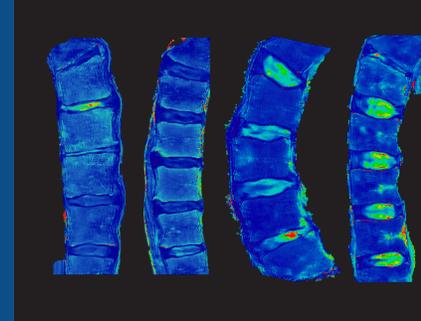
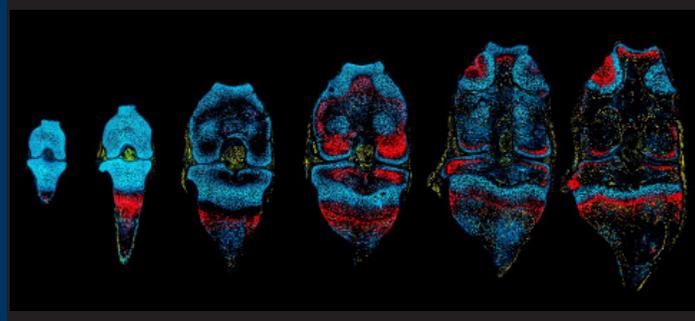
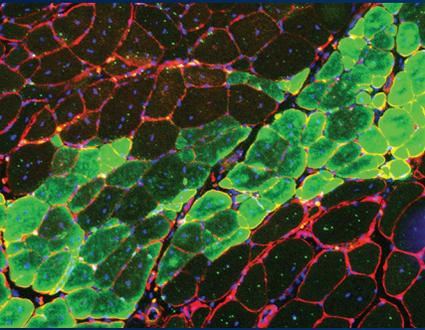


MCKAY
ORTHOPAEDIC
RESEARCH
LABORATORY



Penn Medicine

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WELCOME

MESSAGE FROM LEADERSHIP



Robert L. Mauck, PhD

Mary Black Ralston Professor for Education and Research in Orthopaedic Surgery
Professor of Bioengineering
Director, McKay Orthopaedic Research Laboratory



Louis J. Soslowsky, PhD

Fairhill Professor of Orthopaedic Surgery
Professor of Bioengineering
Associate Dean for Research Integration
Vice Chair, Research, Orthopaedic Surgery
Founding Director, Penn Center for Musculoskeletal Disorders

Welcome to the McKay Orthopaedic Research Laboratory at the University of Pennsylvania

The impact of musculoskeletal-related conditions is hard to overstate: Accounting for nearly \$1 trillion in annual costs, musculoskeletal injuries represent a critical health concern—to say nothing of the indirect impact of a disabling or debilitating injury, such as an individual no longer being able to work, or requiring additional lifelong care. These injuries must be better understood and better treated.

In 1960, the University of Pennsylvania established a program in orthopaedic research. In 1979, the McKay Orthopaedic Research Laboratory was created to house all of our orthopaedic research laboratories in one location. Currently, the McKay Lab is a thriving, multidisciplinary facility that occupies more than 22,000 square feet of space on the Perelman School of Medicine campus. Our multifaceted research programs involve the participation of more than 120 research personnel from 16 distinct laboratories.

Research expenditures in McKay total more than \$15 million per annum, supported largely through extramural funding including grants from the National Institutes of Health, Veteran's Administration, other governmental agencies, private foundations, and industry. We are consistently ranked in the top 5 among Orthopaedic Departments nationally in terms of NIH funding. Our overall mission is to conduct high quality fundamental and translational research and to train the next generation of leaders in our field.

Moreover, the McKay Lab serves as the focal point for the NIH-supported Penn Center for Musculoskeletal Disorders, a university-wide Center that provides resources and a forum for scientific exchange through annual symposia, a year-long seminar series, a pilot grant program and other activities.

We appreciate your interest in our programs and hope you enjoy learning about our efforts to advance orthopaedic care.

Sincerely,

Robert L. Mauck, PhD *Louis J. Soslowsky, PhD*

THE BOERCKEL LAB

ENGINEERING DEVELOPMENT THROUGH MECHANOBIOLOGY

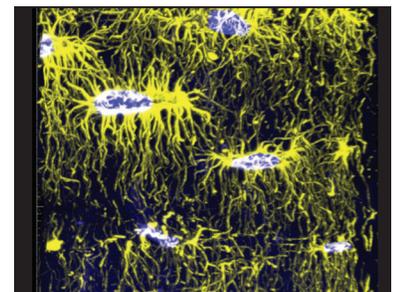
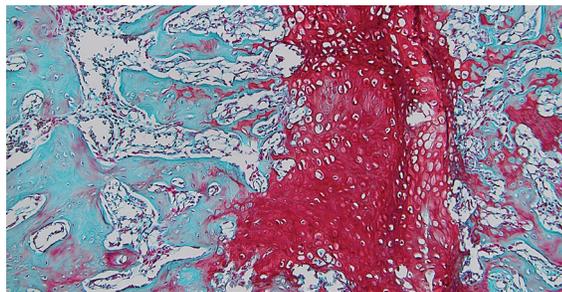
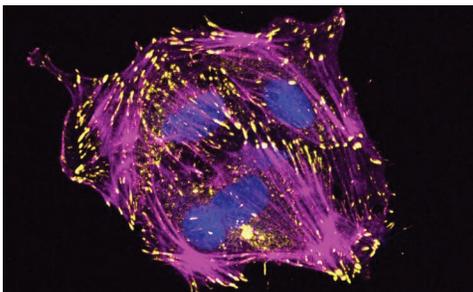


Joel D. Boerckel, PhD
Assistant Professor
Department of Orthopaedic Surgery

Our philosophy is that, if one wants to build a tissue, one should look to how the embryo builds that tissue. Thus the lab seeks to understand the mechanisms by which mechanical cues direct embryonic development toward the goal of creating **new mechanotherapeutic tissue engineering strategies that recapitulate fetal development for regeneration.**

Our work currently focuses on defining the roles of the mechanosensitive transcriptional regulators in mechanotransduction (the conversion of mechanical actions into electrochemical activity), morphogenesis (the development of shapes and structures), and growth, adaptation, and repair in general. In addition, we seek to develop **new tissue engineering strategies for challenging injuries.** We use genetic mouse models to study development and disease, mouse and rat models to study repair and regeneration, and a combination of engineered matrices and bioreactors to study mechanisms of cell mechanotransduction.

We moved our lab to Penn in 2017 in large part because of the remarkable collaborative and collegial environment at McKay Orthopaedic Research Laboratory. Supported by our amazing collaborators and the resources and networks provided by the Penn Center for Musculoskeletal Disorders and the Center for Engineering Mechanobiology, we could not ask for a better place to chase our questions.



LAB HIGHLIGHTS

- **We discovered a mechanotransductive feedback mechanism** that regulates cell motility. In 2019, our paper on this breakthrough was selected as one of the top 10 most influential *Journal of Cell Biology* papers of the year.
- **We solved an important controversy in the field**, revealing that two mechanosensitive transcriptional regulators, YAP and TAZ, exert both compensatory and distinct roles in bone physiology, which regulates bone development.
- Using these observations, **we have developed a new mechanotherapeutic approach to recapitulate development for bone tissue engineering.**
- In two exciting new directions, we are working to **understand how mechanical forces exerted by fetal movement in the womb influence the development of the skeleton** and to understand how mechanotransductive feedback regulates cytoskeletal equilibrium in space and time.
- **Our work has implications for several different classes of clinical problems.** First, we are interested in developing new tissue engineering approaches for the regeneration of large bone defects caused by traumatic injury or tumor resection. We are also interested in developmental and acquired bone diseases, and we hope our work can lead to new understanding of and therapies for the brittle bone disease, osteogenesis imperfecta.

THE DODGE LAB

MOVING MUSCULOSKELETAL RESEARCH INTO CLINICAL PRACTICE



George R. Dodge, PhD

Research Associate Professor
Department of Orthopaedic Surgery

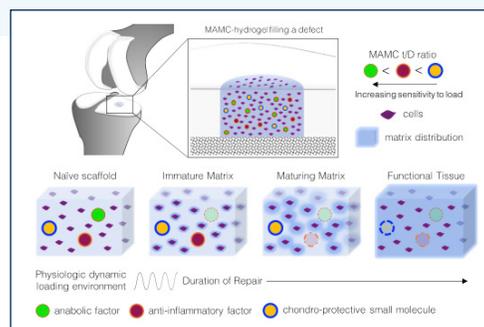
Our lab addresses the translational area of orthopaedic tissue regeneration and focuses on degenerative joint diseases. Over the years, we have deployed state-of-the-art technologies to understand and characterize relevant tissues such as cartilage, bone, and synovium. We have completed seminal work in **a broad range of areas including tissue engineering, novel cartilage imaging, new drug delivery systems, soluble cartilage biomarkers, and the role of nutraceuticals in joint health.**

Alongside clinical colleagues—especially with Penn orthopaedic surgeons John Kelly and Harvey Smith—our research mission has expanded into clinical trials with the firm belief that basic science research and ideas must find their way into practical, clinically significant clinical trials and commercialization to be relevant. To that end, **we have created partnerships with Penn surgeon-scientists in both the Departments of Orthopaedics and Otorhinolaryngology and initiated research and clinical trials that have already impacted clinical practice.**

Penn has a unique collaborative infrastructure and innovation engine that allows new ideas to be explored and commercialized. There are other places this work could happen, but not this rapidly. Together with the Penn Departments of Orthopaedic Surgery and Chemical and Biomolecular Engineering we have formed a new company, Mechano-Therapeutics, LLC. This new enterprise follows up on our recent discovery of mechanically activated microcapsules for drug delivery in joints and tissues. We have begun to commercialize this groundbreaking drug delivery platform through the Penn Center for Innovation.

LAB HIGHLIGHTS

- We focus primarily on what happens during and after joint injury. Specifically, we're looking at impact injuries—and we've designed a method to do that in the lab. As a result, we can generate injuries in a repetitive fashion and more quickly understand the biological processes involved. Our approach means **we can learn how to stop cells from dying or stop or slow inflammation that would lead to joint degeneration.** We have identified bioactive compounds and are developing them as therapeutics for joint injuries and in osteoarthritis.
- Working with fellow McKay Laboratory researcher **Robert L. Mauck, PhD, and Daeyeon Lee, PhD, from Chemical and Biomolecular Engineering**, our lab has also developed a **novel drug delivery platform: microcapsules that can be loaded with anti-inflammatories, antibacterial agents, or other useful compounds and inserted directly into the joint.** These capsules have characteristics no other laboratory has devised. They are designed to only release their contents in the event of mechanical perturbation—meaning if they are loaded under certain physiological pressures.



Mechano-activated microcapsules with varying physical attributes can be tuned to program release in maturing repair tissue exposed to dynamic loading within the joint to potentially release therapeutics and promote tissue regeneration.
DOI: 10.1002/adfm.201807909.

- The potential exists for placing these microcapsules in the joints of healthy individuals as safeguards against injury. However, we believe the more immediate use would be for the prevention of post-surgical infection—an enormous problem in the field of orthopaedic surgery. **Added to a patient's joint at the time of surgery, microcapsules could locally deliver various therapeutics and—their release could be tuned over varying rehabilitation stages.** Through our new company MechanoTherapeutics, LLC, we look forward to moving this innovative drug delivery system into new and exciting translational medicine approaches to tissue regeneration.

THE DYMENT LAB

FROM CELL LINEAGE TO ENHANCED THERAPIES



Nathaniel A. Dymant, PhD

Assistant Professor
Department of Orthopaedic Surgery

Our primary goal is to better understand the genetic, cellular, and mechanical mechanisms that regulate normal development, disease, and repair of tissues in the joint.

Our lab focuses on:

1. Identifying the resident stem/progenitor cell populations that contribute to normal growth, healing, and repair;
2. Determining the mechanical and biological cues that regulate cell fate;
3. Ascertaining the phenotypical markers that define the stages of differentiation from early stem/progenitors to mature cell types.

We work with our clinician colleagues and collaborators to achieve these goals. The new knowledge gained from our studies will **guide future therapeutic strategies** and provide success criteria to assess efficacy moving forward.

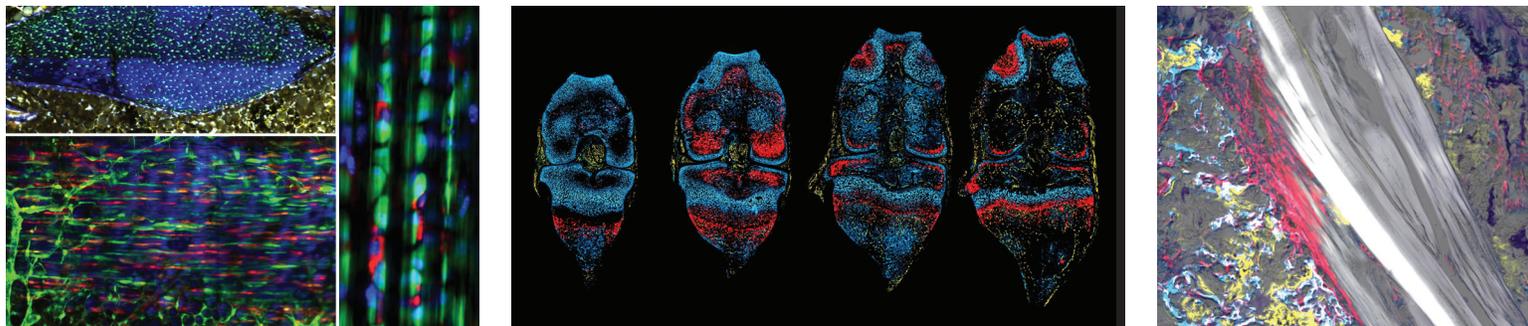


Figure 1 - Tendons from different fluorescent reporter mouse lines demonstrating the heterogeneity of cell populations within this tissue. Figure 2 - Spatiotemporal changes in collagen gene expression (type I: yellow, type II: blue, type X: red) during growth of the knee joint. Figure 3 - Tendon-to-bone integration following anterior cruciate ligament (ACL) reconstruction initiated by progenitor cells (red) originating from the adjacent bone marrow, a process regulated by the hedgehog signaling pathway.

LAB HIGHLIGHTS

- We have identified a new therapeutic target that could be harnessed to improve tendon-to-bone repair. Tendon and ligament injuries account for approximately 1/3 of all musculoskeletal injuries and often require surgical repairs where the tendon is reattached to bone. These repairs have undesirable outcomes in some cases, resulting in significant pain and loss of function. We have demonstrated that a key signaling pathway (Hedgehog pathway) that regulates tendon-to-bone integration during growth and development also plays a similar role during repair in the adult and can be targeted therapeutically to improve repair outcomes.
- We are establishing markers that define specific stages of cell differentiation within tendons/ligaments and other tissues in the joint (e.g., the meniscus). We also are identifying critical biological and mechanical stimuli that regulate differentiation. Interestingly, we are finding that resident macrophages in these tissues may communicate with the resident mesenchymal cells to regulate the development, maintenance, and healing of these tissues.

THE GULLBRAND LAB

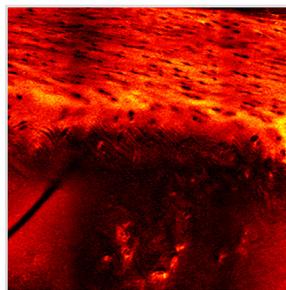
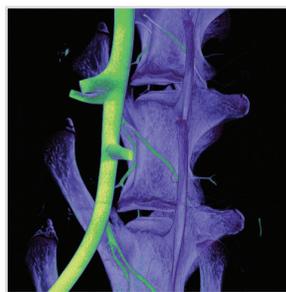
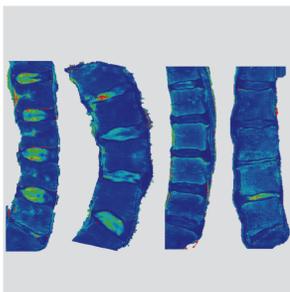
UNDERSTANDING SPINAL DEGENERATION TO INFORM REGENERATIVE APPROACHES

Our lab studies how **aberrant structure-function relationships across anatomical regions of the spine contribute to the initiation and progression of degenerative disc disease**. To do so, we employ a suite of biomechanical and bioimaging tools to probe spinal tissues such as the vertebral bone, cartilage endplate, and spinal facet joints across length scales in both model systems of disease as well as human tissue.

Our group is also focused on **utilizing this knowledge to inform the optimization and development of tissue-engineering-based approaches for disc regeneration**. Central to this work, in collaboration with **Harvey Smith, MD**, and **Robert Mauck, PhD**, is the translation of a whole, tissue engineered intervertebral disc replacement towards clinical utilization in human patients.



Sarah Gullbrand, PhD
Research Assistant Professor
Department of Orthopaedic Surgery



LAB HIGHLIGHTS

- Investigating the **contribution of vertebral endplate remodeling and altered disc nutrition on the progression of disc degeneration**.
- Utilizing quantitative magnetic resonance imaging methods to understand how **altered disc nutrition may predict patients' response to non-operative treatments for back pain**.
- Probing **associations between facet joint osteoarthritis and disc degeneration**.
- **Optimizing the integration of a whole tissue-engineered intervertebral disc replacement** via biomaterial modifications to accelerate bone and vascular ingrowth into the construct's endplate interface.

Photo captions clockwise:

MicroFil enhanced μ CT of the rabbit lumbar spine

Second harmonic generation imaging of organized collagen in the human cartilage endplate

A degenerative human lumbar intervertebral disc

Lumbar spine MRIs from human donors of various ages

THE HAST LAB

ENHANCING REPAIR STRATEGIES WITH MECHANOTRANSDUCTION



Michael Hast, PhD

Research Assistant Professor
Department of Orthopaedic Surgery

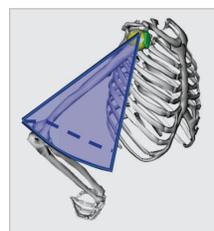
Our laboratory **focuses on bone fracture reconstruction and investigates the interplay between mechanical and biological variables that lead to improved healing.** To perform this research, we use a combination of in vitro, in vivo, and in silico modeling techniques. The major goal of our research is to **develop surgical techniques and novel implants that leverage the principles of mechanotransduction to accelerate bone formation.** Our experiments have spanned a wide variety of orthopaedic injuries, with special attention paid to open reduction internal fixation repair strategies.

Our research is focused on fragility fractures caused by osteoporosis: a metabolic bone disorder which primarily affects the elderly, causes bone weakness, and inhibits robust healing responses. **Osteoporosis represents an emerging healthcare crisis, as the elderly will comprise 20% of the U.S. population by 2030.** Using emergent additive manufacturing technologies, **we are currently investigating how resorbable, patient-specific implants may lead to improvements in congruency of bone-implant mechanical properties and desired temporal increases in loading across the bone callus.**

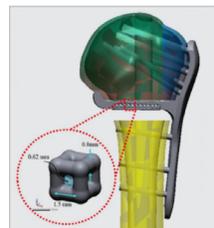
Our experiments are rooted in clinical questions that come from collaborative groups of engineers, biologists, and surgeons working together. As a team, **we are excited to continue challenging the clinical obstacles that osteoporosis presents.** Together, we are confident that our research endeavors hold great promise to fundamentally alter the treatment paradigms associated with fracture fixation.

LAB HIGHLIGHTS

- We have published an extensive collection of mechanical testing studies, which demonstrate the importance of implant design and surgical techniques. For example, we have shown that both surgical positioning and augmentation of proximal humerus locking plates can have direct implications with respect to fixation strength and fatigue life.
- Many of our experiments utilize in vivo 3-D motion capture, in vitro benchtop tests, and in silico musculoskeletal models to make estimates of post-operative implant performance. Results from these investigations have provided guidance for surgical management of soft tissue injuries, such as rotator cuff repairs, as well as bone fracture reconstructions.
- Additive manufacturing has become a major interest for the Lab, as there exists an urgent need for optimization of trauma implant designs in the orthopaedic industry. Most recently, we have begun to explore the creation of 3D printed bioresorbable implants. This research will provide new insights into the role of mechanotransduction while establishing a research framework for developing and optimizing implant designs that will improve patient outcomes.



Computational models provide estimates of post-operative implant performance during activities of daily living.



A computational rendering of a novel 3D printed proximal humerus implant that was biomechanically tested in the Hast lab.

THE HEO LAB

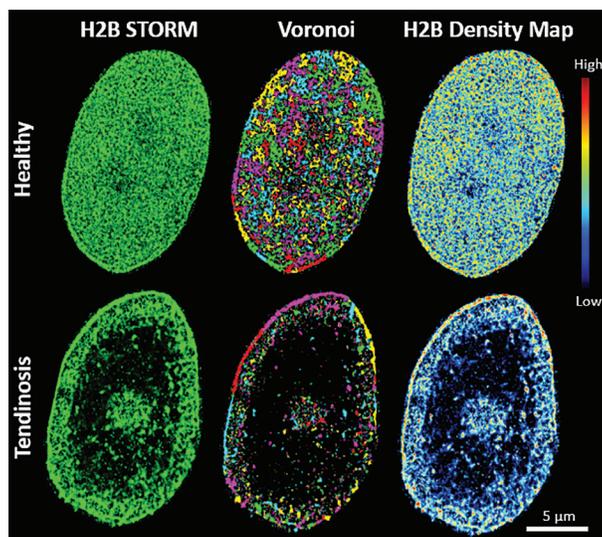
ENGINEERING THROUGH MECHANOBIOLOGY

Our lab focuses on musculoskeletal cell and tissue engineering to develop new therapeutic strategies for the **repair and regeneration of the tendon, ligament and knee meniscus** and other dense fibrous tissues. Our research team explores the feedback between the biophysical environment and cell biology in the context of tissue remodeling with degeneration, repair, and development of musculoskeletal tissues. We are also interested in developing innovative methods to enable **precise control of the cellular microenvironment**, and to address fundamental questions about how biophysical cues regulate cellular behaviors including stem cell differentiation. In addition, our team aims to expand our findings and knowledge **to engineer complex functional tissue constructs** for regenerative medicine applications.



Su Chin Heo, PhD

Research Assistant Professor
Department of Orthopaedic Surgery



Histone-H2B super-resolution stochastic optical reconstruction microscope (STORM) image, and its Voronoi tessellation and density map in human tendon cell nuclei.

LAB HIGHLIGHTS

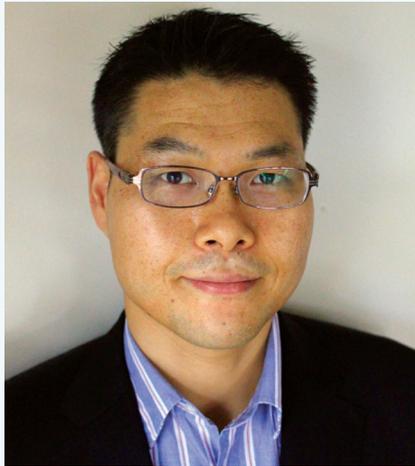
We are now focused on investigating:

1. How chemo-mechanical cues regulate stem cell differentiation with advanced bioreactor and biomaterial systems;
2. How the development or degeneration of fibrous connective tissues alters the spatial genome organization at the nanoscale using a super-resolution microscope; and
3. Multiphasic tissue constructs for regenerative medicine.

We expect that our research programs will enable the development of tissue repair and regeneration tailored for fibrous connective tissues and generate **new therapeutic strategies of musculoskeletal disorders.**

THE JOENG LAB

WHERE MOUSE GENETICS MEETS ORTHOPAEDIC SURGERY



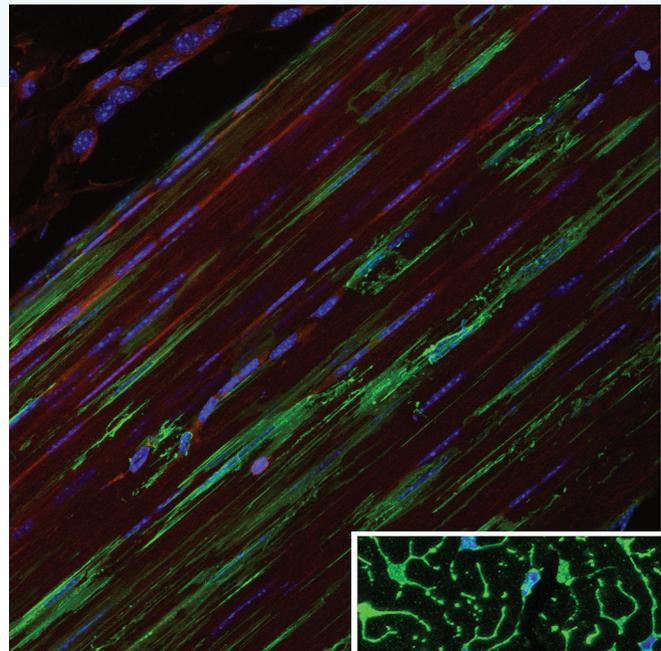
Kyu Sang Joeng, PhD

Assistant Professor
Department of Orthopaedic Surgery

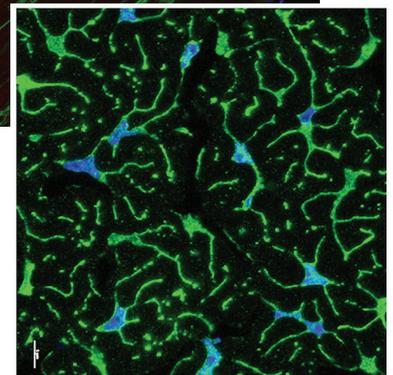
Our laboratory explores the signaling pathways regulating development and homeostasis of the musculoskeletal system. We use mouse genetic models to study the function of ER stress, mTORC1, and Wnt signaling in bone, cartilage, and tendon. We are also interested in **the involvement of these signaling pathways in injury repair**. We expect that our research programs will not only contribute to the understanding of the musculoskeletal system, but also give insight into the advancement of regenerative medicine.

LAB HIGHLIGHTS

- We have demonstrated that developmental signaling pathways are involved in injury repair for musculoskeletal tissue. **We combined several surgery models with mouse genetic models** to investigate the function of molecular signaling pathways in the injury repair mechanism.
- Furthermore, we studied the contribution of abnormal signaling pathways to the pathogenic mechanism of musculoskeletal diseases such as **osteoarthritis, osteoporosis, and tendinopathy**.
- We discovered that the mTORC1 signaling is a critical regulator for tendon development and that activation of mTORC1 can cause a tendinopathy-like phenotype. This finding suggests that **mTORC1 signaling could be one of the major signaling pathways in regulation of tendon healing**, and abnormal activation of mTORC1 can be a pathogenic mechanism of tendinopathy.



High-resolution confocal images of tendon and tenocytes.



THE KAPLAN LAB

NOT ONLY SUPPORTING THE DREAM OF A CURE FOR FOP & POH;
HELPING CREATE IT



Frederick S. Kaplan, MD

Isaac and Rose Nassau Professor of Orthopaedic
Molecular Medicine in Orthopaedic Surgery

The Center for Research in FOP and Related Disorders, under the direction of **Frederick S. Kaplan, MD**, and **Eileen M. Shore, PhD**, is the **world's premier research effort** in two rare and disabling genetic disorders of heterotopic (extraskelatal) bone formation: fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH). Together, we have identified the genetic and molecular causes of FOP & POH. Further, we have used that knowledge to spearhead worldwide research efforts to develop therapies that will transform the care — and the lives — of individuals with those disorders.

LAB HIGHLIGHTS

- **Over the past 25 years, we have moved from the wastelands of little-understood rare diseases to the watershed of clinical trials.** Through the work of our lab, Penn Medicine has led the way in generating breakthrough discoveries about FOP on a genetic and molecular level.
- **After 15 years of work to determine the roots of FOP, our lab was able to announce in 2006 that we discovered its cause: a mutation in a bone morphogenetic protein receptor gene, ACVR1/ALK2.** This led to waves of new investigations, now more directly focused on the molecular and cellular factors behind new bone formation, the cells involved in the process, and the new treatments we can glean from that information.
- **Our laboratory has dramatically reshaped our fundamental understanding of tissue formation, and how those tissues heal.** It's work that has the potential to translate into discoveries across a variety of other disorders.



THE LIU LAB

IMPROVING BONE DISEASE DIAGNOSIS AND TREATMENT STRATEGIES



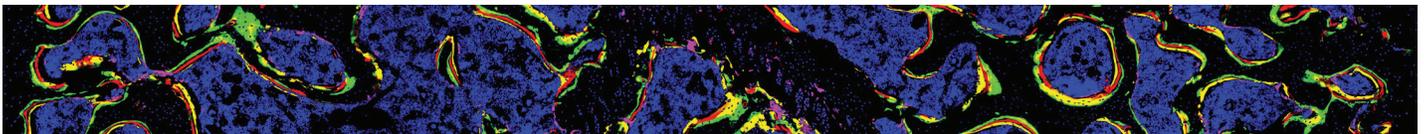
Xiaowei Sherry Liu, PhD

Associate Professor
Department of Orthopaedic Surgery

Our research program focuses on the biological processes within bone and on how they influence bone material, microstructural, and biomechanical properties with aging, disease, and therapies.

Our research team utilizes state-of-the-art imaging, image analysis, and mechanical modeling techniques to explore the mechanisms affecting the mechanical functions of the skeleton at different length scales in both animal models and clinical investigations. Our ultimate goal is to translate new technologies and research findings from bench to bedside to improve the diagnostic and therapeutic strategies for osteoporosis and other serious bone diseases that affect the growing senior population.

Penn's culture encourages researchers with diverse backgrounds to collaborate and cultivate the most innovative ideas. We can ask research questions outside of our expertise because we are confident we can find a colleague with the knowledge we need who is eager to work with us.



Fluorochrome mineralizing labels of active bone formation sites in a post-weaning rat.

LAB HIGHLIGHTS

- Many factors influence a woman's risk of developing post-menopausal osteoporosis. Reproduction, which utilizes the maternal skeleton as a reservoir of mineral for the developing fetus and nursing newborn, may impact the development of post-menopausal osteoporosis. By using a rat model, we demonstrated that a **history of reproduction and lactation prior to menopause resulted in structural adaptations in the maternal skeleton that led to a slower rate of bone loss as compared to virgin rats.** This discovery provides **new insight into osteoporosis prevention and treatment** for post-menopausal women by considering their reproductive histories.
- We are further investigating the long-term effects of reproduction on the bone's response to mechanical loading **to elucidate how exercise can be utilized to maintain bone health** after menopause in women with and without a history of reproduction.

THE MAUCK LABORATORY

TURNING BASIC SCIENCE INTO CLINICAL TRANSLATION

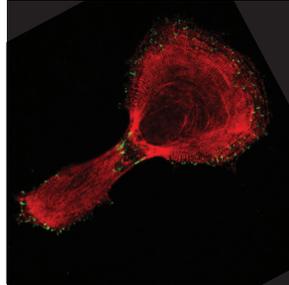
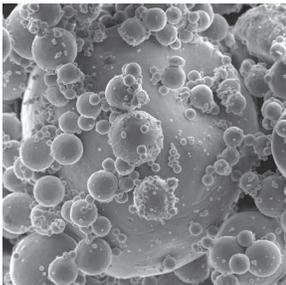
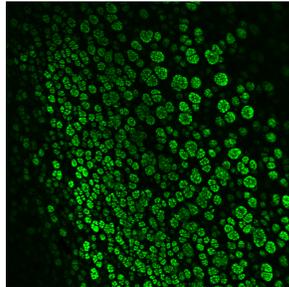
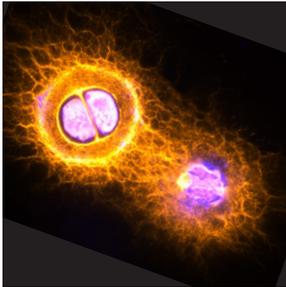


Robert L. Mauck, PhD

Mary Black Ralston Professor for Education and Research in Orthopaedic Surgery
Professor of Bioengineering
Director, McKay Orthopaedic Research Laboratory

Our lab develops **novel tissue engineering and regenerative medicine (TERM) approaches for the restoration of musculoskeletal soft tissues**, with a particular interest in articular cartilage, the knee meniscus and the intervertebral disc. Our team uses rigorous mechanical and molecular analyses to characterize native tissue structure and function and employs this information to enhance the functional properties of engineered constructs through focused technology development. This work employs adult mesenchymal stem cells, custom mechanobiologic culture conditions, and the development of novel cell scaffolding technologies.

Our work also explores **progenitor cell function, differentiation, and efficacy across multiple length scales**, from investigations of subcellular biophysical properties, heterogeneity, and mechanobiology to translation of stem cell-based engineered constructs in large animal models of tissue repair and regeneration. Research team members work both within and across these domains to advance musculoskeletal tissue regeneration.



LAB HIGHLIGHTS

- Investigating how the **R206H mutation in the ACVR1/ALK2 receptor alters progenitor cell mechanobiology** resulting in aberrant differentiation and matrix “read/write” errors during muscle repair that ultimately culminate in an impaired muscle healing response and the formation of disabling heterotopic bone in fibrodysplasia ossificans progressiva.
- Using a series of novel mouse models and micro-scale experimental techniques to **investigate the origin and track the fate and function of cells that comprise the mature meniscus**.
- Developing novel photo-crosslinkable nanofibrous composites with varying mechanics and degradation profiles to deliver agents that influence cell mechanics, so as to **expedite the repair of the meniscus and other dense fiber-reinforced tissues**.
- **Optimizing the use of customized hyaluronic acid hydrogels** to control in vitro and in vivo cartilage formation using adult human mesenchymal stem cells.
- **Developing a hydrogel-based therapeutic for restoration of disc function in early stages disc degeneration**. This project involves the development of a large animal model of disc degeneration, followed by injection of stem cells using a hydrogel carrier.

THE MOURKIOTI LAB

BOOSTING THE REGENERATIVE POTENTIAL OF SKELETAL AND HEART MUSCLES TO FIGHT INJURY, DISEASE, AND AGING



Foteini Mourkioti, PhD

Assistant Professor
Department of Orthopaedic Surgery

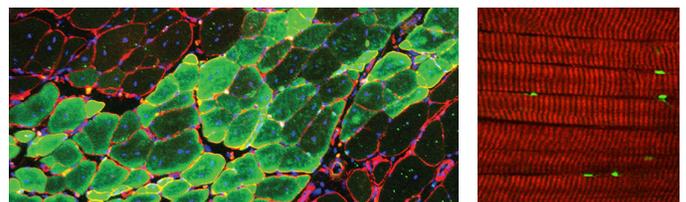
Our lab focuses on regenerative biology and explores the processes that restore damaged or diseased muscle with ultra-modern mouse genetics, stem cell biology, and bioengineering approaches. A major goal of our research is to identify and exploit **interventions that mitigate telomere length changes and other unfavorable gene alterations**. We have **invented many innovative animal models and imaging techniques** that reveal previously unknown processes of disease and regeneration.

Our research is focused on Duchenne Muscular Dystrophy (DMD), the most common inherited form of myopathy: neuromuscular disorders that cause muscle weakness due to dysfunction of muscle fiber. DMD affects both skeletal and cardiac muscles; repeated cycles of muscle damage and repair lead to stem cell dysfunction in skeletal muscles. Using technologies we invented, we demonstrated that telomere shortening is a distinct feature of dystrophic muscle stem cells in both mice and DMD patients, starting at a very young age. We also showed that excessive DNA damage to telomeres results in stem cell exhaustion and severe skeletal muscle defects, similar to that seen in human DMD.

Our discoveries have come through a multidisciplinary approach that includes genetics, mechanobiology, telomere biology, and stem cell biology. Working with a dynamic team of trainees, we are very excited to continue expanding this impactful work to **overcome existing challenges in mammalian cell regeneration** and **advance the development of therapeutics** in patients afflicted by muscle injuries.

LAB HIGHLIGHTS

- The major cause of death in DMD is cardiac failure. We have demonstrated the importance of telomeres in human heart muscle to this disease. With **our new measurement technique**, we discovered shortened telomeres only in heart muscle cells of DMD patients. Furthermore, we provided the **first evidence of a direct correlation between this telomere shortening and human heart failure**. We also demonstrated that telomere shortening is a **previously unrecognized signature** of cardiac diseases. The cardiac mechanisms in these studies are also relevant to the telomeric mechanisms acting in other muscle diseases, and pave the way for enhancing future therapeutic interventions.
- Another major goal is understanding the role of muscle stem cells under injury conditions. We developed a new mouse model that greatly improves the visualization of muscle stem cells. **It is in high demand**, and we are proud to be able to distribute it among the muscle research community.
- With this new model, our lab became the first to visualize the dynamic behavior of muscle stem cells in live animals. **We identified unique and novel properties that had never been reported previously**. We found that these properties are altered during both normal aging and chronic injury conditions. We also identified a novel signaling pathway that controls these properties. Understanding how muscle stem cells use these properties to respond to injuries can provide **major insights into the biology of tissue restoration** that may help us to boost muscle regenerative abilities after injuries and/or aging.



Left image: Muscle stem cells form new myofibers (green) in dystrophic muscles, 3 weeks after transplantation.

Right Image: Imaging of intact skeletal muscles in vivo using 2-photon microscopy show muscle stem cells in green and sarcomeres in red.

THE QIN LAB

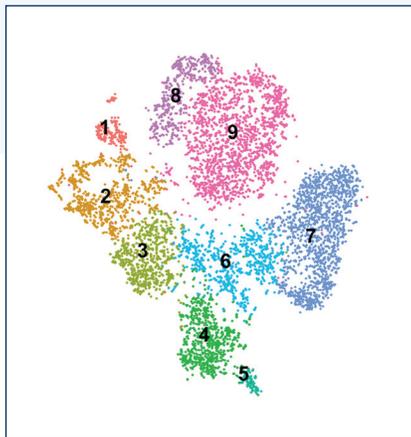
SKELETAL CELL FUNCTION AND FUTURE CLINICAL APPLICATIONS

The Qin lab studies the **cellular and molecular basis for skeletal development, homeostasis, aging, and diseases**. Osteoporosis and osteoarthritis are two common skeletal diseases that cause huge economic and social burdens to our society. We utilize cutting edge techniques, including single-cell transcriptome analysis, 3D fluorescent imaging, and genetically modified animal models, to identify mesenchymal stem and progenitor cells at various musculoskeletal sites and investigate the function of their descendants under normal and disease conditions. In collaborating with a team of multidisciplinary scientists and clinicians, **our ultimate goal is to translate the studies on fundamental mechanisms of skeletal cell function into future clinical applications**. Ongoing projects in our group include:



Ling Qin, PhD

Associate Professor
Department of Orthopaedic Surgery



Single-cell transcriptomics reveals mesenchymal subpopulations in bone. 1: early mesenchymal progenitor; 2: intermediate mesenchymal progenitor; 3: late mesenchymal progenitor; 4: osteoblast; 5: osteocyte; 6: lineage committed progenitor; 7: marrow adipogenic lineage precursor (MALP); 8, 9: chondrocyte.

LAB HIGHLIGHTS

- **Delineating mesenchymal stem and progenitor cells in bone marrow, periosteum, joint, and muscle.** We apply an advanced single-cell transcriptomics approach to identify stem cell and progenitor subpopulations responsible for skeletal tissue homeostasis and regeneration.
- **Investigating a novel adipose cell type (MALP) in bone marrow and its multifaceted actions in regulating bone metabolism.** Our recent work discovered a unique cell type that expresses adipocyte markers but contains no lipid droplets. As adipocyte precursors, they exist abundantly as pericytes and stromal cells that form a ubiquitous 3D network inside the bone marrow cavity to regulate bone formation, resorption, angiogenesis, and hematopoiesis.
- **Understanding the mechanism of radiation-induced osteoporosis and delayed fracture healing.** Focal radiotherapy for cancer patients is frequently associated with skeletal damage within the radiation field. Our research on focal radiation animal models reveals the mechanism of radiation damage on bone structure and fracture repair. More importantly, we have proposed new therapeutic interventions for radiation-induced bone loss.
- **Targeting epidermal growth factor receptor (EGFR) signaling for osteoarthritis treatment.** We are the first group to demonstrate that EGFR signaling is critical for maintaining the superficial layer of articular cartilage and preventing osteoarthritis initiation. In collaboration with bioengineers, we develop a nanoparticle-based drug delivery system that targets EGFR in joint cartilage for osteoarthritis therapy.

THE SCHIPANI LAB

G-PROTEIN COUPLED RECEPTORS AND HYPOXIA BIOLOGY



Ernestina (Stina) Schipani, MD, PhD

Full Professor
Department of Orthopaedic Surgery

I have a long-standing interest in the study of cartilage and bone development. Over the years, I have used cartilage and bone tissues as models to **establish essential principles in the broader fields of G-protein coupled receptors and hypoxia biology.**

In my early years, as a member of Dr. Harald Jueppner's laboratory at MGH-Harvard Medical School, I **cloned the human PTH/PTHrP receptor (PTHR1) and its gene and discovered that gain-of-function mutations of PTHR1 cause Jansen Metaphyseal Chondrodysplasia (JMC)**, a severe form of short-limbed dwarfism associated to hypercalcemia.

As an independent investigator, I **pioneered the notion that gradients of oxygen control tissue morphogenesis during skeletal development.** Oxygen is an essential metabolic substrate in numerous enzymatic reactions, including mitochondrial respiration, and a regulatory signal. My laboratory studies the role of hypoxia-driven pathways and mitochondria metabolism in skeletal development with the overall goal of unveiling both novel aspects of the cellular adaptation to hypoxia and new avenues for treating cartilage and bone diseases. We use genetically modified mice as a model organism, and we analyze their phenotypes with a variety of in vivo, ex-vivo, and in vitro assays.

LAB HIGHLIGHTS

HIFs and Mitochondria in Development, Disease, and Regeneration

- We are studying the **interplay between the mitochondria and HIF1-dependent reprogramming of metabolism in skeletal development.**
- We are also studying **how the loss of HIF2 in mesenchymal progenitors increases bone mass and its translational implications.**
- Our laboratory is investigating whether transient activation of the HIFs contributes to healing articular cartilage defects through the inhibition of hypertrophy.
- In addition, we are looking at the role of the HIFs in the onset of fibroblastic tumors of the soft tissue.
- Finally, we are studying the **interplay between mitochondria and HIF1-dependent reprogramming of metabolism in congenital scoliosis.**

Jansen Disease

- We are working to identify potential therapeutic avenues for the treatment of Jansen Disease.



Staining of a fetal growth plate with the marker of hypoxia EF5.

THE SHORE LAB

LEADING THE WAY IN TAKING ON SOME OF THE WORLD'S RAREST AND MOST DEBILITATING DISEASES

The Shore Lab, as part of the **Center for Research in FOP and Related Disorders** and in collaboration with **Dr. Frederick Kaplan**, investigates the genetic regulation of cell development and differentiation through studies of extra-skeletal (heterotopic) bone formation in two rare genetic diseases, fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH). While several features distinguish POH from FOP, both of these disorders induce ectopic bone formation during early childhood and are progressive throughout life, forming bone in soft tissues such as skeletal muscle. **By identifying the underlying genetic mutations that cause these diseases, we uncovered key regulatory proteins and cell signaling pathways that determine where and when bone forms.**

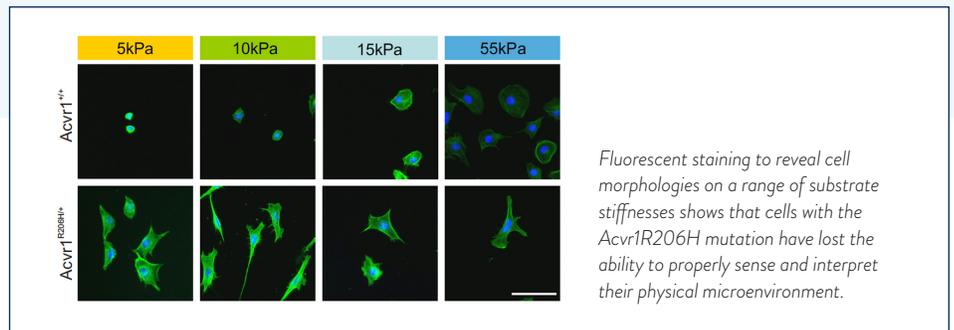
To investigate the cellular and molecular mechanisms of cartilage and bone formation and to identify treatment strategies and conduct pre-clinical drug testing, we develop, characterize, and apply in vitro cell assays and in vivo mouse and zebrafish systems. Ongoing work includes investigating the stem cells that are mis-directed to form bone along with their interactions with other cells and tissues that influence and permit extra-skeletal bone formation, including the tissue microenvironment, biomechanical signaling, and the immune system.

Our work, which began when few knew of FOP, POH, and heterotopic ossification or appreciated the value of understanding rare diseases, has stimulated an active and expanding field of basic research and translational application.



Eileen M. Shore, PhD

Cali and Weldon Professor of FOP Research
Orthopaedic Surgery and Genetics



LAB HIGHLIGHTS

- We made the surprising discovery that **nearly all FOP patients carry the identical mutation in the ACVR1 gene**, indicating that very specific alterations in ACVR1 signaling lead to this disease. Ongoing studies are identifying the molecular mechanisms that are altered by the mutation, bringing new insight into how these signaling proteins normally regulate the necessary and precise signaling control.
- We determined that **FOP mutations enhance differentiation to osteoblast (bone) and chondrocyte (cartilage) fates and that ACVR1 is critical during early cell fate commitment stages.** Importantly, our work has demonstrated that the FOP mutation alters key processes in cells and tissues that precede ectopic bone formation, including immune cells and biomechanical signaling cues, that direct and support the formation of heterotopic bone.
- We determined that **POH is caused by mutations in the GNAS gene and discovered that GNAS inactivation appears to act as a regulatory cell fate ‘switch’** that leads to increased osteogenesis and decreased adipogenesis.
- Both ACVR1 and GNAS regulate signaling pathways that are important during development of skeletal bones. Recent studies identified that GNAS mutations as in POH negatively impact bone maintenance and quality. We additionally determined that FOP ACVR1 mutation alters joint formation during embryonic skeletal development.

THE SMITH LAB

CLINICALLY IMPACTFUL RESEARCH INTO DISORDERS AFFECTING THE SPINE AND SYNOVIAL JOINTS

The broad goal of the Translational Spine and Joint Research Lab is to conduct **clinically impactful research into the pathophysiology and treatment of degenerative and developmental disorders affecting the spine and synovial joints.** The scope of our research includes basic mechanistic studies, translational studies in animal models, and clinical studies in human patients.

We use cutting-edge techniques in molecular biology, biochemistry, and bioengineering, coupled with novel in vitro and in silico model systems, to study disease mechanisms. Our research in the translational space bridges the fields of tissue engineering, biomaterials, drug delivery, and stem cells, and aims to both arrest spine and joint disease progression and restore healthy function. Broad research themes in our lab include 1) Development and preclinical translation of bioactive, injectable therapies for intervertebral disc degeneration and low back pain; and 2) Investigating the pathological mechanisms of skeletal disease in the mucopolysaccharidoses (MPS), a family of rare, genetic, metabolic disorders, and developing novel treatments and diagnostic tools.

We collaborate across the Medical, Veterinary and Engineering Schools, and at the Children's Hospital of Philadelphia. These partnerships, along with access to state-of-the-art technologies and unique model systems, have enabled the rapid translation of our basic science findings towards preclinical and clinical applications.



Lachlan J. Smith, PhD
Associate Professor
Departments of Neurosurgery
and Orthopaedic Surgery



Preclinical evaluation of bioactive injectable therapies for intervertebral disc degeneration.

LAB HIGHLIGHTS

- **Bioactive Injectable therapies for Intervertebral Disc Degeneration and Low Back Pain.** Intervertebral disc degeneration is a major cause of chronic low back pain. We have established a preclinical large animal model that mimics key characteristics of human disc degeneration, and are applying this model to evaluate novel therapies targeting the disc nucleus pulposus that combine stem cells, structural implants and drug delivery fragments in bone disease in MPS and identify therapeutic targets.
- **Developmental Paradigms for Intervertebral Disc Regeneration.** Intervertebral disc cells have a unique development lineage. By studying disc development, we are identifying emergent, regenerative subpopulations of disc cells that can be isolated and enriched for therapeutic application.
- **Mechanisms of Failed Bone Formation in the Mucopolysaccharidoses.** Patients with MPS exhibit failures of endochondral bone formation during postnatal growth, leading to severe skeletal deformity. We are identifying the molecular mechanisms linking abnormal glycosaminoglycan accumulation in MPS tissues to cellular dysfunction and failed bone formation using novel in vitro, in vivo and in silico models.
- **Biomarkers and Diagnostic Imaging of Synovial Joint Disease in the Mucopolysaccharidoses.** Synovial joint degeneration is prevalent in patients with MPS, and often results in profound disability and reduced quality of life. Through concurrent preclinical and clinical studies, we are working to identify novel molecular biomarkers and improved diagnostic imaging of synovial joint degeneration in MPS patients.

THE SOSLOWSKY LAB

COMBINING BASIC RESEARCH AND BIOENGINEERING TO BETTER HEAL TENDONS AND LIGAMENTS

We focus on orthopaedic tissue biomechanics, structure-function relationships, and functional tissue engineering in studies that examine tendons in the shoulder, ankle, and knee, as well as the anterior cruciate ligament. Using a variety of sophisticated and rigorous model systems, **we address both basic and applied research questions in tendons and their associated joints.** Our multidisciplinary research team includes bioengineers, orthopaedic surgeons, and physical therapists, as well as experts in imaging and molecular biology. The overall goals of our research program are to determine fundamental relationships and mechanisms of tendon and ligament injury, healing, repair, and regeneration and to use this information to develop and evaluate potential treatment modalities.



Louis J. Soslowsky, PhD

Fairhill Professor of Orthopaedic Surgery
Professor of Bioengineering
Associate Dean for Research Integration
Vice Chair, Research, Orthopaedic Surgery
Founding Director, Penn Center for
Musculoskeletal Disorders

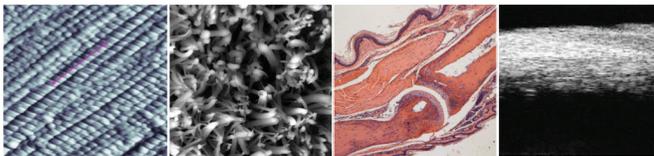


Figure 1 - Patellar tendon collagen fibrils visualized via surface scanning under an atomic force microscope. Custom code can then evaluate fibril deformation and sliding by measuring pixel intensities along fibrils (blue line).

Figure 2 - Transverse crosssection of biodegradable scaffold for supraspinatus injury repair as visualized under a scanning electron microscope.

Figure 3 - Histological visualization of a rat shoulder joint.

Figure 4 - Visualizing the collagen fiber structure of a rat Achilles tendon under a high-resolution ultrasound.

LAB HIGHLIGHTS

- We demonstrated significantly improved rotator cuff tendon healing with the use of non-invasive pulsed electromagnetic field therapy which is now in an **ongoing clinical trial** for rotator cuff repair patients.
- We studied **rotator cuff and Achilles tendon healing** and provided information on the role of immobilization vs exercise and repair vs non-repair to guide clinical treatment strategies.
- We have a series of studies demonstrating the role of various extracellular matrix proteins in tendon structure-function and injury and repair using innovative and rigorous model systems and evaluation tools. These studies are providing important fundamental information for development of targeted pharmacologic and tissue engineering treatment modalities.
- We have **developed several non-invasive, in-vivo measurement systems** that have direct lab-to-clinic parallels to study tendon injury, repair, and regeneration (e.g., gait, range-of-motion, ultrasound, photoacoustic imaging, microdialysis).

TO LEARN MORE ABOUT THE MCKAY
ORTHOPAEDIC RESEARCH LABORATORY, VISIT—
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