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:

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.

Pilot Grant Deadline 2/27/2015
Click on link for more information

http://www.med.upenn.edu/pcmd/pilotgrants.shtml

A Look Back at the PCMD Annual Scientific Symposium — November 12, 2014

We are happy to announce that the 11th Annual Penn Center for Musculoskeletal Disorders Scientific Symposium was a great success. The symposium was held in the BRB Auditorium/Lobby on November 12, 2014.

The keynote speaker, Henry M. Kronenberg, MD, from Harvard Medical School, Professor of Medicine and Chief of the Endocrine Unit at the Massachusetts General Hospital gave a well received lecture titled "*How PTHrP regulates chondrocyte differentiation.*" Symposium attendees enjoyed several scientific presentations from new Center members Drs. Carla Scanzello, Kacy Cullen, and Harvey Smith. While at the symposium, attendees has the opportunity to view more than 50 posters which were judged in five categories.

The following poster winners received prizes:

Julia Haupt (1st place), Brianne Connizzo (2nd place), Corinne Riggin (3rd place) for their winning posters in the Biomechanics Category; Tristan Driscoll (1st place), Salin Chakkalakal (2nd place), Natalie Chernets, Jefferson Ortho (3rd place) for their winning posters in the Histology Category; Chantal de Bakker (1st place), Allison Altman (2nd place), Wenli Sun (3rd place) for their winning posters in the Imaging Category.

Pictures from the Symposium are available at:
http://www.med.upenn.edu/pcmd/2014SymposiumPictures.shtml

See page 4 for details for the 2015 PCMD Annual Scientific Symposium

PCMD Pilot and Feasibility Grant Program Opportunity

The Penn Center for Musculoskeletal Disorders Pilot is once again accepting applications for its Pilot and Feasibility Grant Program. Submissions should be related to musculoskeletal tissue injury and repair which is the broad focus of the Center and Grants are only eligible for Full Members (if you are not a full member but would like to become, please contact us at (pcmd@mail.med.upenn.edu). Pilot grants will be due on February 27, 2015 with a planned start date of July 1, 2015 and we are expecting to award 3 grants in this round. At least 1 of these grants will be awarded at $50,000 per year. This grant will be co-sponsored by the IRM Program in Musculoskeletal Regeneration.

Submissions should be related to musculoskeletal tissue injury and repair which is the broad focus of the Center. For more information on our Cores and Center in general please see our website at http://www.med.upenn.edu/pcmd

(continued on page 2)

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

- Categories of applicants are:

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 must 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 $25-50,000 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. Please note that second year funding will most 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 at:

http://www.med.upenn.edu/pcmd/pilotgrants.shtml

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

Penn Orthopaedics 2015 Cartilage Repair Symposium

Join us for an event dedicated to the latest techniques in cartilage repair– including a hands-on workshop in the Human Tissue Lab

Follow link for registration:
http://www.eventbrite.com/e/penn-orthopaedics-2015-cartilage-repair-symposium-registration-14730600623

Research Updates from PCMD Members

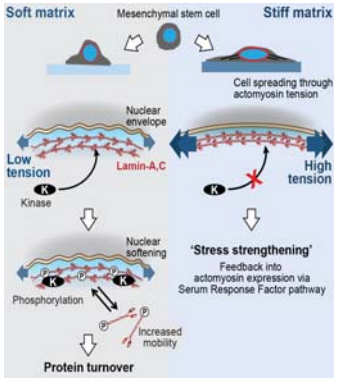
Dennis E. Discher, PhD

Matrix Elasticity Regulates Lamin-A,C Phosphorylation and Turnover with Feedback to Actomyosin

Tissue microenvironments are characterized not only in terms of chemical composition but also by collective proper-ties such as stiffness, which influences the contractility of a cell, its adherent morphology, and even differentiation [1–8]. The nucleoskeletal protein lamin-A,C increases with matrix stiff-ness, confers nuclear mechanical properties, and influ-ences differentiation of mesenchymal stem cells (MSCs), whereas B-type lamins remain relatively constant [9]. Here we show in single-cell analyses that matrix stiffness couples to myosin-II activity to promote lamin-A,C dephosphoryla-tion at Ser22, which regulates turnover, lamina physical properties, and ac-tomyosin expression. Lamin-A,C phos-phorylation is low in in-terphase versus dividing cells, and its levels rise with states of nuclear rounding in which myosin-II generates little to no ten-sion. Phosphorylated lamin-A,C localizes to nucleoplasm, and phosphorylation is enriched on lamin-A,C fragments and is suppressed by a cyclin-dependent kinase (CDK) inhibitor. Lamin-A,C knock-down in primary MSCs suppresses tran-scripts predomi-nantly among actomyosin genes, especially in the serum response factor (SRF) pathway. Levels of myosin-IIA thus parallel levels of lamin-A,C, with phosphosite mutants revealing a key role for phosphoregulation. In modeling the system as a parsimonious gene circuit, we show that tension-dependent stabilization of lamin-A,C and myosin-IIA can suita-bly couple nuclear and cell morphology down-stream of matrix mechanics.

Highlights

- MSCs on soft matrix exhibit a less spread nucleus with low lamin-A,C levels
- Lamin-A,C is rapidly phosphorylated in response to reduced cytoskeletal tension
- Phosphorylation leads to nuclear softening and lamin-A,C turnover
- Levels of lamin-A,C and myosin-IIA are coregulated in response to matrix elasticity



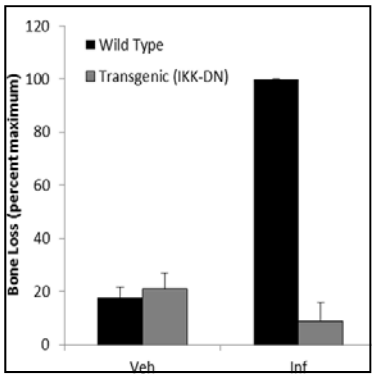
Acknowledgements: Buxboim A, Swift J, Irianto J, Spinler KR, Dingal PC, Athirasala A, Kao YR, Cho S, Harada T, Shin JW

Dana T. Graves, DDS, DMSc

Inhibiting NF-κB activation in osteoblast lineage cells blocks periodontal bone loss induced by bacterial infection.

Periodontitis is caused by bacteria-induced inflammation and is the most common osteolytic disease in humans. Previous studies have identified leukocytes and their products as key factors in this process. We investigated periodontal disease in mice with a dominant negative mutation that blocks NF-kB (nuclear factor kappaB) activation in osteoblast-lineage cells without affecting formation of an inflammatory infiltrate. Lineage specific inhibition of NF-kB in osteoblasts/osteocytes blocked periodontal bone loss. Analysis of in vivo specimens indicated that osteoblast lineage cells were an important source of RANKL whose expression was NF-kB dependent. Moreover, substantially more reparative bone formation (bone coupling) occurred in transgenic than wild-type mice. To examine potential mechanism we determined that inflammation inhibits expression of bone matrix genes by direct repression of transcription. This involves interaction of NF-kB with the promoter region of bone matrix proteins. When NF-kB binding sites were mutated in the promoter region of osteocalcin and bone sialoprotein inflammatory cytokines no longer blocked their transcription. This study establishes for the first time that osteoblast lineage cells play an essential role in periodontal disease and that NF-kB can inhibit expression of bone matrix proteins by directly blocking transcription. These events are critical in periodontal bone loss and may give insight into the formation of osteolytic lesions in other inflammatory diseases.

Periodontitis was initiated in IKK-DN transgenic mice or wild-type control mice by oral inoculation of periodontal pathogens *P. gingivalis* and *F. nucleatum* or vehicle alone. Mice were euthanized 6 weeks after oral inoculation. MicroCT performed in the PCMD Imaging Core examined bone loss between the molar teeth.



Acknowledgements: S. Pacios, R. Tarapore

Upcoming Events

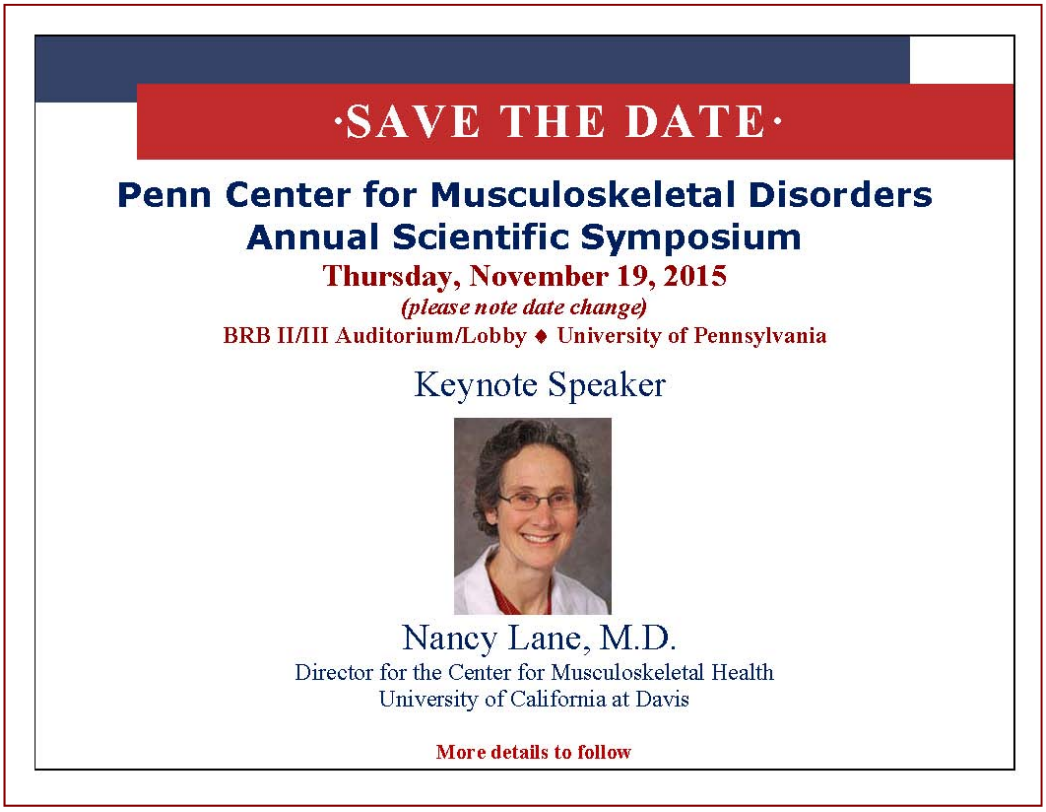
PCMD Visiting Professorship Series 2014-2015 (February—May)

Tuesday, February 10, 2015, 1:30-2:30pm/SCTR 10-146AB
Pluripotent Stem Cell Repair of Osteochondral Defects
Darryl D'Lima, MD, PhD
Associate Professor
Scripps Translational Science Institute

Tuesday, March 10, 2015, 1:30-2:30pm/BRB 251
Title: "Bone Health in Microgravity — Use It or Lose It"
Mary L. Bouxsein, PhD
Associate Professor of Orthopedic Surgery
Harvard Medical School

Tuesday, April 21, 2015, 1:30-2:30pm/TBD
Orthopedic Tissue Engineering by Epigenetic Landscaping
Andre J. van Wijnen, PhD
Professor of Orthopedic Surgery & Biochemistry & Molecular Biology
Mayo Clinic

Tuesday, May 12, 2015, 1:30-2:30pm/TBD
Cell and Extracellular Matrix Dynamics in Skeletal Tissues
Sarah L. Dallas, PhD
Professor of Oral and Craniofacial Sciences
University of Missouri



RELEASE THE PREVIOUS DATE OF NOVEMBER 11TH

Welcome to the 2014 New Members of Penn Center for Musculoskeletal Disorders

Full Members

Oren Friedman, M.D., Associate Professor of Clinical Otorhinolaryngology
Songtao Shi, D.D.S., Ph.D., Professor and Chair of Anatomy and Cell Biology, Dental School
Eric Granquist, D.M.D, M.D., Assistant Professor of Oral & Maxillofacial Surgery
Mark Kahn, M.D., Professor of Medicine
Michael Langham, Ph.D., Research Assistant Professor of Radiology
Ben Prosser, Ph.D., Assistant Professor of Physiology
Sogol Mostoufi-Moab, M.D., MSCE, Assistant Professor of Pediatrics
Marisa Bartolomei, Ph.D., Professor of Cell and Developmental Biology
Victoria Werth, M.D., Professor of Dermatology
Sami Khella, M.D., Professor and Chief of Neurology
Dan Dongeun Huh, Ph.D., Assistant Professor of Bioengineering
Andrew Tsourkas, Ph.D., Associate Professor of Bioengineering
David Peter Cormode, PhD, Assistant Professor of Radiology
Daeyeon Lee, Ph.D., Associate Professor of Chemical and Biomolecular Engineering
George Hajishengallis, D.D.S., Ph.D., Professor of Microbiology
Harvey Smith, M.D., Assistant Professor of Orthopaedic Surgery
John T. Farrar, M.D., MSCE, Ph.D., Associate Professor of Epidemiology, Neurology, and Anesthesia
Hongtao Zhang, Ph.D.,Research Assistant Professor of Pathology and Lab Medicine
Miltiadis H. Zgonis, M.D., Assistant Professor of Orthopaedic Surgery
Christopher T. Plastaras, M.D., Assistant Professor of Physical Medicine & Rehabilitation,
Russ Carstens, M.D., Associate Professor of Medicine and Genetics

Associate Members

Christina Mundy, Ph.D., Postdoctoral Fellow of Orthopaedic Surgery
Jinfei Xu, Ph.D, Research Associate of Physical Medicine & Rehabilitation
Meena Sharma, Ph.D., Lab Manager, Dept of Dermatology Univ. of Pennsylvania
Julianne Huegel Potocek, Ph.D., Postdoctoral Researcher, Department of Orthopaedic Surgery
Anna P. Malykhina, Ph.D., Assistant Professor, Division of Urology, Department of Surgery
Anthony S. Fargnoli, Graduate Student of Bioengineering
Sayantani Sinha, Ph.D., TRP in Pediatric Orthopaedics, Division Of Orthopaedic Surgery, CHOP
Mona Al Mukaddam, MD, MS, CCD, Assistant Professor of Endocrinology, Diabetes and Metabolism
Annamarie D. Horan, PhD, Director of Clinical Research in Orthopaedic Surgery

Affiliate Members

Lin Han, Ph.D., Assistant Professor of Biomedical Engineering, Drexel University, PA
Bin Wang, Ph.D., Assistant Professor for Translational Medicine, Thomas Jefferson University

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