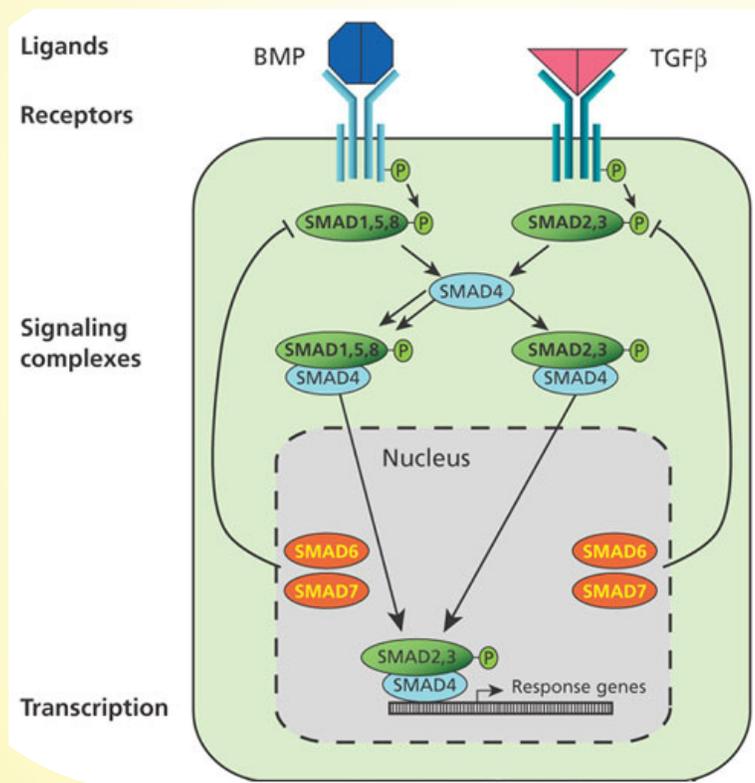


RESEARCH SYMPOSIUM 2013

DISCOVERIES IN
MUSCULOSKELETAL REGENERATION &
BIOMECHANICAL RESEARCH

June 20, 2013



BMP AND TGF BETA SIGNALING IN ARTICULAR CHONDROCYTES

THE LAWRENCE J. ELLISON
MUSCULOSKELETAL RESEARCH CENTER

Department of Orthopaedic Surgery
University of California, Davis School of Medicine

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www.ucdmc.ucdavis.edu/orthopaedics/education/

Established when the department was founded in 1969, the Orthopaedic Research Laboratories became the Lawrence J. Ellison Musculoskeletal Research Center in 1997, made possible through a generous gift by Lawrence J. Ellison, president and chief executive officer of Oracle Corporation, to help develop a world-class research center in musculoskeletal molecular biology and regeneration.

The laboratories provide a facility where faculty, residents, fellows, medical students, graduate and undergraduate students and visiting scholars can conduct broadly interdisciplinary research in tissue and cellular biomechanics, regeneration and repair.

DISTINGUISHED GUEST SPEAKER



Gerard Karsenty, MD, PhD

Professor and Department Chair, Genetics and Development, Columbia University, NY

Professor Gerard Karsenty is the Paul A Marks MD Professor and Chairman of the Department of Genetics and Development in the College of Physicians and Surgeons, Columbia University in New York City. He received his MD and PhD from the University of Paris, France. He was a Postdoctoral Fellow in the NIH and MD Anderson Cancer Center, Houston TX. He was on the faculty of MD Anderson Cancer Center before joining the Baylor College of Medicine as a Professor in 1999. Dr Karsenty moved to Columbia University in 2006. He has received numerous awards including the William Neuman Award in 2011 from the American Society for Bone and Mineral Research and the Herbert Fleisch Award in Basic Sciences of the International Osteoporosis Foundation. He has published over 250 peer-reviewed publications and invited review articles.

Title of Presentation

“Contribution of Bone to Whole Organ Physiology”

PROGRAM

- 7:30 AM Continental Breakfast
- 8:00 AM WELCOME: Richard A. Marder, MD, Professor and Acting Department Chair
- 8:10 AM INTRODUCTION OF GUEST LECTURER: A. Hari Reddi, PhD, Distinguished Professor, Lawrence J. Ellison Chair of Molecular Biology, Acting Lab Director and Acting Vice Chair
- 8:15 AM ELIZABETH C. AND MICHAEL W. CHAPMAN LECTURER: Gerard Karsenty, MD, PhD, Professor and Chair of the Department of Genetics and Development, Columbia University, New York
- "Contribution of Bone to Whole Organ Physiology"*
- 9:15 AM Mark A. Lee, MD, Acting Vice Chair of Operations and Clinical Research and Associate Professor
- "Fracture Healing"*
- 9:45 AM Eric O. Klineberg, MD, Assistant Professor
- "Facet Joint Biology in Spine"*
- 10:15 AM Coffee Break
- 10:30 AM Sean M. McNary, PhD Candidate
- "Role of Cytoskeleton in Superficial Zone Protein Biology in Articular Cartilage"*
- 11:00 AM DENNY AND JEANENE DICKENSON RESIDENT RESEARCH FELLOW: Jose Mejia-Oneto, MD
- "Covalent Targeting Therapy"*
- 11:30 AM Blaine A. Christiansen, PhD, Assistant Professor
- "A Novel Model for Post Traumatic Osteoarthritis"*
- 12:00 PM Dominik R. Haudenschild, PhD, Assistant Professor
- "Early Response to Joint Injury"*
- 12:30 PM Adjournment

THE LAWRENCE J. ELLISON MUSCULOSKELETAL RESEARCH CENTER



Sean McNary

As people live longer, virtually everyone, given enough time, will face painful and debilitating bone diseases, such as osteoporosis, arthritis and other arthropathologies.

For the nation's 77 million baby boomers who are just turning 60 years old, their demand for mobility and flexibility will move medical treatments and research to meet these needs to the forefront in an unprecedented way. Indeed, longitudinal studies confirm that maintaining an active and healthy quality of life is a significant requirement of the aging baby-boomer population group. As such, it is the primary challenge facing orthopaedic medicine today.

The Lawrence J. Ellison Musculoskeletal Research Center at UC Davis is a world-class research center well positioned to address the quality of life concerns through its collaborative research into tissue and cellular biomechanics, regeneration and repair - thanks to the generous support of Larry Ellison, who endowed the Lawrence J. Ellison, the Doris Linn Ellison and the David Linn Chairs.

Over the past 10 years that UC Davis has benefited from Ellison's contributions, the Lawrence J. Ellison Musculoskeletal Research Center has conducted research, trained new scientists, recruited a very talented research team and provided the resources needed to advance bone health. Specifically, these endowments have enabled UC Davis to:

- Recruit top researchers, including internationally renowned skeletal molecular biologist A. Hari Reddi from John Hopkins School of Medicine and biomechanical engineer and researcher David P. Fyhrie. The laboratory staff includes seven basic science faculty, administrative staff, two technicians and typically a dozen postgraduate researchers: fellows, residents, visiting scholars, medical students and graduate students
- Train and assist some 50 postdoctoral candidates and fellows in the development of their research careers while advancing research at UC Davis
- Augment an 8,000 square-foot research facility that includes a machine shop, a materials testing laboratory, cell and molecular biology laboratory, histology laboratory, tissue culture facilities, microscopy laboratory and mechanobiology laboratory
- Conduct dozens of research projects that would not have qualified for government funding due to the "unknown science" involved
- Publish nearly 100 research papers in more than 65 journals, magazines and books
- Secure \$10 million in additional research funding for projects benefiting from endowment funding

The impact of injuries and diseases on bones and joints

- *Musculoskeletal conditions are the number one reason that patients visit doctors*
- *In the US, musculoskeletal conditions cost society up to \$254 billion per year in medical care and lost productivity*
- *About one third of all American report that they have some form of arthritis*
- *Half of all women and one out of every eight men older than age 50 will have osteoporosis-related fractures in their lifetime*
- *Up to 15 million people are injured or disabled each year in road accidents*

REGENERATION LABORATORY

A. Hari Reddi, PhD, Distinguished Professor and Lawrence J. Ellison Chair of Musculoskeletal Molecular Biology

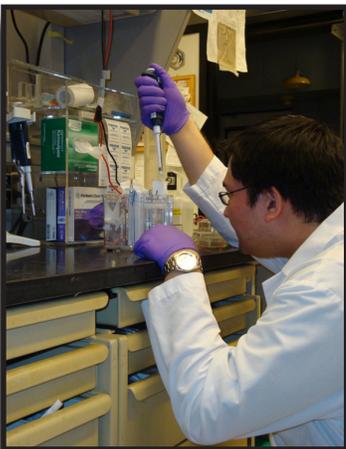


A. Hari Reddi, PhD

Regenerative medicine and surgery are emerging areas of medicine that are based on design and development of spare parts for the human body; our focus being regeneration for the musculoskeletal system to restore function to tissue diseased or damaged from cancer, trauma and arthritis. Regenerative medicine is based on principles of molecular developmental biology and is governed by basic biomechanics and bioengineering. The three key elements of regenerative medicine and tissue engineering are morphogenetic signals, stem cells and scaffolds of extracellular matrix. Regeneration recapitulates embryonic development and morphogenesis.

the Ellison Center. This is being addressed through multiple biological and biomechanical approaches. Superficial zone protein is produced by the top layer of articular cartilage and serves as a boundary lubricant, reducing friction. One segment of the lab is analyzing the relationship between friction and wear of articular cartilage due to changes in mechanical loading, SZP expression and the greater biomechanical environment. Previous work by this lab has shown that SZP is produced by loading-bearing regions of articular cartilage. We continue to

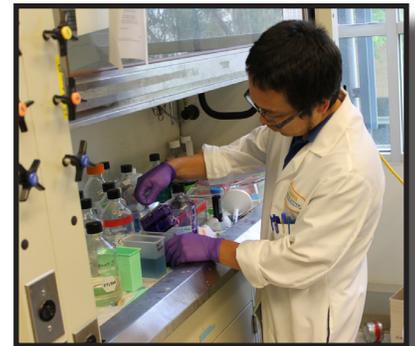
study the biomechanical regulation of SZP by examining its expression in response to a variety of mechanical loading regimes. The mechanotransduction of SZP is also being studied at the cellular level, in relation to cell shape and cytoskeletal morphology. In recent years, the lab has identified stem and progenitor cells in articular cartilage, muscle, and synovial tissues. Building upon this work, we are exploring the differentiation of embryonic and adult stem cells for articular cartilage and bone repair.



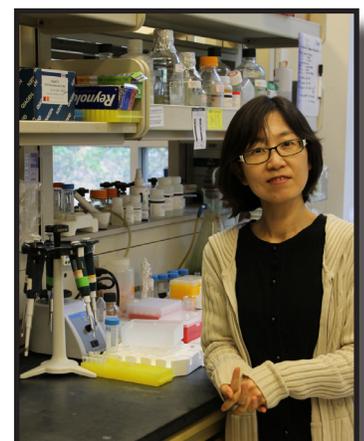
Graduate Student Sean McNary preparing a Western blot

Dr. Reddi is the recipient of the Marshall R. Urist Award for Excellence in Regeneration Research, Orthopaedic Research Society; the NIH Directors Award; the Kappa Delta Award of the American Academy of Orthopaedic Surgeons; and the Nicolas Andry Award of the Association of Bone and Joint Surgeons. He is the founder of the International Conference on Bone Morphogenetic Proteins (BMPs) and he chaired the conference in 1994, 1997, 2000, 2002 and 2008. Dr. Reddi has published over 330 papers.

The research conducted in the Musculoskeletal Regeneration Laboratory is a tripartite collaboration between Dr. Reddi, Dr. Cassandra Lee and Dr. Kyriacos Athanasiou, Chairman, Department of Biomedical Engineering, College of Engineering, UC Davis.



Atsuyuki Inui, MD



Eunmee Hong, PhD

REGENERATION LABORATORY

Araceli Cuellar (PhD Candidate): Is investigating the role of bone morphogenetic proteins (BMPs) in the formation of osteochondromas (benign outgrowths that arise on the surface of long bones). The goal of the study is to examine the molecular mechanism of action of BMP and BMP binding factors in the initiation and maintenance of osteochondroma using a mouse model. The proposed study will seek to elucidate whether the same genetic mechanism found in mouse models applies to humans osteochondromas. Outcomes of the proposed study will aid to further clarify the role BMPs play in the development of an osteochondroma and help provide an insight to the possible involvement of BMPs in the bowing and shortening of long bones, features present in multiple osteochondromas (MO).



Takashi Iwakura, MD, PhD, Visiting Fellow: Modulation of superficial zone protein synthesis by Wnt and Hedgehog signaling. Superficial zone protein (SZP) is produced by surface zone of articular cartilage and serves as a boundary lubricant and plays an important role in cartilage homeostasis and degeneration. Takashi investigated the roles of Wnt or Hedgehog signaling pathways which play an important role in not only skeletal development but also cartilage homeostasis and pathogenesis of osteoarthritis.

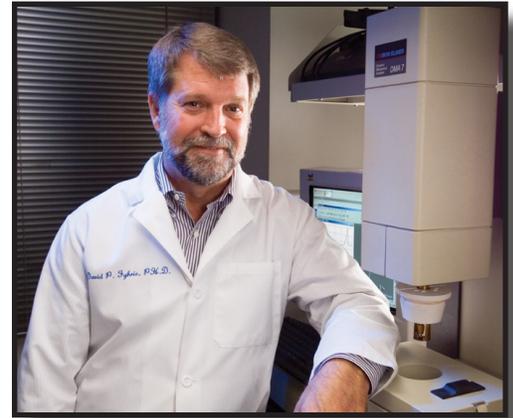
Sean McNary (PhD Candidate): Graduated from University of the Pacific (Stockton, CA in 2007 with a B.S. in Bioengineering. After getting a taste of research through cooperative education experiences at Lawrence Livermore National Lab and Duke University, he decided he needed to learn more about this very interesting and broad field. McNary is pursuing a PhD in Biomedical Engineering so that he may contribute his own novel piece of research to the world. He is entering his fifth year in the graduate program and aims to finish in Winter 2012.



Gordon Peng (PhD Candidate): Lubrication of articular cartilage: One of the two main functions of articular cartilage is to provide lubrication in diarthrodial joints. Boundary lubricants, such as superficial zone protein (SZP), have been proposed to reduce the friction coefficient of cartilage interfaces, minimizing its wear and tear, thereby preventing the early onset of osteoarthritis. Mechanical stimulation and growth factors have demonstrated to upregulate the production of SZP in native cartilage tissue. Gordon's current studies are to elucidate the mechanism behind SZP production in tissue engineered cartilage and determine if SZP production is conserved between native and tissue engineered cartilage. Gordon works closely with Sean McNary and in close collaboration with Dr. Kyriacos Athanasiou.

TISSUE BIOMECHANICS LABORATORY

David P. Fyhrie, PhD, David Linn Chair of Orthopaedic Surgery, was educated at Gonzaga and Stanford University and he worked at Henry Ford Hospital for sixteen years before joining UC Davis in 2004. His research work is to understand and prevent the age related mechanical changes in bone and cartilage that cause osteoporosis and are associated with osteoarthritis and many other orthopaedic diseases.



Mechanical loading to bone and cartilage causes nonlinear viscoelastic deformation. The deformation stimulates cells to release growth factors, causes fluid flow, causes damage and influences repair. With age or disease, healthy young normal bone changes to be porous and more brittle. A similar process occurs in cartilage, ligament and tendon, where the mechanical properties of the tissue degrade causing an increase of injuries with age. Our goal is to measure and determine the causes of mechanical property changes and to help prevent or repair those changes.

OUR PROJECTS



Michael Hardisty (PhD candidate): currently a PhD Candidate within the Department of Biomedical Engineering. His research interests focus on toughening mechanisms within the organic matrix of bone and examines the organic matrix within bone using modeling, mechanical testing and the surface force apparatus. Prior to coming to UC Davis Michael was a Research Engineer at Sunnybrook Health Science Centre in Toronto, pursuing clinical translational research within the department of Orthopedics. Michael obtained his Master's of Applied science in Biomedical Engineering and Bachelor's of Applied Science from the University of Toronto.

Matthew Soicher (PhD candidate): Replacing lost bone material using a tissue engineered replacement. Matthew is determining the best method to demineralize and remove cellular debris from cortical bone tissue and then to remineralize the tissue with embedded growth factors. The goal is to build a cortical bone replacement that is sterile, strong, tough, osteogenic and can be shaped before mineralization. Collaborators: JK Leach



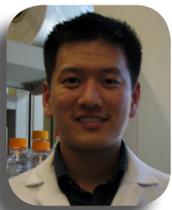
MECHANOTRANSDUCTION AND OSTEOARTHRITIS LABORATORY

Dr. Haudenschild's lab focuses on cartilage mechanobiology, our goal is to understand the mechanisms that explain how exactly moderate mechanical forces are beneficial for cartilage matrix formation and maintenance. We have designed and built an in-vitro bioreactor to simulate the mechanical forces routinely experienced by chondrocytes in healthy joints. We are using this bioreactor to identify that mechanosensitive promoter elements in the DNA of genes that respond to mechanical compression. We have jointly developed a post-traumatic osteoarthritis knee injury model with the Christiansen Lab, and we are using the model to test a new inhibitor of primary response gene transcriptional activation. Our goal is to use this inhibitor to treat joint mild injuries such as ACL tears at the time of injury. The inhibitor decreases the inflammatory response, and our hope is that this will help prevent or delay the future onset and progression of post-traumatic osteoarthritis. Finally, we have ongoing projects to identify the mechanistically how the extracellular matrix affects cellular responses to growth factors. Our goal is to enhance the efficacy of growth factors for tissue engineering applications and stem-cell chondrogenesis.



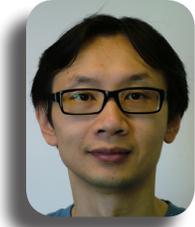
Dominik R. Haudenschild, PhD
Assistant Professor

Kazunari Ishida, MD, PhD, Visiting Post-Doctoral Fellow: Is studying the interaction of COMP with BMP-2, in bone formation. COMP has a newly discovered function to increase the local concentration and activity of TGF- β family growth factors and slow their diffusion. Kazu has used biochemical approaches to characterize the binding of COMP to BMP-2, then used cell-biology approaches to demonstrate that this binding enhances the osteogenic activity of BMP-2 in a variety of assays. Finally Kazu has used an ectopic bone formation assay to demonstrate that COMP enhances BMP-2 mediated osteogenesis in-vivo.



Jeffrey Lu, M.Eng, PhD Candidate: Effect of mechanical stress on gene expression in articular chondrocytes and bone marrow derived stem cells. Jeff is building a bioreactor for application of multi-axial translational and rotational stresses on human cell-seeded hydrogels to simulate physiological forces experienced by articular cartilage. Resulting cellular responses invoked by a mechanoresponsive DNA element within a gene promoter is our target to identify. Target genes of mechanotransduction pathways include extracellularmatrix genes, Cartilage Oligomeric Matrix Protein (COMP), and Superficial Zone Protein (SZP).

MECHANOTRANSDUCTION AND OSTEOARTHRITIS LABORATORY



Jasper H.N. Yik, PhD

Basic research projects in Dr. Yik's lab include the use of molecular and cellular biology approaches to study the mechanisms for chondrocyte differentiation from stem cells. Specifically, we are interested in studying the inter-relationship between positive and negative transcription factors in regulating the expression of cartilage matrix genes, and their effects on chondrogenesis and skeletal development. We are also using conventional biochemical approaches such as affinity chromatography to identify novel proteins important for regulating chondrogenesis from stem cells.

MUSCULOSKELETAL ADAPTATION LABORATORY



Blaine A. Christiansen, PhD
Assistant Professor

Dr. Christiansen's research interest is in the adaptation of musculoskeletal tissues to the mechanical environment, injury, or disease. The musculoskeletal system has an innate ability to repair and optimize itself based on the mechanical demands placed on it. By studying this adaptation, we are able to uncover underlying mechanisms that contribute to diseases such as osteoporosis and osteoarthritis. My research primarily utilizes small animal models of injury, mechanical loading or unloading. Musculoskeletal adaptation is quantified in these models using advanced imaging techniques, histology, and mechanical testing. My current projects include investigation of mechanisms that contribute to the development of post-traumatic osteoarthritis after ACL injury, and the effect of peripheral nerve function on bone metabolism and bone adaptation to mechanical loading.

MATERIAL TESTING LABORATORY

Matthew Anderson: Matt is a specialist in mechanical testing and material evaluation.



SPINE RESEARCH LABORATORIES



Munish C. Gupta, MD
Professor and Chief



Eric O. Klineberg, MD
Assistant Professor



Rolando F. Roberto, MD
Associate Professor

Our Spine Research Group merges cutting edge technology with medicine in major research areas, including stem cells for bone regeneration, biology of spinal fusion, and characterization of disc degeneration. We are investigating the interplay of BMP antagonists during spinal fusion in an animal model of posterolateral lumbar fusion and have discovered the reciprocal interaction between bone grafts and the local microenvironment. We are particularly interested in rhBMP in the posterolateral

spine, and fusion rates in both the adult and pediatric population. Utilizing the AO Spine Hansjorg Wyss Grant, we have investigated the effect of Noggin-targeted RNA Interference on spinal fusion. We also continue to maintain an active clinical research focus, including Atlanto-Occipital Dissociation, Lamnioplasty, Demineralized Bone Fusion, and Adult and Pediatric Scoliosis.

Our laboratory has also placed a great focus on motion preservation technologies and stabilization of spinal disorders. We have developed synergistic relations with the UC Davis Biomedical Engineering graduate group and have been the recipients of several research grants from both corporate sources and from not-for-profit organizations. Additionally, we are collaborating with investigators from Oregon Health Sciences University on upper cervical kinematics and stabilization of the C1-C2 articulation without obliteration of rotation. Finally, we have worked in a collaborative fashion with Reduction Technologies, Inc., on the design and implantation of motion preserving scoliosis correction implants. As spinal motion is crucial to function, we are dedicated to pursue stabilization of spinal pathologies without reduction of motion.

THE DENNY AND JEANENE DICKENSON ORTHOPAEDIC RESIDENT RESEARCH FELLOWSHIP

This fellowship is a unique and extremely important program, which trains one of our outstanding residents each year for a career in academic orthopaedic surgery. Funding for this program was made possible through a generous donation by Denny and Jeanene Dickenson.

The Dickenson Fellowship allows this resident to work on a research project for a year with our world-recognized research clinicians, molecular biologists and engineers. This prepares the resident for a career in translational research where they will work with basic science research to transition novel treatments for disorders of the musculoskeletal system from the laboratory into the clinic for patient care.

This year's fellow, Dr. Jose M. Mejia Oneto, under the supervision of Dr. Gupta, Dr. Lee and Dr. Reddi, and through collaborations with Dr. Leach and Dr. Sutcliffe (Biomedical Engineering), developed an interdisciplinary method to deliver therapeutics in a targeted manner, exploiting the vascular system of the body and novel chemistry.



FRACTURE HEALING AND TRAUMA LABORATORY



Mark A. Lee, MD
Associate Professor

Dr. Lee's lab focuses on a variety of research areas pertaining to fracture healing, including animal models of fracture nonunion, mesenchymal stem cell applications for fracture repair, and biomechanical evaluations of fracture implants. Our lab has optimized a rat models for atrophic nonunions and critical size defect repair and has performed evaluations of mesenchymal stem cells in bone regeneration. We have ongoing studies of critical size defect repair in small and medium size animal models utilizing biocompatible scaffolds with stem cells and growth factors. All of our bone regeneration experiments are focused on translational applications and we have initiated work on autologous stem cell concentration and delivery for fracture nonunions. In addition, we have performed numerous cadaveric and composite bone model biomechanical analyses of fracture implants and are working toward the development of clinically relevant cyclic loading protocols.

NERVE REGENERATION LABORATORY



Robert M. Szabo, MD, MPH
Professor

Professor Szabo's research focus, both clinically and in the laboratory, is on nerve compression syndromes. A major emphasis on his laboratory efforts was focused on examining the effects of compression on the tibial nerve on a rat model. His specific aim had been to characterize the response of peripheral nerves to intermittent compression with a goal of understanding the role of repetitive motion, as seen in cumulative trauma, in the pathophysiology of nerve compression. In the laboratory, he developed an animal model to study end-to-side nerve regeneration and repair. Professor Szabo's second research focus is in biomechanics of fracture fixation, specifically with determining the role of locking, non-locking and hybrid fixation in the hand. Professor Szabo also has a strong interest in clinical research design and outcome studies that can contribute to the foundation of evidence-based medicine.

BIOMEDICAL ENGINEERING

Dr. Athanasiou's research focus is on finding clinically acceptable solutions to treat cartilage injury and diseases and in elucidating how mechanical forces induce cartilage metabolism from the single cell to the tissue level. Long-term cartilage and fibrocartilage regeneration continues to be elusive in musculoskeletal medicine, particularly since these tissues are unable to heal themselves in a way that would allow them to functionally persist within their naturally strenuous and biomechanically difficult environments. It has become clear that exogenous intervention is required for these tissues, and an engineered product may fill the void. On the tissue level, processes have been developed by the Athanasiou Laboratory whereby differentiated cells from both cartilage and fibrocartilage self-assemble to form neocartilage possessing functional properties on par with native tissue. These functional properties are then improved using anabolic, catabolic, and mechanical stimuli. Thresholds of mechanical stimuli that precipitate in metabolic changes have also been determined on the single cell level. Skin-derived cells, in addition to mesenchymal and embryonic stem cells, are under examination for their utility in regenerating or repairing articular cartilage and fibrocartilages of the knee and the temporomandibular joints. Dr. Athanasiou is the Distinguished Professor of Biomedical Engineering and Orthopaedic Surgery and Chair of the Department of Biomedical Engineering.



Kyriacos A. Athanasiou, PhD
Distinguished Professor



Pasha Hadidi (PhD Candidate): Chemical and Mechanical Stimulation of Knee Meniscus Cartilage: The knee meniscus is a piece of cartilage important for load transmission and joint stability. Recent studies have suggested several methods for producing significantly enhanced meniscus tissue grown in the lab. Mechanical testing of cultured constructs has shown hydrostatic pressure stimulation and TGF- β 1 growth factor application to lead to beneficial effects on bulk tissue properties. Pasha's current studies deal with looking for synergistic effects in these stimuli and optimizing them, by manipulating their temporal application, for multiple treatments.

Gina MacBarb (PhD Candidate): Comparison of Stem Cell Sources in Cartilage Tissue Engineering for the Equine Athlete: Gina is comparing the chondrogenic potentials of four different sources of equine mesenchymal stem cells. The four sources include bone marrow, adipose, cord blood, and cord tissue derived equine mesenchymal stem cells. Using the Athanasiou Laboratory's previously established self-assembly method, tissue engineered cartilage constructs will be created using the most promising of the four cell sources. Collaborators: C Yellowley, LD Galuppo, GL Ferraro



Jerry C. Hu, PhD, Principal Development Engineer: The focus of Dr. Hu's research is to tissue engineer, *in vitro*, cartilage and fibrocartilages to restore joint function. These soft tissues do not mount a sufficient healing response, and tissue loss from trauma or disease results in function loss that is seldom naturally restored. Using differentiated chondrocytes, fibrochondrocytes, mesenchymal stem cells, or skin derived cells, Dr. Hu's research has determined chemical and mechanical cues necessary in improving matrix production, organization, and, finally, mechanical properties such that the engineered neotissues can withstand loading in the native environment. He has examined the progression of matrix development and changes in mechanical properties in scaffold-free, self-assembled chondrocyte constructs to

note that collagen content and organization are particularly important parameters in the function of these joint tissues. These principles have allowed for the engineering of articular cartilage with biochemical and biomechanical properties that are on par with native tissues. The remodeling of collagens and glycosaminoglycans in these tissues are reminiscent of those seen in cartilage morphogenesis. The engineered neocartilage also synthesizes superficial zone protein and exhibit a coefficient of friction that is on the same order as native articular cartilage. Toward the translation of these engineered tissues, Dr. Hu is also examining new agents to effect cartilage adhesion and integration.



J. Kent Leach, PhD
Associate Professor

Research in the Leach laboratory is primarily in the broad area of cellular and tissue engineering. Within our research program, we seek to engineer functional replacement and temporary bridge tissues while also developing model systems to study physiological and pathophysiological tissue formation. We initially develop many of our projects with an eye toward bone tissue engineering, and these findings are subsequently applied to other areas of tissue repair including cartilage, cardiovascular, and neural tissue engineering.

All projects in the lab are linked by the hypothesis that combinatorial approaches to tissue formation are superior to individual stimulation. More specifically, successful tissue engineering approaches will be realized upon the proper spatial and temporal presentation of cells, signaling molecules, biomaterials, and mechanical stimulation.

Dr. Leach's research interests include the normal formation and repair of human tissues is the result of a complex series of intra- and extracellular events culminating in functional tissue. The experimental strategy of delivering a single molecule to stimulate the body's own mechanisms of growth and repair, either systemically or from a matrix, has assisted in our biological understanding of organogenesis. However, there is accumulating evidence that a single growth factor delivered as a protein for a short duration or as gene therapy for a slightly longer duration may not be sufficient for functionally significant regeneration of tissues such as heart, bone, cornea, and others. The presence of multiple factors (i.e. growth factors, cytokines, and cells) in varied concentrations during native repair suggests the combinatorial delivery of multiple signaling molecules coupled with the exposure of cells to biomimetic surfaces may enhance the formation, growth, and function of new tissues. Consequently, the guiding theme of my research is the engineering of tissues through the combination of synthetic and natural materials, bioactive moieties such as growth factors and cells, and physical stimulation in order to achieve a more natural engineered tissue.

Dr. Leach is also interested in the development of pharmacologic formulations that can assist in the treatment of heart attack and stroke. Encapsulation of clot-busting drugs in a variety of vehicles has previously demonstrated significant improvement over clinically used treatment options. We are developing new techniques to deliver these drugs which may result in viable treatment alternatives.

ABSTRACTS

A Novel Model for Post Traumatic Osteoarthritis

Blaine A. Christiansen, PhD

In our laboratory we have developed a mouse model of knee injury that uses a single non-invasive mechanical load to induce ACL rupture, creating a joint injury response that is relevant to post-traumatic osteoarthritis (PTOA) in humans. Using this model we have observed articular cartilage degeneration and osteophyte formation by eight weeks post-injury, as well as a rapid subchondral bone changes that begin within one week of injury. Ongoing studies in our laboratory are utilizing this model to investigate biomechanical and biological mechanisms of PTOA progression, as well as potential therapies that target the early bone turnover response observed following injury. Results from these studies will help establish the "window of opportunity" for treatments aimed at slowing or preventing the onset of PTOA, and will establish potential therapeutic targets by identifying the relative contributions of biological and biomechanical changes on PTOA initiation. This research will greatly expand our understanding of processes that can lead to PTOA following joint injuries, and could lead to a fundamental change in the way traumatic joint injuries are treated in human subjects.

Early Response to Joint Injury

Jasper Yik, PhD, Ethan Hu, and Dominik Haudenschild, PhD

Although the etiology of osteoarthritis (OA) is unknown, it is often associated with joint injuries. The mechanical damage during joint trauma immediately causes cell death and physical damage to the surrounding tissues. This is followed by an acute cellular response, which occurs within a time-scale of minutes to hours. In the acute response phase, inflammatory mediators are released from the injured joint tissues, including IL-1, IL-6, TNFa, and iNOS. This causes the transcriptional activation of primary response genes, and increased production of matrix-degrading enzymes such as MMPs, collagenases and aggrecanases that contribute to OA.

Using our non-invasive mouse joint injury model, this study characterizes the temporal changes in gene expression shortly after knee trauma.

When analysis was limited to cartilage, ligaments and subchondral bone, IL-6 expression peaked at 8-hours and returned to base line at 3-day post-injury. IL-1b, TNFa and MMP13 expression did not change significantly throughout the 7-days time course. When synovium and other joint tissues were also included in the analysis, we observed a much larger and more comprehensive response that included IL-1b, but with a delayed onset and peak.

This suggests an initial response in the injured ligament/cartilage/subchondral-bone tissue that then gets amplified in adjacent joint-lining tissues. IL-6 may play an important role in this acute phase, and the subsequent development of PTOA. Thus, a window for therapeutic intervention may exist shortly after injury, during which attenuating the acute cellular response will decrease the production of matrix degrading enzymes and thus decrease the likelihood of developing PTOA.

Characterization of Spinal Zygoapophyseal Joints

Klineberg, E, Maitra, S, Reddi, AH, Hu, J, Athanasiou, K

The spinal zygoapophyseal joints or facet joints have been a neglected area of research due to the difficulty in isolating the joints from other pathology and due in part to the interest in the intervertebral disc. However, facet joint can be the source of significant pain, and clinically dorsal rami blocks, medial branch blocks and rhizotomy can be successful in the management of back and facet mediated pain. Corroborating these techniques, there are animal and human studies that have identified nociceptive nerve fibers, and inflammatory mediators in the articular cartilage of facet joints. Biomechanical studies allow for understanding and characterizing the facet joints, and interestingly there is significant species variability. Even within the species, facet joints from different areas of the spine: cervical, thoracic, lumbar; display different biomechanical and functional characteristics. In the human spine, the facet joints use their gliding properties to allow for rotational, sagittal and coronal motion. They undergo significant stress during these movements and can develop hypertrophy due to pathologic loads. This study will characterize the properties of human spinal facets and focus on the surface gliding properties of the spinal facet.

Fracture Healing

Mark Lee, MD

An estimated 5% to 10% of fractures experience delayed union and nonunion and many of the most severe fractures we care for in our trauma center have significant bone loss and require surgical treatment to restore function. Many of these patients will require open bone grafting procedures to induce bone regeneration in fractures that have failed to heal (nonunions) or in patients who have lost bone secondary to trauma or related infection. The current treatment of choice for these patients is surgical harvest and open application of cancellous autogenous iliac crest graft; however, this procedure has well documented morbidity and procedural complications. Currently, a safe and reliable alternative is lacking. We have sought novel and essential solutions that can restore basic function to many injured patients.

Bone marrow aspirate concentration has long been utilized in the treatment of nonunions. We have explored this technique using point of care concentration systems to rapidly isolate and deliver enriched MSC via anterior iliac crest bone marrow aspirate on allograft as an alternative to autogenous cancellous crest grafting.

We performed a prospective single site, single surgeon study on 19 patients with fracture nonunions or critical size bone defects. We performed pre- and post-concentration cell analysis. Additionally, patients were followed for radiographic and functional outcomes.

The high efficiency concentration created a 4x enrichment of CD34 cells and a 11x enrichment for the CFU-F assay. There was a high level of variability in total cells isolated from the different patients.

We were able to demonstrate good efficacy of cell concentration with this point of care system. We are continuing to analyze the relationship between number of cells delivered and other host factors with radiographic and functional outcomes.

Covalent Targeting Therapy

José Manuel Mejía Oneto, MD

This project focuses on core strengths of University of California, Davis in orthopaedic surgery, solid carrier development and in-vivo imaging to address the following research question: can therapeutics be delivered selectively to specific areas of the body in-vivo in a minimally invasive fashion?

Two chemical entities can react selectively through “click chemistry” in vivo to deliver detectable radioactivity levels to subcutaneous tumors in mice. Our work explores the application of this chemical reaction for delivery of small molecules to specific areas of the body for potential orthopaedic applications.

We designed and synthesized new “click chemistry” reagents (trans-cyclooctenes [TCO] and tetrazines [Tz]). One reaction partner (TCO) was attached to hydrogels. Mice were implanted gels subcutaneously, followed by intravenous injection with Tz probes labeled with either Cu-64 or In-111 for positron emission tomography (PET) or single photon emission computed tomography (SPECT) respectively, as well as biodistribution studies. Our results indicate that we have achieved an in-vivo click reaction (TCO-Tz) with delivery of ~2% intravenous injected dose per gram to a specific site in a murine model.

In conclusion, this is the first time a TCO-Tz reaction has been used in-vivo outside of a tumor & antibody model. This work represents proof of concept that covalent targeting delivery can be used to deliver a pharmaceutical load to a specific anatomic site using a solid carrier and open the door for optimization and therapeutic uses.

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“TGFβ-Induced Superficial Zone Protein Accumulation is Synergistically Enhanced by Lysophosphatidic Acid”

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Articular chondrocytes have a context-dependent phenotype that is mediated through the cytoskeleton. Chondrocytes in monolayer culture undergo dedifferentiation and gradually experience a decrease in the expression of type II collagen and aggrecan, hallmarks of the articular chondrocyte phenotype. This process can be reversed with cytochalasin, an inhibitor of actin polymerization. Superficial zone chondrocytes differ from middle and deep zone cells through their secretion of the cartilage boundary lubricant, superficial zone protein (SZP). Our previous studies have demonstrated that alteration of cytoskeletal dynamics or Rho-family GTPase activity modulated the synthesis of SZP in a TGFβ-dependent manner in monolayer cultures. Most significantly lysophosphatidic acid (LPA), a signaling phospholipid and activator of RhoA, enhanced TGFβ-induced SZP synthesis. LPA and TGFβ, individually and in combination, promoted proliferation of primary, superficial zone chondrocytes in serum-free, monolayer culture conditions; the cell number doubled within seven days. While LPA did not have an effect on basal SZP synthesis, TGFβ-induced SZP

was synergistically enhanced by LPA treatment after media accumulation was normalized to cell number. The synergistic effects of LPA were found to be mediated primarily through TGF β . LPA and TGF β -induced media accumulation was abrogated in the presence of TGF β receptor kinase I inhibitor SB431542. An increase in Smad3 phosphorylation was observed in response to LPA+TGF β treatment, compared to TGF β alone. TGF β is a key regulator of superficial zone protein. Determining the effects of LPA on TGF β -mediated SZP synthesis is an important step in elucidating the biochemical regulation of SZP and articular cartilage lubrication.

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