Volume 1, Issue 1

September 2009

Musculoskeletal Messenger

University of Pennsylvania Penn Center for Musculoskeletal Disorders

Inside this issue:

Have you already registered and submitted abstracts and posters for our **Annual Scientific Symposium to be held on October 14, 2009**? The deadline is September 23, 2009 and you can register at www.med.upenn.edu/pcmd/registration_form.shtml

Did you know that you can e-mail all 75+ faculty members of our Center with a question, comment, request for help or announcement by e-mailing the distribution list at ccmd@upenn.edu?

Did you know that funds are available to support projects within each Research Core (in addition to the formal Pilot Grant Program described at right)? Contact the Core Directors for more information (see p.2).

Do you know what BoneHeaDs is?

BoneHeaDs is a monthly gathering, sponsored by the PCMD, which features seminars and discussions of the Philadelphia Bone and Hard-Tissue group. For more information please email Kurt Hankenson at kdhank@vet.upenn.edu.

Welcome to the Newsletter and Overview of the Penn Center for Musculoskeletal Disorders

Director: Louis J. Soslowsky, PhD

soslowsk@upenn.edu

Welcome to the inaugural edition of the Musculoskeletal Messenger, our new, newsletter for our research community! In addition to our continued communications through e-mail, regular mail, and the always present web site at www.med.upenn.edu/pcmd which is a great source of information, the Musculoskeletal Messenger will serve as another contact for our Center membership.

As a brief history, the Penn Center for Musculoskeletal Disorders was formed in 2006 based on receipt of an NIH P30 Center grant (National Institute of Arthritis, Musculoskeletal, and Skin Diseases) and became official at Penn in 2008 to provide resources for established and new investigators to address multidisciplinary research strategies for musculoskeletal problems. The overall goal of the Center is to promote cooperative interactions among investigators to enrich the effectiveness of ongoing research and promote new research within the theme of "Musculoskeletal Tissue Injury and Repair". This theme is both broad (as it includes all musculoskeletal tissue types) and focused (as it includes similarities of approaches across all tissue types, with particular emphasis on applications using animal models).

As a reminder, the aims of this Center are to enhance and advance the research productivity of investigators in musculoskeletal tissue injury and repair by:

- ◊ Developing three research core facilities (Microarray, Structure Function Biomechanics, and Imaging).
- ◊ Developing a pilot and feasibility grant program whereby new approaches, ideas, and collaborations can be developed prior to seeking extramural funding, and,
- ◊ Developing educational, training, and research enrichment programs for the musculoskeletal community.

Please do not hesitate to let us know if you have any questions or concerns. You can reach us at our e-mail address at centermd@upenn.edu.

PCMD Pilot and Feasibility Grant Program

The Penn Center for Musculoskeletal Disorders is once again accepting applications for its Pilot and Feasibility Grant Program. **Pilot grants will be due by 5pm on October 15, 2009** with a planned start date of January 1, 2010 and we are expecting to award up to 4 new grants in this round. Submissions should be related to musculoskeletal tissue injury and repair which is the broad focus of the Center and Grants are only eligible for Center members (if you are not a member but would like to become one, please contact us at:

centermd@upenn.edu).

For more information on our Cores and Center in general, please see our web site at:

www.med.upenn.edu/pcmd.

Eligibility

- Only Center members are eligible. If you are not currently a member, please e-mail Lou Soslowsky (centermd@upenn.edu), who can send you information on becoming a member.
- Categories of applicants include: 1) Established investigators with a proposal to test the feasibility of a new or innovative idea in musculoskeletal tissue injury and repair representing a clear and distinct departure from their ongoing research, 2) Established investigators with no previous work in musculoskeletal tissue injury and repair interested in testing the applicability of their expertise on a problem in this area, and 3) New investigators without significant extramural grant support as a Principal Investigator to develop a new project.
- Pilot and Feasibility Grants should use at least one of the Center's Research Cores.
- Pilot project awardees are eligible for one year, with a second year to be considered (budgets will be for $20-35,000 per year and timelines should be for one or two years). The second year of funding, the dollar amount of which would only be for up to half the year one budget, will be considered based on the progress report submitted after the first year of funding and funding availability in the Center.

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Overview of the Microarray Core

Microarray Facility on campus

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The Penn Microarray Facility and the Molecular Diagnosis and Genotyping Facility are existing resource laboratories in the School of Medicine at the University of Pennsylvania that provide instrumentation and expertise for many genomic assays. The Facilities primarily support RNA and microRNA profiling by microarrays, DNA polymorphism genotyping, and massively parallel sequencing applications. This catalog of services reflects our goal of offering a range of cost and performance options suitable for a variety of experimental questions. The overall objective of this Microarray Core Facility for our Penn Center for Musculoskeletal Disorders is to develop and utilize genomic analyses directed toward problems of musculoskeletal tissue injury and repair. The Specific Aims are:

◊ To provide guidance and training on the capabilities, advantages, and disadvantages of various genomic protocols and analyses for musculoskeletal research through formal educational enrichment programs and one-on-one interactions.

◊ To provide expertise and service for Affymetrix GeneChip assays.

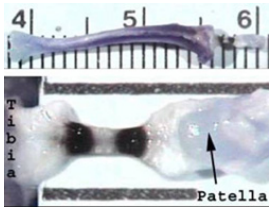
◊ To provide expertise and service for the development and use of custom-printed and other commercial microarrays.

◊ To facilitate access to training and bioinformatics tools appropriate for analyzing the data produced in Aims 2 and 3.

◊ To provide funding for development of new projects and collaborations and to facilitate development of preliminary and/or feasibility data for investigators.

Please note that funds are available within this Core for small or feasibility studies. Please contact the Core Director for further information on accessing these funds.

Overview of the Structure-Function Core



Mouse patellar tendon ready for biomechanical testing in the SFBC

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Robert Pignolo, M.D., Ph.D.,
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The overall objective of this Structure Function Biomechanics Core (SFBC) is to develop and utilize a wide range of functional mechanical and structural (including histological) assays of musculoskeletal tissue injury and repair, and to provide training and funding for new projects and collaborations utilizing these assays. The Specific Aims are:

◊ To provide guidance and training on the capabilities, advantages, and disadvantages of the various methodologies to assess musculoskeletal tissue biomechanical function and structure through formal educational enrichment programs and one-on-one interactions.

◊ To provide expertise and service for biomechanical function assays of musculoskeletal tissues.

◊ To provide expertise and service for structural assays of musculoskeletal tissues, including histological characterization.

◊ To provide funding for development of new projects and collaborations and to develop preliminary and/or feasibility data for investigators.

Please note that funds are available within this Core for small or feasibility studies. Please contact the Core Director for further information on accessing these funds.

Overview of the Imaging Core

Micro-CT scan at 28 µm isotropic resolution of a transgenic mouse presenting a Paget's disease-like phenotype with osteopenia of femoral trabeculae, visualized by red glass volume rendering. (J.P. Taylor, et al.)

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Formerly the "Small Animal Imaging Core," the new "Imaging Core" has been expanded in order to address an unmet need in the musculoskeletal research community at Penn. The capabilities allowing researchers to perform imaging studies in small animals have been expanded to include services for examining larger animals and humans. This extension of scope broadens the capabilities and opportunities for our colleagues.

The Specific Aims are:

◊ To provide guidance and expertise on the use of imaging for musculoskeletal research through educational enrichment programs and one-on-one interactions.

◊ To provide a range of imaging resources for the study of structure, function and physiology of the musculoskeletal system in laboratory animals and humans.

◊ To provide pilot funding for development of new projects and collaborations and to develop preliminary and/or feasibility data with investigators.

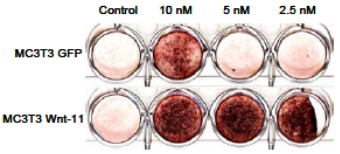
Please note that funds are available within this Core for small or feasibility studies. Please contact the Core Director for further information on accessing these funds.

Spotlight: Selected Current Pilot and Feasibility Grants

Regulation of Bone Formation by Novel Activators of Canonical Wnt Signaling

Kurt D. Hankenson, DVM, PhD, (PI) kdhank@vet.upenn.edu

Wnt proteins signal through either canonical or non-canonical pathways. Recent work indicates that canonical Wnt signaling promotes osteoblast differentiation and bone formation. While non-canonical Wnt signaling has been shown to inhibit adipogenesis, the role of non-canonical Wnts in regulating bone mass is poorly understood. Our global hypothesis is that Wnt-11, through activation of the novel osteogenic growth factor, Rspo2, promotes osteoblast differentiation via the canonical Wnt signaling pathway. Our specific aims are: I. Define the role of Rspo2 in Wnt-11 enhanced osteoblast differentiation. We hypothesize that Wnt-11 signaling activates the canonical pathway, in part through increased R-spondin 2 expression, thereby promoting osteoblast differentiation. II. Determine if Wnt-11 and Rspo2 regulate osteoblast differentiation in uncommitted mesenchymal stem cells. We hypothesize that Wnt-11 and Rspo2 will promote osteoblast differentiation of MSC through the canonical pathway. III. Determine if Wnt-11 regulates bone formation in vivo. We hypothesize that loss of Wnt-11 will result in decreased bone mass, while overexpression of Wnt-11 in osteoblasts will promote bone formation.



Wnt-11 enhances osteoblast differentiation. Wnt-11 or GFP control pre-osteoblast cells were cultured for two days. The media was changed and supplemented with ascorbic acid (25 μg/mL) and β-glycerophosphate (BGP, 3mM). BMP-2 was added at the indicated concentration for the first 3 days of induction only. Media was changed every 2-3 days to fresh media with ascorbate BGP, but no BMP-2. Red staining is mineral stained with Alizarin Red-S.

Analysis of an ACVR1 Knock-in Mouse Model for FOP

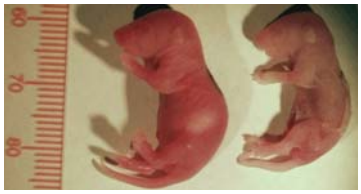
Eileen M. Shore, PhD (PI) shore@upenn.edu

Fibrodysplasia ossificans progressiva (FOP) is a genetic disorder characterized by skeletal malformations during embryonic development and progressive extra-skeletal (heterotopic) endochondral ossification after birth. Using genetic linkage and positional cloning strategies, we identified the ACVR1/ALK2 gene, which encodes a BMP type I receptor, as the mutated gene in FOP. All patients with a classic clinical presentation of FOP carry the identical single nucleotide change in ACVR1. In order to investigate the functional consequences of this mutation *in vivo*, we have generated chimeric mice with a knock-in allele of the mutation. Our specific aims are: 1. To evaluate the effects of the mutation on skeletal development and the formation of extra-skeletal bone. Complete skeletal and heterotopic ossification surveys will be conducted using X-rays, microCT, and specific staining for bone and cartilage. Skeletal bone quality also will be assessed by mechanical testing. 2. To identify soft tissues and cells altered by the mutation. Tissues will be examined by histology and for BMP signaling activity. Bone marrow MSCs will be examined *in vitro* for altered osteogenic potential. Our investigations of a mouse model that carries the mutation found in FOP allows us to examine the *in vivo* effects of the mutation on bone formation as well as on other tissues and organ systems. This animal model will be further developed and used as an important component for therapeutic drug development and evaluation.

Collagen III-deficient Mice as a Model for Musculoskeletal Wound Repair

Sherril L. Adams, PhD (PI) sherri@biochem.dental.upenn.edu

Col3-deficient mice provide a model to test the role of this protein in wound healing and to define the mechanisms by which it acts. We propose the following hypotheses: 1) Col3 serves as a reservoir for the growth factors TGFβ and/or BMPs; and 2) the regulation of TGFβ/BMP availability by Col3 plays an important role in structuring the marrow environment, thus regulating the availability of MSCs for wound healing processes in bone, tendon and skin. There are three aims: 1. Determine whether the cysteinerich domain in the Col3 N-propeptide binds TGFβ itself or other members of the TGFβ superfamily. 2. Define the impact of Col3 deficiency on TGFβ and BMP signaling, global gene expression and cell proliferation in immortalized fibroblasts and MSCs. 3. Characterize the alterations in the bone marrow environment and in marrow derived MSCs from wild-type and Col3-deficient mice. These experiments will provide unique information on the role of Col3 in regulating the availability of TGFβ family members and in structuring the marrow environment.



A newborn Col3 -/- pup (right) is ~20% smaller than its wildtype littermate.

PENN
CENTER for
MUSCULOSKELETAL
DISORDERS

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

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continuation of Pilot and Feasibility Grant Program from page 1

The second year of funding, the dollar amount of which would only be for up to half the year one budget, will be considered based on the progress report submitted after the first year of funding and funding availability in the Center. Please note that second year funding will often not be awarded, and when awarded, will be done so primarily to new investigators; second year funding to senior investigators will be quite rare.

• It is expected that these Pilot grants will lead to funding through other independent, extramural mechanisms. Therefore, the likelihood of future extramural funding will enter into the evaluation of these proposals.

For format guidelines please visit our website www.med.upenn.edu/pcmd.

Upcoming Events

Visiting Professorship Series

Tuesday, September 22, 2009, 1:00-2:00pm/JMB Class of '62
Making Cartilage: Architecture, Scaffolding and Builders
Brian Johnstone, Ph.D.

Director of Research, Department of Orthopaedics and Rehabilitation

Oregon Health & Science University

Tuesday, September 22, 2009, 2:00-2:30pm/JMB Class of '62

Technology Transfer at Penn

Robert H. Schenkel, Ph.D.

Director Life Sciences Licensing, Center for Technology Transfer

University of Pennsylvania

ANNUAL SCIENTIFIC SYMPOSIUM
Wednesday, October 14, 2009, 8:00am-2:45pm/BRB Auditorium
Molecular and Cellular Control of Skeletal Morphogenesis
Bjorn R. Olsen, M.D., Ph.D.

Hersey Professor of Cell Biology, Harvard Medical School

Professor and Chair of Oral and Developmental Biology, Dean for Research

Harvard School of Dental Medicine

Tuesday, November 17, 2009, 1:00-2:00pm/JMB Class of '62
Using Mechanical Loading to Enhance Bone Mass
Marjolein CH van der Meulen, Ph.D.

Professor, Sibley School of Mechanical and Aerospace Engineering, Cornell University

Senior Scientist, Laboratory for Biomedical Mechanics & Materials

Hospital for Special Surgery, New York NY

Tuesday, December 15, 2009, 1:00-2:00pm/BRB 251
Integration of Signaling Pathways in the Growth Plate

Karen M. Lyons, Ph.D.
Professor of Orthopaedic Surgery, Department of Biological Chemistry

University of California, Los Angeles

Tuesday, January 19, 2010, 1:00-2:00pm/Room TBA
Why Tissues in Joints Don't Heal
Martha M. Murray, M.D.

Assistant Professor and Clinical Associate

Orthopaedic Surgeon,

Children's Hospital and Harvard Medical School, Boston, MA

Tuesday, February 16, 2010, 1:00-2:00pm/Room TBA
Exploiting the Physical Environment to Optimize Stem Cells for Skeletal Regeneration

Henry J. Donahue, Ph.D.

Baker Professor and Vice Chair for Research

Director, Division of Musculoskeletal Sciences

Director, Department of Orthopaedics and Rehabilitation

Pennsylvania State University College of Medicine

Tuesday, March 16, 2010, 1:00-2:00 pm/Room TBA
The Biomechanics of Osteoarthritis: Progress vs. Progression?
Joel A. Block, M.D.

The Willard L. Wood M.D. Professor of Rheumatology

Director, Section of Rheumatology

Rush Medical College, Rush University Medical Center, Chicago, IL

Tuesday, April 13, 2010, 1:00-2:00pm/Room TBA
TBA

Tuesday, May 18, 2010, 1:00-2:00pm/Room TBA
TBA

5th Annual Philadelphia Spine Research Symposium
8:00am – 6pm, December 9, 2009

BRB II/III Auditorium

The Philadelphia Spine Research Symposium provides a forum to present cutting-edge multidisciplinary Spine research in a collegial atmosphere that disseminates scientific information, encourages informal exchange, educates scientific and clinical trainees, and develops future collaborations. The meeting includes clinicians, biologists, and engineers from across the greater Philadelphia and surrounding mid Atlantic region. The Keynote presentation "There Is No Such Thing as Non-specific Back Pain" will be by Dr. Stuart M. McGill from Waterloo University.
Breakfast, Lunch, hors d'oeuvres, poster session included. More information soon including registration link at:
http://www.med.upenn.edu/pcmd/

Fall Genomics Workshop

9:30am – 1pm, October 30, 2009

BRB II/III Auditorium

Experiment design and bioinformatics for microarray and massively parallel sequencing applications to profile RNA and DNA.

Lunch, poster session and vendor tables included, register at:

http://bioinformatics.upenn.edu/workshop/index.do