Summer 2013

Musculoskeletal Messenger

University of Pennsylvania Penn Center for Musculoskeletal Disorders

Inside this issue:

Penn Center for Musculoskeletal Disorders
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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 2013 PCMD Annual Scientific Symposium — November 13, 2013

Preparations are underway for the 10th Annual Penn Center for Musculoskeletal Disorders Scientific Symposium in the BRB Auditorium/Lobby to be held on November 13, 2013.

The keynote speaker will be Joan A. McGowan , Ph.D., Director, Division of Musculoskeletal Diseases, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health (NIH) . Her lecture is titled "*Managing Science and Innovating in Challenging Times*."

The day will begin at 10:45 am with registration and poster set-up followed by scientific presentations from new Center 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 check the PCMD website in the upcoming months for more information.

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 each for their pilot grant projects with a start date of July 1, 2013.

The first recipient in our newest round, X. Sherry Liu, Ph.D., will receive funding for her grant titled "Structure and Strength Recovery in Post-Lactation Bone." Dr. Liu's project will investigate structural and cellular processes that lead to remarkable bone structure and strength recovery after lactation by using advanced imaging techniques.

The second new recipient, Ling Qin, Ph.D., will receive funding for her pilot grant titled "novel anabolic treatment for radiation-induced osteoporosis." Dr. Qin's study will establish a clinically relevant rodent model of radiation-induced bone damage to determine whether PTH treatment prevents radiation-induced bone loss and to delineate changes in the bone marrow microvasculature after radiation and PTH treatment.

The third new recipient is Lachlan Smith, Ph.D., whose pilot grant is titled

PCMD Pilot and Feasibility Grant Recipients Announced (cont'd)

"Molecular Mechanisms of Failed Vertebral Bone Formation in Mucopolysaccharidosis VII." Dr. Smith's goal is to establish the underlying molecular mechanisms of failed cartilage-bone conversion in MPS VII vertebrae, with the goal of identifying new therapeutic targets.

The fourth new recipient is Hansell H. Stedman, M.D., whose pilot grant is titled "Molecular Pattern Recognition in Acute and Chronic Injury to Muscle and Myotendinous Junction." Dr. Stedman's study will To investigate the role of selected innate immune mechanisms in the initial detection of DAMPs in acutely injured muscle and dystrophic (dystrophin-null) and myotendinous junction.

Congratulations to all pilot grant recipients!

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 "P" grants such as P20, P50, P60 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 turnaround 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

In addition to the one page proposal, the PDF of the complete summary statement must be provided. Funding through this mechanism is available by submitting the one page proposal and summary statement to pcmd@mail.med.upenn.edu.

Core Seed Grant Funding Available!

The purpose of this program is to provide small seed grants to PCMD investigators who are active in musculoskeletal research that fits within the scope of the Center's overall objectives, as a means to generate pilot data in support of a future grant application.
If you wish to benefit from this opportunity with a small project that uses one of our core resources, please provide a brief description including specific aims and budget, not exceeding one page. to the appropriate core director (see below for contact information). There are no restrictions as far as the use of the funds are concerned except that they cannot be spent on equipment. The current cap is $6,000.

Core Director Contact Information
Molecular Profiling Core Director - Vivianna Van Deerlin, M.D., Ph.D. (vivianna@mail.med.upenn.edu)

Imaging Core Director — Felix W. Wehrli, Ph.D. (wehrli@mail.med.upenn.edu)

Biomechanics Core Director — Robert Mauck, Ph.D. (lemauck@mail.med.upenn.edu)

Histology Core Director — Robert Pignolo, M.D., Ph.D. (pignolo@mail.med.upenn.edu)

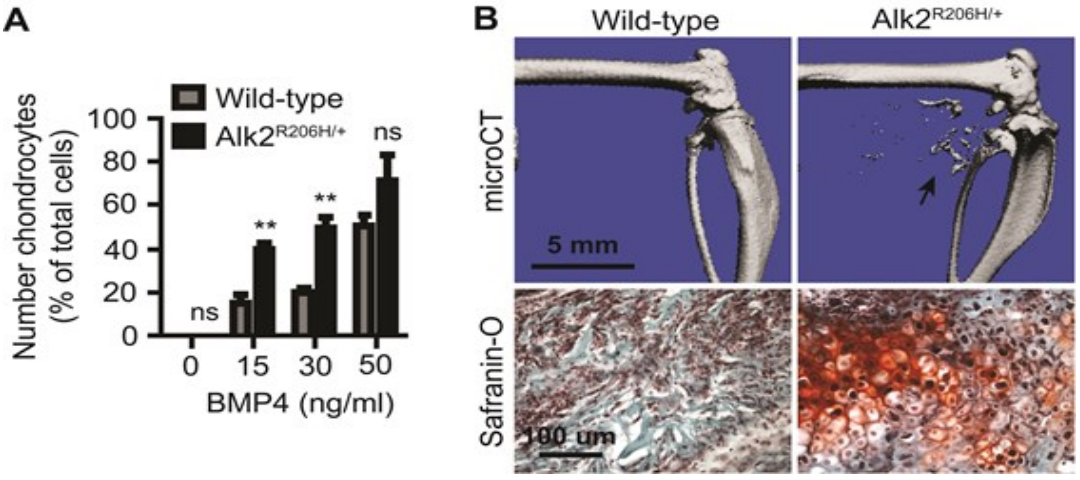
Research Updates from PCMD Members

Gain-of-function Alk2 mutation enhances chondrocyte differentiation

Andria L. Culbert and Eileen M. Shore, Ph.D.

A rare genetic disorder, though directly impacting relatively small numbers, can provide critical insight into fundamental cellular mechanisms with wider clinical implications. One such disease, fibrodysplasia ossificans progressiva (FOP) is a disabling disorder characterized by congenital skeletal malformations and progressive extraskeletal (heterotopic) endochondral ossification. FOP is caused by gain-of-function mutations in ALK2, a highly conserved type I bone morphogenetic protein (BMP) receptor. As part of our studies to determine the cellular mechanisms that direct the transformation of soft connective tissues to cartilage and bone, we are investigating whether the gain-of-function FOP ALK2 R206H mutation modulates cell differentiation, specifically to promote endochondral bone formation. We developed Alk2R206H/+ mouse embryonic fibroblasts as a mesenchymal progenitor cell model. In vitro, these cells showed leaky and enhanced BMP/Smad signaling as well as accelerated and heightened sensitivity toward chondrogenic differentiation in response to low, non-osteoinductive levels of BMP. In vivo, Alk2R206H/+ cells, but not wild-type, differentiated to cartilage and promoted robust heterotopic ossification in a skeletal muscle cell-implant model. Furthermore, we determined that knock-out of Alk2 severely suppressed differentiation and that Alk2 function is critical specifically for early chondrogenesis. Together, these data suggest that Alk2 signaling modulates differentiation potential under normal circumstances but that leaky low-level Alk2R206H signaling directly promotes accelerated chondrogenesis. These investigations support the onset of chondrogenic differentiation as an important therapeutic target for preventing heterotopic bone formation in FOP patients and suggest that activation of ALK2 may be a useful strategy for maintaining bone and cartilage formation and integrity during aging.

These investigations were supported in part through a pilot grant for the Penn Institute for Aging (IOA) and the Penn Center for Musculoskeletal Disorders (PCMD).



(A) Quantification of chondrocytes differentiated in vitro by increasing BMP concentration shows a dose effect, with Alk2$^{R206H/+}$ cells showing increased sensitivity at low concentrations.

(B) In vivo induction of mineralized heterotopic ossification by Alk2$^{R206H/+}$ implanted cells, but not wild-type cells, is seen by microCT (top; arrow), and evidence of endochondral ossification is provided by cartilage matrix staining (red; safranin-O) of histological sections.

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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

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Upcoming Events

PCMD Visiting Professorship Series 2013-2014

Tuesday, September 17, 2013, 1:30-2:30pm/TBD

Engineering human osteochondral grafts
Gordana Vunjak-Novakovic, PhD
Mikati Foundation Professor of Biomedical Engineering; Professor of Medical Sciences (in Medicine)
Columbia University

Tuesday, October 22, 2013, 1:30-2:30pm/TBD

The Biomolecular Science and Engineering of Bone's Extracellular Matrix
Deepak Vashishth, PhD
Director, Center for Biotechnology & Interdisciplinary Studies
Professor & Department Head of Biomedical Engineering
Rensselaer Polytechnic Institute

Annual Scientific Symposium

Wednesday, November 12 2013, 10:45-5:30pm/BRB Auditorium

Managing Science and Innovating in Challenging Times

Joan A. McGowan, PhD
Director, Division of Musculoskeletal Diseases, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health (NIH)

Tuesday, December 10, 2013, 1:30-2:30pm/TBD

Epigenetic regulation of stem cell phenotypic plasticity and hedgehog signaling during early cartilage development
Andrew Lasser, PhD
Professor of Biological Chemistry and Molecular Pharmacology
Harvard Medical School

Tuesday, January 21, 2014, 1:30-2:30pm/TBD

Title: TBA
Mathias Bostrom, MD
Professor of Orthopaedic Surgery
Hospital for Special Surgery

Tuesday, February 18, 2014, 1:30-2:30pm/TBD

Solid State MR Spectroscopy and Imaging of Bone Mineral and Matrix
Jerome L Ackerman, PhD
Associate Professor in Radiology
Harvard Medical School

Tuesday, March 25, 2014, 1:30—2:30pm/ TBD

Title: TBA
James C. Iatridis, Ph.D.
Professor or Orthopaedics and Neurosurgery
Mount Sinai Hospital

April 2014/ TBD
May 2014 / TBD