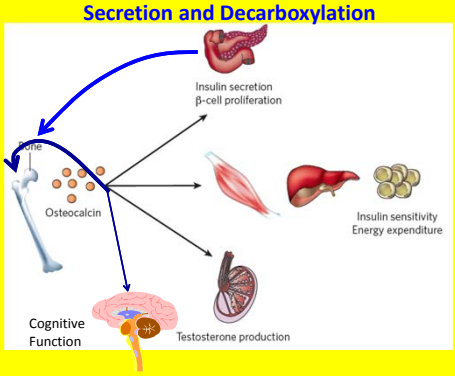
Highlights
Basic Science at ASBMR 2014, Houston

Roland Baron, Harvard

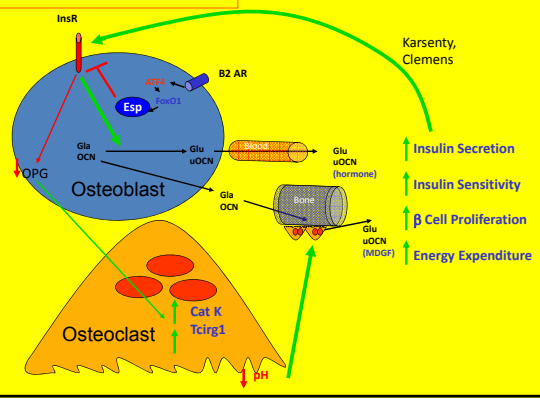
- 24 Abstracts
- Osteocalcin as a hormone
- Bone/Brain/Fat and SNS
- Muscle and Bone
- Wnt Signaling
- Bone and Cancer
- siRNA as Therapeutics

Bone as an Endocrine Organ via Osteocalcin Secretion and Decarboxylation



Adapted from Karsenty and Ferron, Nature 2012

Bone and Insulin



1121

DLK1 Exerts a Negative Feedback Regulation on The Osteocalcin-Insulin Loop

Concurrent Orals: Energy Metabolism and Bone
Presenter: Basem Abdallah, (Dr Kassem Lab) DENMARK

Hypothesis: This endocrine mechanism must have a negative feedback loop

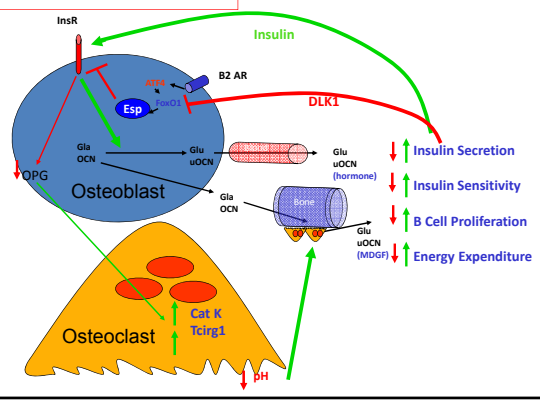
Question: **What is the nature of the negative regulatory signal of this loop ?.**

Results:

- **DLK1 is a circulating factor produced by β cells together with insulin.**
- **Glu-OCN stimulated Dlk1 gene expression by pancreatic islets**.
- **Insulin-induced OB differentiation and OCN expression were blocked in OB from Col1-Dlk1mice** while it was significantly up-regulated in OB from Dlk1-/- mice.
- Serum **Glu-OCN was 43% reduced in Col1-Dlk1 mice and 48% elevated in Dlk1-/-mice.**
- **Insulin secretion and sensitivity were reduced in Col1-Dlk1 mice and increased in Dlk1-/-mice**.
- In OB, **DLK1 antagonizes insulin signaling by inhibiting the AKT phosphorylation of FoxO1**, decreasing OCN expression.

Conclusion: **Glu-OCN-controlled production of DLK1 by pancreatic β cells acts as a negative feedback mechanism** to counteract the stimulatory effects of insulin on OB production of GLU-OCN, **preventing osteocalcin-induced hypoglycemia**.

Bone and Insulin



Expression of Glucose Transporter-4 by the osteoblast is required for global glucose metabolism

Presentation Number: 1044
Presenting Author: **Zhu Li**, T Clemens, Johns Hopkins (USA)

Recent studies have identified the osteoblast as a major insulin responsive cell that regulates global energy metabolism by secreting osteocalcin that alter insulin secretion and sensitivity.

Question: **What are the major fuel requirements of osteoblasts?**

- **Insulin increases metabolism of 14C-glucose in osteoblasts.**
- **Osteoblasts express Glut1 and Glut3 at low levels whereas Glut4 mRNA increased 6-fold during osteoblast differentiation.** In vivo, Glut4 was expressed by osteoblasts, osteocytes and chondrocytes at levels similar to muscle.
- Insulin induced **Glut4 translocation to the plasma membrane**.
- **Disruption of Glut4 in osteoblasts** eliminated insulin-stimulated glucose uptake, reduced proliferation and **diminished osteoblast maturation**
- **Mice lacking Glut4 in osteoblasts/osteocytes (Glut4 Ob-KO) had no change in cortical and trabecular bone architecture**
- **Glut4 Ob-KO mice exhibited increased adiposity and mild hyper-insulinemia and insulin resistance**. In the liver and fat of Glut4 Ob-KO mice insulin sensitivity was not altered.

Conclusion: **Resistance to insulin is the result of decreased Glut4-mediated uptake of glucose in bone.** Thus, the osteoblast-lineage contributes to the clearance of glucose in response to insulin, regulating whole body metabolism **beyond the secretion of osteocalcin**.

Last year # 1077

Bone as a Site of Insulin resistance in Type 2 Diabetes

Wei J and Karsenty G, New York

Question: T2D is characterized by insulin resistance at target cells: Adipocytes, Myoblasts, Hepatocytes. Since Osteoblasts are also target cells, which regulate glucose metabolism via osteocalcin, is insulin resistance in OBs contributing to T2D?

- Insulin resistance (increased pAKT and OPG, decreased uOcn) occurs in Obs from mice rendered diabetic through High Fat Diet
- Mice with Gain- of function of InsR in OBs were protected from insulin resistance
- Mice with Loss-of function of InsR in OBs were more insulin resistant
- In vitro OBs uptake glucose in an insulin-dependent manner, decreased by HFD
- **Glut1 is the main glucose transporter in OBs**

Conclusion: Insulin resistance takes place in osteoblasts in diet-induced type 2 diabetes **and insulin favors glucose uptake in these cells via Glut1**

1090

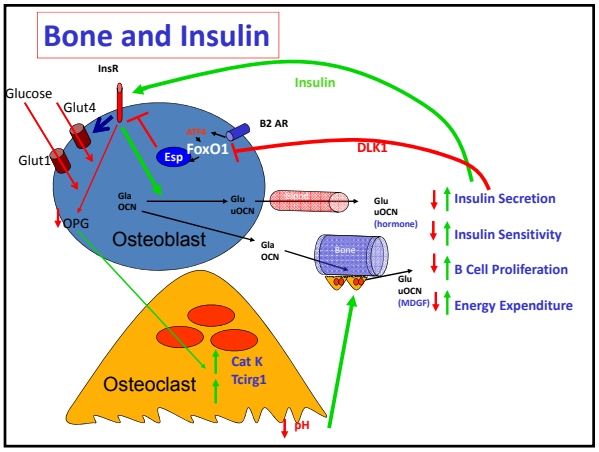
Glut1-dependent glucose uptake in osteoblasts is necessary for bone formation before and after birth and for whole-body glucose homeostasis

Plenary Orals: Translational Science II
Presenter: Jianwen Wei, (Karsenty's lab) Columbia University, USA

Question: **Why does bone regulate glucose metabolism?** **First step**: define the functions of glucose in bone.

- **Bone uptakes glucose, mostly in an insulin-independent manner**
- The amount of glucose up-taken by bone is 1/5 of what is up-taken by muscle.
- Osteoblasts or osteoclasts uptake 1/3 of the amount of glucose up-taken by myoblasts.
- **Glut1 (insulin-independent transporter) is 100 fold more abundant than other glucose transporters in bone cells**.
- Accordingly, **glucose uptake is decreased 70% in OBs lacking Glut1** and is increased 20% in OBs overexpressing Glut1.
- Deletion of Glut1 in OBs delays and **decreases bone formation and bone mass** in Glut1osb-/- mice **and induces an OCN-dependent glucose intolerance and insulin resistance**.
- The converse is true in mice overexpressing Glut1 in osteoblasts.
- **Glucose** limits AMPK activity, **favors** mTOR signaling in OBs and thereby **collagen synthesis and bone formation, osteocalcin synthesis and glucose metabolism**.

Conclusion: **Insulin-independent Glut1-dependent glucose uptake in OBs is a regulator of bone formation and of whole-body glucose homeostasis**.



1146

Osteocalcin regulates muscle function and mass

Plenary Orals: Basic Bone Biology II
Presenter: Paula Mera, (Karsenty's lab) Columbia University, USA

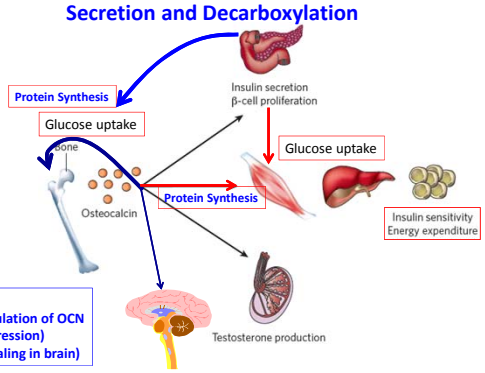
Muscle function and mass decrease with aging at the same time bone mass decreases. **GPRC6A**, a receptor for OCN, **is expressed in muscle fibers and satellite cells**.

Question: **Does osteocalcin regulate muscle function and mass in the mouse**.

- **Ocn-/- mice exhibit a decrease in muscle function and mass.**
- Converse is true in Esp-/- mice, a model of OCN gain-of-function.
- mice lacking GPRC6A, in all cells or in myocytes display the same muscle phenotype.
- As in β cells and in Leydig cells of the testis, **OCN activates the cAMP/PKA pathway** in primary myotubes and this is **dependent on GPRC6A**.
- OCN also in a GPRC6A-dependent manner, inhibits the energy sensor AMPK in primary myotubes, activating mTOR and increasing phosphorylation of S6K, an activator of protein synthesis.
- Concomitantly, OCN promotes tyrosine incorporation into cellular proteins in wild type, but not in Gprc6a-/- primary myotubes.

Conclusion: **osteocalcin is a regulator of muscle function and mass through GPCR6A-dependent inhibition of AMPK in muscle (directly or via insulin?)**

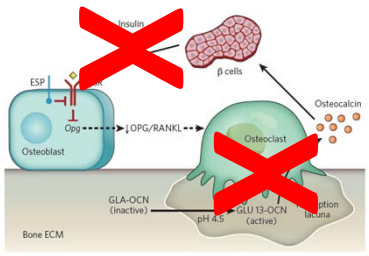
Bone as an Endocrine Organ via Osteocalcin Secretion and Decarboxylation



See Also
1016 (Regulation of OCN expression)
1017 (signaling in brain)

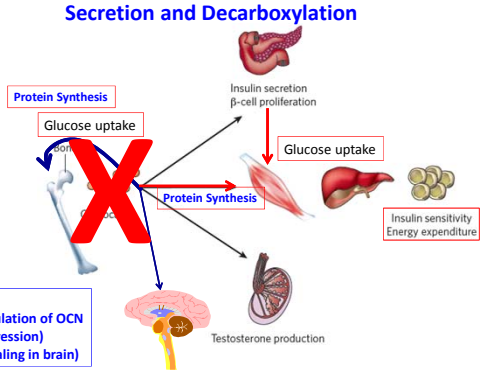
Adapted from Karsenty and Ferron, Nature 2012

Osteocalcin as a Matrix-Derived Growth Factor in coupling



Karsenty and Ferron, Nature 2012

Bone as an Endocrine Organ via Osteocalcin Secretion and Decarboxylation



See Also
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1017 (signaling in brain)

Adapted from Karsenty and Ferron, Nature 2012

1104
Effect of Dmab on Fasting Glucose Concentrations in Postmenopausal Women with Osteoporosis: Results From Subjects With Diabetes or Prediabetes From the FREEDOM Trial
Concurrent Orals: Diabetes and Skeletal Health
Presenter: Nicola Napoli, Amgen, Inc., USA

High sRANKL was a predictor of T2DM in a population-based study, and blockage of RANKL signaling improved glucose tolerance by enhancing hepatic insulin sensitivity in mouse T2DM models (Kiechl et al. Nature Med 2013;19(3):358-366).
In a prior post-hoc analysis of the FREEDOM trial, that enrolled 7808 women with osteoporosis, **DMAb had no effect on incident diabetes or fasting serum glucose (FSG) in women without diabetes at baseline**. Based on the favorable effect of blockage of RANKL on glucose tolerance in mouse T2DM models, **we tested the hypothesis that DMAb might decrease FSG in FREEDOM subjects with diabetes or prediabetes**.

- Baseline characteristics were similar between DMAb and PBO in the subpopulations with diabetes and prediabetes.
- The avg FSG across visits was not different between DMAb and PBO in women with diabetes or in women with prediabetes (p=0.20 and p=0.42, respectively);
- However, when censoring FSG values after ADM use in women with diabetes, estimated **average postbaseline FSG across visits was lower with DMAb than PBO (p=0.02)**.

BUT THIS IS OPPOSITE TO THE MOUSE OBSERVATIONS:
1/ Suppressing resorption and formation (OCN!) does not lead to significant glucose metabolism alterations whether in normal or diabetic women (and no worsening!)
2/ In contrast Dmab may actually favor glucose metabolism in women with diabetes (not worsen it!)

1020
Targeting RANK/RANKL as a novel treatment for muscle weaknesses and dystrophic conditions
Concurrent Orals: Neuromuscular Regulation of Bone
Presenter: Jérôme Frenette, Université Laval, CAN

RANK, RANKL and OPG are the key regulators of osteoclast differentiation. Although there is a **strong association between osteoporosis and skeletal muscle atrophy/dysfunction**, a biological pathway that regulates synchronously bone and muscle is still elusive.

Question: Does the RANK/RANKL pathway play a role in muscle function?

- **Deletion of RANK in skeletal muscle increases** the activity of the sarco/endoplasmic **reticulum Ca2+ ATPase** (SERCA, > 200% increase) in fast-twitch muscles.
- **Selective deletion of RANK in these muscles increased force production**.
- inhibition of RANKL/RANK with **OPG-Fc increases force in muscles from dystrophic mdx mice** (233% gain) and prevents the loss of SERCA expression and activity.
- a RANK/dystrophin double-deficient mouse model showed that **RANK deletion preserves muscle force, reduces muscle damage** and increases SERCA activity in dystrophic mice.

Conclusion: **RANK/RANKL is a key actor in several models of muscle weaknesses** and myopathies **and its inhibition is a new therapeutic avenue for several muscular diseases**.

Here again, but this time in the same species, inhibition of RANK/RANKL should lead to decreased OCN and decreased decarboxylation by Osteoclasts, decrease insulin sensitivity, glucose uptake and protein synthesis in muscle, thereby decreasing (not increasing) muscle function!

1021
Sarcopenia and Increased Body Fat in Sclerostin Deficient Mice
Plenary Orals: Basic Bone Biology 1
Presenter: Andrew Krause, Penn State College of Medicine, USA

The absence of mechanical load results in muscle and bone loss. Sost KO mice are resistant to unloading by hind limb suspension (HLS) as were mice given sclerostin antibody.

Question: **Are bone and muscles from Sost KO mice resistant to HLS-induced atrophy?**

- Sost KO mice and controls were exposed to HLS or maintained in control cages for 2 weeks.
- **Sost KO displayed reduced loss of trabecular BV/TV** (-4% vs. -47%, p<0.05), trabecular thickness (-2% vs. -41%, p<0.05), and trabecular number (+6% vs. -15%, p<0.05).
- Sost KO mice displayed significantly **more adipose tissue** and **less lean tissue** than WT mice.
- **HLS resulted in a further gain of fat and loss of muscle in Sost KO**.

Conclusion: Sost KO gained bone and were **resistant to unloading** but they displayed dramatic **sarcopenia and increased adiposity**. Our results suggest that **long term sclerostin deficiency, while having positive effects on bone, may have deleterious effects on muscle**.

If confirmed, these findings should be considered when developing therapeutic protocols using sclerostin antibody.

1092
Exercise regulation of marrow fat in the setting of PPARγ agonist treatment
Plenary Orals: Translational Science II
Presenter: Maya Styner, University of North Carolina, Chapel Hill, School of Medicine, USA

Marrow adipose tissue (MAT), remains poorly understood. Exercise prevents MAT accumulation while promoting bone formation, a response that may depend on caloric expenditure.

Question: **Can exercise overcome the adipogenic biasing of MSCs and increased MAT in PPARg agonist therapy (Rosiglitazone)?**

- Female mice were treated with Rosi. Exercise groups were provided running wheels (RD-E, Rosi-E), running ~12 km/d
- Total femur **MAT was 4.5-fold higher in Rosi relative to RD** (p<0.0001). **Exercise suppressed MAT in RD-E mice by half** (p<0.01).
- MAT acquisition **in Rosi** responded to exercise in all regions tested, although **MAT did not return to control levels** (p<0.001 for total femur)..

Conclusion: **Rosi induced MAT accumulation** in the femur and **exercise partially limited Rosi induction of MAT, perhaps through fuel usage, but not the negative effects of Rosi on bone quantity**. MAT supplies fuel for energy needs of exercise, but exercise cannot overcome the effects of PPAR agonists on bone.

1125
Muscle, Bone, and Nerve Differentially Interact to Achieve Trabecular and Cortical Bone Homeostasis
Concurrent Orals: Mechanobiology
Presenter: Ted Gross, University of Washington, USA

Muscle atrophy precipitates bone loss. The reduction in skeletal loading concomitant with sarcopenia has been presumed to be a primary mediator of bone catabolism.

Question: **Does diminished muscle function modulate bone homeostasis independent of loading?**

- Mice received transient paralysis of the right calf (C) or quadriceps (Q) muscles (BTxA) or peripheral nerve injury (PNI) of the right sciatic nerve.
- Gait-induced strains were diminished by Q than C paralysis, but not by PNI.
- Calf muscle volume was diminished more by C than Q paralysis, but not altered by PNI.
- C and Q **paralysis decreased trabecular BV/TV, while PNI induced less BV/TV loss**.
- C and Q **paralysis induced endocortical resorption, while PNI did not**.
- **Diminished normal strains and decreased trabecular BV/TV were minimally correlated** (r2<0.19), **but the relation between diminished normal strains and endocortical expansion was significant** (r2=0.62, p<0.01).

Conclusion: **cortical and trabecular bone are differentially regulated by muscle, bone and nerve interactions.** For **cortical homeostasis, muscle function is a potent modulator** via gait-induced mechanical stimuli. However, **neuronal pathways serve an essential role in trabecular homeostasis.**

1054

BMP-Alk3 signaling exerts opposite effects on trabecular versus cortical bone formation in postnatal mice

Concurrent Orals: Signaling Pathways in Skeletal Development

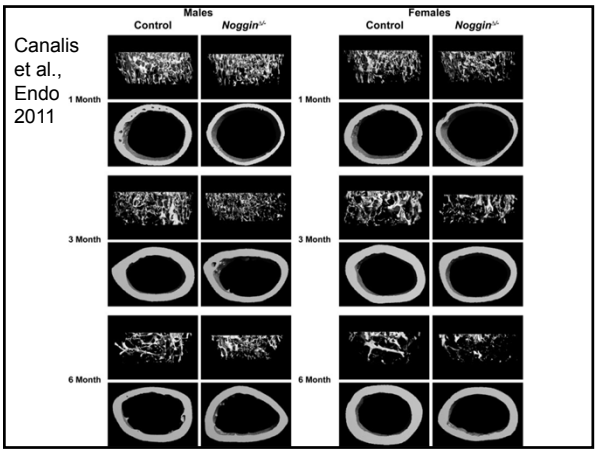
Presenter: Joohyun Lim, (Fanxin Long) Washington University in St. Louis, USA

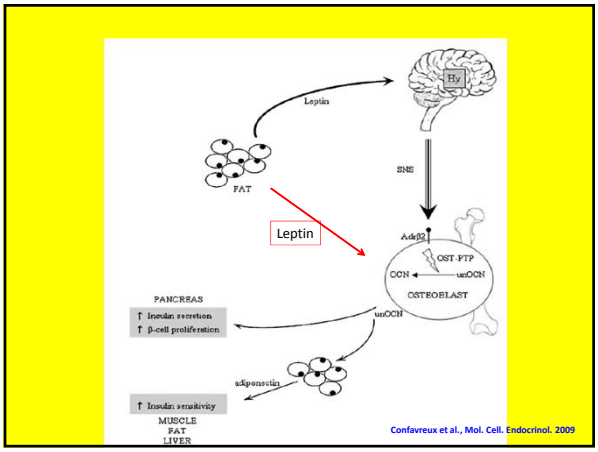
Bone morphogenetic proteins (BMPs) induce ectopic bone.

Question: **Does BMP signaling directly regulate bone formation in postnatal mice?.**

- Mice with deleted BMPR1 (Alk3) in OB-lineage cells were normal in size and weight but had **thinner cortical diameter due to reduced periosteal OB activity**.
- **Alk3 deletion increased cancellous bone formation**, without affecting OC numbers and function.
- Alk3 deletion significantly **increased BrdU-positive OB precursors**.
- Alk3 deletion also **suppressed Sost expression** by osteocytes, restricting the proliferation of osteoblast progenitors in trabecular bone through Sost-mediated inhibition of Wnt signaling.
- **Deletion of Smad4** in osteoblast-lineage cells **also increased cancellous bone formation** and reduced cortical diameter, **but less than Alk3 removal**.

Conclusion: **BMP-Alk3 signaling exerts opposite effects on trabecular versus cortical bone formation in postnatal mice, through both Smad-dependent and independent mechanisms.**





1120

Leptin is crucial for ventral hypothalamic delta FosB-mediated regulation of glucose and energy homeostasis but not for bone homeostasis

Concurrent Orals: Energy Metabolism and Bone

Presenter: Kazusa Sato, Harvard, USA

Leptin signals via the VHT, affects positively energy and glucose metabolism and has been reported affect bone negatively. Expression of ΔFosB in the VHT induce a high bone, low glucose and high energy phenotype, **despite lower levels of leptin**.

Question: What is the **role of leptin in the bone, energy and glucose metabolism** phenotypes? And **can energy and bone homeostasis be dissociated**?

- **In the absence of leptin, ΔFosB- ob/ob double transgenic mice lost the ΔFosB metabolic improvement whereas the increased bone mass remained.**
- VHT injected AAV- ΔFosB mice had increased energy expenditure but **ob/ob-AAV-ΔFosB mice failed to respond** and to correct the ob/ob glucose metabolism alterations.
- **AAV-ΔFosB in the VHT did not improve the obesity and adiposity of ob/ob mice.**
- **In contrast**, like the AAV-ΔFosB mice, the **ob/ob-AAV-Delta;FosB mice showed significant increases in BV/TV.**

Conclusion: **signaling from the VHT downstream of ΔFosB affects separately bone homeostasis and energy/glucose metabolism**: it increases **bone in a leptin-independent** manner whereas its **regulation of energy and glucose metabolism is leptin-dependent**.

1091

Brown Adipose Tissue Induces a Bone Anabolic Effect Through an Uncoupling Protein 1-Mediated Elevation of Central Neuropeptide Y Expression and Reduced Sympathetic Tone.

Plenary Orals: Translational Science II

Presenter: Paul Baldock, Garvan Institute of Medical Research, AUSTRALIA

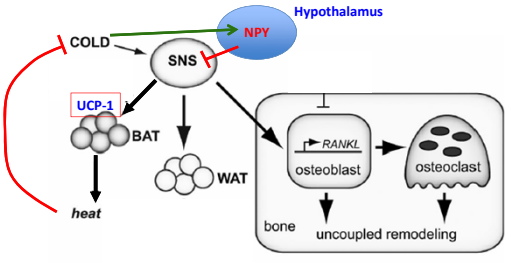
BAT dissipates energy through the actions of UCP-1 in mitochondria of brown adipocytes. A positive correlation between BAT and bone mass has been identified, linked to the bone anabolic effect of reduced sympathetic tone (Rosen)

Questions: i) **what component of BAT is responsible for the bone anabolic effect**, and ii) **what is the pathway by which BAT activity regulates sympathetic tone.**

- **UCP1-KO** or WT mice are housed at thermoneutrality **(30ºC), where UCP-1 is inactive**, or mild **cold-stress (22ºC), where UCP-1 is activated** for thermogenesis.
- **At 30ºC, no differences in cancellous or cortical bone**.
- **At 22ºC, UCP-1 KO mice displayed reduced TBV** (21%, p<0.05), mineralizing surface and cortical periosteal and endosteal perimeters..
- in WT **cold-stress elevates NPY**, which inhibits neurons **in the hypothalamus**, reducing sympathetic tone and protecting bone, but **cold-stressed UCP-1 KO displayed reduced hypothalamic NPY**
- **low NPY would release the sympathetic inhibition**, raising sympathetic output as in the BAT-deficient Misty mouse (Motyl et al., 2013).

Conclusion: UCP-1 activity protects bone mass. Thermogenesis initiated during cold-stress plays a positive role in bone mass and the **central NPY/sympathetic circuit is involved** in this BAT-Bone pathway.

Cold stress increases SNS output, affecting BAT and Bone



Adapted from Motyl et al., JBMR 2013

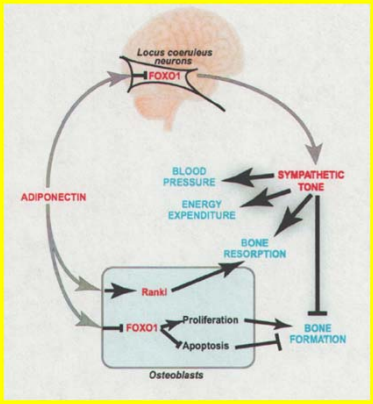
1128
Inner ear vestibular signals contribute to bone loss through the sympathetic nervous system
Concurrent Orals: Mechanobiology
Presenter: Guillaume Vignaux, (F Elefteriou lab) Vanderbilt University, USA

Elderly population is affected by bone loss and high risk of fracture. **The vestibular system is degenerating with age and is known to influence SNS outflow**.

Hypothesis: **Since SNS activation induces bone loss, microgravity-induced bone loss in space may be, at least in part, caused by disturbance in vestibular signals**.

- A mouse model of vestibular lesion (VBX) was subjected to a bilateral transtympanic injection of sodium arsenilate whereas Sham animals were injected with PBS.
- **VBX animals** had a significant vestibular syndrome. **Micro-CT revealed a reduction in TBV in with a decrease in ObS and an increase in OCs**.
- **UCP1 expression was increased 2X after VBX whereas serum TNFα levels were not** affected, suggesting an **increase in SNS outflow** and no chronic inflammation
- **Propranolol** (a beta blocker) or **b2AR deficiency** (global and specific) **blunted the vestibular-induced bone loss**.

Conclusion: **Vestibular signals, via SNS, modulate bone remodeling**, and **vestibular dysfunction may contribute to bone loss occurring with aging**. These results may also shed a new light on patients with vestibular disease.



Karsenty, Cell Metabolism, 2013

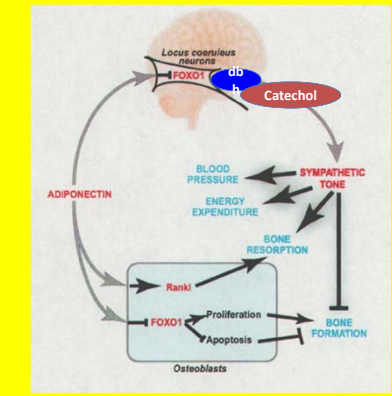
1026
FoxO1 inhibits bone mass accrual through its expression in neurons of the locus coeruleus.
Plenary Orals: Basic Bone Biology 1
Presenter: Daisuke Kajimura, (Karsenty lab) Columbia University, USA

FoxO1 is relevant to the regulation of bone mass because the hormone **adiponectin triggers the phosphorylation of FoxO1 in neurons of the locus coeruleus** and this may be one mechanism whereby **adiponectin inhibits SNS output and protects bone**.

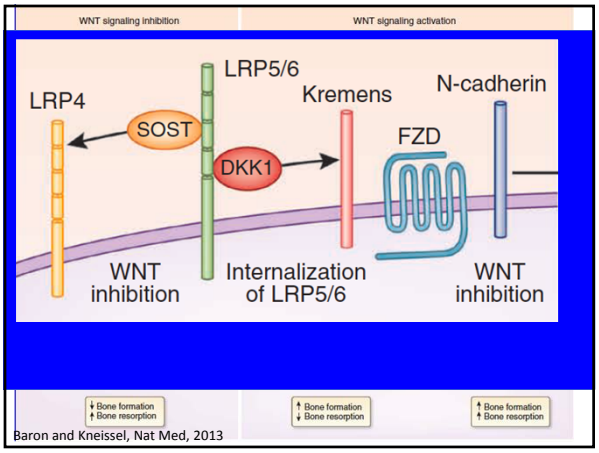
Question: **Does FoxO1 regulate the sympathetic tone? And how?**

- **Mice lacking FoxO1 only in neurons of the locus coeruleus** (FoxO1LC-/-) demonstrate a marked **decrease in the activity of the SNS, with low UCP 1 in BAT**.
- As a consequence of this decrease **FoxO1LC-/- mice have a high bone mass** because of a **decrease in bone resorption and an increase in bone formation**.
- **Gene expression survey identified Dbh**, a locus coeruleus-specific gene that encodes the initial and **rate-limiting enzyme in the synthesis of catecholamines**, as being **down regulated** in the FoxO1LC-/- mice.
- A molecular study showed that **FoxO1 binds to and trans-activates the promoter of Dbh**.

Conclusion: These results uncover a **transcriptional mechanism responsible for the sympathetic regulation of bone mass** and **identify a novel mechanism whereby FoxO1 regulates bone mass in vivo**.



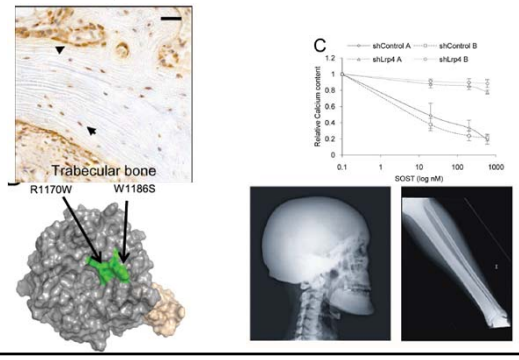
Karsenty, Cell Metabolism, 2013



Baron and Kneissel, Nat Med, 2013

Bone Overgrowth-associated Mutations in the *LRP4* Gene Impair Sclerostin Facilitator Function[S]

Leupin et al. J Biol Chem, 2010



Pharmacological Blockade of LRP4 Sclerostin Facilitator Function Is Bone Anabolic

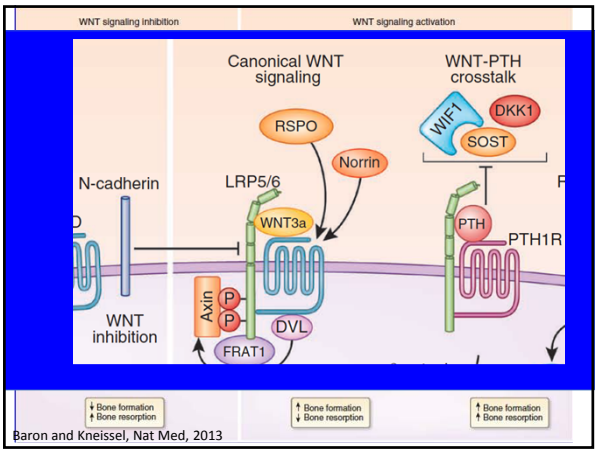
Ming-Kang Chang (Kneissel lab, Van Hul) Novartis, Basel, Switzerland[1]

LRP4 is a sclerostin facilitator and **mutations disrupting this LRP4 function cause HBM in humans** similar to patients lacking SOST/sclerostin.

Objective: **further delineate the role of LRP4 (previously known as NMJ protein) in bone,**

- **cKO mice that lack *Lrp4* in OBs/osteocytes (*Lrp4*$^{flox/flox}$;*Oc-cre*) or osteocytes (*Lrp4*$^{flox/flox}$;*Dmp1-cre*) showed** cancellous and cortical bone gain.
- OBs harvested from *Lrp4*$^{flox/flox}$;*Oc-cre* mice exhibited **higher mineralization *in vitro***.
- OB/osteocyte *Lrp4* deficiency resulted in **elevated serum sclerostin**, while ***Sost* gene expression in bone was unaltered**, indicating that **OB LRP4 retains sclerostin within bone** to present it to LRP5/LRP6 WNT co-receptors.
- To **explore the therapeutic potential of LRP4 inhibition we generated two anti-Lrp4 Abs**, which **selectively block sclerostin facilitator**, but not NMJ **function *in vitro***.
- **Anti-Lrp4 Abs increased bone mass** in aged rats in both cancellous and cortical bone, due to **increased bone formation**.
- This despite the fact that serum sclerostin levels were increased as a result of Lrp4 antagonism.

Conclusion: This demonstrates **a pivotal role of LRP4 in bone homeostasis** through its interaction with sclerostin, providing a **novel avenue for bone anabolic therapy** by antagonizing LRP4 sclerostin-facilitator function.



Baron and Kneissel, Nat Med, 2013

1008

N-cadherin Restrains Parathyroid Hormone (PTH) Activation of Lrp6/β-catenin Signaling and Its Bone Anabolic Action

Concurrent Orals: Biomechanics and Hormonal Effects

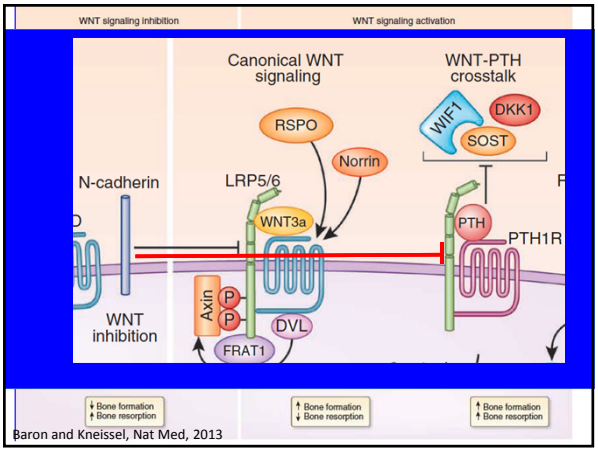
Presenter: Leila Revollo, (Civitelli lab) Washington University Division of Bone and Mineral Diseases, USA

Formation of a complex between parathyroid hormone (PTH), PTH/PTHrP 1 receptor (PTH1R), and Lrp6 has been linked to PTH signaling and anabolic action. Also, N-cadherin regulates canonical Wnt/β;-catenin pathway by interacting with Lrp5/6 via axin.

Question: **Does N-cadherin modulate PTH signaling by interfering with Lrp6 ?**

- **In N-cadherin-ablated BMSCs** (Cdh2flox/flox::Osx-Cre; cKO), Co-IP showed **that PTH1R interacts with Lrp6, but not Lrp5 or N-cadherin**.
- **PTH1-34 enhances this interaction in cKO cells**, but not in control.
- PTH1-34 promoted PKA-dependent **β-catenin stabilization** via C-terminus phosphorylation (S675), and Tcf/Lef transcriptional activity and **this was accentuated in cKO BMSC**.
- In vivo intermittent treatment with **PTH1-34 increased trabecular BV/TV, MAR and BFR in cKO more than in control mice**.
- **sCTX increased to a similar extent** in response to PTH in mice from both genotypes, but **P1NP was significantly increased in cKO mice compared to control**.

Conclusion: **N-cadherin restrains PTH activation of bone formation, but not bone resorption, buffering Lrp6/PTHR1 interaction** and consequently PTH-induced activation of Lrp6/β-catenin responses.



Baron and Kneissel, Nat Med, 2013

1055

TGIF Is Required for Canonical Wnt Signaling-induced Bone Formation

Concurrent Orals: Signaling Pathways in Skeletal Development

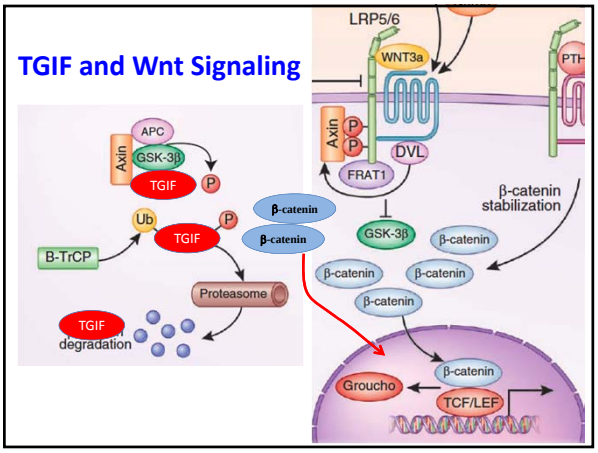
Presenter: Ming-zhu Zhang, (A Atfi, Mississipi, R Baron, Harvard)) School of Medicine,

The homeodomain protein TGIF plays crucial roles in cell fate determination and tissue homeostasis.

Question: Does it play a role in Bone Homeostasis and How?

- **GSK3β phosphorylates TGIF at T235 and T239 and mutation decreases TGIF turnover**.
- similar to βcatenin, **GSK3β phosphorylation leads to TGIF ubiquitination and degradation**; suppressing GSK3β stabilizes TGIF.
- expression of **TGIF enhanced Wnt-induced gene expression**, whereas TGIF deficiency had opposite effects.
- **TGIF promotes βCatenin accumulation by interfering with the assembly of the destruction complex.**
- Activation of **Wnt signaling induced TGIF, revealing a Wnt signaling feed-forward loop**.
- **TGIF increased OB differentiation via Wnt signaling**, blunted by TGIF depletion.
- **In vivo, TGIF-/- mice display decreased OB differentiation and low bone mass**, and deletion of TGIF prevented the high bone mass phenotype in DKK1+/- mice.

Conclusion: **TGIF is a component of the Wnt signaling machinery and is required for efficient Wnt-induced osteoblast differentiation and bone formation.**



Meta-Analysis of Genome-Wide Scans for Total Body BMD in Children and Adults Reveals Allelic Heterogeneity and Age-Specific Effects at the *WNT16* Locus

Carolina Medina-Gomez[1,2,3,4], John P. Kemp[5,6], Karol Estrada[1,3,4], Joel Eriksson[7], Jeff Liu[8], Sjur Reppe[9], David M. Evans[5,6], Denise H. M. Heppe[2,3,10], Liesbeth Vandenput[11], Lizbeth Herrera[1], Susan M. Ring[5], Claudia J. Kruithof[2,3], Nicholas J. Timpson[5,6], M. Carola Zillikens[10], Ola K. Olstad[9], Hou-Feng Zheng[12,13], J. Brent Richards[11,14,15], Beate St. Pourcain[5], Albert Hofman[2,3,4], Vincent W. V. Jaddoe[2,3,10], George Davey Smith[5,6], Mattias Lorentzon[16], Kaare M. Gautvik[9,17], André G. Uitterlinden[1,3,4,5], Robert Brommage[8], Claes Ohlsson[16], Jonathan H. Tobias[18], Fernando Rivadeneira[1,2,3,4].

WNT16 Influences Bone Mineral Density, Cortical Bone Thickness, Bone Strength, and Osteoporotic Fracture Risk

Hou-Feng Zheng[1,2], Jon H. Tobias[3], Emma Duncan[4,5], David M. Evans[6,7], Joel Eriksson[8], Lavinia Paternoster[6,7], Laura M. Yerges-Armstrong[9], Terho Lehtimäki[10], Ulrica Bergström[11], Mika Kähönen[12], Paul J. Leo[5], Olli Raitakari[13], Marika Laaksonen[14], Geoffrey C. Nicholson[15], Jorma Viikari[16], Martin Ladouceur[17], Leo-Pekka Lyytikäinen[10], Carolina Medina-Gomez[18,19], Fernando Rivadeneira[18,19], Richard L. Prince[20,21], Harri Sievanen[22], William D. Leslie[23], Dan Mellström[24], John A. Eisman[25], Sofia Movérare-Skrtic[26], David Goltzman[26], David A. Hanley[28], Graeme Jones[27], Beate St. Pourcain[7], Yongjun Xiao[29], Nicholas J. Timpson[6,7], George Davey Smith[6,7], Ian R. Reid[30], Susan M. Ring[7], Philip N. Sambrook[31], Magnus Karlsson[32], Elaine M. Dennison[33], John P. Kemp[6,7], Patrick Dandy[4], Adrian Sayers[6], Scott G. Wilson[34,35,36], Maria Nethander[24], Eugene McCloskey[28,29], Liesbeth Vandenput[24], Richard Eastell[29], Jeff Liu[37], Tim Spector[38], Braxton D. Mitchell[9], Elizabeth A. Streeten[9,39], Robert Brommage[40], Ulrika Pettersson-Kymmer[26,41], Matthew A. Brown[4], Claes Ohlsson[26], J. Brent Richards[1,2,42], Mattias Lorentzon[26]

PLoS Gen, 2012

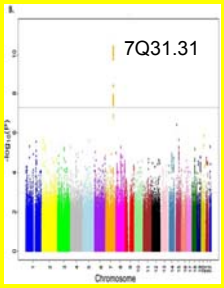
Meta-Analysis of Genome-Wide Studies Identifies *WNT16* and *ESR1* SNPs Associated With Bone Mineral Density in Premenopausal Women **JBMR, 2013**

Daniel L. Koller,[1] Hou-Feng Zheng,[2,3] David Karasik,[4,5,6] Laura Yerges-Armstrong,[7] Ching-Ti Liu,[8] Fiona McGuigan,[9] John P. Kemp,[10,11] Sylvie Giroux,[12] Dongbing Lai,[1] Howard J. Edenberg,[1] Munro Peacock,[1] Stefan A. Czerwinski,[13] Audrey C. Choh,[13] George McMahon,[14] Beate St Pourcain,[11] Nicholas J Timpson,[15] Debbie A Lawlor,[11] David M. Evans,[11] Bradford Towne,[13] John Blangero,[16] Melanie A Cortes,[16] Candace Kammerer,[16] David Goltzman,[17] Christopher S Kovacs,[18] Jerilynn C Prior,[19] Tim D Spector,[20] Francois Rousseau,[21] Jon H Tobias,[22] Kristina Akesson,[9] Michael J Econs,[1] Braxton D Mitchell,[13] J Brent Richards,[2,23,24] Douglas P Kiel,[3,25] and Tatiana Foroud[1]

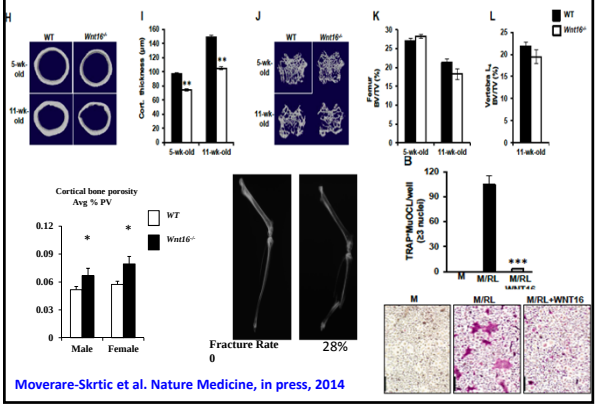
Missense polymorphisms of the WNT16 gene are associated with bone mass, hip geometry and fractures

C. García-Ibarbia · M. I. Pérez-Núñez · J. M. Olmos · C. Valero · M. D. Pérez-Aguilar · J. L. Hernández · M. T. Zarrabeitia · J. González-Macías · J. A. Riancho

Osteoporos Int, 2013



Last year two WNT16 knockout papers :



Moverare-Skrtic et al. Nature Medicine, in press, 2014

1028

Osteoblast-specific Overexpression of Human WNT16 Increases both Cortical and Trabecular Bone Density and Improves Bone Structure in Mice

Plenary Orals: Translational Science 1

Presenter: Imranul Alam, (M Econs lab) Indiana University School of Medicine, USA

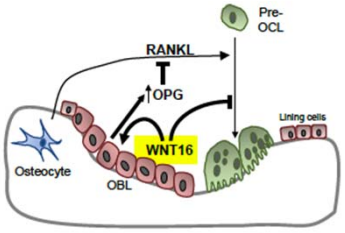
GWAS have identified common variants in genes associated with bone mineral density (BMD) and risk of fracture and identified SNPs in WNT16 that were associated with peak BMD in premenopausal women.

Objective: **To further identify the role of WNT16 in bone mass regulation**

- **WNT16-TG (Col1,2.3) mice exhibited higher BMD** (16-21%) **and BMC** (16-28%) at 6 and 12 weeks of age in both male and females. microCT **revealed 3-fold (male) and 14-fold (female) higher trabecular BV/TV in femurs**.
- The femur **cortical bone also showed 22% (male) and 14% (female) higher BA/TA and 14% (male) and 8% (female) higher cortical thickness in the TG mice**.
- Ca and P levels were similar between male WT and TG mice but **female TG mice had 11% higher P level and male TG mice had 20% higher serum ALP and 23% higher OCN** compared to WT mice.
- **CTX/TRAPc5b ratio was 14% (male) and 22% (female) lower in TG mice** compared to WT animals, suggesting that **WNT16 affects both bone formation and resorption parameters.**

Conclusion: WNT16 is a positive regulator of both cortical and trabecular bone mass, and can be targeted for anabolic therapeutic intervention.

WNT16 Regulation of Bone Homeostasis



- **WNT16 Deletion did not affect trabecular BFR, probably due to redundancy with other WNTs**
- **Overexpression of WNT16 increases BFR, due to added WNT stoichiometry**

Moverare-Skrtic et al. Nature Medicine, in press, 2014

1051

Heterozygous deletion of Wntless in the osteoclast lineage causes osteopenia demonstrating that osteoclasts are a critical source of Wnt proteins in the developing skeleton

Concurrent Orals: Signaling Pathways in Skeletal Development

Presenter: Megan Weivoda, (MJ Oursler lab) Mayo Clinic, USA

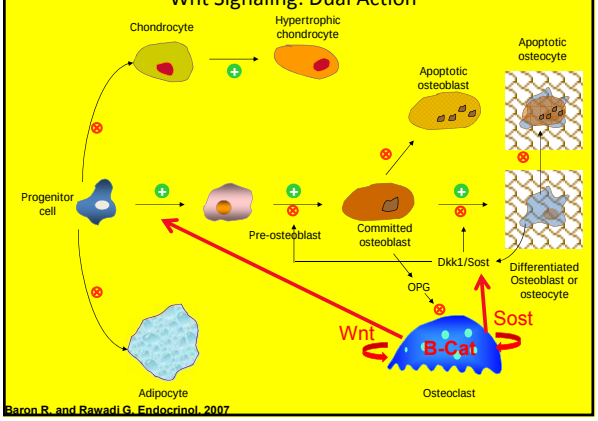
Although several cell types in the skeleton are known to produce Wnts, the contribution of these cellular sources to skeletal Wnt signaling is not clear. **Osteoclasts secrete multiple Wnts including Wnt1, Wnt3a, and Wnt10b.**

Question: **Are osteoclasts a critical source of Wnts in skeletal development?**

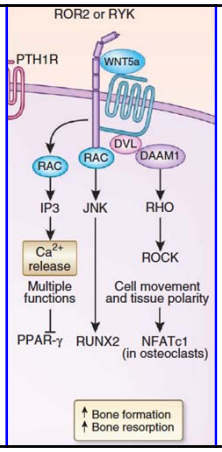
- Wntless (Wls), is required for Wnt secretion.
- **Cd11b or cathepsin K (Ctsk)-Cre Wls-flox mice exhibited decreased BMD at 6wo**.
- **Total protein secretion by Ctsk/WlsHet mature OCs was unaltered but secretion of Wnt1, Wnt3a, and Wnt10b was reduced.**
- pQCT showed **reductions in cortical bone** area, thickness, and density, as well as **decreases in total bone and trabecular density**.
- MicroCT showed a **60% reduction in cortical thickness** but trab BV/TV was unchanged.
- **Endocortical OB numbers were decreased by 70%, and OC numbers were increased**.

Conclusion: **Osteoclasts are a source of anabolic Wnts in the cortical region** and osteoclast lineage-derived Wnts play an essential role in skeletal development.

Wnt Signaling: Dual Action



Baron R. and Rawadi G. Endocrinol. 2007



1034

WNT5A Inhibits Skeletal Metastases of Prostate Cancer in Mice and Is Associated with a Longer Patient Survival

Concurrent Orals: Bone and Cancer
9/13/2014, 2:30 - 4:00 PM
Presenter: Stefanie Thiele, , GERMANY

Prostate cancer often metastasizes to bone. It is important to find prognostic markers that predict the aggressiveness of prostate cancer. Wnt proteins are implicated in carcinogenesis and WNT5A may influence prostate cancer as it stimulates osteogenic differentiation.

Question: Is WNT5A involved in prostate cancer development and in the formation of skeletal metastases?

- A tissue microarray using 397 high-risk prostate cancer patients showed that expression of WNT5A was higher as compared to patients with benign prostatic hyperplasia ($p<0.05$).
- Patients with high WNT5A levels had a higher probability for a longer survival than those with low WNT5A expression ($p=0.025$).
- In vitro, WNT5A overexpression in PC3 cells reduced proliferation by 39%, and induced apoptosis 2-fold. Knock-down of WNT5A yielded opposite results.
- In vivo, subcutaneous tumor growth and tumor growth within bone was inhibited in nude mice injected with WNT5A-overexpressing PC3-Luc cells (-90% and -85%, $p<0.05$).
- Moreover, while 80% of the mice receiving PC3-Luc cells developed bone metastases and bone lesions, overexpression of WNT5A abolished this process.

Conclusion: WNT5A has anti-tumor effects in prostate cancer and may be suitable as a prognostic marker and novel therapeutic target (treatment?) for prostate cancer and associated skeletal metastases.

Leukemogenic Transformation of Hematopoietic Stem Cells by Constitutive Activation of Canonical Wnt signaling in Osteoblasts

Presentation Number: **1005** **Most Outstanding Abstract Award**
Presenting Author: **Aruna Kode**, S Kousteni Columbia University (USA)

Question: Osteoblasts have been implicated in self-renewal and expansion of hematopoietic stem cells (HSCs) and the fate of malignant stem cells. What are the molecular basis of these functions?

- Constitutive **activation of Wnt/b-catenin in osteoblast precursors** in mice (***β*cat(ex3)$_{osb}$**) shifts HSC progenitors to the myeloid lineage, **leading to acute myeloid leukemia (AML).**
- AML is associated with clonal evolution in all ***β*cat(ex3)$_{osb}$** mice examined.
- **Transplantation of bone marrow from *β*cat(ex3)$_{osb}$ mice to irradiated WT mice induces AML.**
- **b-catenin-activated osteoblasts increased proliferation of human HSCs** in co-cultures, with accumulation of immature myeloid cells.
- **Nuclear accumulation of β-catenin in bone marrow biopsies were identified in 38% of patients with myelodysplasia (MDS) or AML.**

Conclusion: **Genetic alterations in osteoblast precursors can induce AML in mice and are associated with AML development in humans**.

Thus…antagonizing Sclerostin or Dkk1 could have a negative impact on leukemia!

1088

Foxo1 Expressed in Osteoblasts Promotes the Leukemogenic Properties of B-Catenin by Activating Notch Signaling

Plenary Orals: Translational Science II
9/14/2014, 10:00 - 11:30 AM
Presenter: Aruna Kode, (Kousteni lab) Columbia University Medical Center, USA

Osteoblasts affect HSCs and homing of healthy hematopoietic and tumor cells into the bone marrow.
In the mouse, constitutive activation of β-catenin (Ctnnb1CAosb mice) in Obs alters the differentiation potential of myeloid and lymphoid progenitors and triggers acute myeloid leukemia (AML) and the same genetic event is associated with AML development in humans

Question: Does FoxO1, a transcription factor known to interact with β-catenin, affect AML inducing properties?

- Deleting one allele of FoxO1 mice from the OBs of leukemic Ctnnb1CAosb mice prevented anemia, monocytosis, neutrophilia and lymphocytopenia.
- It also prevented the shift in the differentiation of HSCs to the myeloid lineage and the increase in long term repopulating HSC progenitors (LT-HSCs).
- myeloid and megakaryocyte dysplasias observed in Ctnnb1CAosb mice and associated with AML were also rescued.
- FoxO1 haploinsufficiency in OBs prevented the early lethality of Ctnnb1CAosb mice.
- FoxO1 interacts with β-catenin in OBs to induce the Notch ligand Jagged-1 in LT- HSC progenitors and the leukemogenic transformation of HSCs initiating the dysmyelopoiesis leading to AML.

Conclusion: FoxO1 in OBs affects hematopoiesis and the FoxO1/ activated β-catenin interaction results in AML. Targeting the bone marrow niche may help treat leukemia.

1057

FGF23 regulates bone mineralization in a vitamin D and Klotho-independent fashion

Concurrent Orals: Bone Remodeling and Mineral Homeostasis
9/13/2014, 4:30 - 6:00 PM
Presenter: Sathish Kumar Murali, (R Erben lab) AUSTRIA

Lack of Fgf23 (secreted by OB and Ocytes) or of Klotho (Kl), the co-receptor for FGF23, leads to severe impairment of bone mineralization in mice but the mechanisms are still poorly understood.

Question: What is the vitamin D independent role of FGF23 and Klotho in bone mineralization?

- we crossed Fgf23-/- or Kl-/- mice with mice expressing a non-functioning vitamin D receptor (VDR Δ/Δ).
- As expected, Fgf23-/- and Kl-/- mice had increased serum 1,25 (OH)2D3, and impaired bone mineralization, with increased expression of ANK, ENPP1, ENPP3, and osteopontin (OPN), increased pyrophosphate and OPN expression in bones of Fgf23-/- and Kl-/- mice.
- Ablation of vitamin D signaling in Kl-/-/VDR Δ/Δ mutants normalized serum Fgf23 levels, bone mineralization, pyrophosphate levels, ANK, ENPP1, ENPP3, and OPN. suggesting that the mineralization defect observed in Kl-/- mice is entirely due to 1,25(OH)2D3-driven upregulation of the mineralization inhibitor OPN, and of the pyrophosphate-regulating factors ANK, ENPP1, ENPP3.
- Despite normalization of pyrophosphate levels, bone mineralization remained impaired and OPN expression increased in Fgf23-/-VDR Δ/Δ mutants.
- osteoblasts isolated from Fgf23-/- mice, but not those isolated from Kl-/- mice, showed cell autonomous increases in OPN expression as compared to wild-type cells.
- Treatment of osteoblasts isolated from wild-type mice with FGF23 decreased OPN expression.

Conclusion: Fgf23 but not Klotho has a vitamin D-independent role in bone mineralization through direct regulation of OPN.

1029

Gut Microbiota Plays a Pivotal Role in the Bone Loss Induced by Sex Steroid Deficiency

Plenary Orals: Translational Science 1
9/13/2014, 10:00 - 11:30 AM
Presenter: Jau-Yi Li, Emory University School of Medicine, USA

PMOP results, in part, from the chronic inflammatory state caused by sex-steroid deficiency, with increased production of TNFα by activated T cells, but the nature of the antigens (Ags) driving T cell activation is unknown. The intestine contains trillions of microbes known as the microbiota, crucial for the induction, training, and function of the host immune system, contributes to inflammatory processes, and regulates bone mass accrual.

Objective: Determine the role of microbiota to the bone loss of sex-steroid deficiency.

- germ-free (GF) mice and control mice were treated with vehicle or Leuprolide, a GN-RH agonist that blocks sex-steroid production mimicking ovariectomy, for 10 weeks starting at 10 weeks of age.
- GF mice had a higher trabecular bone volume (BV/TV), and cortical bone volume (Ct.Vo) in the distal femur and the spine, as compared to controls.
- Leuprolide caused a 20-40% greater bone loss in control mice than in GF mice in all regions of interest.
- s CTX was increased ~2-fold by Leuprolide in control but not in GF mice.
- GF mice had a ~50 % smaller increase in bone marrow (BM) cells in response to Leuprolide.
- Leuprolide increased the frequency of TNFα;+CD4+ and TNFα;+CD8+ T cells in the BM in control mice but not in the BM of GF mice.

Conclusion: gut microbiota plays a significant role in bone loss and bone turnover in sex-steroid deficient mice by providing the Ags required for BM T cell expansion and increased TNFα; production. The gut microbiota may be involved in regulating the magnitude of bone loss in PMOP.

1038

Intravital 2-photon imaging reveals tumour-associated macrophages as the cellular targets underlying the anti-tumour activity of bisphosphonates in vivo

Concurrent Orals: Bone and Cancer
9/13/2014, 2:30 - 4:00 PM
Presenter: Michael J Rogers, Garvan Institute of Medical Research, AUSTRALIA

Bisphosphonates (BPs) target rapidly to the skeleton and inhibit bone resorption in patients with metastatic bone disease. BPs also decrease tumour growth and metastasis outside the skeleton in mouse tumour models. In recent clinical trials, adjuvant treatment with zoledronic acid alongside standard therapy also increased disease-free survival, and reduced local tumour recurrence and soft tissue metastases in estrogen-deficient women with early breast cancer.

Question: What are the mechanisms underlying these anti-tumour effects of BPs?

- Within minutes of tail vein injection of fluorescently-labelled BP in 4T1 mammary tumours in live mice, intravital 2-photon imaging revealed the flow of BP into mammary tumours via the vasculature. BP then diffused into mammary tumour tissue from leaky vessels and bound to microcalcifications that were rapidly engulfed by F4/80+ tumour-associated macrophages.
- Intravital imaging of individual macrophages in tumours of live mice also revealed the **uptake of BP by pinocytosis**. Flow cytometric analysis confirmed that cellular uptake of BP occurred predominantly by CD11b+F4/80+ macrophages, but not by tumour cells or CD11b+F4/80- tumour-infiltrating leukocytes.
- BP did not accumulate in normal mammary tissue.

Conclusion: BPs can be rapidly internalised by tumour-associated macrophages outside the skeleton, enhanced by the presence of microcalcifications. The anti-tumour activity of BPs in vivo occurs via effects on tumour-associated macrophages rather than by direct effects on tumour cells.

1106

Aptamer-Functionalized Lipid Nanoparticles (LNPs) Targeting Osteoblasts as a Novel RNA Interference-Based Bone Anabolic Strategy

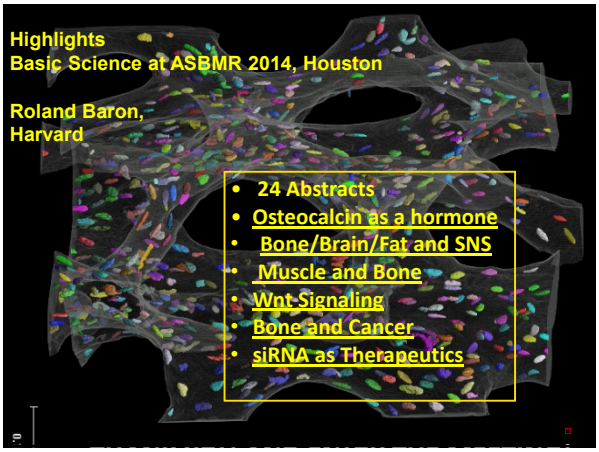
Concurrent Orals: Novel Targets and Treatments
9/14/2014, 2:30 - 4:00 PM
Presenter: Liang Chao, , HONG KONG

Objective: Our osteogenic siRNA delivery system (AspSerSer)6-liposome has concerns on efficacy and safety due to lack of osteoblast-specific delivery at cellular level (Zhang G, Nat Med 2012; Wang X, Nat Med 2013). The objective of this project is to develop novel aptamer-functionalized LNPs directly targeting osteoblasts at cellular level for RNAi-based bone anabolic therapy.

- Aptamers were screened by cell-SELEX with osteoblasts as target cells and hepatocytes and PBMCs as non-target cells. Osteoblast-specific aptamer was conjugated to LNPs that encapsulated osteogenic Plekho1 siRNA (Lu K, Nat Cell Bio 2008), i.e., Aptamer-LNPs-siRNA.
- In vitro evaluation of Aptamer-LNPs-siRNA was conducted
- aptamer (CH6) could target osteoblasts but not hepatocytes and PBMCs (Fig. 1).
- CH6-functionalized LNPs encapsulating Plekho1 siRNA, i.e., CH6-LNPs-siRNA. facilitated osteoblast-specific uptake of the encapsulated siRNA mainly via macropinocytosis in vitro (Fig. 2).
- in vivo data further confirmed that CH6 facilitated skeleton/osteoblast-specific delivery of Plekho1 siRNA (Fig. 3) and long persistence of gene knockdown (Fig 4), promoting bone formation and bone micro-architecture (Fig. 5), increased bone mass and enhanced mechanical properties in osteopenic rats with no obvious toxicity.

Conclusion: CH6 aptamer-functionalized LNPs is a targeting system for directly delivering siRNA to osteoblasts for anabolic treatment.

- Also : **1108 Therapeutic silencing intra-osseous Ckip-1 for promoting bone formation in an aged rat model of male osteoporosis** ,Baosheng GUO, Hong Kong Baptist University, HONG KONG
- **1107 Efficacy of an Experimental small interfering RNA Therapy for Autosomal Dominant Osteopetrosis type 2 (ADO2)** Mattia Capulli, University of L'Aquila, ITALY



ASBMR- Annual Meeting
Houston, Texas
September 12, 2014

Highlights of the ASBMR 2014 Annual Meeting

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

Larry Raisz (1925-2010)

- Founding Member of ASBMR, 1977
- Founding President of ASBMR, 1980-1981
- Leader Extraordinaire
- Founding Editor of JBMR, 1986
- Scientific Leader
- Mentor
- Friend
- The "guru" of this program for Health Professionals!
- In Memoriam (Bilezikian et al., J Bone Miner Res 2011;26:903-911)

The ASBMR Program for 2014

- **Special Sessions**
  - **Special Symposium: Diabetes (9/11)**
  - **Special Workshop: Rare Bone Diseases (9/11)**
  - **Special Ancillary Program: NOF Fracture Liaison Service (FLS) Model of Care Training (9/11)**
  - **Named plenary lectures (Louis V. Avioli Lecturer: H. Takayanagi; Gerald D. Aurbach Lecturer: A. Cuervo)**
  - **Plenary Symposia**
  - **Symposia**
  - **Round Tables**
  - **Clinical and Basic Science Evening at ASBMR**
  - **Debate (ASBMR-ECTS)**
  - **Grant Writing Workshop**
  - **Special Reports (NHBA, ASBMR)**

The ASBMR Program for 2014

- **Meet The Professors (17 clinical/translational; 9 basic- Fri, Sat, Sun, Mon)**
- **Working Groups (7: Fri, Sun eves)**
- **Oral abstracts 152 (10.4% of total 1448)**
- **Late-breaking abstracts 90**
- **Plenary Oral Posters ("mini-orals'): 30 (3 concurrent sessions; Fri @ 4:30-5:30)**

Distribution of all abstract presentations (orals and posters)

- **A. *Osteoblasts 125 (9.%)***
- ***B. Osteocytes 42 (3.0%)***
- ***C. Osteoclasts 68 (5.0%)***
- **D. *Bone, Cartilage and Connective Tissue Matrix & Development 88 (6.0%)***
- ***E. Modulators of Bone Remodeling 60 (4.0%)***
- ***F. Hormonal and Paracrine Regulators 86 (6.0%)***
- ***G. Energy Metabolism, Bone, Bone Marrow Niche 61 (4%)***
- ***H. Genetic Disorders of the Musculoskeletal System 70 (5.0%)***
- **I. *Bone Tumors and Metastases 52 (3.0)***

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

- *J. Osteoporosis – Assessment 66(4.0%)*
- *K. Osteoporosis – Epidemiology 97 (7.0%)*
- *L. Osteoporosis - Treatment 122 (8.0%)*
- *M. Osteoporosis – Pathophysiology 54 (4.0%)*
- *N Osteoporosis- Secondary causes 23 (2%)*
- *O. Osteoporosis- Health Care Delivery (21 (1%)*
- *P. Osteoporosis- Nutrition and Dietary Supplements 26 (2%)*
- *Q. Aging, Osteoarthritis and Muscle/Bone Interactions 90(6.0%)*
- *R. Biomechanics, Mechanobiology, and Quality 148 (10.0%)*
- *S. Bone Acquisition and Pediatric Bone Disease 27 (2.0%)*
- *T. Adult Disorders of Mineral Metabolism 48 (3.0%)*
- *U. Muscle biology and bone 24 (2 %)*
- *V. Rare and Other Bone Diseases 46 (3%)*

All osteoporosis related categories = 27% (2012: 34%; 2013- 31%)
Abstract #s reduced by 4% in 2013: 6% in 2014

Trends and special emphasis that you may notice at the 2014 ASBMR meeting

- Clinical Trial Results and Therapeutics
- Epidemiology of Osteoporosis
- Vitamin D, Calcium and Nutrition
- Musculoskeletal Biology

Trends and special emphasis that you may notice at the 2014 ASBMR meeting (continued)

- Pediatrics and developmental aspects of bone accrual
- Application of high resolution imaging to key clinical situations
- Bone turnover markers and signaling molecules
- Adverse effects of drugs

Highlights of the ASBMR 2014 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*

- Cristiana Cipriani
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- Bill Leslie
- Barbara Silva
- Ethel Siris
- Emily Stein
- Laura Targownik
- Ji Wang
- Renaud Winzenreith

*Provided me with material relevant to their presentations

Topics to be covered

- EFF-ASBMR Fellows' Symposium
- Vitamin D, Calcium, Nutrition and Exercise
- Epidemiology and Outcomes Research
- Frailty, Biomechanics, Muscle, and Bone
- Imaging, Microstructure, Bone Material Properties
- Bone Biomarkers
- Osteoporosis Therapeutics
- Metabolic Bone Diseases/Secondary Causes of Osteoporosis
- Diabetes, Obesity and Bone
- Rare Bone Diseases and Other Conditions
- Pediatrics/Adolescents/Development
- Clinical Genetics
- Cancer

8th EFF-ASBMR FELLOWS FORUM ON METABOLIC BONE DISEASES
September 10-11, 2014

62 Attendees
12 countries represented
36% International
50/50 MDs and PhDs
3 Plenary Lectures and 8 workshops
12 Faculty (basic & clinical)
Fellows presented 44 abstracts!

VITAMIN D, CALCIUM, NUTRITION AND EXERCISE

Sun: 9/14 11:30 AM	MTP: Nutritional and Bone Health in Adolescents	J. Pettifor
Mon: 9/15 11:30 AM	MTP: Diet and the Microbiome	C. Weaver
Sun: 9/14 7:15 PM	Working Group: Nutrition	S. Shapses

Abstracts of note: #s **1013**, 1014, 1075, 1076, 1077

Abs #1013: Allison et al. The influence of Exercise and the 3D distribution of Cortical and Trabecular Bone across the Proximal Femur: The HipHop Study (Young Investigator Award)

Background: Exercise doesn't change BMD very much in adults.
Question: Are there localized structural changes at the cortex of the femoral neck with exercise?
Design: 50 men- age 70; 1 year of daily single-legged hopping for 1 year (50 multidirectional hops per session on randomly allocated leg)
Assessment: By QCT: cortical mapping and adjacent trabecular density distribution
Compliance: 34 men finished; 92% compliance
Results: density in regions that might be critically important to structural integrity do change

Abs #1013: Allison et al. The influence of Exercise and the 3D distribution of Cortical and Trabecular Bone across the Proximal Femur: The HipHop Study

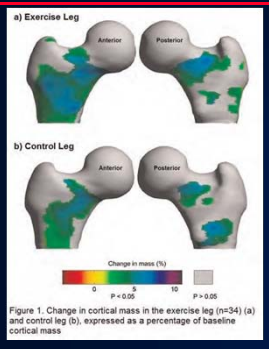


Figure 1. Change in cortical mass in the exercise leg (n=34) (a) and control leg (b), expressed as a percentage of baseline cortical mass

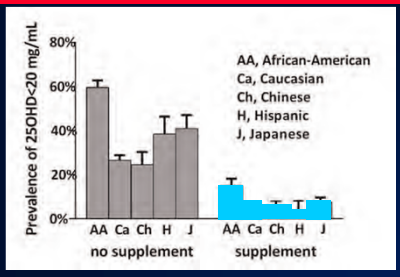
Results: Selective increase in femoral neck and proximal shaft mass: cortical and trabecular gains

Conclusions: repetitive, hopping leads in a short time to increases in cortical mass and trabecular density in regions that might be critically important to structural integrity

#1075: Mitchell et al. Increasing 25-hydroxyvitamin D levels over time: The Study of Women's Health Across the Nation (SWAN)

- 1582 women had 25-OH Vitamin D measured over two time periods spanning 11 years in an ethnically diverse population.
- Measurement of 25-OH Vitamin D by liquid chromatography-mass spect in single batch
- All groups increased: by 5.2 ng/mL (Caucasian) to 8.7 ng/mL (Chinese)
- Among supplement users (49%), increase was 10.1 ng/mL (vs 3.2 ng/mL).
- Standard of sufficiency set at 20 ng/mL (IOM)

#1075: Mitchell et al. Increasing 25-hydroxyvitamin D levels over time: The Study of Women's Health Across the Nation (SWAN)



By IOM, prevalence of vitamin D deficiency fell markedly among supplement users from 35% to 6%. Among non-supplement users from 43% to 24%

#1076: Cauley et al. Serum 25-hydroxyvitamin D, BMD, and Fracture Risk across the menopausal transition (SWAN)

- 1620 women: 80% pre- early-late perimenopausal; mean age 48 years
- Followed for 9 years
- Average 25-OH D 21 ng/mL
- 88 incident fractures: radiographically confirmed
- **For each 10 ng/mL increment in 25 vitamin D, fracture risk was lower by 25%. (multivariate adjustment)**
- A subgroup of 791 women: 10 years spanning 5 years before and 5 years after documented menopause: no relationship between change in BMD and vitamin D level.

Table: 25(OH)D and fracture over the menopausal transition

25(OH)D	Base Model[1] HR(95% CI)	Multivariate Model[2] HR(95% CI)
per 10 ng/ml increase	0.75(0.58, 0.96)	0.75(0.57, 0.997)
≥ 20 vs <20 ng/ml	0.55(0.35, 0.86)	0.58(0.35, 0.96)

[1] Adjusted for age, site, race.
[2]Base model + fracture history, prior and current hormone therapy, BMI, physical activity, education, total hip BMD, calcium and D supplements, corticosteroids, diabetes.

CONCLUSION:

Vitamin D is good for us!
(subtext: hopping on a sunny day may be even better!)

EPIDEMIOLOGY AND OUTCOMES RESEARCH

Sat: 9/13 11:30 AM	MTP: Strong Risk Factors for Clinicians	S. Cummings
Sun: 9/14 11:30 AM	The Clinical Diagnosis of Osteoporosis: Report of an NBHA Working Group	E. Siris

Abstracts related to Epidemiology and outcomes research:
1012, 1015,1063,1065,1066,1067,1068, 1076,1080,1084,1085,1101,1135,1136,1137, 1138,1139,1140

1015: Sundh et al. Hypnotics and SSRIs are associated with risk of osteoporotic and hip fractures, independent of FRAX risk factors (Swedish registry study)

1137. Morin et al. Previous fractures are associated with subsequent fractures, particularly during the first year. Effect mitigated by advanced age (competing mortality is likely explanation)

EPIDEMIOLOGY AND OUTCOMES RESEARCH

Sat: 9/13 11:30 AM	MTP: Strong Risk Factors for Clinicians	S. Cummings
Sun: 9/14 11:30 AM	The Clinical Diagnosis of Osteoporosis: Report of an NBHA Working Group	E. Siris

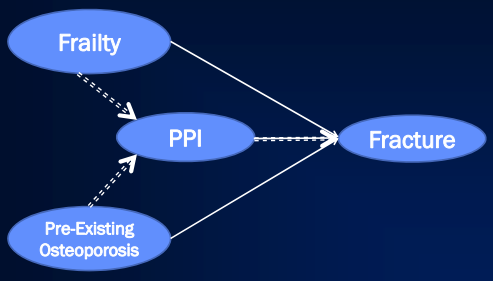
Summary of several abstracts:

1067: Dufour et al. Soft tissue thinness of the trochanter as determined by DXA is a risk factor for hip fracture, independent of BMD. Used together, though, soft tissue thinness and BMD improved risk prediction best

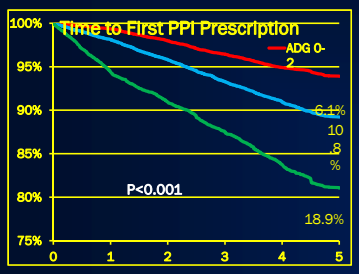
The Clinical Diagnosis of Osteoporosis: Sunday at 11:30 (Ethel Siris, presenter)

- An NBHA Working Group proposes an expansion of the criteria for making a clinical diagnosis of osteoporosis in the US to reflect the definition of the disease as a problem of reduced bone strength predisposing to high risk for fracture.
- The diagnosis of osteoporosis should be made in postmenopausal women and men age 50 or older if any one of the following are present:
  - T-score ≤-2.5 at the spine or hip
  - Hip fracture, with or without BMD
  - Vertebral, proximal humerus, pelvis or some distal forearm fractures in the setting of osteopenia
  - FRAX score in a patient with osteopenia meeting or exceeding the NOF Guide treatment cut points

#1080: Targownik L. et al. Medical Comorbidity and Osteoporosis Are Associated With Subsequent Initiation of Proton Pump Inhibitors



#1080: Targownik L. et al. Medical Comorbidity and Osteoporosis Are Associated With Subsequent Initiation of Proton Pump Inhibitors



- Persons with severe medical comorbidities are approximately 3 times more likely to start on PPIs than those with no or mild comorbidity (prior to the occurrence of fracture)
- Osteoporosis increases the risk of subsequent PPI prescription by ~20%
- Persons who receive PPI may therefore be at increased baseline risk for fracture
- This provides evidence for a non-causal explanation for the PPI-fracture association

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

- Diabetes mellitus appears to be a risk factor for fracture independent of FRAX
- Does it add to or simply modify other clinical risk factors?
- Population: 62,413- mean age 64. 6,455 (10%) had diabetes.
- Over 6 years, 7.6% with and 6.7 without diabetes developed major osteoporotic fracture.

#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

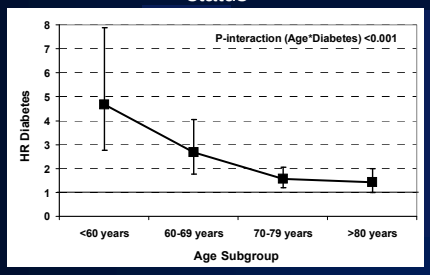
	Without diabetes	With diabetes	p-value
	N=55,958	N=6455	
Incident hip fracture	954 (1.7%)	154 (2.4%)	*<0.001*
Any incident MOF	3726 (6.7%)	492 (7.6%)	*0.004*

- 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)

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

HR (95% CIs) for incident hip fracture by diabetes status *



* adjusted for age, sex, BMI, glucocorticoid use, rheumatoid arthritis, high alcohol use, any prior fracture and femoral neck T-score.

Frailty, Biomechanics, Muscle, and Bone

Fri: 9/12 10 AM	MTP: Sarcopenia: definition and assessment	R. McLean
Fri: 9/12 11:30 AM	Symposium: Muscle and Bone	L. Bonewald, M. Hamrick, T Guise, M. Brotto, T. Harris
Fri: 9/12 7:30 PM	Working Group: Muscle and Bone	C. Gordon
Fri: 9/12 7:15 PM	Working Group: Bone Strength	R. Kremers,A Cheung

Frailty, Biomechanics, Muscle, and Bone

Sat: 9/13 11:30 AM	To Mars and Beyond: How will we preserve the musculoskeletal system in long term space flights?	R. Gagel, J. Sibonga, J. J. Robinson, E. Orwoll, A. Licata, J. Myers, ISS Astronauts et al.
Sun: 9/14 8:00 AM	Symposium: Falls and Fall-related Injuries	M. Hannon, E. Samuelson, M. Karlsson, S. Lord, E. Becker
Mon 9/15 11:30 AM	NIH: Geroscience Summit	R. Jilka, J. McGowan, J Williams
	Abstracts of note: 1011, 1012, 1014, 1067	

IMAGING, MICROSTRUCTURE, BONE MATERIAL PROPERTIES

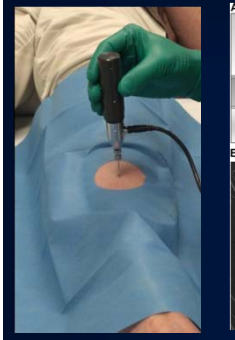
Sat 9/13 11:30 AM	MTP: In Vivo Microindentation	M. Bouxsein
Sun 9/13 11:30 AM	MTP: Bone Microdamage	C. Hernandez
Mon: 9/15 11:30 AM	MTP: Cortical Bone Modeling (and remodeling)	E. Seeman

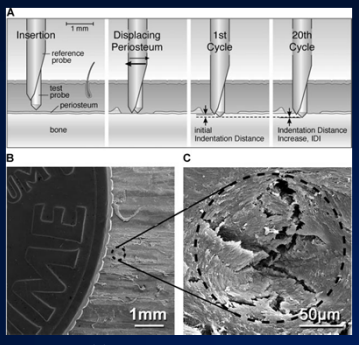
Related Abstracts:
#s 1013, 1046,1047,1048,1049,1050,**1064**,
1065,**1079**,**1085**,1093,1102,1136,1073

Quantitative Imaging Technologies

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

Microindentation Methodology





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

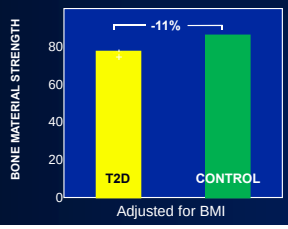
Last year

Abstract # **1084:** Farr et al. Bone Material Strength Measured by In Vivo Microindentation is Compromised in Postmenopausal Women with Type 2 Diabetes Mellitus.

DXA: no differences

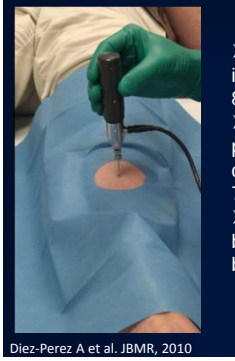
HRpQCT: no differences in cortical or trabecular bone microstructure

Bone Material Strength (BMS) by microindentation was reduced, even after adjustment for BMI (-10.5%; p< 0.001)



Adjusted for BMI

#1064: Malgo et al. Bone Material Strength as measured by microindentation in vivo is decreased independently of BMD in patients with fractures.



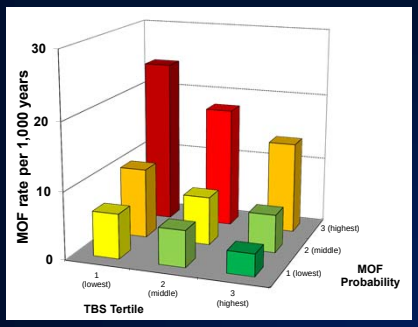
- BMS by microindentation was lower in those who fractured (78.5 ± 0.9 vs 84.1 ± 4.6 p<0.01)
- It was similarly lower among fx patients with osteopenia or osteoporosis by DXA (79.3 ± 0.9 vs 76.7 ± 2.1, p=0.267).
- Altered bone quality (as determined by microindentation) contributes to bone fragility independent of BMD

Diez-Perez A et al. JBMR, 2010

IMAGING AND BIOMECHANICS

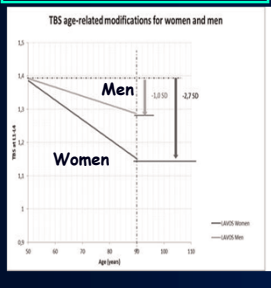
TRABECULAR BONE SCORE (TBS)

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

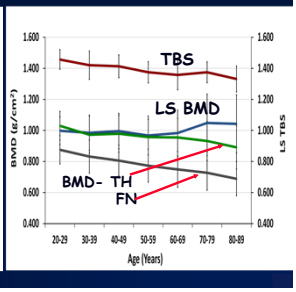


Adapted from WD. Leslie et al. Osteoporos Int. 2014 Jun 21

Abs # SU 291Clark et al. Comparison between normative spine TBS data for men and women: LAVOS

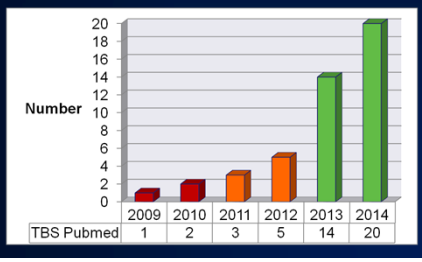


Abs #SA 293 Silva et al. Age-related changes in LS TBS in Chinese American men



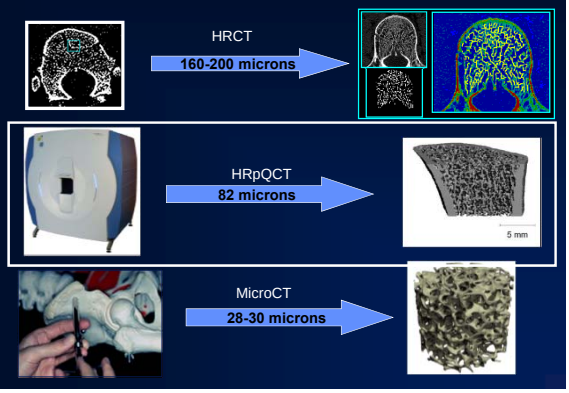
TBS reports at ASBMR and Publications since 2009…

- ASBMR 2011 -- 1 abstract
- ASBMR 2012 -- 19 abstracts
- ASBMR 2013 -- 30 abstracts
- ASBMR 2014 - 34 abstracts



	2009	2010	2011	2012	2013	2014
TBS Pubmed	1	2	3	5	14	20

Resolution of HRCT vs HRpQCT vs Bone Bx



#1085: Chapurlat et al. Bone Microarchitecture by HR-pQCT as Predictor of Fracture Risk in Postmenopausal Women: The OFELY Study

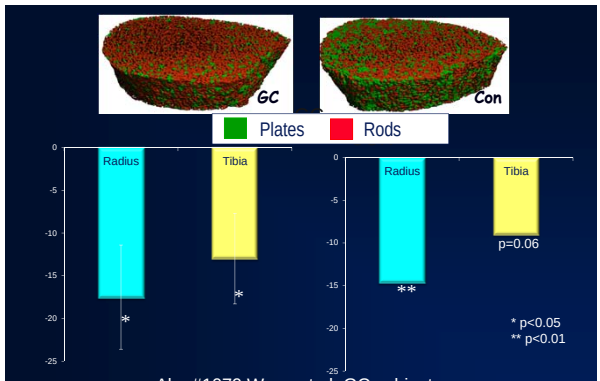
- Prospective independent contributions of cortical and trabecular bone microarchitecture to fracture risk not known
- 7-yr prospective follow up of 588 women (age 68)
- 101 incident fractures
- After adjustments, for each quartile decrease in several parameters fracture risk was increased [e.g. at radius for major osteoporotic fracture: Tb vBMD and TbN in lowest quartile: HR 2.25 (1.21-4.18) and 2.05 (1.11-3.78) respectively]
- Conclusion: HRpQCT has predictive value

Further resolution of microstructure by HRpQCT using Individual Trabecula Segmentation (ITS)- Guo and Liu, 2010

- ITS can differentiate between plate- and rod-like trabeculae type
  - More plates are associated with greater strength

#1079: Wang et al. Trabecular Plate-Rod Morphology and Connectivity are Abnormal and Associated with Reduced Bone Stiffness in Women Treated with Glucocorticoids

- By DXA in GIO, fractures occur at higher BMDs
- By HRpQCT in GIO, abnormal trabecular and cortical indices are seen
- Question: Are there microarchitectural abnormalities (plates vs rods) by ITS and reduced stiffness by FEA in GIO?
- 30 women Rxed with prednisone (av daily dose 8 mg) for >3 mos (age 68)



Abs #1079 Wang et al. GC subjects:
Lower stiffness and failure load both radius and tibia

BONE BIOMARKERS

Fri 9/12: 3 PM	ASBMR/ECTS Clinical Debate: Biochemical Markers are of Practical Value in the Routine Management of Osteoporosis	K Akesson and B Langdahl: Co-chairs W. Fraser: YES! D. Bauer: NO!
Fri 9/12: 7:30 PM	Working Group: Bone Turnover Markers	D. Bauer

Noteworthy Abstracts: 1063,1066,1099,1100

OSTEOPOROSIS THERAPEUTICS

Fri: 9/12 10 AM	MTP: How long should we treat osteoporosis?	D. Black
Sat: 9/13 11:30 AM	Clinical Roundtable: Management of Premenopausal Women with Low Bone Density	S. Khosla, K. Miller, E. Shane
Sat: 9/13 11:30 AM	Clinical Roundtable: Breaking Through: Closing the Care Gap in Secondary Fracture Prevention	E. Siris, J. Eisman, P. Mitchell, D. Lee

OSTEOPOROSIS THERAPEUTICS

Sat: 9/13 6:30 PM	Clinical Evening: Personalizing Treatment of Osteoporosis	M. McClung, F. Cosman, E. Eriksen, K. Saag, R. Eastell
Sun: 9/14 Noon	Report: International ONJ Taskforce- 2014 Consensus on Diagnosis and Management	
Mon: 9/15 11:30 AM	Report: ASBMR Task Force: Long-term Bisphosphonate Treatment: Goals for Osteoporosis Treatment	
Mon: 9/15 2:30 PM	Next Gen Therapies	D. Black, B. Langdahl,S. Jamal, L. Rejnmark, M. Lewiecki

OSTEOPOROSIS THERAPEUTICS

Mon: 9/15 11:30 AM	MTP: Management of Atypical Fractures	A. Cheung

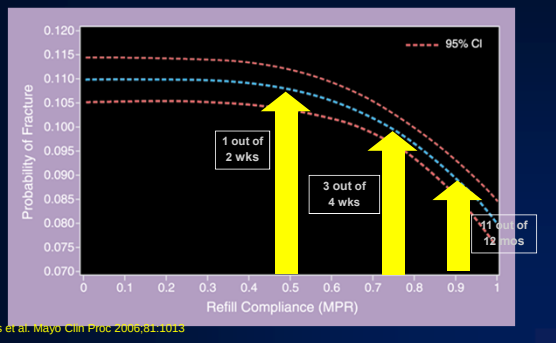
Noteworthy Abstracts:

- Bisphosphonates: **1045** (Outstanding Clinical Abs); FR 398 (Oral Poster)
- Denosumab: **1047**,1104,1150,1152
- Teriparatide: 1048,1049
- Romosozumab: **1049**,1152
- Blosozumab: **1151**
- Abaloparatide: **1050**
- Odanacatib: **1147,1148,1149**
- Antimyostatin Ab: 1011
- Combination Therapy: **1046**
- Sequential Therapy: 1150, 1152
- Vitamin K: 1078

#1045: Adams et al. Bisphosphonate Drug Holiday and Fracture Risk *

- Retrospective cohort study of 28,620 women >45 yrs: 3 yrs exposure to BP
- Drug Holiday: no Rx x 12 months (0% adherence): 40.2%
- (fewer co-morbidities, higher baseline T-scores, lower fracture and fall risk scores)
- Persistence: Rx for an additional year (50% adherence): 59.8%
- Primary outcome: 1st incident clinical OP fragility Fx
- Multiple adjustments
- Conclusion: "Women who undertake a drug holiday from BP use are not at greater risk of osteoporosis-related fragility fractures, nor hip fractures specifically, than women who continue to use BPs persistently."

The greater the compliance, the greater the reduction in fracture probability with bisphosphonates

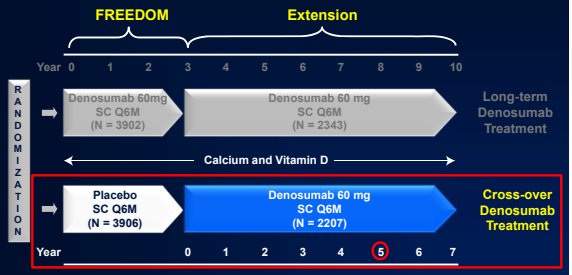


Siris et al. Mayo Clin Proc 2006;81:1013

OSTEOPOROSIS THERAPEUTICS
#1047: Bilezikian et al. Denosumab Restores Cortical Bone Loss at the Distal Radius Associated with Aging and Reduces Wrist Fracture Risk: Analyses from the FREEDOM Extension Cross-over Group

Abs # 1047. FREEDOM Extension Study Design

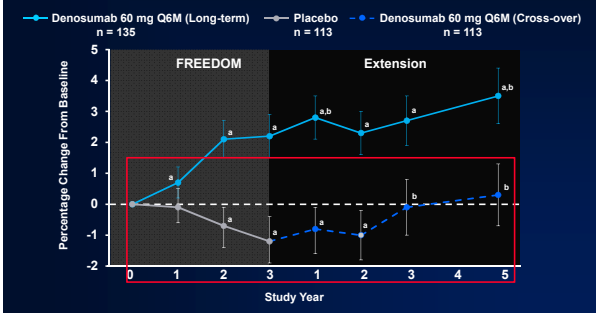
International, multicenter, open-label, single-arm study



Key Inclusion Criteria for the Extension:

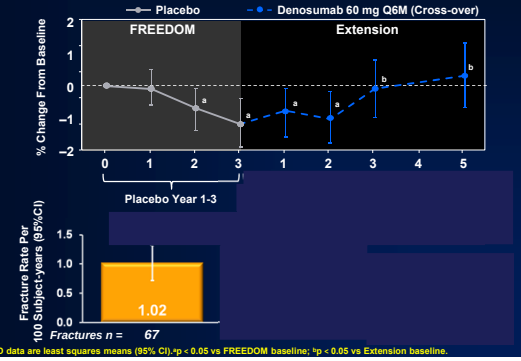
- Completed the FREEDOM study (completed their 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
- Not receiving any other osteoporosis medications

Abs #1047. 1/3 Radius BMD Percentage Change From FREEDOM Baseline Through Extension Year 5



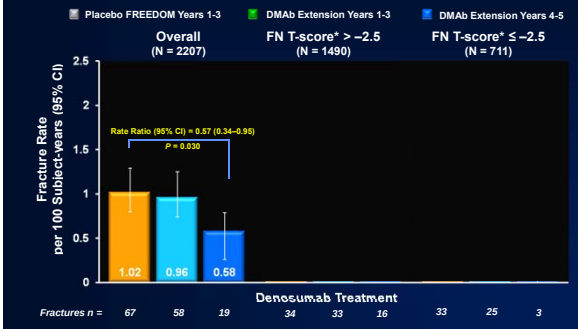
BMD data are least squares means (95% CI). [a]p < 0.05 compared with FREEDOM baseline; [b]p < 0.05 compared with Extension baseline. Q6M = every 6 months. n = number of subjects with observed data at the start of the DXA substudy.

Abs #1047. 1/3 Radius BMD Percentage Change and Wrist Fracture Rate Through Extension Year 5



BMD data are least squares means (95% CI).[a]p < 0.05 vs FREEDOM baseline; [b]p < 0.05 vs Extension baseline.

Abs #1047. Wrist Fracture Rates in the Cross-over Group by Femoral Neck T-score



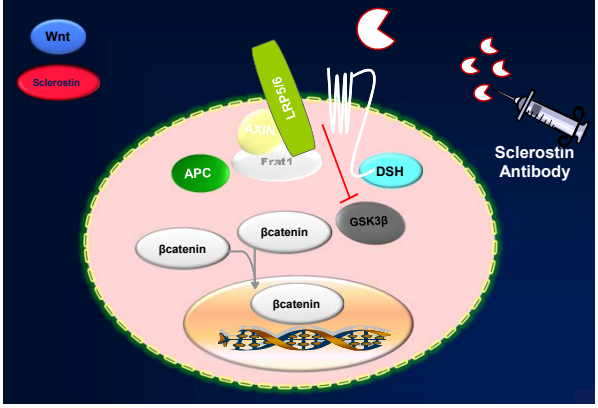
FN = femoral neck. *Femoral neck T-score assessed at FREEDOM baseline.

Summary

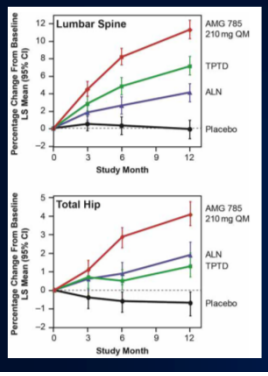
- These data provide evidence, for the first time, of a clinical endpoint of reversing cortical bone loss.

OSTEOPOROSIS THERAPEUTICS

#1049: Whitmarsh et al. Romososumab and Teriparatide Effects of Vertebral Cortical Mass, Thickness, and Density in Postmenopausal Women with Low BMD



CLINICAL TRIALS AND MECHANISMS OF THERAPEUTICS: ANTISCLEROSTIN ANTIBODY



Romosozumab

#1025: McClung MR et al. (2012); N Eng J Med,2014

OSTEOPOROSIS THERAPEUTICS

#1049: Whitmarsh et al. Romososumab and Teriparatide Effects of Vertebral Cortical Mass, Thickness, and Density in Postmenopausal Women with Low BMD (Young Investigator Award)

- Cortical Parameters at L1 by CT
- Vertebral surface mapped at baseline and after 1 year
- Romo at 210 mg monthly (teriparatide and placebo controls)
- N=17-20
- Results for Romo: CTh +11.2%; CMass +12.7%;TBMD +22.2%
- Significantly greater than for teriparatide which showed effects and placebo which did not show positive effects

OSTEOPOROSIS THERAPEUTICS

#1151: Benson et al. Effect of Blosozumab on Bone Mineral Density: 52 Week Follow-up of a Phase 2 Study of Postmenopausal Women with Low Bone Mineral Density

- 52-week follow up of Phase 2 study and 52–week extension without further therapy
- 4 doses 180 mg q4W; 180 mg q2W; 270 mg q2W; Plb
- 120 women; mean age 66 yrs, LS T-score -2.75

Abs #1151: Blosozumab

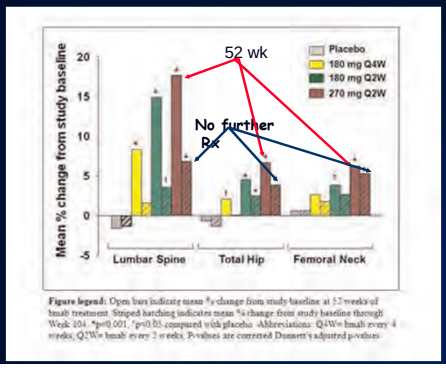


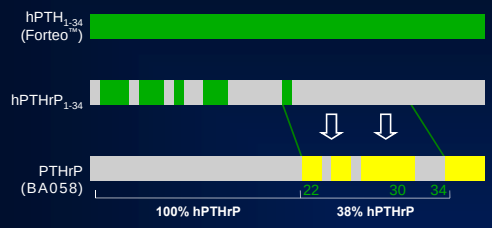
Figure legend: Open bars indicate mean % change from study baseline at 52 weeks of bmab treatment. Striped hatching indicates mean % change from study baseline through Week 104. *p<0.001, †p<0.05 compared with placebo. Abbreviations: Q4W= bmab every 4 weeks; Q2W= bmab every 2 weeks. P-values are corrected Dunnett's adjusted p-values

OSTEOPOROSIS THERAPEUTICS

#1050: Varela et al. The Long Term Effects of Abaloparatide (BA058) on Micro-CT and Histomorphometry in Osteopenic Cynomolgus Monkeys

Functional optimization of PTHrP: Hattersley G et al.,

The Endocrine Society 94th Annual Mtg Houston, 2012: OR08-1

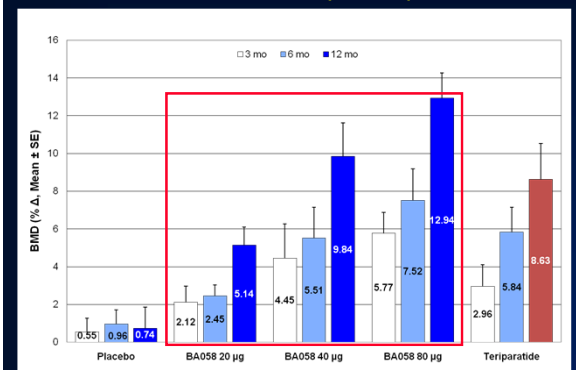


based on amino acid replacements between residues 22-34

Hattersley G et al.,

The Endocrine Society 94th Annual Mtg Houston, 2012: OR08-1

Results of a Phase 2 clinical trial in postmenopausal women

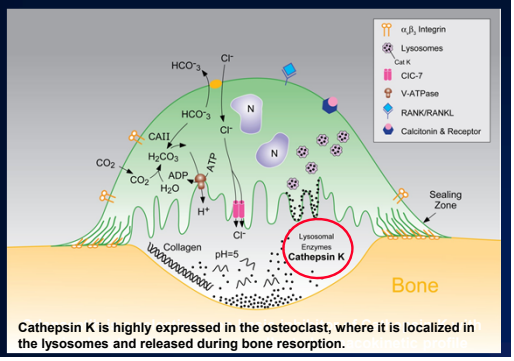


OSTEOPOROSIS THERAPEUTICS

#1050: Varela et al. The Long Term Effects of Abaloparatide (BA058) on Micro-CT and Histomorphometry in Osteopenic Cynomolgus Monkeys

- Aged osteopenic, ovx'ed monkeys
- Sham and ovx'ed non-treated controls
- 3 doses of ABL (0.2, 1, 5 ug/kg) for 16 mos
- Histomorphometry at L2, FN, and femur mid-diaphysis
- **Results:**
  - **ABL restored ovx-induced cancellous and cortical bone loss by increasing bone formation without affecting cortical porosity**

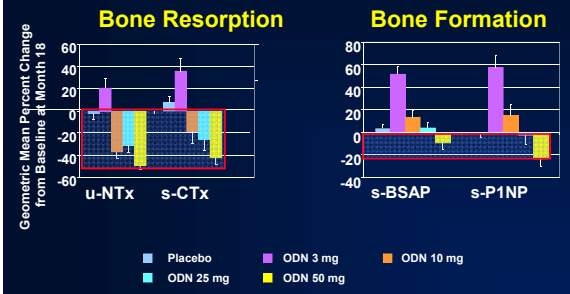
OTHER WAYS TO TARGET THE OSTEOCLAST



Rodan & Duong. BoneKey 2008

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

Biochemical Markers at 18 Months



OSTEOPOROSIS THERAPEUTICS

#1147: McClung et al. Odanacatib Anti-Fracture Efficacy and Safety in Postmenopausal Women with Osteoporosis. Results from the Phase III Long-Term Odanacatib Fracture Trial (LOFT)

#1148: Papapoulos et al. Safety and Tolerability of Odanacatib Therapy in Postmenopausal Women with Osteoporosis: Results from the Phase III Long-Term Odanacatib Fracture Trial (LOFT)

#1149: Orwoll et al. Randomized Controlled Trial to Assess the Safety and Efficacy of Odanacatib in the Treatment of Men with Osteoporosis

OSTEOPOROSIS THERAPEUTICS
#1147: McClung et al.
#1148: Papapoulos et al.

- **Randomized, double-blind placebo-controlled, event-driven**
- **50 mg weekly**
- **Primary endpoints: new morphometric vertebral fractures, hip, and clinical non-vertebral fractures**
- **Secondary endpoints: safety/tolerability, clinical VFx, spine and hip BMD, bone turnover markers**

OSTEOPOROSIS THERAPEUTICS
#1147: McClung et al.
#1148: Papapoulos et al.

- **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**
- **7,081 completed at least 4 years of follow-up**
- **Pre-planned blinded extension (after 70% of targeted events)**
- **50 mg weekly**

OSTEOPOROSIS THERAPEUTICS
#1147: McClung et al.
#1148: Papapoulos et al.

- **RESULTS:**

- **None presented in the abstract**
- **Await presentation on Monday, Sept 15!**

OSTEOPOROSIS THERAPEUTICS
#1149: Orwoll et al. Odanacatib and Male Osteoporosis

- Randomized, double-blind placebo-controlled, 24-mos trial
- 50 mg weekly; n=292 men, aged 69
- T-score <-2.5 (FN or TH); <-1.5 (FN or TH) with prior radiographic VFx
- Primary endpoint: LS BMD

OSTEOPOROSIS THERAPEUTICS
#1149: Orwoll et al. Odanacatib and Male Osteoporosis

Results:
- AEs and Safety Profile similar between drug and placebo
- Results:
  - LS +6.9%; TH +1.9%; FN 1.7% (all p<0.01 vs Plb)
  - BTMs- after 3 mos
    - Resorption: UNTx/CR -68%; s-CTx -77%
    - Formation: s-P1NP -16%; sBSAP -8%
    - After 3-24 months, BTMs returned towards baseline

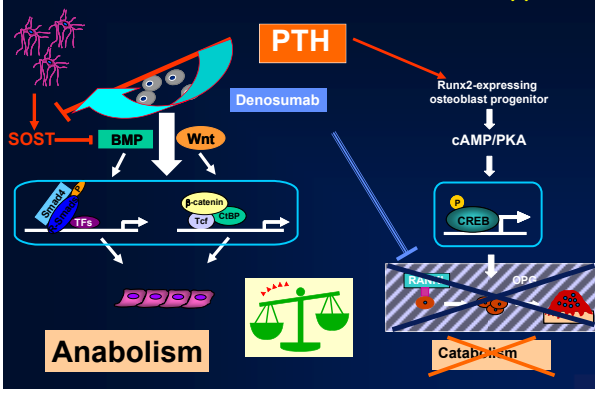
Antiresorptive

PTH

Combination therapy with an antiresorptive and osteoanabolic agent

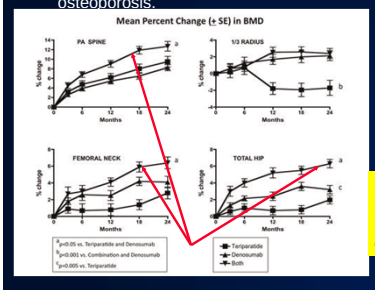
- **Rationale is clear but the results…**
  - Raloxifene: possible small benefit
  - Estrogen: possible small benefit
  - Alendronate: reduced benefit
  - Risedronate (in men): possible hip BMD benefit
  - Zoledronic acid: early benefit primarily
  - **Denosumab: promising (Tsai et al, Lancet, 2013;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

Combination Denosumab and PTH Therapy



CLINICAL TRIALS AND MECHANISMS OF THERAPEUTICS: COMBINATION THERAPY WITH DENOSUMAB AND TERIPARATIDE

1019 Leder et al. DATA Extension Trial: 2 years of combined denosumab and teriparatide in postmenopausal women with osteoporosis.



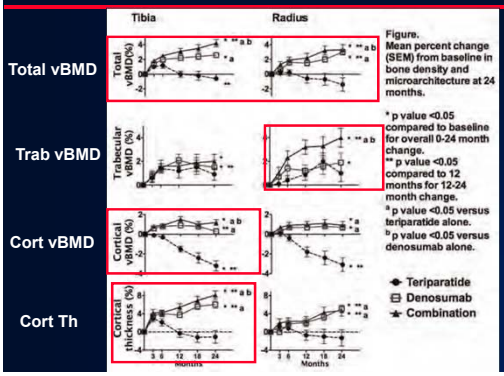
N=100 divided equally among Teriparatide (20 ug daily); Denosumab (60 mg q 6mos); and combination. 83 completed the study

Fr 0372: Tsai et al. By HRpQCT Microstructural improvements in the cortical compartment

OSTEOPOROSIS THERAPEUTICS
#1046: Tsai et al. Effects of Two Years of Teriparatide, Denosumab and Combination Therapy on Peripheral Bone Density and Microarchitecture: The DATA-HRpQCT Extension Study (Young Investigator Award)

- Aim: Effect of combination Rx on perpheral cortical and trabecular BMD and microstructure
- 95 postmenopausal women; Teriparatide or Denosumab or both for 24 months.
- HRpCT at 0,3,6,12,18, and 24 months
- Results of combination therapy:
  - Increased TvBMD, Radius Tb vBMD and Tibia Ct.Th. More than either drug alone

OSTEOPOROSIS THERAPEUTICS
#1046: Tsai et al.



METABOLIC BONE DISEASES
SECONDARY CAUSES OF OSTEOPOSIS

Thurs 9/11 All day	Special Symposium: The Effects of Diabetes and Disordered Energy Metabolism on Skeletal Health	Epstein, Lecka, Czernik et al.
Fri 9/12 11:30 AM	Symposium: Bone and Inflammation	Goldring M, Pacifici R,Schett, Gravellese, Lane
Sun 9/13 11:30 AM	Clinical Roundtable: Management of Bone Health in CKD-MBB	Hruska, Miller, Sprague

Abstracts: Primary Hyperparathyroidism: 1086
GIO: 1079,1069
Diabetes Mellitus: 1083,1102,1099,1100,1101, 1103,1104,1007

Abs. #1086:Cipriani et al. Clinical Presentation of Primary Hyperparathyroidism: a Five-Year Study

AIM: To evaluate the prevalence of kidney stones (by abdominal imaging) and vertebral fractures (by vertebral X-rays) in a cohort of 140 patients diagnosed with asymptomatic and symptomatic primary hyperparathyroidism (PHPT)

Abs #1086. Cipriani et al. RESULTS

Characteristics	Symptomatic (n=64)	Asymptomatic (n=76)	p
Weight (kg)	68.2±11.9	64.2±9.6	<0.05
Height (cm)	162.7±9.3	159.6±7	<0.05
Osteoporosis[a] (%)	59.4	65.8	NS
VFs (%)	34.4	34.7	NS
KS (%)	78.1	35.5	<0.0001

[a]T-score<2.5 at any site; evaluated by DXA

4th International Workshop on:
THE MANAGEMENT OF ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM
Florence (Italy), September 19th – 21st, 2013

Organized by

All papers JCEM on line August, 2014.
In print- October, 2014

Bilezikian et al. Guidelines Statement of the 4th International Conference On the management of Asymptomatic PHPT

Eastell R et al. Diagnostic Considerations PHPT

Silverberg et al. Clinical Presentations of PHPT

Udelsman et al. Surgery in PHPT

Marcocci et al. Medical Management of PHPT

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Http: www.fondazione-menarini.it

Skeletal evaluation, in addition to DXA will be recommended in the evaluation of PHPT: VFA, TBS or vertebral X-rays

Renal system: 24-hour urine for calcium and other stone risk factors Abdominal imaging

(Bilezikian et al. JCEM, 2014)

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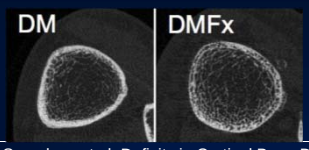
DIABETES AND BONE

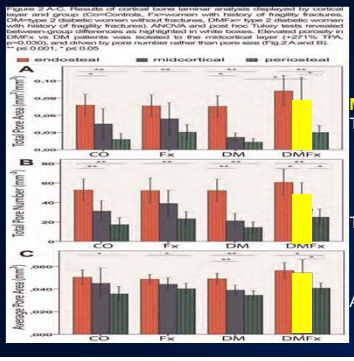
2012: #1127: Patsch et al. D. mellitus associated with increased cortical porosity



Abstract # **1083:** Samelson et al. Deficits in Cortical Bone Density and Microstructure in Type 2 Diabetes: Framingham HRpQCT Study

Lower cortical bone density and greater cortical porosity in tibia, not radius, in T2 DM. Correlated with HgA1c levels.

Abs #1102: Heilmeier et al. Cortical Laminar analysis reveals increased midcortical porosity in Type 2 DM with history of fractures



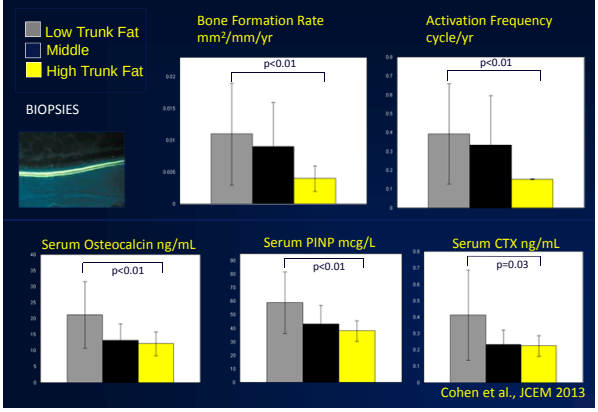
Mid-cortical region:
Total Pore area: + 271%*

Total pore Number: +126%*

Avg Pore Area: +39% **(NS)**

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

Visceral fat is bad for bones!



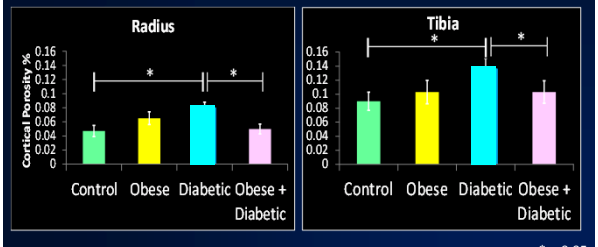
Cohen et al., JCEM 2013

Abs # 1103. Furst et al. Type 2 Diabetes and Obesity Each Contribute Separately to Adverse Skeletal Health: adverse effects of cortical bone microarchitecture

- **4 groups of postmenopausal women**

Group	BMI kg/m²	A1c (%)
Control	18.5-25	<6.0
Obese (no DM)	>30	<6.0
Diabetic (not obese)	<30	>7.0
Obese + diabetic	>30	>7.0

Abs #1102. Furst et al. Cortical Porosity as determined by HRpQCT is worse in Type 2 DM independent of obesity



*p<0.05
** p<0.01
***p<0.001

RARE BONE DISEASE/OTHER CONDITIONS

Thurs 9/11: All day	Special NBHA Rare Bone Disease Patient Network Workshop	NHBA
Sun 9/14: 8AM	Symposium: Lessons from Brittle Bone Diseases: Control of Bone Mass and Quality	Lee, Krakow, Eyre, Glorieux
Sun 9/14: 4:30 PM	Symposium: Heterotopic ossification	Hsiaso, Jueppner, Forsberg, Yang, M Pacifici
Mon 9/15 2:30 PM	Symposium: In Next-Gen Therapies (Treatment of hypoparathyroidism)	L Rejnmark

RARE BONE DISEASE/OTHER CONDITIONS

Fri 9/12 10 AM	MTP: Fibrous Dysplasia	M Collins
Fri 9/12 10 AM	MTP: Monoclonal gammopathies and bone health	D. Roodman
Sat 9/13 11:30 AM	MTP: Osteopetrosis	U Kornak
Sun 9/14: 11:30 PM	MTP: Clinical management of phosphorus disorders	M Drezner
Sun 9/14 7:30 PM	Adult Bone and Mineral Working Group	V. Tangpricha

Abstracts: 1082,1095,1097

PEDIATRICS/ADOLESCENTS AND DEVELOPMENT

Fri 9/12: 7:15 PM	Working Group: Pediatric Bone and Mineral	Tebben, Perwad
Sun 9/14 11:30 AM	MTP: Nutrition and Bone Health in Adolescents	Pettifor
Mon 9/15 11:30 AM	Clinical Roundtable: Management of Osteoporosis in Pregnancy and Pediatrics	Brandi, Kovacs, Ward

Abstracts related to pediatrics and development:
#s 1081,1097- Hypophosphatasia
1093,1094,1095,1096,1098

OTHER TOPICS

Clinical Genetics	Abs # 1027,1030,1068	
Cancer Sun 9/14 11:30 AM	MTP: Bone Metastases and the Bone Microenvironment Abs# 1034,1036	R Faccio

Topics to be covered

- EFF-ASBMR Fellows' Symposium
- Vitamin D, Calcium, Nutrition and Exercise
- Epidemiology and Outcomes Research
- Frailty, Biomechanics, Muscle, and Bone
- Imaging, Microstructure, Bone Material Properties
- Bone Biomarkers
- Osteoporosis Therapeutics
- Metabolic Bone Diseases/Secondary Causes of Osteoporosis
- Diabetes, Obesity and Bone
- Rare Bone Diseases and Other Conditions
- Pediatrics/Adolescents/Development
- Clinical Genetics
- Cancer

ENJOY THE MEETING!