Summer 2018

Musculoskeletal Messenger

University of Pennsylvania Penn Center for Musculoskeletal Disorders

Inside this issue:

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

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Remember to include reference to support from the Center in your abstracts and publications.

Cite Grant NIH/NIAMS P30AR069619 from the National Institute Of Arthritis And Musculoskeletal And Skin Diseases of the NIH.

Looking Forward to the 2018 PCMD Annual Scientific Symposium — November 7, 2018

Preparations are underway for the 15th Annual Penn Center for Musculoskeletal Disorders Scientific Symposium in the Smilow Rubenstein Auditorium and Commons (note new location for us) to be held on November 7, 2018.

The keynote speaker will be Brendan H. Lee, M.D., Ph.D. from Baylor College of Medicine. Dr. Lee is the Robert & Janice McNair Endowed Chair and Professor of Molecular and Human Genetics and Director of the Center for Skeletal Medicine and Biology. His keynote lecture will be *"Skeletal Dysplasias: Informing Skeletal Function & Homeostasis."*

The day will begin at 8am 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 in the Commons area of Smilow.

Registration is free but is required.

Stay tuned for more information on registration.

2018 PCMD Pilot and Feasibility Grant Recipients Announced

The Penn Center for Musculoskeletal Disorders Pilot and Feasibility Grant Program has awarded two investigators with one year of funding for their pilot grant projects with a start date of *July 1, 2018*

Miltiadis Zgonis, M.D. will receive funding for his grant titled "Development, Maturation, and Function of Meniscal Radial Elements".

Joel Boerckel, Ph.D. will receive funding for his grant titled "Role of YAP/TAZ in osteoprogenitor cell-induced angiogenesis for vascularized bone repair".

Research Updates from PCMD Members

Tejvir Khurana, M.D., Ph.D.

Role of Interleukin-15 receptor alpha (IL15RA) in the musculoskeletal system

The Khurana lab is interested in the role of Interleukin-15 (IL15) and IL15 receptor alpha (IL15RA) in the musculoskeletal system. IL15 and IL15RA are mostly known for their role as pro-inflammatory molecules in the immune system. However, their expression is detected in cell types not directly involved in immunity. IL15 and IL15RA are expressed in metabolically active tissues such as muscle where, we and others, have shown they participate in modulating muscle contractility, exercise performance and energy metabolism. Silencing *Il15ra* improves exercise capacity and protects against diet-induced obesity. In the skeletal system, a tissue highly responsive to loading and changes in muscle secretome during exercise, IL15RA was previously shown to be important for osteoclastogenesis. However, little is known about its role in osteoblasts and bone mineralization.

In collaboration with Dr. Eileen Shore from the Department of Orthopaedic Surgery, we evaluated the bone structural and mechanical properties of *Il15ra* whole-body knock out mice (Il15ra$^{-/-}$). We used a variety of in vivo, in vitro and bioinformatic analyses to define the role IL15/IL15RA signaling on osteoblast function and have recently published our results [Loro *et al.* 2017 **Bone** *103*, 20-30]. We showed that lack of IL15RA decreased bone mineralization *in vivo* and in isolated primary osteogenic cultures, suggesting a cell-autonomous effect on osteoblasts (Fig.1). Il15ra$^{-/-}$ osteogenic cultures also had reduced *Rankl/Opg* mRNA ratio, indicating defective osteoblast / osteoclast coupling. We analyzed the transcriptome of primary pre-osteoblasts from normal and Il15ra$^{-/-}$ mice and identified 1150 genes that were differentially expressed at a False Discovery Rate (FDR) of 5%. Using DAVID analysis, we grouped these genes into functional clusters related to metabolism, immune response, bone mineralization and morphogenesis. The transcriptome analysis was validated by qPCR of some of the most significant hits. Using bioinformatic approaches, we identified candidate genes, including *Cd200* and *Enpp1*, that could contribute to the reduced mineralization (Fig.2). Silencing *Il15ra* using shRNA in the calvarial osteoblast MC3T3-E1 cell line decreased ENPP1 activity. Together, these data highlight an important cell-autonomous role for IL15RA in bone mineralization and osteoblast function. In the future, we will extend these studies focusing on the role of IL15 and IL15RA in osteocyte biology, signaling and mechanosensing as well as to determine whether these pathways can be targeted to modulate bone remodeling in response to inactivity / unloading.

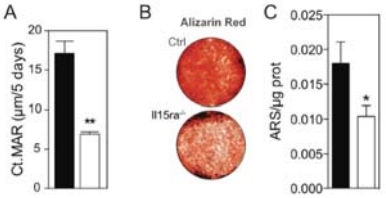


Figure 1:(A) *In vivo* cortical mineral apposition rates. (B) Alizarin red mineralization staining performed on primary osteogenic cultures after 12 days of differentiation and quantified in (C).

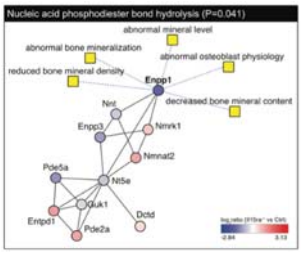


Figure 2: Diagram of protein-protein interaction network for "Nucleic acid phosphodiester bond hydrolysis" from Phenomescape analysis.

Acknowledgement: The study was supported in part through a pilot grant for the Penn Center for Musculoskeletal Disorders (PCMD).

Mary Mullins, Ph.D.

Pathogenic signaling mechanism of the Fibrodysplasia Ossificans Progressiva (FOP) altered receptor using a zebrafish model

FOP is a rare genetic disorder characterized by extra-skeletal ossification. FOP is caused by gain-of-function mutations in the Type I BMP receptor gene, ACVR1, which result in over-activation of Bone Morphogenetic Protein (BMP) signaling. However the mechanism by which the FOP mutation causes disease is still unknown. Zebrafish have been used extensively in the study of BMP signaling and more recently have been recognized as a model of human disease. In collaboration with Dr. Eileen Shore and Dr. Fred Kaplan of the Department of Orthopaedic Surgery, we use zebrafish development as a method to determine the aberrant FOP signaling mechanism and develop potential therapeutics. We tested the activity of the human FOP-causing ACVR1 R206H, G328R, G328E, and G328W mutations in our zebrafish assays. We found that all FOP mutant receptors cause BMP signaling overactivity in wild-type embryos, embryos defective for endogenous Acvr1 function, as well as embryos lacking BMP ligand. The results show that the human FOP receptors signal independently of BMP ligand and the endogenous Acvr1 receptor. We are now testing if BMP and other TGFb ligands enhance activity of these mutant receptors, as well as examining the roles of the Type II and other Type I BMP receptors in this aberrant signaling mechanism.

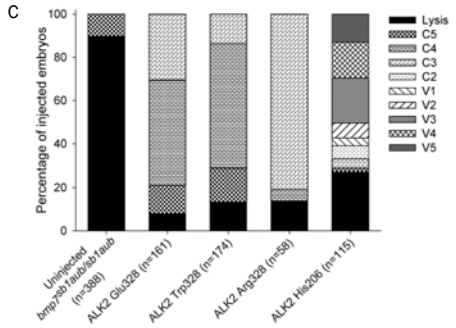
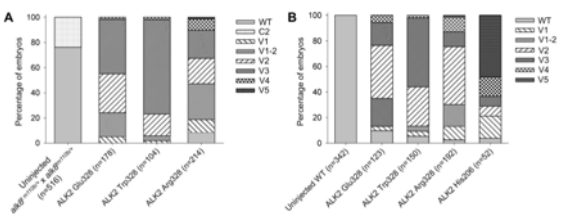


Figure 1. Overactivity of human FOP mutant ACVR1 receptors in a zebrafish development assay. A. Overactivity of BMP signaling causes ventralization (V) in *acvr1* (*alk8*) mutant (A), wild-type (WT) (B), and *bmp7* ligand mutant (C) zebrafish embryos. Increasing severe ventralization (V1 low, V5 high) reflects increasing BMP activity. Loss of BMP signaling causes an opposite dorsalization defect (C2 weak to C5 strong, lysis most severe).

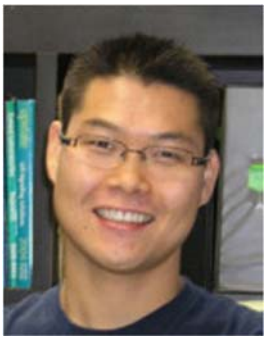


Acknowledgement: Studies performed by Dr. Bettina Mucha-LeNy and supported by a T32 Postdoctoral Research Training Grant (NIH/NIGMS "Medical Genetics Research Training") to BML and a Cali Developmental Grant to MM.

In the News!

Orthopaedic Surgery New PhD Faculty Recruited

Please welcome Kyu Sang Joeng, Ph.D. who has joined Penn as Assistant Professor of Orthopaedic Surgery in April 2018. Dr. Joeng obtained his Ph.D. from Washington University in St. Louis majoring in Developmental Biology. He mainly studied endochondral bone development at WashU using mouse genetic models. After his Ph.D., he moved to Baylor College of Medicine to study bone-related human genetic diseases and developed a mouse model to study Osteogenesis Imperfecta (brittle bone disease). Dr. Joeng is interested in signaling pathways regulating development and homeostasis of the musculoskeletal system. He uses mouse genetic models to study the function of ER stress, mTORC1, and Wnt signaling in bone, cartilage and tendon.



If you would like to contact Dr. Joeng, please do so at joeng@pennmedicine.upenn.edu

Louis J. Soslowsky receives the H. R. Lissner Medal from the American Society of Mechanical Engineers (ASME)

In making its selection, the Society cited Soslowsky "for outstanding contributions toward the understanding, prevention, and treatment of musculoskeletal injuries to tendinous [tendon] and ligamentous [ligament] tissues; and for internationally recognized leadership in the biomechanics community."

An expert in orthopaedic bioengineering and functional tissue engineering, Soslowsky focuses his research on soft connective tissue and joint mechanics, seeking to identify the causes of tendon and ligament injury, healing, repair, and regeneration. He also studies shoulder joint mechanics, examining relationships between tissue injury and joint loading in normal and abnormal states.

Soslowsky will deliver a plenary lecture and receive his award at the World Congress of Biomechanics in Dublin, Ireland next month. He has published more than 200 peer reviewed articles in professional journals. His honors and awards include the American Academy of Orthopaedic Surgeons Kappa Delta Ann Doner Vaughan Award, Charles S. Neer Award for Excellence in Basic Science Research (twice), American Orthopaedic Society for Sports Medicine Hughston Award, Whitaker Foundation Special Opportunity Award, the ASME Y.C. Fung Young Investigator Award, and the Outstanding Mentorship Award from the Orthopaedic Research Society. Soslowsky is a Fellow of the American Society of Mechanical Engineers and of the American Institute for Medical and Biological Engineering.

Congratulations to Dr. Soslowsky!

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@pennmedicine.upenn.edu or for more information please visit the website at www.med.upenn.edu/pcmd

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U.S. Department of Health and Human Services

Supported by the
National Institutes of Health
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Upcoming Events

PCMD Visiting Professorship Series Fall/Winter 2018-2019

Tuesday, September 25, 2018 1:30-2:30pm/CRB Austrian Auditorium
TBD
Christopher Hernandez, PhD
Associate Professor, Sibley School of Mechanical and Aerospace Engineering and Meinig School of Biomedical Engineering
Cornell University

Tuesday, October 23, 2018 1:30-2:30pm/CRB Austrian Auditorium
"Comparative and MRI Studies of Developmental Orthopedic Disease"
Cathy Carlson, DVM, PhD, DACVP
Professor, Department of Veterinary Clinical Sciences
University of Minnesota

Wednesday, November 7, 2018,
Annual Scientific Symposium
Smilow Rubenstein Auditorium
8am-6:30pm

Tuesday, December 11, 2018, 1:30-2:30pm/CRB Austrian Auditorium
"A novel Hyaluronan-binding Peptide improves Cartilage Repair"
Thorsten Kirsch, PhD
Professor and Vice Chair for Research
Musculoskeletal Research Center
Department of Orthopaedic Surgery
Hospital for Joint Diseases
NYU Langone Medical Center

Tuesday, January 2019 TBD
Tuesday, February 2019 TBD
Tuesday, March 2019 TBD
Tuesday, April 2019 TBD

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