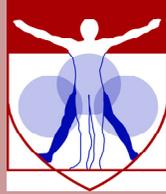
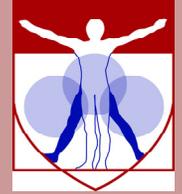


Spring 2020



Musculoskeletal Messenger



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University of Pennsylvania Penn Center for Musculoskeletal Disorders

PCMD and the COVID-19 Pandemic!

In these challenging times with the COVID-19 pandemic, please note that the PCMD is available for certain services. If you need a consultation or data analysis related to one of our research core facilities, we are available! Our core educational programs are still ongoing as well. If you have any questions requests, please contact us at pcmd@penmedicine.upenn.edu or visit our website <https://www.med.upenn.edu/pcmd/>.

From the PCMD family, stay safe and we wish you and your family well!

New Home for Penn Center for Musculoskeletal Disorders!

It is with great pleasure that we announce that the renovation of Stemmler Hall is complete and the Penn Center for Musculoskeletal Disorders is fully operational. All Cores (Administrative, Biomechanics, Histology, and Micro-CT Imaging) are all now located on the 3rd floor of Stemmler Hall in beautiful new space. Core space and capabilities have been expanded and are available for use. Please see our website at www.med.upenn.edu/pcmd for more information on the Center and its Cores.

A Look Back at the PCMD Annual Scientific Symposium – November 13, 2019

We are pleased that the 16th Annual Penn Center for Musculoskeletal Disorders Scientific Symposium was a great success. The symposium was held in the Smilow Rubinstein Auditorium on Wednesday, November 13, 2019

The keynote speaker, Anthony Ratcliffe, Ph.D. President and CEO of Synthasome, Inc. gave a well received lecture titled “Strategic approaches for the Translation of Concept to Product in Regenerative Medicine”. Symposium attendees enjoyed scientific presentations from new

Center members Drs. Veronique Lefebvre, Peter B. Tseng (1st place), Beth Noël, Shuying Yang While at the symposium, attendees had the opportunity to view more than 70 posters which were judged in four categories. The following poster presenters received prizes: Hannah Zlotnick(1stplace), Nikolas Di Caprio (2nd place) and Jonathan Gallaraga (3rd place) for their winning posters in the Biomechanics Category; Joseph Collins (1stplace), Anna Lia Sullivan (2nd place), Ana Peredo (3rd place) for their winning posters in the His-

tology Category; Wei-Ju Ashinsky (2nd place), Thomas Leahy (3rd place) for their winning posters in the MicroCT Category. Elisia Tichy (1st place), Claudia Loebel (2nd place) and Marco Angelozzi (3rd place) for their winning posters in the Miscellaneous Category.

Pictures from the Symposium are available on the website at www.med.upenn.edu/pcmd/past-pcmd-annual-symposia.html

Penn Center
for
Musculoskeletal Disorders
University of Pennsylvania
Stemmler Hall, 3rd floor
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@penmedicine.upenn.edu

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.

Research Update from PCMD Member

Nat Dymant, Ph.D.

Leveraging hedgehog signaling to improve adult tendon-to-bone repair

The coordinated events that give rise to zonal tendon/ligament insertions into bone (i.e., entheses) during development are well established. These mechanisms are less known in the adult because traditional reattachment surgeries of avulsed tendon to bone result in disorganized scar and do not re-establish a zonal enthuses. Instead of direct repair, injuries to ligaments are often repaired via reconstructions with tendon grafts (e.g., anterior cruciate ligament reconstruction). In this procedure, a tendon graft is used to replace the ligament and is anchored to adjacent bones within tunnels drilled through the bone marrow. During this tunnel integration process, zonal attachments are produced between the graft and adjacent bone. Therefore, ligament reconstructions can serve as a test platform to better understand the mechanisms that drive adult zonal tendon-to-bone repair.

The hedgehog signaling pathway is a key positive regulator of zonal tendon-to-bone insertion formation during growth and development. It promotes the formation of mineralized fibrocartilage, which is a key step in creating a zonal insertion. However, we do not know whether this pathway has a similar role in adult tendon-to-bone repair. Therefore, our lab reconstructs anterior cruciate ligaments in transgenic mouse models to better understand the key mechanisms that drive zonal tendon-to-bone formation. Our current studies aim to define the origin of cells that participate in the formation of the zonal attachments and then target hedgehog signaling in these cells to modulate the healing process.

We found that quiescent mesenchymal progenitor cells within the bone marrow that express alpha smooth muscle actin (aSMA) are the primary contributors to tendon-to-bone repair (Fig. 1B-C). These cells activate in response to the bone tunnel injury, expand, and migrate toward the tendon graft surface. They then infiltrate the tendon graft and assemble collagen fibers that anchor to the adjacent bone (Fig. 1B). At later stages, these cells differentiate within the attachments and produce mineralized fibrocartilage (MFC in Fig. 1C), resulting in a zonal insertion site similar to normal enthesis development. We then targeted these cells both genetically and pharmacologically to stimulate the Hh pathway and found that stimulating the pathway leads to improved tunnel integration (Fig. 2A), as measured by MFC formation within the tunnels, and tunnel pullout strength (Fig. 2B). Therefore, Hh signaling is a positive regulator of tendon-to-bone integration and future studies aim to develop therapies to leverage this pathway to improve repair outcomes.

Acknowledgement: Studies performed by Mr. Tim Kamalitinov and Dr. Keitaro Fujino. Funding provided by PCMD pilot grant (P30 ARO69619), NIH R00 ARO67283, and start up funds from Orthopaedic Surgery Department at Penn

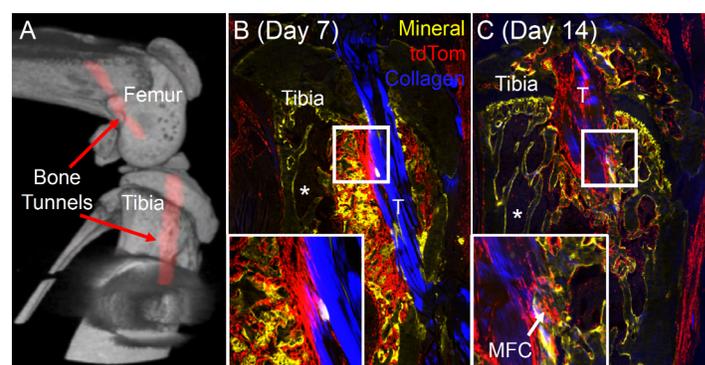


Fig. 1: Formation of zonal tendon-to-bone attachments following ACL reconstruction. A. Location bone tunnels (red) in the femur and tibia following reconstruction procedure. B. aSMA-labeled progenitor cells (red) from bone marrow infiltrate tendon graft (T, collagen in blue) to initiate attachments at day 7 post-surgery. C. Cells produce mineralized fibrocartilage (MFC) as they differentiate within attachments, yielding a zonal attachment with mineralized tidemark (yellow) separating unmineralized and mineralized zones of the attachment. aSMA progenitors do not activate in un-injured regions of the bone marrow (*).

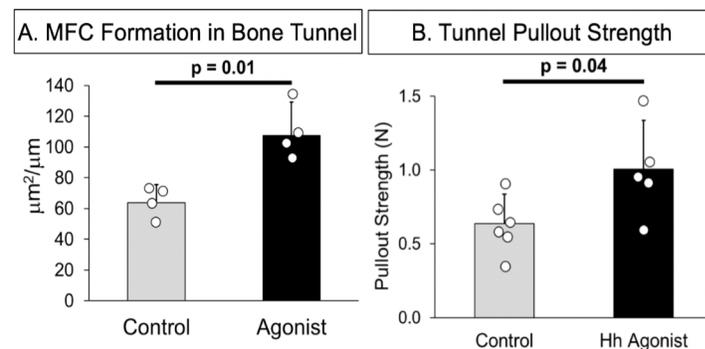


Fig. 2: Stimulating Hh signaling improves tunnel integration. Daily delivery of Hh agonist improved mineralized fibrocartilage (MFC) formation (A) and pullout strength (B).

In the News!

2020 PCMD Annual Symposium - November 18, 2020 SAVE THE DATE



Preparations are underway for the 17th Annual Penn Center for Musculoskeletal Disorders Scientific Symposium in the Smilow Rubinstein Auditorium and Commons to be held on Wednesday, November 18, 2020.

The keynote speaker will be Richard L. Lieber, Ph.D., Chief Scientific Officer and Senior Vice President, Shirley Ryan Ability Lab, Northwestern University. 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.

2020 PCMD Pilot and Feasibility Grant Recipients Announced

The Penn Center for Musculoskeletal Disorders Pilot and Feasibility Grant Program has awarded three investigators with one year of funding for their pilot grant projects with a start date of *July 1, 2020*.

Patrick Seale, Ph.D. will receive funding for his grant titled “Fat and synovial tissue development and disease remodeling in joints”

Kyu Sang Joeng, Ph.D. will receive funding for his grant titled “The function of mTORC1 signaling in the regulation of the provisional matrix during tendon healing”

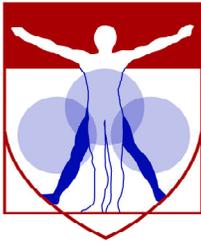
Josh R. Baxter, Ph.D. will receive funding for his grant titled “Stimulating muscle-tendon healing by prescribing mechanical loading.”

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@pennteam.upenn.edu



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University of Pennsylvania
3rd Stemmler Hall, 3450 Hamilton Walk
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U.S. Department of Health
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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 P30AR069619 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.

PCMD Visiting Professorship Series

Tuesday, September 17, 2019 1:30-2:30pm/CRB Austrian Auditorium
Towards a better understanding of Musculoskeletal development and arthritis pathogenesis: A Systems approach **Hiroshi Asahara, MD, PhD**, Professor of MEM Department of Molecular Medicine, Scripps Research, California Campus

Tuesday, October 15, 2019 1:30-2:30pm/CRB Austrian Auditorium
Osteocytes and connexin channels in mechanotransduction and hormonal response in bone. **Jean Jiang, PhD** Professor and Zachry Distinguished University Chair; Department of Biochemistry and Structural Biology, UT Health San Antonio

Wednesday, November 13, 2019, Annual Scientific Symposium
Smilow Rubinstein Auditorium
830am-5:30pm; Keynote Speaker:
Anthony Ratcliffe, PhD President and CEO of Synthasome, Inc.

Tuesday, December 10, 2019, 1:30-2:30pm/CRB Austrian Auditorium
Osteoarthritis: Thinking Beyond the Cartilage. **Kyle Allen, PhD** Associate Professor, Associate Chair for UG Studies, ABET Coordinator J. Crayton Pruitt Family, Biomedical Engineering, University of Florida

Friday, January 21, 2020 1:30pm – 1:30pm, CRB Austrian Auditorium
Imaging across scales: visualizing tissue to subcellular mechanobiology in cartilage health and disease. **Corey Neu, PhD**, Donnelly Family Endowed Associate Professor, Mechanical Engineering, University of Colorado, Boulder

Tuesday, February 25, 2020, 1:30pm – 2:30pm, CRB Austrian Auditorium
Microtubules, Osteocyte Mechanotransduction, and the Surprising Regulation of Sclerostin". **Joseph Stains, PhD**, Associate Professor of Mechanical Engineering, Iterim Director of Musculoskeletal Research, University of Maryland

Tuesday, March 17, 2020, 1:30pm – 2:30pm, CRB Austrian Auditorium
Cancelled Rescheduled 12/8/2020
Skeletal Dysplasia in Neurofibromatosis Type 1. **Florent Elefteriou, PhD**, Associate Professor of Orthopaedic Surgery and Molecular and Human Genetics; Associate Director for the Center for Skeletal Medicine and Biology, Baylor University

Tuesday, April 14, 2020, 1:30pm – 2:30pm, CRB Austrian Auditorium
Cancelled Rescheduled 9/8/2020
Regenerative Rehabilitation: Applied biophysics meets stem cell therapeutics. **Fabrisia Ambrosio, PhD, MPT**, Associate Professor of Physical Medicine &

Rehabilitation; Director of Rehabilitation for UPMC International, University of Pittsburgh.

Tuesday, May 5, 2020, 1:30pm – 2:30pm, CRB Austrian Auditorium
Cancelled Rescheduled 10/20/2020
Gauging Tendon Mechanics by Observing Tissue Dynamics. **Darryl Thelen, PhD**, Professor, Mechanical and Biomedical Engineering; Affiliate Professor: Orthopedics and Rehabilitation, University of Wisconsin-Madison

Tuesday, June 2, 2020, 1:30pm – 2:30pm, CRB Austrian Auditorium
Cancelled Rescheduled 01/12/2021
Biomanufacturing, Biomaterials and Biomechanics for Improved Treatment of Volumetric Muscle Loss Injuries **George Christ, PhD**, Professor of Biomedical Engineering and Orthopaedic Surgery; Mary Muilenburg Stamp Professor of Orthopaedic Research; Director of Basic and Translational Research in Orthopaedic Surgery; University of Virginia