Summer 2015

Musculoskeletal Messenger

University of Pennsylvania Penn Center for Musculoskeletal Disorders

Inside this issue:

Penn Center
for
Musculoskeletal Disorders
University of Pennsylvania
424 Stemmler Hall,
3450 Hamilton Walk
Philadelphia, PA 19104-6081

Phone: 215-898-8653
Fax: 215-573-2133
www.med.upenn.edu/pcmd

If you have any news or information that you would like included in the next issue of this newsletter, please email us at:

pcmd@mail.med.upenn.edu

Remember to include reference to support from the Center in your abstracts and publications. Cite Grant NIH/NIAMS P30AR050950 from the National Institute Of Arthritis And Musculoskeletal And Skin Diseases of the NIH.

Looking Forward to the 2015 PCMD Annual Scientific Symposium — November 19, 2015

Preparations are underway for the 12th Annual Penn Center for Musculoskeletal Disorders Scientific Symposium in the BRB Auditorium/Lobby to be held on November 19, 2015.

The keynote speaker will be Nancy Lane, M.D. from the

University of California at Davis, Endowed Professor of Medicine and Director for the Center for Musculoskeletal Health. Her lecture is titled *"Targeted delivery of mesenchymal stem cells to the bone."*

The day will begin at 930am with registration and poster set-up followed by scientific presentations from new Center Full and Affiliate members and PCMD Pilot Grant recipients.

The symposium will also include lunch and a judged poster session with prizes awarded in four categories.

The day will conclude with a reception from 4:00-5:30pm in the BRB lobby.

Please register (no charge, but registration is required) by going to: http://www.med.upenn.edu/pcmd/PCMD-scientific-symposium-registration-form.shtml .

Co-sponsored by:

Institute on Aging
University of Pennsylvania

2015 PCMD Pilot and Feasibility Grant Recipients Announced

The Penn Center for Musculoskeletal Disorders Pilot and Feasibility Grant Program has awarded four investigators with one year of funding for their pilot grant projects with a start date of July 1, 2015.

Yejia Zhang, MD, PhD, will receive funding for her grant titled "Inhibition of ADAM-8 to reduce intervertebral disc degeneration"

Harvey Smith, MD, will receive funding for his pilot grant titled "Impact of Pre-Culture and *In Vivo* Remobilization on Engineered Disc Replacement"

Oren Friedman, MD, will receive funding for grant titled " Effect of injury to cartilage and recovery treatment with FGF-18"

Tejvir Khurana, MD, PhD, will receive funding for his grant titled "Role of the IL-15 / IL-15Rα axis in modulating muscle-tendon-bone adaptation and repair"

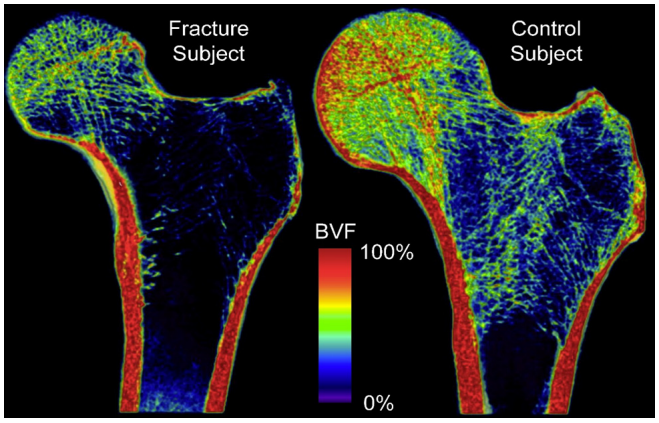
Research Updates from PCMD Members

Chamith S. Rajapakse, PhD

MRI-based biomechanics of proximal femur microstructure can detect lower elastic modulus in subjects with fragility fractures compared to controls

Hip fracture is a devastating manifestation of osteoporosis. Within a year of a hip fracture, 20-30% of patients die and 50% lose the ability to walk. The standard-of-care test for osteoporosis diagnosis—Dual energy X-ray absorptiometry (DXA) derived bone mineral density (BMD)—is used as a surrogate for bone strength but has many limitations. Consequently, a majority of women who suffer hip fractures are classified as having "normal" bone quality by DXA BMD. We developed a method to determine the strength of the proximal femur in human subjects by using magnetic resonance imaging (MRI) and finite element analysis. We applied this technique to determine the feasibility of detecting lower bone strength in subjects with clinically-defined fragility fractures (N=22) compared to controls (N=22). Fracture cases demonstrated lower elastic modulus compared to controls in all proximal femur regions—femoral head, femoral neck, Ward's Triangle, intertrochanteric region, and greater trochanter. Interestingly, DXA BMD T-scores failed to show any significant difference between the two groups. This study highlighted that direct assessment of proximal femur strength may provide information about bone quality that is not captured by DXA BMD.

Figure: Volume-rendered MRI bone volume fraction map of an osteoporotic fracture subject showing low regional bone volume and deterioration in trabecular microarchitecture compared to the control subject.

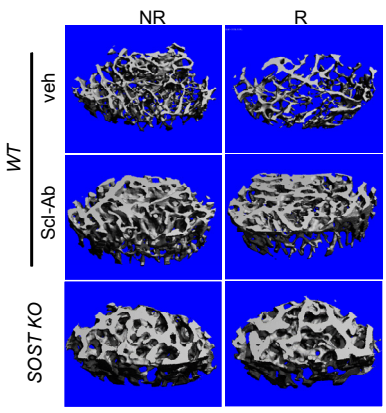


Acknowledgement:
PCMD Pilot grant, R01 AR 066008, R01 AR 068382

Ling Qin, PhD

Mechanism of radiotherapy-induced osteoporosis and its treatment

Radiotherapy eliminates tumor cells but can have untoward effects on neighboring normal tissues including bone, causing osteoradionecrosis, osteoporosis and fractures. We recently established a rodent focal radiation model that reproduces many aspects of radiotherapy-induced damage on bone, such as loss of mineralized bone, decreased marrow cellularity, loss of vascular integrity, and increased marrow adiposity. Further studies demonstrated that radiation causes local trabecular bone loss by drastically and persistently reducing the number of osteoblast lineage cells, including osteoblasts and their progenitors. We initially found that daily injections of parathyroid hormone (PTH1-34) largely prevented such bone loss and structural deterioration in irradiated bone and that the major mechanism appeared to be the protection of osteoblasts from radiation-induced apoptosis via stimulating the PKA/β-catenin pathway. Radiation exposure directly or indirectly generates a large amount of DNA lesions in cells, among which DNA double strand break (DSB) is the most deleterious one that causes cell death. Mechanistic studies showed that activating the canonical Wnt/β-catenin signaling is capable of blocking radiation-induced apoptosis in osteoblast lineage cells by enhancing the repair of DSBs through a non-homologous end-joining (NHEJ) pathway. Sclerostin is an osteocyte-secreted Wnt antagonist whose loss-of-function mutation is associated with a high bone mass phenotype. Interestingly, administration of antibody against sclerostin (Scl-Ab) elicited the same robust radioprotective actions on trabecular bone as PTH1-34. Most strikingly, the damaging effects of radiation were completely abrogated in *sclerostin* (*SOST*) *knockout* mice. Taken together, our studies provide proof-of-principle evidence for a novel use of Scl-Ab as a therapeutic treatment for radiation-induced osteoporosis and establish molecular and cellular mechanisms that support such treatment.



Scl-Ab reverses trabecular bone loss in mouse long bones induced by focal radiation.

Two-month-old mice were irradiated (d1: 8 Gy; d3: 8 Gy) at the right distal femoral metaphyseal region and received weekly injections of Scl-Ab for 4 weeks. *SOST KO* mice at the same age received the same focal irradiation without any treatment. Their trabecular bone at d28 was scanned for 3D mCT images. NR: non-radiated femur; R: radiated femur.

Announcements

Louis J. Soslowsky, PhD named as Associate Dean for Research Core Facilities

Louis J. Soslowsky, PhD has been appointed Associate Dean for Research Core Facilities in the Perelman School of Medicine. As Associate Dean for Research Core Facilities, Dr. Soslowsky will oversee all aspects of biomedical research core facilities within the PSOM and his reporting relationship will be to the Executive Vice Dean and Chief Scientific Officer. Dr. Soslowsky's research program in orthopaedic biomechanics and functional tissue engineering relates to injury, repair, healing, and regeneration of soft connective tissues through a series of multidisciplinary studies that span molecular and cellular structure to biomechanics, and bridge basic and clinical research. Dr. Soslowsky is a distinguished investigator with multiple accolades and awards. He has authored over 170 peer-reviewed publications, speaks widely at national and international venues, and has served on numerous scientific committees both inside and outside of Penn. Dr. Soslowsky's experience with research core facilities — in combination with his strong track record of leadership in a variety of roles — makes him the ideal candidate to lead our research core facilities, and to act as an advocate on behalf of our faculty. Dr. Soslowsky invites you to explore the exciting resources available at the Biomedical Research Core Facilities.

http://www.med.upenn.edu/cores/

PCMD FUNDS AVAILABLE: Summary Statement Driven Funding Request

If you have a recent summary statement from an NIH grant (eligible NIH mechanisms include all "R" grants such as R03, R21 and R01 and "K" grants such as K01, K08 on their first submission—please inquire regarding eligibility of other proposal mechanisms) which requires you to run additional experiments, gather additional data, provide feasibility for an approach, or similar, we can provide small funds ($1,000-$15,000) with a very short turn-around time in order to allow you to complete these experiments and resubmit your proposal with the best chance of success. Requests for funding will be evaluated on a rolling basis and priority will be given to Assistant Professors with encouraging initial review priority scores better than ~30-35%. The format of the "Summary Statement Driven Funding Request", which is limited to **one page**, is as follows:

- Name of PI (must be a PCMD full member)
- Title of Project Request
- Specific Purpose of Request with Stated Outcome/Goal Referring Explicitly to the Summary Statement for Justification
- Research Design and Methods
- Budget with Brief Justification

Funding through this mechanism is available by submitting the one page proposal to pcmd@mail.med.upenn.edu

Robert L. Mauck, PhD appointed as Director of the McKay Orthopaedic Research Laboratory

The McKay Orthopaedic Research Laboratory is proud to announce the appointment of our new director, Dr. Robert Mauck. Rob is an Associate Professor of Orthopaedic Surgery and Bioengineering, and he now takes the reigns as the director of McKay Labs. Rob began as director of the McKay Lab on July 1, 2015 and looks forward to carrying on the traditions of the McKay Labs and building on and further expanding its exemplary record of excellence in Orthopaedic Research. We are pleased to welcome him to his new position.

COMING SOON!!

NEW AND EXCITING UPDATED WEBSITE FOR THE PENN CENTER FOR MUSCULOSKELETAL DISORDERS

PENN
CENTER for MUSCULOSKELETAL DISORDERS

Penn Center for Musculoskeletal Disorders
University of Pennsylvania
424 Stemmler Hall, 3450 Hamilton Walk
Philadelphia, PA 19104-6081

Phone: 215-898-8653
Fax: 215-573-2133
www.med.upenn.edu/pcmd

If you have any news or information that you would like included in the next issue of the Musculoskeletal Messenger newsletter, please email the information to:
pcmd@mail.med.upenn.edu

U.S. Department of Health and Human Services

Supported by the
National Institutes of Health
NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Remember to include reference to support from the Center in your abstracts and publications. Cite Grant NIH/NIAMS P30AR050950 from the National Institute Of Arthritis And Musculoskeletal And Skin Diseases of the NIH. Support has also been provided by the Perelman School of Medicine at the University of Pennsylvania.

Upcoming Events

PCMD Visiting Professorship Series 2015-2016

Tuesday, September 8 2015, 1:30-2:30pm/ 8-146 SCTR
Evolving roles of Prolyl Hydroxylases in Intervertebral Disc Health and Disease
Makarand Risbud, Ph.D.
Professor of Orthopaedic Surgery
Professor and Co-Director, Cell and Developmental Biology Graduate Program
Jefferson University

Tuesday, October 20, 2015, 1:30-2:30pm/8-146 SCTY
TITLE : TBD
M. Hicham Drissi Ph.D.
Professor of Orthopaedic
Director of Orthopaedic Research
UConn Musculoskeletal Institute

Thursday, November 19, 2015
Annual Scientific Symposium
BRB Auditorium/Lobby
930am-4:00pm (Reception 4:00-5:30)
Targeted delivery of mesenchymal stem cells to the bone.
Nancy Lane, M.D.
Director, Center for Musculoskeletal Health
Endowed Professor of Medicine and Rheumatology
Director: Academic Geriatric Resource Program
UC Davis Health System

Tuesday, December 15, 2015, 1:30-2:30pm/8-146AB
TGF-beta Integration of Physical and Biochemical Cues in the Skeleton
Tamara Alliston, Ph.D.
Associate Professor of Orthopaedic Surgery, University of California, San Francisco

Tuesday, January 19, 2016, 1:30-2:30pm/TBD
Role of Connexin43 in Cortical Bone Adaptation to Mechanical Load
Roberto Civitelli, M.D.
Sydney M. and Stella H. Schoenberg Professor of Medicine, Professor of Orthopaedic Surgery and Cell Biology and Physiology, Washington University in St. Louis

Tuesday, February 16, 2016, 1:30-2:30pm/TBD
Unravelling the neurobiology of osteoarthritis pain
Anne-Marie Malfait, M.D., Ph.D.
Associate Professor of Medicine and Biochemistry, Rush University Medical Center

Tuesday, March 2016
TBD

Tuesday, April 2016
TBD

Tuesday, May 2016
TBD