Poster #12

"Holey Bones": How osteocytes might cause the development of cortical bone porosity

Robert L. Jilka, Annick DeLoose, Kanan Vyas, Leslie Climer, Linda Liu, Robert S. Weinstein, Charles A. O'Brien, and Stavros C. Manolagas

Cortical bone becomes porous in the elderly leading to skeletal fragility. Cortical porosity must be due to excessive osteoclastic bone resorption, but the underlying pathophysiology has not been established. It is now known that osteocytes buried within the bone matrix are an important source of the pro-osteoclastogenic cytokine RANKL, and that apoptotic osteocytes stimulate the synthesis of RANKL by viable neighboring osteocytes. In view of evidence that osteocyte apoptosis increases with advancing age, we measured cortical porosity in mice with osteocytes that are resistant to apoptosis due to deletion of Bak and Bax – two proteins essential for apoptotic death. Femoral cortical porosity in aged (21-22 month old) Bak/Bax-deficient mice was dramatically increased, as compared to aged wild type mice, and was associated with increased expression of RANKL by cortical osteocytes. The cortical pores contained osteoclasts and bone-forming osteoblasts, as well as blood vessels that deliver osteoclast and osteoblast progenitors into the pores. Consistent with the latter, cortical osteocytes of Bak/Bax-deficient mice also exhibited increased expression of the pro-angiogenic cytokine VEGF. Preliminary studies suggested that the synthesis of RANKL and VEGF by osteocytes is enhanced with advancing age by activation of the unfolded protein response to endoplasmic reticulum stress – a response that normally protects cells against noxious conditions such as hypoxia and oxidative stress. We propose that the development of cortical porosity with advancing age is due to excessive RANKL and VEGF production by damaged osteocytes, and that the increased porosity of aged Bak/Bax-deficient mice is due to exaggeration of the normal effect of aging on osteocyte function due to artificial prolongation of the life span of damaged osteocytes.

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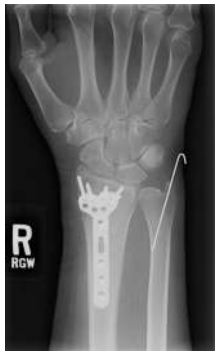
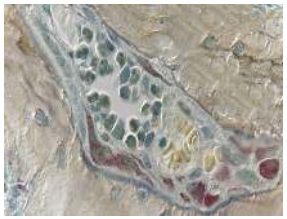
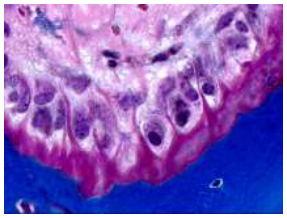
UAMS College of Medicine Series

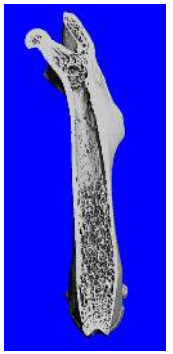
Showcase of Medical Discoveries:

A focus on Bone Health









A Wine and Cheese Reception Featuring

UAMS Investigators Discussing

Their Research and Discoveries.

Winthrop P. Rockefeller Cancer Institute

10th Floor Rotunda

Wednesday, June 12, 2013

4:00—5:30 p.m.

Poster #1

Loss of Insulin Signaling in Osteoprogenitor Cells Impairs Structural Strength of Bone

Jeffry S. Nyman, R. Clay Bunn, Kathryn M. Thrailkill, Charles K. Lumpkin, Jr., Elizabeth Wahl, Gael E. Cockrell, Lindsey M. Clark, and John L. Fowlkes

Type 1 diabetes mellitus (T1DM) is associated with decreased bone mineral density (BMD), a deficit in bone structure, and subsequently an increased risk of a fragility fracture. Mouse models demonstrate that severe reductions in bone formation occur in the context of insulin-deficiency and altered metabolic state and normalization of systemic insulin levels stimulates new bone formation through RUNX2 and RUNX2 target genes in diabetic animals despite persistent hyperglycemia. To examine the specific action of insulin signaling on bone, an osteoblast-specific insulin receptor knockout (OIRKO) mouse model was engineered and the resulting architectural, structural, and biomechanical properties of bone were studied. OIRKO mice display a significant dwarfing phenotype with normal appearing growth plates. In the metaphyseal compartment, the loss of IR in osteoblasts resulted in lower trabecular bone volume fraction with thinner, more rod-like trabeculae. In the diaphyseal compartment, the cortex of femurs from the OIRKO mice was thinner with much lower structural parameters than the cortex from control mice. OIRKO bones were not as strong in bending as bones from control mice. The skeletal phenotype of the OIRKO mouse appears more severe than that reported using the *Col1a1-Cre* or the *OC-Cre* constructs, suggesting that insulin signaling plays an important role during the early stages of osteoblast development.

Poster #2

The UAMS Center for Osteoporosis and Metabolic Bone Diseases

Stavros C. Manolagas, Robert L. Jilka, Robert S. Weinstein, Charles A. O'Brien, Maria Almeida, Haibo Zhao, and Paula K. Roberson

The Osteoporosis and Metabolic Bone Diseases Center of UAMS was established in 1994, with the recruitment of authorities in the field from around the world. Within a very short period of time, it became an internationally renowned center of excellence and a premier facility for research in osteoporosis and other metabolic bone diseases, as well as a patient referral center for treatment of these conditions. The primary objective of the research undertaken by the center's interdisciplinary faculty has been the understanding of the cellular and molecular mechanisms behind the development of osteoporosis and other bone diseases in women after menopause and women and men with old age, as well as in patients developing osteoporosis as a side-effect of steroid therapy. Using such an understanding, the investigators are developing more effective therapies for treatment of this common metabolic bone disease. The Center's faculty has the combined research experience of almost 200 years, has a collective record of more than 1,200 publications, and it represents a highly synergistic team with complimentary expertise in molecular and cellular biology, molecular genetics, the biology of bone as a tissue, and the clinical diagnosis and treatment of osteoporosis.

Poster #11

New genes causing osteoporosis and brittle bone disease

Roy Morello, Roberta Besio, and Milena Dimori

In my laboratory, we study the function of novel genes, with a focus on those likely involved in bone formation, development, homeostasis and disease. We utilize standard genetic techniques to generate ubiquitous or tissue-specific gene mutations in the mouse and then, with the use of multi-disciplinary approaches, including those of cell biology, biochemistry and cell microscopy, we characterize the phenotype of these mice. The ultimate goal is to understand the function of the protein encoded by the novel gene and its functional network of interactions. We then try to translate what we learned from the animal model into relevant pathological aspects of human diseases that affect our skeleton.

We recently characterized the function of the *Crtap* gene, a member of a recently described family of genes. *Crtap* inactivation in mice causes dramatic low bone mass and a functional defect in bone forming cells, the osteoblasts. We showed that Crtap forms an intracellular complex with two enzymes and that this complex is essential for proper collagen synthesis. Importantly, type I collagen is an essential 'scaffolding' molecule that gives rigidity to our bones and its mutations in humans cause autosomal dominant Osteogenesis imperfecta (OI or brittle bone disease), a congenital disease characterized by recurrent frequent fractures. We identified *CRTAP* as the first gene whose mutations cause rarer, recessive forms of OI. Our discovery led the way to the more recent identification of several new genes causing less common forms of OI. Currently, we continue to study the function of the Crtap protein, including its potential contribution to extracellular matrix mineralization and mesenchymal stem cell homeostasis in the bone marrow.

Given the importance of Crtap in bone homeostasis and human disease, we have now started to characterize a novel but evolutionarily related gene, called Sc65. It encodes a protein highly similar to Crtap and we hypothesized that it may have retained a similar function. We generated mice that do not produce Sc65 protein and showed that they also have low bone mass. Current experiments are aimed at the identification of the cellular and molecular defects with the hope that these studies will provide us with novel biological insights into how bone is formed and maintained and how these processes can be affected in human skeletal disease.

Poster #10

Orthopaedic Research at UAMS: It's All about the Bone!

Robert A. Skinner, William R. Hogue, Frances L. Swain, Sandra G. McLaren, Archana Kamalakar, Charity Washam, Nisreen S. Akel, Jaclyn Vander Schilden, Corey O. Montgomery, C. Lowry Barnes, Richard McCarthy, Shahryar Ahmadi, Dana Gaddy, Richard W. Nicholas, and Larry J. Suva

The skeletal consequences of disorders such as cancer, bone infection and osteoporosis as well as complications from the associated bone fractures are a major cause of pain and suffering leading to diminished quality of life across the population of Arkansas. The Center for Orthopaedic Research (COR) at UAMS is focused on research into a myriad of skeletal complications of disease employing collaborators and colleagues from across the campus, state and country. Our research efforts have addressed skeletal conditions in people with Down Syndrome, Scoliosis, breast cancer, osteosarcoma, multiple myeloma, osteomyelitis infection, disuse and osteoporosis. The faculty of the Department of Orthopaedic Surgery are expert in the identification, management and treatment of a variety of these skeletal issues. The UAMS COR, in combination with our renowned orthopaedic investigative discovery, strong collaborators, technical expertise and state-of-the-art analytical tools, is a major ally for the interrogation of the mechanisms of disease progression in bone. The COR provides both in vivo and ex vivo imaging of the skeleton, biomechanical testing, and in vivo multispectral image analysis. The COR provides translational research capabilities combining state-of-the-art hard tissue histology and morphometry with specialized expertise specifically applied to investigations related to bone pathology. In all, the UAMS COR provides shared infrastructure for education, training and research to investigators across all disciplines to optimize efficiency, accelerate the pace and accuracy of data acquisition, and facilitate the translation of important research discoveries to the bedside.

Poster #3

HMOX1 is a targeted therapy for myeloma-induced bone disease

Xin Li, Wen Ling, Sharmin Khan, Sathisha Upparahalli venkateshaiah, Rakesh Bam, Bart Barlogie, Joshua Epstein and Shmuel Yaccoby

Multiple myeloma (MM) bone disease is characterized by increased activity of osteoclasts and reduced osteoblast numbers. We recently reported that cytotherapy with mesenchymal stem cells (MSCs) promotes bone formation, inhibits bone disease and reduces MM growth (Yaccoby et al., 2006; Li et al., 2011) and that MSCs secrete bone remodeling associated factors such as decorin that directly inhibits osteoclastogenesis and promotes osteoblastogenesis (Li et al., 2012). To shed light on molecular mechanisms associated with the cytotherapeutic effects of MSCs we exploited the SCID-hu model engrafted with MM cells from various patients and cytotherapeutically treated with fetal or healthy donors MSCs. Human global gene expression profile was performed in nonmyelomatous implanted bones (n=5) and in myelomatous implanted bones injected with human MSCs ($1x10^6$ cells/bone) and analyzed immediately (control group, n=17) or 24 hours later (n=16). We indentified heme oxygenase 1 (HMOX1) as one of the top significant upregulated genes consistently induced by 24 hours cytotherapy using fetal MSCs or MSCs from 3 different donors. HMOX1 induction was confirmed by qRT-PCR and immunohistochemistry and was also found to be consistently induced by MSCs cytotherapy in myelomatous bones engrafted with MM cells from different patients (n=4). Further analysis revealed lower expression of HMOX1 in myelomatous versus nonmyelomatous bones. HMOX1, an inducible antioxidant, degrades intracellular heme into carbon monoxide, free iron and biliverdin and is involved in oxidative stress response and intracellular iron homeostasis both of which are known to regulate osteoclastogenesis. Culture of human blood mononucleated cells or committed osteoclast precursors with MSCs (non-contact co-culture) in osteoclastogenic medium supplemented with RANKL and M-CSF inhibited multinucleated osteoclast formation by 70% ($p<0.0001$) and 97% ($p<0.0001$), respectively. MSCs induced HMOX1 expression in osteoclast precursors by 3 folds ($p<0.02$) and HMOX1 levels remained higher in these cells during osteoclast formation. Concurrently, RANK (RANKL receptor) and NFATC1 (osteoclast main transcription factor) were constantly downregulated in osteoclast precursors by MSCs by 65±10% ($p<0.01$) and 42±11% ($p<0.05$), respectively, followed by reduced expression of the osteoclastic markers cathepsin K ($p<0.0002$), acid phosphatase 5 ($p<0.01$) and vitronectin receptor ($p<0.02$) at the end of the differentiation process (7 days). Similar to MSCs, overexpression of HMOX1 in osteoclast precursors using lentiviral vector markedly reduced their ability to form osteoclasts while HMOX1 inducer, hemin (50 μM), induced HMOX1 in osteoclast precursors and inhibited their differentiation into osteoclasts by 49±2% ($p<0.0001$). In MM-bearing SCID-rab mice (9 mice/group) bone mineral density (BMD) was reduced by 17±3% from pretreatment levels in control group whereas in hosts treated with hemin for 3 weeks BMD was reduced by 2±3% ($p<0.005$). Histological bone sections revealed reduced number of TRAP-expressing osteoclasts in myelomatous bones from hemin-treated hosts ($p<0.01$). These data suggest that HMOX1 is suppressed in myelomatous bone and that therapeutic induction of HMOX1 is a promising approach to control MM-induced osteoclastogenesis and osteolytic bone disease.

Poster #4

Understanding Bone Health Across Age and the Menopause: If You Don't Use It, You Lose It!

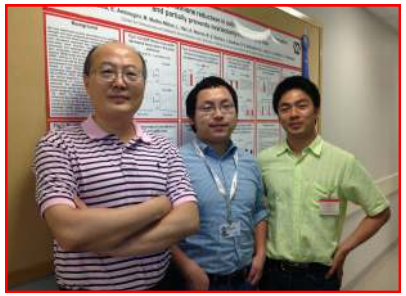
Nisreen S Akel, Archana Kamalakar, Robert A Skinner, Frances Swain, William R Hogue, Larry J Suva, and Dana Gaddy

Bone health is critical to quality of life, as it enables us to maintain an independent, active lifestyle. Aging in both men and women is associated with reduced bone mass. This bone loss is worsened in women as they go through the menopause, and can be further worsened with decreased activity or bed-rest (common in elder nursing home patients). Our NIH-funded research focus is 2-fold: 1) to understand the impact of aging and decreased activity on the musculoskeletal system, and to determine the ability of activity and exercise to restore bone loss due to inactivity, and 2) to understand the contributions of non-estrogenic reproductive hormones on normal bone metabolism and in particular, menopausal bone loss. We were the first to discover that menopausal bone loss is not all dues to the loss of estrogen, but that other ovarian hormones, such as Inhibins contribute to bone metabolism. Their decrease at the onset of menopause in women is associated with the initial phase of bone loss. Using mouse models, we demonstrated that treatment with Inhibins prevents the bone loss associated with loss of ovarian function, further demonstrating the importance of Inhibins in bone.

To investigate aging effects on bone, we have utilized state-of-the-art bone imaging, biomechanical testing and histomorphometric analysis of adult and aged rats, undergoing disuse, followed by reambulation to determine the effects of inactivity and aging on the skeleton. In fact, we have determined that aged rats are severely compromised in their ability to reambulate and to restore the loss of muscle and bone due to inactivity. Our findings demonstrate that trabecular bone loss is greatest in young adult rat, whereas cortical bone is lost in aged rats in response to disuse. Both of these effects contribute to decreased bone strength. In addition, trabecular bone is more responsive to 2 weeks reambulation than cortical bone, increasing bone formation and decreasing the number of cells capable of resorbing bone. Perhaps most importantly, the aged rats take longer to fully reambulate, resulting in a delay in the attainment of bone strength, as well as muscle mass. These data suggest that muscle and bone loss in the elderly due to inactivity, particularly in nursing homes where patients spend up to 20 hours in bed per day, may be much more difficult to restore to normal support function and capacity than in younger adults. We are currently working on discovering what type and duration of exercise is most able to restore musculoskeletal mass, strength, and function in the aged.

Poster #9

Lis1 Regulates Osteoclastogenesis through Small GTPase Cdc42



Shiqiao Ye, Stavros Manolagas, and Haibo Zhao

Haploinsufficiency of LIS1, also known as platelet-activating factor (PAF) acetylhydrolase isoform 1b subunit 1 (PAFAH1b1), causes lissencephaly, a severe human developmental brain disorder due to impaired neuronal migration. LIS1 has been shown to regulate microtubule dynamics, PAF, and Cdc42 in neurons. Since these molecules/pathways are critical for osteoclast differentiation, survival, and/or function it is likely that LIS1 regulates osteoclastic bone resorption. To test this hypothesis, we have generated LIS1 macrophage conditional knockout (cKO) mice by crossing LIS1-floxed mice with LysM-Cre mice. LIS1 expression was abolished in macrophages and osteoclasts from LIS1 cKO mice but not in those from control mice, as shown by western blots. LIS1 cKO mice had no gross skeletal abnormality during development, but at 5-month old of age, they exhibited increased bone mass measured by micro-CT, as compared to their control littermates. The level of serum TRAP5b, an in vivo marker of osteoclast number, was decreased in cKO mice, indicating that loss of LIS1 impairs osteoclastogenesis. Consistent with this finding, macrophages isolated from cKO mice had intrinsic defects in osteoclast differentiation as revealed by a decreased number of $TRAP^{+}$ osteoclasts and reduced level of TRAP 5b in culture medium. The attenuated osteoclast formation in LIS1-null macrophages was associated with a significant decrease in macrophage proliferation, osteoclast differentiation and survival, due to reduced activation of ERK and AKT by M-CSF and prolonged RANKL-induced JNK activation. These defects were cell autonomous because reconstitution of wild type LIS1 in cKO macrophages by retro-viral transduction rescued osteoclastogenesis and M-CSF/RANKL signaling. Next, we searched for downstream pathway(s) of LIS1 critical for osteoclast formation. Neither ectopic PAF nor overexpression of NDE1 and NDEL1, two LIS1 binding partners in regulating microtubule dynamics, rescued the osteoclast formation defect in cKO cultures. On the other hand, expression of a constitutively active form of Cdc42 dramatically increased osteoclastogenesis in cKO macrophages. Moreover, M-CSF- and RANKL-stimulated Cdc42 activation was blunted in cKO pre-osteoclasts as measured by a GST-pull down assay. We conclude that LIS1 regulates bone remodeling in mice and is an essential molecule for the activation of Cdc42 during osteoclast differentiation.

Poster #8

Overcoming the Growing Problem of Biofilm-Associated Infection

Mark S. Smeltzer, Karen Beenken, Michelle Griffin, Alice Matthews, Allister J. Loughran, Aga Zielinska, Allison Anthony, Danielle Atwood, Robert Skinner, Lara Mrak, and Sandra McLaren

Treatment of bacterial infections has relied on conventional antibiotic therapy for over 70 years, but recent emergence of bacterial pathogens therapeutically resistant to all available antibiotics has severely limited clinical treatment options. As a result, many bacterial pathogens are more threatening now than at any time since the pre-antibiotic era. Indeed, the Infectious Disease Society of America has designated certain "ESKAPE" pathogens based on their prominence as a cause of human disease *and* absence of available antibiotics to treat resulting infections. Most prominent is *Staphylococcus aureus*, which has now passed HIV/AIDS as a cause of death in the United States.

S. aureus has the capacity to cause multiple forms of life-threatening infection including necrotizing pneumonia, endocarditis, osteomyelitis, and infections associated with indwelling medical devices. These include catheters, prosthetic heart valves, vascular grafts, prosthetic joints, and the orthopaedic hardware required for the repair of traumatic injuries. As if antibiotic resistance were not trouble enough, these infections form a biofilm (i.e., multiple layers of bacterial cells encased within an extracellular matrix) that protects bacteria from conventional antibiotics and host defenses. The treatment of these infections requires not only long-term, intensive antibiotic therapy, assuming an appropriate antibiotic is even available, but surgical intervention to remove infected tissues and/or indwelling devices. The rate of therapeutic failure remains unacceptably high. Established at UAMS in 1993, the Smeltzer laboratory has been devoted to solving these clinical problems. Although a primary focus of this effort has been on orthopaedic infections, indwelling devices are a critical component of all medical specialties including cancer treatment, thus extending the clinical impact of this work well beyond orthopaedics.

Our comprehensive and interdisciplinary research approach has a clinical corollary with cancer. Specifically, both tumors and biofilms represent "growths" within the human body with pathological consequences and therefore must be selectively destroyed without collateral damage to healthy host tissues. Early detection, a critical factor in both cases, is being addressed through development of non-invasive methods for the detection of *S. aureus* infections in their earliest stages. It is also imperative to understand how these diseases occur, thereby allowing development of methods to prevent their occurrence. To this end, we are intensively investigating how *S. aureus* forms biofilms. Development of novel antibiotics and improved methods of delivering antibiotics to the targeted cells is also a critical part of our research effort. Finally, we are exploring novel nanotherapeutic methods to treat infections caused by an antibiotic-resistant strain or protected within a biofilm, thus significantly reducing the current reliance on conventional antibiotics. Descriptions of our research efforts can be found at http://www.ncbi.nlm.nih.gov/pubmed using the search term "smeltzer ms".

Poster #5

Vitamin D Supplementation Prevents Hypocalcaemia and Cortical Bone Loss Associated with Chronic Alcohol Feeding in Female Mice

Kelly E. Mercer, Rebecca A. Wynne, Oxana P. Lazarenko, Charles K. Lumpkin, Jr., William B. Hogue, Larry J. Suva, Jin-Ran Chen, Thomas M. Badger, and Martin J. Ronis

Chronic alcohol abuse is known to contribute to increased risk of osteoporosis and fractures in the older populations, particularly in women as prevalence rates for alcohol abuse disorders increase steadily in younger cohorts. Dietary cholecalciferol supplementation alone or combined with calcium has shown great promise in reducing osteoporotic fractures in older patients, which has been attributed to endocrine actions involved in calcium regulation and/or paracrine/autocrine actions within bone, and dietary supplementation may also be an effective strategy in protecting against EtOH-mediated bone loss in young females. Previously, we have reported bone loss in cycling females receiving EtOH diets through intragastric infusion. EtOH-mediated bone loss was associated with excessive reactive oxygen species (ROS) production in osteoblastic populations resulting inhibition of bone formation and increased bone resorption. In addition, EtOH-generated ROS in the kidney increased CYP24A1 mRNA expression, which resulted in a reduction of circulating 1,25 hydroxyvitamin D3 ($1,25(OH_2)D_3$) concentrations to below normal baseline levels, thus contributing to the disruption of vitamin D and calcium homeostasis. In the current study, 6 wk old, female C57BL/6J mice were pair-fed (PF) Lieber-DeCarli liquid diets containing 0% or 30% EtOH supplemented with 400 IU (EtOH/400) or 2000 IU (EtOH/2000) of cholecalciferol (VitD) for 40 d. In the EtOH/400 group, chronic EtOH feeding resulted in decreased bone strength and stiffness ($p<0.05$), reductions in trabecular BV/TV and cortical volumetric BMD ($p<0.05$), increased biochemical markers of bone resorption, and decreased circulating $1,25(OH)_2D_3$ and ionized calcium in the serum ($p<0.05$), and increased apoptosis in bone cells when compared to PF controls. In contrast, increasing daily cholecalciferol intake from 400 to 2000 IU/kg/kg, prevented cortical bone loss by reducing EtOH-mediated increases in bone resorption and apoptosis in bone cells and protected against EtOH-mediated hypocalcaemia. In the EtOH/2000 mice, circulating $1,25(OH)_2D_3$ was significantly lower compared to mice receiving EtOH alone, suggesting increased sensitivity to feedback control of vitamin D metabolism in the kidney. Therefore, increasing the daily vitamin D recommendation for heavy and chronic alcohol users may reduce the risk of fracture in these populations. *Supported by NIH AA018282 to MJR.*

Poster #6

Abscopal Bone Marrow Stroma Suppression and Acute Death in Gut-Irradiated Mice

Robert J. Griffin, Dan Jia, Roopa Halakatti, Leah Hennings, Cassie Johnson, Christina Thompson, Eduardo Moros, Sunil Sharma, and Peter M. Corry

Gastrointestinal (GI) injury is a major cause of acute death after total-body exposure to large doses of ionizing radiation that could occur following clinical error or a terrorist attack. Additionally, localized pelvic-abdominal cavity irradiation is a common treatment modality for malignancies in these regions with associated co-morbidity leading to GI problems and increased risk of bone fracture. In two separate studies we investigated the effect of GI-only exposure to radiation on survival and bone mineral density and the role of anti-oxidants to block these events; and underlying mechanisms that lead to GI injury and bone fracture risk after pelvic-abdominal cavity irradiation.

Following high-dose exposure of the abdomen to ionizing radiation we found non-irradiated bone marrow had elevated reactive oxygen species (ROS) and suppressed *ex vivo* colony formation of bone marrow stromal cells. Massive loss of duodenal villi was also seen histologically. NAC (a potent anti-oxidant) diminished these radiation-induced abscopal effects and improved 10- and 30-day survival rates to >50% compared with <5% in vehicle-treated animals after radiation exposure. Additional studies investigating bone fracture risk after pelvic-abdominal cavity irradiation indicated a decrease in the serum bone formation marker and *ex vivo* osteoblast differentiation. However, little change in the serum bone resorption makers and *ex vivo* osteoclast formation was seen. These radiation-induced abscopal effects led to a loss of bone mineral density (BMD) of up to 4.1% in the whole skeleton, 7.3% in tibia, and 7.7% in the femur within 14 days of exposure. Taken together these studies indicate GI exposure to radiation in a clinical setting or accidental/terroristic exposure leads to loss of intestinal villi, increased ROS in the bone marrow, suppression of bone building cells, reduced bone mass and in some cases animal death. However, these effects may be partly rescued with the addition of an antioxidant such as NAC. Our data suggests a role for NAC as an adjuvant in pelvic-abdominal cavity irradiation of malignancies to reduce co-morbidity rates in addition to the extreme case of accidental exposure high doses of radiation.

Poster #7

Osteocyte Control of Bone Remodeling

Jinhu Xiong, Melda Onal, Yiying Wang, Marilina Piemontese, Rajamani Selvam, Priscilla Baltz, Stavros C. Manolagas, and Charles A. O'Brien

A major function of the human skeleton is to protect other organs from damage. It is also vital for our ability to move about and acts as a source of important minerals when they are not available in our diet. Because of these important functions, the skeleton is constantly undergoing renewal via a process known as bone remodeling. During this process, large cells known as osteoclasts resorb old bone and cells known as osteoblasts lay down new bone in the cavities created by osteoclasts. Many conditions that cause osteoporosis, such as advanced age, estrogen-deficiency, and therapeutic use of glucocorticoids, do so by creating an imbalance between bone resorption and bone formation during bone remodeling.

Osteocytes are another type of cell present in the skeleton that is created when a subset of osteoblasts is buried within the new bone matrix that they produce. These cells remain alive within the bone and stay connected with each other and with cells on the bone surface, creating a network within the bone matrix. The precise role of the osteocyte network has, until recently, been unclear.

The major goal of the studies in my laboratory is to identify the mechanisms that control bone remodeling in pathophysiological conditions. To accomplish this goal we rely on mouse models of aging, estrogen-deficiency, and glucocorticoid therapy. In each of these models, the bone loss that occurs closely resembles the bone loss that occurs in humans. We also use a variety of genetically-modified mice to address specific hypotheses. Recently, we have determined that, under normal physiological conditions, osteocytes control the formation of osteoclasts by producing a cytokine known as RANKL. Our ongoing studies seek to under seek to understand the molecular mechanisms that control RANKL production by osteocytes and to identify the cellular sources of RANKL that drive osteoclastogenesis in pathophysiological conditions.