2019 Interdisciplinary Symposium on Osteoporosis

Friday, May 17, 2019

1:15 pm – 2:15 pm

Bone Modeling: An Old Idea Revisited with Implications for Osteoporosis Treatment

David Dempster, PhD, FRMS

Evaluate this session via the app!

Modeling-based Bone Formation: An Old Concept Revisited

- with Implications for the Treatment of Osteoporosis

David W. Dempster, BSc (Hons), PhD, FRMS

Columbia University
and
Helen Hayes Hospital
New York

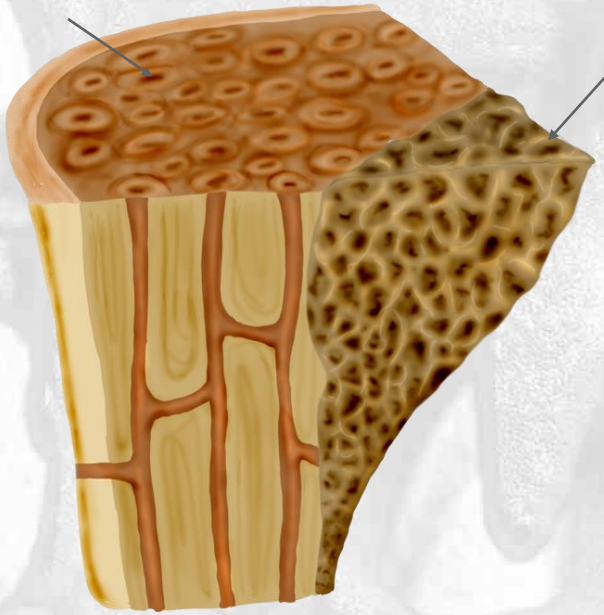
ISO2019 La Jolla, CA, May 17, 2019

Disclosures

- Eli Lilly & Co.: Consultant, Research Grants
- Amgen Inc.: Consultant, Speaker's Bureau, Research Grants
- Radius Health: Consultant, Speaker's Bureau, Research Grants

Cortical and Cancellous Bone

80% of the human skeleton is Cortical Bone[1]



Thoracic spine
>75% cancellous

Lumbar spine
>66% cancellous

Femoral neck
75% cortical
25% cancellous

1/3 distal radius
>95% cortical

Ultradistal radius
75% cortical
25% cancellous

Trochanter
50% cortical
50% cancellous

Image courtesy of © David W. Dempster, PhD, 2000

1. Dempster DW. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 6th ed; 2006:7-11.

Bone Remodeling

- Bone is a complex, continuously remodeled tissue
  - The adult skeleton is completely regenerated every 10 years
  - 3-4 million bone remodeling units (BRUs) are initiated each year
  - 1 million BRUs are actively engaged in bone turnover at any time

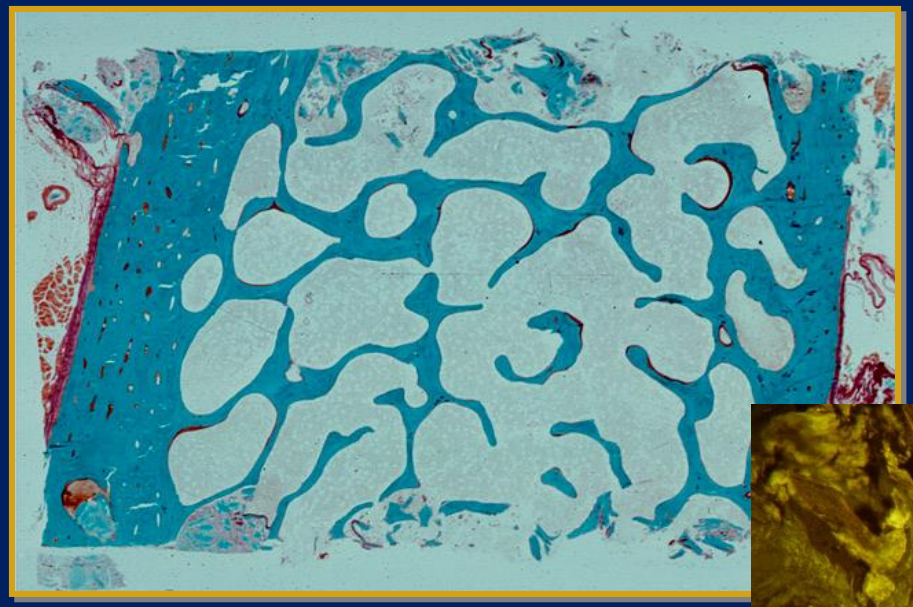
Manolagas SC. *Endocr Rev.* 2000;21:115-137.

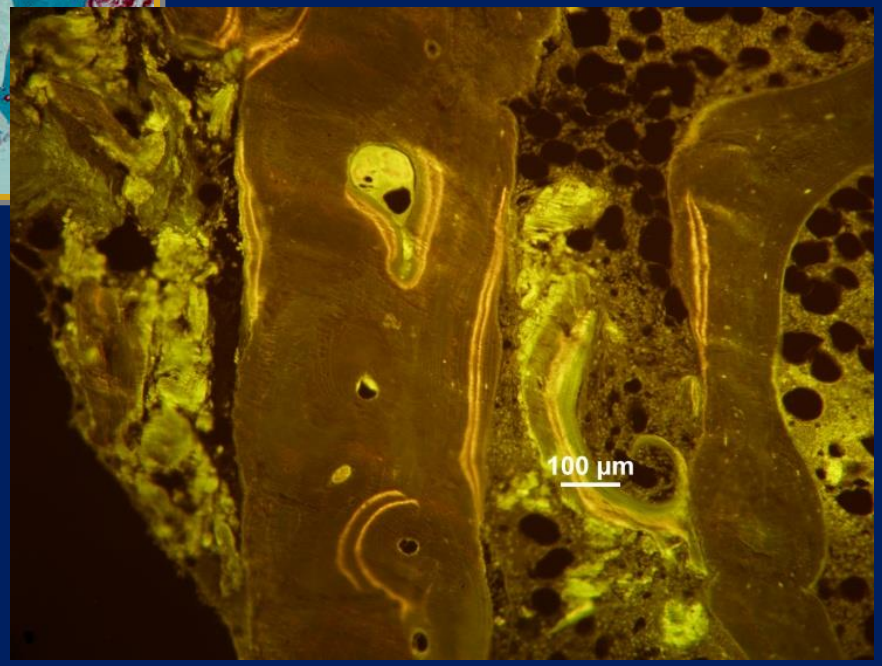
Bone Remodeling

- Replacement of old or damaged bone with new bone
  - Osteoclasts and osteoblasts in the same remodeling units
  - Persists for a lifetime
  - Abnormalities cause low or high bone mass syndromes

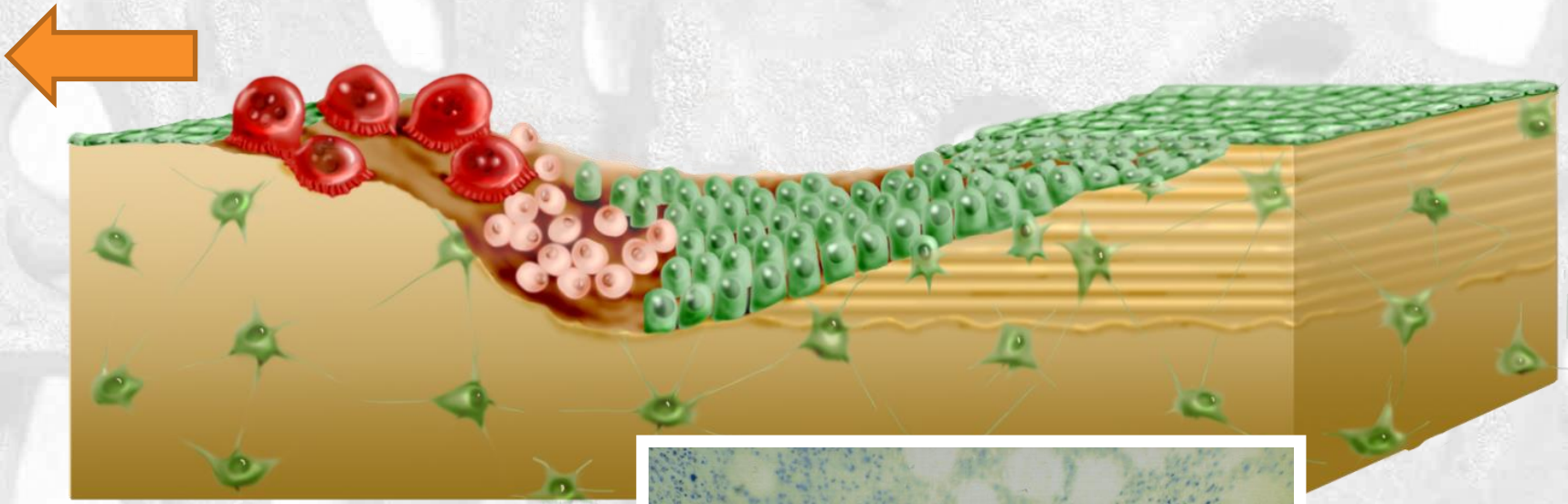
Courtesy of Roberto Civitelli, MD

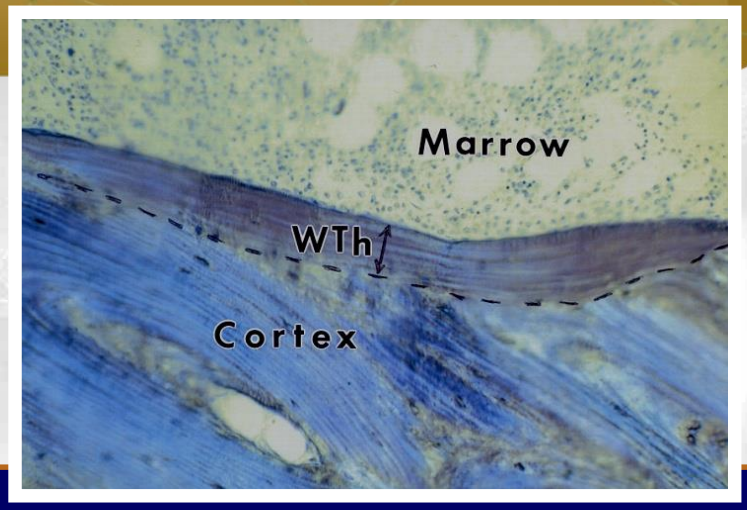
Remodeling on Endocortical, and Periosteal and Cancellous Surfaces





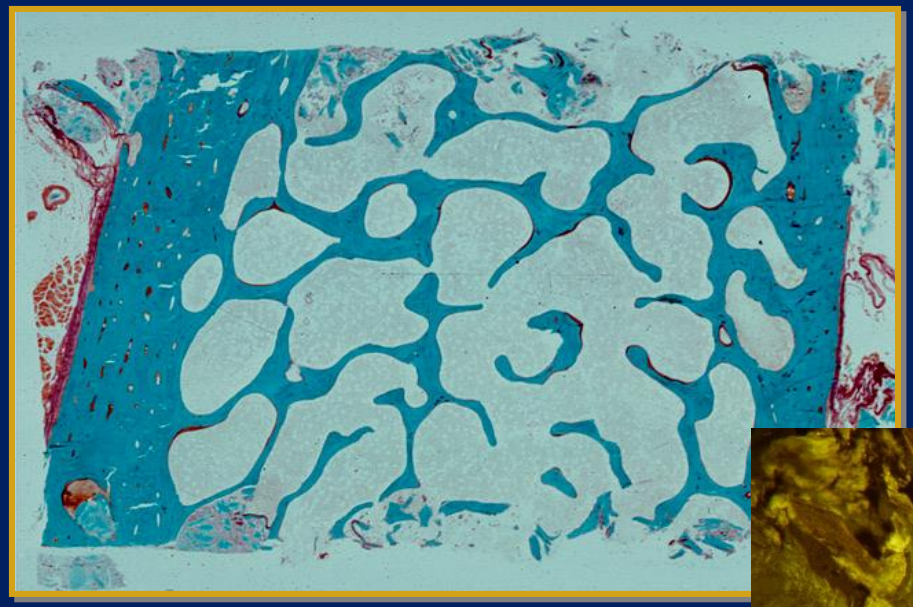
Hemi-osteonal Remodeling on Endocortical, Periosteal and Cancellous Surfaces

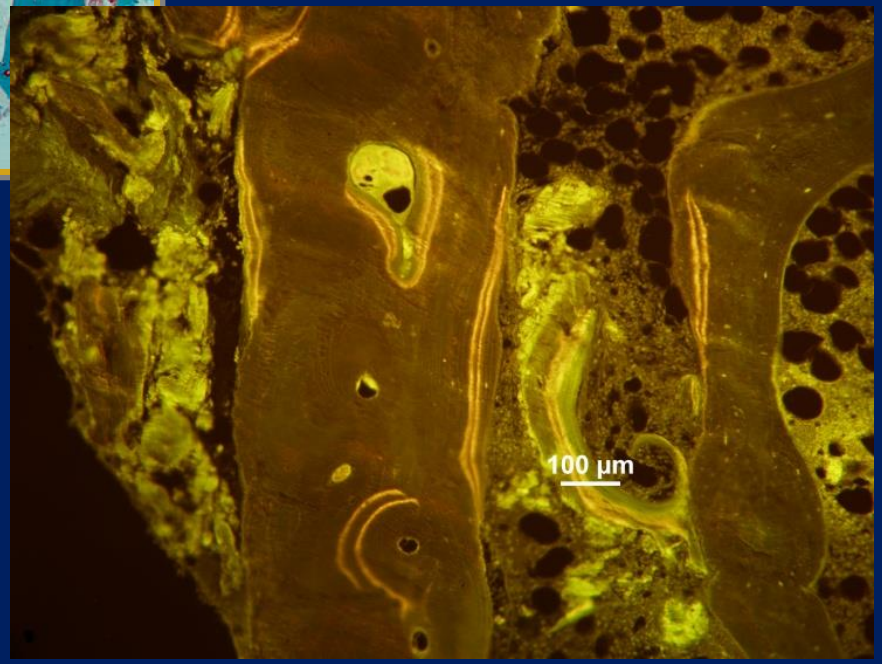




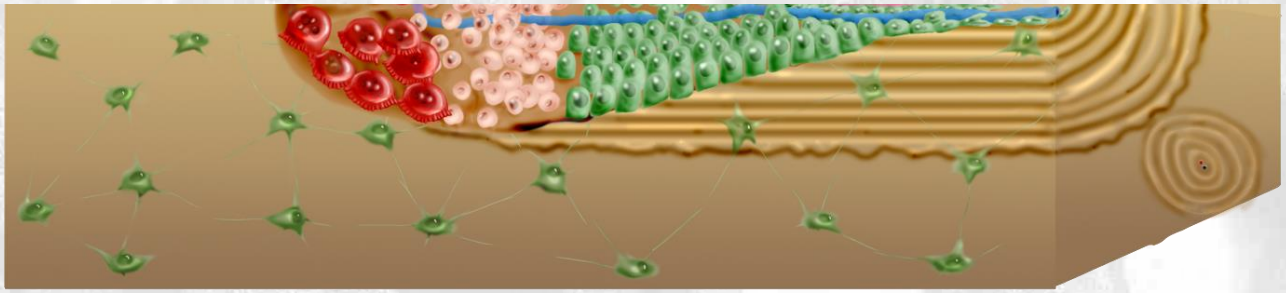
Dempster et al, JBMR 2001; 16:846

Intracortical Remodeling

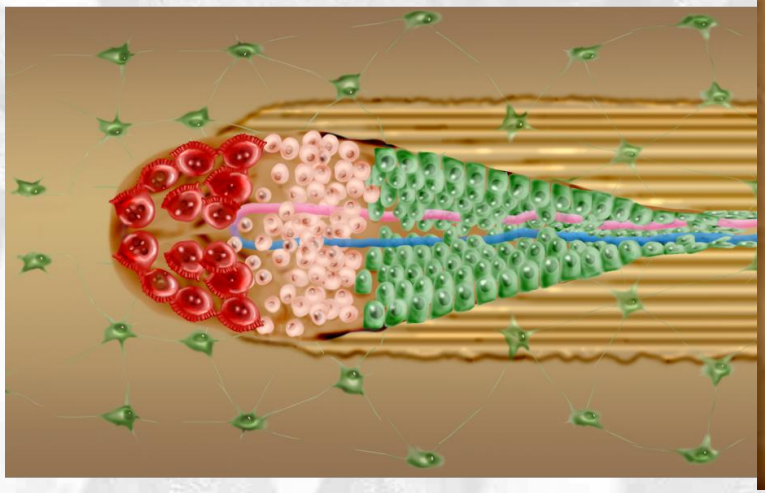


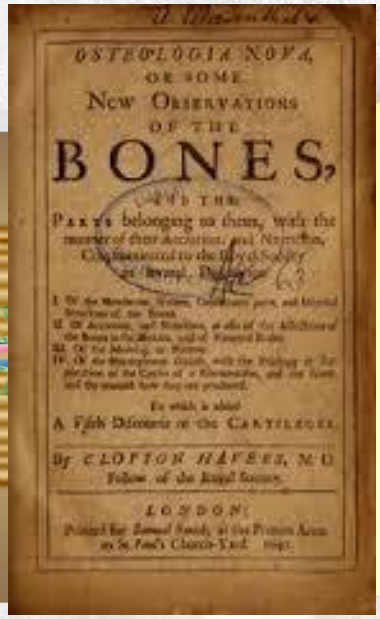


Osteonal Remodeling in Cortical Bone



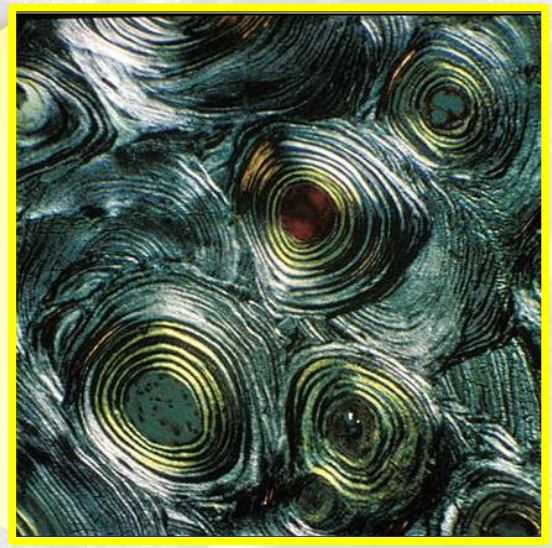
Osteonal Remodeling in Cortical Bone





OSTEOLOGIA NOVA,
OR SOME
NEW OBSERVATIONS
OF THE
BONES,
AND THE
PARTS belonging to them, with the manner of their Accretion, and Nutrition,
By CLOPTON HAVERS, M.D.
Fellow of the Royal Society.
LONDON:

Clopton Havers, 1691



Reprinted from *The Lancet*, Dempster DW, Lindsay R. 1993;341: 797-801. Copyright 2011, with permission from Elsevier.

Osteonal Remodeling in Iguanodon Bone from the Cretaceous Period (~130 M yr)

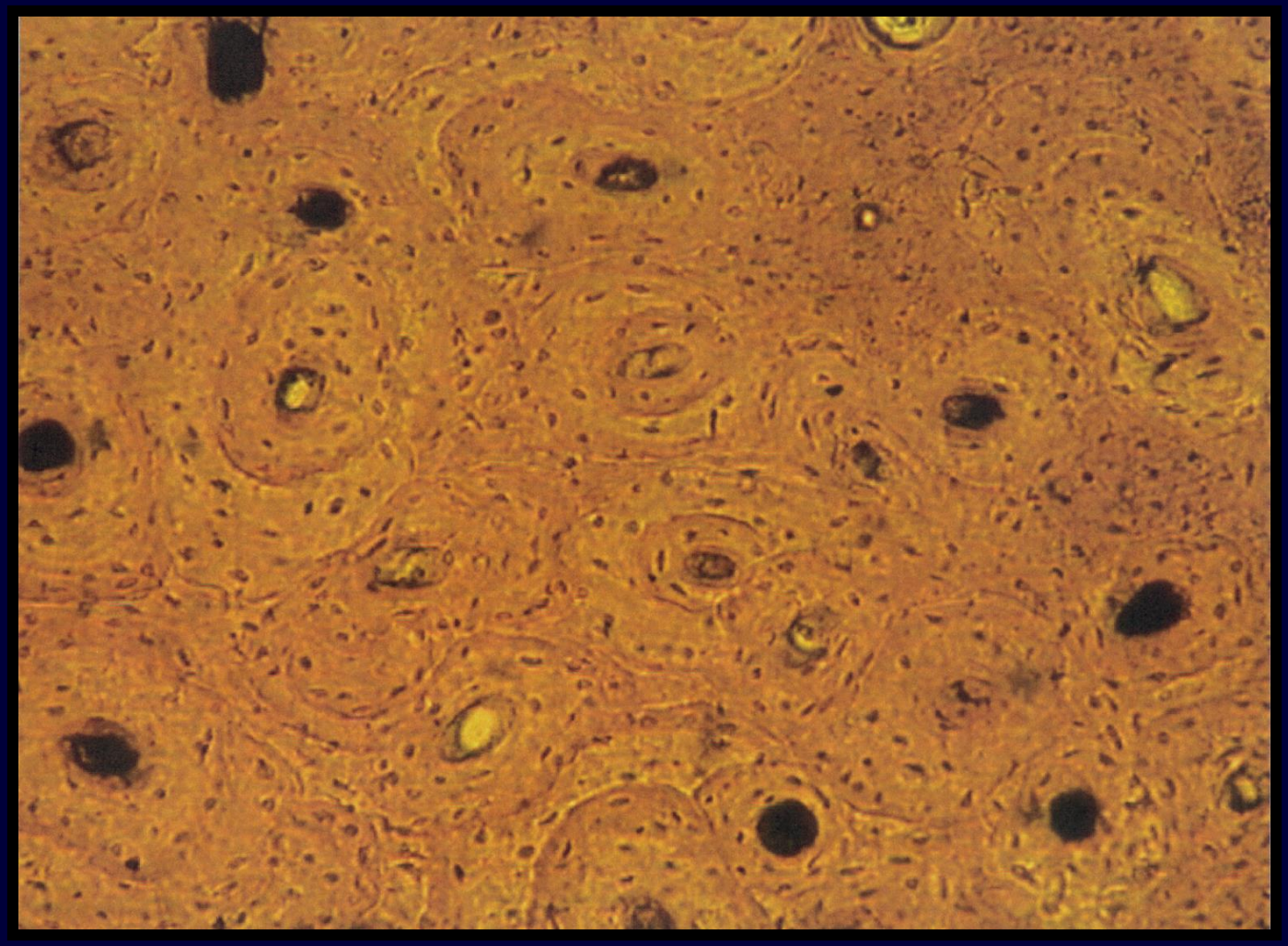


Image courtesy of Tim Skerry and John Currey.

Functions of Remodeling

- Calcium homeostasis (long-term)
- Maintain mechanical strength
- Acid/base balance
- Release growth factors
- Provide reservoir of labile mineral (short-term homeostasis)
- Replace osteocytes
- ???

Functions of Remodeling

- Calcium homeostasis (long-term)
- Maintain mechanical strength
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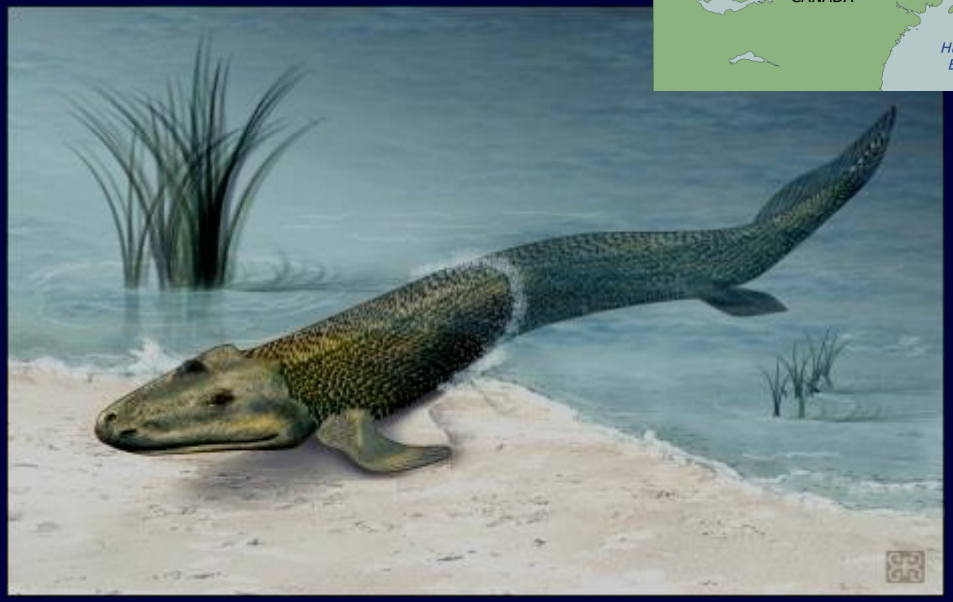
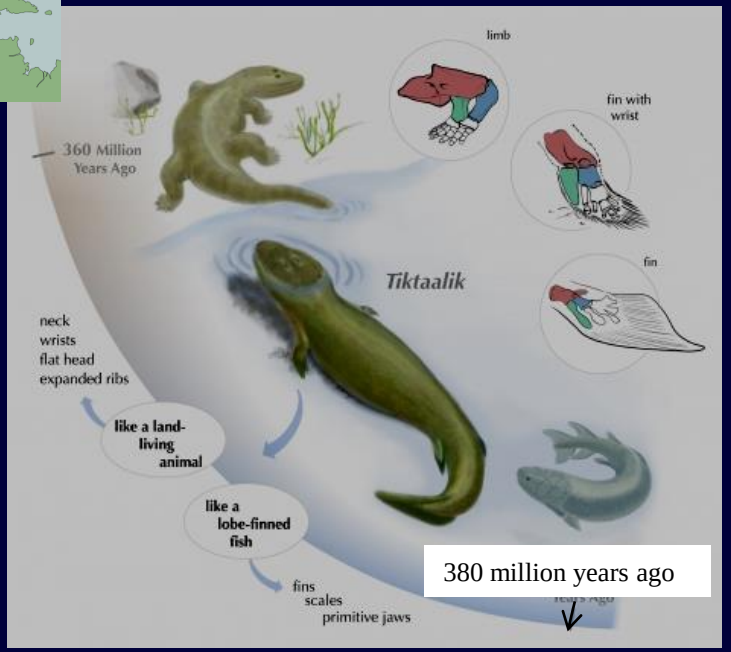
- Replace osteocytes
- ???

Tiktaalik
"From Fins to Limbs"

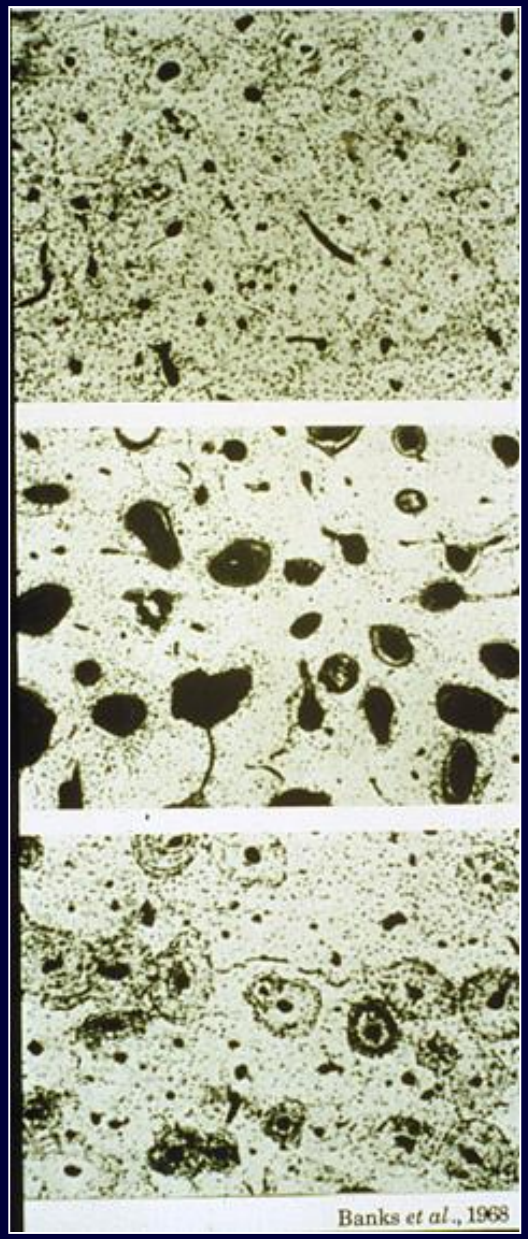
Neil Shubin





National Science Foundation
University of Chicago

Remodeling Participates in Mineral Homeostasis



Before antler formation

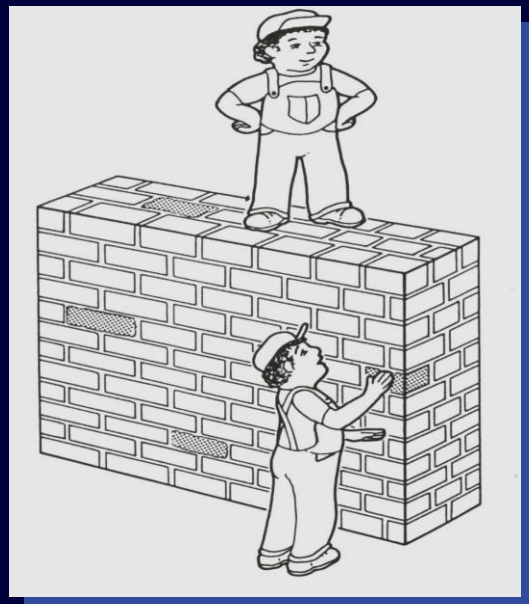
During antler formation

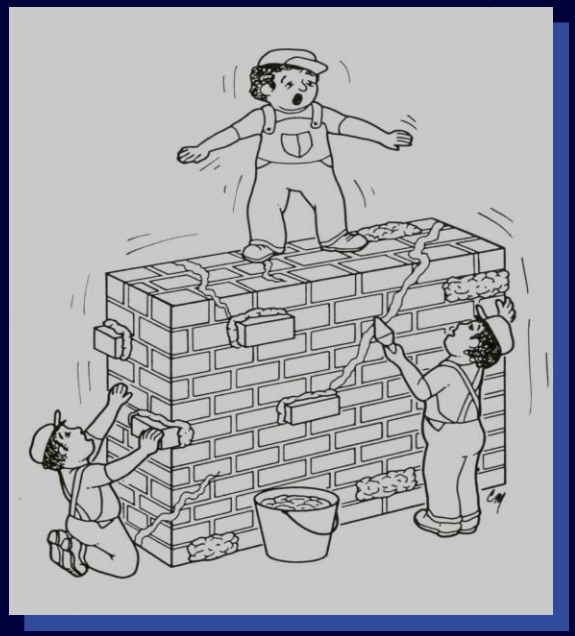
After antler formation

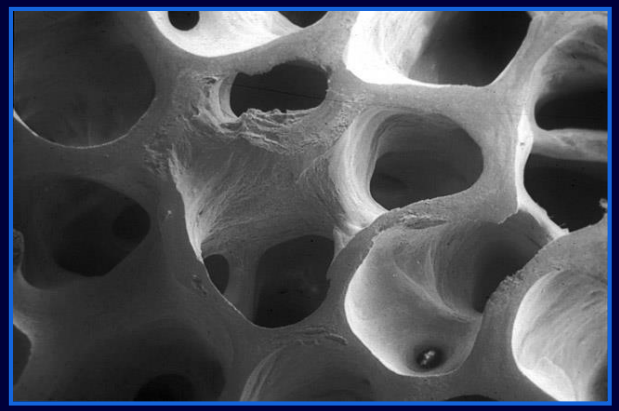
Banks WJ, Jr., et al. *Anat Rec*. 1968;162:387-398.

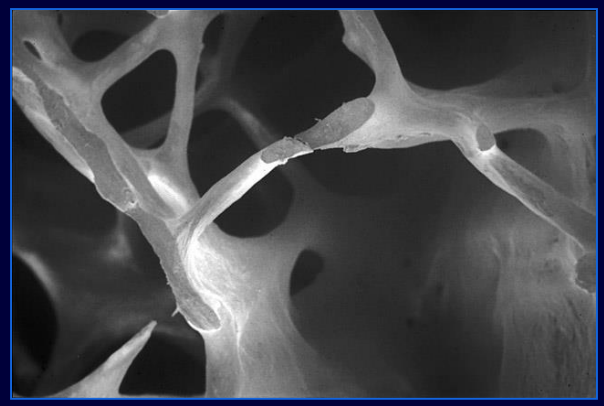
Remodeling Maintains Mechanical Strength

“Excessive Repair is a Risky Business”





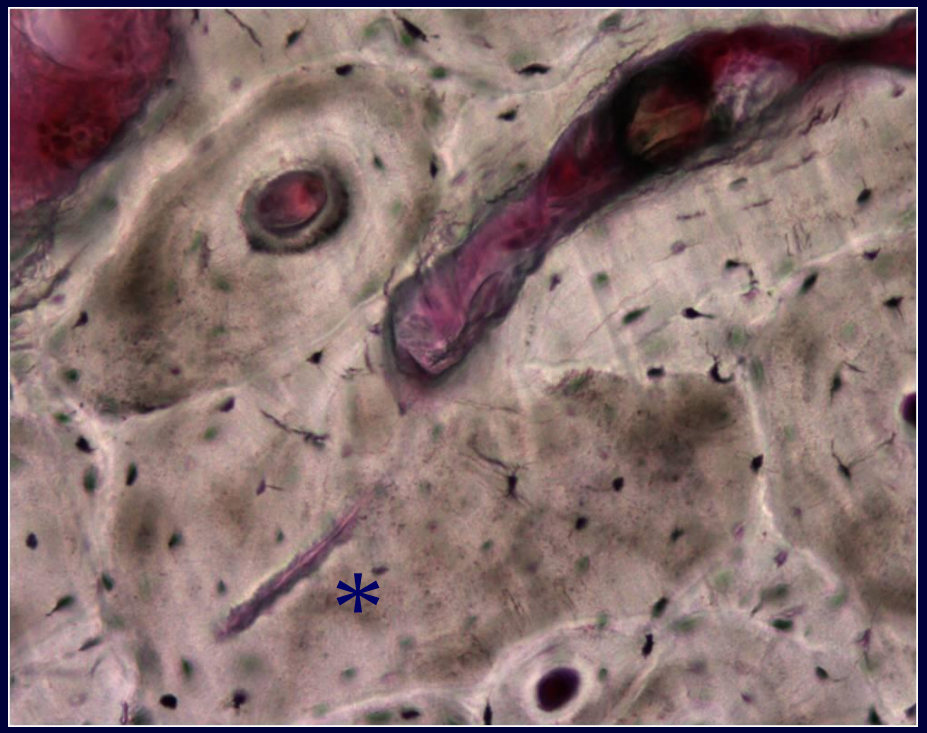




Einhorn TA. *Calcif Tiss* Int. 51:333-339, 1992.

Dempster et al, JBMR 1986;1:15

Targeted Remodeling

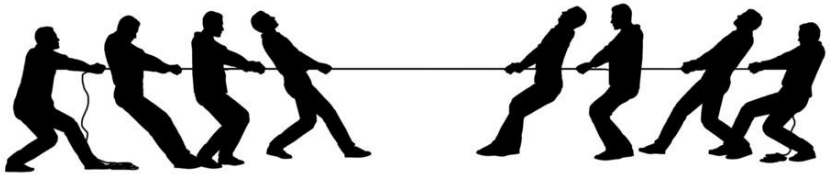


Allen MR and Burr DB. *Clin Rev Bone Miner Metab.* 2008;6:24-30.

- Excessive strain causes regional microdamage
- Targeted remodeling removes a volume of bone that greatly exceeds that of damaged region
- Resulting volume deficit increases strain in neighboring bone

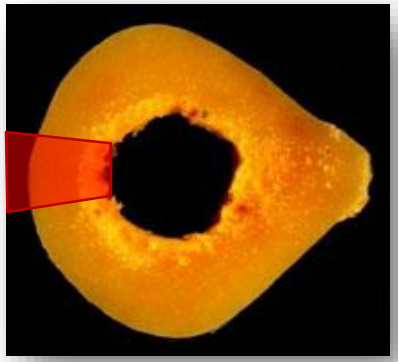
B. Martin, JOR 1995

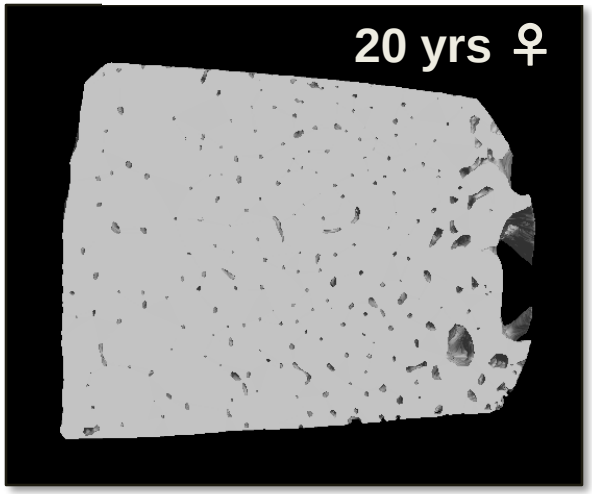
Age-Related Changes in the Human Femoral Midshaft

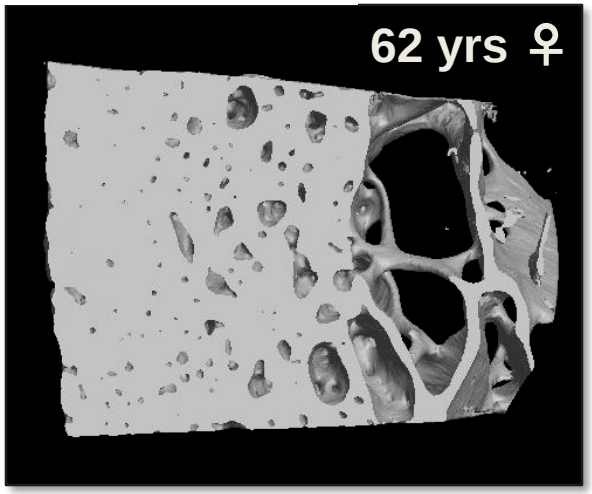


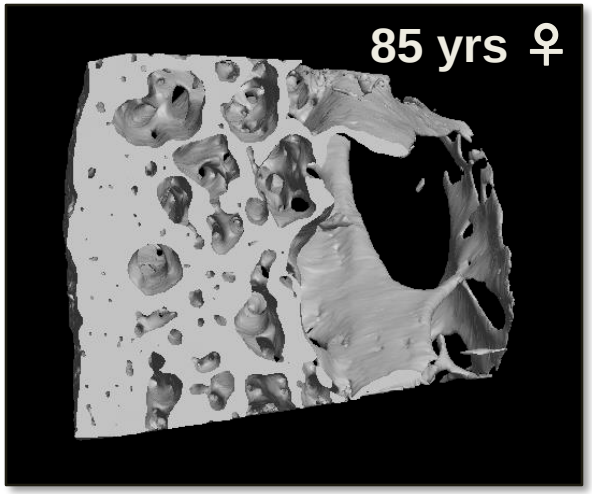
Skeletal Integrity

Calcium Homeostasis









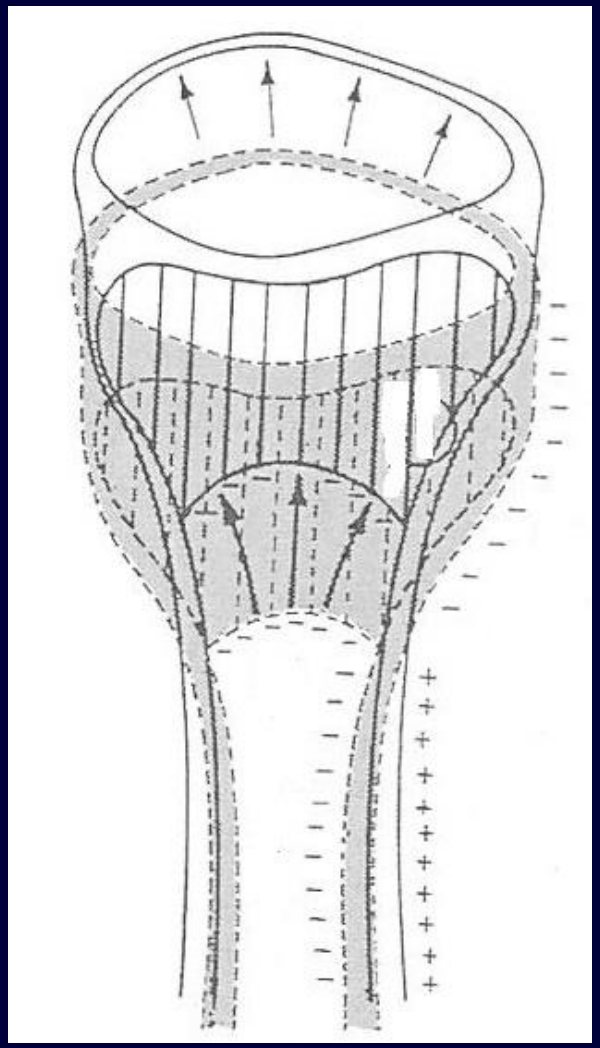
Images courtesy of Dr. David Cooper. University of Saskatchewan.

Bone Modeling

- The shaping of bone segments and their movement through space
  - Defines skeletal development and growth
  - Osteoblasts and osteoclasts need not be anatomically and temporally tethered
  - Abnormalities cause skeletal dysplasias or dismorphysms

Courtesy of Roberto Civitelli, MD

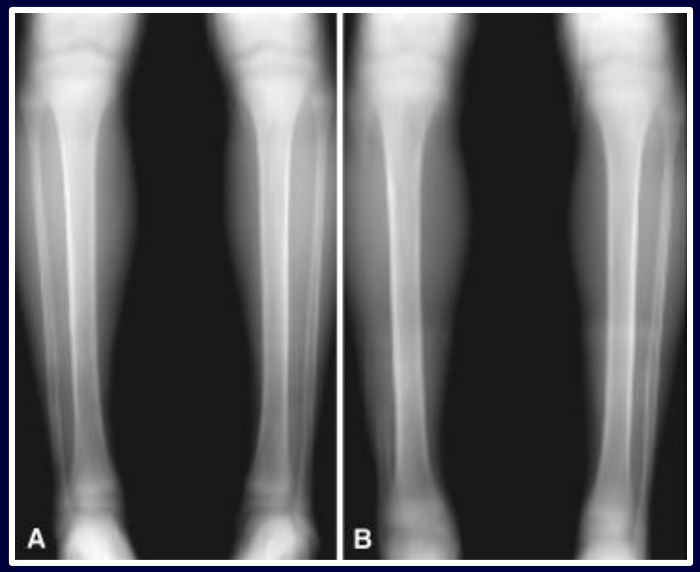
The Erlenmeyer Flask Deformity

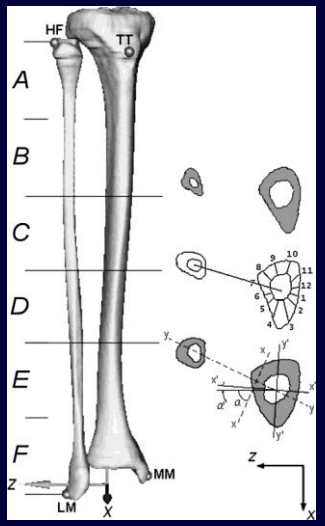


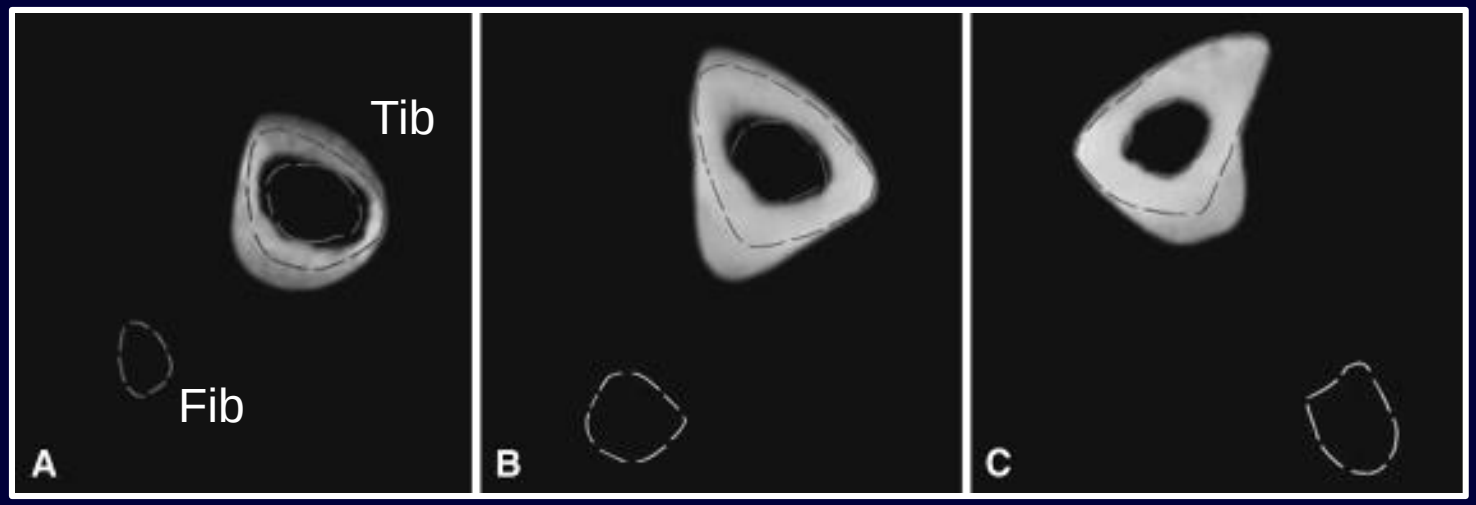
Jean-François Ganghoffer (2011).

Faden et al, *Am. J. Med. Genet*. 2009;149A: 1334–1345.

Tibial Modeling after Fibula Harvesting

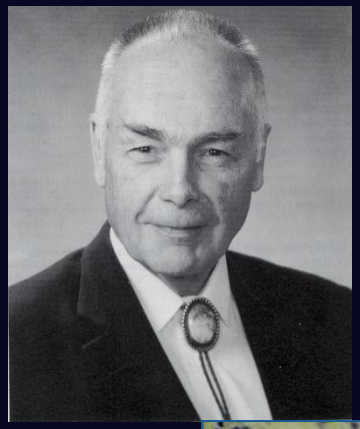






Taddei F, et al, Clin Orthop Relat Res 2009;467:2149

A Touch of Frost



Harold M
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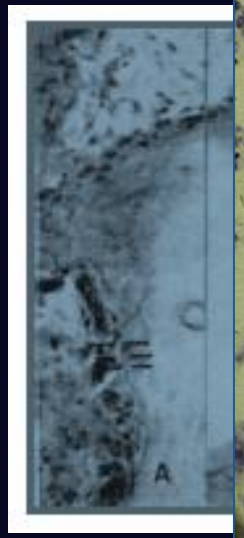
SUGGESTED SEQUENTIAL MODE OF CONTROL OF CHANGES IN CELL BEHAVIOUR IN ADULT BONE REMODELLING

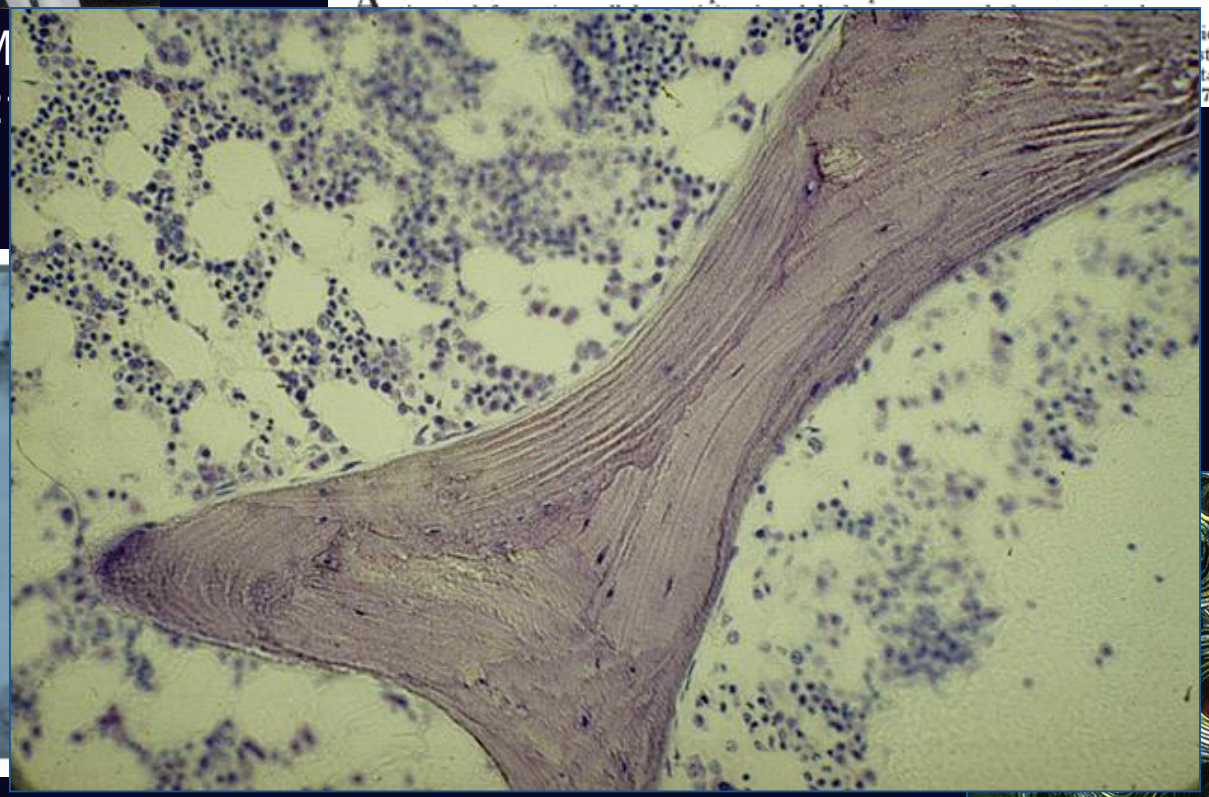
By R. HATTNER, B. N. EPKER and Dr. H. M. FROST

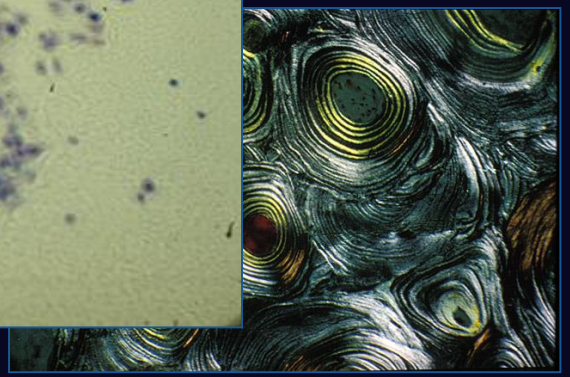
Wayne State University College of Medicine, University of Detroit School of Dentistry, and Henry Ford Hospital, Detroit, Michigan

A SPECIFIC functional relationship between resorp- cement lines reveals whether resorption has or has not

ied out in 150 mineralized
tained with basic fuchsin,
tabolically normal people
75 years[3]. The sexes were

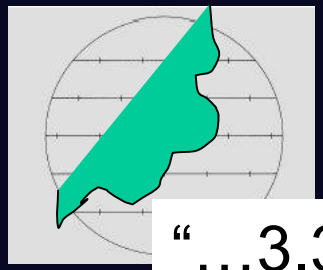


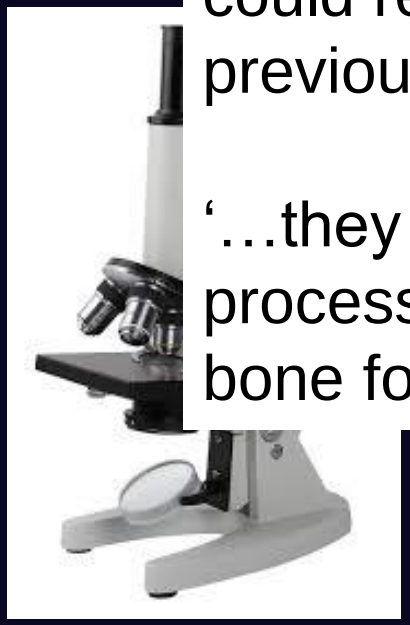




Hattner, Epker and Frost, *Nature* 1965

A Touch of Frost





"…3.3% of the cement lines that were smooth could represent bone being formed without previous resorption…"

'…they could also represent "overflow" of formation processes extending beyond the perimeter of the bone formation preceded by resorption…"

Table 1

Cement lines in trabeculae

Median	No.	Total No.	No. scal- loped	Cement lines
		5,357	5,181	(96.7%)
Standard deviation				0·65
Precision				0·5

75 normal subjects, aged 20-75 (ribs, femoral heads, iliac crests, humeri, and vertebrae)

Hattner, Epker, Frost, *Nature* 1965

Rat Bone: Modeling or Remodeling?

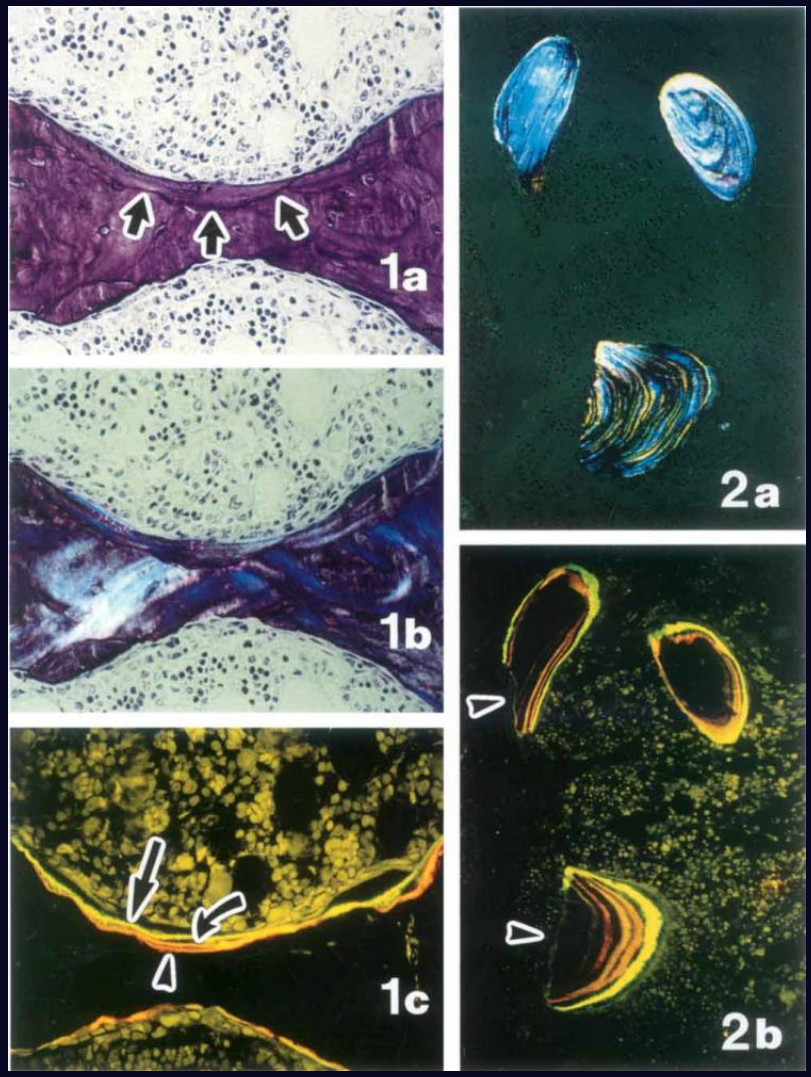
Trabecular and Endocortical Bone Surfaces in the Rat: Modeling or Remodeling?

REINHOLD G. ERBEN
Institute of Physiology, Physiological Chemistry, and Animal Nutrition, University of Munich, Germany

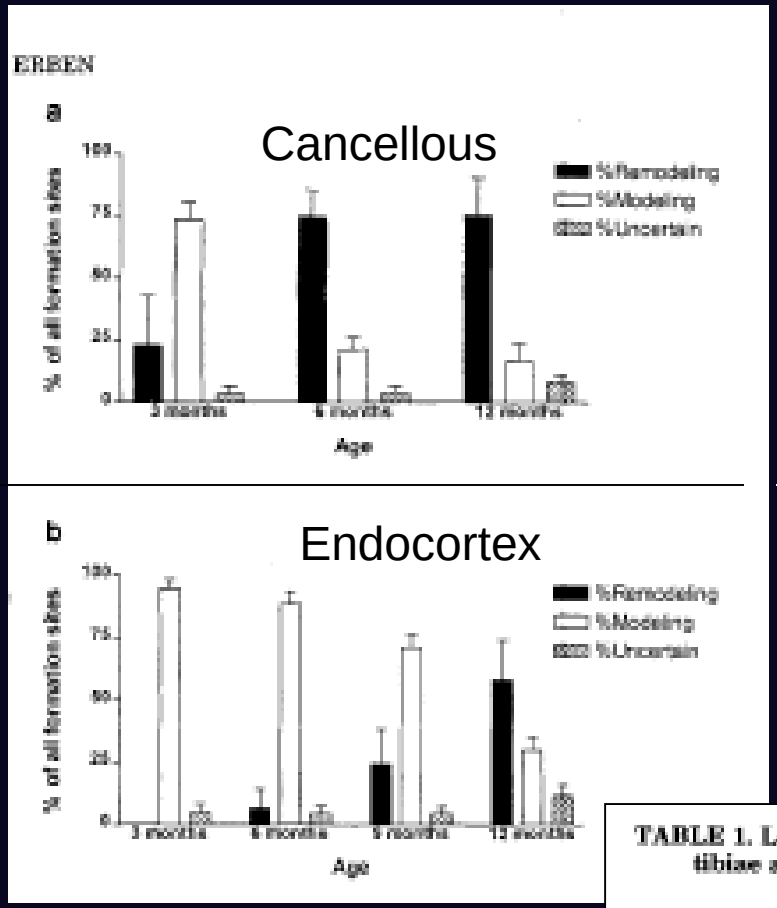
ABSTRACT ***Background:*** **There is conflicting evidence as to whether bone resorption and bone formation are coupled in the site-specific manner that is typical of bone remodeling in the rat. The aim of this study was to elucidate this controversy further by analysis of tibial and vertebral cancellous and endocortical bone in rats of different age groups with a combination of in vivo fluorochrome labeling with cement line staining.**

Erben et al, *Anat Rec* 1996

Remodeling Modeling



Rat Bone: Modeling or Remodeling?



L1 vertebra

Proximal tibial metaphysis

TABLE 1. Longitudinal bone growth in the proximal tibiae and first lumbar vertebrae of female Fischer-344 rats[1]

Age	Proximal tibia (μm/day)	Caudal vertebra (μm/day)	Cranial vertebra (μm/day)
3 months	29.5 ± 1.2	4.10 ± 0.24	2.34 ± 0.20
6 months	9.98 ± 0.62	1.09 ± 0.24	0.74 ± 0.32
9 months	3.30 ± 0.60	n.d.[2]	n.d.
12 months	1.27 ± 0.59	n.d.	n.d.

[1]Means ± SEM, n = 6–7 in each age group.
[2]Not detectable.

Erben et al, *Anat Rec* 1996

Trabecular Mini-modeling in Human Bone

34 normal subjects undergoing THR

Modeling

Remodeling & Modeling

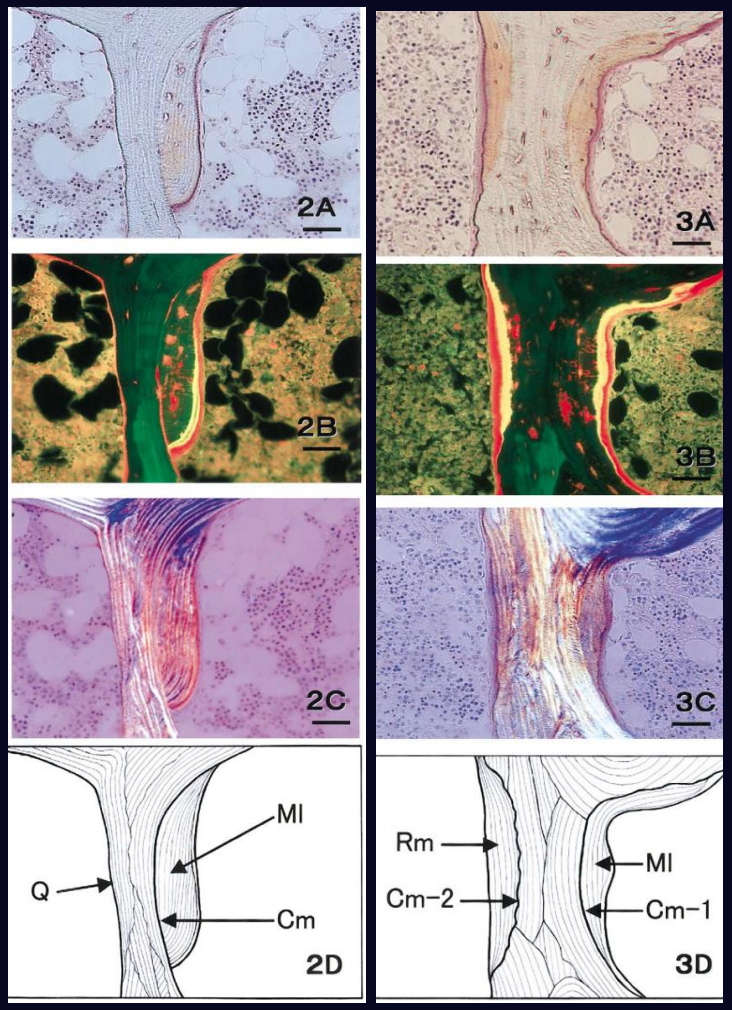


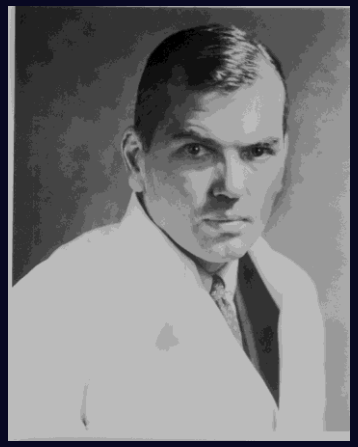
Table 1
Histomorphometric data for minimodeling (me

Variables	In 34 patients
Bone structure	
N.M1/BS (/mm)	0.053 ± 0.085
N.M1/TV (/mm^2)	0.113 ± 0.193
N.M1/BV (/mm^2)	0.906 ± 1.360
M1.BV/TV (%)	0.084 ± 0.156
M1.BV/BV (%)	0.639 ± 1.096
M1.OV/BV (%)	0.152 ± 0.328
M1.OV/OV (%)	9.03 ± 12.59
M1.OV/M1.BV (%)	21.5 ± 8.1
Bone surfaces	
M1.BS/BS (%)	1.46 ± 2.43
M1.OS/BS (%)	1.36 ± 2.29
M1.OS/M1.BS (%)	94.0 ± 30.6

M1 = Mini-modeling

Kobayashi et al, *Bone* 2003

PTH - Discovery of Anabolic Action

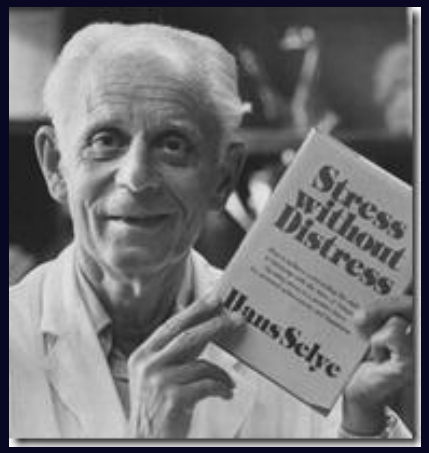


Albright

1929: Bauer, Aub, and Albright

Parathyroid extract increased trabecular number in growing rats

(*J Exp Med*. 1929;49:145-161.)

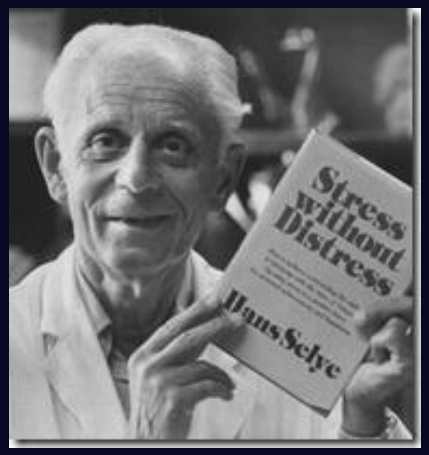


Selye

1932: Selye

Histological evidence that parathyroid extract stimulates bone formation

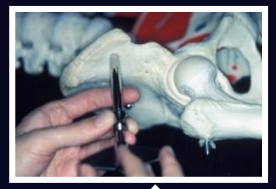
(*Endocrinology*. 1932;16:547-558.)

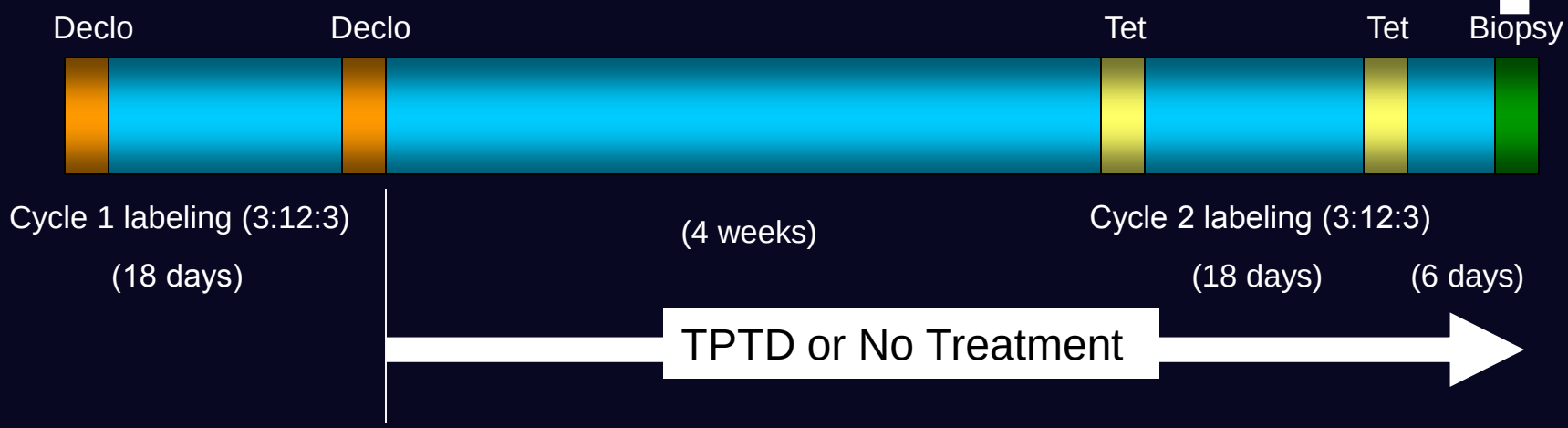


"This experiment shows that *if parathyroid hormone is administered in very small doses it will lead to a stimulation of the osteoblasts and thereby to bone apposition without previous osteoclast formation…"*

Hans Selye, 1932

Quadruple Tetracycline Labeling



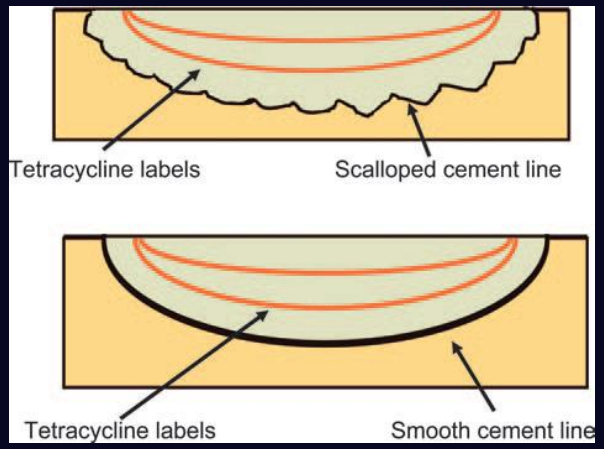


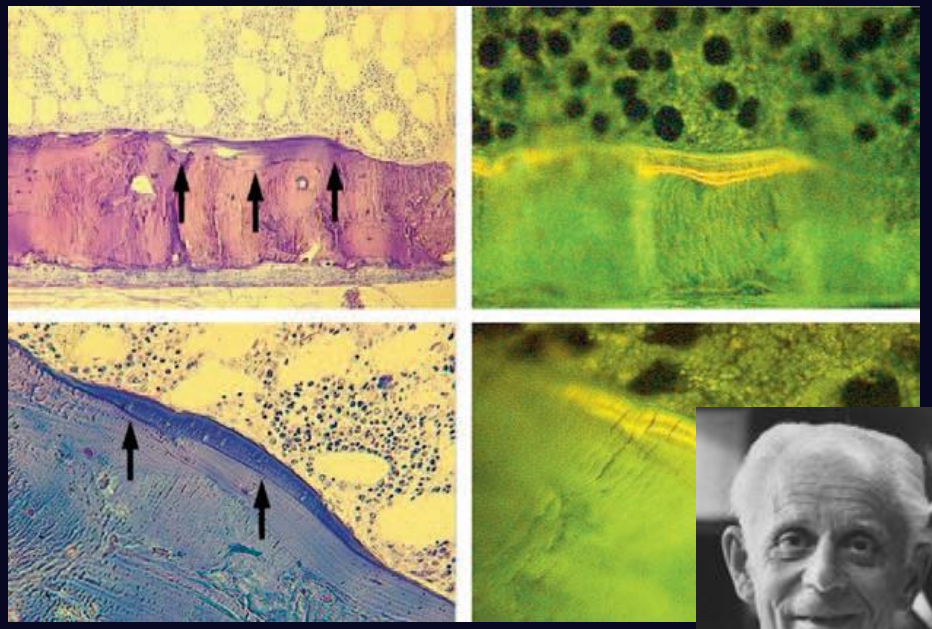
Cycle 1 labeling (3:12:3): Declomycin (Declo) 150 mg, 4 times a day for 3 days. The doses were repeated after 12 days of no antibiotic.

Cycle 2 labeling (3:12:3): Tetracycline (Te) 250 mg, 4 times a day for 3 days. The doses were repeated after 12 days of no antibiotic.

Lindsay R et al, JBMR 2006

Early Effects of Teriparatide on Bone Formation





Remodeling

Modeling

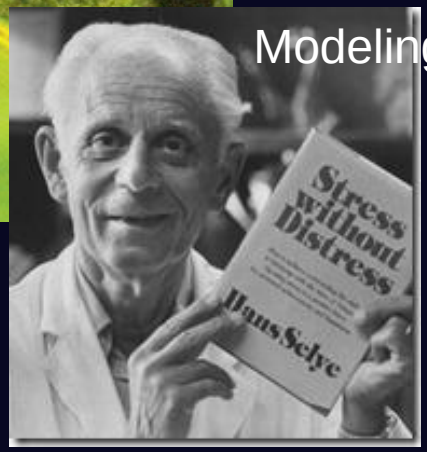


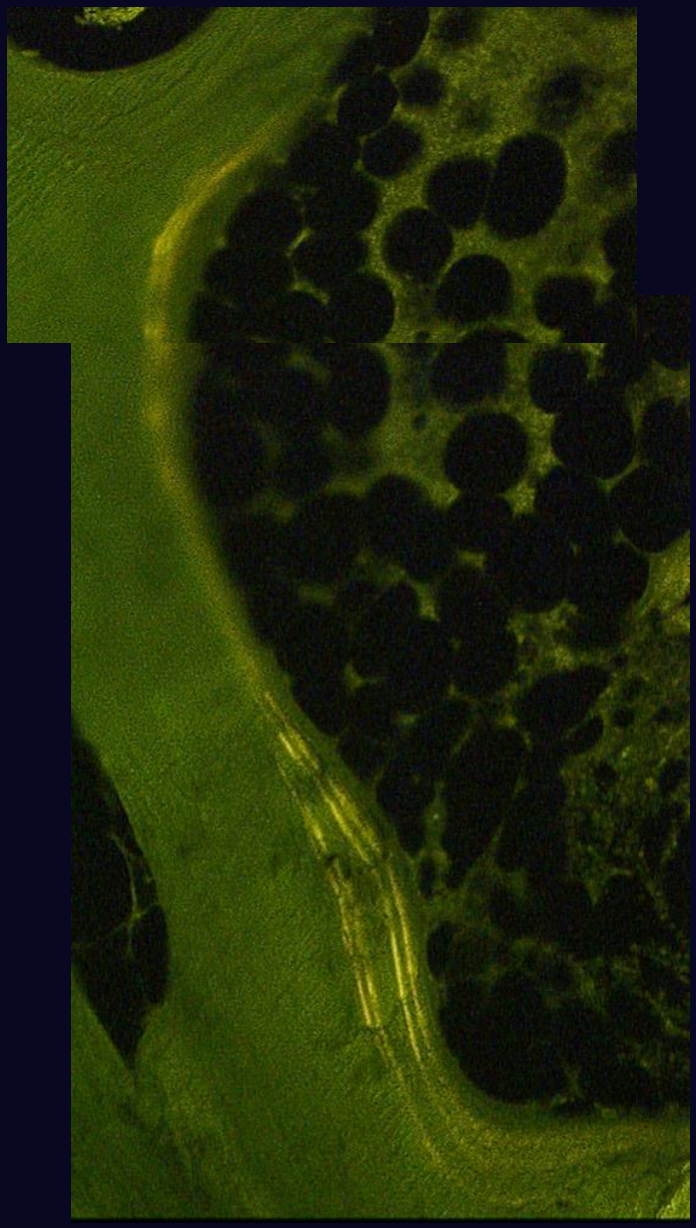
TABLE 4. REMODELING- AND MODELING-BASED FORMATION IN hPTH(1-34)–TREATED PATIENTS AND CONTROLS

	hPTH(1-34) (n = 10)			*Controls (n = 9)*		
Group	*Cn*	*Ec*	*Ct*	*Cn*	*Ec*	*Ct*
Remodeling-based formation (%)	69.2*	77.8	100	100	100	100
Modeling-based formation (%)	30.8*	22.2	0	0	0	0

" …bone apposition without previous osteoclast formation…"

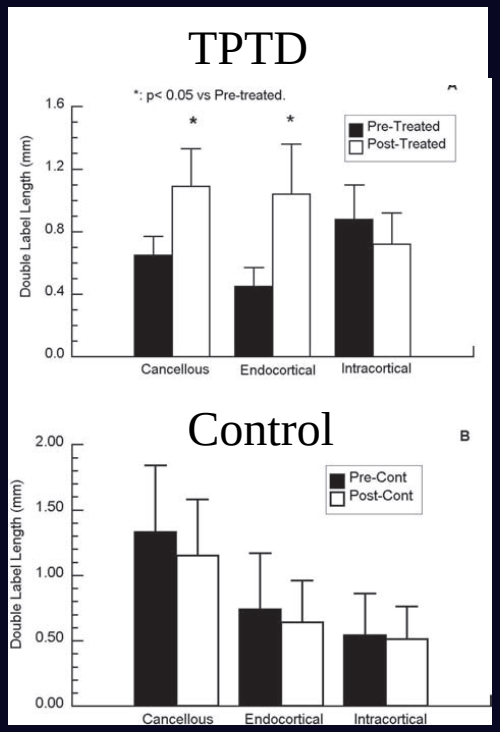
Lindsay R et al, JBMR 2006

Quadruple Labels in Teriparatide-Treated and Control Subjects



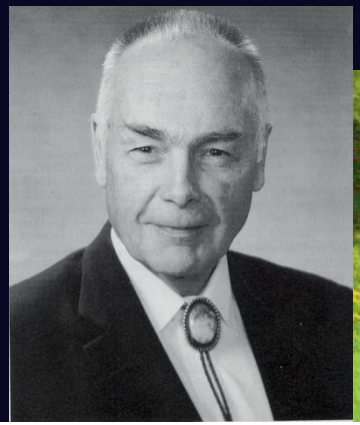
Teriparatide

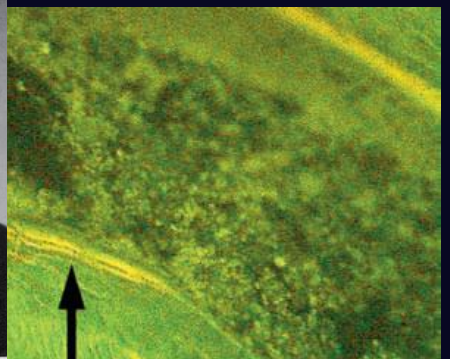
Control



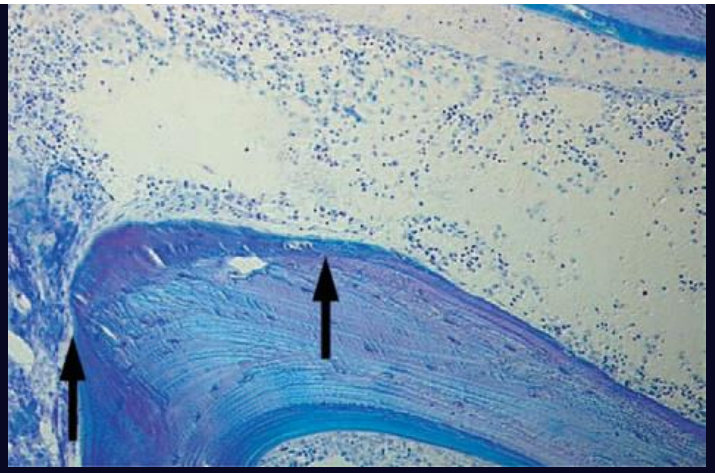
Lindsay R et al, JBMR 2006

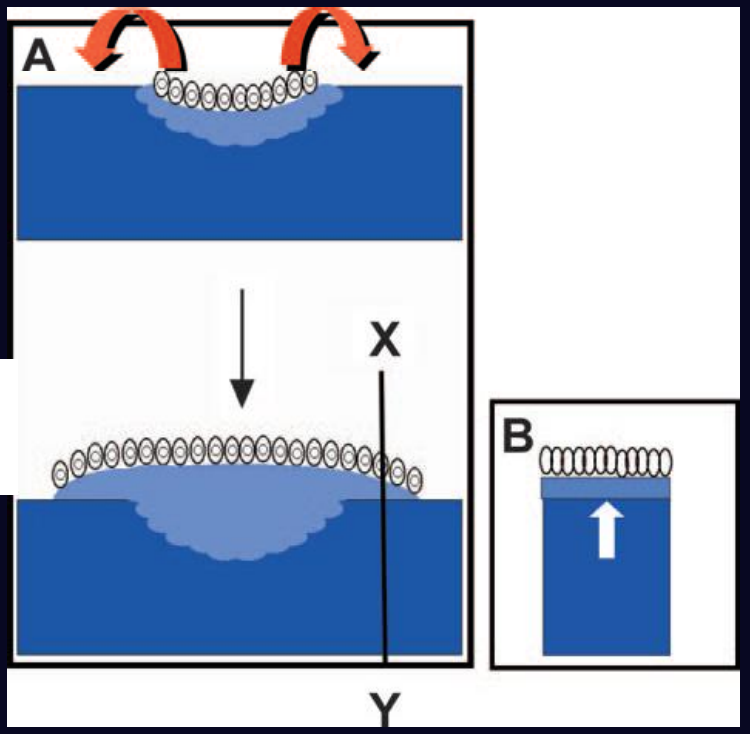
Early Effects of Teriparatide on Bone Formation





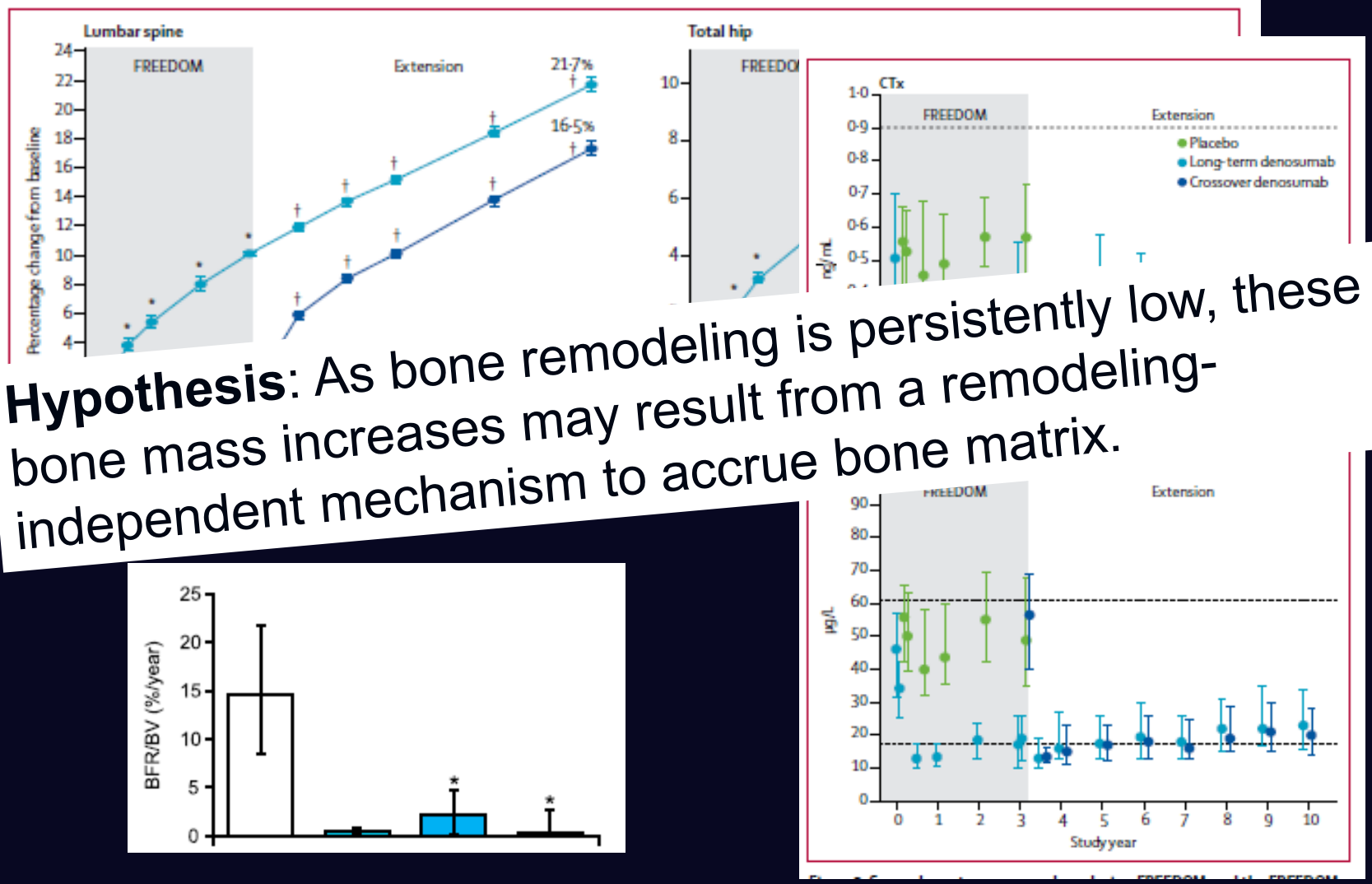
"…they could also represent "overflow" of formation processes…"





Lindsay R et al, JBMR 2006

Long Term Effects of DMAb on BMD



Hypothesis: As bone remodeling is persistently low, these bone mass increases may result from a remodeling-independent mechanism to accrue bone matrix.

Dempster et al, 2018

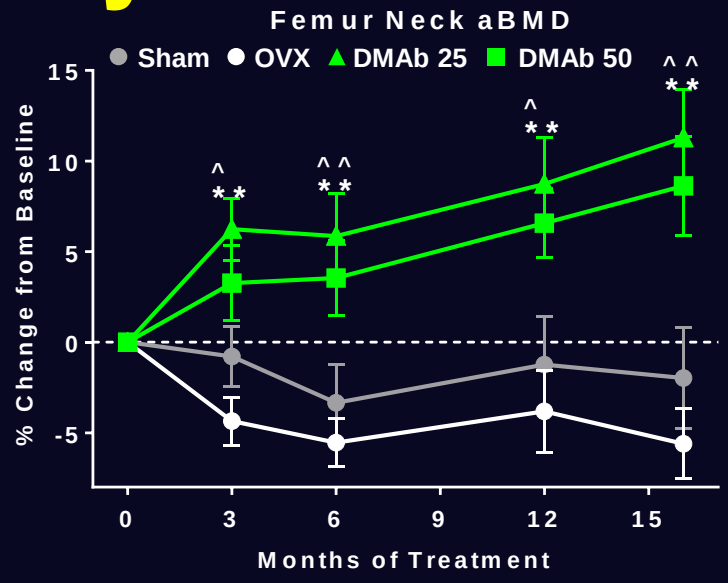
Bone et al, *Lancet Diabetes Endocrinol 2017;* 5: 513–23

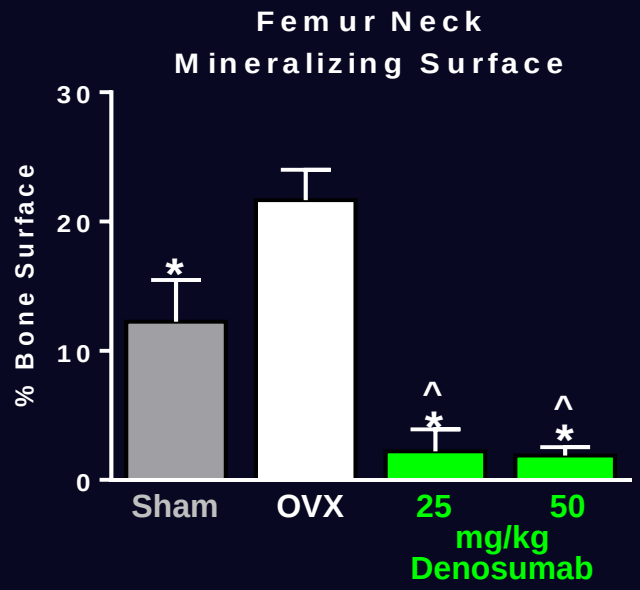
16-Month Bone Quality Study in OVX Cynomolgus Monkeys

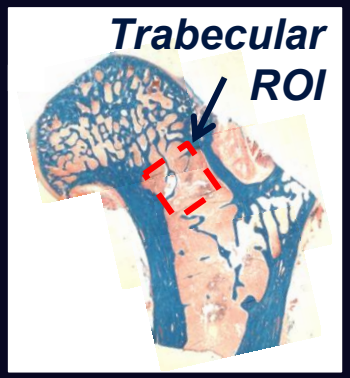
Mature (9+ year old) cynos:

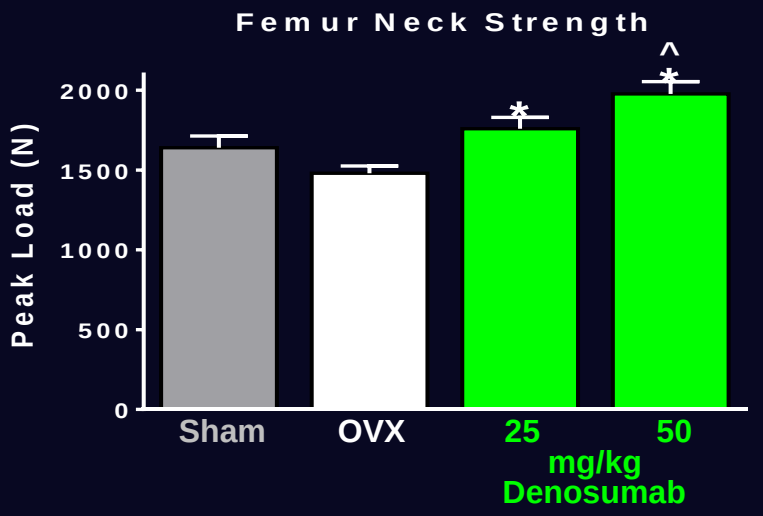
- Group 1: Sham + vehicle
- Group 2: OVX + vehicle
- Group 3: OVX + DMAb (25 mg/kg)
- Group 4: OVX + DMAb (50 mg/kg

(All groups dosed Q4W)





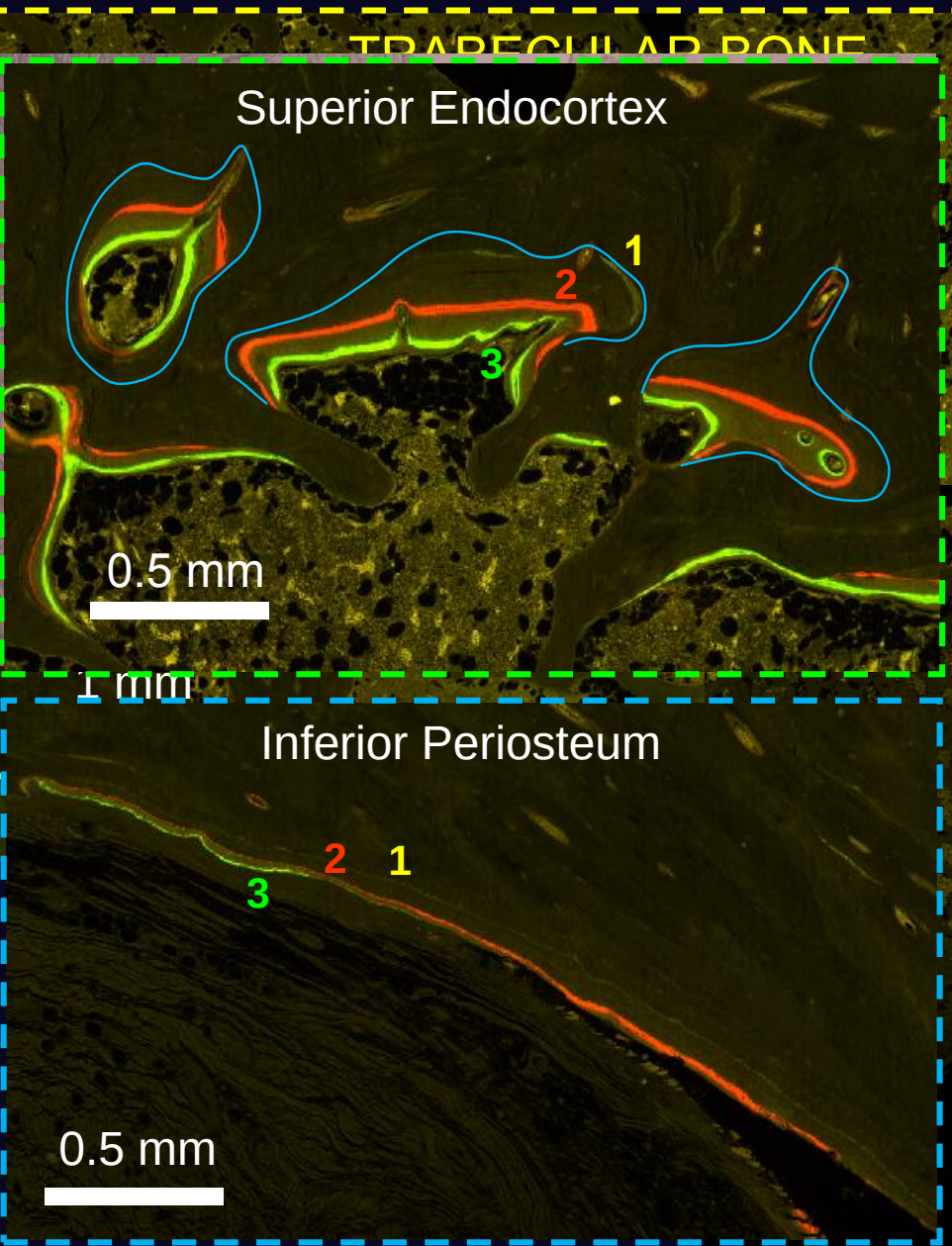




Mean ± SE; n = 14 - 20/group; *$P < 0.05$ vs OVX, ^$P < 0.05$ vs Sham

Kostenuik et al, *Bone* 2011

Fluorochrome Labeling: Femur Neck



Fluorochrome Labels

1. Tetracycline (6 mo)
2. Alizarin (12 mo)
3. Calcein (16 mo)

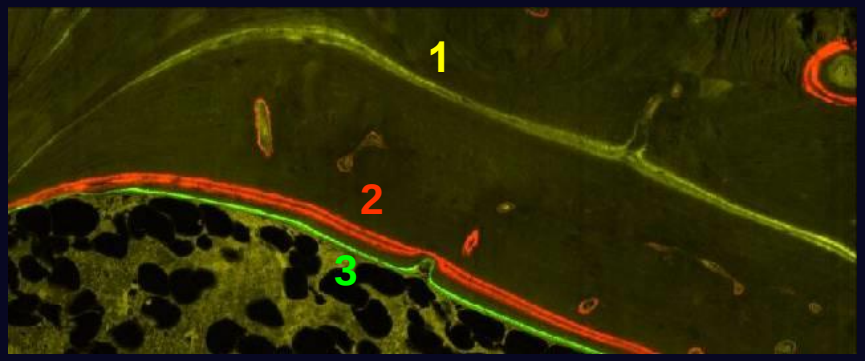
DMAb 25 mg/kg

Ominsky et al, *JBMR* 2015

Additional Examples of Stacked Labels in Sham and DMAb-treated Animals

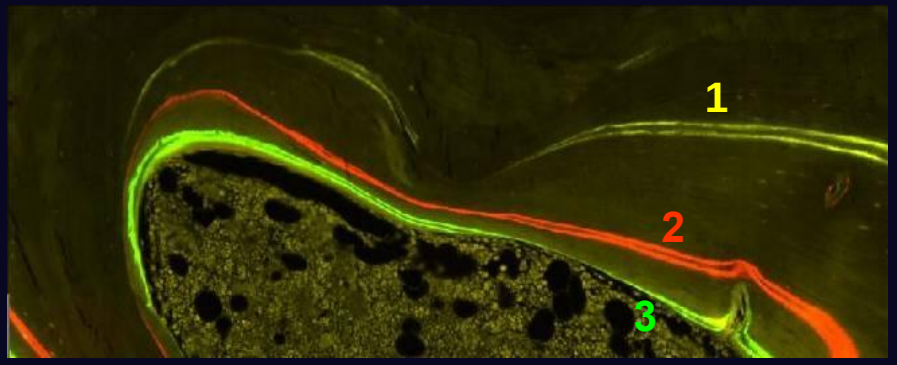
Labels
1. 6 mo
2. 12 mo
3. 16 mo

Sham

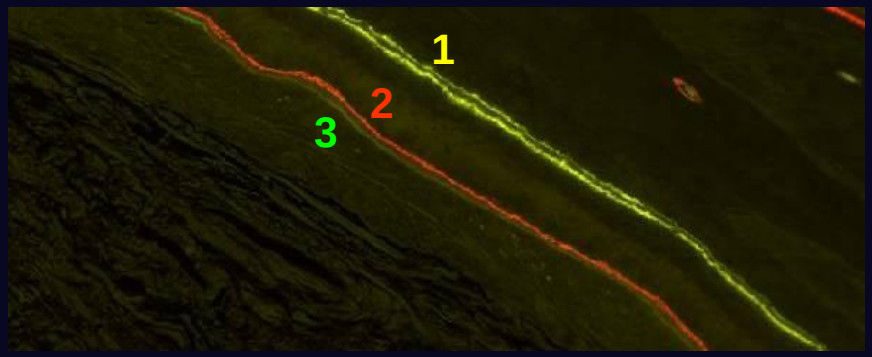


Superior Endocortex

DMAb 25 mg/kg



Superior Endocortex



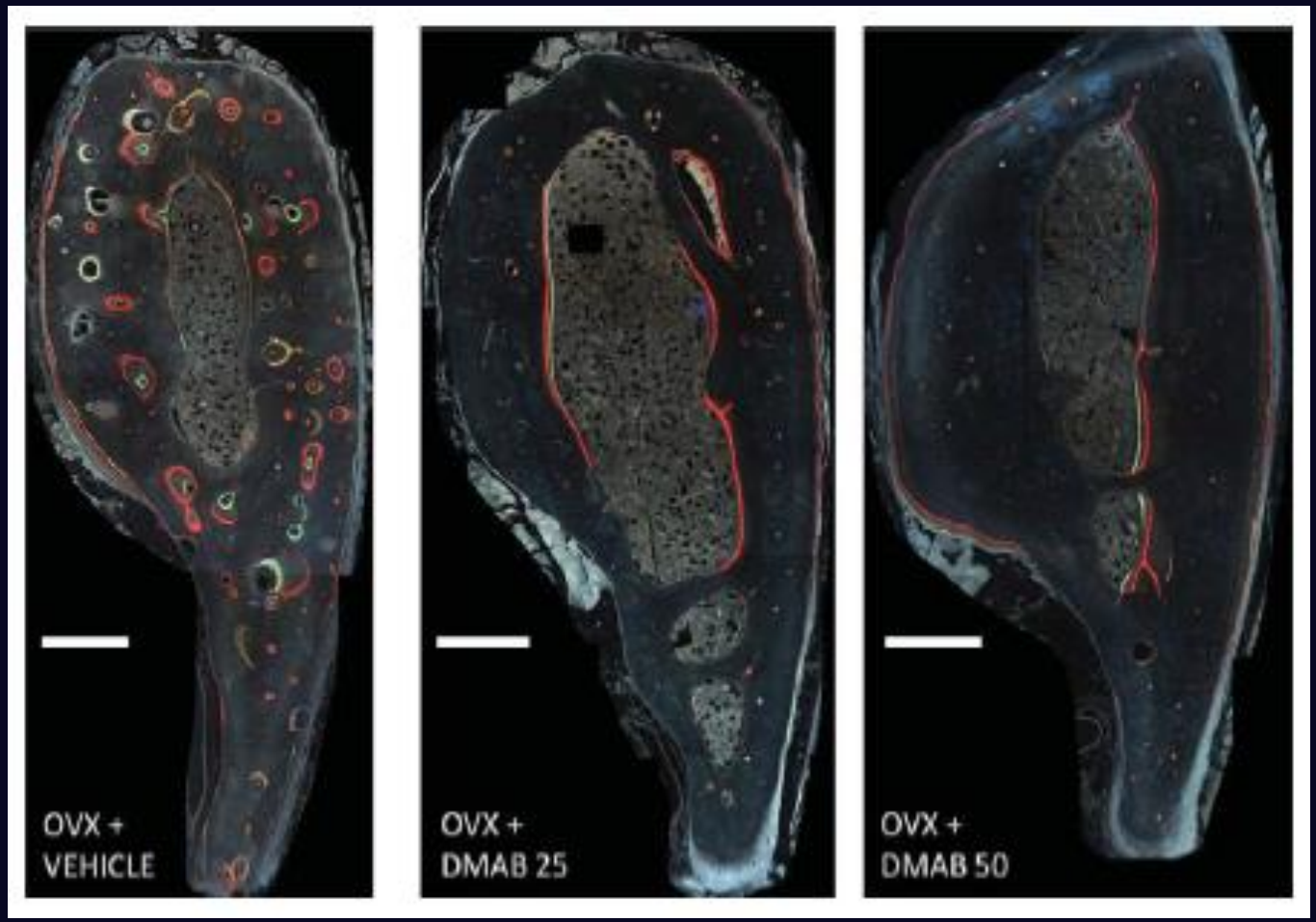
Inferior Periosteum

Inferior Periosteum

Stacked labeling on one or both surfaces was observed in 65% of Sham and 70% of DMAb–treated samples

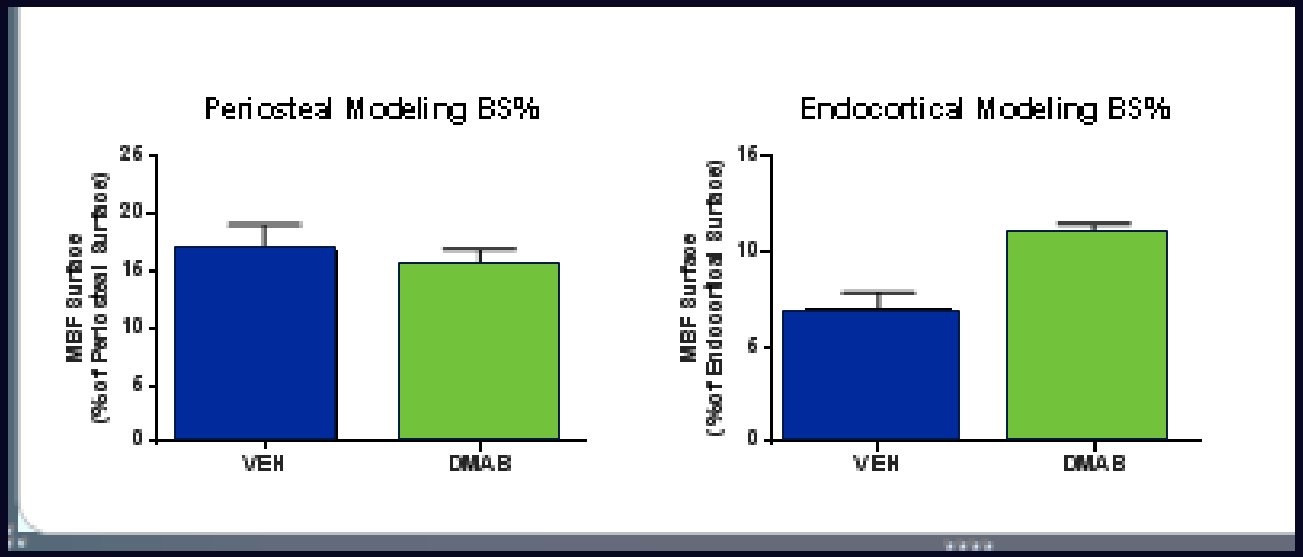
Ominsky et al, *JBMR* 2015

Effects of DMAb on Bone Formation in Cynomolgus Monkeys – 9th Rib



Ominsky et al, *JBMR* 2015

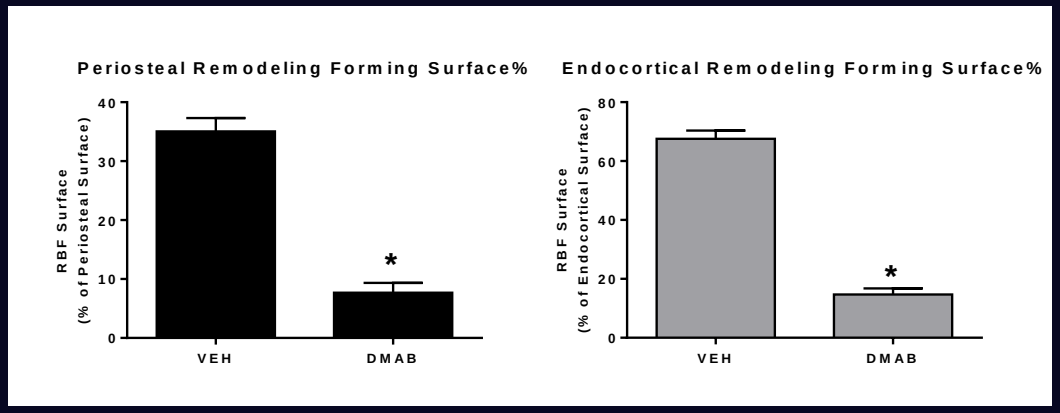
Effects of DMAb on Bone Formation in Cynomolgus Monkeys - Rib

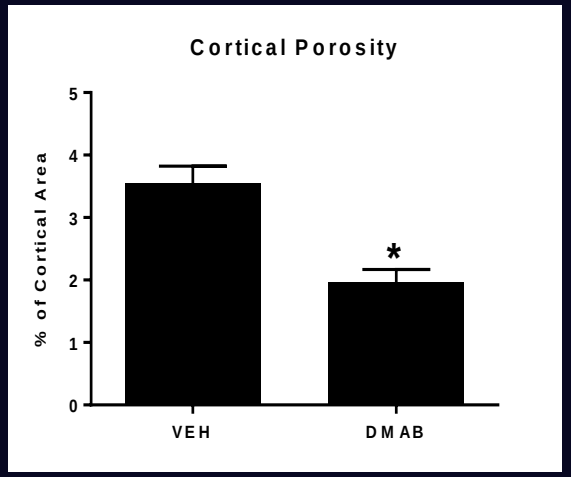


Ominsky et al, *JBMR* 2015

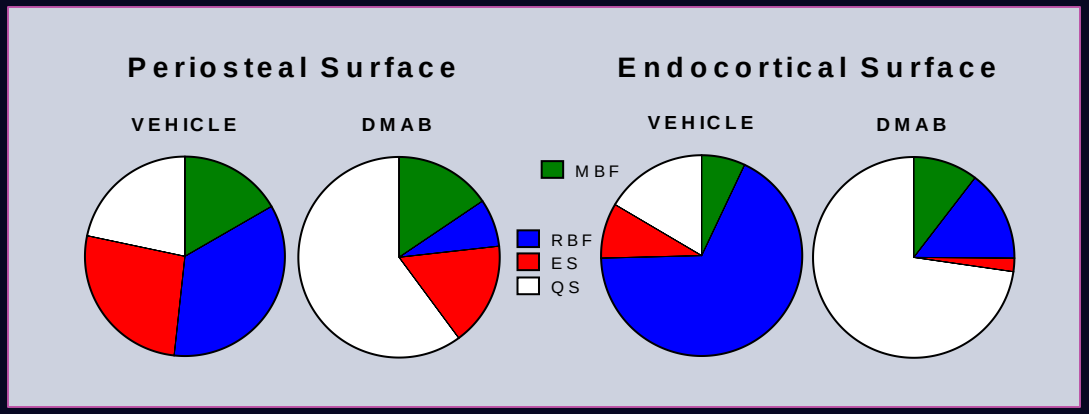
Effects of DMAb on Bone Formation in Cynomolgus Monkeys – 9th Rib

Remodeling-based formation



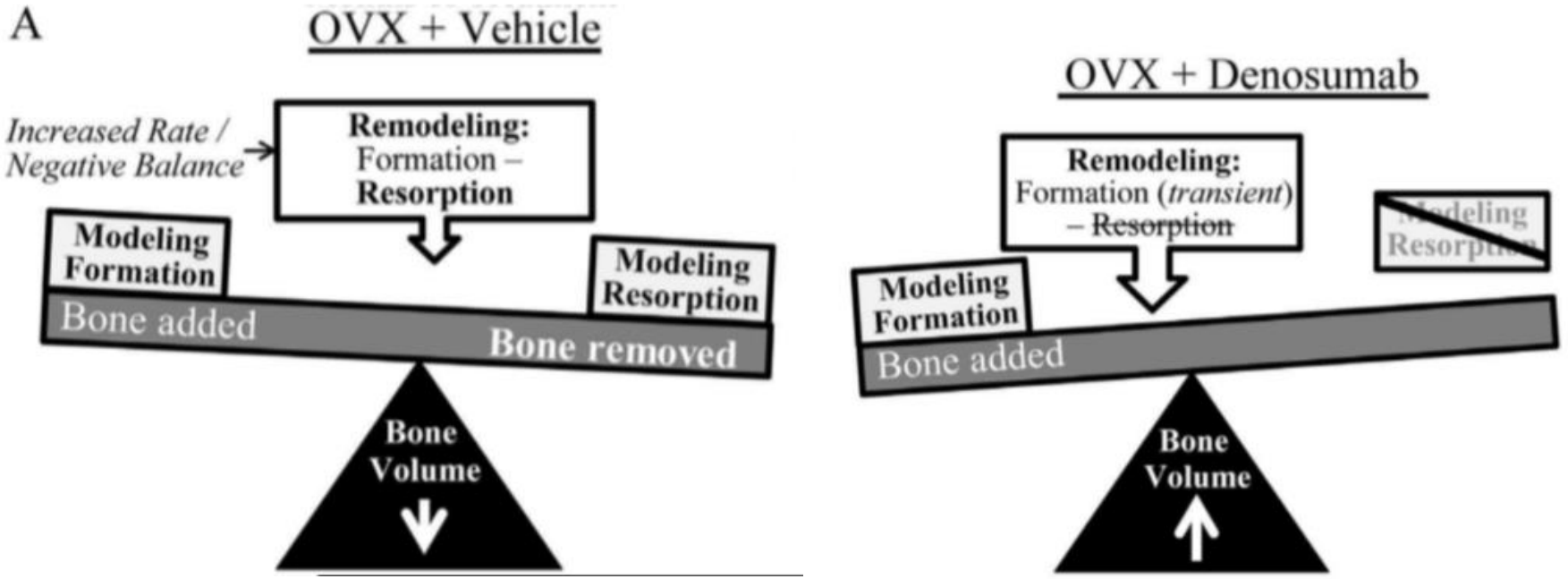


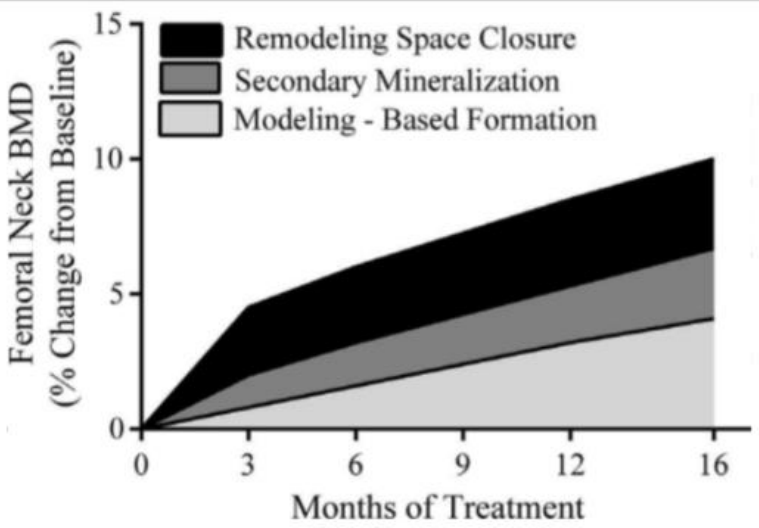
*Mean ± SEM; *p<0.05 vs VEH*



Ominsky et al, *JBMR* 2015

Hypothetical Model of the Potential Contributions to BMD Increases with Denosumab





Ominsky et al *JBMR*, 2015

Effect of TPTD on Human Femoral Neck

ORIGINAL ARTICLE

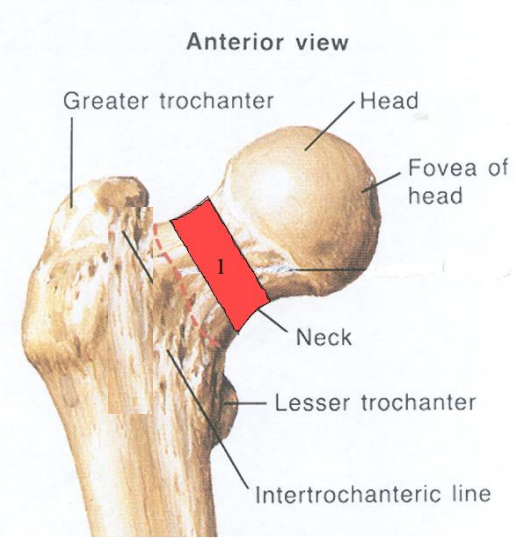
Effect of Teriparatide on Bone Formation in the Human Femoral Neck

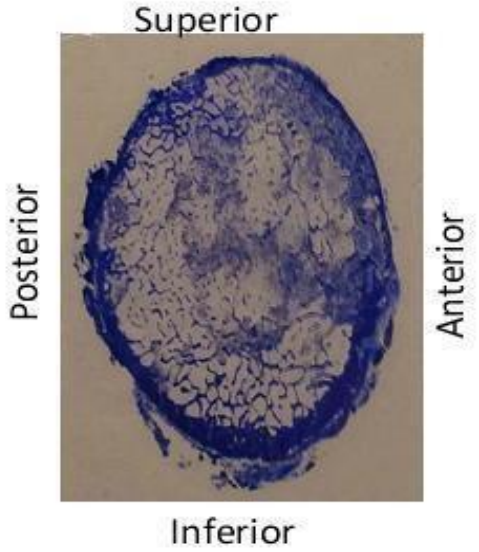
Felicia Cosman, David W. Dempster, Jeri W. Nieves, Hua Zhou, Marsha Zion, Catherine Roimisher, Yvonne Houle, Robert Lindsay, and Mathias Bostrom

Regional Bone Center, Helen Hayes Hospital (F.C., D.W.D., J.W.N., H.Z., M.Z., C.R., R.L.), West Haverstraw, New York 10993; Department of Medicine (F.C., R.L.), Department of Pathology (D.W.D.), and Department of Epidemiology (J.W.N.), Columbia University, New York, New York 10032; and Department of Orthopedics (Y.H., M.B.), Hospital for Special Surgery, New York, New York 10021

Purpose: Teriparatide (TPTD) improves bone mass and microstructure resulting in reduced risk of vertebral and nonvertebral fractures. However, hip bone mineral density improvements are modest and there are no data confirming that TPTD reduces hip fracture risk. To study the effects of TPTD on the proximal femur, we performed a double-blind trial of TPTD vs placebo (PBO) in patients with osteoarthritis from whom femoral neck (FN) samples were obtained at total hip replacement (THR) surgery.

Methods: Participants were randomly assigned to receive TPTD or PBO for an average of 40 days before THR. Double tetracycline labeling was initiated 21 days prior to THR to allow histomorphometric assessment of bone formation. During the THR, an intact sample of the FN was procured, fixed, and sectioned transversely. Serum levels of bone turnover markers were measured at baseline and during the THR. Standard histomorphometric parameters were measured and calculated on four bone envelopes (cancellous, endocortical, intracortical, and periosteal). The primary outcome measure was bone formation rate/bone surface (BFR/BS).

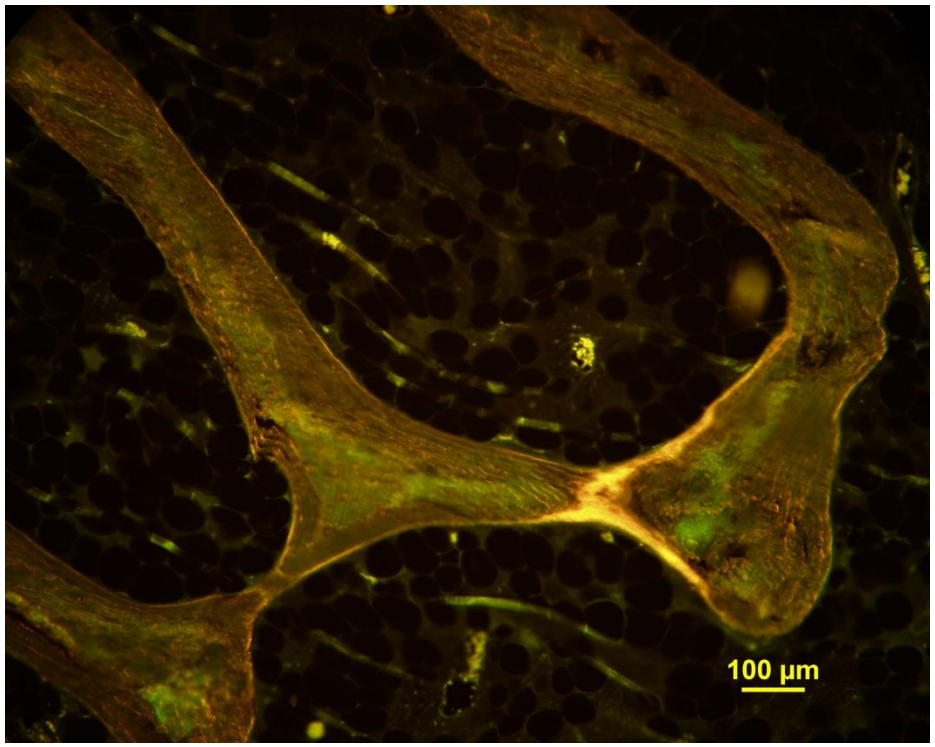




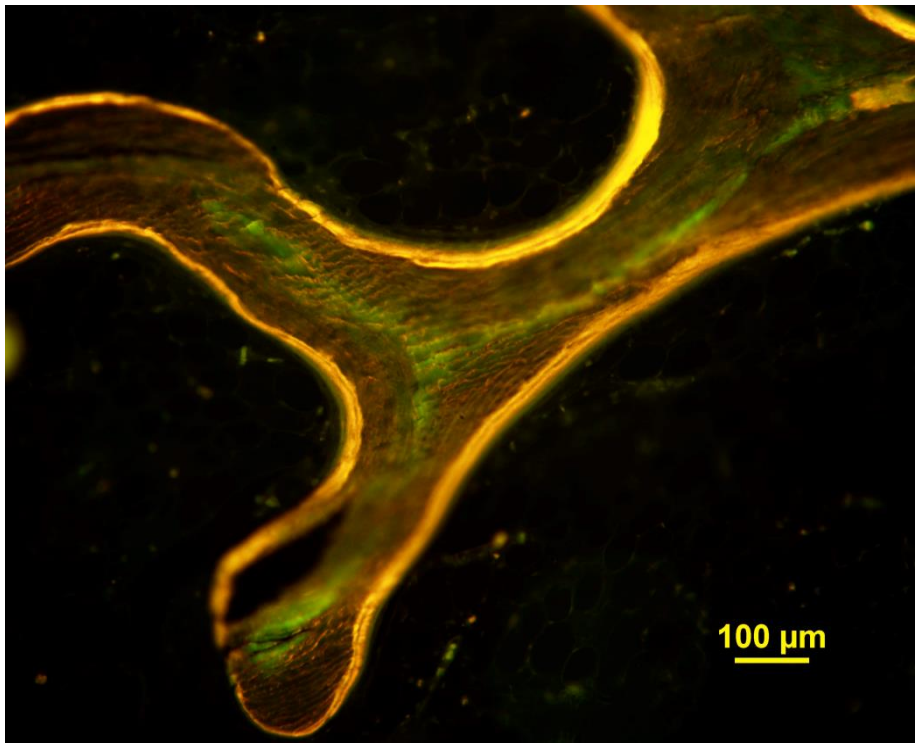
J Clin Endocrinol Metab 101: 1498 –1505, 2016

Tetracycline Labels with PBO and TPTD in Human Femoral Neck

PBO



TPTD



J Clin Endocrinol Metab 101: 1498 –1505,

Effect of DMAb Treatment on Bone Remodeling and Modeling in the Human Femoral Neck

ORIGINAL ARTICLE

JBMR®

Remodeling- and Modeling-Based Bone Formation With Teriparatide Versus Denosumab: A Longitudinal Analysis From Baseline to 3 Months in the AVA Study

David W Dempster,[1,2] Hua Zhou,[1] Robert R Recker,[3] Jacques P Brown,[4] Christopher P Recknor,[5] E Michael Lewiecki,[6] Paul D Miller,[7] Sudhaker D Rao,[8] David L Kendler,[9] Robert Lindsay,[1,2] John H Krege,[10] Jahangir Alam,[10] Kathleen A Taylor,[11] Thomas E Melby,[12] and Valerie A Ruff[11]

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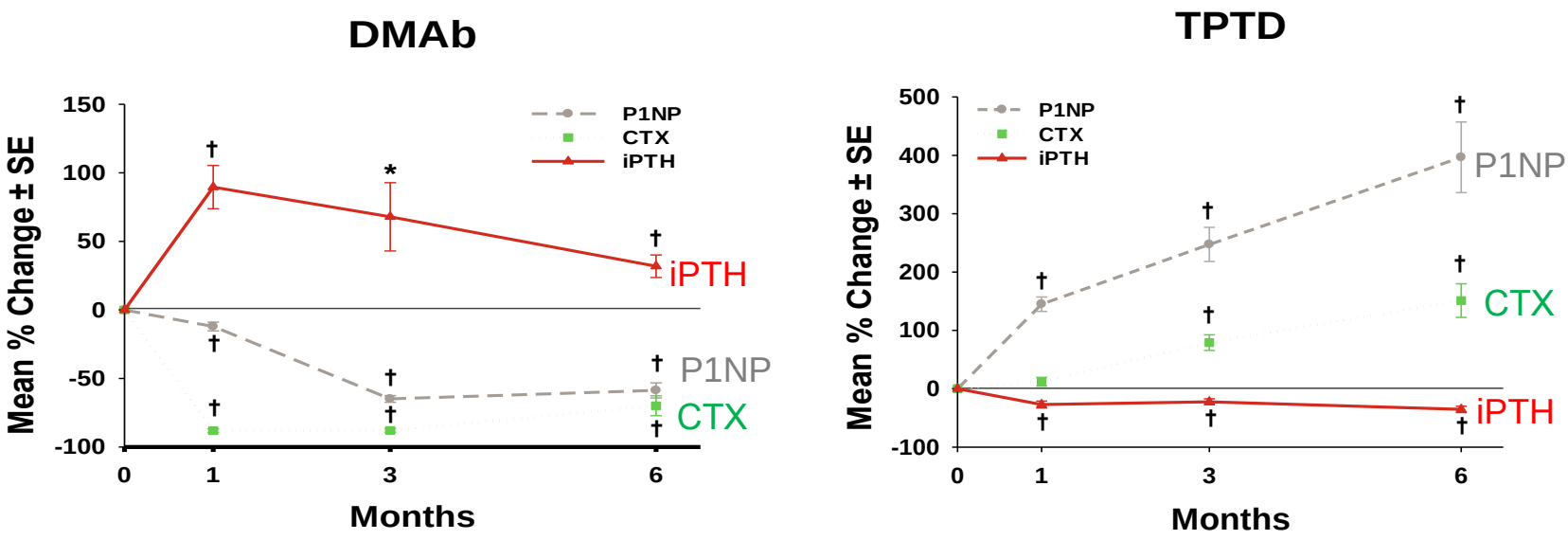
[2]Department of Pathology and Cell Biology, College of Physicians and Surgeons of Columbia University, New York, NY, USA
[3]Department of Medicine, Division of Endocrinology, School of Medicine, Creighton University, Omaha, NE, USA
[4]Rheumatology and Bone Diseases Research Group, CHU de Québec (CHUL), Research Centre and Department of Medicine, Laval University, Quebec City, Canada
[5]United Osteoporosis Centers, Gainesville, GA, USA
[6]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA
[7]Department of Medicine, Colorado Center for Bone Research, Lakewood, CO, USA
[8]Bone & Mineral Research Laboratory, Henry Ford Hospital, Detroit, MI, USA
[9]Department of Medicine (Endocrinology), University of British Columbia, Vancouver, Canada

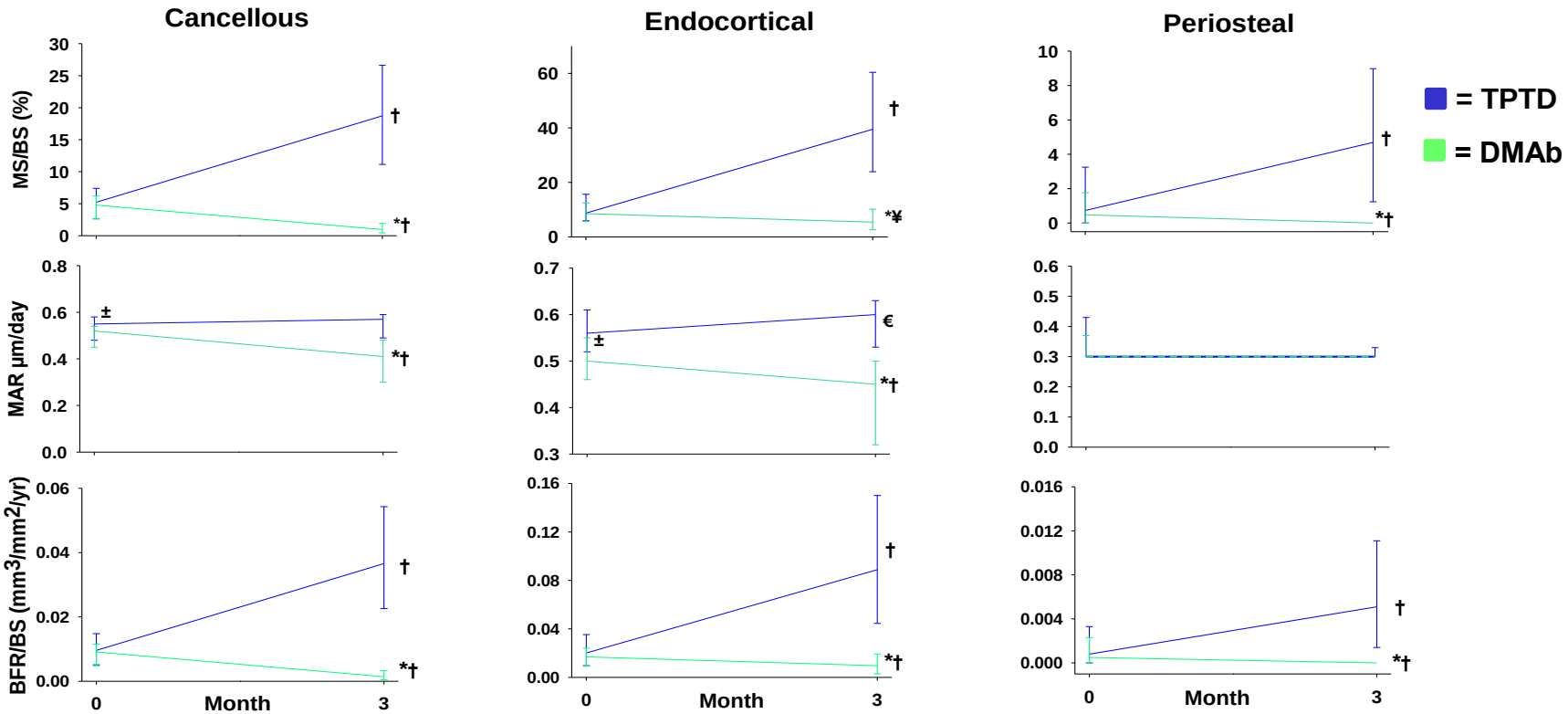
Intact PTH and Bone Turnover Markers



*p=0.01 for within treatment group comparison from baseline to each time point using t-test
†p<0.001 for within treatment group comparison from baseline to each time point
Abbreviations: iPTH = intact parathyroid hormone; P1NP = procollagen type 1 N-terminal propeptide; CTX = carboxyterminal cross-linking telopeptide of type 1 collagen; SE = standard error

Dempster et al. *J Clin Endocrinol Metab*. 2016;101(4):1353-1363

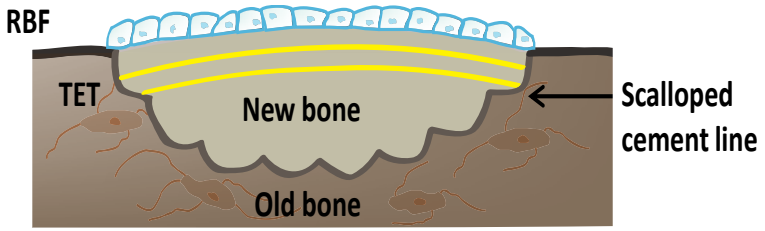
Results – Histomorphometry



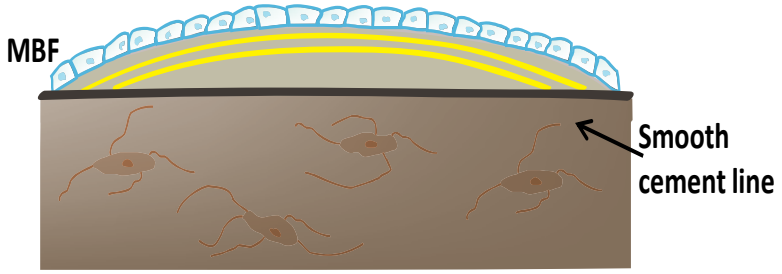
Values are medians with interquartile range. *p<0.001 for between treatment group comparison at baseline or Month 3 in each envelope †p<0.001 for within treatment group comparison from baseline to Month 3 in each envelope ¥p<0.01 for within treatment group comparison from baseline to Month 3 in each envelope. ±p<0.05 for between treatment group comparison at baseline or Month 3 in each envelope.
€p<0.05 for within treatment group comparison from baseline to Month 3 in each envelope. Between group testing by Wilcoxon rank-sum test; within group by Wilcoxon signed-rank test.
Abbreviations: MS/BS = mineralizing surface/bone surface; MAR = mineral apposition rate; BFR/BS = bone formation rate per bone surface

Cartoon Illustrating Three Types of Bone Formation

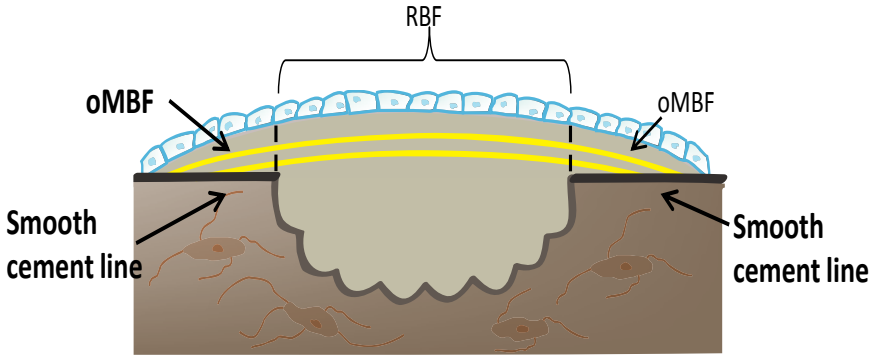
RBF = Remodeling-based formation



MBF = Modeling-based formation

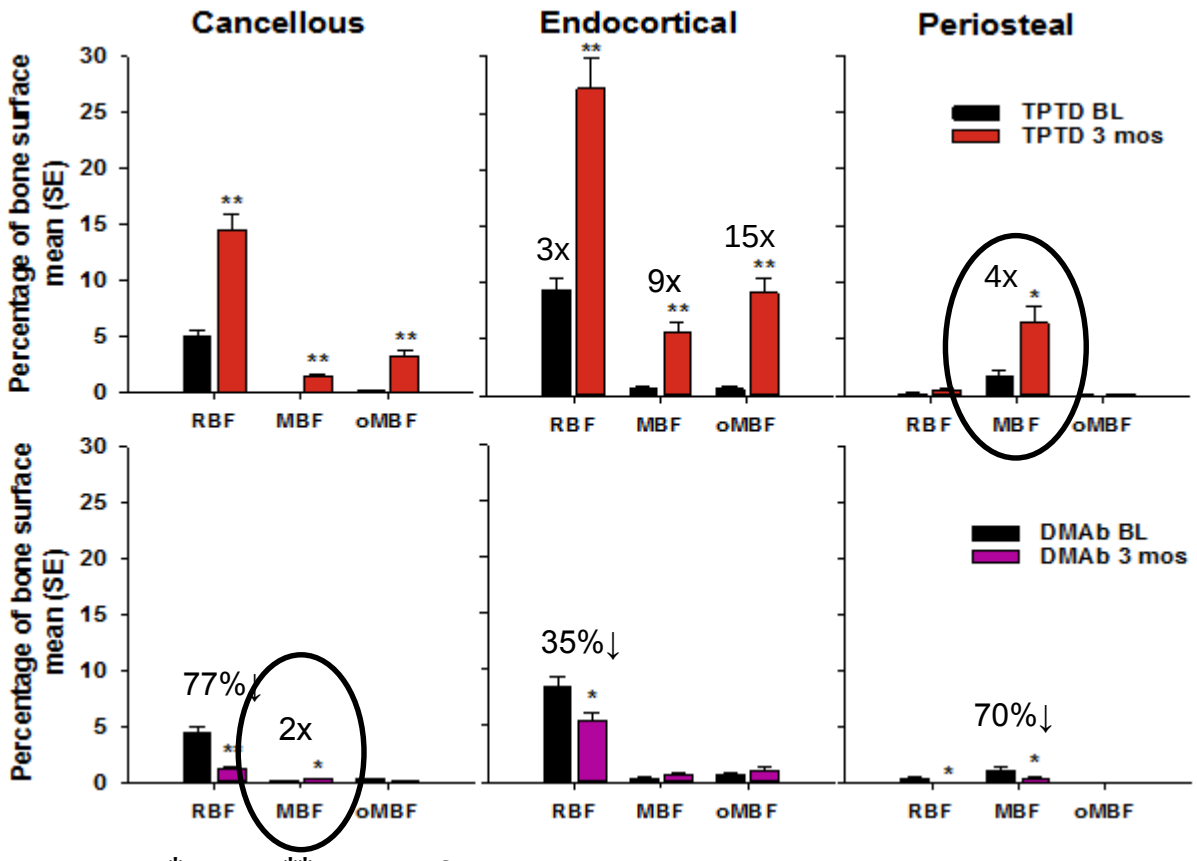


oMBF = Overflow Modeling-based formation



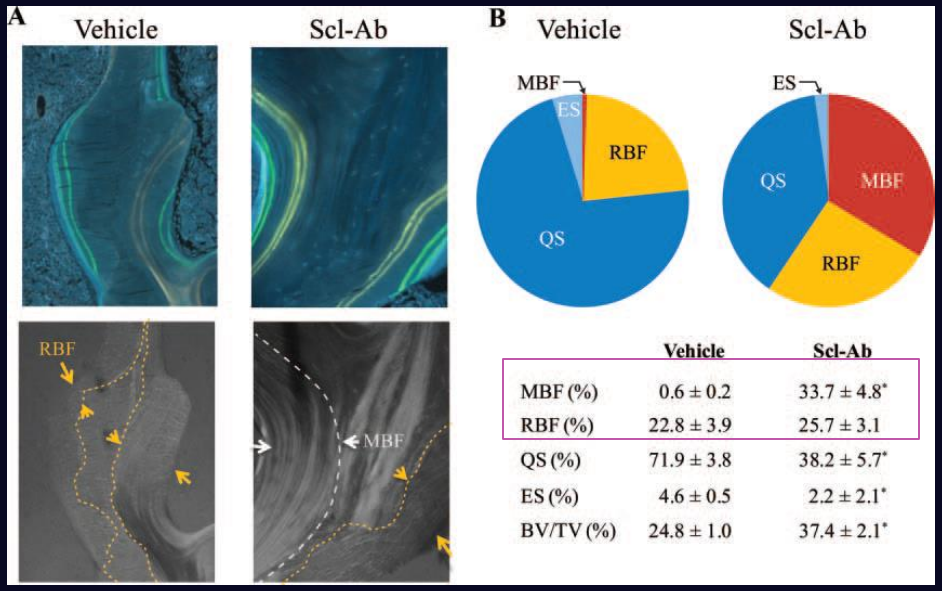
Dempster DW et al Longitudinal Effects of Teriparatide or Zoledronic Acid on Bone Modeling- and Remodeling-Based Formation in the SHOTZ Study. J Bone Miner Res. 2017 Nov 30. 10.1002/jbmr.3350. [Epub ahead of print]

Results – Bone Formation from Baseline to 3 Months Within Groups



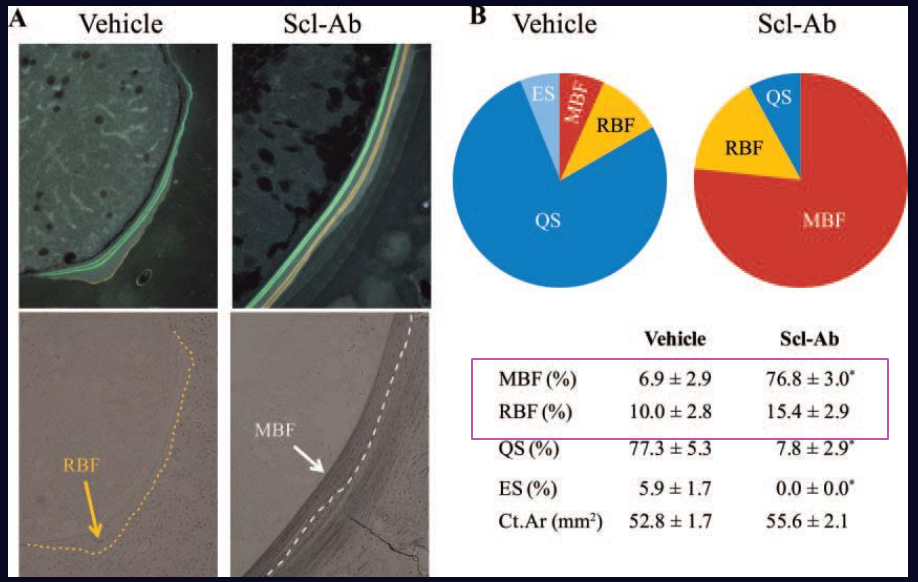
*<0.05; **<0.0001 for within group p-value by paired t-test

Modeling in Monkeys Treated with Sclerostin Antibody



	Vehicle	Scl-Ab
MBF (%)	0.6 ± 0.2	33.7 ± 4.8*
RBF (%)	22.8 ± 3.9	25.7 ± 3.1
QS (%)	71.9 ± 3.8	38.2 ± 5.7*
ES (%)	4.6 ± 0.5	2.2 ± 2.1*
BV/TV (%)	24.8 ± 1.0	37.4 ± 2.1*

Trabecular Envelope



	Vehicle	Scl-Ab
MBF (%)	6.9 ± 2.9	76.8 ± 3.0*
RBF (%)	10.0 ± 2.8	15.4 ± 2.9
QS (%)	77.3 ± 5.3	7.8 ± 2.9*
ES (%)	5.9 ± 1.7	0.0 ± 0.0*
Ct.Ar (mm²)	52.8 ± 1.7	55.6 ± 2.1

Endocortical Envelope

Ominsky et al, *JBMR* 2014

Romosozumab – Bone Histomorphometry

Effects of Romosozumab in Postmenopausal Women With Osteoporosis After 2 and 12 Months: Bone Histomorphometry Substudy

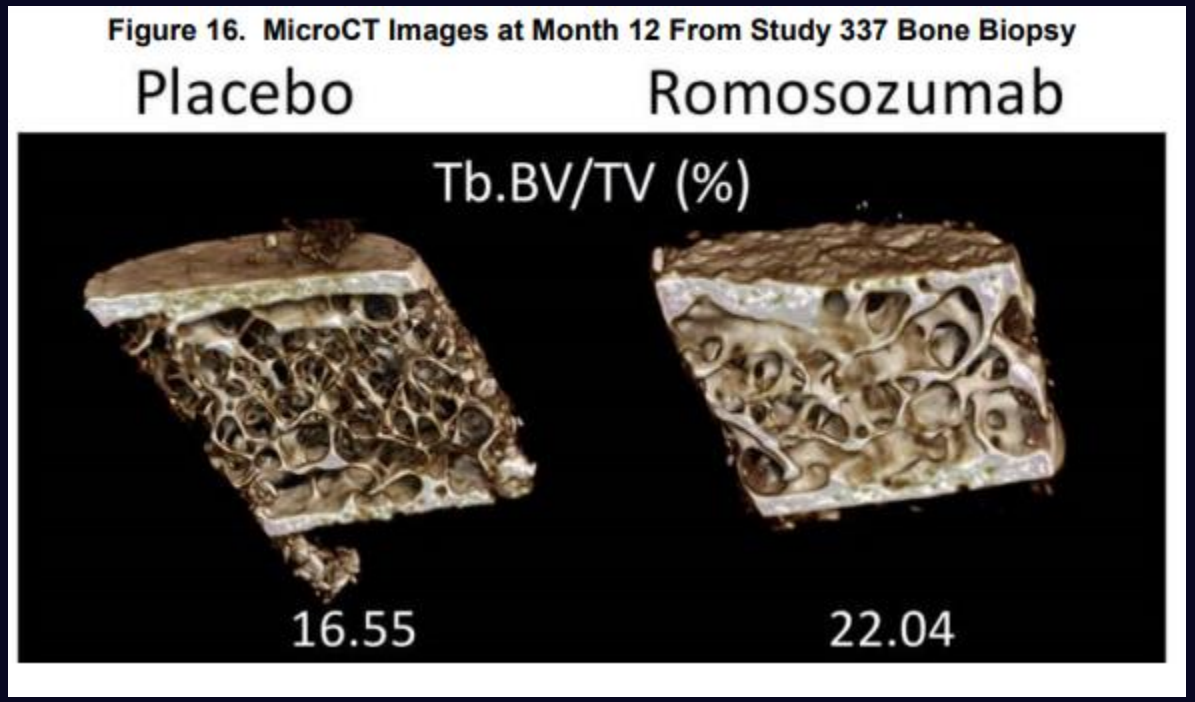
Pascale Chavassieux[1], Roland Chapurlat[1], Nathalie Portero-Muzy[1], Pedro Garcia[2], Jacques P. Brown[3], Stéphane Horlait[4], Cesar Libanati[5], Rogely Boyce[6], Andrea Wang[6], Andreas Grauer[6]

[1]INSERM UMR 1033, Université de Lyon, Lyon, France ; [2]Hospital Universitario de Monterrey, Monterrey, [4]Amgen, E
Thousand

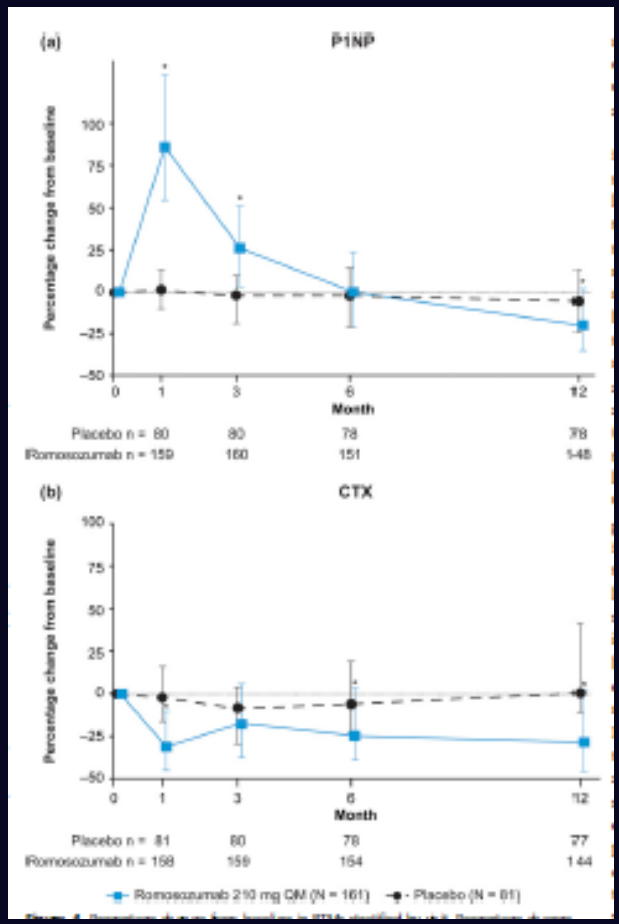
	Month 2 median (Q1, Q3)			Month 12 median, (Q1, Q3)		
	Placebo (N = 14)	Romosozumab (N = 15)	p-value	Placebo (N = 31)	Romosozumab (N = 39)	p-value
Cn-BV/TV (%)	12.3 (10.9, 17.0)	15.5 (9.0, 19.1)	0.98	11.4 (9.4, 15.5)	15.4 (11.0, 20.1)	0.03
Cn-Tb.Th (µm)	99.5 (85.0, 133.4)	105.9 (95.8, 125.4)	0.35	100.2 (86.1, 125.2)	132.0 (101.9, 158.4)	0.006
Cn-W.Th (µm)	31.7 (30.4, 33.9)	31.6 (30.7, 33.6)	0.91	29.5 (27.8, 32.3)	31.8 (30.8, 34.1)	0.014
Cn-MS/BS (%)	2.3 (0.7, 3.1)	5.6 (3.7, 8.4)	0.002	3.0 (0.9, 5.4)	0.6 (0.0, 2.2)	0.004
Cn-BFR/BS ($\mu m^3/\mu m^2$/year)	5.2 (2.9, 7.2)	12.1 (7.3, 16.1)	0.004	6.8 (2.7, 13.2)[a]	1.6 (0.9, 6.5)[b]	0.014

ASBMR 2018

Romosozumab – CT and Biochemical Markers

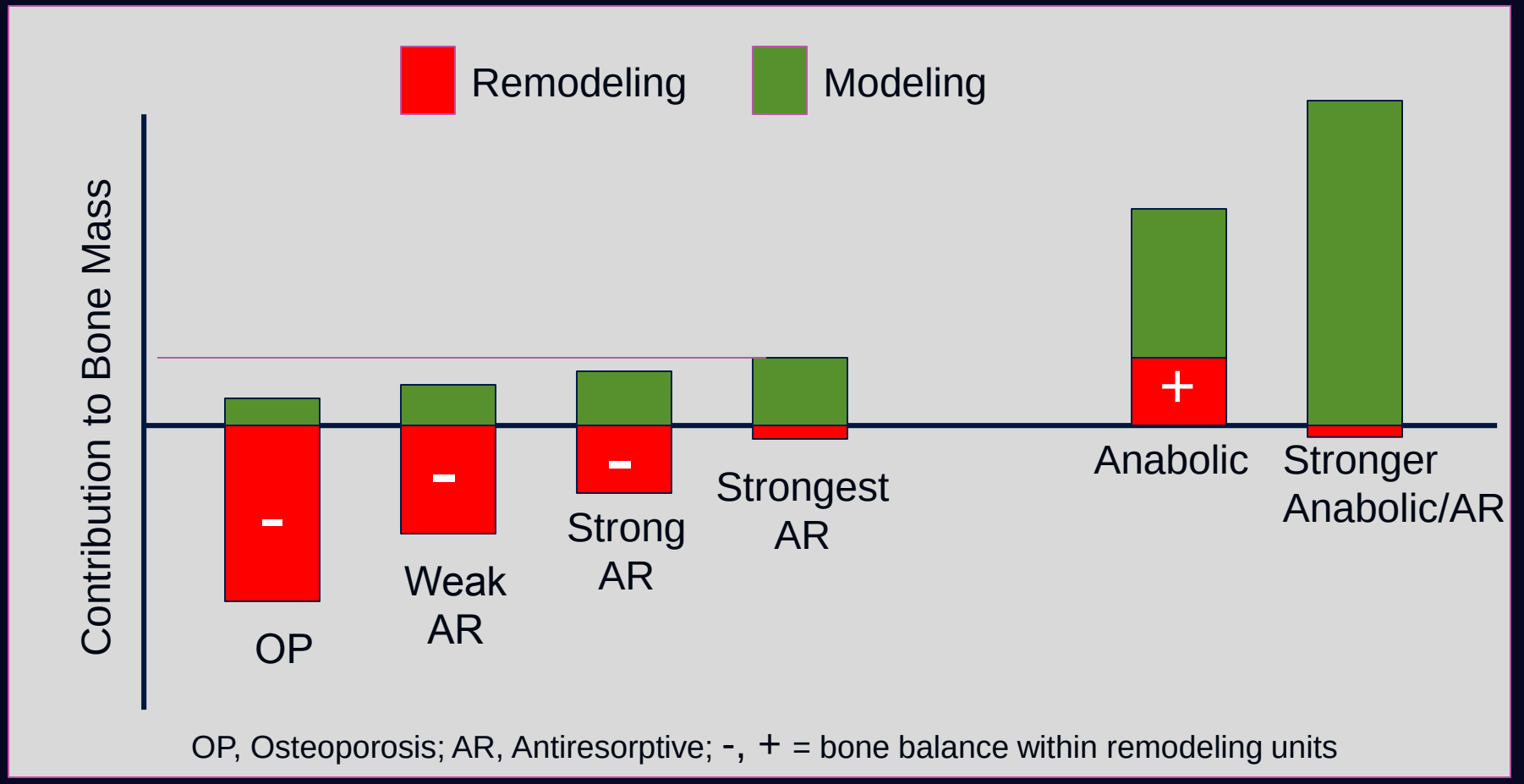


https://www.fda.gov/media/121255/download



Lewiecki EM, et al J Clin Endocrinol Metab. 2018 Sep 1;103(9):3183-3193.

Modeling and Remodeling in Osteoporosis and Following Treatment



OP, Osteoporosis; AR, Antiresorptive; -, + = bone balance within remodeling units

Langdahl B, Ferrari S, Dempster DW,*Ther Adv Musculoskel Dis* 2016;8:225-235

Summary I

- Bone remodeling plays an important role in calcium homeostasis and maintenance of skeletal integrity – as we age, these functions may be in conflict
- Modeling-based bone formation (MBF) in the adult skeleton has been largely ignored.
- MBF persists in the ileum and femur of adult humans. Under normal conditions, MBF in cancellous bone represents a tiny fraction of total bone formation. Other surfaces and skeletal sites need to be explored.

Summary II

- MBF is the most efficient mechanism to increase bone mass in osteoporosis. However, it does not replace older bone and does not replenish the osteocyte pool.
- Potent antiresorptive agents (e.g., DMAb) may be permissive to MBF and, coupled with a low rate of remodeling, may account for prolonged gains in bone mass with such agents.
- Anabolic agents (e.g., PTH 1-34; Scl Ab's) stimulate modeling in both cancellous and cortical bone.

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Thank You!

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