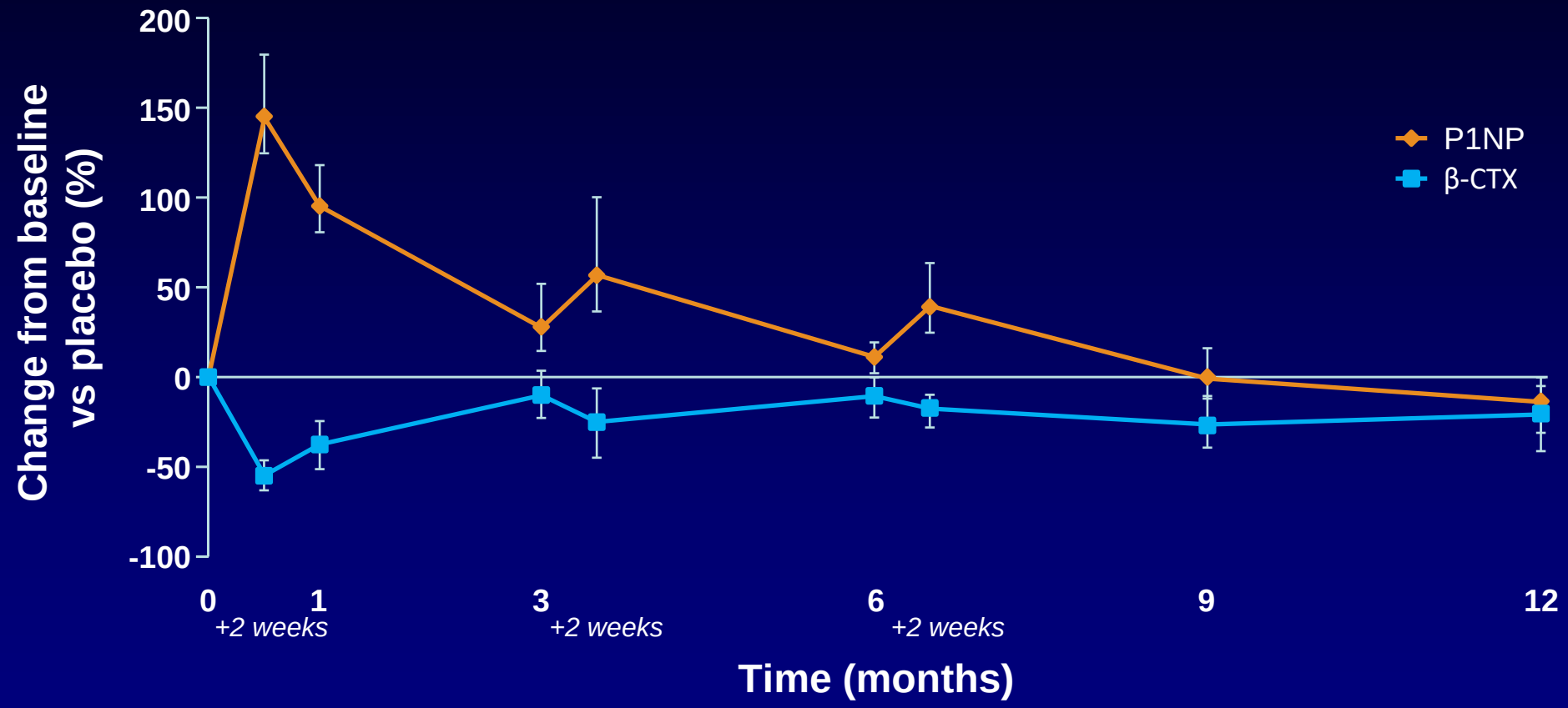
Romosozumab: Fracture reduction in FRAME and ARCH Clinical Trials



Cosman F. et al., New England J Med 2016; Saag G. et al., New England J Med, 2017

FRAME Phase 3 study: Despite Continued Treatment the Increase in Bone Formation Marker Fades Out

Change in serum P1NP and β-CTX with romosozumab relative to placebo

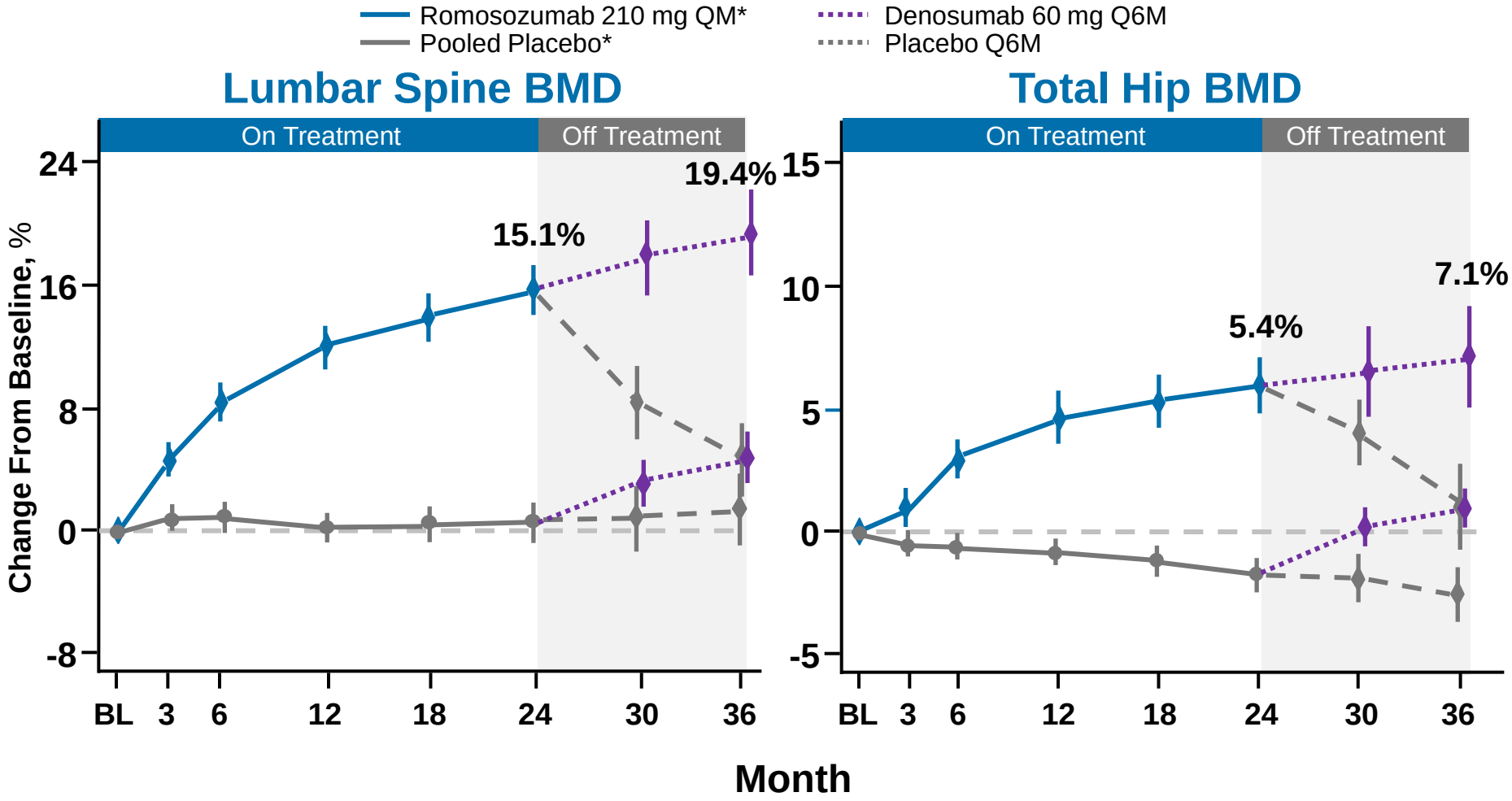


P1NP: romosozumab n = 62, placebo n = 62;
CTX: romosozumab n = 61; placebo n = 62.
Data presented as bootstrapped median treatment difference and 95% CI.

β-CTX, β-isomer of C-terminal telopeptide of type 1 collage; CI, confidence interval;
P1NP, procollagen type 1 N-terminal propeptide.

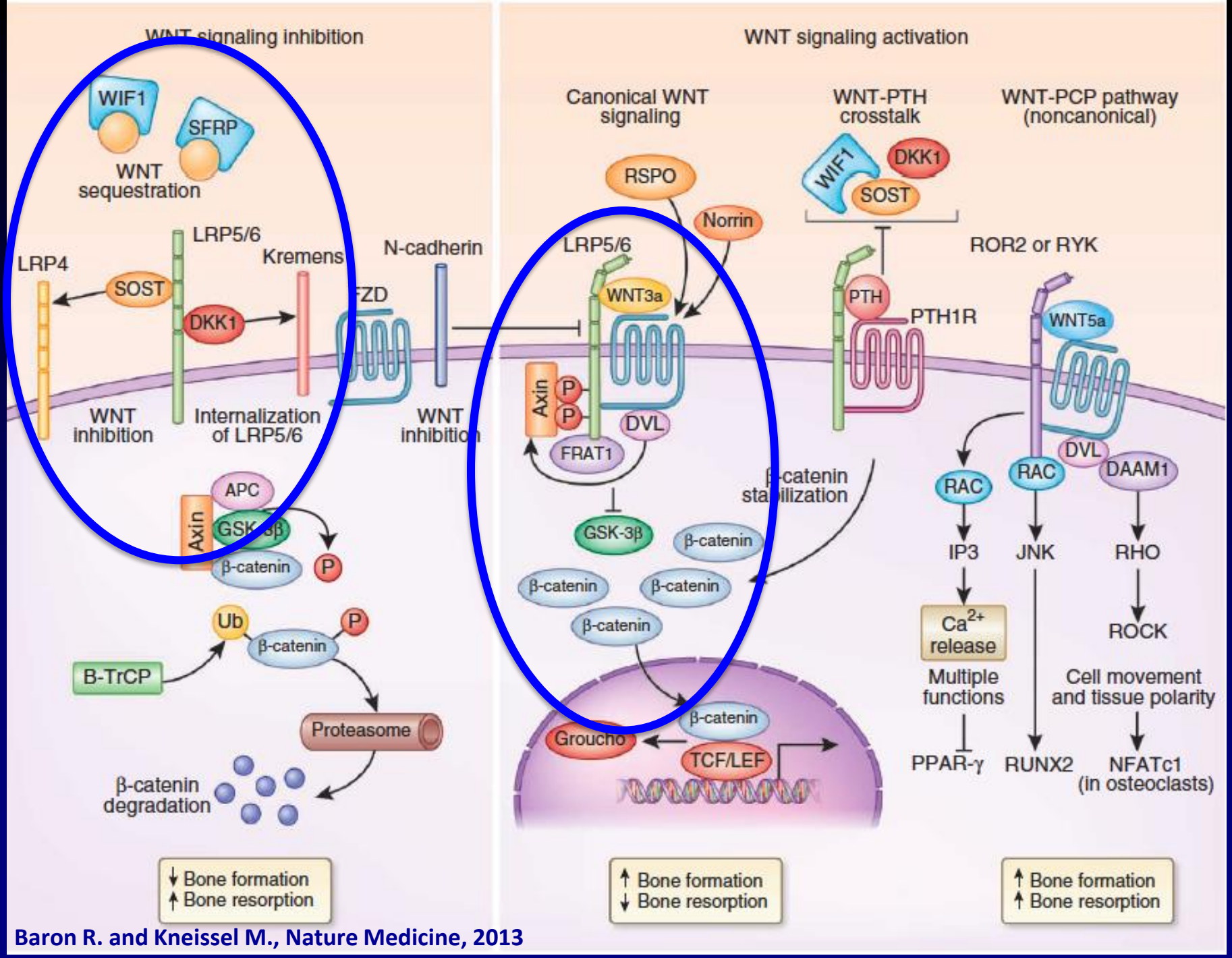
Cosman F, et al. *N Engl J Med* 2016;375:1532-43.

Lumbar Spine and Total Hip BMD Declined Towards Baseline After Discontinuation of Romosozumab Treatment[1]



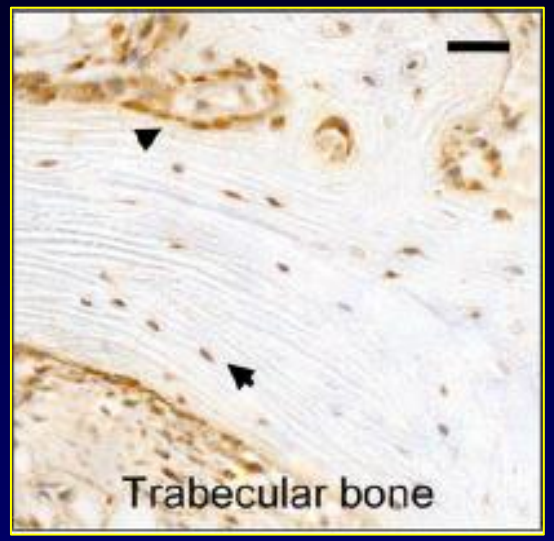
*Randomized treatment group up to month 24. Romosozumab 210 mg QM (N = 40), pooled placebo (N = 36).
Results include only subjects re-randomized at month 24. Data are means and 95% CI.
BL=baseline; BMD=bone mineral density; CI=confidence interval; Q6M=once every 6 months; QM=once monthly

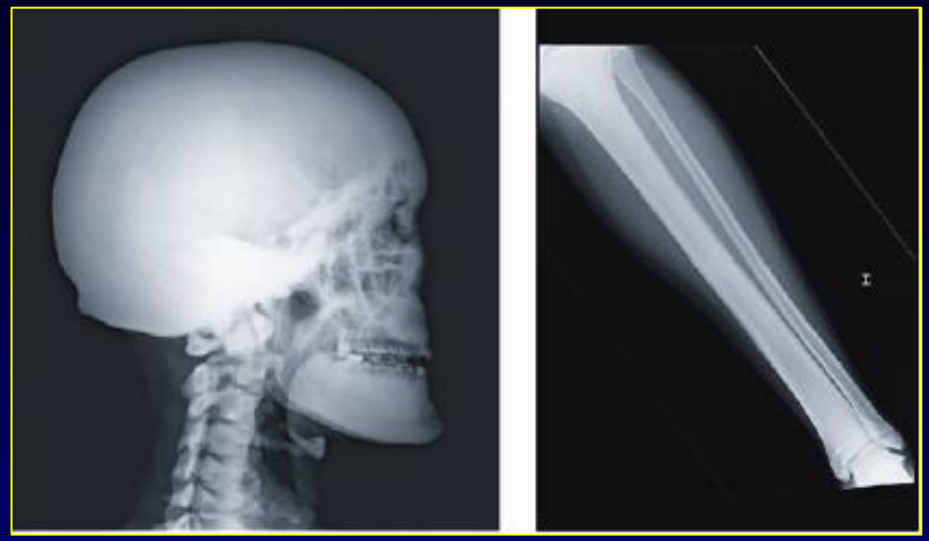
1. Adapted from: McClung MR, et al. *J Bone Miner Res.* 2018;33:1397-1406.

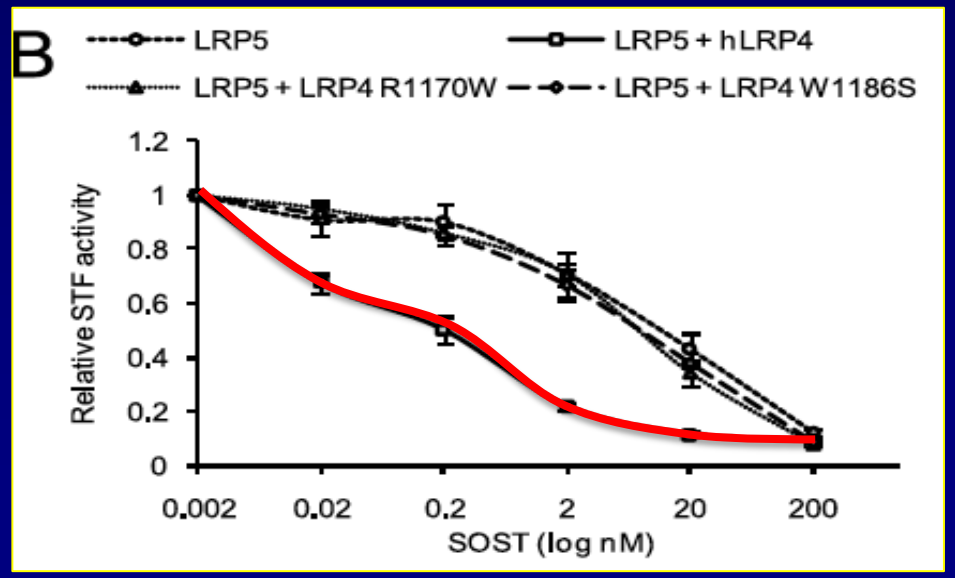


Baron R. and Kneissel M., Nature Medicine, 2013

LRP4 is in Osteocytes, Enhances Sost Inhibition of LRP5 And LRP4 Mutations or Inhibition Increase Bone Mass



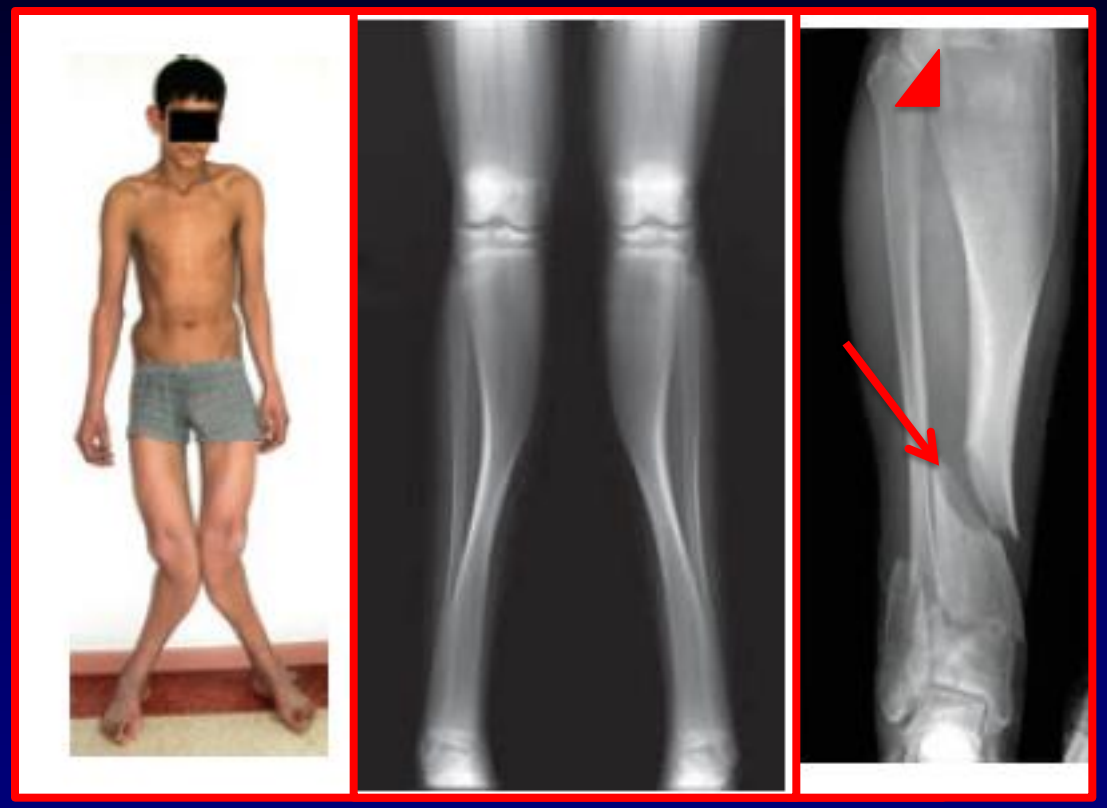


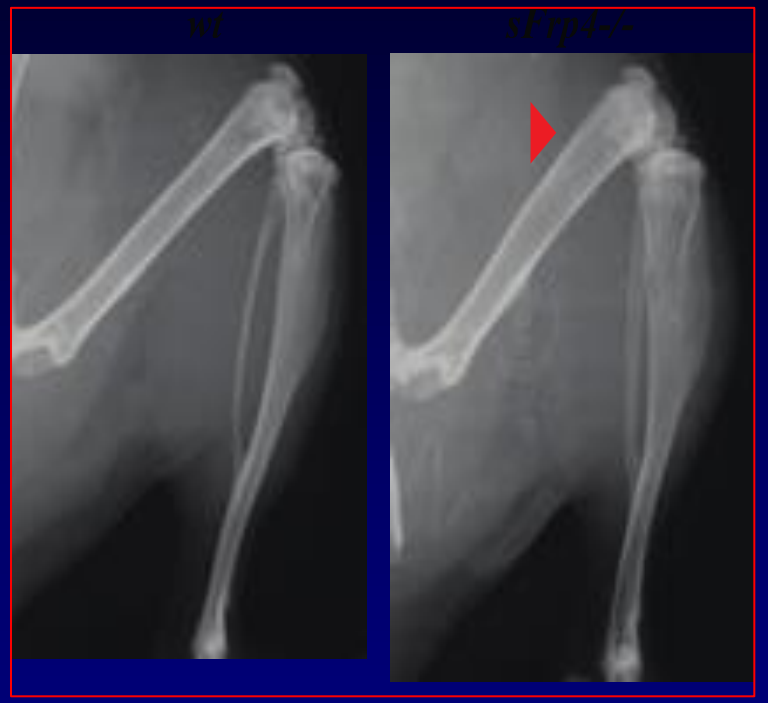


Forced expression of LRP4 enhances the ability of SOST to inhibit WNT signaling

Leupin et al., JBC 2011

Cortical-Bone Fragility — Insights from sFRP4 Deficiency in Pyle's Disease



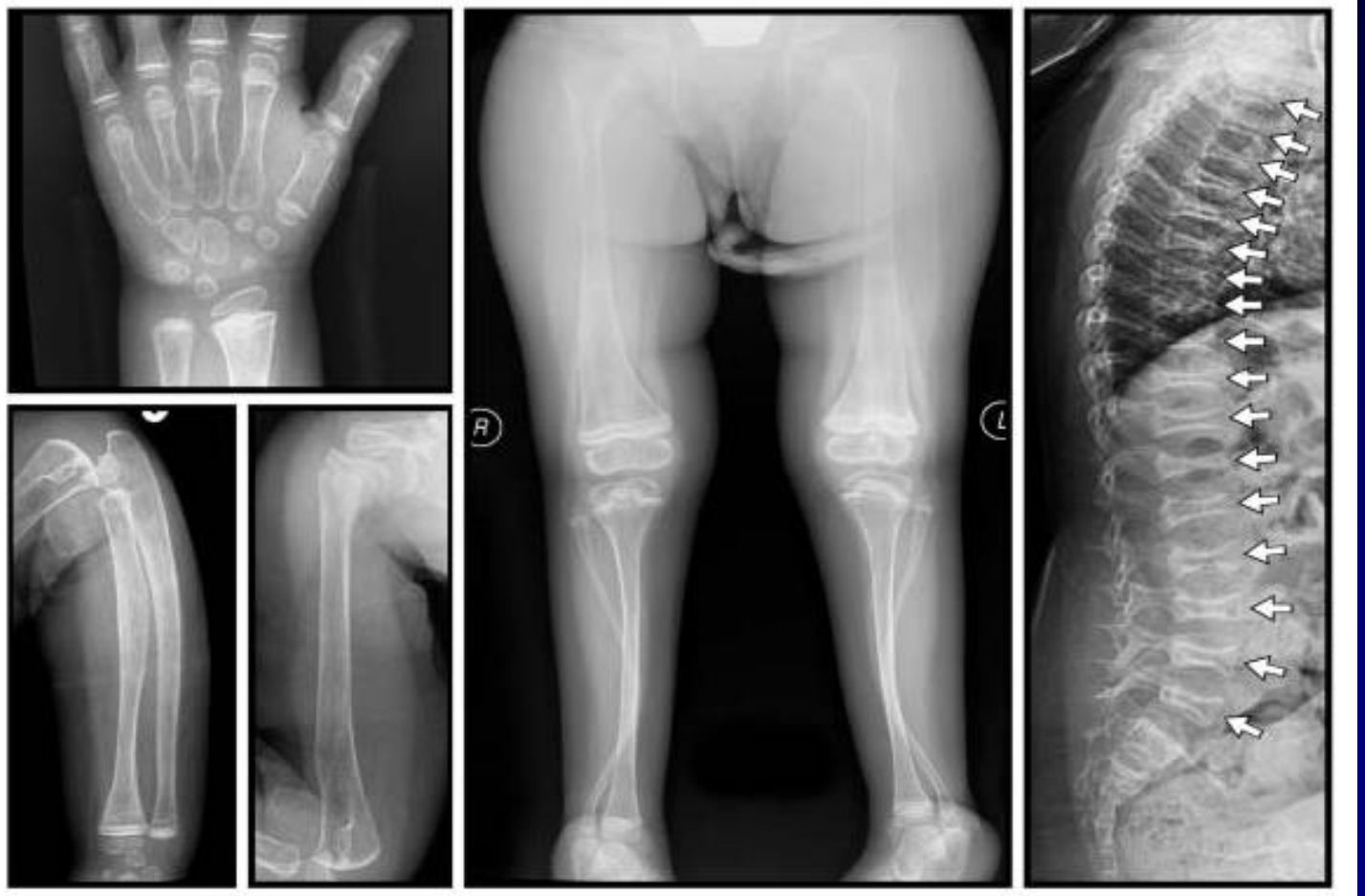


Pyle Disease: sFrp4 null **sFrp4 null Mice**

Kiper , Saito et al., NEJM 2016

Mutations in WNT1 are a cause of osteogenesis imperfecta

Somayyeh Fahiminiya,[1] Jacek Majewski,[1] John Mort,[2] Pierre Moffatt,[2] Francis H Glorieux,[2] Frank Rauch[2]



J Med Genet 2013;**50**:345–348.

Mutations in *WNT1* Cause Different Forms of Bone Fragility

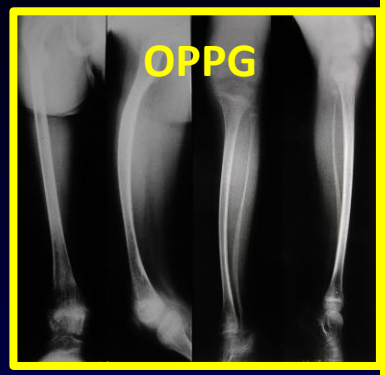
Keupp et al., Am J Hum Gen 2013

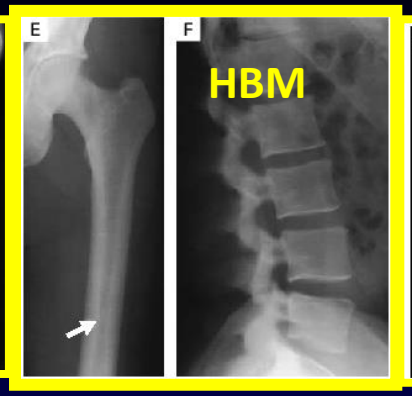
WNT1 Mutations in Families Affected by Moderately Severe and Progressive Recessive Osteogenesis Imperfecta

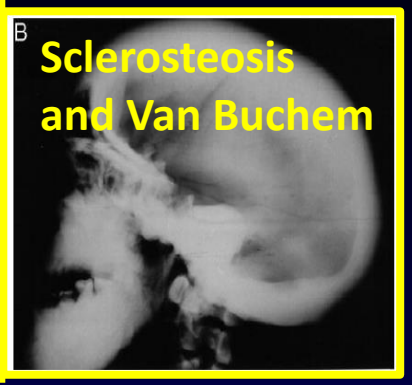
Pyott et al., Am J Hum Gen 2013

WNT1 Mutations in Early-Onset Osteoporosis and Osteogenesis Imperfecta

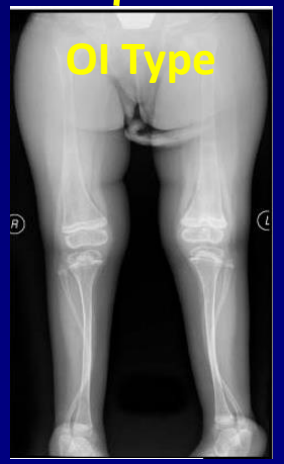
Laine et al. NEJM, 2013







WNT Signaling is essential!



OI Type II and III

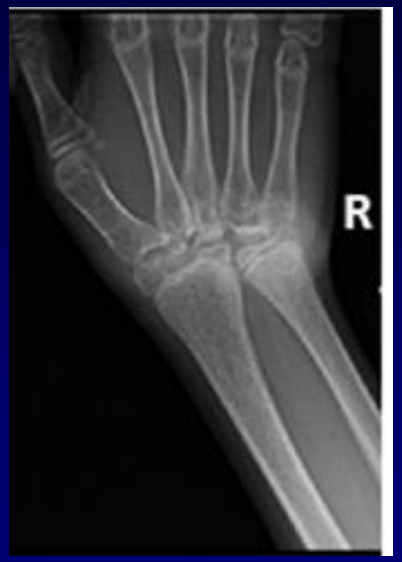
Other Rare Skeletal Diseases Have Been Successfully Treated in the Last Few Years

• Hypophosphatasia	Alkaline Phosphatase	Asfotase α (Strensiq)
• Achondroplasia	FGF3 Receptor	vosoritide (Voxzogo)
• X-Linked Hypophosphatemia	Phex/FGF23	Burosumab (Cryssvita)
• Osteogenesis Imperfecta II/III	Collagen	Setrusumab

Many other skeletal rare diseases are not yet fully understood or treated

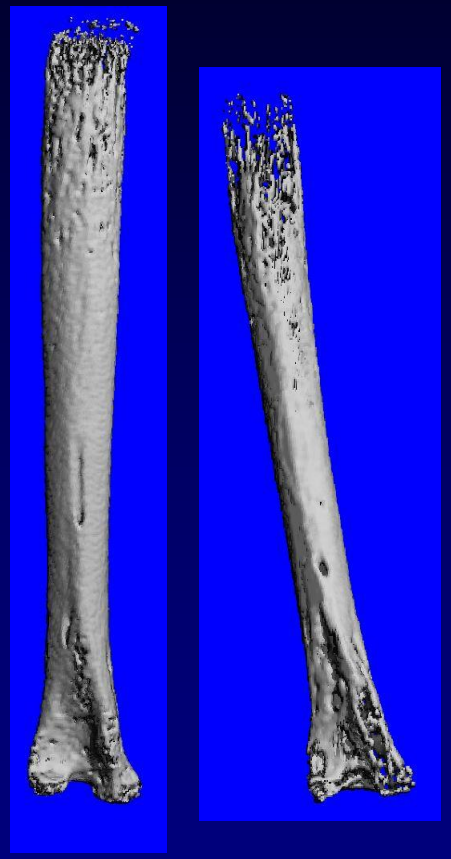
Multicentric Carpo-Tarsal Osteolysis (MCTO) Mouse Model (*MafB Pro59Leu* KI) S. Takahashi

13 yr old boy



Regev et al,
Bone Reports 2021

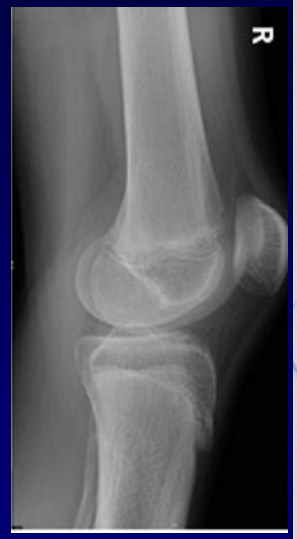
4 week old female mice



WT KI

Metatarsal

13 yr old boy



Regev et al,
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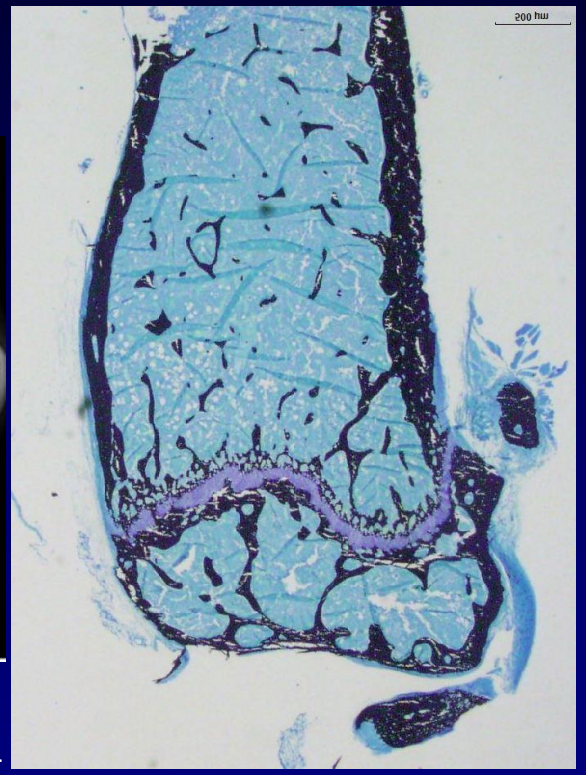

WT KI

Distal Femur

The quest: …understand the disease to find a treatment…

Thank you for your attention!