NEWS AND RESEARCH:
FERGUSON LABORATORY FOR ORTHOPAEDIC AND SPINE RESEARCH

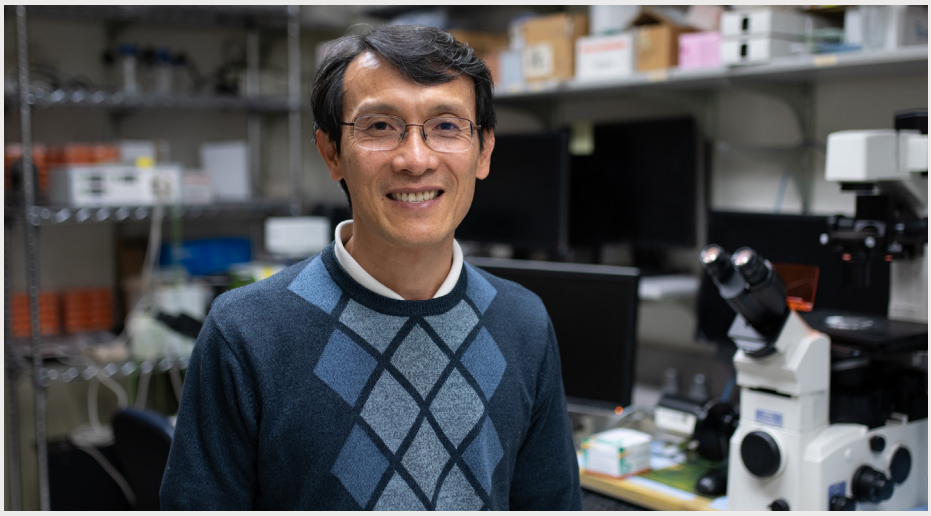
WINTER 2024

EXPANDING THE BOUNDARIES OF BASIC SCIENCE AND CLINICAL SPINE RESEARCH

Does Cellular Senescence Drive Aging in Intervertebral Discs?

New R01 Grant is Exploring Molecular Mechanisms at Play in IDD.

Nam V. Vo, PhD, co-director of the Ferguson Laboratory for Orthopaedic and Spine Research was awarded a 2023 National Institutes of Health R01 grant that will further his ongoing research into the cellular and molecular mechanisms that lead to intervertebral disc degeneration (IDD).



The grant, titled "Mechanisms of Cellular Senescence Driving Intervertebral Disc Aging Through Local Cell Autonomous and Systemic Non-Cell Autonomous Processes," is designed to more fully characterize how the process of cellular senescence associated with aging leads to degradation of intervertebral disc tissues and ultimately pathological spine conditions and low back pain.

The project builds on prior findings that link persistent DNA damage in aging cells to the onset of cellular senescence and their subsequent acquisition of the senescence-associated secretory phenotype (SASP). SASP is characterized by the release of inflammatory and catabolic factors by senescent cells, which are implicated in the degradation of disc matrix, which is a core aspect of IDD.

What is Cellular Senescence?

Cellular senescence (CS) occurs when cells cease to divide and undergo distinctive biological changes. CS is a hallmark of the aging process, acting as a protective mechanism, primarily against the development of cancer. When cells sense damage or stress, such as DNA damage, they take on a senescent state to prevent the changed or mutated cell from replicating and propagating its damaged genomic DNA. Senescent cells remain metabolically active but no longer replicate themselves, but their SASP can have deleterious effects on surrounding tissues, for example intervertebral discs.

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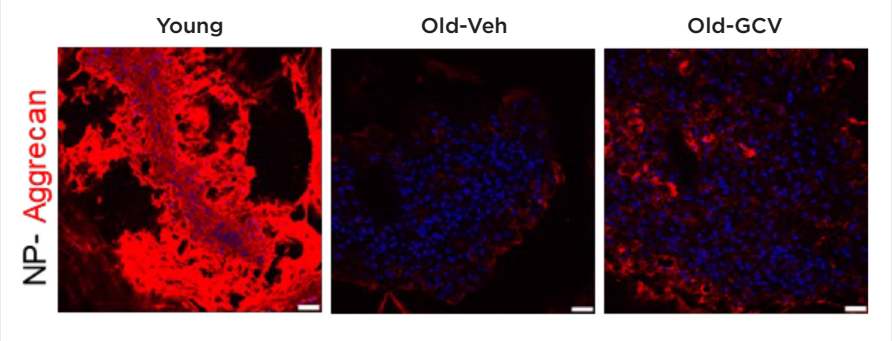


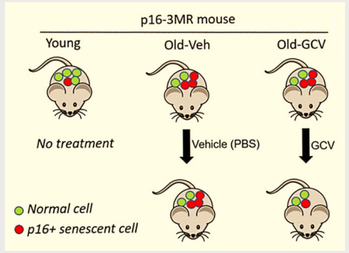
Clearance of cellular senescence by GCV improves intervertebral disc proteoglycan matrix.

Red: Aggrecan
Blue: Nuclei

Grant Details – Aims and Potential Clinical Applications

Dr. Vo's study is investigating the dual role of cellular senescence - whether it predominantly acts through local, cell-autonomous processes within the disc tissue, or through systemic, non-cell autonomous mechanisms via senescent cells in other tissues-in driving age-related IDD.

This distinction is crucial for understanding the pathophysiology of disc aging and devising targeted interventions. For example, if IDD is influenced systemically, then treating IDD locally without account for other body tissues would not be effective. Additionally, the study also explores the contributions of two distinct cellular senescence mechanisms, p16INK4a and p21Cip1-mediated pathways, in IDD.



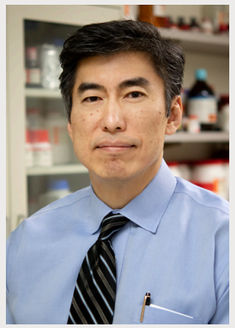
Treatment of aging mice with the nucleotide analog GCV eliminates senescent cells (red circles) without harming normal cells (green).

Dr. Vo's research has significant potential implications for clinical practice. By characterizing the exact role of cellular senescence in driving age-related IDD and understanding which pathways - p16INK4a vs. p21Cip1 - contribute locally and globally to the formation of IDD, it may potentially lead to the identification of novel senolytic therapies that are more effective and targeted approaches to treating IDD.

Grant Reference

Mechanism of Cellular Senescence Driving Intervertebral Disc Aging Through Local Cell Autonomous and Systemic Non-Cell Autonomous Processes. Project Number: 1R01AG081293. Principal Investigator: Nam V. Vo, PhD. Funding: National Institute on Aging – Skeletal Biology Structure and Regeneration Study Section.

Visit fergusonlab.pitt.edu to learn more.



Creating a Hub for Musculoskeletal Research: The Orland Bethel Family Musculoskeletal Research Center at the University of Pittsburgh

The University of Pittsburgh, in collaboration with the Department of Orthopaedic Surgery, has established the Orland Bethel Family Musculoskeletal Research Center (BMRC), funded by a $25 million donation from the Orland Bethel Family Foundation and matched by the university. This $50 million initiative, led by **Joon Y. Lee, MD**, aims to revolutionize musculoskeletal disorder research and treatment.

The BMRC differs from traditional research centers by integrating basic science with clinical research, facilitating translational research that quickly moves scientific discoveries to practical clinical applications. Dr. Lee, the center's founding executive director and Orland Bethel Professor in Spine Surgery, emphasizes the center's wide-ranging focus on musculoskeletal issues, from spinal disorders to knee joint, cartilage, and tendon problems – every aspect of the musculoskeletal system will be prepresented.

Central to the BMRC's approach is collaboration, involving various departments within the university to ensure a multidisciplinary perspective. A critical aspect of this collaborative effort is the Bethel Research Fellows program, which supports up to four external researchers annually.

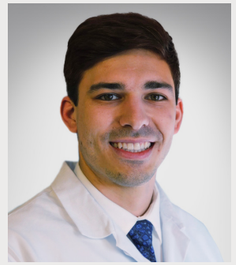
Education is also a priority, with plans to provide grants to undergraduates and medical students, encouraging early interest in musculoskeletal research. The center will host annual conferences and seminars and plans to establish an accessible online journal.

Research at the BMRC will concentrate on areas such as molecular and genetic mechanisms in spine-related diseases, the effects of gender and age on musculoskeletal disorders, development of osteoarthritis therapies, and applying technologies like machine learning in orthopedics.

Scheduled to open in 2024, the BMRC is the culmination of Dr. Lee's 30-year vision. It aims to be a leading force in musculoskeletal research, blending basic and clinical research with a collaborative, educational framework to translate research breakthroughs into effective patient treatments.

Visit bethel.pitt.edu to learn more.

Ferguson Lab Spotlight: *Christopher Como, MD*



Pittsburgh native and current Ferguson Laboratory for Orthopaedic and Spine Research trainee, **Christopher Como, MD**, is currently a second year of resident in the University of Pittsburgh Department of Orthopaedic Surgery's six-year research track.

Dr. Como's journey in medicine began with an undergraduate degree in biomedical engineering from the University of Michigan, followed by a medical degree from the University of Pittsburgh, his top choice due to its quality, opportunities, and proximity to family.

Early Work in Orthopaedics at the ORL and Biodynamics Labs

During his undergraduate years, Dr. Como's interest in orthopaedic surgery and research was sparked by volunteering in various labs within the Department of Orthopaedic Surgery. His early work at the Orthopaedic Robotics Lab (ORL) under the guidance of Richard Debski, PhD, and Volker Musahl, MD, involved revamping the STAR-IV a shoulder and knee testing apparatus that was originally designed and built by the Department's late chair Freddie Fu, MD, more than two decades ago. The testing apparatus, designed for examining joint mechanics, had become outdated and dysfunctional. Dr. Como's work involved extensive mechanical repairs and coding, leading to the successful restoration of this important research tool by the end of the summer.

"Every time I go over to the lab, I see that rekindled device in operation," says Dr. Como. "It's immensely satisfying to have been a part of rehabilitating something Dr. Fu built and used for research."

Dr. Como's second project at in ORL focused on analyzing the effectiveness of different sizes of interference screws in ACL surgeries, particularly for osteoporotic patients. This research linked bone mineral density with insertion torque and load to failure, indicating that larger screws could yield better surgical outcomes.

Taking a year off between his third and fourth years of medical school, Dr. Como interned at the Biodynamics Laboratory (BDL), directed by William Anderst, PhD. Dr. Como's main project involved tracking hip and spine data for patients who underwent total hip arthroplasty. The study focused on analyzing changes in patients' movements and pain levels before and after the surgery, particularly in the context of hip-spine syndrome, a phenomenon where hip surgery alleviates concurrent low back pain. The research led to published findings about spinal alignment changes after hip surgery.

Dr. Como also contributed to a novel trapeziectomy study at BDL, involving motion tracking in cadaver wrists and hands, a first for the lab.

Residency Research in the BDL and the Ferguson Lab

In his residency, Dr. Como joined both the BDL and Ferguson Lab, focusing on spinal research. At the BDL, his work involves studying the motion between the skull base and upper cervical vertebrae in the context of upper cervical spine trauma. In the Ferguson Lab, under co-director Nam Vo, PhD, and principal investigator Peter Alexander, PhD, Dr. Como is primarily involved in a study using a rat model to understand ligamentum flavum hypertrophy (LFH) in spinal stenosis. This project aims to develop a reproducible model of spine instability to test treatments for LFH, using MRI and histology to assess changes in the ligamentum flavum.

About Being in the Ferguson Lab

As Dr. Como explains, there's an undercurrent of enthusiasm, collaboration, and mentorship at work in the Ferguson Lab.

"There's so much going on in the lab – basic science, cutting edge technologies, so many studies occurring simultaneously, but the atmosphere and the attitude of everyone here is just so collegial and helpful," says Dr. Como. "And its one that's really focused on the end goal of improving care for patients. It's a tremendous place to study and grow."

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ABOUT THE FERGUSON LABORATORY FOR ORTHOPAEDIC AND SPINE RESEARCH

The Ferguson Laboratory for Orthopaedic and Spine Research at the University of Pittsburgh studies the complex developmental mechanisms, etiologies, and basic biology behind intervertebral disc degeneration (IDD), and it works to develop biological, biomechanical, and cell-based therapies for IDD. Leading the laboratory's multidisciplinary research efforts are co-directors Joon Y. Lee, MD, FAOA; Gwendolyn A. Sowa, MD, PhD; and Nam V. Vo, PhD.

The Ferguson Laboratory explores distinct but complementary research areas to dissect and clarify the physiological processes that lead to disc degeneration. Dr. Vo leads the lab's efforts studying the contribution of aging on IDD and loss of disc extracellular matrix (ECM) proteoglycans, with a special focus on cellular senescence and autophagy in regulating aggrecan homeostasis. Dr. Sowa oversees investigations involving the mechanisms of mechanical strain on disc cell metabolism, with an emphasis on how mechanical strain-induced inflammation controls ECM collagen expression and breakdown. As a practicing orthopaedic surgeon, Dr. Lee explores minimally invasive treatment of trauma and conditions in the spine.

The lab is named in honor of Albert B. Ferguson Jr., who held the Silver Chair of Orthopaedic Surgery at the University of Pittsburgh from 1953 until his retirement in 1986. Dr. Ferguson was a visionary force behind the evolution and growth of the clinical, research, and training programs of the University of Pittsburgh Department of Orthopaedic Surgery into the internationally respected program of excellence it is today.

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