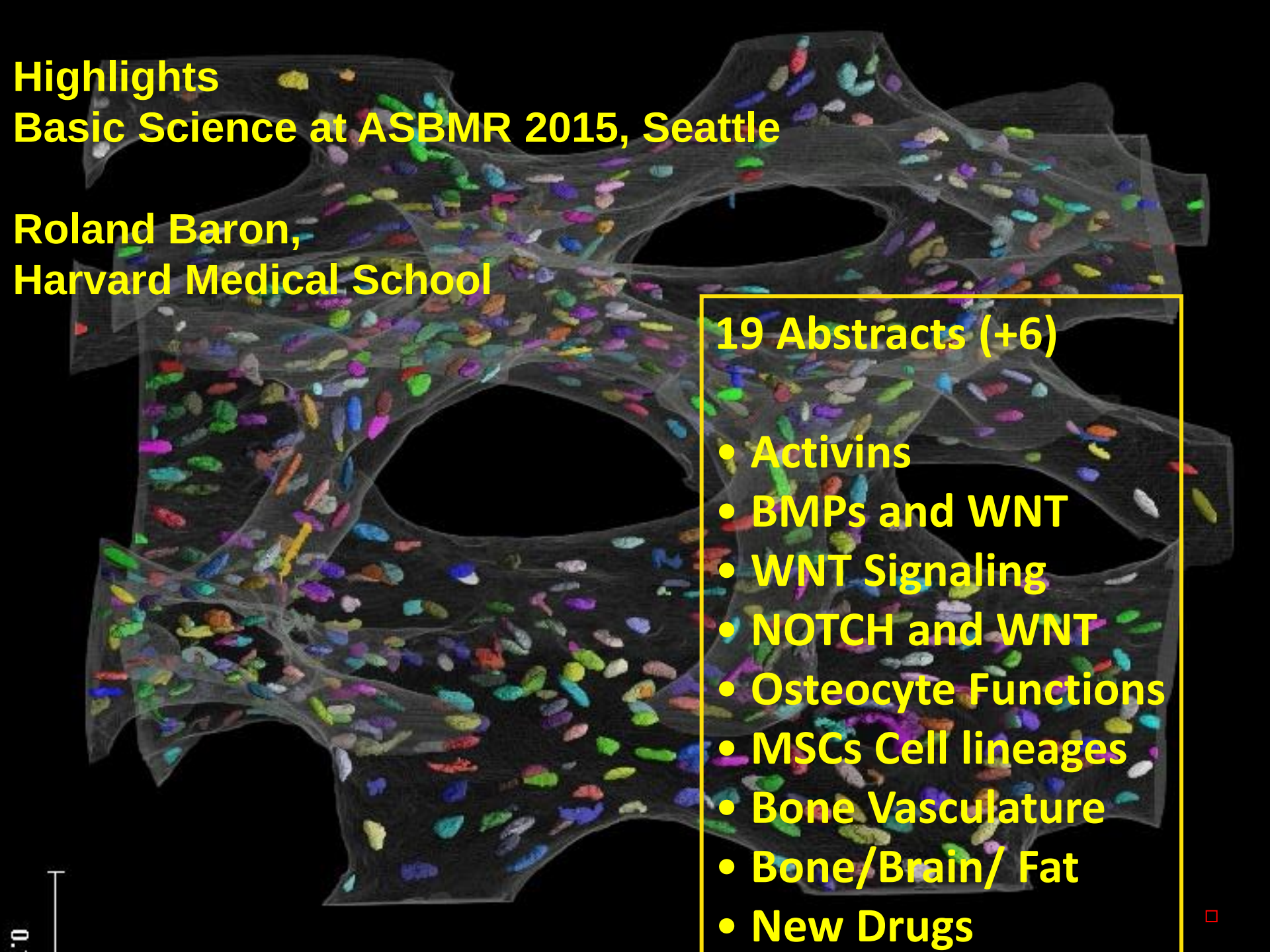
Betsy Mc Clung

Highlights
Basic Science at ASBMR 2015, Seattle

Roland Baron,
Harvard Medical School



19 Abstracts (+6)

- Activins
- BMPs and WNT
- WNT Signaling
- NOTCH and WNT
- Osteocyte Functions
- MSCs Cell lineages
- Bone Vasculature
- Bone/Brain/ Fat
- New Drugs

How Selected?

- **Selection is made from the pool of abstracts blindly selected for oral presentation by the Program Committee, composed of over 100 physicians and scientists among ASBMR members**

- **Restricted by limited time for presentation**

- **Thus…if you are not an oral, you could not be selected here, but this does not mean you work is not exciting!**

- **If you are an oral and were not selected here for presentation, this clearly means your work is exciting… …but I missed it!**

How Selective ?

- **Total Abstracts 1410 + 116 Late = 1526**

Plenary Orals: 36 presentations, **2.3%**

Concurrent Orals: 116 presentations, **7.6%**

Oral Posters: 30 presentations, **2%**

Late-Breaking Abstracts: 5 presentations, **0.3%** (4.3% of late pool)

11.9%

12.2%

Highlights

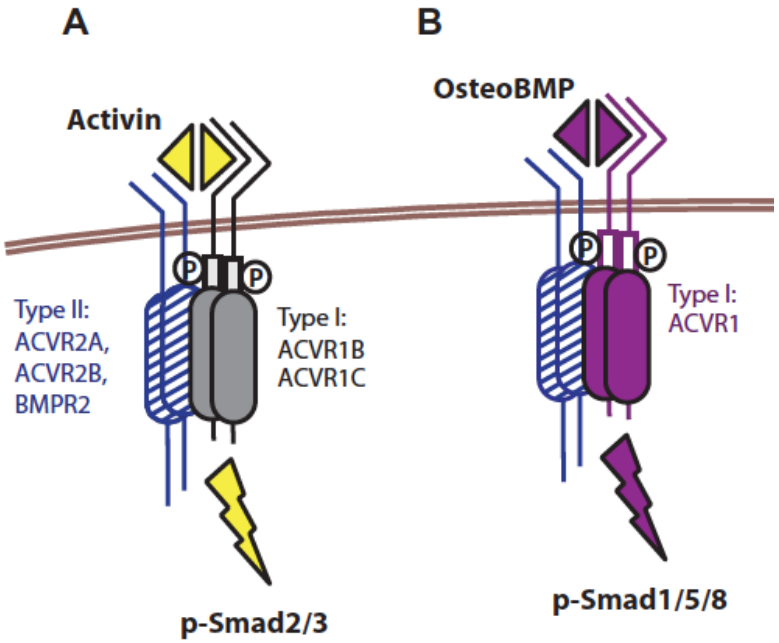
10 = 28% (0.6%)

14 = 12% (1%)

1 = 20% (0.06%)

1.7%

ACTIVINS



Adapted from Hatsell S.J. et al., Sci Translat Med Sept 2015

[1011] YOUNG INVESTIGATOR AWARD

Activin Receptor Type IIA (ACVR2A) Functions Directly in Osteoblasts as a Negative Regulator of Bone Mass

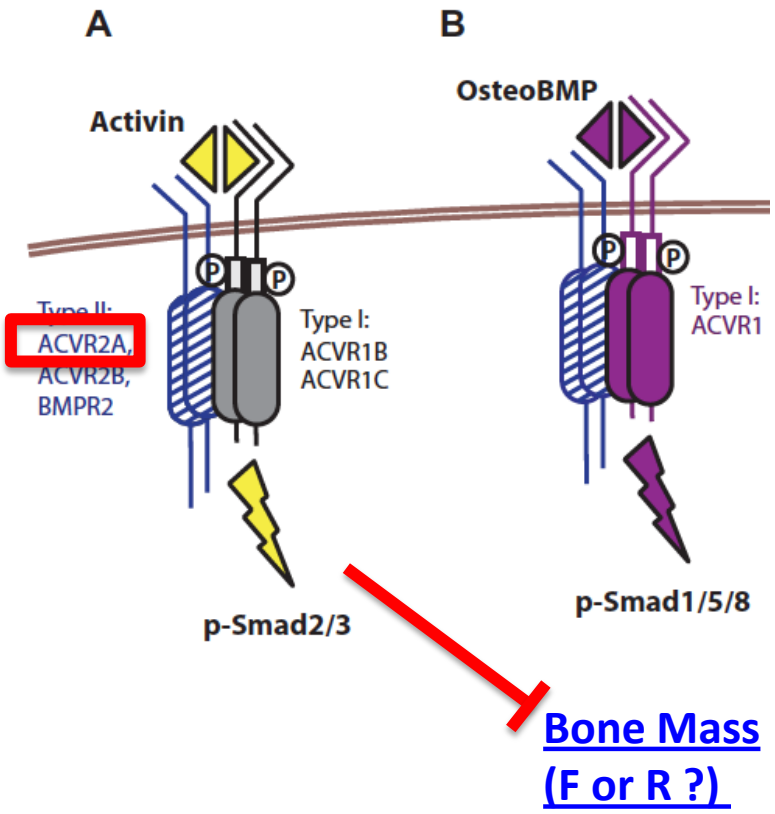
Author(s) Brian Goh, (DiGirolamo lab) Johns Hopkins University School of Medicine, UNITED STATES

Background: Bone and skeletal muscle mass are highly correlated in mammals, suggesting **common anabolic signaling** networks. Mice treated with soluble activin receptors (**blocking activin signaling) demonstrate both increased skeletal muscle mass and bone mass**.
Question: what is the contribution of activin signaling in osteoblasts in the regulation of bone mass.
Results:

- Primary mouse **OBs expressed activin receptors**, including **ACVR2A, ACVR2B, and ACVR1B (ALK4**), and **phosphorylated Smad2/3** upon exposure to activin ligands.
- **OBs deficient in ACVR2A (not ACVR2B) exhibited enhanced differentiation**.
- mice **lacking ACVR2A, not ACVR2B, in OBs and osteocytes** (Osteocalcin-Cre) **had increased trabecular bone volume**.
- Mice **lacking both ACVR2A and ACVR2B demonstrated increases in TBV, similar to ACVR2A single mutants.**

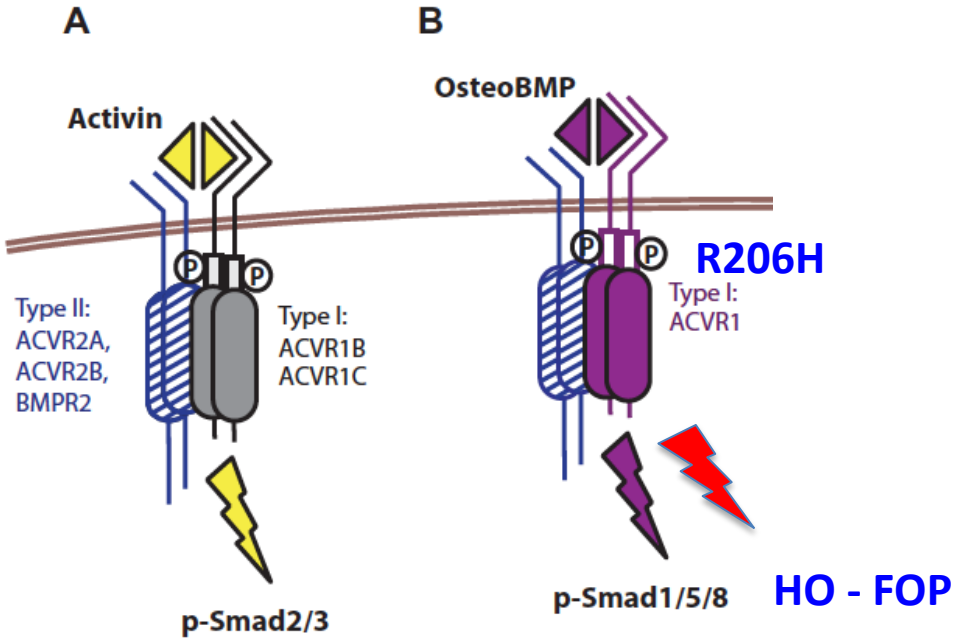
Conclusion: Activin signaling, predominantly through ACVR2A, functions in osteoblasts as a negative regulator of bone mass.

Activins also block BMP signaling



Adapted from Hatsell S.J. et al., Sci Translat Med Sept 2015

…And a mutation of ACVR1 causes FOPand is thought to drive BMP receptor hyperactivity



Adapted from Hatsell S.J. et al., Sci Translat Med Sept 2015

1155

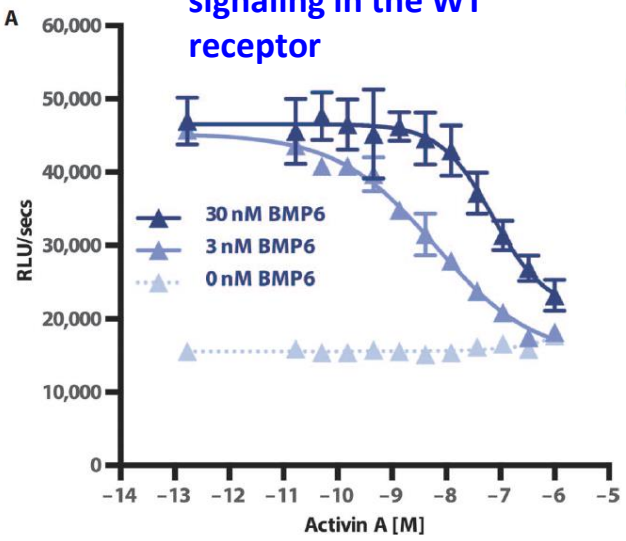
The *ACVR1^{R206H}* mutant receptor causes Fibrodysplasia Ossificans Progressiva by gaining responsiveness to Activin A

Author(s) Aris Economides et al., Regeneron Pharmaceuticals, USA

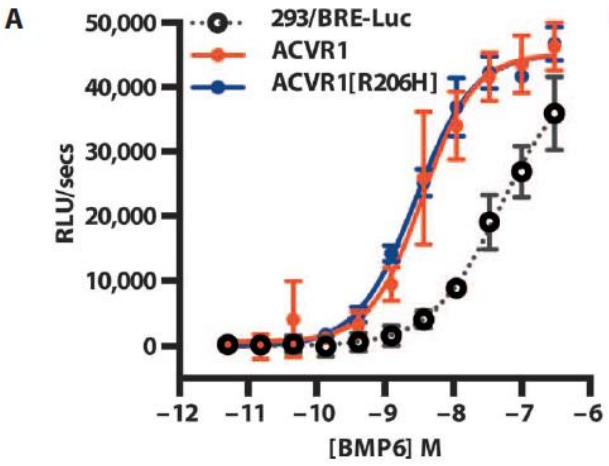
Background: Fibrodysplasia Ossificans Progressiva **(FOP) is a rare bone disease with exuberant heterotopic ossification (HO)** (muscles, fascia, ligaments, and tendons are converted into bone). The cumulative effect is **progressive immobility with catastrophic consequences**. FOP results from mutations in the intracellular domain of the type I BMP receptor **ACVR1 (ALK2)**. The most common mutation, ***ACVR1^{R206H}*** **is thought to drive receptor hyperactivity.**

Question: What is the mechanism by which this mutated receptor activates signaling, and can we prevent it ?

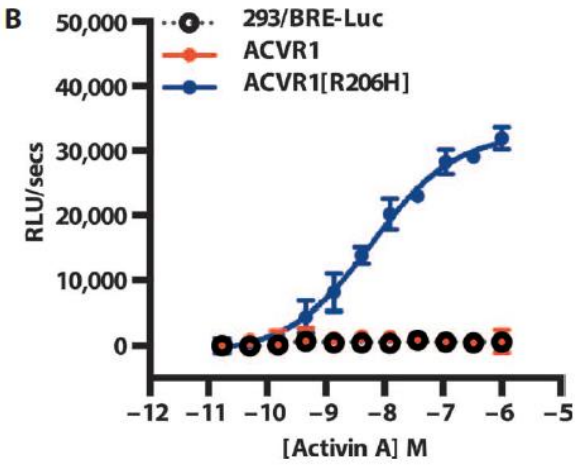
Activin blocks BMP signaling in the WT receptor



The mutated receptor responds normally to BMP



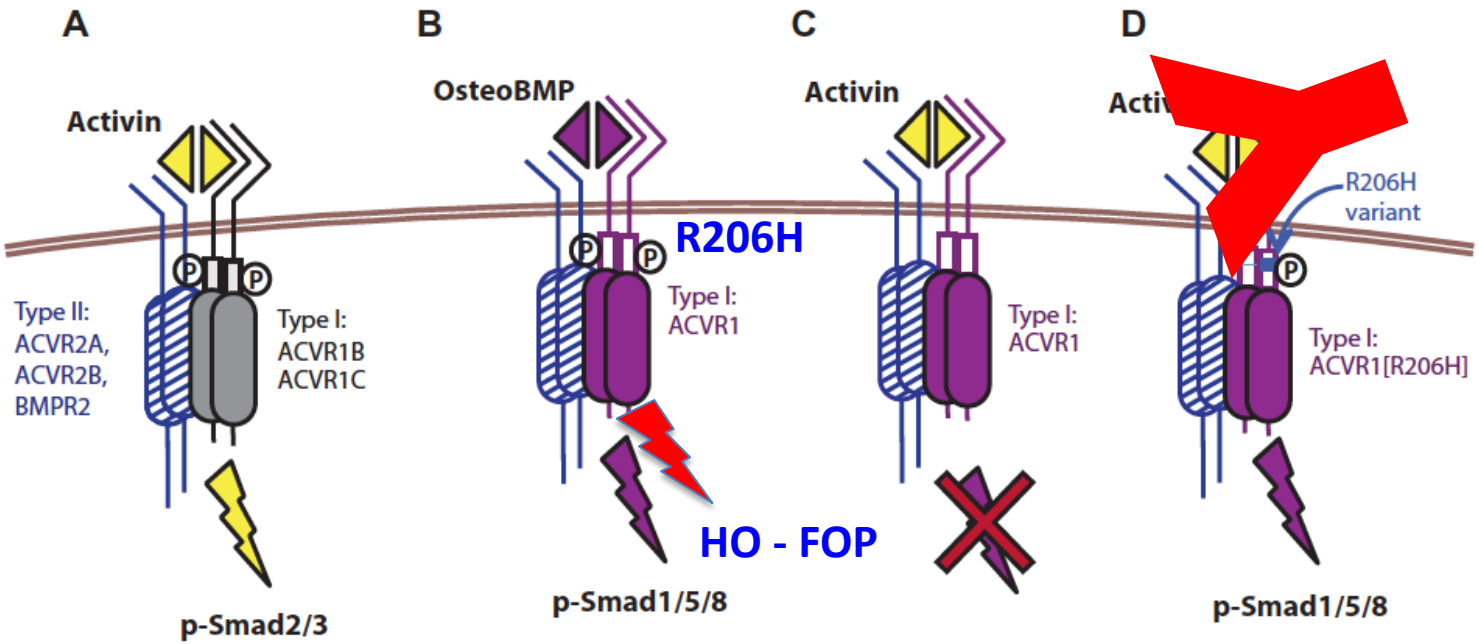
The mutated receptor is activated by Activin A



Results: **In contrast, this mutation renders ACVR1 responsive to Activin A, AB, AC, and B**, ligands that **normally antagonize BMP signaling**, and do not induce bone formation.

- When Acvr1[R206H] expression was induced in a a Cre/lox-based conditional-on knock-in model of *ACVR1*^{R206H}, mice developed HO, spontaneously or after trauma.
- **Local administration of Activin A also triggered HO in the *Acvr1*$^{R206H/+}$ mice but not in controls.**

Adapted from Hatsell S.J. et al., Sci Translat Med Sept 2015



Both spontaneous and trauma-induced HO in *Acvr1*$^{R206H/+}$ mice was blocked by a fully human neutralizing antibody specific to Activin A.

Adapted from Hatsell S.J. et al., Sci Translat Med Sept 2015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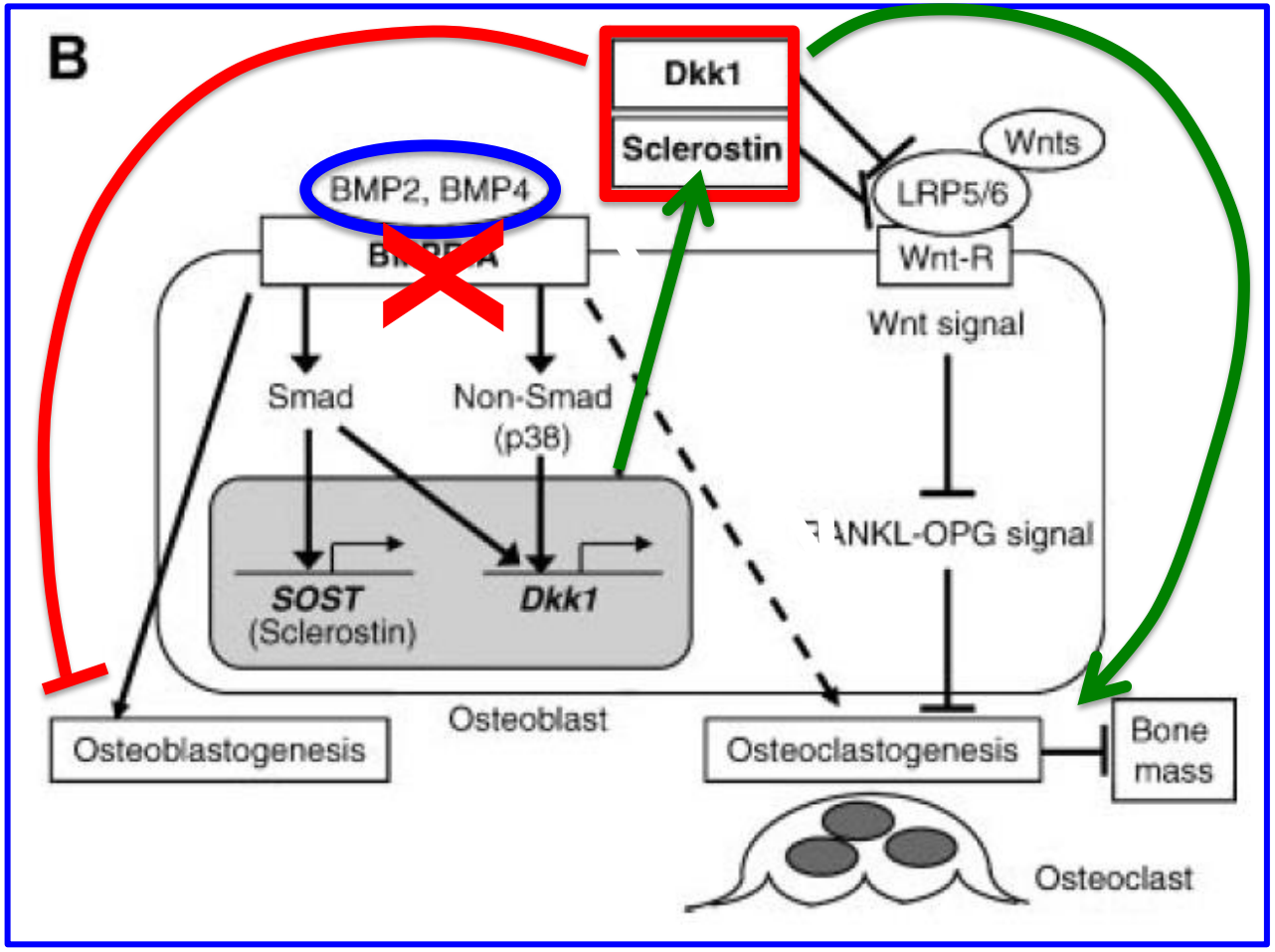
BMPs also CROSS TALK with WNT signaling



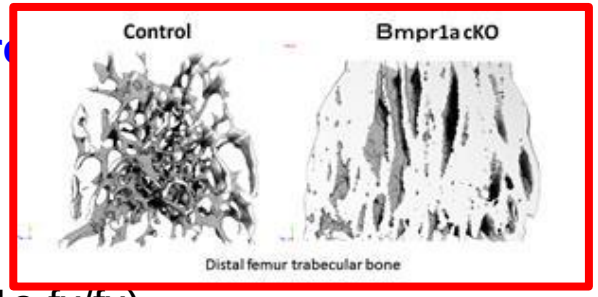
Adapted from Kamiya et al., JBMR 2010

[1048]

Targeted Disruption of BMP Signaling Through Type IA Receptor (BMPRIA) in Osteocyte Suppresses SOST and RANKL, Leading to a Dramatic Increase in Bone Density and Mechanical Strength

Author(s) Nobuhiro Kamiya, Tenri University, JAPAN

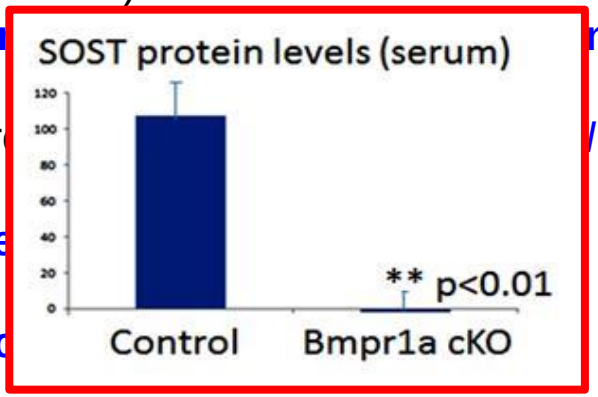
Although more than 90% of bone cells are osteocytes ,**the r**
osteocytes is largely unknown.



Purpose: investigate BMP function in osteocytes.

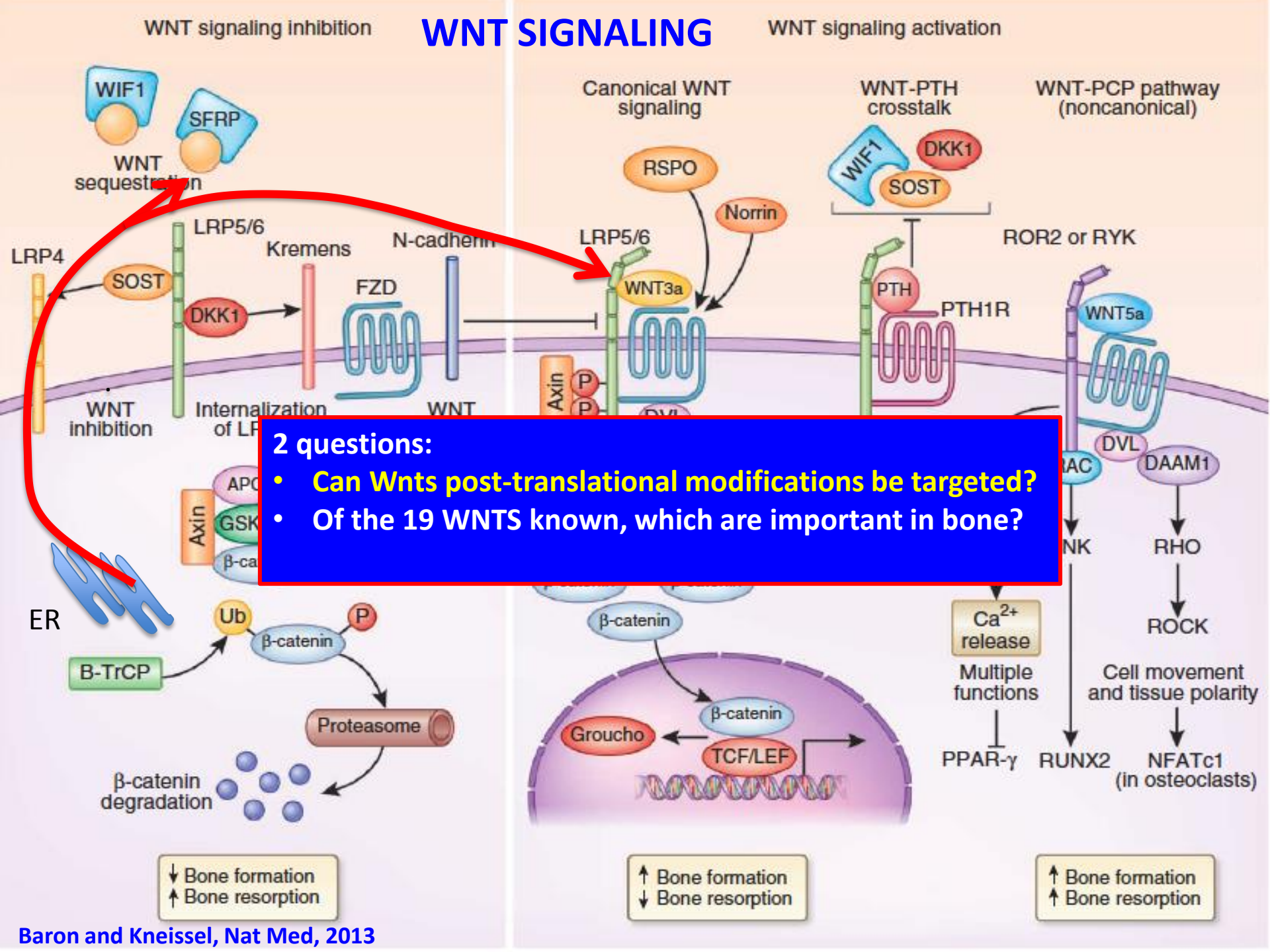
Results: deleted BMPR1A in osteocytes (Dmp1Cre+:Bmpr1a fx/fx)

- cKO femur and spine show **100% increase in Trab BV a** **ne**.
- **Osteoclast number and BFR were reduced**.
- Serum levels of **SOST and RANKL,** as well as gene expr **/** in bones, were **significantly reduced**.
- Beta-catenin levels and **Wnt target genes were increase**
- Mechanical **strength was improved**.
- Osteocyte **shape was disorganized and dendrite netwo**



Conclusion: BMP signaling through BMPR1A plays a role in osteocytes by controlling RANKL and SOST. This study confirms that BMP signaling can negatively regulate bone mass *in vivo*.

WNT SIGNALING



2 questions:

- **Can Wnts post-translational modifications be targeted?**
- **Of the 19 WNTS known, which are important in bone?**

Baron and Kneissel, Nat Med, 2013

NATURE | VOL 519 | 12 MARCH 2015

Disarming Wnt

The secreted enzyme Notum has been found to inhibit the Wnt signalling pathway through removal of a lipid that is linked to the Wnt protein and that is required for activation of Wnt receptor proteins. SEE ARTICLE P.187

ROEL NUSSE

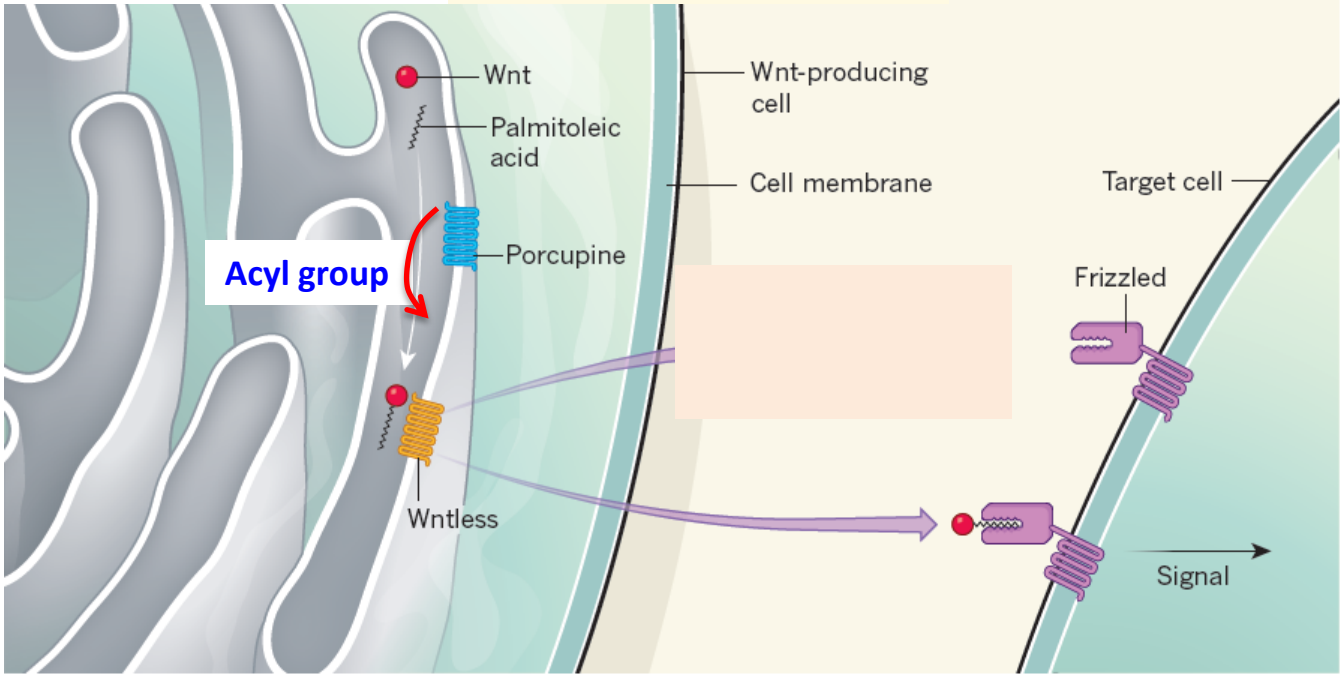


Figure 1 | Notum shoots the messenger in Wnt signalling. In Wnt-producing cells, the Wnt protein is made in a cellular compartment called the endoplasmic reticulum. There, an acyl group from palmitoleic acid is added to Wnt by the membrane-spanning enzyme Porcupine. The Wntless protein then transports palmitoleoylated Wnt out of the cell. Secreted Wnt binds to its receptor protein Frizzled, which spans the membrane of Wnt target cells. This binding depends on the acyl group in Wnt, and triggers an intracellular signalling cascade. Kakugawa *et al.*[2] report that the Wnt–Frizzled interaction is inhibited by the extracellular enzyme Notum, which specifically removes the acyl group from Wnt.

[1020]

Neutralizing Antibody and Orally Active Small Molecule Inhibitors of the Secreted WNT Inactivating Lipase NOTUM Stimulate Cortical Bone Formation in Ovariectomized Rodents

Author(s) Robert Brommage, et al. Lexicon Pharmaceuticals, UNITED STATES

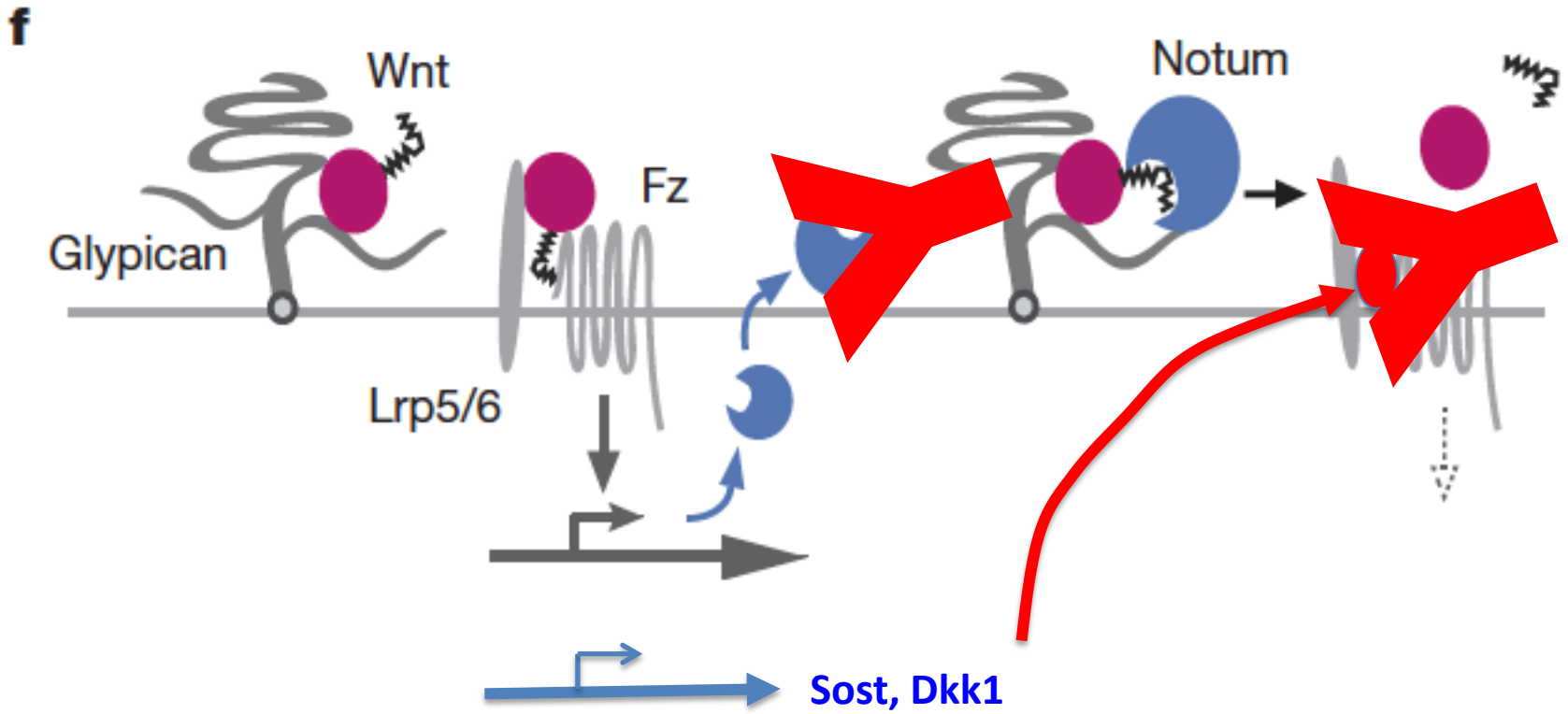
Background: NOTUM is a secreted enzyme that inactivates WNTs by removing an acyl group from palmitoleic acid.

Question: Would antagonizing NOTUM increase bone formation and density?

Results:

- **Notum KO mice have normal bone length and trabecular bone, but high cortical bone thickness (9 cohorts, total KO N=165) with increased strength.**
- **Neutralizing antibody** 2.78.33 had IC50 potencies of 37 and 4 nM and **Small molecule antagonist** (SM) LP-935001 had IC50 potencies of 0.4 and 12 nM in enzymatic and cell-based assays, respectively.
- **8 and 63 weeks following OVX mice treated with Ab (10 mg/kg weekly) for 4 or 12 weeks respectively showed increased cortical thickness ($P < 0.01$) in femur, vertebrae and femoral neck. Endocortical BFR was elevated 4-fold .**
- **Bone strength was elevated at all sites** ($P < 0.01$)

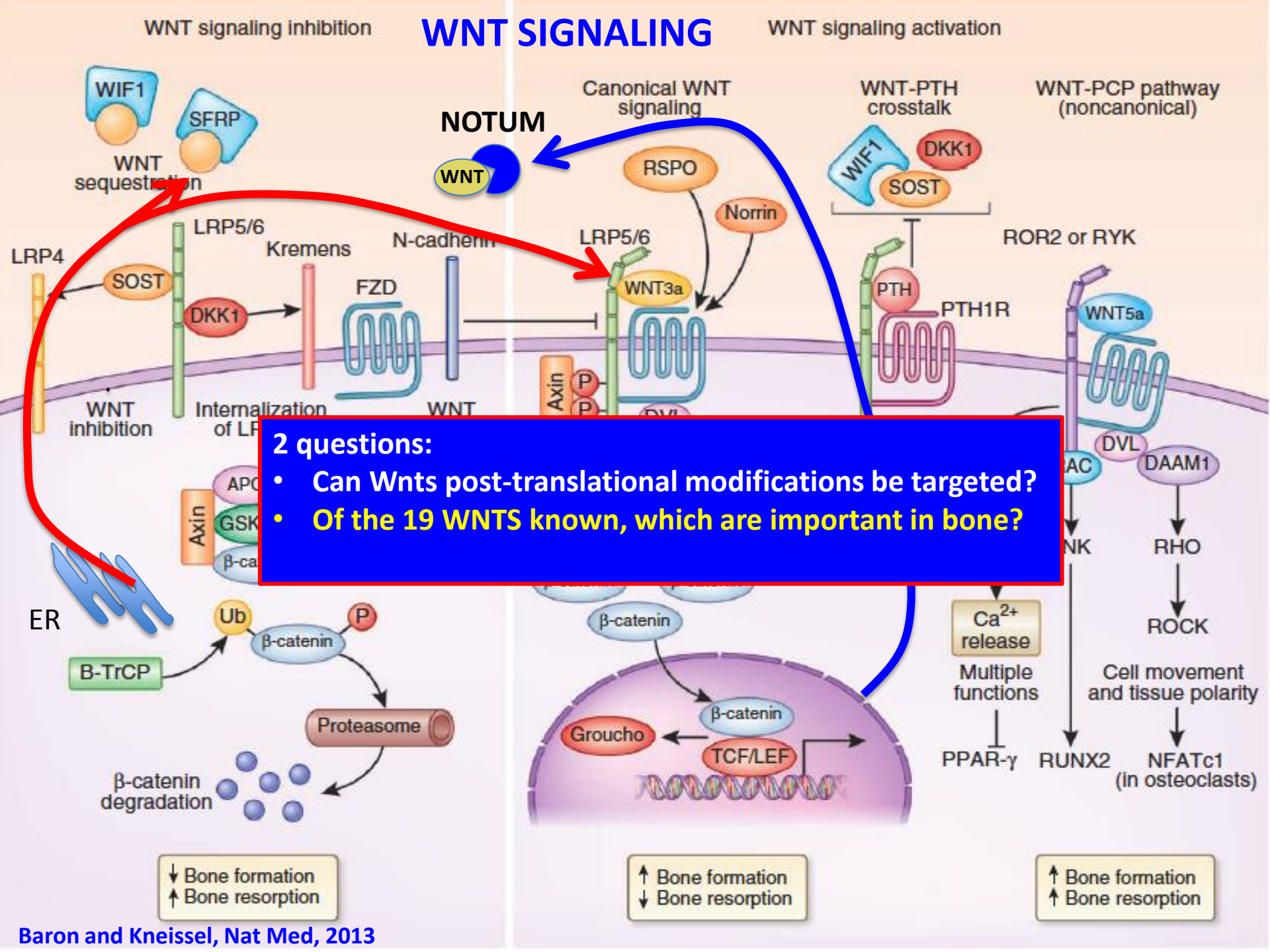
Notum Deacetylates WNT ligands to Suppress WNT signaling



Conclusion: **NOTUM is a WNT inhibitory factor reducing bone formation. As a secreted enzyme inhibitable by neutralizing antibodies and orally active SMs, NOTUM is a potential drug target for stimulating endocortical bone formation and treating osteoporosis.**

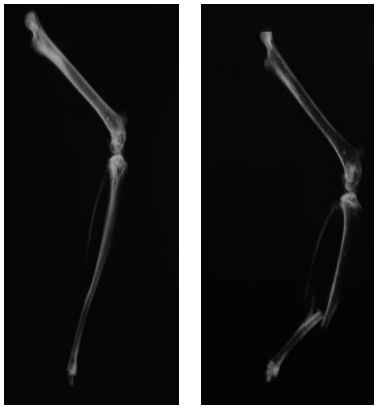
NOTE: NOTUM is ubiquitous, in contrast to Sclerostin…

Adapted from Kakugawa et al., Nature 2015

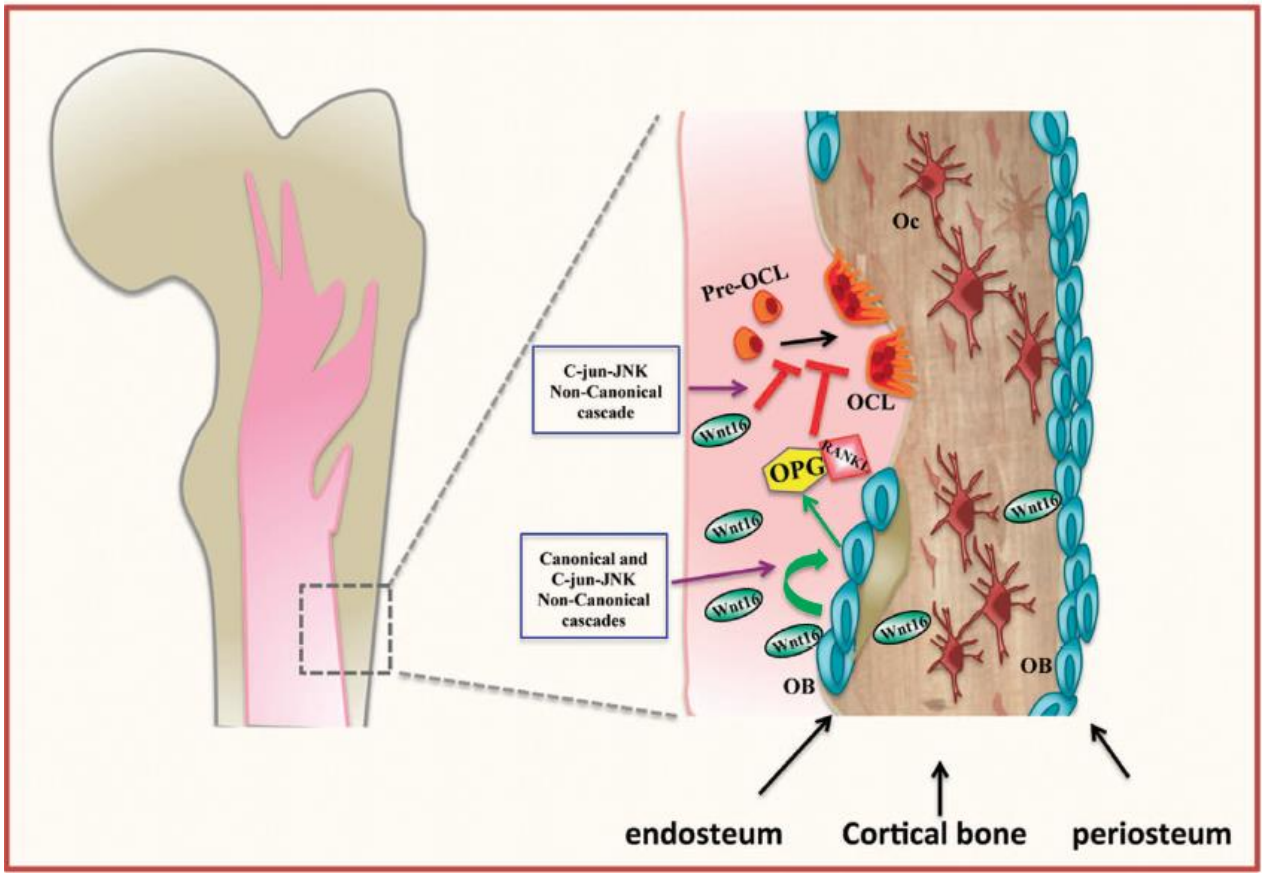


Baron and Kneissel, Nat Med, 2013

WNT16 Regulation of Bone Homeostasis



Fracture Rate **0** 28%



- **WNT16 Deletion did not affect trabecular BFR, probably due to redundancy with other WNTs, but increased resorption in cortex, leading to spontaneous fractures**
- **LAST YEAR: Overexpression of WNT16 increases BFR in both compartments, due to added WNT stoichiometry (M Econs' lab, Abstract # 1028 ASBMR 2014)**

Moverare-Skrtic et al. Nature Medicine, 2014; **Gori F et al. BoneKey, 2015**

1016

Inducible WNT16 Inactivation Demonstrates that WNT16 is a Major Regulator of Cortical Bone Thickness in Adult Mice

Author(s) Sofia Moverare Skrtic, Petra Henning, (Ulf Lerner, Claes Ohlsson labs), Sweden

Background: Non-vertebral fracture risk remains an unmet medical need.

- The WNT16 locus is a major determinant of cortical bone thickness and non-vertebral fracture risk.
- Global and cell-specific deletion of *Wnt16* in mice demonstrated that osteoblast-derived WNT16 is a key regulator of cortical bone thickness and fracture susceptibility.

Question: Can we separate developmental effects and effects on adult bone?

Results:

- ***Wnt16* was conditionally ablated in adult males by tamoxifen for 4 days at 2 doses.**
- At 14 weeks **Tamoxifen dose-dependently decreased *Wnt16* mRNA in cortical bone**
- **Tamoxifen dose-dependently decreased *Wnt16* mRNA and femur cortical bone thickness** in the adult *Wnt16*$^{flox/flox}$ mice
- **Cortical bone thickness was directly associated with *Wnt16* mRNA levels** (r=0.52, p=0.006).

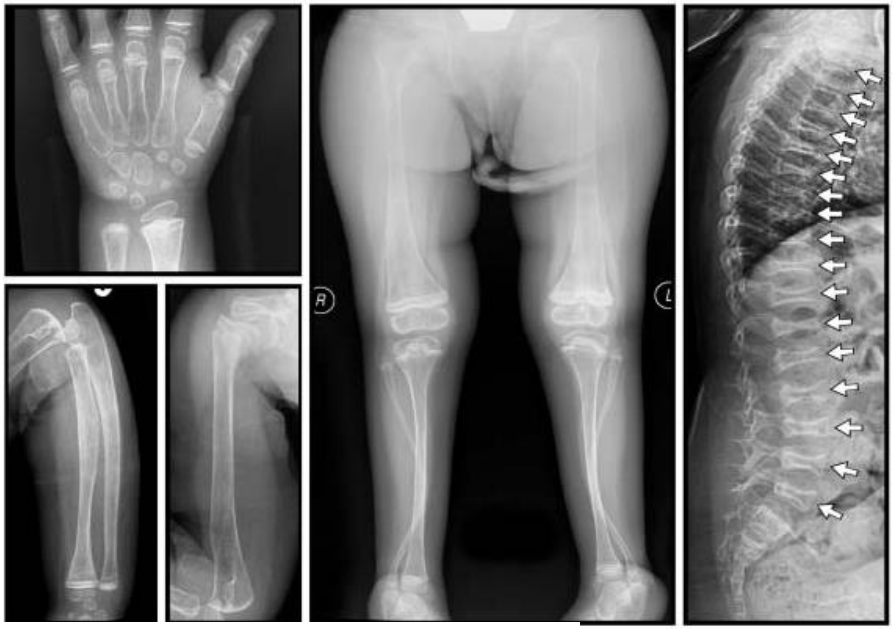
Conclusion: **WNT16 regulates cortical bone thickness in adult mice. New treatment strategies targeting the adult regulation of WNT16 might be useful to reduce fracture risk at cortical bone sites.**

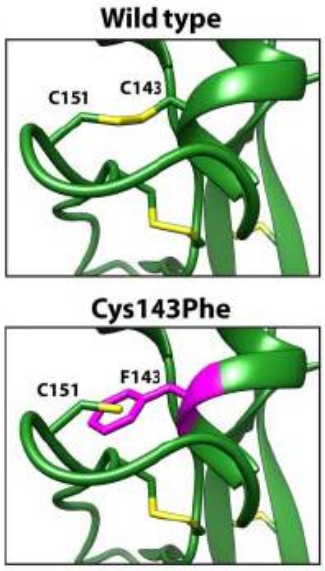
Mutations in WNT1 are a cause of osteogenesis imperfecta

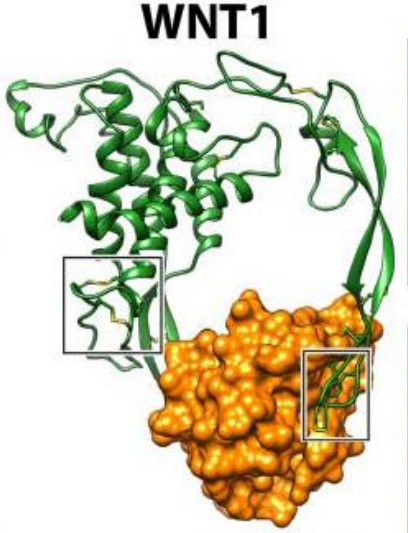
2 years ago…

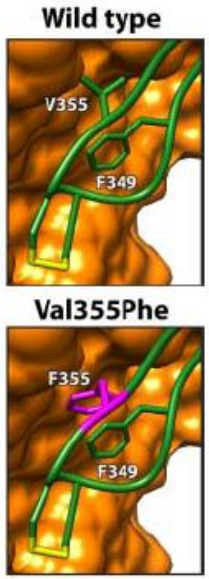
Somayyeh Fahiminiya,[1] Jacek Majewski,[1] John Mort,[2] Pierre Moffatt,[2] Francis H Glorieux,[2] Frank Rauch[2]

J Med Genet 2013;**50**:345–348.





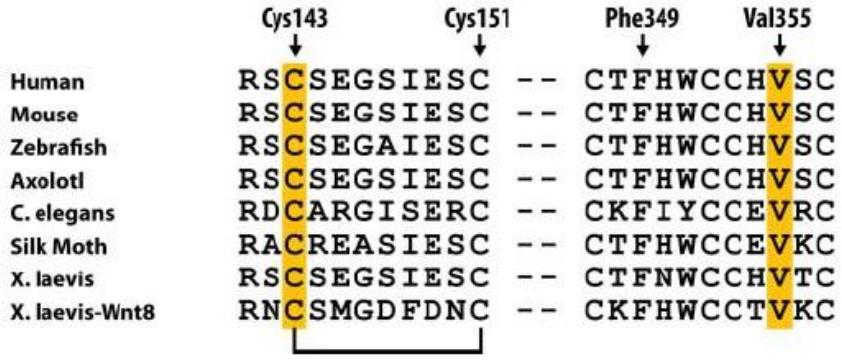




Mutations in *WNT1* Cause Different Forms of Bone Fragility
Keupp et al., Am J Hum Gen 2013

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



[1148]

Wnt1 Regulates Bone Homeostasis by Regulating the Function of Osteoblasts

Author(s) Kyu Sang Joeng, Brendan Lee, Yuqing Chen labs Baylor College of Medicine, USA

*WNT1*mutations have been reported to cause Osteogenesis Imperfecta (OI) and early-onset osteoporosis and lineage tracing experiments suggested that *Wnt1* is expressed in osteocytes.

Question: **Does *Wnt1* expression in osteocytes regulate bone homeostasis?**

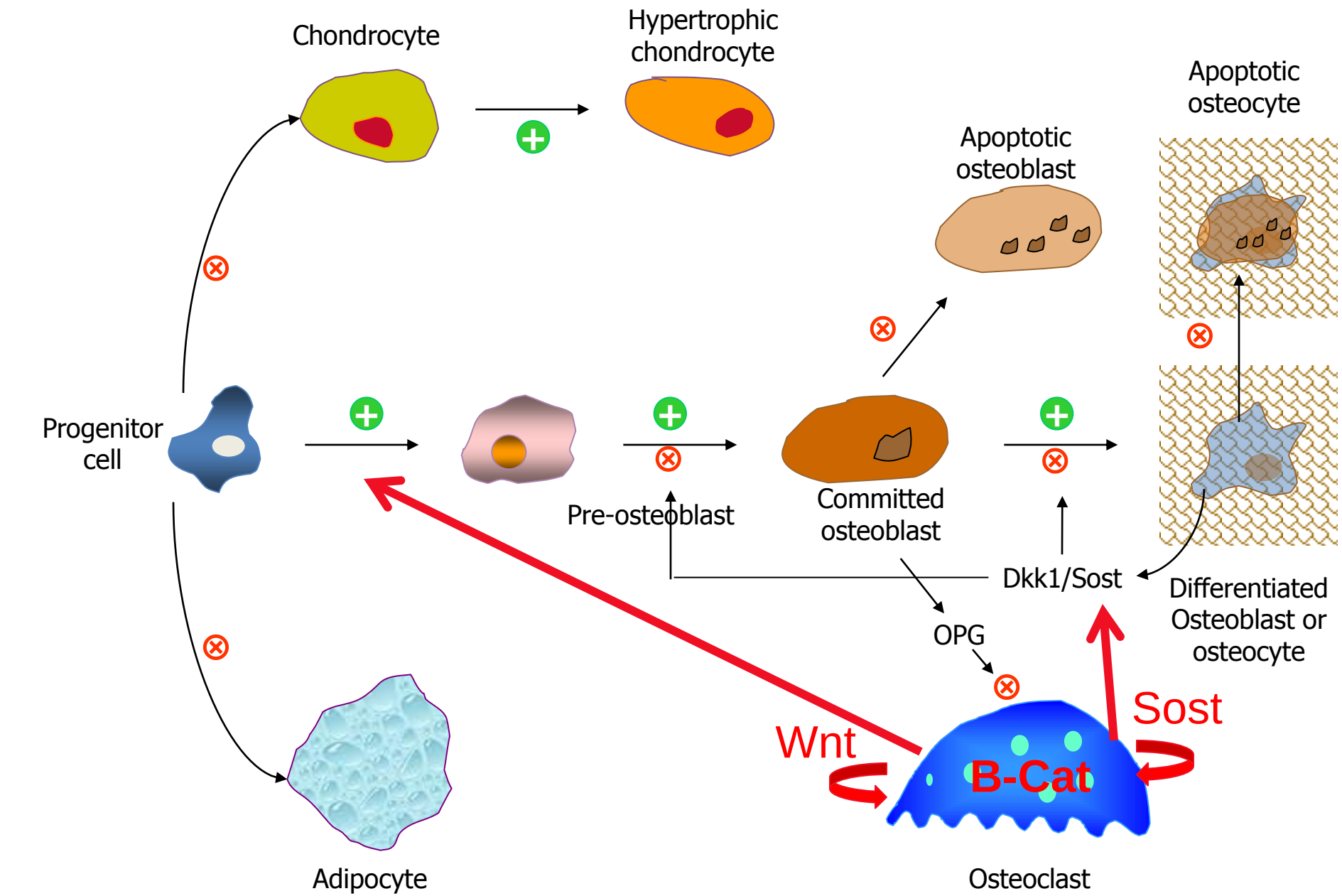
Results:

- ***Mice 1*: *DMP1-Cre; Wnt1$^{f/f}$*** mice exhibit **spontaneous tibial fractures** (70% rate), **low bone mass with reduction in cortical bone diameter due to decreased osteoblast activity, not to changes in osteoclasts.**
- ***Mice 2*: osteocyte-specific *Wnt1* gain-of-function mouse exhibited a 5-fold increase in TBV and 50% increase in cortical bone diameter solely from increased osteoblast activity.**
- ***Mice 3*: Deletion of B-catenin in these mice phenocopied the trabecular phenotype of *DMP1-Cre; β-catenin$^{f/f}$* mice, whereas the cortical bone diameter was significantly higher**

Conclusion: β-catenin mediates WNT1 function in trabecular bone formation, while both β-catenin-dependent and independent mechanisms mediate WNT1 function in cortical bone.

See also: **1018**
Sclerostin Antibody (Scl-Ab) Increased Bone Mass and Strength in a Mouse Model of Osteogenesis Imperfecta Caused by Wnt1 Mutation by the same group

Osteoclasts and WNT Signaling



Adapted from Baron R. and Rawadi G. Endocrinol, 2007

[1031]

Reduced osteoclast TGFβ signaling in the aged skeleton impairs the coupling of bone resorption to bone formation through reduced osteoclast Wnt1 expression

Author(s) Megan Weivoda, Merry Jo Oursler lab, Mayo Clinic, UNITED STATES

Background: Osteoclasts secrete factors that couple bone resorption and formation. These processes are uncoupled with age, resulting in age-related bone loss. TGFβ is abundant in bone and is released and activated by osteoclasts.

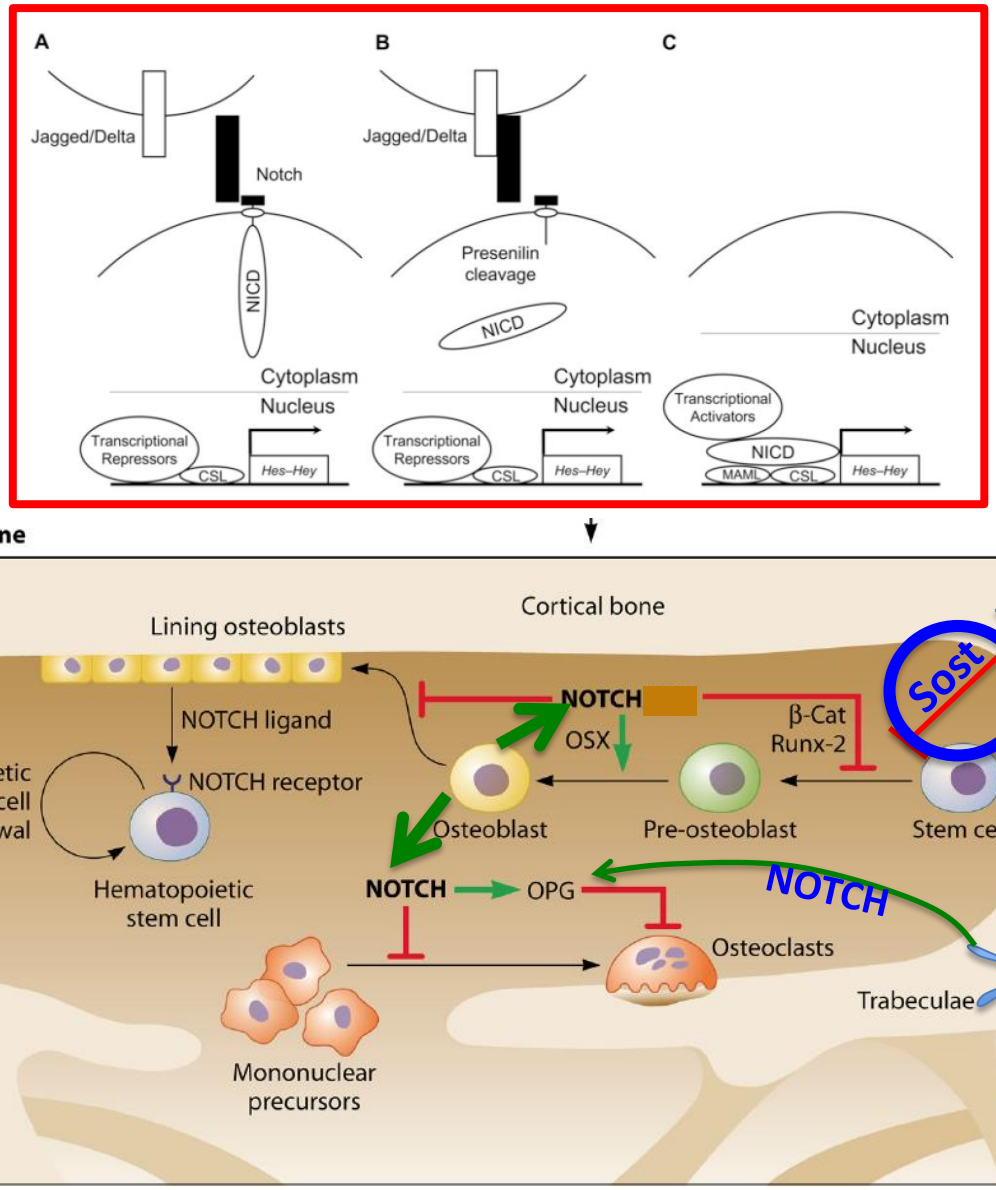
Question: **Does osteoclast TGFβ signaling contribute to age-related uncoupling of bone resorption and formation, and by what mechanism?**

Results:

- **DNeg TGFβ receptor expressed in osteoclasts (Tgfbr2^{OclKO}) in mice induces osteopenia**. **with no change in osteoclast** numbers, but **OB numbers and BFR were reduced 60%.**
- In vitro,**TGFβ induced Wnt1 expression >1000-fold.** This induction was **impaired in Tgfbr2^{OclKO} osteoclasts , with a 53% reduction in osteoclast Wnt1 in vivo.**
- **Tgfbr signaling, was significantly reduced in old bone osteoclasts in vivo.**
- Culture of **osteoclasts derived from young bone marrow** on **old bone matrix** resulted in a **72% reduction in matrix-induced Wnt1**, and osteoclast **Wnt1 expression was reduced 64% in old mice in vivo**.

Conclusion: **TGFβ-stimulated osteoclasts are a key source of Wnt1 that promote osteoblastic bone formation at sites of bone resorption, which decreases with age in mic.**

NOTCH and Crosstalk with WNT SIGNALING



Adapted from Zanotti S and Canalis E, Mol Cell Biol, 2010; Eur. J. Endocrinol., 2013

[1047]

SOST Downregulates Notch Signaling and Reverses the Effects of Notch in Osteocytes

Author(s) Stefano Zanotti, Lauren Schilling, Ernesto Canalis, UConn Health, USA

Background: Activation of Notch1 in osteoblasts impairs osteoblast differentiation/function, whereas Notch activation in osteocytes causes an increase in bone mass due to suppression of cancellous bone resorption and enhanced cortical bone formation attributed to a downregulation of Sost and upregulation of OPG expression in the bone microenvironment.

Question: Is Sost downregulation critical to the effects of Notch in osteocytes?

Results: Notch1 signaling was activated in osteocytes (**DMP1Cre-Notch**), allowing expression of the **NICD**, with **SOST overexpression** (**cross with DMP1-Cre Sost**).

- The **increase in TBV** in Dmp1-Cre+/-;RosaNotch mice **was no longer observed with SOST overexpression**
- **60 to 80% inhibition of Notch target gene** expression, suggests that **sclerostin reverses the effects of Notch1 in osteocytes by downregulating Notch signaling**.

Conclusion: **Sclerostin downregulates Notch signaling** and reverses the high bone mass in osteocyte-specific Notch1 phenotype, indicating that **intact Wnt signaling is required for Notch activity in osteocytes**.

See also: 1032: A Hadju Cheney mutant mouse (*gain of function of NOTCH2*) exhibits profound osteopenia, Canalis E.

[1013] YOUNG INVESTIGATOR AWARD

Osteolineage Notch ligand Jagged1 is critical for maintaining homeostatic trabecular bone mass

Rialnat Lawal,, Laura Calvi's lab, University of Rochester Medical Center, USA

Background: Notch signaling regulates osteoprogenitors and osteoblastic differentiation. The **specific contribution of individual Notch ligands is unknown**. PTH regulates the expression of the Notch ligand Jagged1 in osteoblastic cells.

Question: **Does loss of osteolineage Jagged1 in vivo affects bone homeostasis and responses to PTH?**

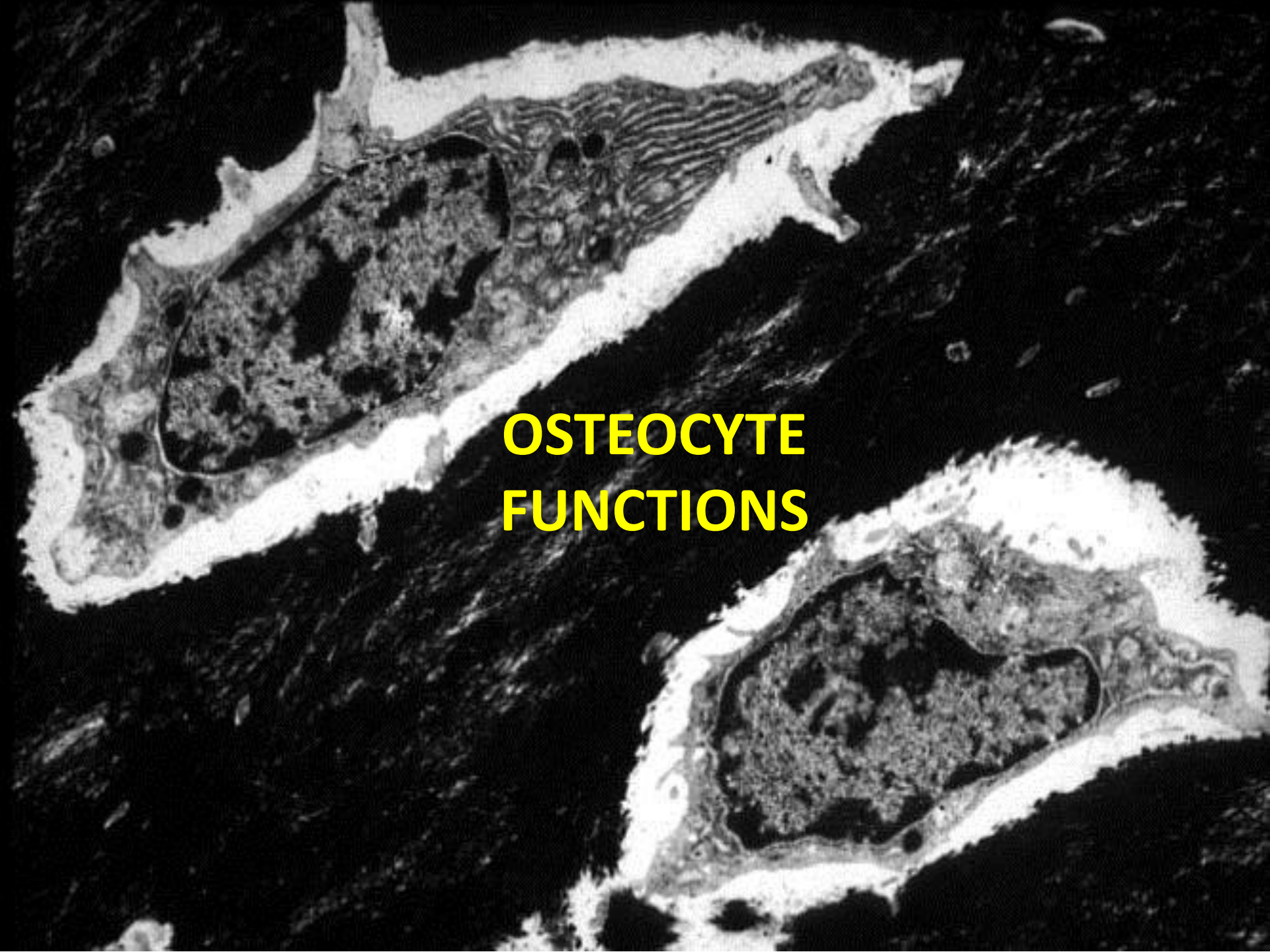
Results:

- Prx1 Cre:Jag1deleted mice had **increased TBV without changes in cortical bone**. **OB activity and numbers were increased**.
- **MSCs were unchanged**, while **osteoprogenitors were decreased.**
- Coupled with the increase in OB numbers and activity, the mice had **increased osteoclastic activity**.
- **PTH-dependent** bone anabolism resulted in a significantly **greater increase in BV/TV in Jag1-deleted mice**.

Conclusion: **Jagged1 restricts the transition of OPs to OBs**, **maintaining appropriate populations of osteolineage cells. Deletion increases TBV, more in combination with PTH.**

See Also: **1123** **OB-activated Notch1 signaling in hematopoietic cells induces Acute Myeloid Leukemia** (Galan Diez, Kousteni lab)

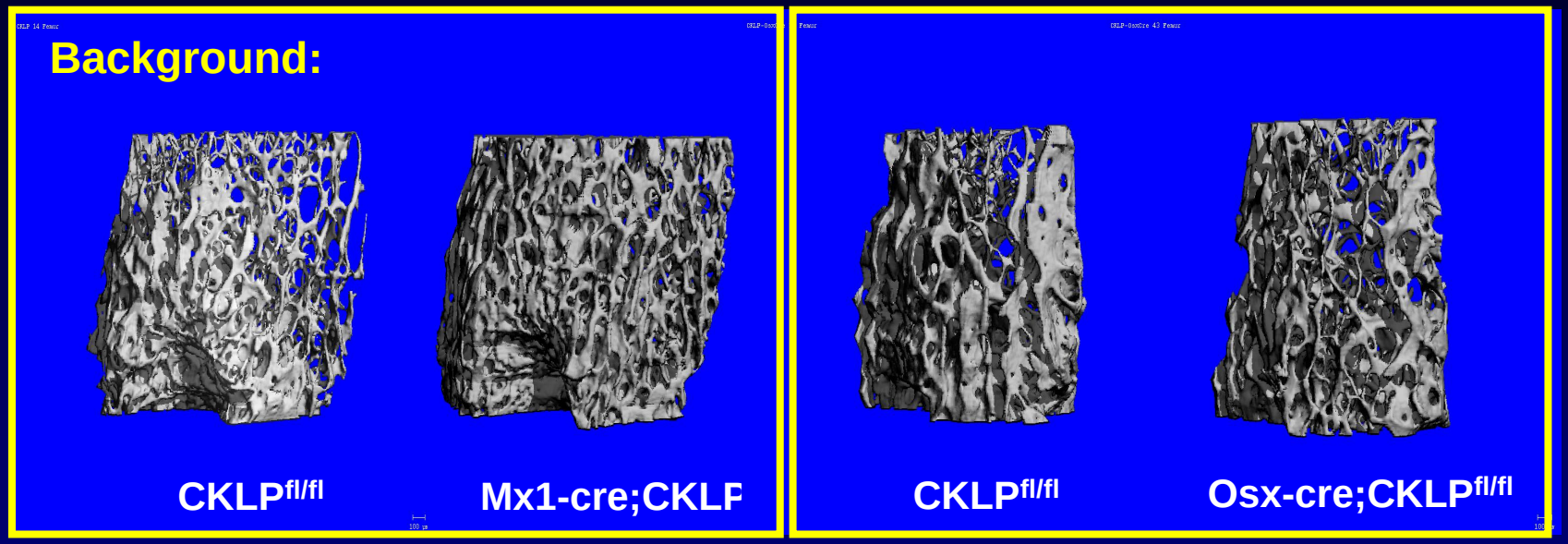
1124 **Notch signaling in OPs is a critical determinant of fracture repair and nonunion** (C Wang, Hilton lab)

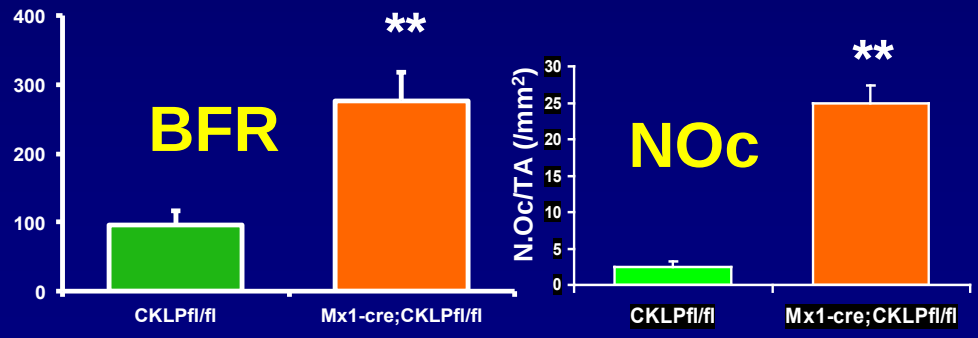

OSTEOCYTE
FUNCTIONS

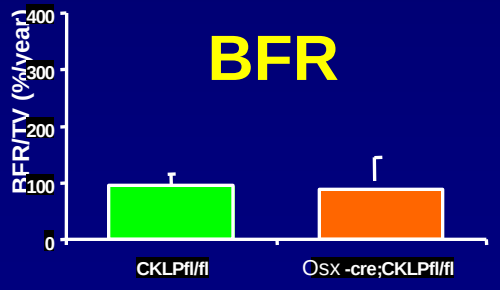
[1025]

Osteocyte-specific Deletion of Cathepsin K Prevents Increased Bone Turnover, Bone Loss and Bone Fragility during Lactation in Mice

Author(s) Sutada Lotinun, Baron' Lab, Harvard, USA

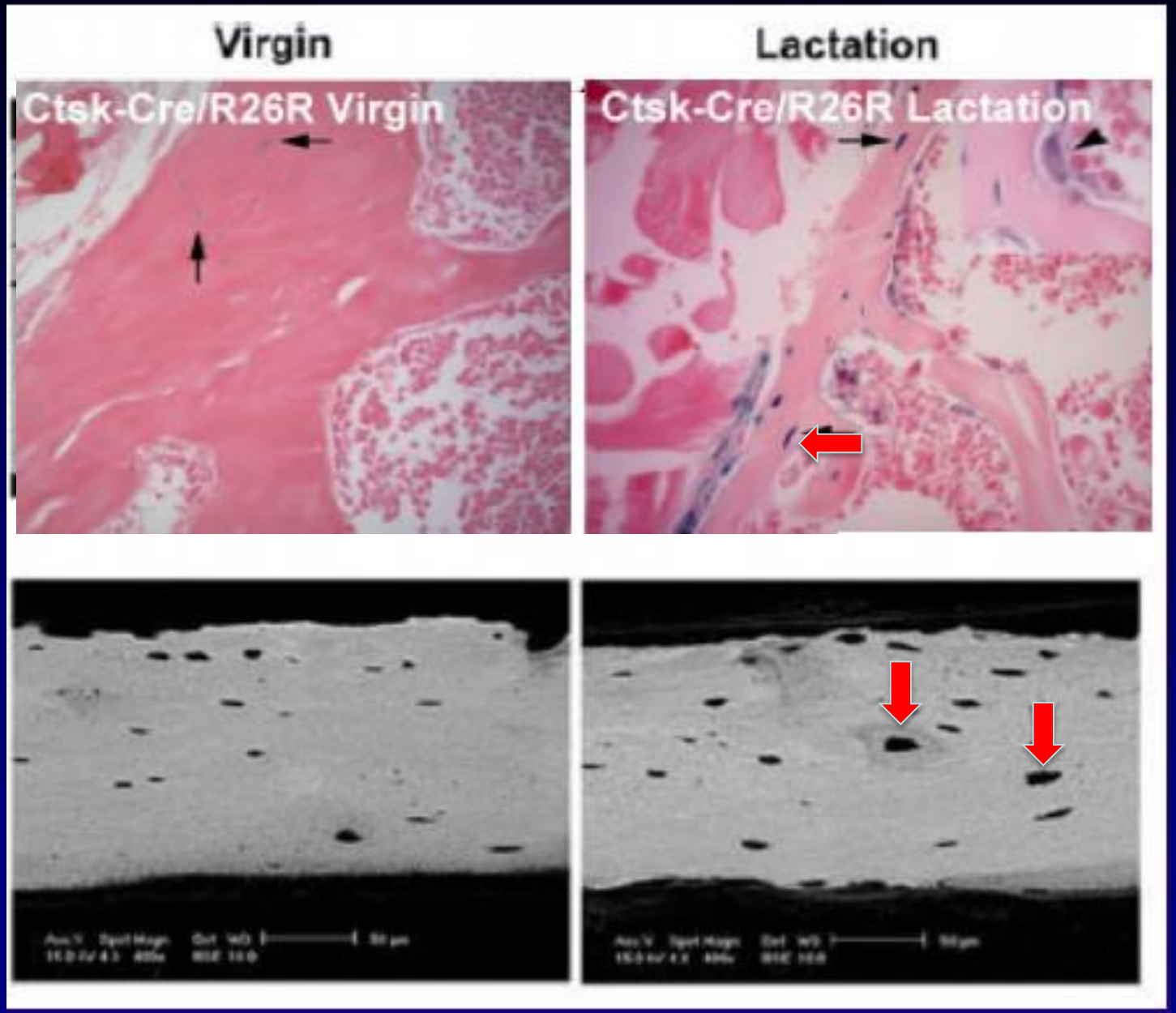






Lotinun, Kiviranta et al. J Clin Invest, 2013

Background: Osteocytes from Lactating Mice Express Cathepsin K and increase Osteolysis



Qing H et al., JBMR 2012

[1025]

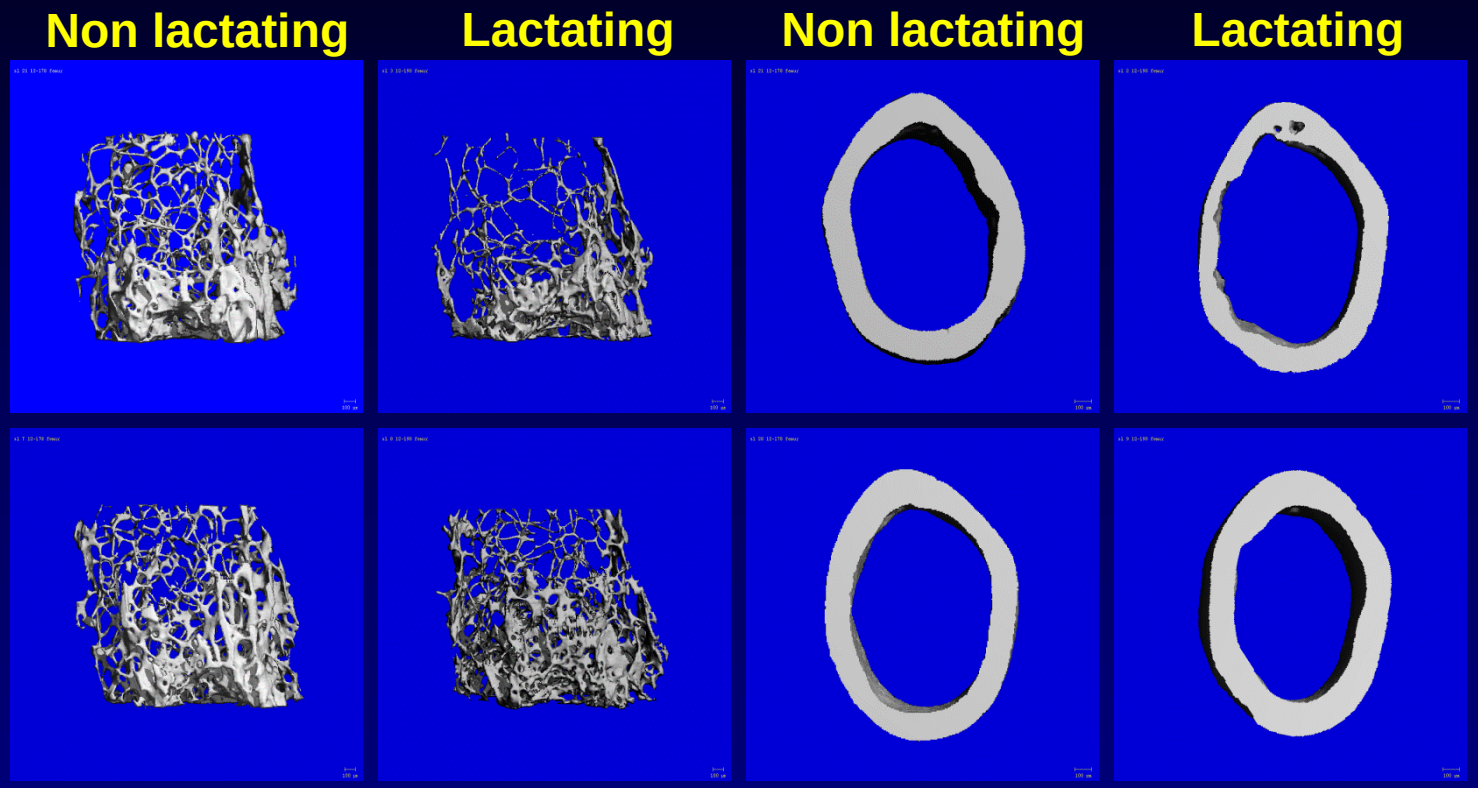
Osteocyte-specific Deletion of Cathepsin K Prevents Increased Bone Turnover, Bone Loss and Bone Fragility during Lactation in Mice

Author(s) Sutada Lotinun, Baron's Lab, Harvard, USA

Question: Is the induction of Ctsk in osteocytes contributing to the increased osteoclastic resorption and/or perilacunar osteolysis induced by lactation?

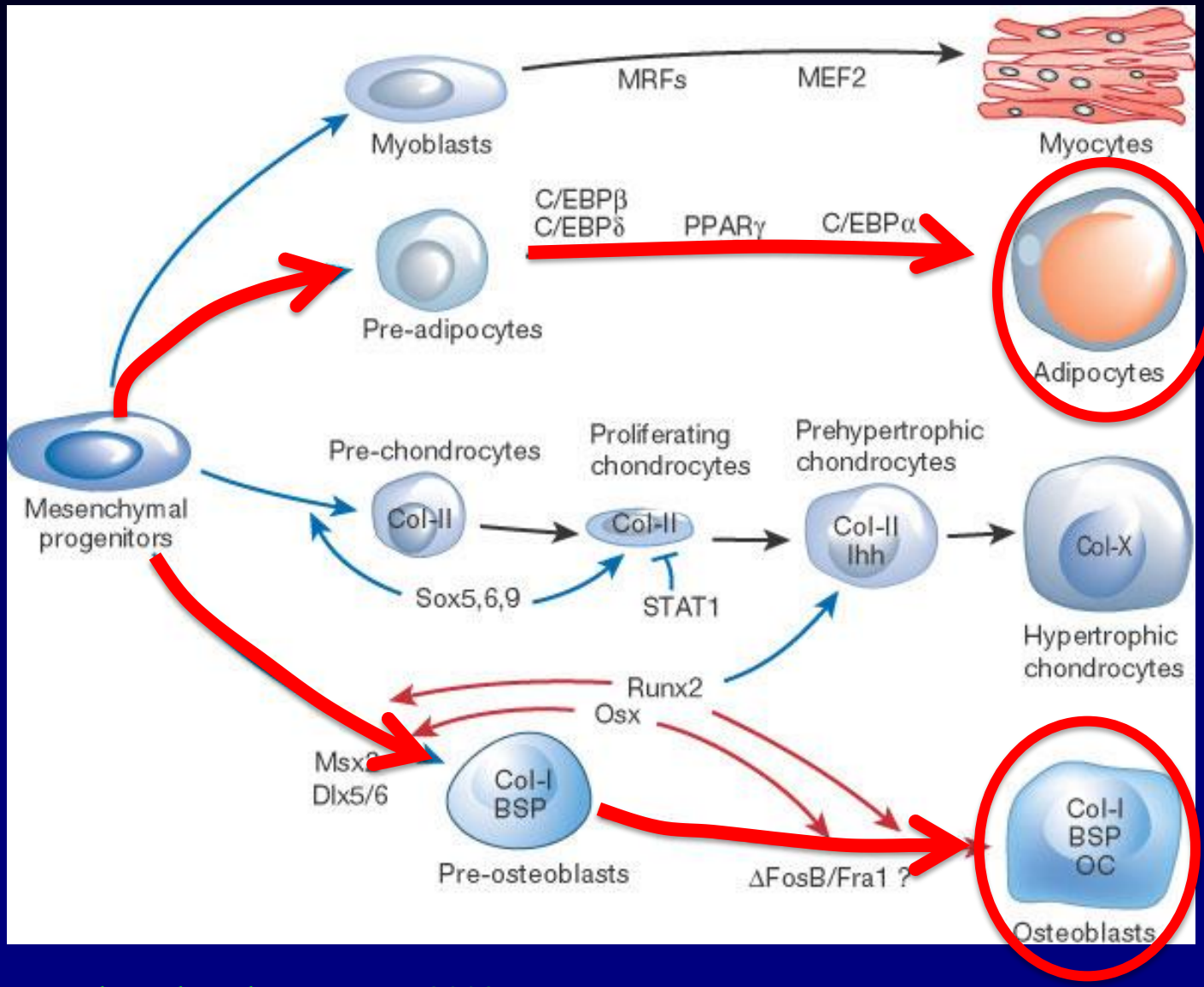
- At **steady state**, **deletion of Ctsk in osteocytes had no effect on bone remodeling and homeostasis**.
- As expected, **lactating control mice showed increased bone resorption and decreased BFR, leading to decreased TBV and altered mechanical properties**.
- This lactation-induced increased remodeling and bone loss **was prevented by deletion of Ctsk in osteocytes**
- **Lactation also increased osteocyte lacunar area (26%, $p<0.01$) in cortical bone and deletion of Ctsk in osteocytes prevented these changes.**
- Deletion of Ctsk in osteocytes **also prevented the negative effects of lactation on mechanical properties.**

Deletion of Cathepsin K in Osteocytes Protects from Lactation-induced Bone Loss



See Also : 1014 YOUNG INVESTIGATOR AWARD
MMP14 Is a Novel Target of PTH Required for Osteocytic PTH Receptor-Driven Bone Remodeling and Mineral Apposition
Jesus Delgado-Calle, Teresita Bellido's lab

Mesenchymal Progenitor Cell Lineages



Adapted from Harada and Rodan, *Nature*, 2003

[1021] MOST OUTSTANDING BASIC ABSTRACT AWARD

PTH administration regulates osteoprogenitor numbers and decreases their differentiation into the adipocytic lineage *in vivo*

Author(s) Deepak Balani (Kronenberg lab), MGH and Harvard, Boston, USA

Background: Mature OBs contribute to the PTH anabolic response but the role of osteoprogenitors is poorly understood. Sox9 promoter/enhancer labels progenitors with multi-lineage and self-renewing potential *in vivo*.

Question: Does PTH regulate the number of Sox9$^+$ progenitors *in vivo* and direct them towards the osteoblastic lineage?

Results: creER-mediated lineage-tracing strategy using 6-8 week old **Sox9**creER^{T2};Rosa26-td**Tomato**, **Ocn-GFP triple transgenic mice.**

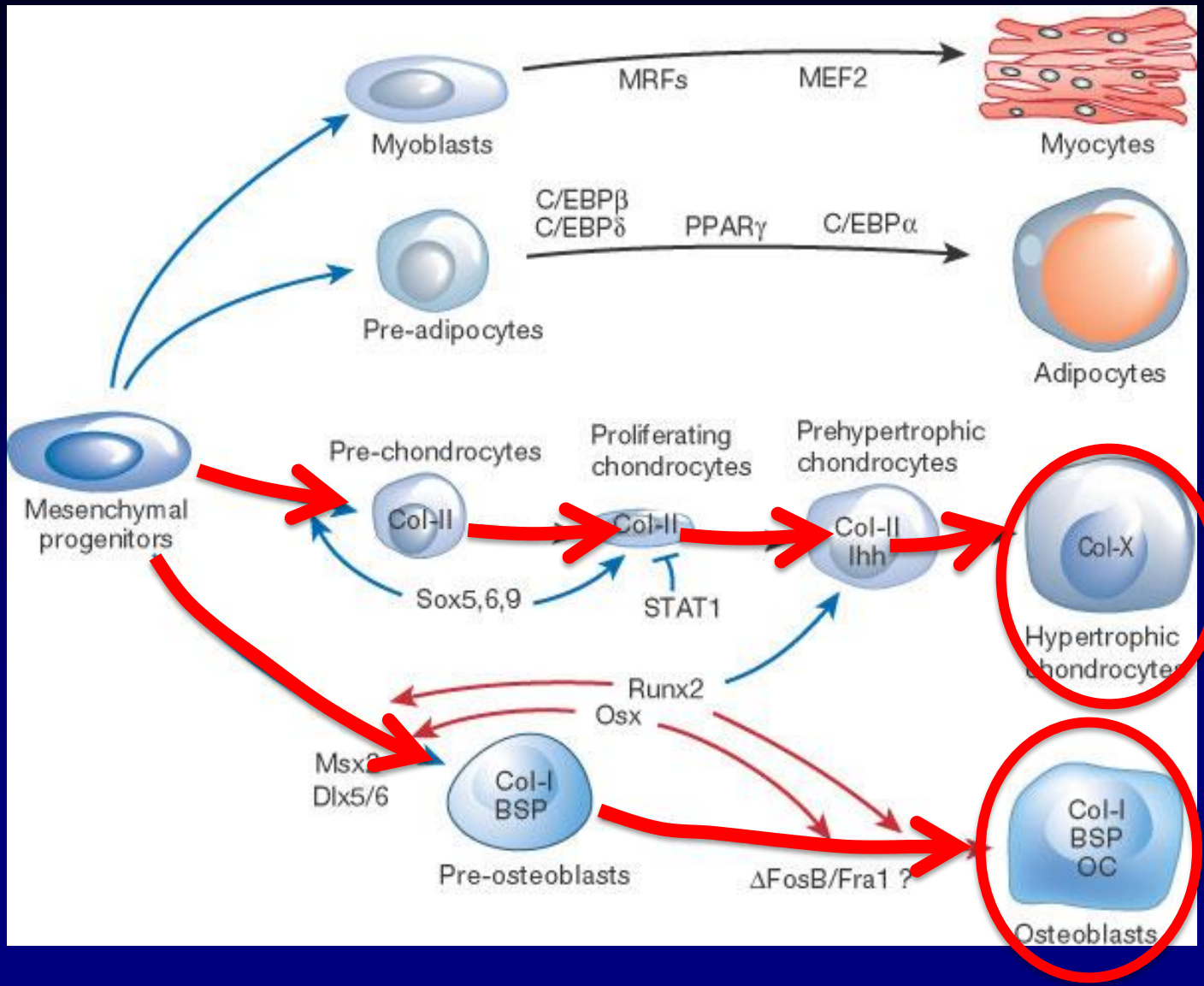
- **Tomato$^+$ cells were increased by PTH** in a dose and time-dependent manner.
- **PTH increased their proliferation**. The increase in Tomato$^+$ cells was seen in the primary spongiosa, periosteal and endocortical surfaces.
- On Day 7 and 21 several **Tomato$^+$ cells also expressed Ocn-GFP** as OBs or as osteocytes.
- At 21d of PTH and after PTH withdrawal for 4 weeks there was a **significant increase in bone marrow adiposity. A fraction of adipocytes was Tomato$^+$**.

See Also [1126] Identification of a Distinct Progenitor Cell within Long Bones that Gives Rise to Bone Marrow Adipocytes In Vivo

Authors: Ryan Berry, Mark Horowitz's lab, Yale University, USA

Conclusion: 1) There is a bi-potent "MSC" lining the endosteum that generates both osteoblasts and BM adipocytes 2) MAT, distinct from brown or white adipose tissue.

Mesenchymal Progenitor Cell Lineages



Harada and Rodan, *Nature*, 2003

[1110]

Transition of Chondrocytes into Osteoblasts in Endochondral Bones Requires Active Canonical Wnt Signaling

Authors: Xin Zhou, de Crombrugghe, Andreeff labs, MD Anderson Houston, UNITED STATES

Background: Recent **lineage tracing studies** demonstrated that **mature chondrocytes**, both in cartilage primordia, in growth plates and in bone repair calluses, **are a major source of osteoblasts during endochondral ossification.**

Question: Are chondrocyte-derived cells present in the bone marrow compartment?

Results:

- In ***Col10a1-Cre; ROSA26-YFP*** mice **0.1% of the bone marrow cells were YFP$^+$. Likewise for GFP+ cells in *Col10a1-Cre;Osx GFP* mice. Both** the YFP$^+$ and the GFP$^+$ bone marrow cells **were positive for MSC markers.**
- **YFP$^+$or GFP$^+$ bone marrow cells displayed clonogenic osteogenic, chondrogenic and adipogenic** capacities *in vitro*. Thus, **hypertrophic chondrocyte-derived MSCs are present in the bone marrow** and a fraction of **MSCs were *Osx*-expressing cells derived from mature hypertrophic chondrocytes.**
- **After inactivation of β-catenin in hypertrophic chondrocytes, BFR decreased and only tomato$^+$ bone marrow cells, but no tomato$^+$ osteoblasts or osteocytes were observed**

Conclusion: chondrocyte-derived cells are present in the bone marrow and Wnt signaling is needed for chondrocyte-derived progenitors to differentiate into mature osteoblasts.

[1150] ASBMR'S PRESIDENT AWARD

Chondrogenesis is an essential physiological phase of endochondrogenesis but not separated from osteogenesis

Author(s) Yinshi Ren, Jian Feng's lab, MD Anderson, Texas UNITED STATES

Background: hypertrophic chondrocytes undergo apoptosis prior to endochondral bone formation and chondrogenesis is considered a separate process from osteogenesis. However, cell lineage studies suggest that chondrocytes can directly transform into bone cells.

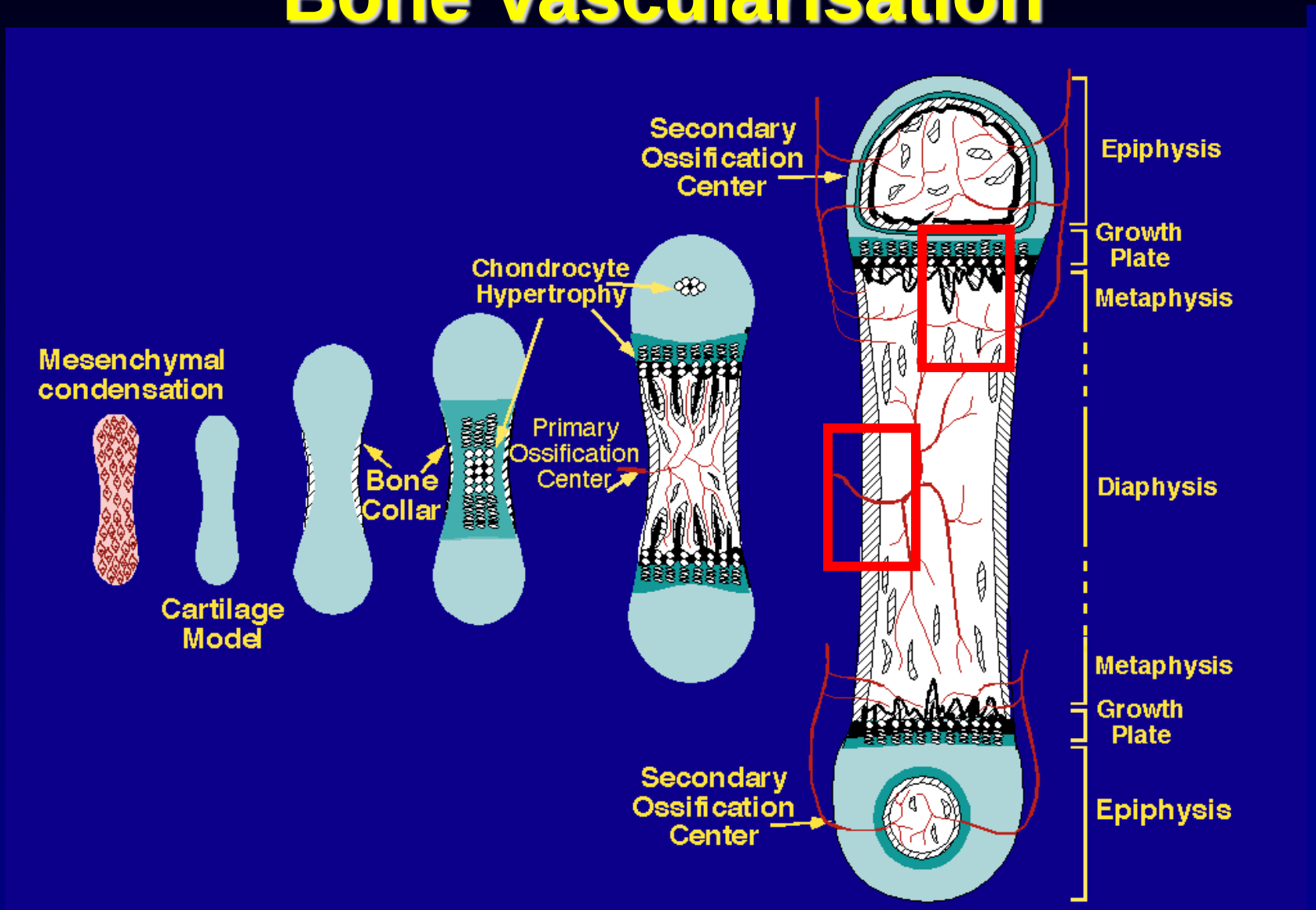
Question: Are chondrogenesis and osteogenesis two separate processes?

Results:

- **Not all hypertrophic chondrocytes undergo aopotosis**
- hypertrophic chondrocytes **divide and express high ALP activity (early bone marker)**.
- **In culture of newborn cartilage** on chick chorioallantoic membrane, **cells express *Col1* (bone marker) and produce bone-like matrix.**
- Cartilage-specific **cell lineage tracing in mice showed direct transformation of chondrocytes into bone and endothelial cells in vivo.**

Conclusion: chondrogenesis is an initial phase of "endochondrogenesis", where chondrocytes undergo apoptosis, divide, become bone cells, or give rise to endothelial cells for de novo vessel formation in subchondral bone formation. This challenges the dogma that chondrogenesis is a separate process from osteogenesis during endochondral bone formation.

Endochondral Ossification and Bone Vascularisation



1127

Deletion of PTH/PTHrP Receptor in Osteoprogenitors Deregulates Local Bone Marrow Vasculature in Mice

Author(s) Cristina Panaroni, Stanford University School of Medicine, UNITED STATES

Background: Osteogenesis and angiogenesis in skeletal tissues are coupled. **(Osx) cells, (osteoprogenitors), co-invade cartilage with growing vessels during endochondral bone formation and are adjacent to blood vessels. Disruption of the PTH1R** in mature osteoblasts and osteocytes **reduces bone formation and impairs endochondral angiogenesis**.

Question: Does ablation of PTH1R in osteoprogenitors alter bone vasculature?

- **Osx-PPR KO mice show a reduction in BM blood vessels**, especially along the endosteal bone surface, with a reduction of CD31+ endothelial cells.
- **In vitro, Osx cells increased the vascular tubes** length, number, branching and the loops **formed by endothelial cells.**
- in sorted osteoprogenitors, **genes involved in vasoconstriction, coagulation, chemotactic activity and inflammatory response were significantly upregulated in Osx-PPR KO cells, whereas the expression of VEGF-A, was reduced.**

Conclusion: Osterix-expressing cells (osteoprogenitors) actively support angiogenesis, and PPR signaling in these cells locally regulates the BM vasculature.

[1050] **YOUNG INVESTIGATOR AWARD**

Osteocyte-specific HIF-1alpha Signaling Regulates Bone Mass and Protects Mice From Osteoporotic Bone Loss

Author(s) Steve Stegen, Peter Carmeliet and Geert Carmeliet's labs, KU Leuven, BELGIUM

Background: osteocytes depend on adequate oxygen and nutrient delivery. **Cells respond to decreases in oxygen tension by activating hypoxia-inducible factor (HIF), which is regulated by the prolyl hydroxylase (PHD) oxygen sensors.**

Question: What is the role of PHDs in osteocytes ?.

Results:

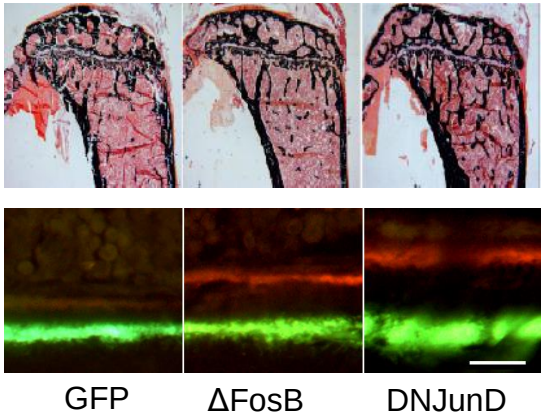
- **Deletion of *Phd2* in osteocytes** (PHD2^{ot-}), results in **osteocytic HIF-1alpha stabilization**.
- **Trabecular and cortical bone mass was increased from enhanced bone formation and decreased resorption.**
- **PHD2^{ot-} mice displayed an increase in the number of viable osteocytes in cortical bone**.
- ***Sost* expression was decreased**, but not *Dmp1* or *Phex*, explaining the changes in bone mass.
- The **number and size of blood vessels was increased** in the bones of PHD2^{ot-} mice, **due to elevated bone *Vegf* levels.**
- **PHD2^{ot-} mice were protected from bone loss after hindlimb suspension or ovariectomy.**

Conclusion: activation of the HIF pathway in osteocytes increases bone formation and mass and protects mice during hindlimb unloading and ovariectomy.

BRAIN

AAV Expression of **ΔFosB**
In the ventral hypothalamus (VHT) blocks AP1 signaling

BONE



↑ Bone mass

?

Which neuronal circuit? What Mechanism?

METABOLISM

↓ Body weight
↑ Insulin sensitivity
↑ Energy expenditure
↑ Feeding
↓ Locomotion

(Rowe et al., JBMR 2012)

[1083]

Critical Role of Galanin in the Hypothalamic Neuronal Regulation of Bone Density and Energy Expenditure by AP-1 Antagonists

Author(s) Anna Idelevich, Roland Baron's lab, Harvard, Boston, USA

Purpose: **identify the individual AP1- responsive neurons in the VHT that mediate the metabolic and/or skeletal effects, and determine the mechanisms by which they exert their actions.**

Results:

- **Cre-inducible lentiviral vectors expressing AP1 antagonists** (ΔFosB, Δ2ΔFosB and DNJunD) **or the AP-1 agonist FosB** were constructed.
- Their **expression was restricted by stereotaxic delivery into the VHT of mice expressing Cre- in specific neurons AgRP-Cre, NPY-Cre, CART-Cre, POMC-Cre.**
- **AP-1 inhibition in any of the 4 ARC neurons decreased fat and increased energy expenditure and bone density**.
- **VHT gene expression identified galanin as a downstream neuromediator of ΔFosB effects.**
- **Deletion of galanin,** VHT delivery of galanin **receptor antagonist or silencing of galanin in the same Cre-inducible neurons blocked the metabolic and the bone effects.**
-

Conclusions: 1) Inhibition of AP-1 in any ARC neuron subtype stimulates metabolism, decreases fat and increases bone density 2) Downstream of AP1, galanin acts as a central neuromediator, common to several hypothalamic neurons, to regulate bone and energy.

[1084]

Osteocyte-specific ablation of Pparγ increases bone mass and improves energy metabolism

Author(s) Nicolas Bonnet, Serge Ferrari's lab, University Geneva Hospital (HUG), SWITZERLAND

Background: Pparγ is a master transcriptional regulator of energy metabolism, and both Pparγ haploinsufficient mice and osteoblast-targeted Pparγ-deficient mice have increased bone mass and osteoblastogenesis.

Question: What is the role of Pparγ in late osteoblast/osteocytes (ocy) on bone (re)modeling and energy metabolism?

Results:

- At 3 months DMP1-Cre- Pparg -/- mice **metabolism was unchanged** but femoral **BMD was higher** in both Trabecular and cortical bone.
- From 3 to 9 months, BMD remained higher and **age-related changes in fat and lean mass were attenuated.**
- At 9 months, **heat production was higher** without changes in food intake. Body temperature was **higher in the BAT-rich neck region and in the limbs**. As a result, **GTT was improved**.

Conclusion: **Deletion of Pparγ in Ocy increases periosteal BFR and lowers bone turnover, resulting in high bone mass. Moreover, Pparγ in osteocytes regulates energy, causing age-related changes in body composition and glucose homeostasis, suggesting a role for osteocyte Pparγ in diabetes bone disease.**

[1027] MOST OUTSTANDING TRANSLATIONAL ABSTRACT AWARD

Maternal Obesity Programs Senescence Signaling and Glucose Metabolism in Fetal Osteoblastic Cells

Authors: Jin-Ran Chen, et al., University of Arkansas, USA

Background: Nutritional status during intrauterine and early postnatal life impacts the risk of chronic diseases, presumably via epigenetic mechanisms. However, evidence for an impact of gestational events on regulation of bone development is sparse.

Question: Does maternal obesity affect bone development in mice and in humans?

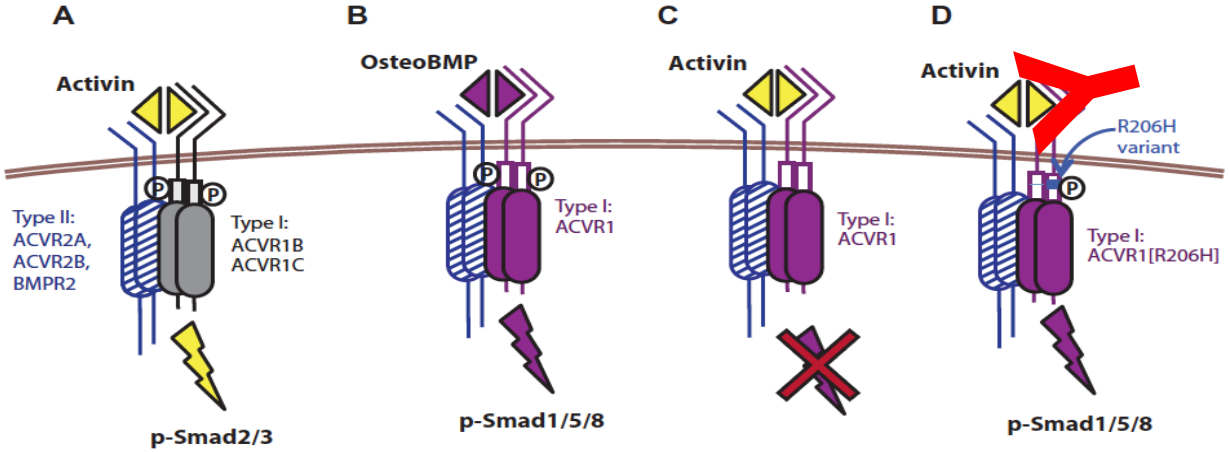
Results:

- **Female rats fed a low- or a high fat diet (HFD), were time-impregnated by control diet male rats. At day E18.5, embryonic osteogenic calvarial cells (EOCCs) were isolated**.
- **in EOCCs epigenetic regulation of polycomb-regulated genes was increased**, **associated with increased cell senescence signaling.**
- **This increase of cell senescence and decreased aerobic glycolysis were imprinted in HFD-EOCCs resulting in decreased OB differentiation.**
- **MSCs (umbilical cord) were isolated from 12 obese and 12 lean pregnant women. The UC MSCs of obese mothers displayed less osteoblastogenesis and more adipogenesis.**
- **UC MSCs and placentas exhibited increased cell senescence signaling, decreased glucose metabolism and high insulin resistance.**

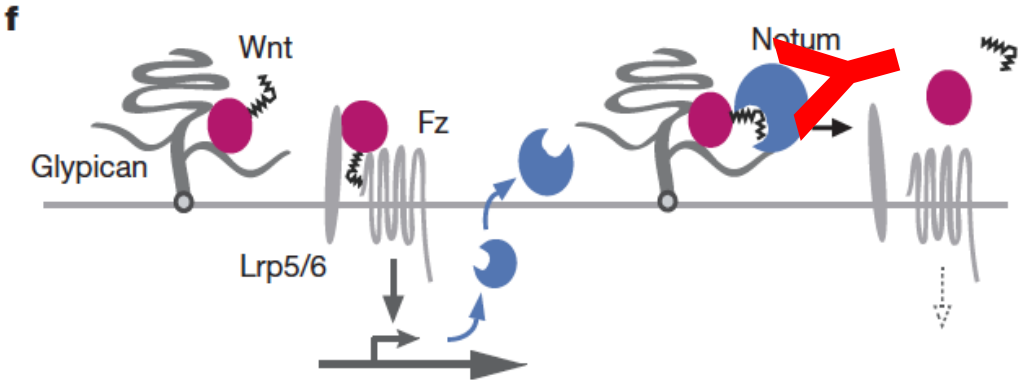
Conclusion: Fetal pre-osteoblastic cell senescence signaling and glucose metabolism are programmed by maternal obesity in both rodents and humans.

NEW DRUGS

- **Activin antibodies for FOP and other HOs**



- **Notum antagonists for Osteoporosis**



[1029]

PCO371, an orally active small-molecule PTH1R agonist for the treatment of hypoparathyroidism

Author(s) Hiroshi Noda, et al., Chugai Pharmaceutical Co., Ltd., JAPAN

Background: Hypoparathyroidism (hypoPT) is a rare disease characterized by hypocalcemia. **Conventional therapy of hypoPT** (oral Ca and active vitamin D analogs) **increase the risk of hypercalciuria.** Since hypoPT is a chronic disorder, there is **a need for an orally bioavailable small-molecule which can mimic PTH.**

Question: Can orally active small molecule agonists of the PTH1R be developed? .

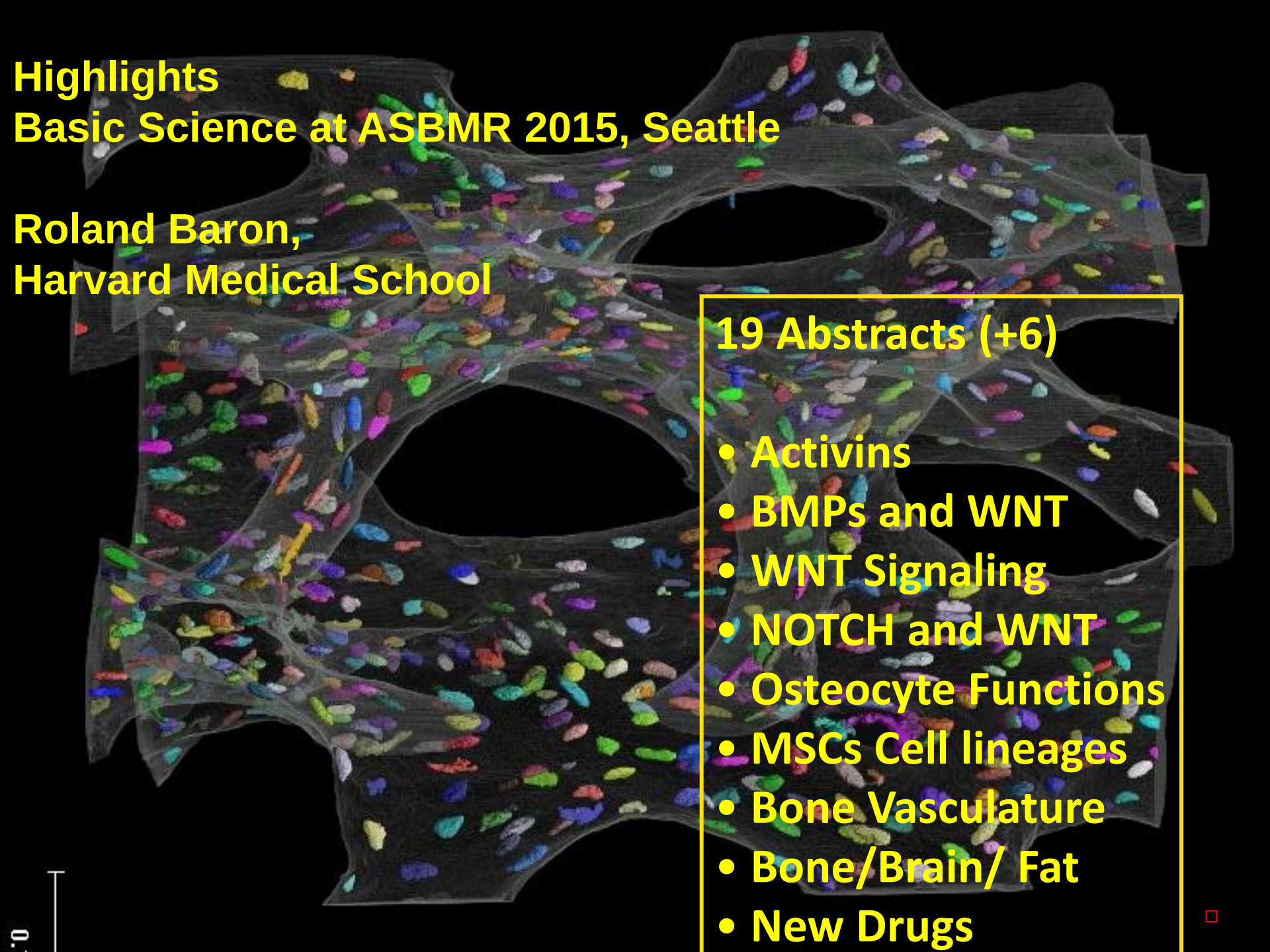
Results:

- **High throughput screening** with LLC-PK1 cells expressing the human PTH1R (hPTH1R) identified Hit-compounds, then optimized to identify a clinical candidate**, PCO371.**
- **PC0371 stimulated cAMP production and PLC activation** in a dose-dependent manner and **displaced ^{125}I-labeled hPTH(1-15)**.
- **PCO371 stimulated Ca release in fetal rat long bone cultures as well as hPTH(1-34).**
- **Single oral administration of PCO371 showed calcemic and hypophosphatemic actions in TPTX rats that were more potent and long-lasting than those of hPTH(1-34).**
- In **repeated dosing** studies in TPTX rats, **once-daily oral PCO371 normalized serum Ca**.

Conclusion: PCO371 is the first example of an orally active small-molecule PTH1R agonist that can mimic the biological functions of PTH. It provides a new treatment option for hypoPT patients.

Highlights
Basic Science at ASBMR 2015, Seattle

Roland Baron,
Harvard Medical School



19 Abstracts (+6)

- Activins
- BMPs and WNT
- WNT Signaling
- NOTCH and WNT
- Osteocyte Functions
- MSCs Cell lineages
- Bone Vasculature
- Bone/Brain/ Fat
- New Drugs

ASBMR- Annual Meeting
Seattle, Washington
October 9, 2015

Highlights of the ASBMR 2015 Annual Meeting

John P. Bilezikian, MD
Roland Baron, DDS, PhD

The ASBMR Program for 2015

- **Special Sessions**
  - **Special Symposium: Kidney and Bone Symposium (10/8)**
  - **Named plenary lectures (Gerald D. Aurbach Lecturer: B. Spiegelman-10/9; Louis V. Avioli Lecturer: M. Whyte-10/11)**
  - **Plenary Symposia**
  - **Symposia**
  - **Clinical and Basic Science Evening at ASBMR**
  - **Debate (ASBMR-ECTS)**
  - **Grant Writing Workshop**
  - **Special Reports (ASBMR Task Forces: Vertebral Augmentation; Cell-based Therapies)**

The ASBMR Program for 2015

- **Special Sessions (cont'd)**
  - **NIH K Awards- Challenges and Opportunities**
  - **Small Ways to Utilize Big Data in Your Research**
  - **Increase Your Chances of Getting Published**
  - **Scientific Integrity**
  - **Career Development: How to Make Successful Transitions**
  - **ASBMR Annual Town Hall Meeting**

The ASBMR Program for 2015

- **Networking Sessions**
  - **Welcome Reception**
  - **New Member Reception**
  - **Young Investigator Networking Hour**
  - **Young investigator Networking Breakfast**
  - **Networking Event**
  - **Diversity Happy Hour**

The ASBMR Program for 2015

- Meet The Professors (16 clinical/translational; 8 basic- Fri, Sat, Sun, Mon)
- Working Groups (8: Fri, Sun eves)
- Oral abstracts 152 (10.8% of total 1410*)
- Late-breaking abstracts 115

2015: Total (not including late breaking abstracts) = 1448

Distribution of all abstract presentations (orals and posters)

- A. *Osteoblasts 102 (7%)*
- *B. Osteocytes 39 (3.0%)*
- *C. Osteoclasts 71 (5.0%)*
- D. *Bone, Cartilage and Connective Tissue Matrix & Development 85 (6.0%)*
- *E. Modulators of Bone Remodeling 102 (7.0%)*
- *F. Hormonal and Paracrine Regulators 86 (6.0%)*
- *G. Energy Metabolism, Bone, Bone Marrow Niche 75 (5%)*
- *H. Genetic Disorders of the Musculoskeletal System 31 (2.0%)*
- I. *Bone Tumors and Metastases 36 (3.0)*

Distribution of all abstract presentations (orals and posters)- cont'd

- J. *Osteoporosis – Assessment* *63(4.0%)*
- K. *Osteoporosis – Epidemiology* *92 (7.0%)*
- *L. Osteoporosis - Treatment 76 (5.0%)*
- M. *Osteoporosis – Pathophysiology 35 (2.0%)*
- *N Osteoporosis- Secondary causes 16 (1%)*
- *O. Osteoporosis- Health Care Delivery 35 (2%)*
- *P. Osteoporosis- Nutrition and Dietary Supplements 33 (2%)*
- *Q. Osteoporosis in Special Populations 45 (3%) – new category*
- R. *Aging, Osteoarthritis and Muscle/Bone Interactions 68(4.0%)*
- S. *Biomechanics, Mechanobiology, and Quality 147 (10.0%)*
- *T. Bone Acquisition and Pediatric Bone Disease 32 (2.0%)*
- *U. Adult Disorders of Mineral Metabolism 69 (4.0%)*
- *V. Muscle biology and bone 23 (2 %)*
- *W. Rare and Other Bone Diseases 58 (4%)*

All osteoporosis-related categories: 26% (2015), 27% (2014), 31% (2013), 34% (2012)

All Abstracts reduced by 4% in 2013: 6% in 2014; 2.7% in 2015 (not including late-breaking abstracts)

Trends and special emphasis that you may notice at the 2015 ASBMR meeting

- Therapeutics of Osteoporosis (including Randomized Clinical Trials)
- Epidemiology of Osteoporosis
- Vitamin D, Calcium and Nutrition
- Musculoskeletal Biology

Trends and special emphasis that you may notice at the 2015 ASBMR meeting (continued)

- Pediatrics and developmental aspects of bone accrual
- Application of high resolution imaging to clinical situations
- Genetics as applied to clinical aspects of skeletal health
- Rare Bone Diseases

Highlights of the ASBMR 2015 Annual Meeting*

Bilezikian:

Clinical Science Meeting Overview

Baron:

Basic Science Meeting Overview

***Data presented at this session in anticipation of the actual abstract presentations are embargoed until the time of the abstract presentations**

Acknowledgements*

- Jessica Bihuniak
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- Didier Hans
- Karl Insogna
- Tony Keaveny
- Bill Leslie
- Nicola Napoli
- Tom Nickolas
- Hiroshi Noda
- Mike Ominsky
- Rachel Wagman

*Provided me with material relevant to their presentations

Topics to be covered

- EFF-ASBMR Fellows' Symposium
- Vitamin D, Calcium, Nutrition
- Epidemiology and Outcomes Research
- Exercise, Muscle, Sarcopenia, Frailty Biomechanics, Aging
- Imaging, Microstructure, Material Properties, Histomorphometry
- Therapeutics of Osteoporosis
- Diabetes, Obesity and Bone
- Rare and Other Metabolic Bone Diseases
- Pediatrics/Adolescents/Development
- Clinical Genetics
- Osteoarthitis
- Others

9th EFF-ASBMR FELLOWS FORUM ON METABOLIC BONE DISEASES
October 7-8, 2015

ASBMR®
The American Society for Bone and Mineral Research

ENDOCRINE FELLOWS FOUNDATION

55 Attendees
11 countries represented
35% International
50/50 MDs and PhDs
3 Plenary Lectures and 7 workshops
11 Faculty (basic & clinical)
Fellows presented 39 abstracts!

VITAMIN D,CALCIUM,NUTRITION

Sun: 10/11 **7:15 PM**	**Working Group: Nutrition (registration fee)**	**S. Shapses**
Mon: 10/12 **11:30 AM**	**MTP: Calcium and Vitamin D: Current Status**	**C. Gallagher**

Abstracts of note: #s **1087, 1088***, **1089**,1090,**1091**,**1092**,1096

* Most outstanding Clinical Abstract (see Genetics)

Vitamin D: the highs and the lows!

#1089: Rasmussen et al. High dose vitamin D Supplementation on Bone Metabolism in Pregnant women with low vitamin D (< 20 ng/mL); [3 grps: 2800IU, 1400IU or PLB daily.

Post partum bone loss not prevented by vitamin D:
At 2800 IU dose, femoral neck BMD fell more:

#1091: Fuleihan et al. A Randomized Trial Investigating Impact of Vitamin D Replacement on Indices of Insulin Resistance in Elderly Overweight subjects.

High dose (3500 IU daily vs 600 IU vs Plb) did not improve insulin resistance. An increase in FBS correlated with the rise in 25(OH)D.

Abs #1087: Binkley et al. Vitamin D Status and Bone Mineralization: A Histomorphometric Analysis

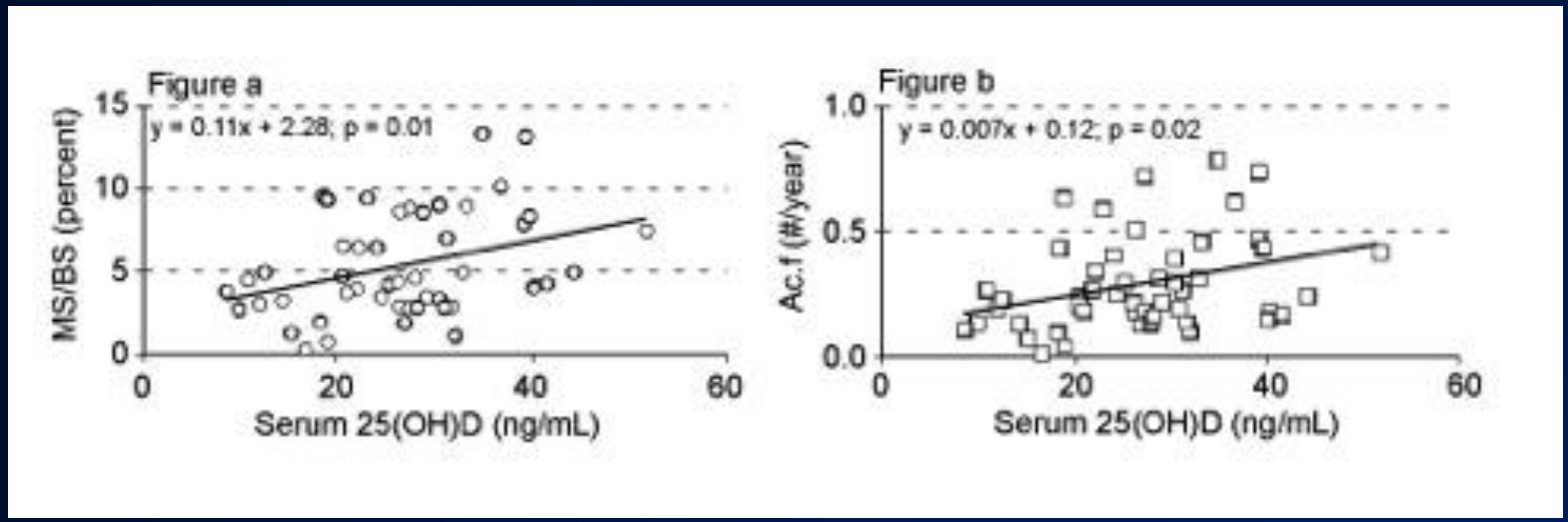
Background: Defining Vitamin D insufficiency is controversial (!).

Question: Is there an association between serum 25(OH)D and histomorphometric data in early postmenopausal women? (leading to a new definition of sufficiency?)

Design: 50 early PM women underwent bone biopsies 12 mos after their last menses. 25(OH)D levels vs static and dynamic indices were studied in relationship to each other

Abs #1087: Binkley et al. Vitamin D Status and Bone Mineralization: A Histomorphometric Analysis

- Static histomorphometric parameters related to bone mineralization, (i.e., osteoid thickness, osteoid volume and osteoid surface) were unrelated to 25(OH)D (data not show)
- **Mineralizing surface and activation frequency positively correlated ($p < 0.05$) with 25(OH)D**

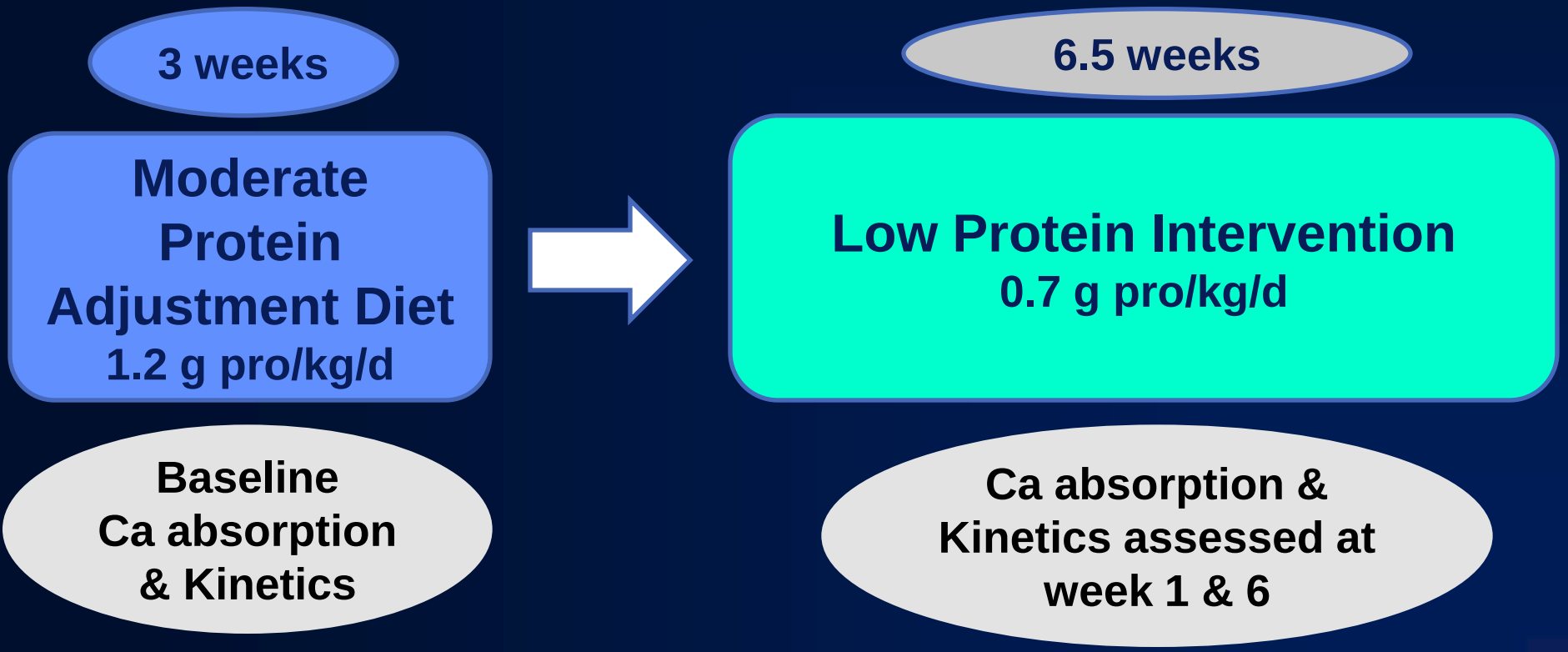


Conclusion: Optimal value to facilitate bone mineralization remains to be defined

Abs #1092: Bihuniak et al. The effects of a Longer-Term, Low-Protein Diet on Calcium Absorption and Kinetic Measures of Bone Turnover in Young Women (11 premenopausal women)

Background: Increases in dietary protein lead to increased Uca due to increased Ca absorption, not increased bone resorption

Question: What are the consequences of low protein diets?



Abs #1092: Bihuniak et al.

- Low protein consumption resulted in:
  - ↓ urinary Ca
  - ↓ intestinal Ca absorption
  - ↑ serum CTX (trend)
  - ↓ bone balance (trend)
    all subjects in negative Ca balance at 6.5 weeks
  - ↑ fraction of UCa from **bone**

Conclusion: Initial effects of low protein diets are to reduce calcium absorption and to increase bone resorption

Abs #1088*: Hsu et al. Interactions of Genetics Variants and Vitamin D Intake on Serum Vitamin D Level: (*Most Outstanding Clinical Abstract)

Background: Concentrations of 25(OH)D_3 depend upon many factors, including possible genetic factors

Question: Are there interactions between genetic variants and vitamin D intake on 25(OH)D_3 concentration?

Design: GWAS meta-analysis in 34,915 Caucasian men and women.

Results: Several SNVs were identified for 25(OH)D_3 levels and for vitamin D intake.

Conclusion: The relationship between vitamin D intake and 25(OH)D concentration may be mediated by genetic variation.

CONCLUSION:

Optimal Vitamin D levels and clinical endpoints are still controversial!

Genetics continue to hold promise

EPIDEMIOLOGY AND OUTCOMES RESEARCH

Sat: 10/10 **11:30 AM**	**Symposium: Small Ways to Utilize Big Data in Your Research**	**L. Bonewald, F. Rivedeneira, M. Brown, M. Mourano**
Mon: 10/12 **11:30 AM**	**Implementing a Fracture Liaison Service**	**P. Geusens**

Abstracts related to Epidemiology

1063, **1065,1067 (in diabetes),**1068,1112,1115,1116,1137,**1138**,**1140**,LB 1153

Abstracts related to Outcomes Research

1066, 1073,1146,**1116**,**1145**, **LB 1153**

#1065: Leslie et al. Are Psychiatric Illnesses and the Medications Used to Treat Them FRAX-Independent Risk Factors? The Manitoba BMD Cohort

Background: Psychiatric illnesses and medications have not been systematically investigated as independent risk factors for fracture

Question: Do psychiatric illnesses and medications influence fracture risk assessment by FRAX?

Design: Manitoba Study. 68,730 women and men: 15 yrs. 8.1% MOF, 2.2% HF.

Abs # 1065. Leslie et al. Hazard Ratios Diagnoses and Drugs Analyzed Separately

	MOF HR (95% CI)*	HF HR (95% CI)*
Depression	**1.39 (1.27-1.51)**	**1.43 (1.22-1.69)**
Anxiety	**1.19 (1.09-1.30)**	1.08 (0.90-1.28)
Schizophrenia	**1.82 (1.16-2.85)**	**2.34 (1.05-5.21)**
SSRI	**1.47 (1.32-1.63)**	**1.51 (1.22-1.85)**
Tricyclics	1.06 (0.94-1.20)	1.21 (0.97-1.52)
Other antidepressants	**1.30 (1.09-1.55)**	1.09 (0.74-1.60)
Lithium	0.82 (0.46-1.44)	Insufficient #
Mood stabilizers	**1.41 (1.12-1.77)**	1.25 (0.80-1.94)
Antipsychotics	**1.48 (1.21-1.81)**	**2.18 (1.58-3.02)**
Benzodiazepines	**1.16 (1.05-1.28)**	**1.23 (1.04-1.45)**

* Adjusted for FRAX probability with BMD and prior osteoporosis drug use.

#1065: Leslie et al. Are Psychiatric Illnesses and the Medications Used to Treat Them FRAX-Independent Risk Factors? The Manitoba BMD Cohort

Results: FRAX underestimated 10-yr Fx risk in those with depression or taking SSRIs, mood stabilizers, antipsychotics, or benzodiazepines.

Conclusion: FRAX underestimates Fx risk in those with depression or who are taking several different kinds of psychotropic drugs.

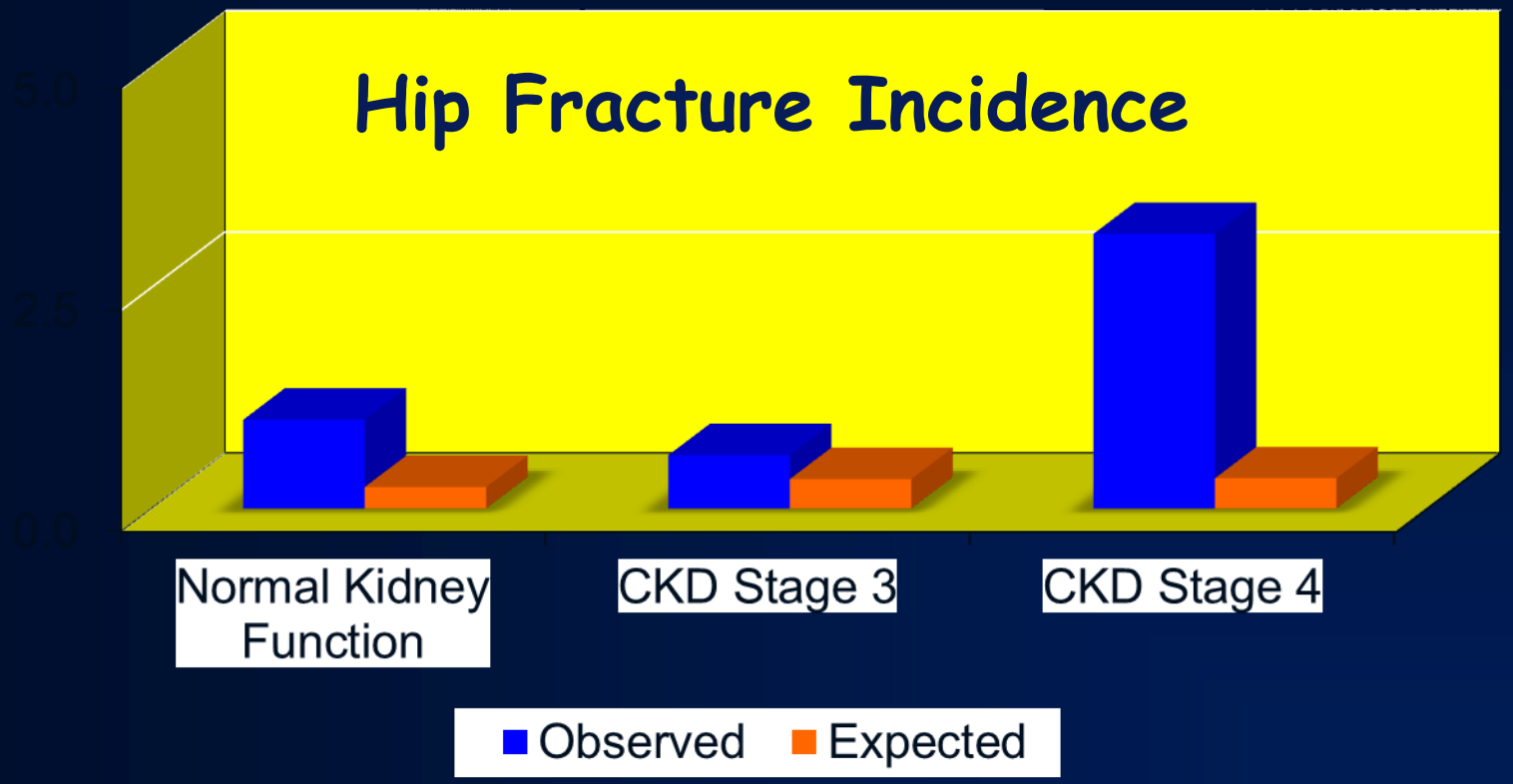
#1138: Nickolas et al. FRAX Underestimates Hip Fracture Risk in Older Men with CKD

Background: KDIGO does not recommend BMD testing in severe CKD

Question: Can a cohort be used to assess MOF and Hip Fx risk without BMD in severe CKD?

Design: Veterans Aging Cohort Study (13,668 with/wo HIV). Modified FRAX (without BMD, parental or secondary OP hx) used. Stages 3,4, and 5 CKD

#1138: Nickolas et al. FRAX Underestimates Hip Fracture Risk in Older Men with CKD



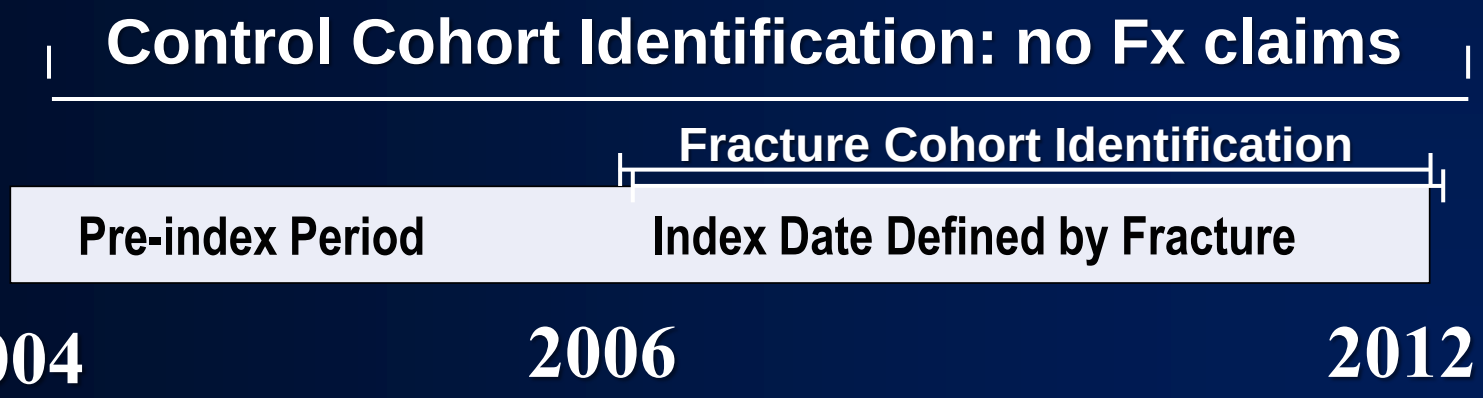
- **For Healthy Kidney Function and CKD Stage 3 there was mild to moderate underestimation of hip fracture incidence by the FRAX Tool**
- **For CKD Stage 4, FRAX underestimated by 8-fold hip fracture incidence**

#1066: Bonafede et al. Predicting Imminent Risk for Fracture in Patients With Osteoporosis Using Commercially Insured Claims Data

Background: Factors contributing to imminent fracture risk (occurring within a 12 month period) are not well defined

Question: What factors contribute to imminent fracture risk?

Design: Retrospective: Commercial and Medicare claims databases over 6 years for those who did or did not claim a new fragility fracture.



#1066: Bonafede et al. Predicting Imminent Risk for Fracture in Patients With Osteoporosis Using Commercially Insured Claims Data

(code-733- 1.3 million: 162K =incl criteria; 32K with Fx)

Table. Factors Associated With Imminent Risk of First Fracture Within 12 and 24 Months

Pre		
Fal		
Nar		
Eve		
Wh		
SS		
Cha		
Mo		
CNS disease	1.41 (1.30–1.52)	1.34 (1.25–1.43)
Muscle relaxant use	1.40 (1.34–1.47)	1.29 (1.25–1.35)
Charlson comorbidity index score* 3	1.40 (1.31–1.50)	1.42 (1.32–1.52)

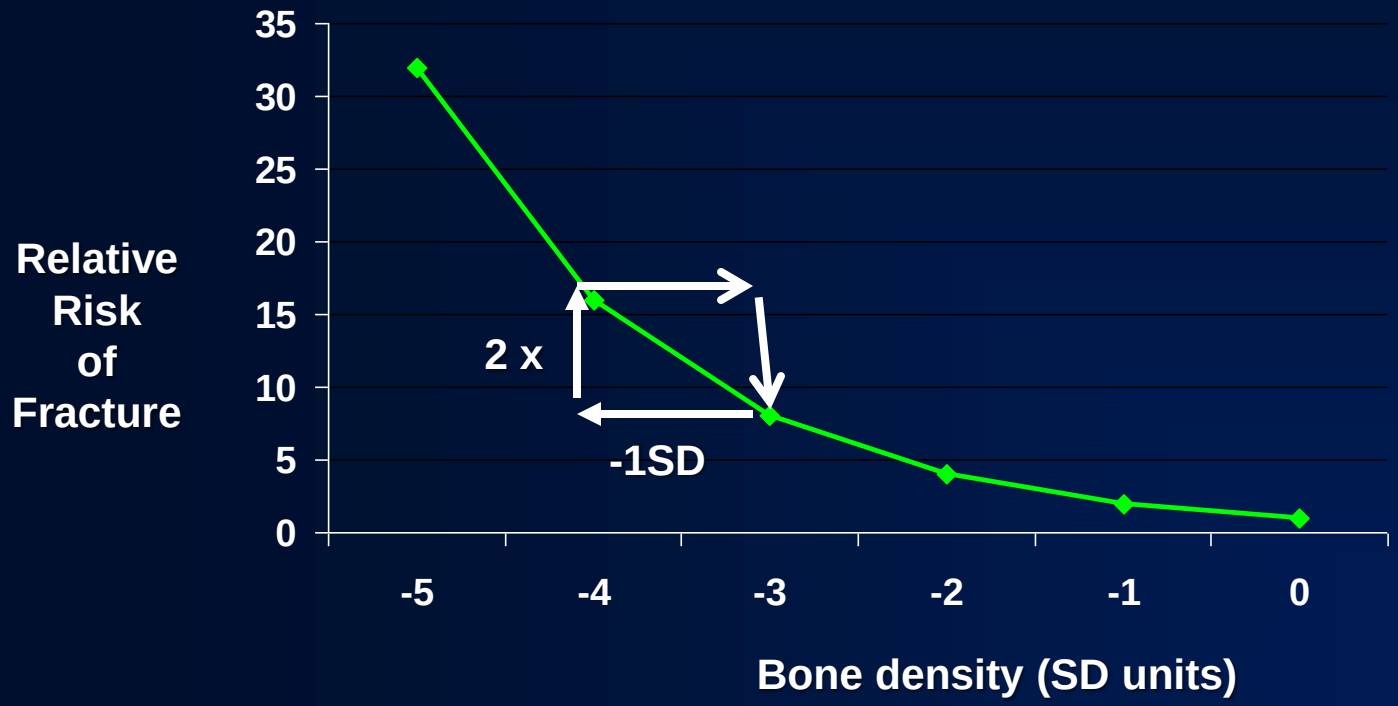
$p < 0.0001$ for all.
*Reference category: Charlson comorbidity index = 0.

Results: For the first Fx, all risk factors were fall related (previous falls, wheelchair use, psychoactives, age, and mobility impairment).

Conclusion: Fall-related risk factors help to predict imminent first fracture risk

DCI, Deyo-Charlson comorbidity index. Odds ratio > 1 indicates increased risk for fracture.

Revisiting the relationship between a therapeutic increase in BMD and reduction in fracture Risk

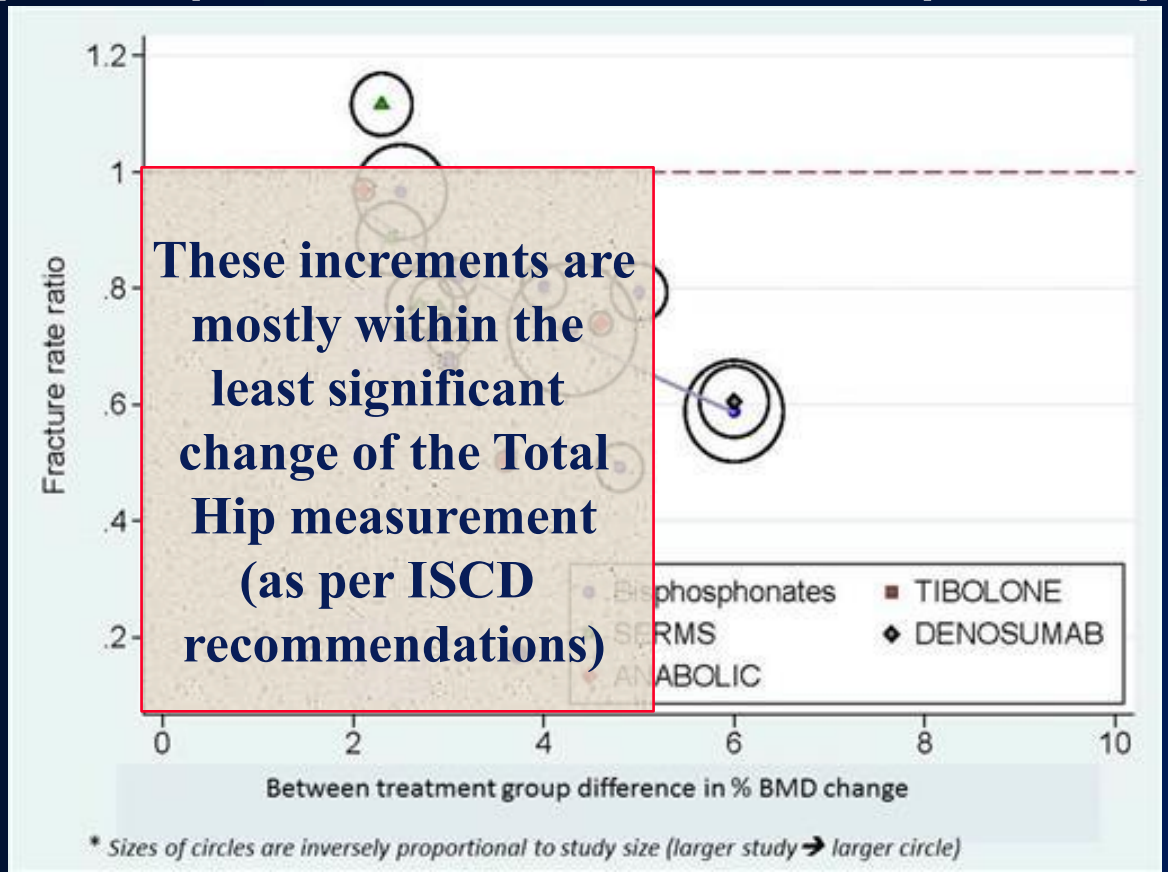


Adapted from Faulkner KG. *J Bone Miner Res.* 2000;15:183-187

#1145: Black et al. Hip BMD by DXA Can Reliably Estimate Reduction in Hip Risk in Osteoporosis Trials: A Meta-Regression

Mega Meta-regression analysis of Total Hip BMD changes with treatment and hip and non-Vert Fx. 14 trials for Hip; 30 trials for non-vert Fxs.

Changes in Total Hip BMD correlated with reduction in hip Fx: (r^2=0.57 p<0.001); for Non-vert much weaker (r^2=0.14, p=0.004)



These increments are mostly within the least significant change of the Total Hip measurement (as per ISCD recommendations)

#LB-1153: van Geel et al. Reduced Mortality and Subsequent Fracture Risk with Oral Bisphosphonates Treatment in Secondary Fracture Prevention: an Observational 8-Year Follow-up Study

- Long term follow up of about 9500 patients who were prescribed calcium/ vitamin D (50%) or that plus BPs.
- BP group at much greater risk for fracture.
- After all variables adjusted (age, gender, BMD, fracture location, alcohol, glucocorticoid use, smoking…)
- BP was associated with lower fracture risk (HR 0.59) and mortality (HR 0.79)
- Conclusion: there are long term benefits of BP Rx on fracture and mortality

Exercise, Muscle, Sarcopenia, Frailty Biomechanics, Aging

Fri: 10/9 10 AM	MTP: Osteosarcopenia: Managing Frailty	N. Binkley
Fri: 10/9 10 AM	MTP: Skeletal Aging	S. Manalagas
Fri: 10/9 7:15 PM	Working Group: Muscle and Bone	C. Gordon
Sat: 10/10 10 AM	MTP: Treating Osteoporosis in the Elderly: Is the Horse Ever Out of the Barn?	S. Greenspan
Sun: 10/11 7:15 PM	Working Group: Bone Strength	A. Cheung, R. Kremer

Exercise, Muscle, Sarcopenia, Frailty Biomechanics, Aging

Abstracts of Note: #s 1010, **1012**, **1064**, 1097, 1111, 1112, 1113,1114, **1115**			

#1012: Vico et al. Six-month of Spaceflight and 1 Year Follow-up Revealed Differential Responses of Cortical and Trabecular Bone Dependent on Bone Localization and Starting Bone Status

Background: 6-mos of space flight: tibial bone loss (cortical and trabecular) did not recover; radius no loss

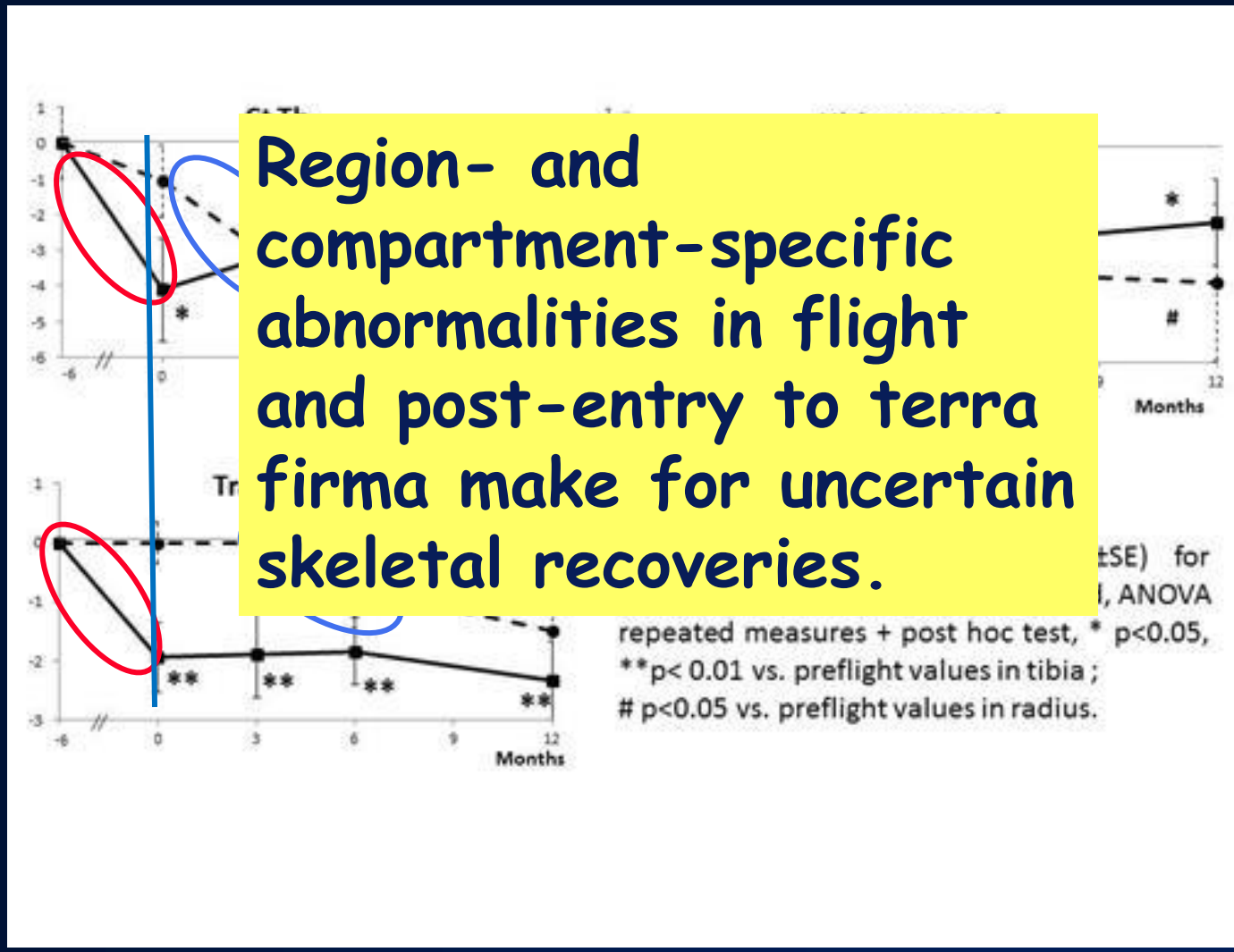
Question: Does it take longer for tibial bone loss to recover?

Design: 13 new astronauts in space for 6 mos with baseline and follow up HRpQCT measurements for up to 12 months.

#1012: Vico et al. Six-month of Spaceflight and 1 Year Follow-up Revealed Differential Responses of Cortical and Trabecular Bone Dependent on Bone Localization and Starting Bone Status

Tibia- losses in cortex and trab with recovery after 12 month for cortical thickness but not for Tb BV/TV or density

Radius- no inflight losses but 12 mos later, cortical and trabecular losses were seen



#1064: Coster et al. Increased Physical Activity in Childhood Reduces Fracture Risk- an 8-Year interventional Study in 3534 Children

Background: Exercise increases bone mass in children

Question: Does it influence fracture risk?

Design: 40' of exercise/school day x 8 yrs in 1339 children (6-8 yrs old). Control: 2,195 children in other schools 60 minutes/school week.

Results: RR for fx fell every year: at end RR reduction 0.48 (CI 0.25-0.91). Bone mass higher in the exercisers. Muscle strength greater

Conclusion: EXERCISE LEADS TO BETTER SKELETAL HEALTH IN CHILDREN.

#1115: Trombetti et al. Sarcopenia Predicts Fracture Risk in 65-Year Old Healthy Community Dwellers

- Sarcopenia leads to falls; falls lead to fractures
- Lean body mass is defined variously
- In this study, low lean body mass was a predictor of incident fractures, independent of the FRAX score, by two different scales (EWGSOP, Baumgartner) but not another (FNIH)
- **Conclusion: Sarcopenia as a risk factor for fracture is a function of the threshold for defining low lean body mass.**

IMAGING, MICROSTRUCTURE, MATERIAL PROPERTIES, HISTOMORPHMETRY

Fri 10/9 10 AM	**MTP: Bone Quality: Raman, FTIR,SAXS, BSEM: What do They Mean?**	**E. Paschalis**	

Related Abstracts:

#s **1008**, 1009,1010,1012,1019,1028,1051,1052,1055,1056,1067, 1087, 1098, 1114,1135,1139,**1140**,1143

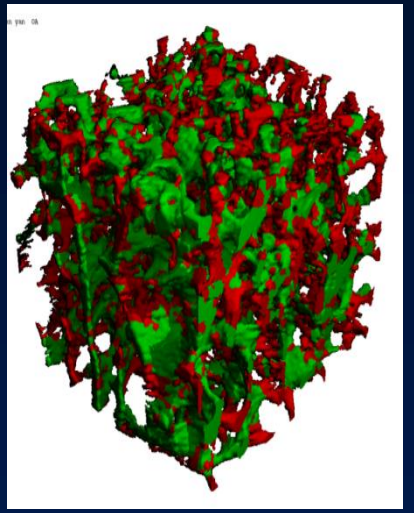
* All abstracts also “fit” into other categories illustrating the rapid translational strengths of imaging technology to clinical disorders of bone

Innovative, clinically applicable imaging technologies

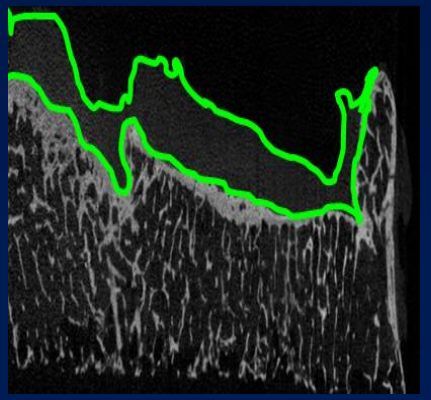
- High Resolution peripheral Quantitative Tomography (HRpQCT)
- Individual Trabecula Segmentation Analysis (ITS)
- Reference point microindentation
- Trabecular Bone Score

#1008: Chen et al. Subchondral Bone in Human Osteoarthritic Knees is Characterized by Trabecular Rod Loss and Trabecular Plate Stiffening

- To investigate changes in subchondral trabecular plate and rod microstructure in human OA knees compared with normal knees

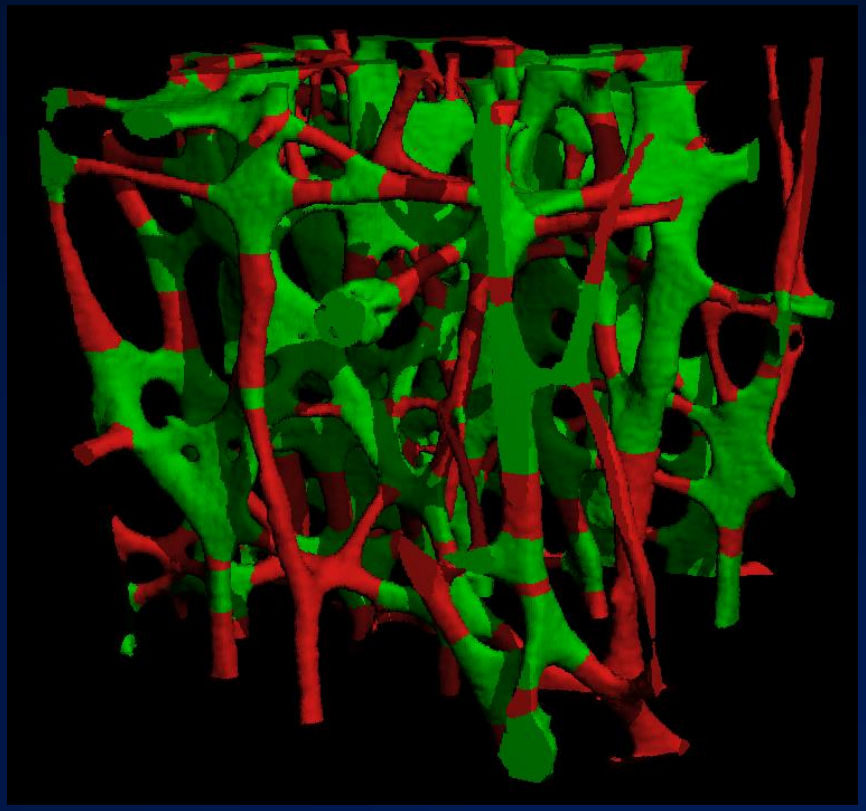


- To examine subtle trabecular plate and rod abnormalities in subregions beneath intact/mildly damaged cartilage



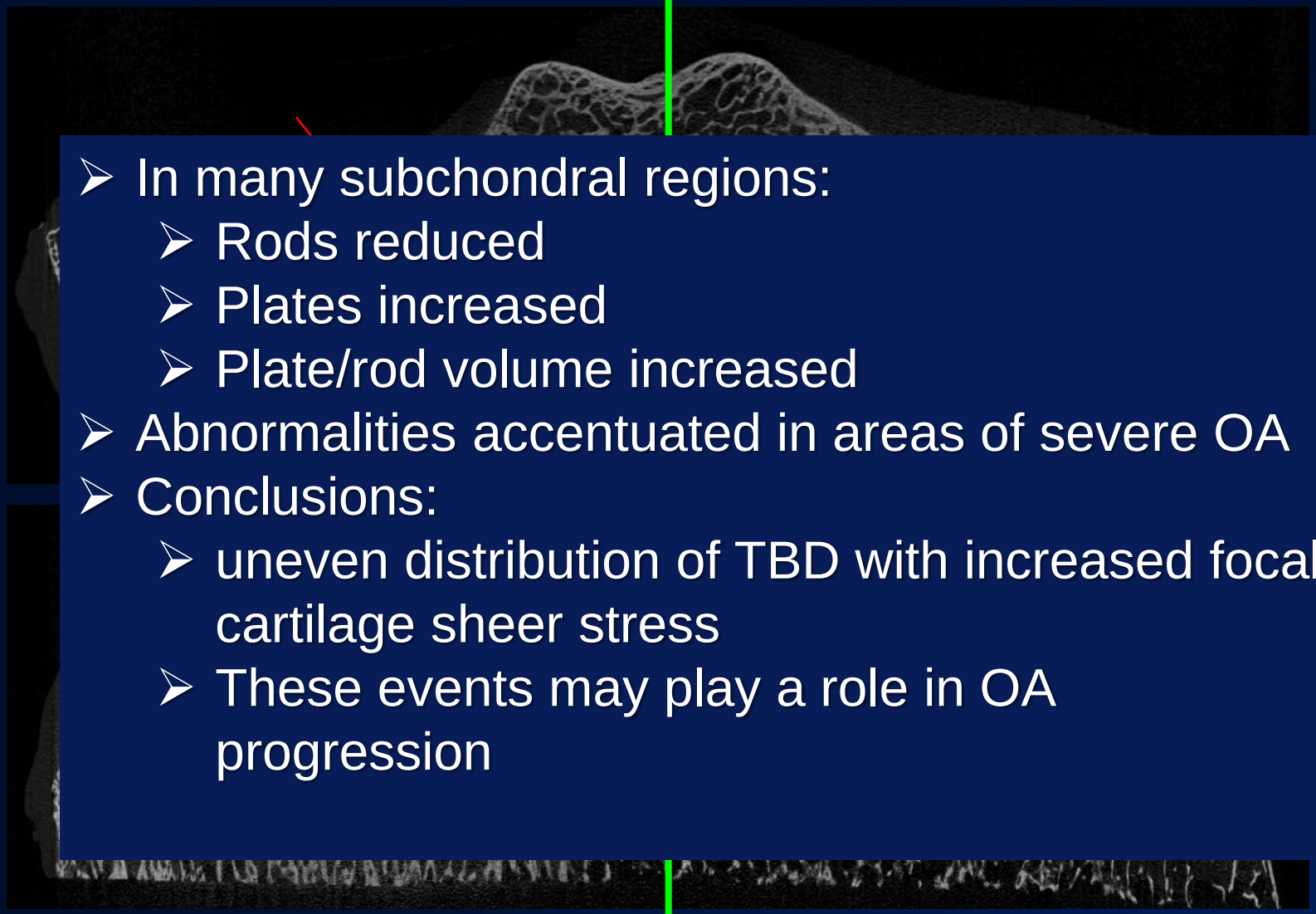
ITS Based Morphological Analysis

- Trabecular Plate/Rod Bone Volume Fraction
- Trabecular Plate/Rod Orientation
- Trabecular Plate Thickness/Rod Diameter
- Trabecular Plate/Rod Number Density
- Junction Density



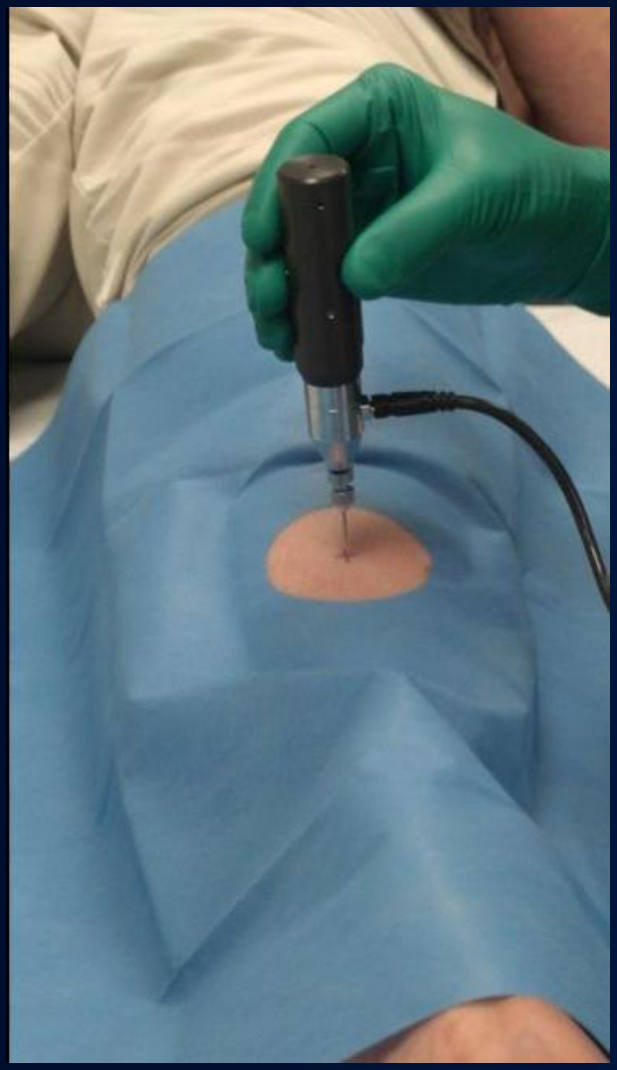
Green: Plate Bone Volume Fraction = pBV/TV
Red: Rod Bone Volume Fraction = rBV/TV

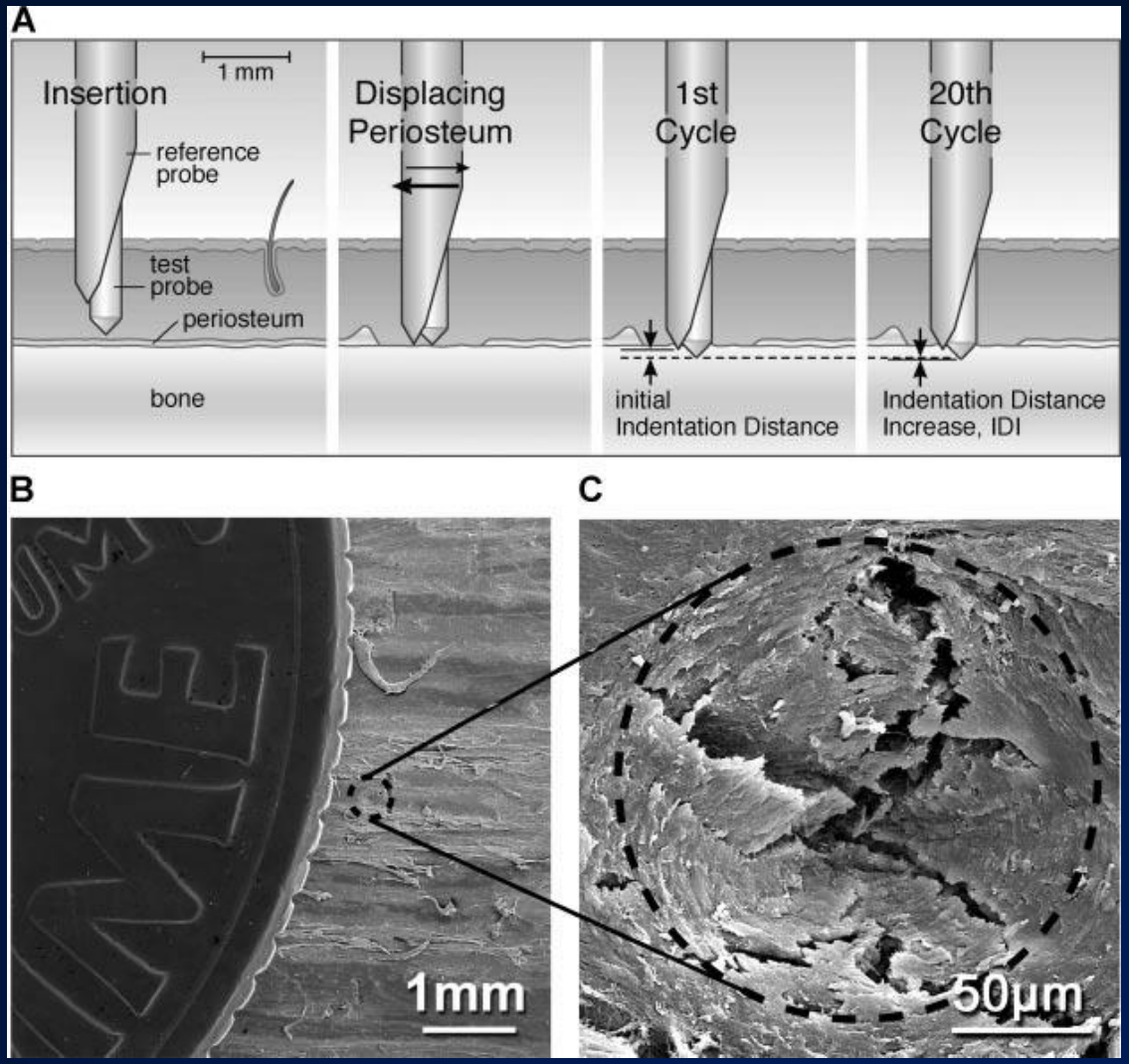
#1008: Chen et al



- In many subchondral regions:
  - Rods reduced
  - Plates increased
  - Plate/rod volume increased
- Abnormalities accentuated in areas of severe OA
- Conclusions:
  - uneven distribution of TBD with increased focal cartilage sheer stress
  - These events may play a role in OA progression

Microindentation Methodology





Diez-Perez A et al. J Bone Miner Res. 2010;25(8):1877-85.

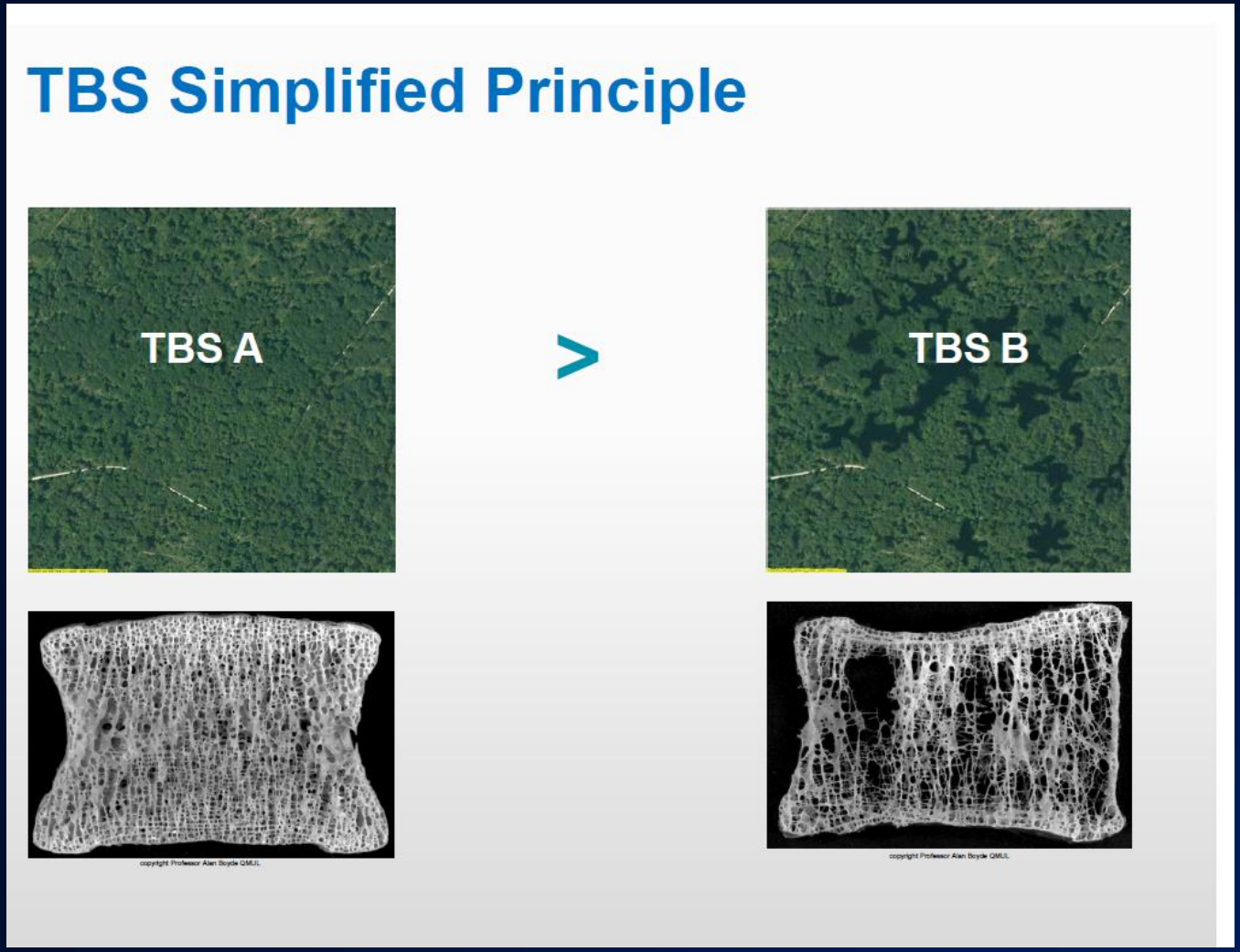
Reference point indentation (RPI) oral presentations at ASBMR: 2013, 2014 and 2015

2013: Farr et al. Bone Material Strength reduced in T2 DM
2014: Malgo et al. BMS is reduced independently of BMD in patients who fracture

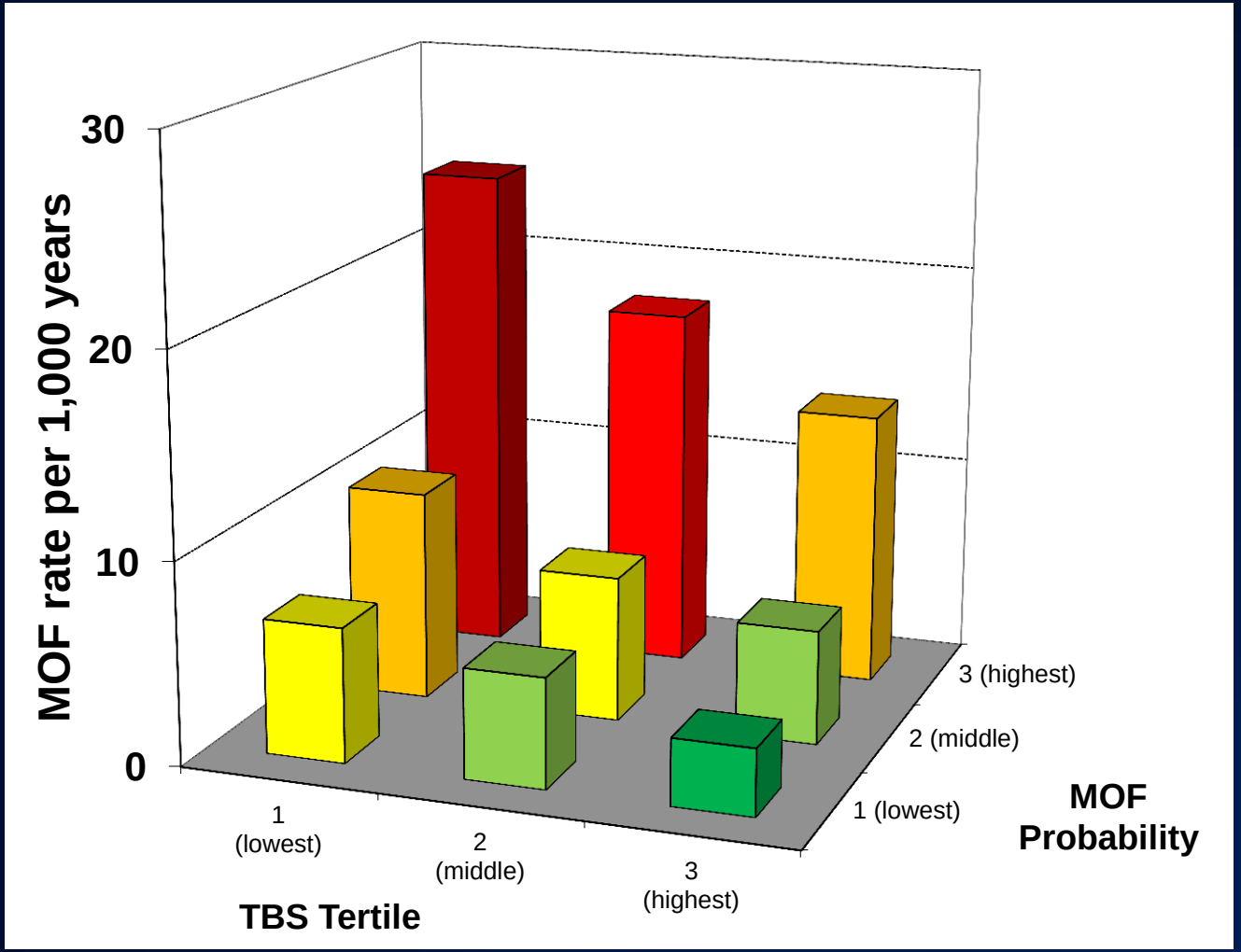
2015: #1140: Thurner et al. RPI Supplements Existing Clinical Factors for Improved Fracture Risk Assessment at the Femoral Neck

- **Applied to femoral neck tissue (post fx) and compared to cadaveric tissue without bone disease**
- **RPI added to clinical threshold probabilities for fx by FRAX and BMD**
- **Potential clinical applicability**

IMAGING:TRABECULAR BONE SCORE (TBS)



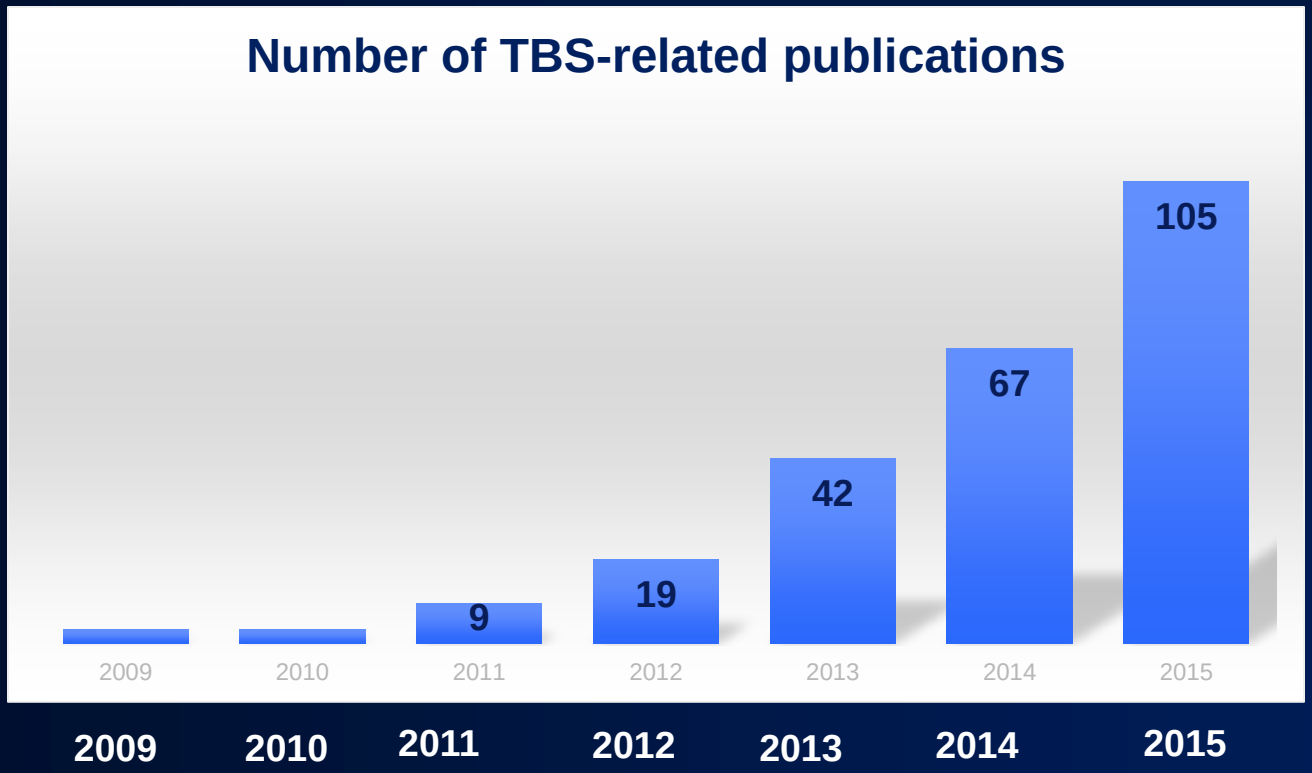
Fracture rates per 1,000 woman-years according to FRAX and TBS tertiles



Adapted from WD. Leslie et al. Osteoporos Int. 2014 Jun 21

TBS reports at ASBMR and Publications since 2009…

- 2011 -- 1 abstract
- 2012 -- 19 abstracts
- 2013 -- 30 abstracts
- 2014 -- 34 abstracts
- 2015 - 21 abstracts



TBS ABSTRACTS AT ASBMR 2015

#248: Leslie et al. Improved Risk Assessment Using Lumbar Spine TBS to Adjust Fracture Probability: The Manitoba BMD Cohort

Conclusion: A small but significant improvement in MOF and HF Risk assessment is achieved by using lumbar spine TBS to adjust FRAX probability

355: Neumann et al.

357 Del Rio et al.

255 Alvarenga et al.

033 Johannesdottir et al.

059 Gordon et al.

332 Rodriguez et al.

016 Munoz-Torres

265 Muschitz et al.

014 Abraham et al.

015 Cipriani et al.

LB 19 Chen et al.

251 Vokes et al.

333 Watanabe et al.

253 Schousboe et al.

OSTEOPOROSIS THERAPEUTICS

Fri: 10/9 10 AM	MTP: Communicating Benefits and Risks of Osteoporosis Treatments	M. Lewiecki
Sat: 10/10 11:30 AM	MTP: Treating Osteoporosis in the Elderly: Is the Horse Ever out of the Barn?	S. Greenspan
Sun: 10/11 11:30 AM	MTP: Drug Holidays: When and How	R. Josse
Sun: 10/11 11:30 AM	MTP: Estradiol and Mechanical Loading	M. Van der Meulen

OSTEOPOROSIS THERAPEUTICS

Mon: 10/12 11:30 AM	MTP: Implementing a Fracture Liaison Service	P. Geusens
Sat: 10/10 6:30 PM	Clinical Evening: Controversial Issues in Osteoporosis:	S. Harris, M. Luckey,T. deVillers, B. Leder, F. Cosman
Sun: 10/11 11:30 AM	Report: ASBMR Task Force: Long Term Safety and Efficacy of Vertebral Augmentation	
Mon: 10/12 11:30 AM	Report: ASBMR/ORS Task Force: Cell-Based Therapies	

OSTEOPOROSIS THERAPEUTICS

Noteworthy Abstracts:

- Bisphosphonates: 1141 ; LB 1153, LB 1156
- Denosumab: 1054**,1146, LB 1157**
- Combination Therapy: **1055**
- Odanacatib: **1056,1146**
- Teriparatide: 1021 (Basic Abs Award),1037
- Abaloparatide: **1053,1143**
- Romosozumab: **1019,1043**
- Vitamin K: 1051

OSTEOPOROSIS THERAPEUTICS

Antiresorptives

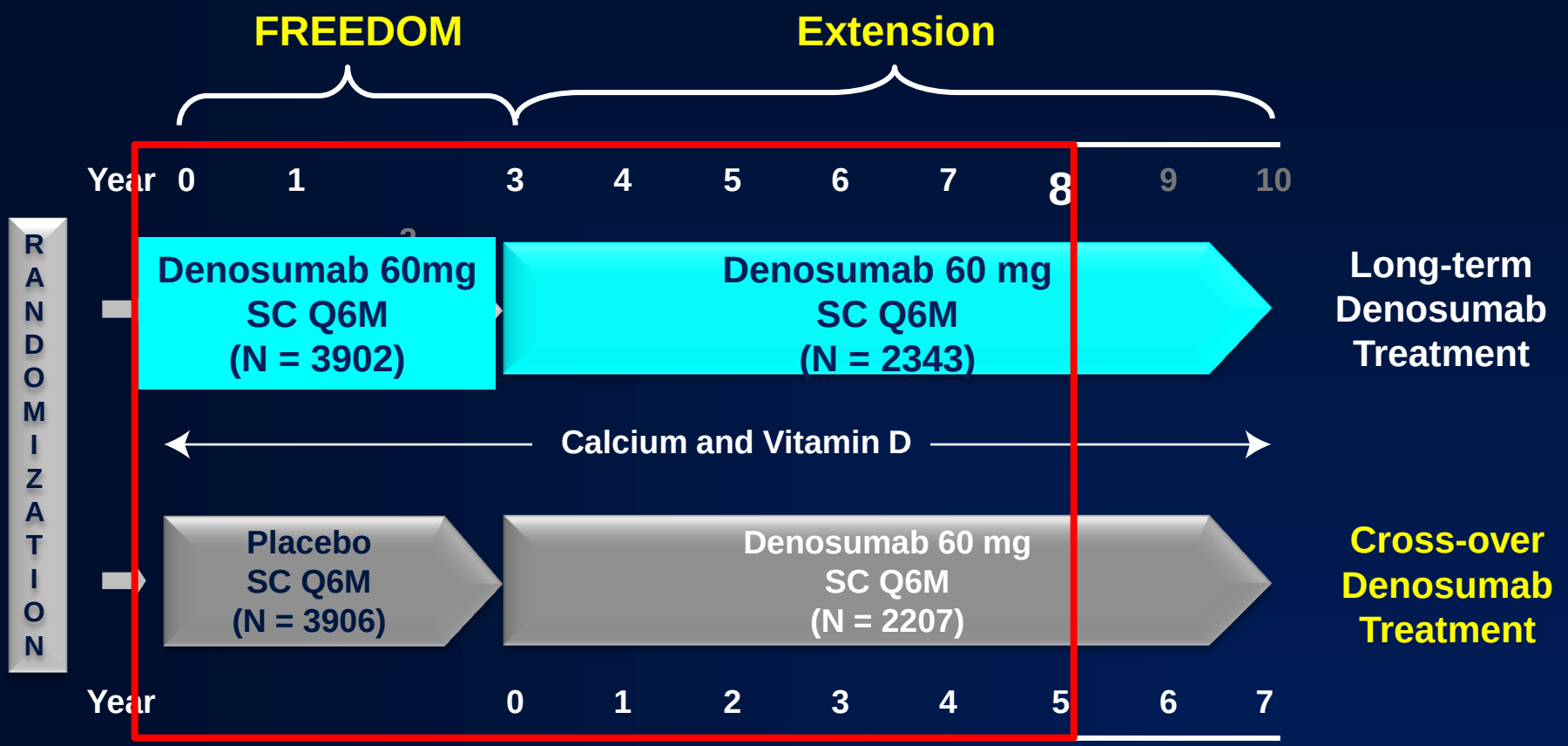
- **Denosumab (incl combination Rx)**
- **Odanacatib**

Osteoanabolics:

Combination Therapy

A “pure’ osteoanabolic approach

#1046: Ferrari et al. Relationship Between Total Hip BMD T-Score and the Incidence of Non-Vertebral Fracture with up to 8 Years of Denosumab Treatment

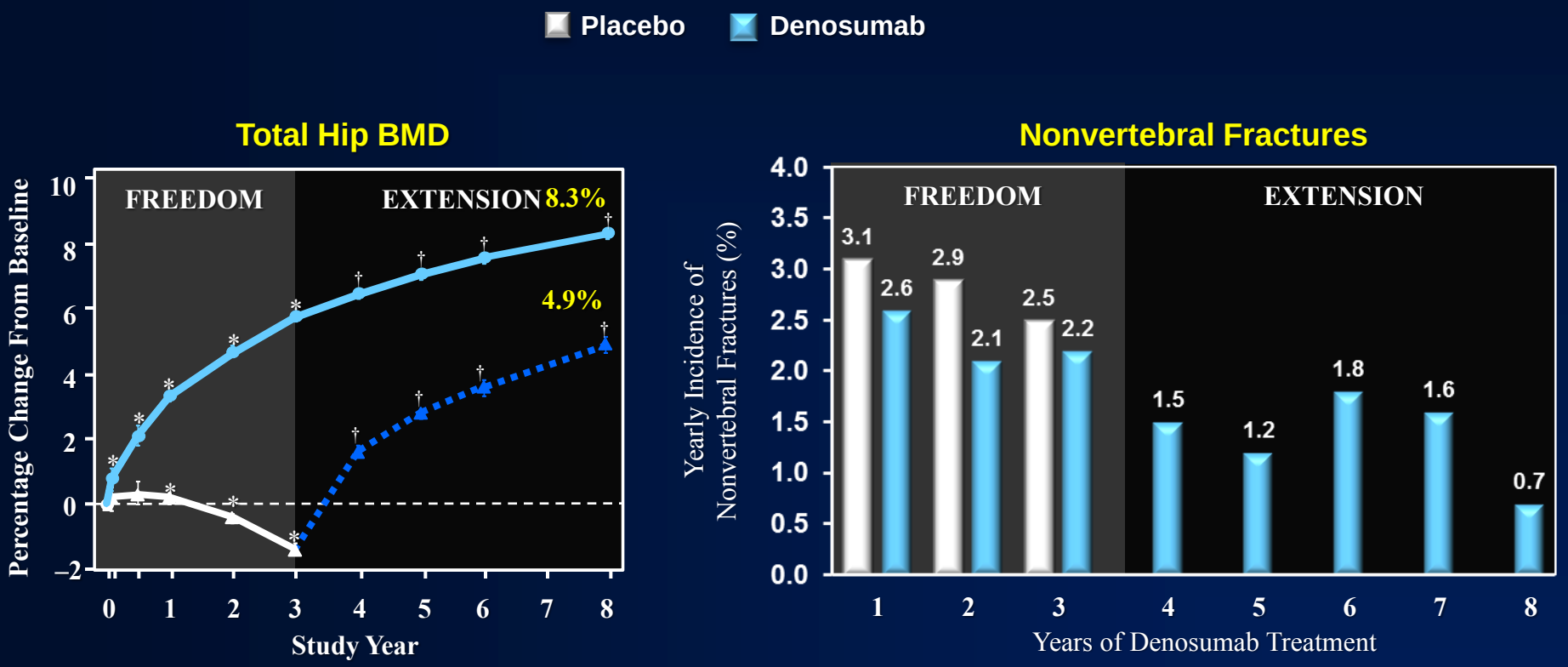


Key Inclusion Criteria for the Extension:

- Completed the FREEDOM study (completed their 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
- Not receiving any other osteoporosis medications

International, multicenter, open-label, single-arm study

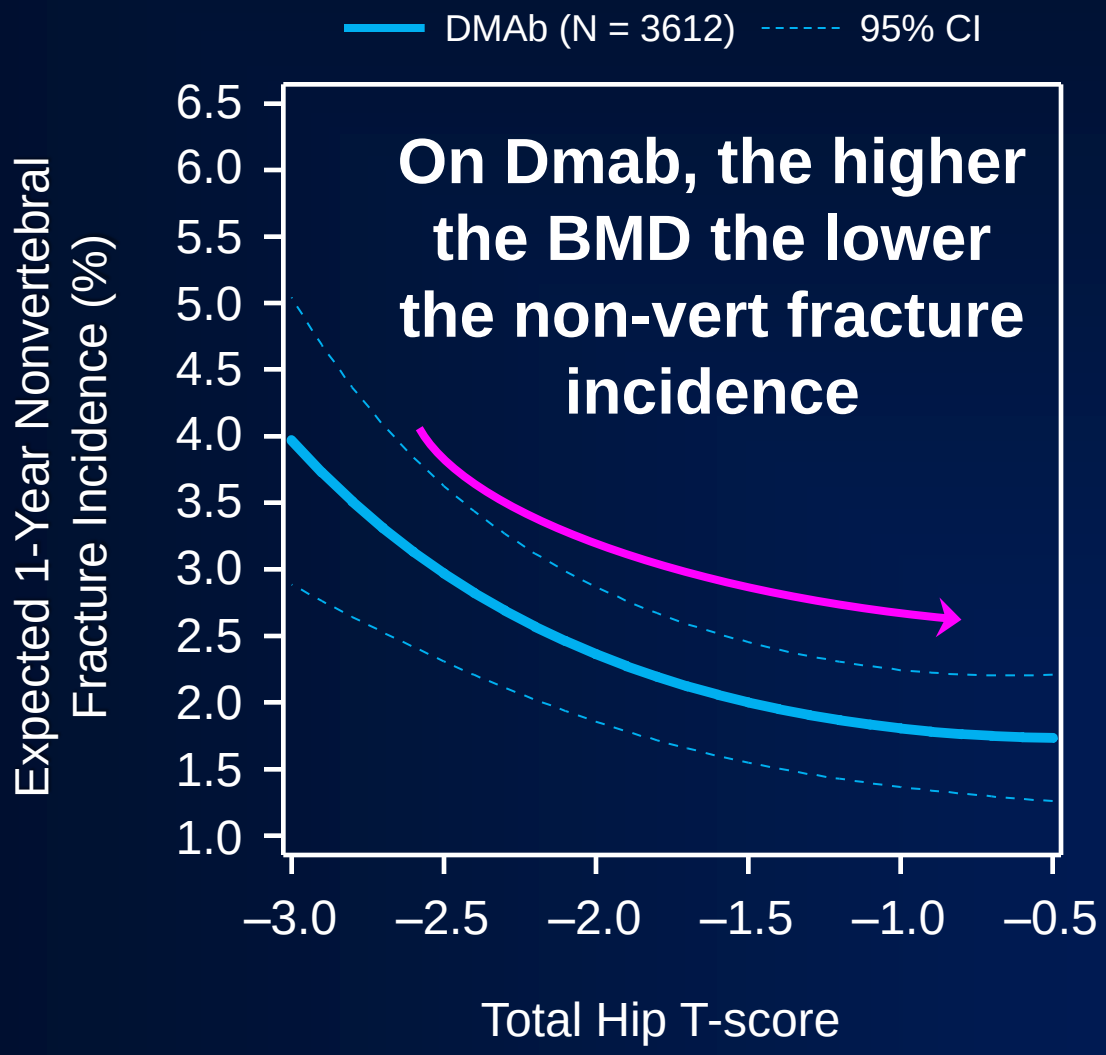
Long-term Denosumab Treatment Continuously Increases Total Hip BMD and Results in Reduced Nonvertebral Fracture Incidence



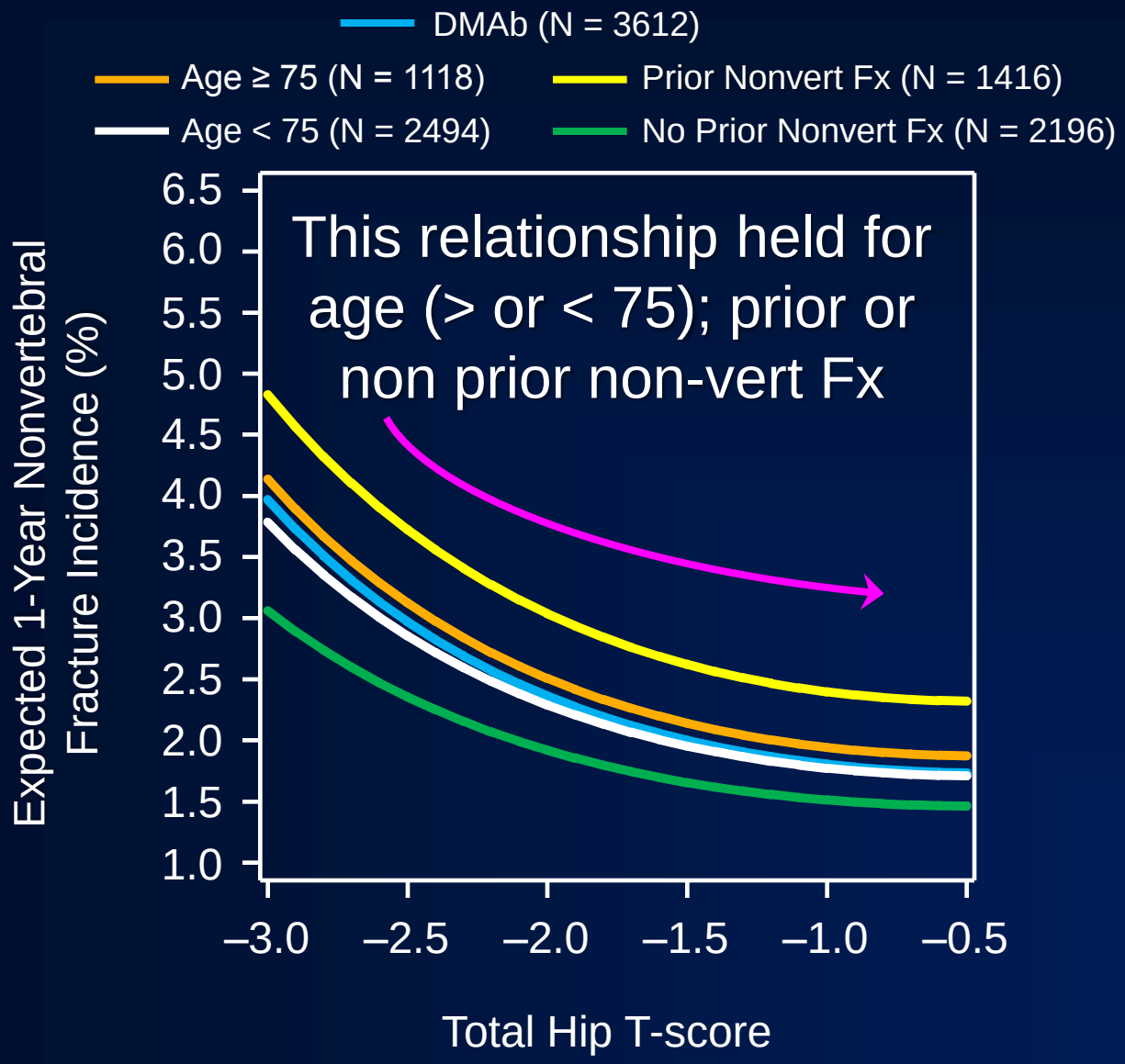
Papapoulos S et al. *Osteoporos Int* 2015. DOI 10.1007/s00198-015-3234-7.

LS Means and 95% confidence intervals. **P* < 0.05 vs FREEDOM baseline; †*P* < 0.0001 vs FREEDOM baseline and extension baseline. Percentages for nonvertebral fractures are Kaplan-Meier estimates.

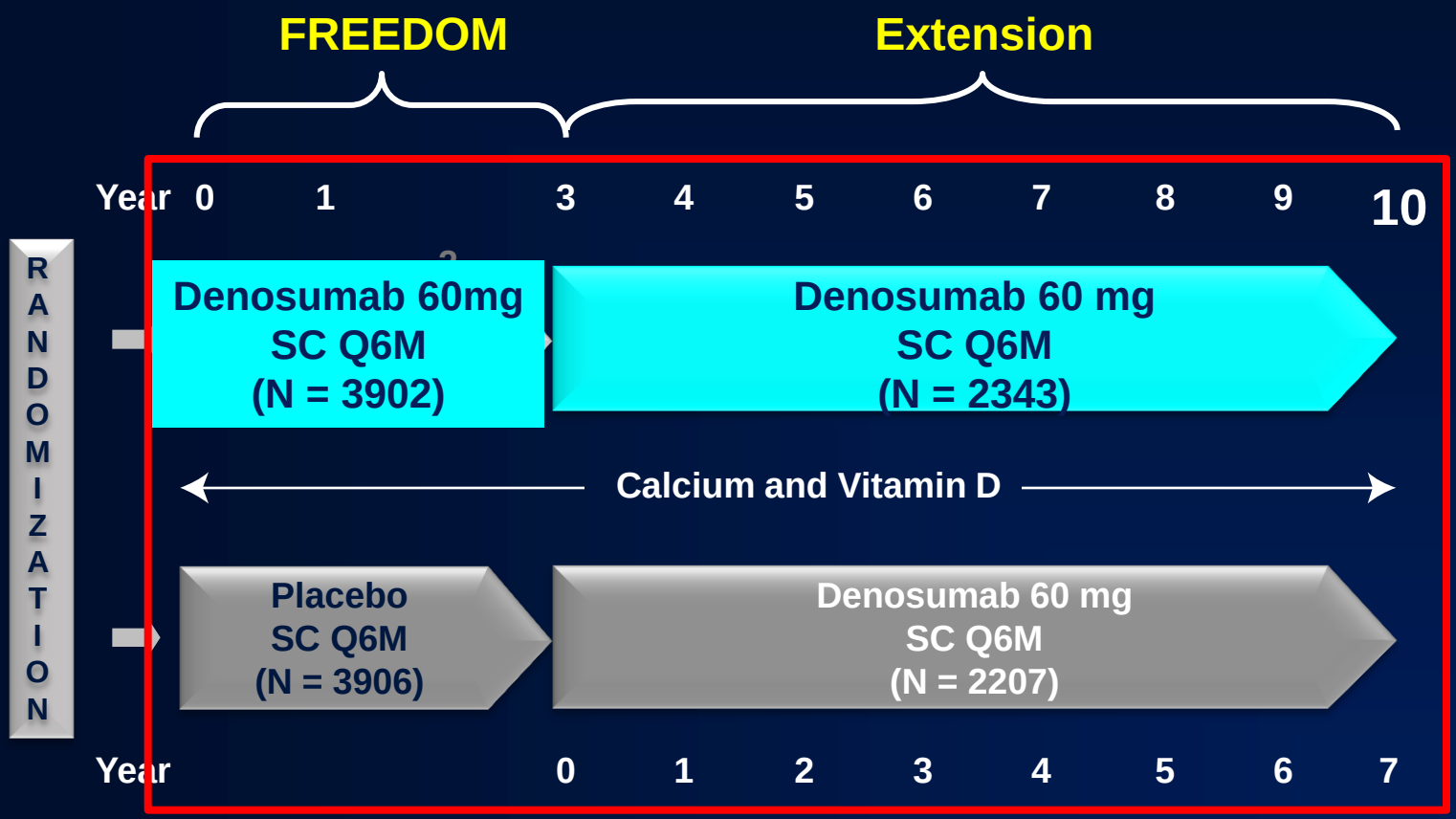
#1146: Ferrari et al. Relationship Between Total Hip T-score and Nonvertebral Fracture



#1146: Ferrari et al. Relationship Between Total Hip T-score and Nonvertebral Fracture



#LB 1157: Bone et al. Ten Years of Denosumab Treatment in Postmenopausal Women with Osteoporosis: Results From the Freedom Extension Trial:



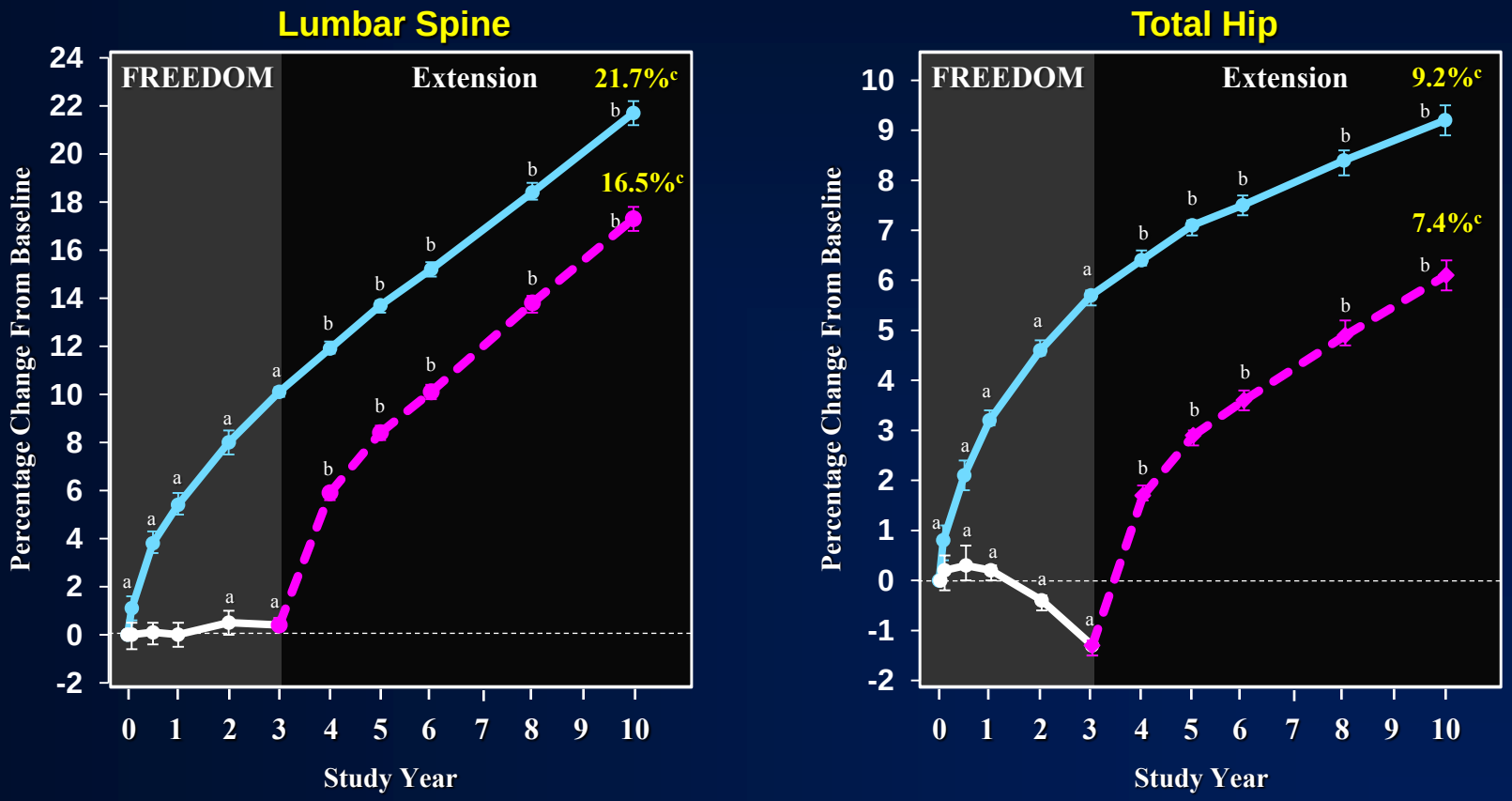
Key Inclusion Criteria for the Extension:

- Completed the FREEDOM study (completed their 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
- Not receiving any other osteoporosis medications

International, multicenter, open-label, single-arm study

#LB 1157: Bone et al. Ten Years of Denosumab Treatment in Postmenopausal Women with Osteoporosis: Results From the Freedom Extension Trial: LUMBAR SPINE AND HIP BMD

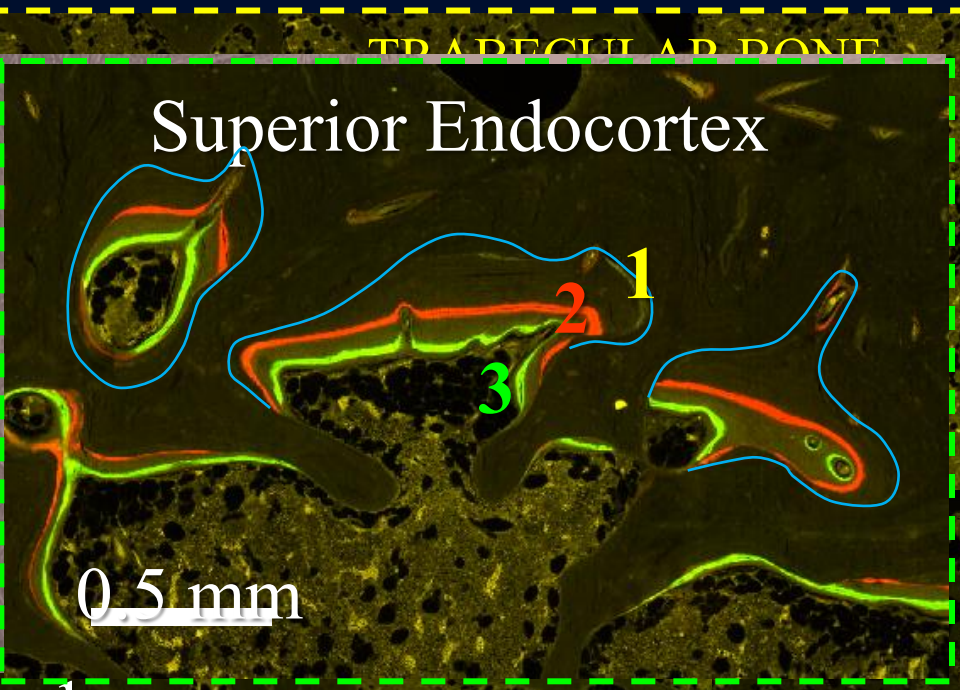
Placebo Long-term Denosumab Cross-over Denosumab

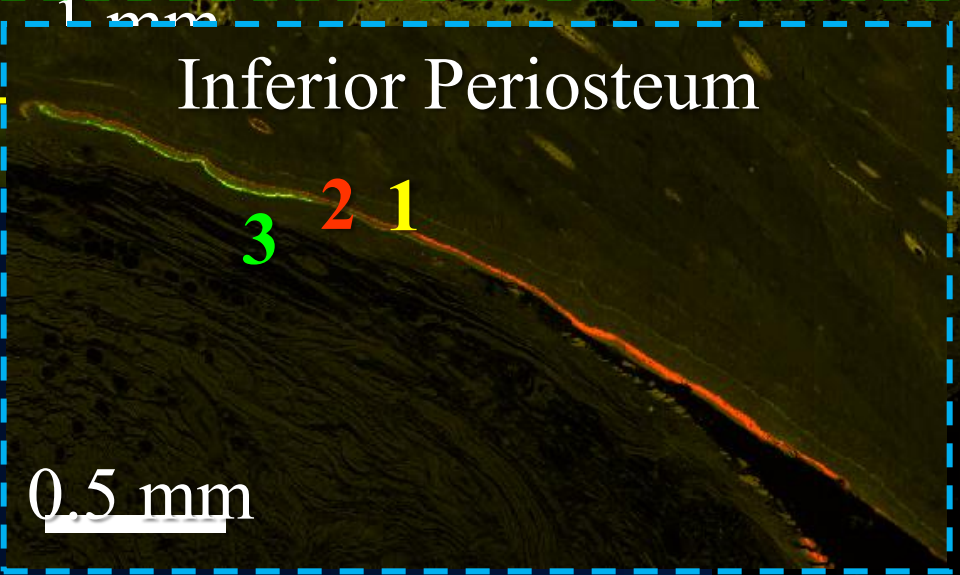


BMD data are LS means and 95% confidence intervals. [a]$P < 0.05$ vs FREEDOM baseline. [b]$P < 0.05$ vs FREEDOM and Extension baselines. [c]Percentage change while on denosumab treatment. [d]Annualized incidence: (2-year incidence) / 2. Lateral radiographs (lumbar and thoracic) were not obtained at years 4, 7, and 9 (years 1, 4, and 6 of the Extension).

What could account for the relentless increase in BMD over a decade: an unprecedented observation not duplicated by any therapeutic for osteoporosis?

Fluorochrome Labeling: Femur Neck





Fluorochrome Labels

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

Formation Period

Modeling: ≥ 10 mo

Remodeling: 1-2 mo

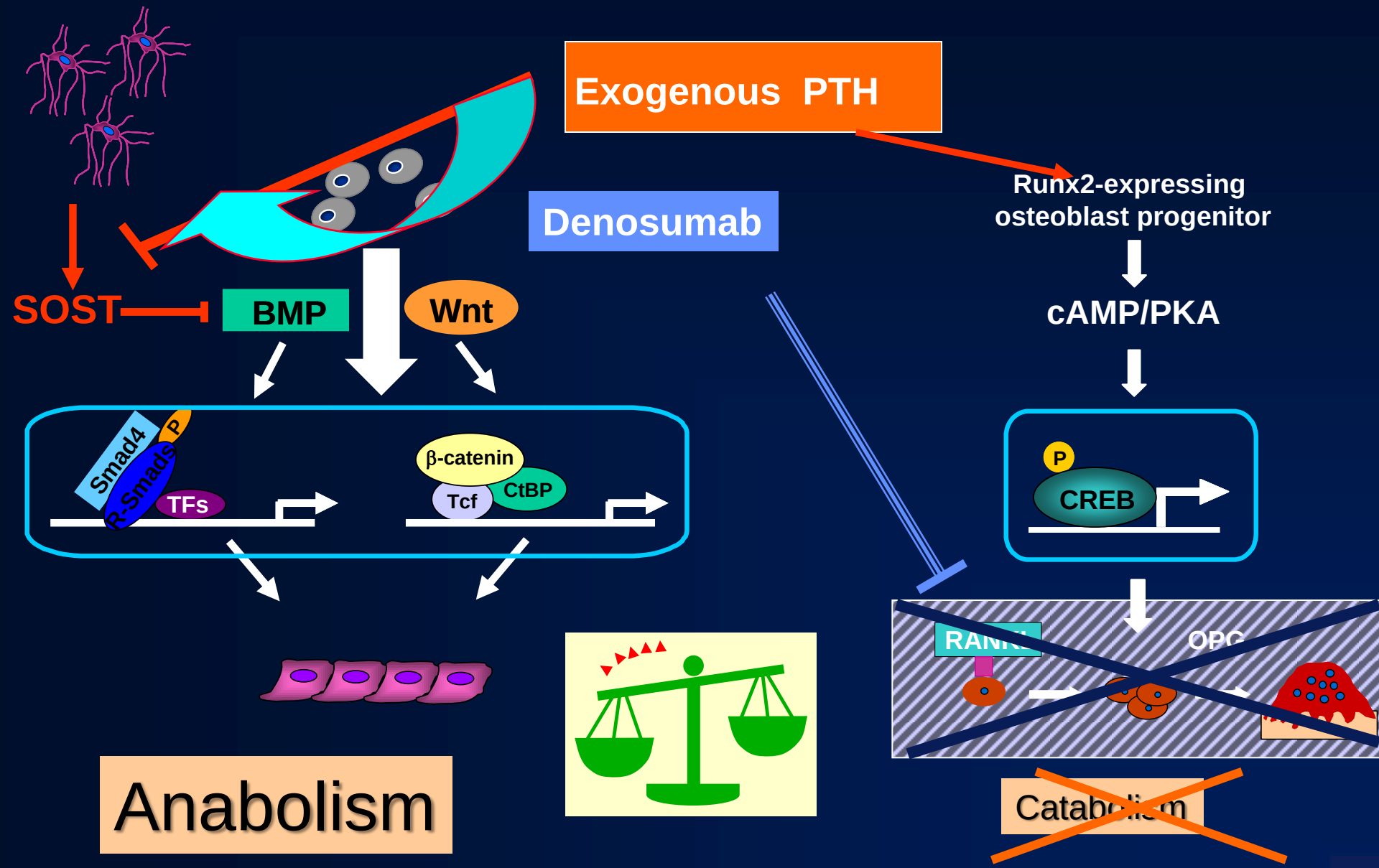
DMAb 25 mg/kg

Ominsky et al, *JBMR* 2015

Combination therapy with an antiresorptive and osteoanabolic agent

- **Rationale is clear but the results…**
  - Raloxifene: possible small benefit
  - Estrogen: possible small benefit
  - Alendronate: reduced benefit
  - Risedronate (in men): possible hip BMD benefit
  - Zoledronic acid: early benefit primarily
  - **Denosumab: promising** (Tsai et al, Lancet, 2013; Leder, JCEM, 2014, Tsai et al, JBMR, 2015)

Denosumab may shift exogenous PTH pathways



#1055: Tsai et al. Effect of Denosumab (DMAB) and Teriparatide (TPTD) Transitions on Peripheral Bone Mineral Density (BMD) and Microarchitecture: The DATA-Switch HR-pQCT Study

- BMD: Comb > Dmab or TPTD
- Microstructure: Comb > Dmab or TPTD
- Switch (after 2 yrs):
  - Comb to Dmab or TPTD to Dmab: gains
  - Dmab to TPTD: loss
- This study: Switching and changes in microstructure (by HRpQCT)

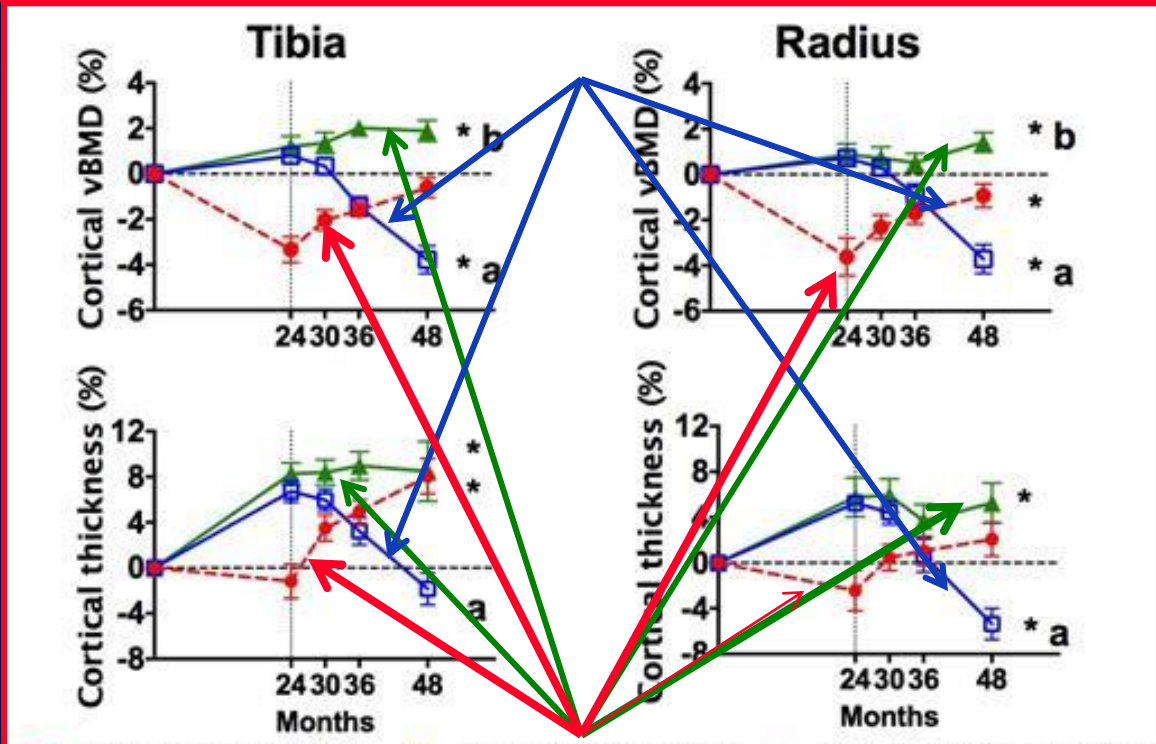
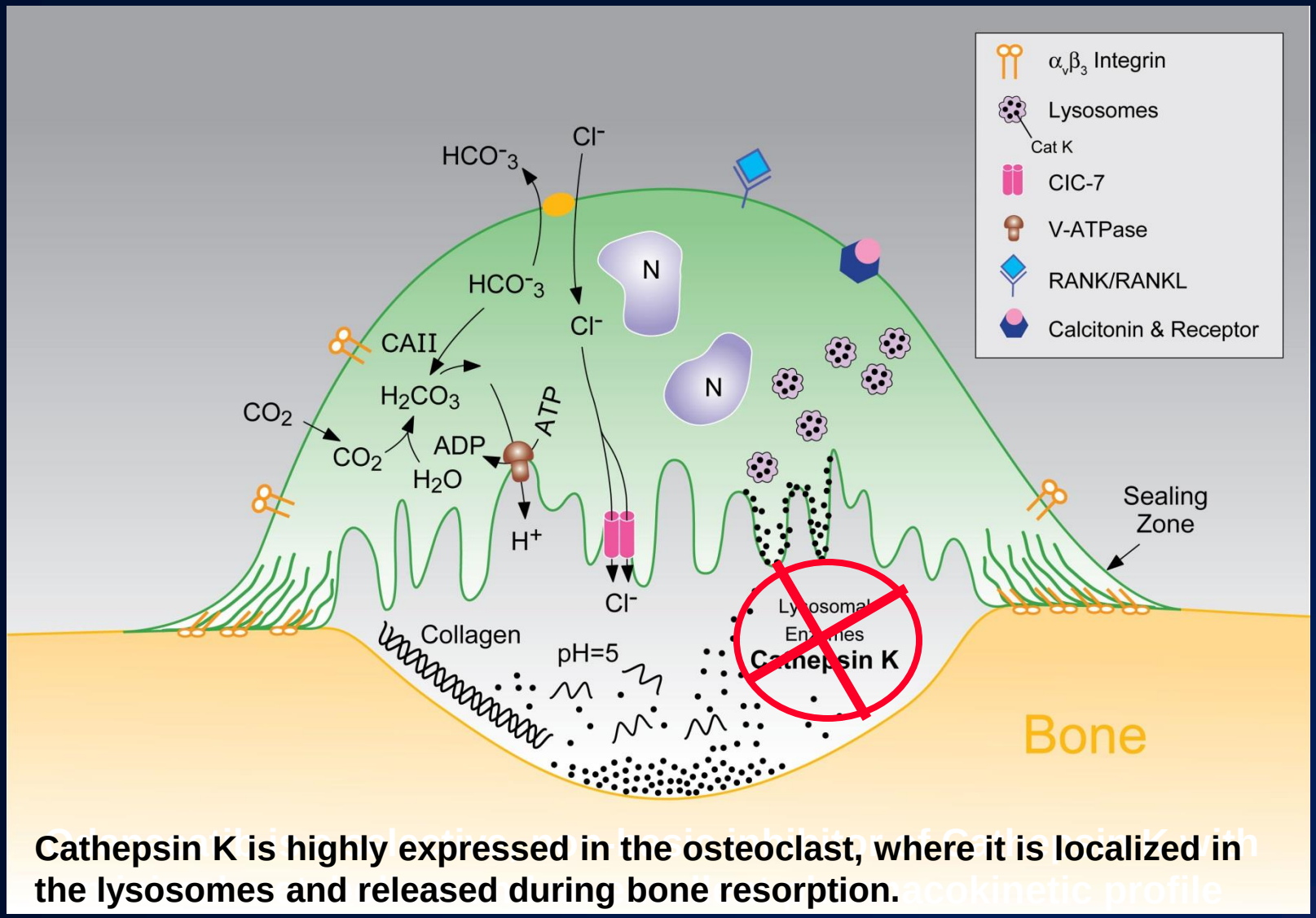


Figure. Mean percent change (SEM) from baseline in bone density and microarchitecture at 48 months. [a] p value <0.05 vs both other groups. [b] p value <0.05 versus TPTD-to-DMAB group. * p value <0.05 compared to baseline for overall 0-48 month change.

OTHER WAYS TO TARGET THE OSTEOCLAST



Cathepsin K is highly expressed in the osteoclast, where it is localized in the lysosomes and released during bone resorption.

Rodan & Duong. BoneKey 2008

#1144: Saag et al. Efficacy of Odanacatib in Postmenopausal Women with Osteoporosis: Subgroup Analyses of Data From the Phase 3 Long-Term Odanacatib Fracture Trial

- Age: 72.8
- T-score <-2.5 (FN or TH); <-1.5 (FN or TH) with prior radiographic VFx (46%)
- N= 16,713; 387 centers; 40 countries

- RR Reductions in:
  - Vert Fx 54%
  - Hip Rx 47%
  - Non-Vert: 23%

Current Study: subgroup analyses:
Bottom line: Consistency across all subgroups for morphometric fracture reductions:

- With or without previous fx
- Age < or > 70
- Baseline LS BMD
- BP intolerant subjects

#1056: Langdahl et al. Effect of Odanacatib on Bone Density and Estimated Bone Strength in Postmenopausal Women: a CT-based Sub-Study of the Phase 3 Long-Term Odanacatib Fracture Trial

- Substudy of 164 women (78 ODN; 86 PBO)
- Similar baseline characteristics to entire study
- CT indices and FEA analyses
- **Estimated strength by FDA at vertebrae and total hip increased at 24 months**

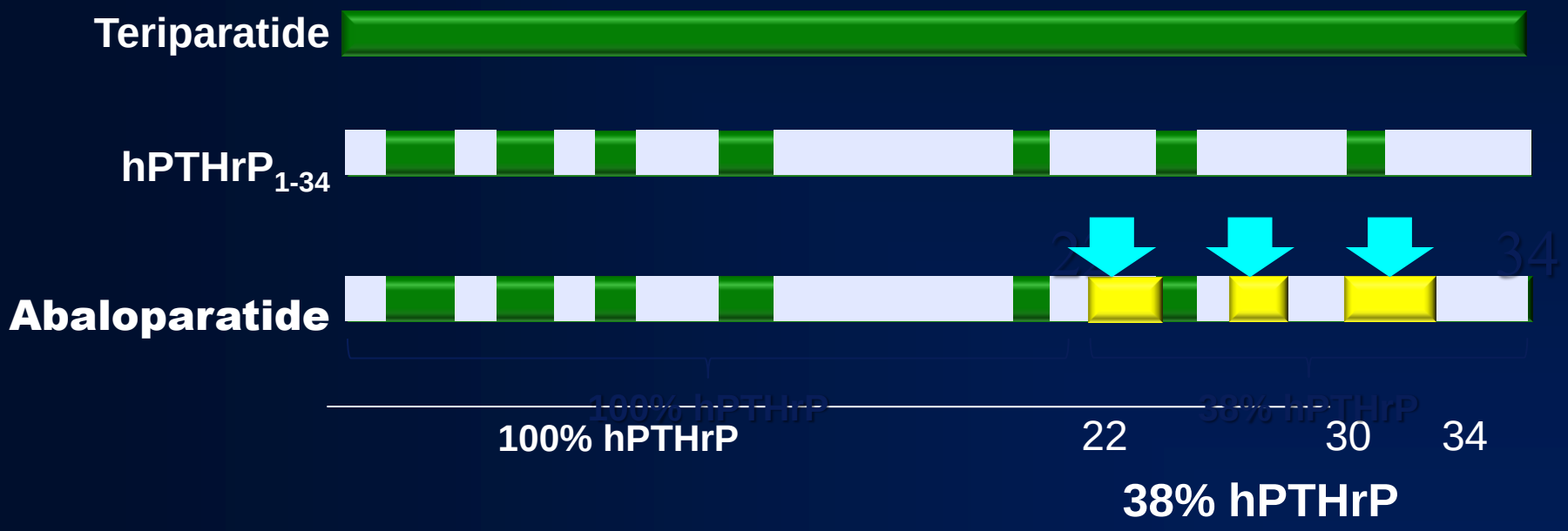
Table 2. QCT measurements of estimated strength by FEA of the vertebral body and total hip after 24 months of treatment with ODN 50 mg once weekly or placebo (FAS population)

	N	Mean % change from baseline (95% CI)[a]	
Compressive strength of vertebral body (L1)			
ODN 50 mg weekly	46	8.98 (5.99, 11.98)	**Compressive strength at vertebral body**
Placebo	47	-0.77 (-4.16, 2.61)	
Strength under fall loading conditions at total hip			
ODN 50 mg weekly	55	3.80 (2.29, 5.31)	**Strength at Total Hip**
Placebo	56	-3.10 (-4.43, -1.77)	

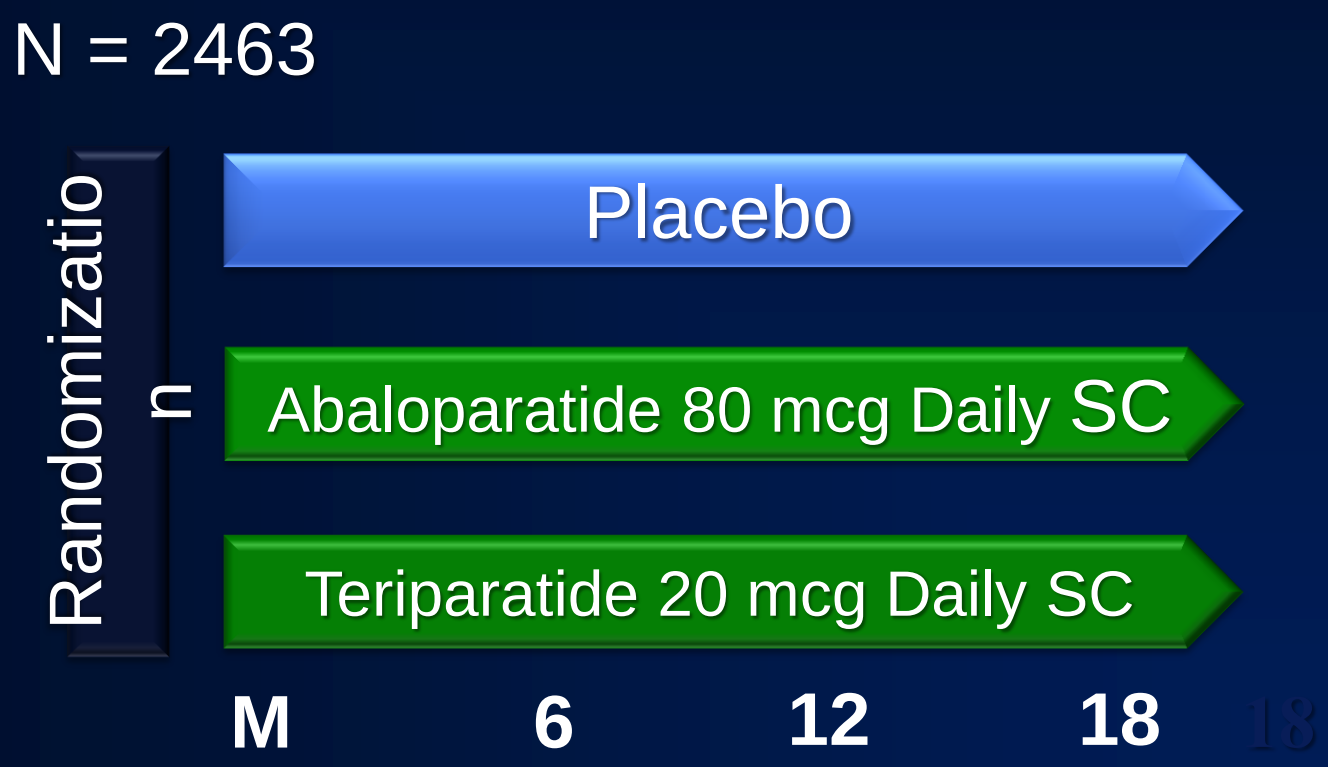
As there were no pre-specified hypotheses for FEA endpoints, analysis was restricted to descriptive statistics.

[a]Confidence intervals assuming normality.

Emergence of a new osteoanabolic Abaloparatide, an analogue of PTHrP



Phase 3 Trial Design of Abaloparatide Clinical Trial



Miller et al, Endo Soc 3-15

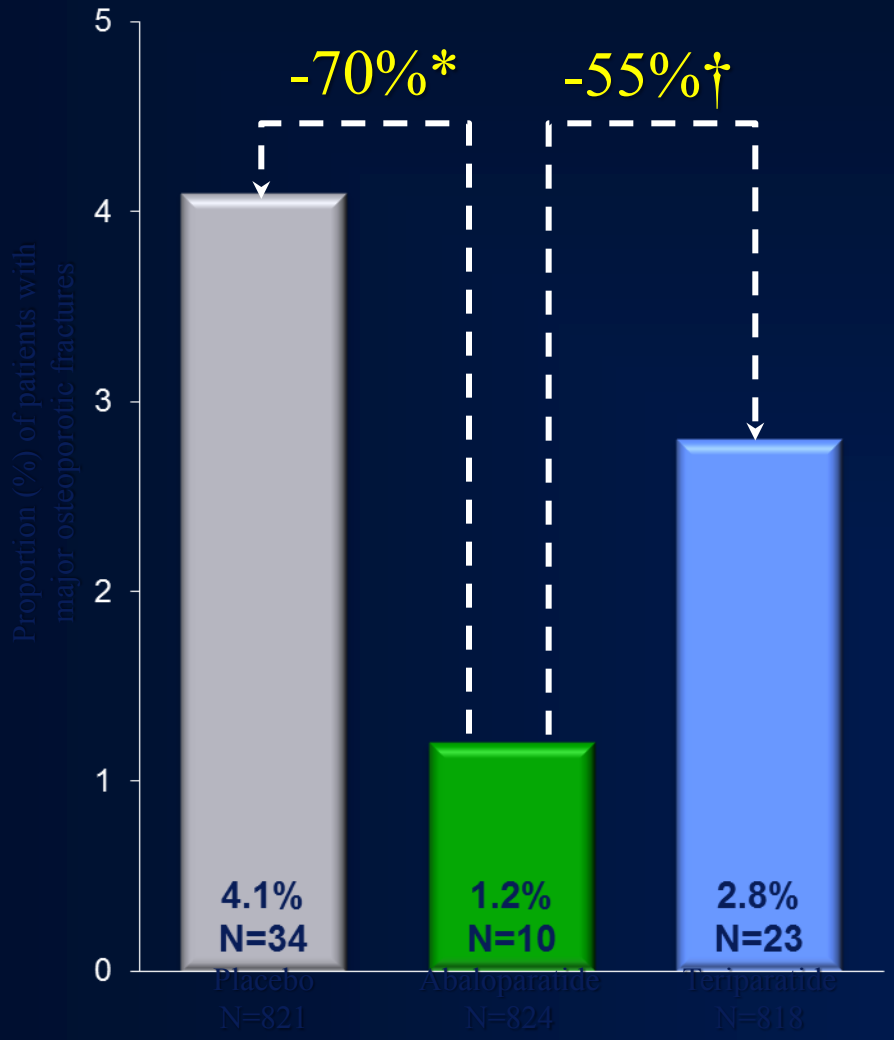
#1053: Williams, Fitzpatrick et al. Effects of Abaloparatide on Major Osteoporotic Fracture Incidence in Postmenopausal Women with Osteoporosis- Results of the Phase 3 ACTIVE Trial

Bkgd: Significant reductions in Vert, Non-verts, Clin Fxs (similar to teriparatide)- Miller et al. March, 2015

Objective: Effect of Abaloparatide or Teriparatide on ***Major Osteoporotic Fractures*** (high or low trauma clinical fxs; upper arm, forearm, hip, shoulder, and/or spine)

Results: Abaloparatide vs PBO (70% reduction: p=0004)
Teriparatide vs PBO (no significant reduction)
Abaloparatide vs Teriparatide (P < 0.05)

#1053: Williams, Fitzpatrick et al. Effects of Abaloparatide on Major Osteoporotic Fracture Incidence in Postmenopausal Women with Osteoporosis- Results of the Phase 3 ACTIVE Trial

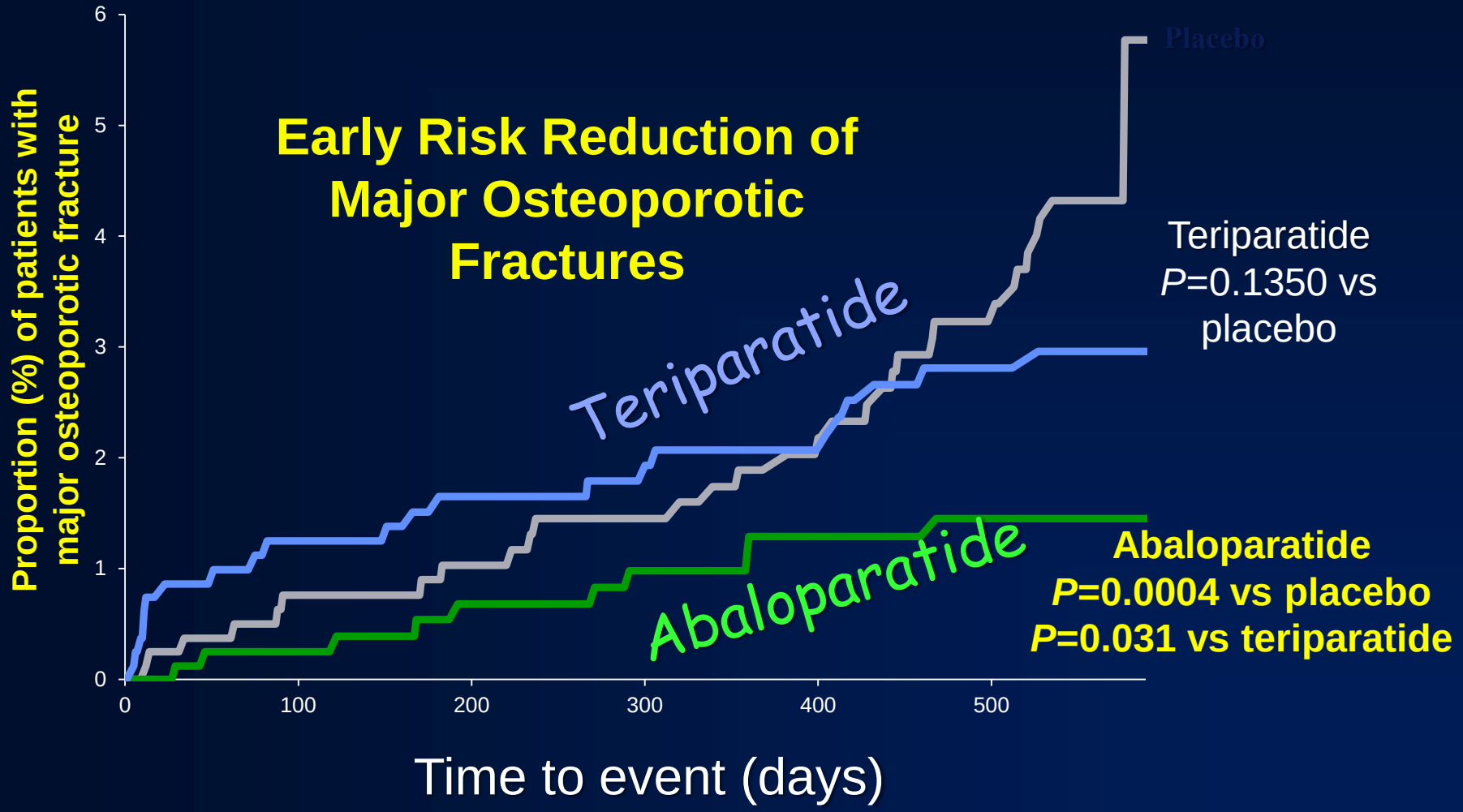


*P=0.0004, abaloparatide vs placebo.

†P=0.031, abaloparatide vs teriparatide.

Teriparatide NS vs placebo.

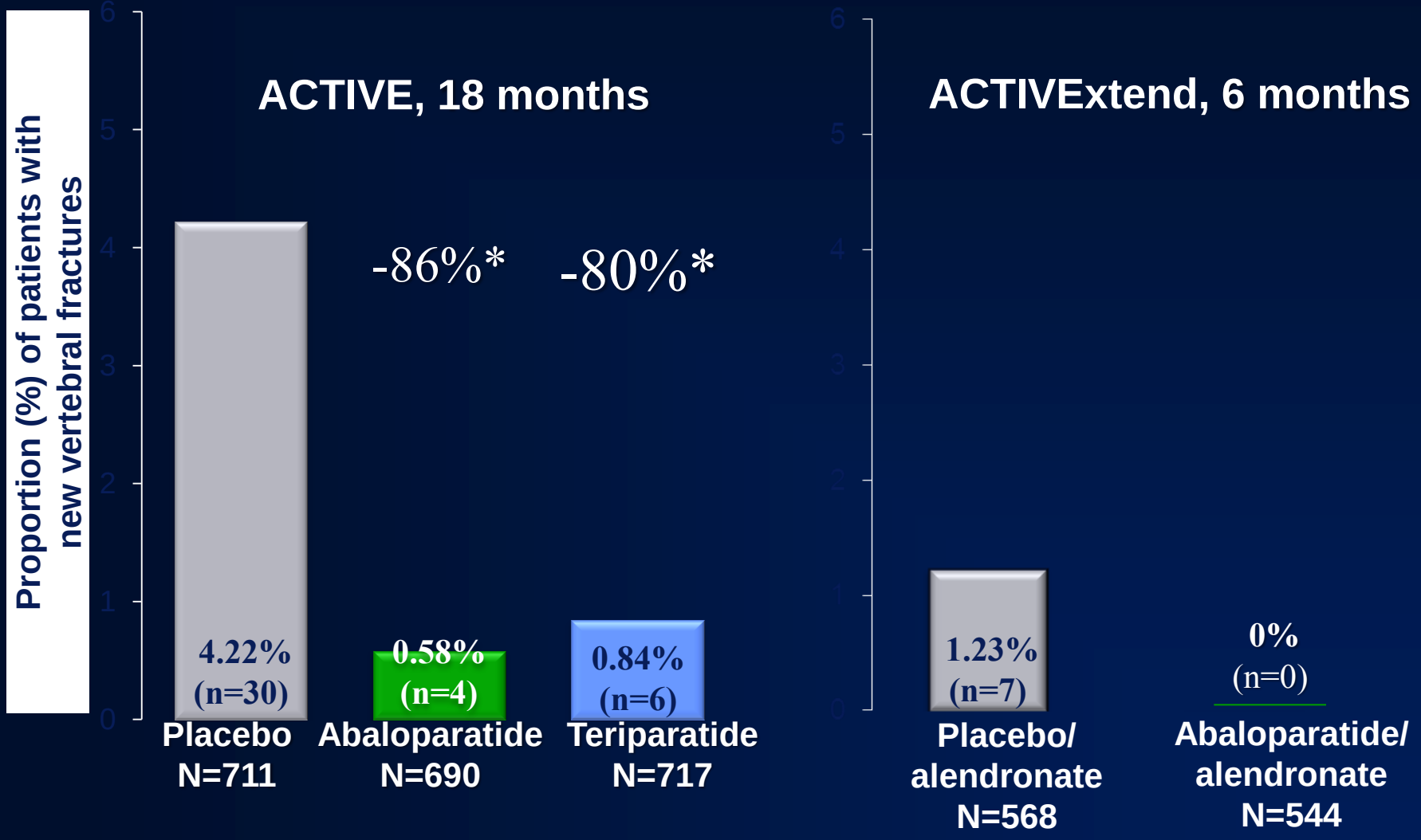
#1053: Williams, Fitzpatrick et al. Effects of Abaloparatide on Major Osteoporotic Fracture Incidence in Postmenopausal Women with Osteoporosis- Results of the Phase 3 ACTIVE Trial



#1142: Cosman, Miller et al. Eighteen Months of Treatment with Abaloparatide Followed by Six Months of Treatment with Alendronate in Postmenopausal Women with Osteoporosis-Results of the ACTIVExtend Trial

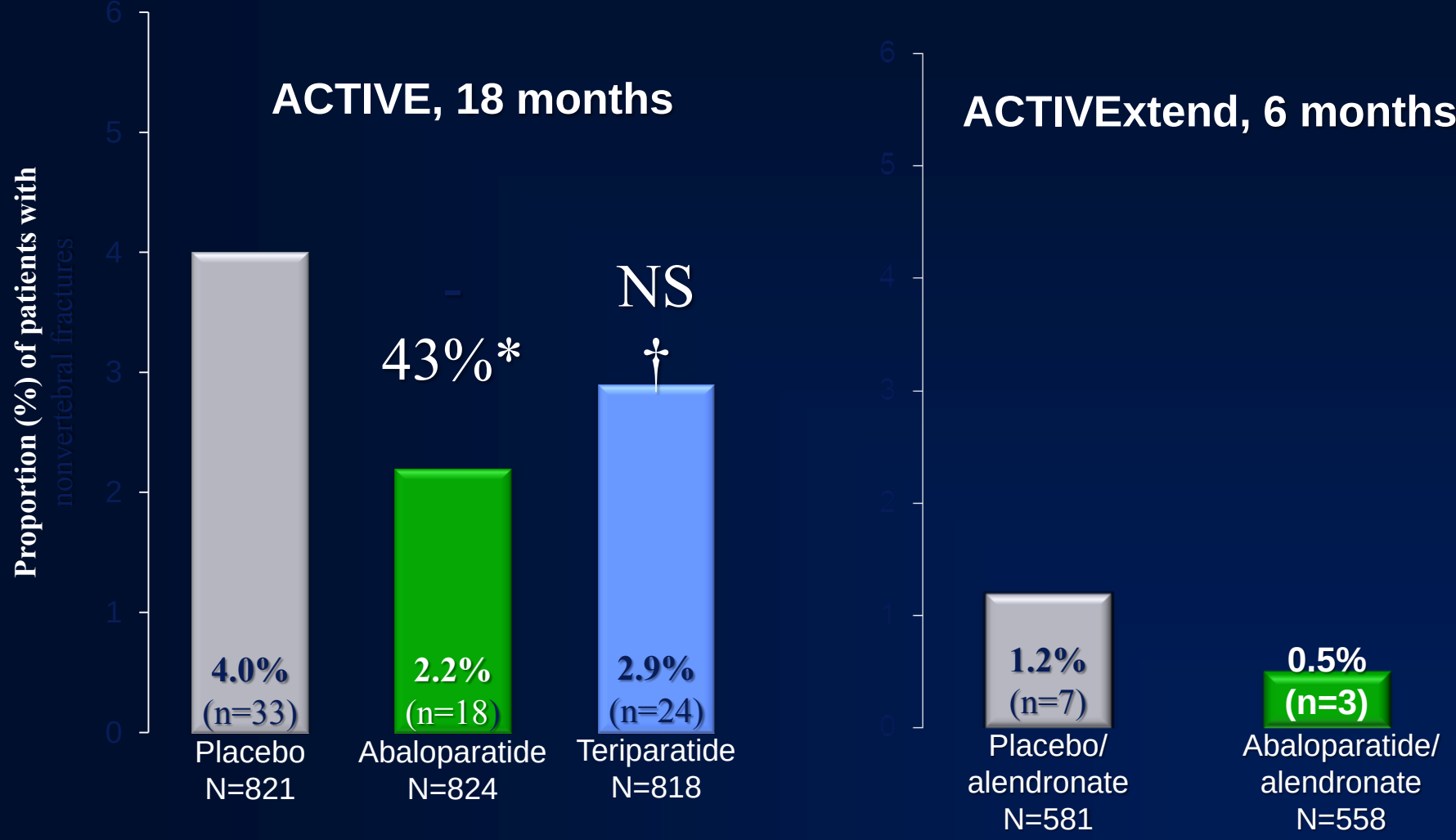
*1-month gap in treatment was allowed for rollover from ACTIVE to ACTIVExtend.

#1142: Cosman, Miller et al. ACTIVExtend Trial with Abaloparatide: Risk Reduction of Vertebral Fractures

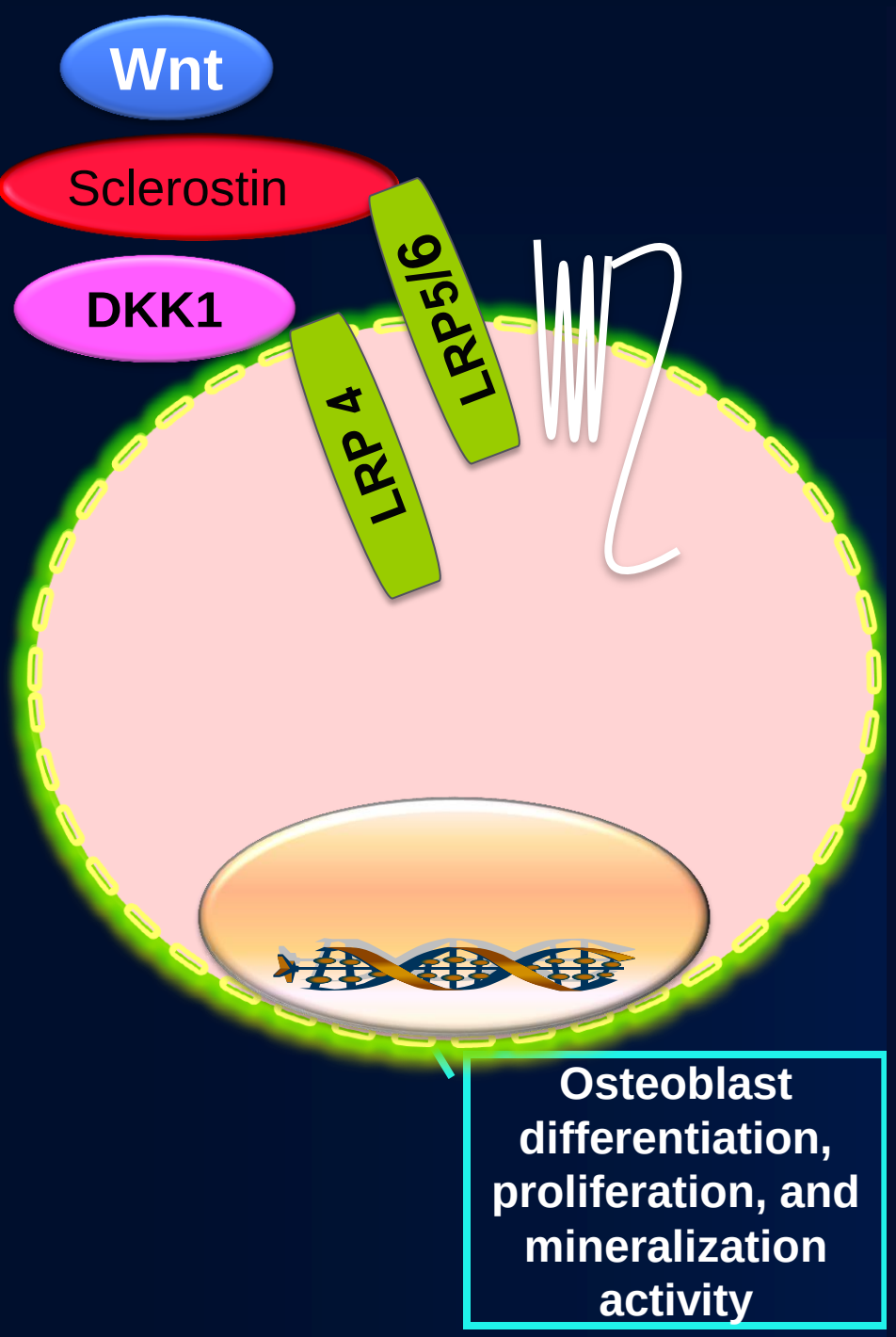


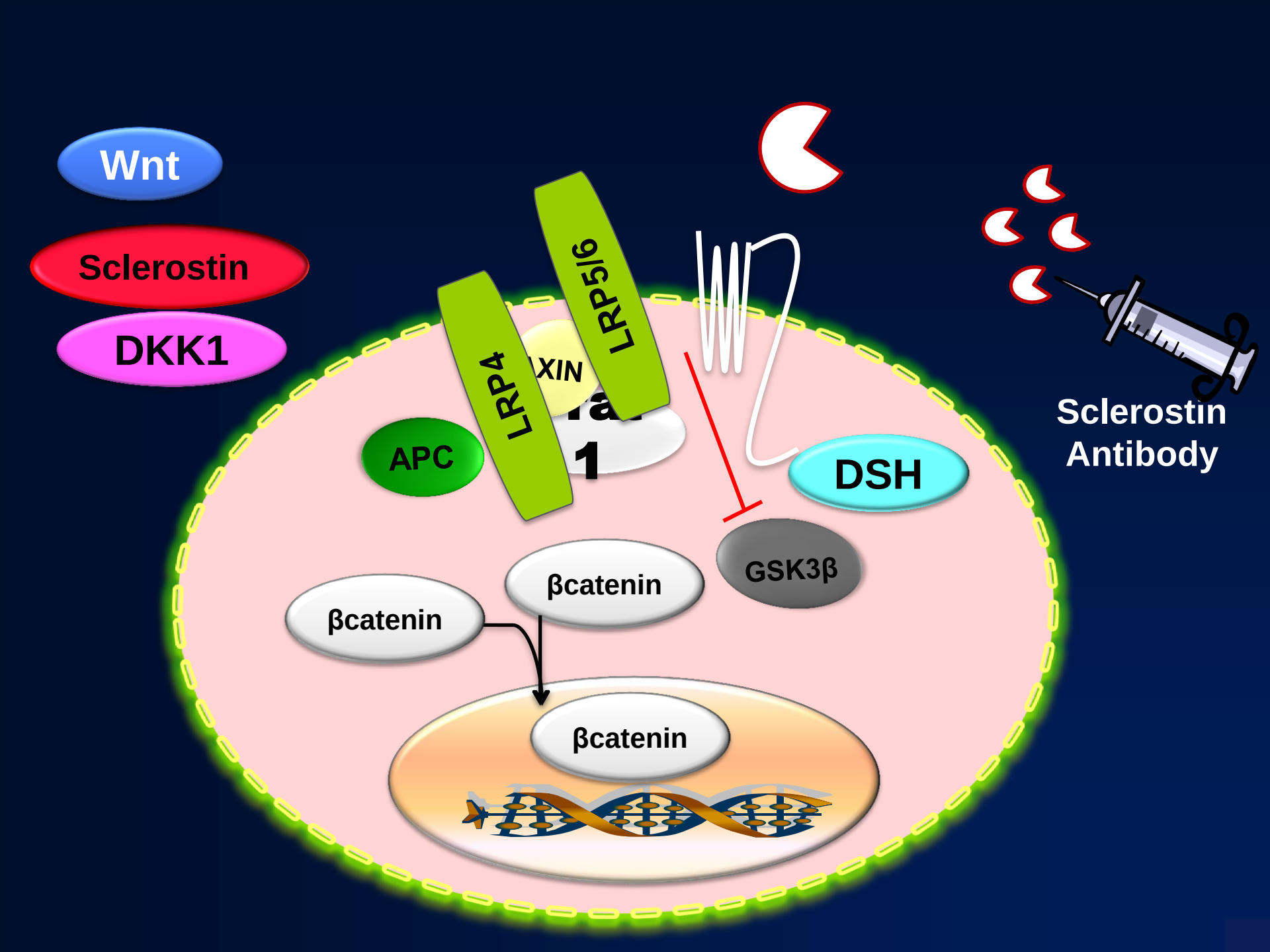
*$P<0.0001$ vs placebo.

#1142: Cosman, Miller et al. ACTIVExtend Trial with Abaloparatide: Risk Reduction of Non-Vertebral Fractures



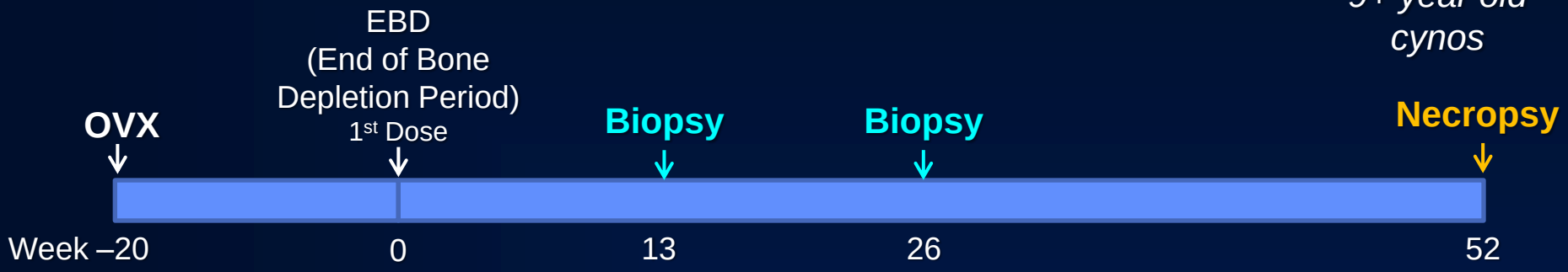
*P= 0.0489 vs placebo ; †P=0.2157 vs placebo


Wnt
Sclerostin
DKK1
LRP 4
LRP5/6
LRP 4
Osteoblast differentiation, proliferation, and mineralization activity


Wnt
Sclerostin
DKK1
LRP4
LRP5/6
APC
DSH
GSK3β
βcatenin
βcatenin
βcatenin
Sclerostin
Antibody

#1019: Ominsky et al. Romosozumab (Sclerostin Antibody) Improves Bone Mass and Bone Strength in Ovariectomized Cynomolgus Monkeys After 12 Months of Treatment

Skeletally mature 9+ year old cynos



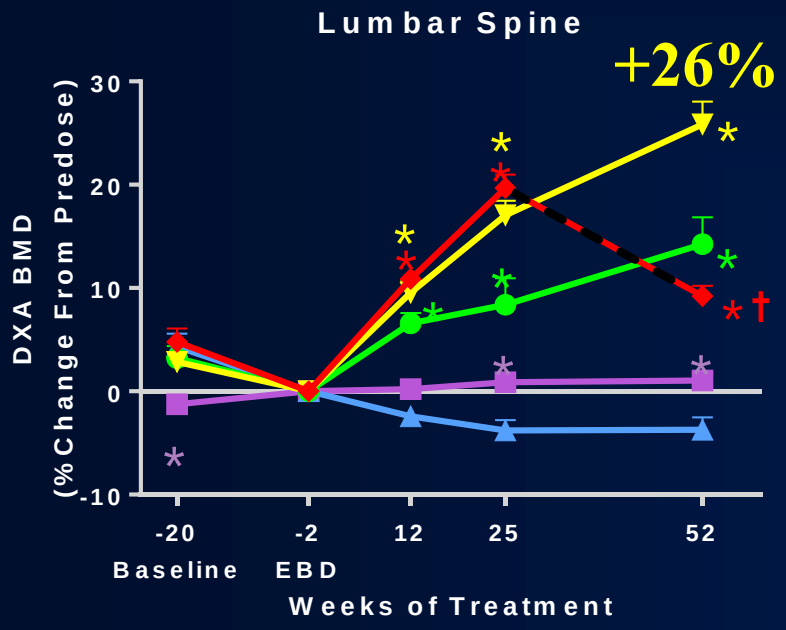
#	Group	Month 0–6 (Weekly SC Dosing)	Month 6–12 (Weekly SC Dosing)	Final n
1	Sham + Veh	Vehicle	Vehicle	16
2	OVX + Veh	Vehicle	Vehicle	16
3	OVX + 3 mg/kg	3 mg/kg	3 mg/kg	6
4	OVX + 30 mg/kg	30 mg/kg	30 mg/kg	15
5	OVX + 30 / 0 mg/kg	30 mg/kg	Vehicle	14

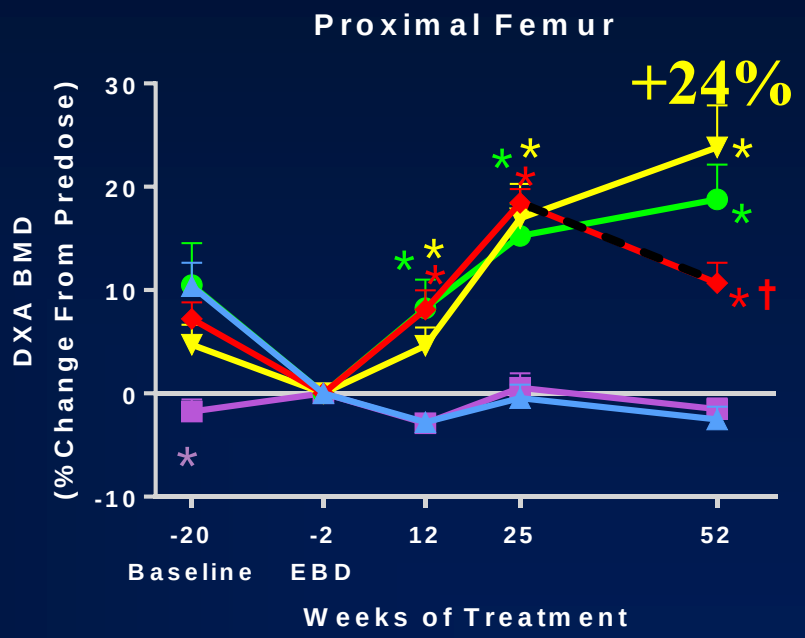
10 ADA+

Endpoints

- In vivo: serum biomarkers, DXA/pQCT
- Ex vivo: microCT, strength, ash analysis, histomorphometry

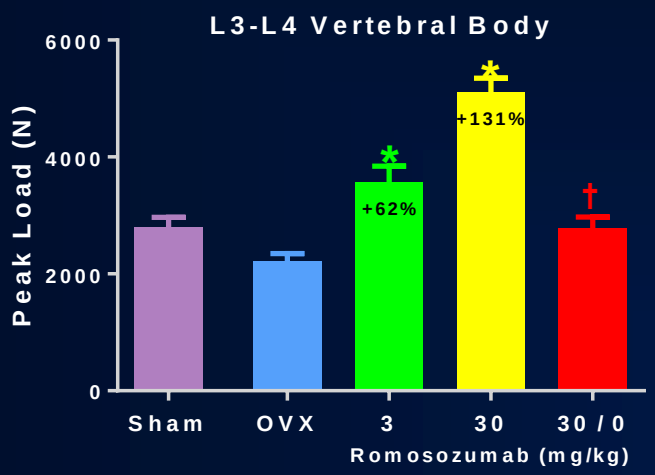
#1019. Ominksy et al. Romosozumab Increased DXA BMD at the Spine and Hip

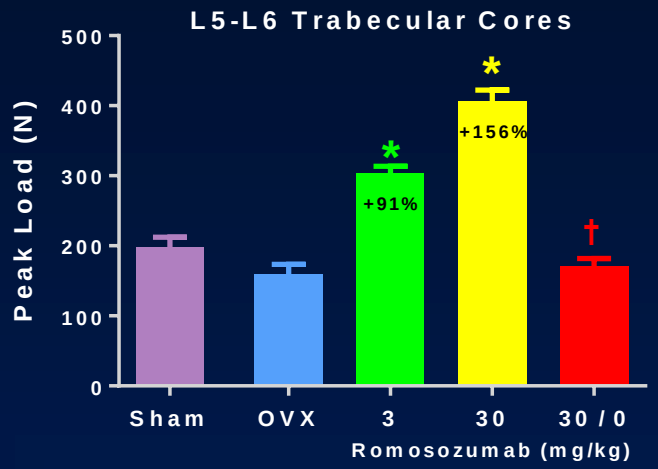


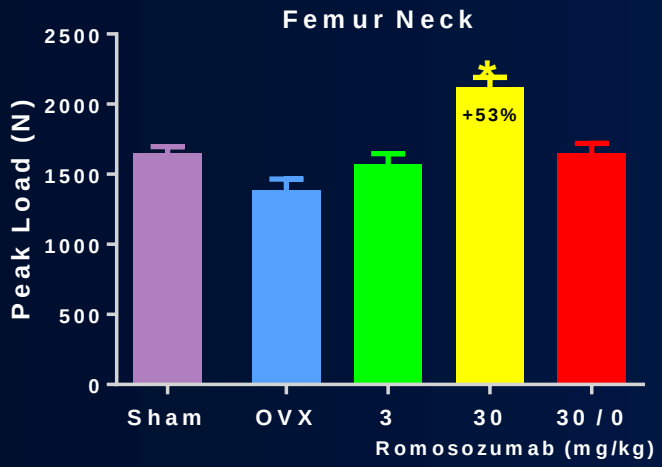


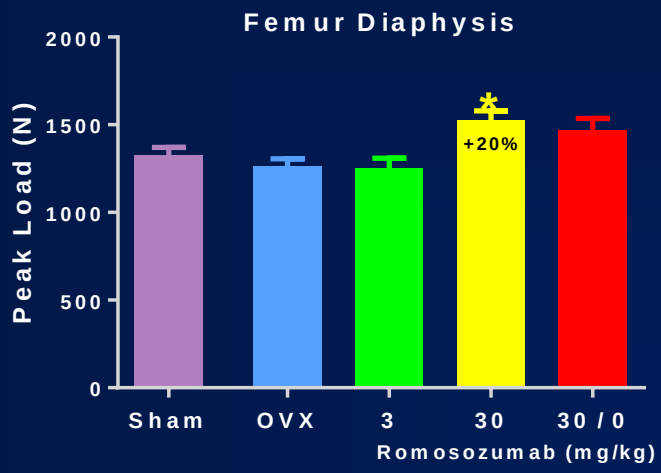
Mean ± SE, *$p < 0.05$ vs OVX, †$p < 0.05$ vs 30 mg/kg.

#1019. Ominsky et al. Romosozumab Increased Bone Strength at Cancellous and Cortical Sites









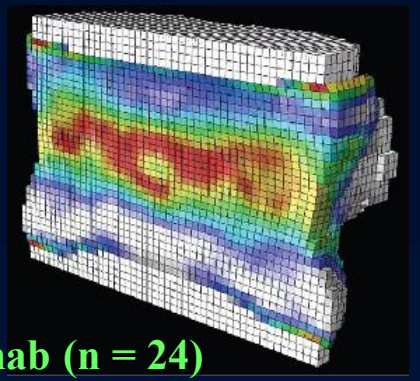
Mean ± SE, *$p < 0.05$ vs OVX, †$p < 0.05$ vs 30 mg/kg.

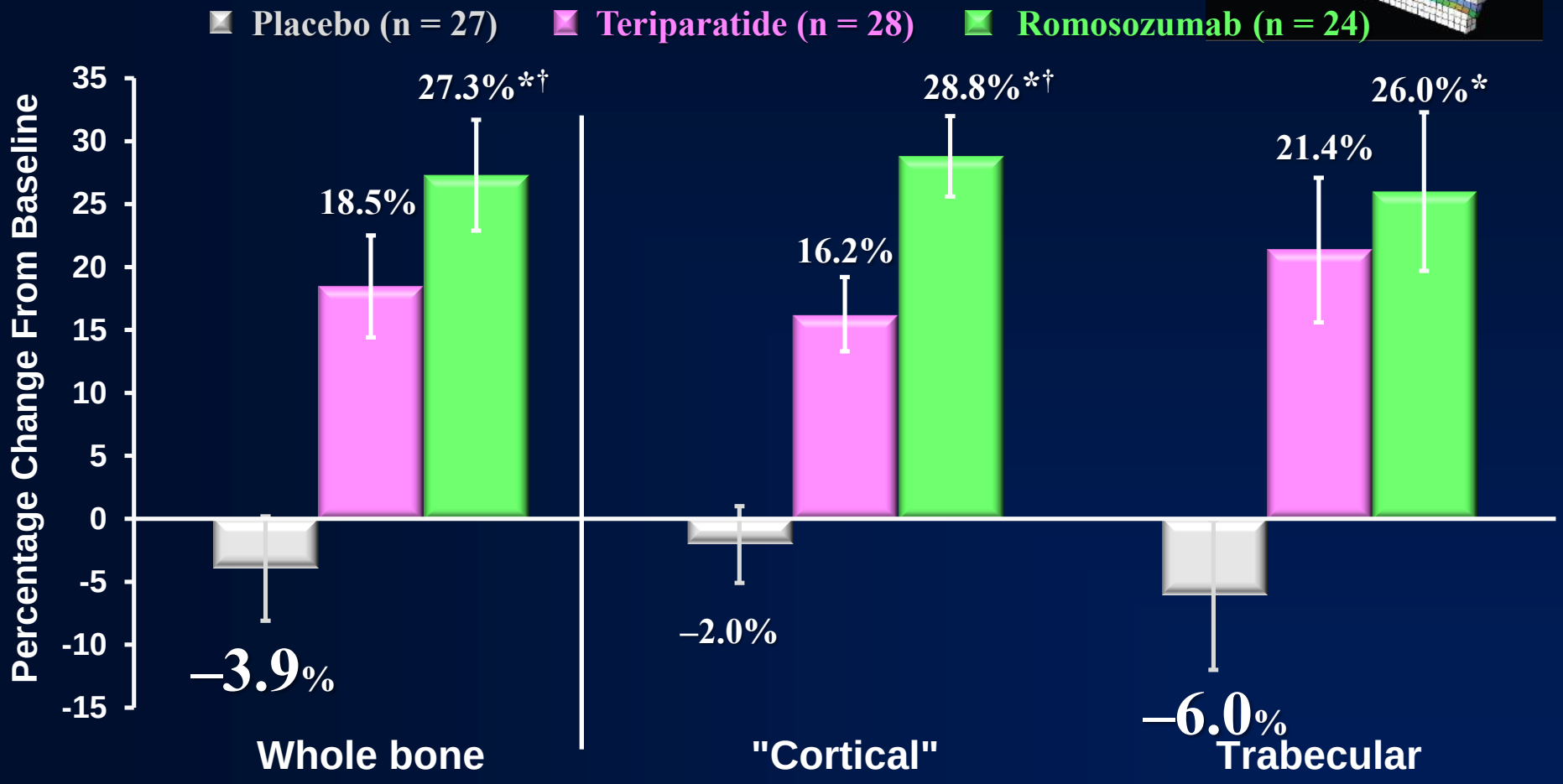
#1143: Keaveny et al. Romosozumab Improves Strength at the Lumbar Spine and Hip in Postmenopausal Women With Low Bone Mass Compared with Teriparatide

Objective:

To compare changes in estimated strength by finite element analysis (FEA) at the lumbar spine and total hip in postmenopausal women with low bone mass treated with romosozumab, teriparatide, or placebo for 12 months

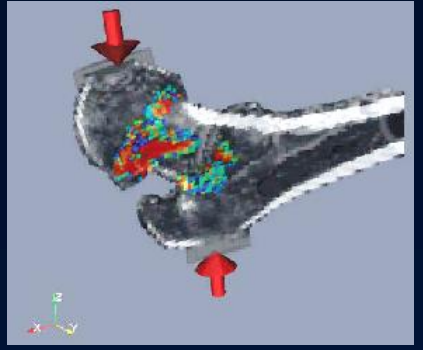
#1143 Keaveny et al. Romosozumab Increased Estimated Strength by FEA at the Lumbar Spine at Month 12

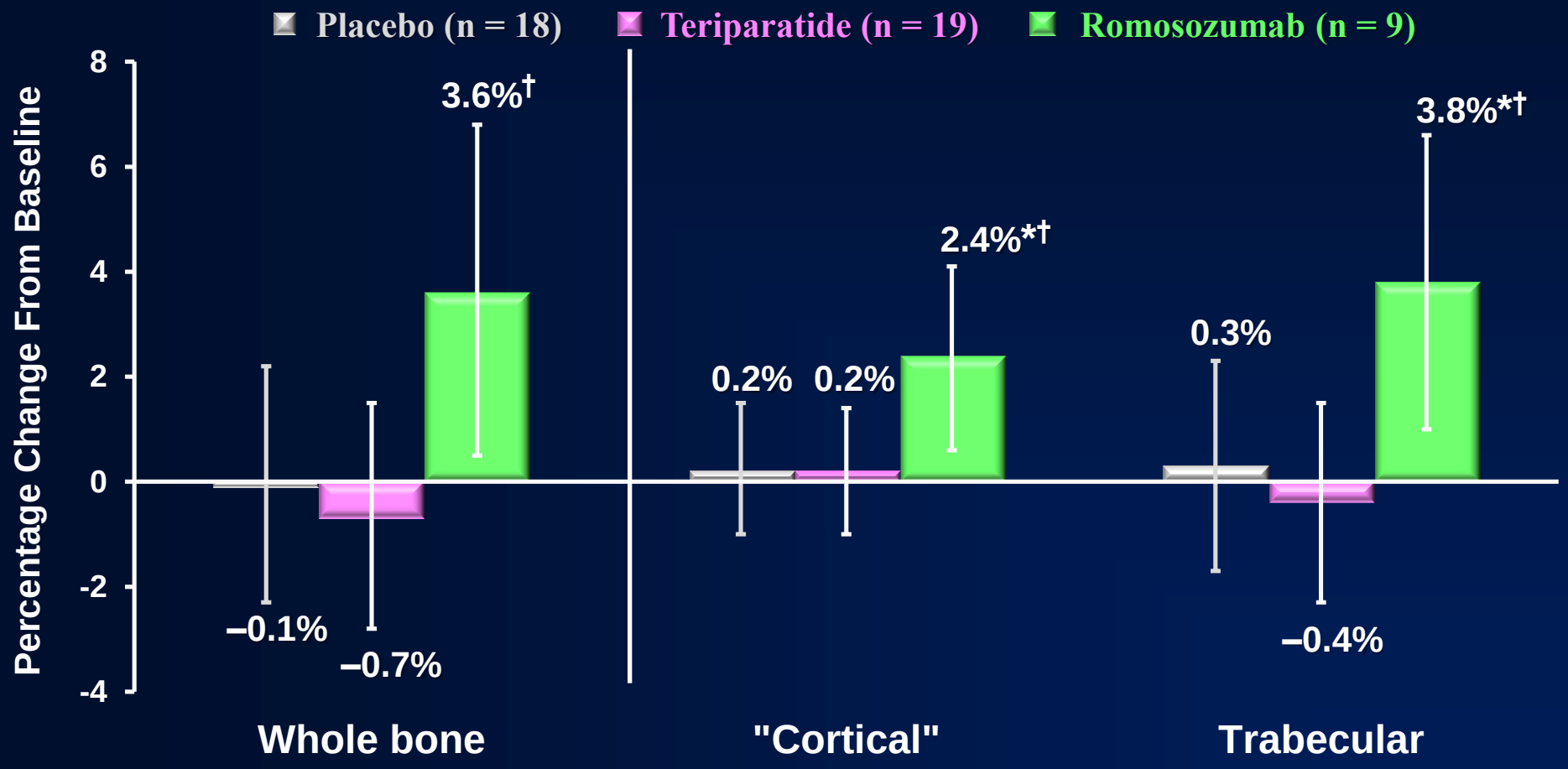




Data are LS means and 95% CIs. *$P < 0.05$ compared with placebo; †$P < 0.05$ compared with teriparatide.
ANCOVA model adjusting for baseline QCT FEA value and geographic region.
Teriparatide 20 µg QD, romosozumab 210 mg QM.

#1143. Keaveny et al. Romosozumab Increased Estimated Strength by FEA at the Hip at Month 12





Data are LS means and 95% CIs. *$P < 0.05$ compared with placebo; †$P < 0.05$ compared with teriparatide.
ANCOVA model adjusting for baseline QCT FEA value and geographic region.
Teriparatide 20 µg QD, romosozumab 210 mg QM.

DIABETES, OBESITY AND BONE

Fri : 10/9 **8 AM**	**Gerald D. Aurbach Plenary Lecture**	**B. Spiegelman**
Fri: 10/9 **11:30 AM**	**Symposium: Skeletal Consequences of Diabetes and Obesity**	**V. Borba, D. Schneider, S. Ferrari, J. Compston, B. Leslie**
Mon: 10/12 **11:30 AM**	**MTP: Fat-Bone Connection**	**C. Rosen**

Abstracts: 1027 (Most Outstanding Translational Abstract), **1067**, **1073**, 1094, **1139,.1141**, 1091

LAST YEAR:

#1101: Leslie et al. Does Diabetes Modify the Effect of FRAX Risk Factors for Major Osteoporotic and Hip Fracture Prediction? The Manitoba BMD Cohort

Incident Fractures

	Without diabetes	With diabetes	p-value
	N=55,958	N=6455	
Incident hip fracture	**954 (1.7%)**	**154 (2.4%)**	***<0.001***
Any incident MOF	**3726 (6.7%)**	**492 (7.6%)**	***0.004***

- Diabetes was a significant risk factor for fracture:
  - Hip fracture adjusted HR 1.40 [95% CI 1.18-1.66]
  - MOF adjusted HR 1.32 [95% CI 1.20-1.46]

(adjusted for FRAX risk factors including BMD)

#1067: Napoli et al. Vertebral Fracture Risk in Diabetic Elderly Men: The MrOS Study

Bkgd: Fracture risk increased in T2DM. Not studied well in men.

Cohort: Mr. Os.

Objective: to determine: if VF increased

b. whether BMD is correlated with VFs

Design: DXA and QCT at baseline and after 4.6 yrs

Results:

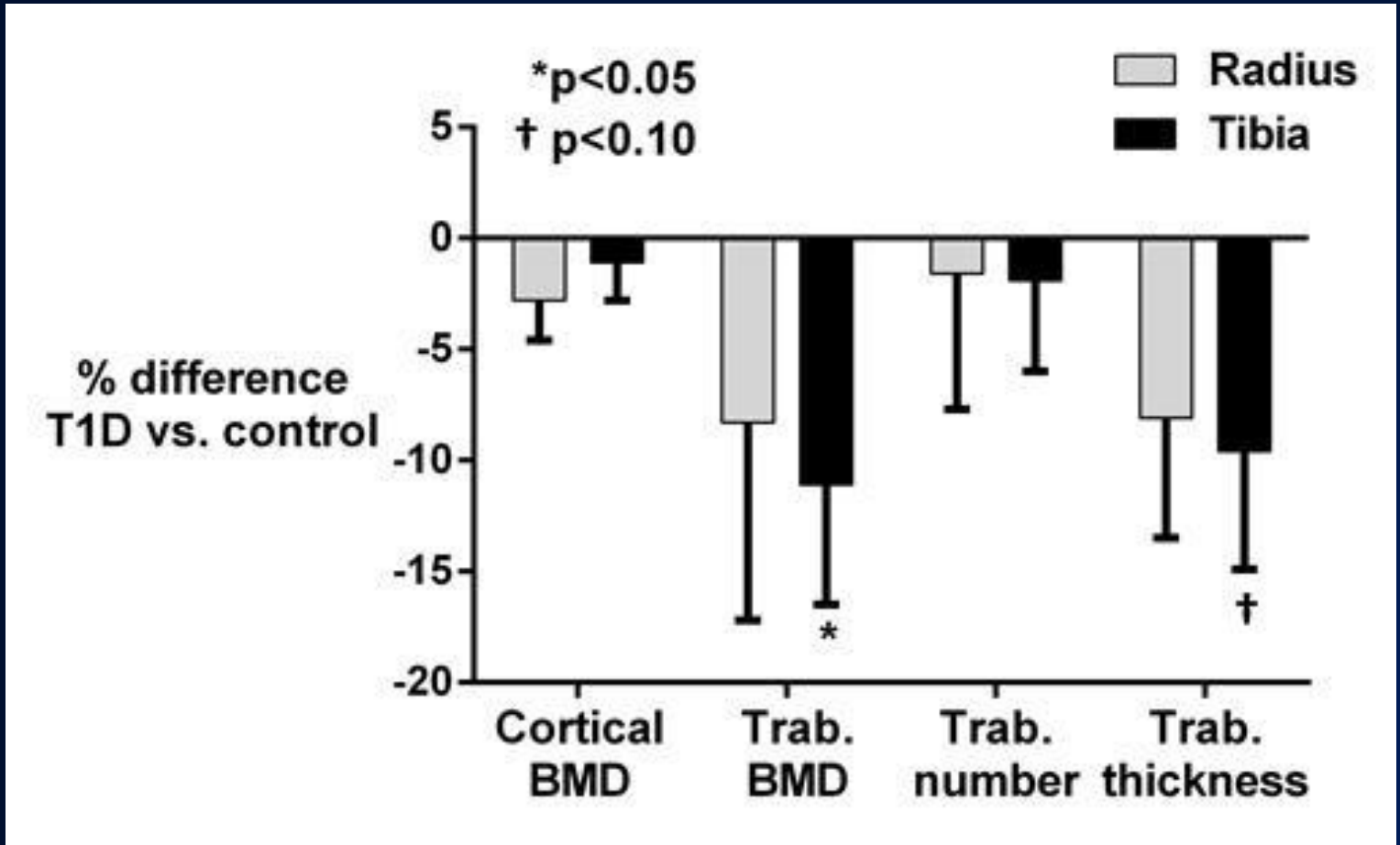
- Prevalence and incidence of VFs not higher in men with DM
- Spine BMD by DXA or QCT correlated with prevalent VFs

#1067: Napoli et al. Vertebral Fracture Risk in Diabetic Elderly Men: The MrOS Study

	Prevalent vertebral fractures	Incident vertebral fractures
Model adjusted for	**OR (95%CI)**	**OR (95%CI)**
Model 1: age, race, clinic site	0.91 (0.74-1.18)	1.05 (0.68-1.62)
Model 2: Model 1, BMI	0.93 (0.70-1.25)	1.10 (0.71-1.71)
Model 3: Model 2, spine aBMD	1.05 (0.78-1.40)	1.28 (0.81 -2.00)
Model 4: Model 2, spine vBMD	1.30 (0.89-1.88)	1.40 (0.78 -2.53)

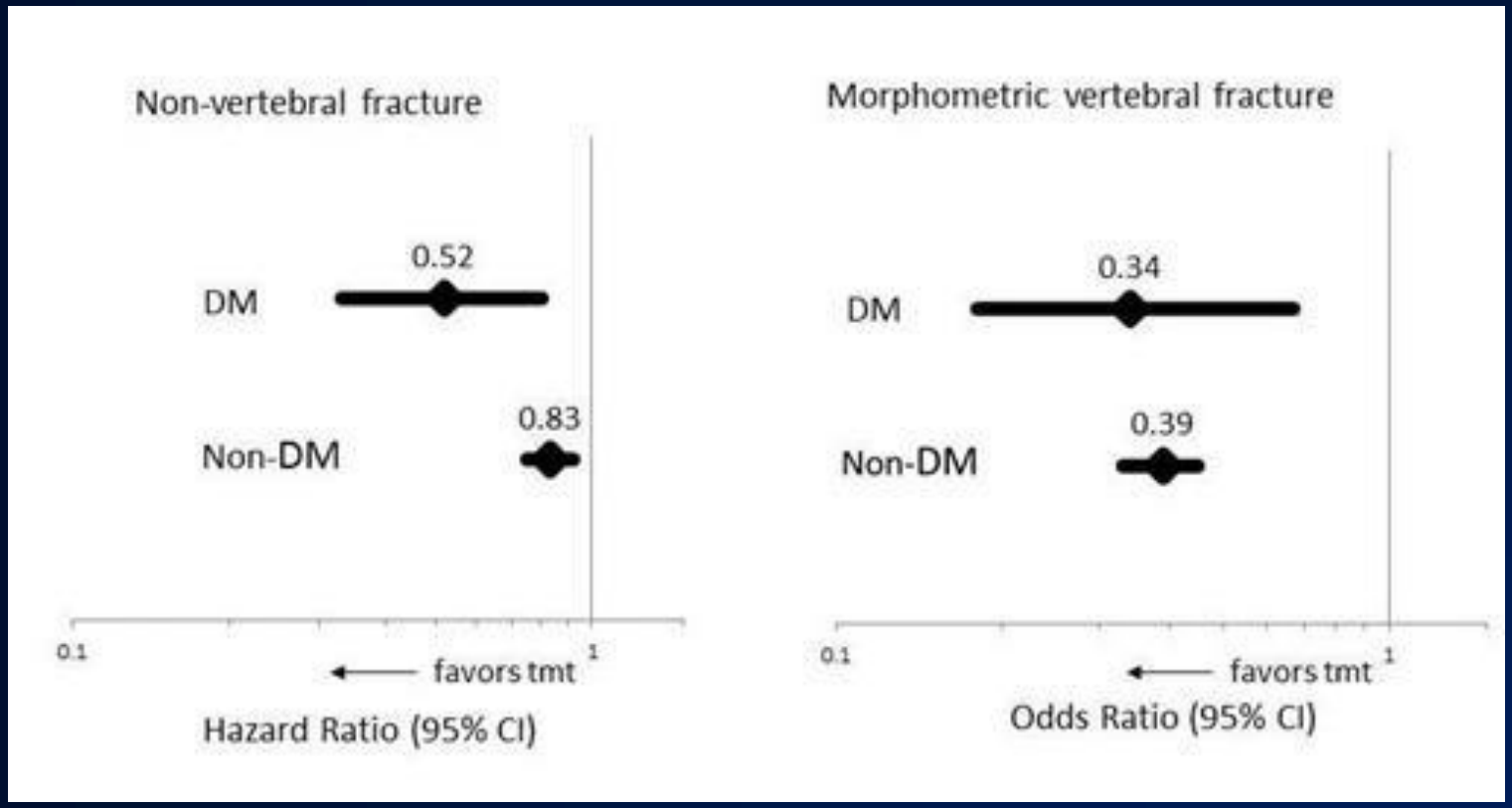
#1139: Mitchell et al. Altered Trabecular Microarchitecture in Youth with Type 1 Diabetes Mellitus

Design: 83 girls, 10-16 (16 T1D; 67 Controls)
T1 DM at least 1 yr
Method: HRpQCT



#1141: Schwartz et al. Bisphosphonates Reduce Fracture Risk in Postmenopausal Women with Diabetes: Results from FIT and HORIZON Trials

Post Hoc analysis: from FIT and Horizon Trials
Total n= about 13,000; DM = about 900



Conclusion: BPs reduce Vert and NonVert Fxs in DM

How to distinguish skeletal effects when both Type 2 DM and obesity coexist and both are bad for bones?

#1073: Rousseau et al. Changes in Fracture Risk After Bariatric Surgery from a Pattern Associated with Obesity to a Pattern Typical of Osteoporosis.

	Obesity + Bariatric Surgery vs non-obese controls		Obesity: no bariatric surgery vs non obese controls	
	Before	After	Baseline	later
Upper Ext Fx				
Central				
Lower Ext Fx				

RARE METABOLIC BONE DISEASES

Fri: 10/9 7:15 PM	Working Group: Rare Bone Diseases (Registration Fee)	C. Waldman
Sun: 10/11 8:00 AM	Plenary Louis V. Avioli Lecture: Hypophosphatasia: The Journey to Treatment	M. Whyte
Sun: 10/11 11:30 AM	MTP: Management of Hypoparathyroidism	D. Shoback

RARE METABOLIC BONE DISEASES

Abstracts:

Hypoparathyroidism: **1029***

Achondroplasia: LB1154

Fibrodysplasia Ossificans Progressiva: LB 1155

Hypophosphatasia: 1071

X-Linked Hypophosphatemia; 1070

Fibrous Dysplasia: 1074

Osteogenesis Imperfecta: 1072

#1029: Noda et al. Discovery of PCO371; an Orally Active Small-molecule PTH1R Agonist for the Treatment of Hypoparathyroidism

Bkgd: PTH(1-84), a **daily** injectable, has been approved for the treatment of hypoparathyroidism.

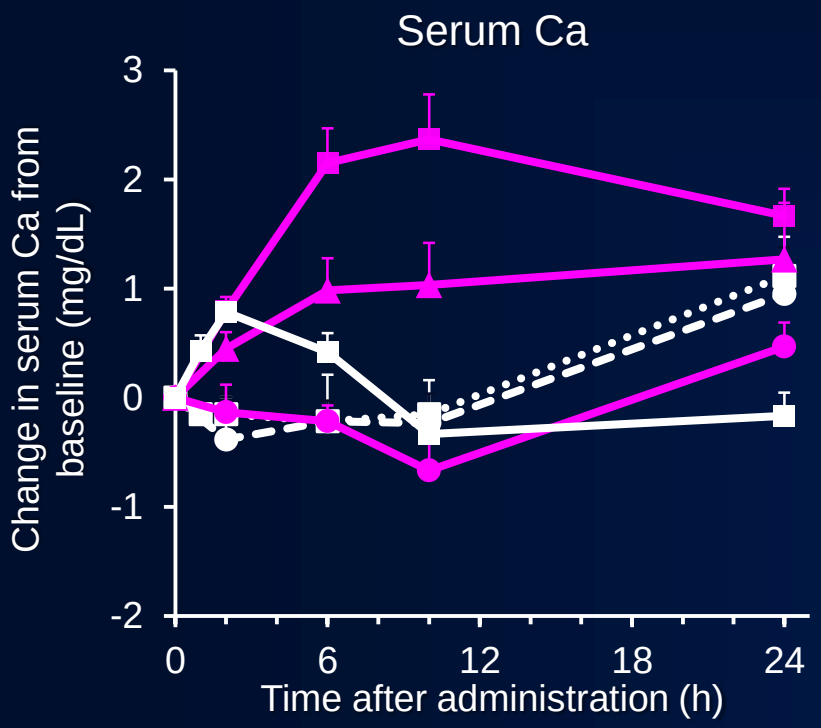
Question: can an **oral** agent that recognizes the PTH1R receptor be developed?

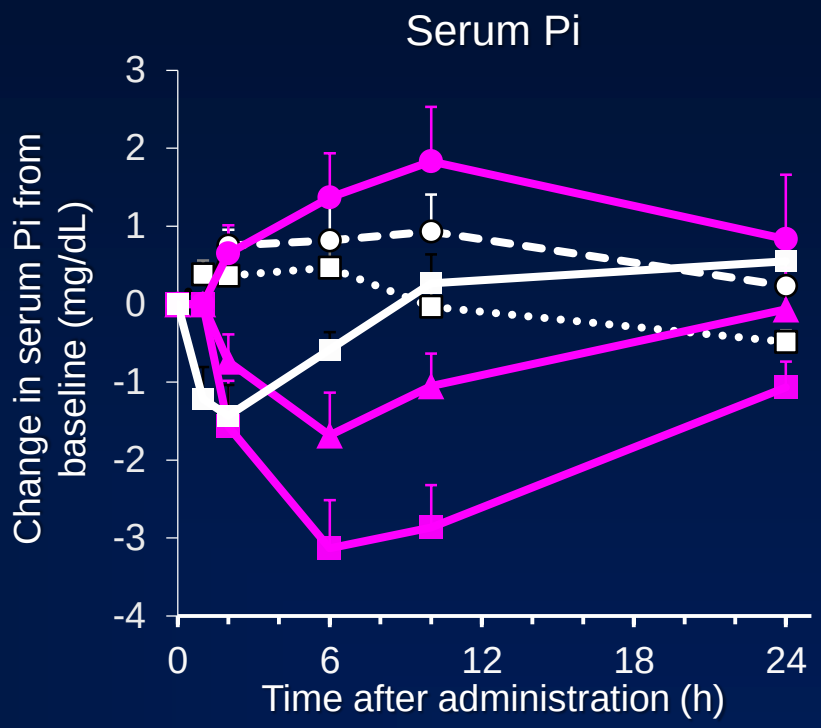
Method: high throughput screening withLLC-PK1 cells transfected with the PTH1R.

Test animal: thyroparathyroidectomized rat

#1029

Single oral dosing of PCO371 showed calcemic and hypophosphatemic effects in TPTX rats





Mean + SE, n=6
7-week old female SD rats

PO Control
PO PCO371 (1.3)
PO PCO371 (6.5)
PO PCO371 (33 mg/kg)
SC Control
SC PTH(1-84) (9 nmol/kg)

OTHER METABOLIC BONE DISEASES

Thurs: 10/8 All Day	**Symposium: Crosstalk between Kidney and Bone (Reg Fee)**	**B. Lanske, K. Hruska et al.**
Fri: 10/9 7:15 PM	**Working Group: Adult Bone and Mineral (Registration Fee)**	**A. Malaban**
Fri: 10/9 7:30 PM	**Working Group: Bone Turnover Markers (Registration Fee)**	**D. Bauer**
Sat: 10/11 11:30 AM	**Primary Hyperparathyroidism: An Update**	**J. Bilezikian**

Abstracts: 1069 (Paget Disease); **1138 (CKD)**

PEDIATRICS/ADOLESCENTS AND DEVELOPMENT

Sun: 10/11: 8 AM	**Louis V. Avioli Plenary Lecture: Hypophosphatasia: The Journey to Treatment**	**M. Whyte**
Sun: 10/11 4:30 PM	**Symposium: Low BMD and Fractures in Young People**	**A. Cheung, J. Jan de Beur, L. Bachrach, E. Shane, E. Orwoll**
Sun: 10/11 7:15 PM	**Working Group: Pediatric Bone and Mineral (Registration Fee)**	**F. Perward, P. Tebben**

Abstracts related to pediatrics and development:

#s 1063, **1064 (exercise in children),** 1071,1089,.1093,1094,1095,1096, 1097,1098,1139, LB 1154

OTHER TOPICS

Clinical Genetics	**Abs#1038,1088 (MO clinical abstract),1094,1097,1135,1136**	
Cancer **Mon: 10/12** **2:30 PM**	Plenary Symposiium: Bone Health in Patients Treated for Cancer Abs# 1086	J. Bruder, B. Edwards, P. Hadji, M. Smith, M. Drake
Osteoarthritis: Abs #s 1006,1007,1008,1009,1010 **Osteoporosis in Men: 1067,**1137,1138 **Falls:** 1067**,1066,** 1116 **High Bone Mass**: 1006,1072		

Topics covered

- EFF-ASBMR Fellows' Symposium
- Vitamin D, Calcium, Nutrition
- Epidemiology and Outcomes Research
- Exercise, Muscle, Sarcopenia, Frailty Biomechanics, Aging
- Imaging, Microstructure, Material Properties, Histomorphometry
- Therapeutics of Osteoporosis
- Diabetes, Obesity and Bone
- Rare and Other Metabolic Bone Diseases
- Pediatrics/Adolescents/Development
- Clinical Genetics
- Osteoarthitis
- Others

ENJOY THE MEETING!