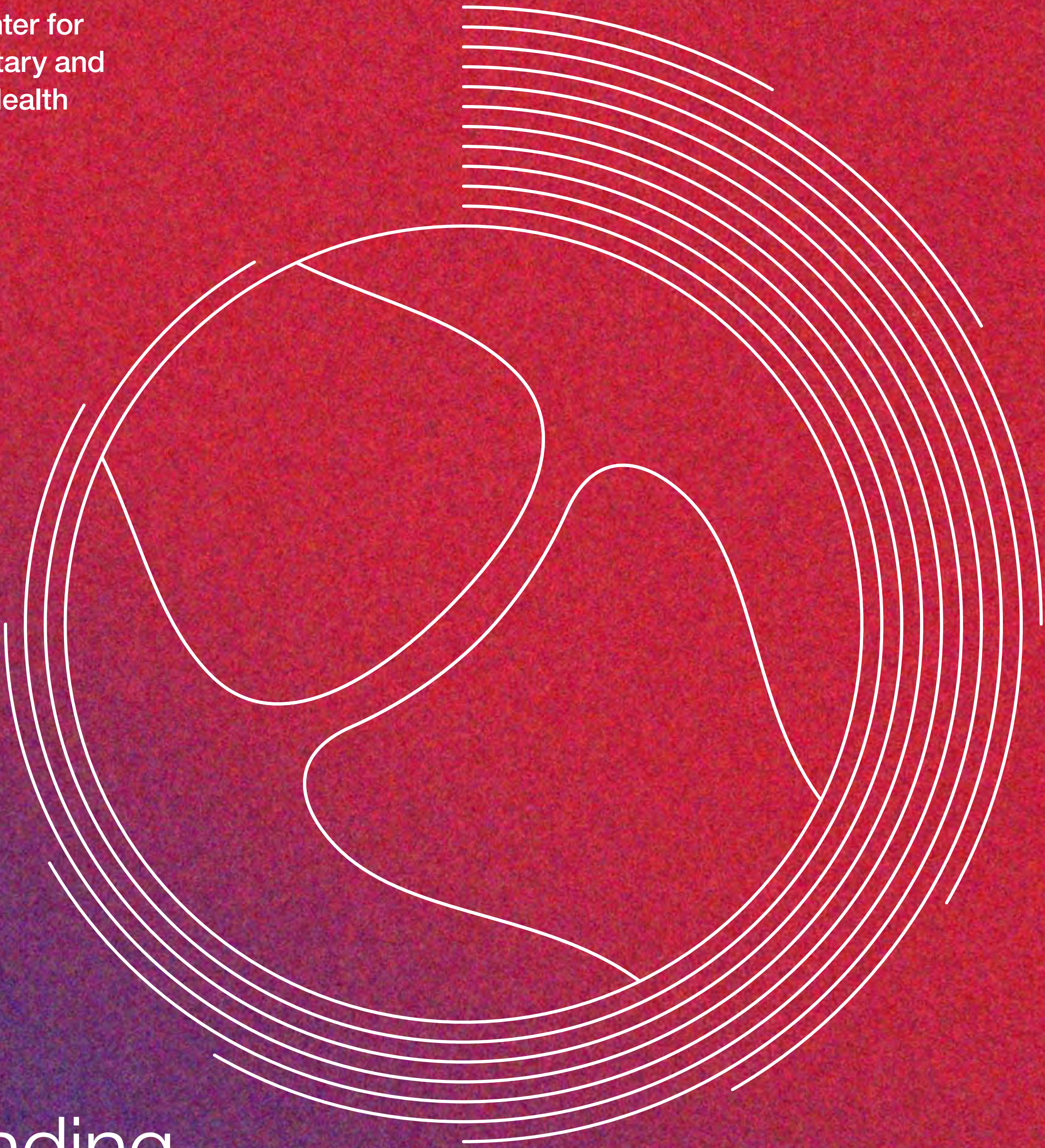
NIH National Center for Complementary and Integrative Health



Understanding and Restoring Whole Joint Health in Pain Management:

An NIH HEAL Initiative Workshop

July 25–26, 2023

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Tuesday, July 25, 2023

10:00 a.m. Welcome and NIH HEAL Overview: **Rebecca Baker, Ph.D.,** Director, National Institutes of Health (NIH) Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®

10:15 a.m. Opening Remarks: **Helene M. Langevin, M.D.,** Director, National Center for Complementary and Integrative Health (NCCIH)

10:30 a.m. Opening Remarks: **Lindsey A. Criswell, M.D., M.P.H., D.Sc.,** Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

10:45 a.m. *Session One: Structural and Mechanical Factors in Joint Pain*

Chair: Rebecca Lenzi, Ph.D., NIAMS

Co-Chair: Melissa Ghim, Ph.D., National Institute of Dental and Craniofacial Research (NIDCR)

External Co-Chair: Richard F. Loeser, M.D., University of North Carolina School of Medicine

10:50 a.m. **Richard F. Loeser, M.D.,** University of North Carolina School of Medicine. *Osteoarthritis pathobiology*

11:02 a.m. **Hai Yao, Ph.D.,** Clemson University/Medical University of South Carolina. *Deciphering relationships between joint structure, function, and pain through whole joint biomechanical modeling*

11:14 a.m. **Ali Guermazi, M.D., Ph.D.,** Boston University Chobanian and Avedisian School of Medicine. *Structural damage in osteoarthritis and relationship with pain*

11:26 a.m. **David Walsh, Ph.D.,** University of Nottingham. *Subchondral bone as a source of pain*

11:38 a.m. Panelist Comments for Additional Perspectives

Farshid Guilak, Ph.D., Washington University School of Medicine in St. Louis

Joel A. Block, M.D., Rush University Medical Center

Thomas L. Clemens, Ph.D., University of Maryland School of Medicine

Laura Stone, Ph.D., University of Minnesota

Tristan Maerz, Ph.D., University of Michigan

11:48 a.m. Panel Discussion

12:20 p.m. Questions and Answers From the Zoom and VideoCast Audiences

12:30 p.m. LUNCH

1:30 p.m. *Session Two: Mechanisms of Whole Joint Pathology*

Chair: John Williams, Ph.D., National Institute on Aging

Co-Chair: Wen Chen, Ph.D., NCCIH

External Co-Chair: Martin Lotz, M.D., Scripps Research

1:35 p.m. **Carla Stecco, M.D.,** University of Padua. *Myofascial component of joint pain*

1:47 p.m. **Anne-Marie Malfait, M.D., Ph.D.,** Rush University Medical Center. *Structural neuroplasticity in joint innervation*

1:59 p.m. **Kelsey H. Collins, Ph.D.,** University of California, San Francisco. *The role of adipose tissue crosstalk and systemic factors in knee joint damage and pain*

2:11 p.m. **Martin Lotz, M.D.,** Scripps Research. *Intertissue communication*

2:23 p.m. Panelist Comments for Additional Perspectives

Dana Orange, M.D., M.Sc., Rockefeller University

Nick J. Willett, Ph.D., University of Oregon

Marcas Bamman, Ph.D., Florida Institute for Human and Machine Cognition

Alisa J. Johnson, L.M.T., Ph.D., University of Florida

Tuhina Neogi, M.D., Ph.D., Boston University Chobanian and Avedisian School of Medicine

2:33 p.m. Panel Discussion

3:05 p.m. Questions and Answers From the Zoom and VideoCast Audiences

3:15 p.m. BREAK

3:30 p.m. *Session Three: Differences Among Joint Types and Joint Pain Populations*

Chair: Melissa Ghim, Ph.D., NIDCR

Co-Chair: Miguel R. Ossandon, Ph.D., National Cancer Institute

External Co-Chair: Clair A. Francomano, M.D., Indiana University School of Medicine

3:35 p.m. **Clair A. Francomano, M.D.,** Indiana University School of Medicine. *Heritable disorders of connective tissue as models for human joint disease*

3:47 p.m. **Beth A. Winkelstein, Ph.D.,** University of Pennsylvania. *Temporomandibular joint and spinal facet joint pain: lessons learned from their similarities and differences*

3:59 p.m. **Vijay Goel, Ph.D.,** University of Toledo. *Structure and function: spine and sacroiliac joint*

4:11 p.m. **Amanda Nelson, M.D., M.S.C.R., Rh.M.S.U.S.,** University of North Carolina. *Differences by sex and race in multiple joint osteoarthritis*

4:23 p.m. Panelist Comments for Additional Perspectives

Leslie Russek, P.T., D.P.T., Ph.D., Clarkson University

Anna Shmagel, M.D., M.Sc., AbbVie

Kendi Hensel, D.O., Ph.D., Texas College of Osteopathic Medicine

Laura C. Cappelli, M.D., M.H.S., Johns Hopkins University School of Medicine

Gary F. Bouloux, D.D.S., M.D., Emory University School of Medicine

4:33 p.m. Panel Discussion

5:05 p.m. Questions and Answers From the Zoom and VideoCast Audiences

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5:30 p.m. ADJOURN

Wednesday, July 26, 2023

10:00 a.m. Welcome Back: **Walter Koroshetz, M.D.,** Director, National Institute of Neurological Disorders and Stroke (NINDS)

10:15 a.m. *Session Four: Interventions to Address Joint Pain and Disease*

Chair: Alex Tuttle, Ph.D., NCCIH

Co-Chair: Michael L. Oshinsky, Ph.D., NINDS

External Co-Chair: Kathleen Sluka, P.T., Ph.D., University of Iowa

10:20 a.m. **Kathleen Sluka, P.T., Ph.D.,** University of Iowa. *Does transcutaneous electrical nerve stimulation work for pain control?*

10:32 a.m. **Dan Rhon, P.T., D.P.T., D.Sc., Ph.D.,** Uniformed Services University of the Health Sciences. *Manual therapy for treating lower extremity osteoarthritis-related joint pain: effectiveness and proposed therapeutic mechanisms*

10:44 a.m. **Stephen Messier, Ph.D.,** Wake Forest University. *Diet and exercise interventions: effects on pain*

10:56 a.m. **Preeti Raghavan, M.B.B.S.,** Johns Hopkins Medicine. *Mechanisms underlying a novel pharmacologic approach to restoring whole joint health*

11:08 a.m. Panelist Comments for Additional Perspectives

Gunnar Brolinson, D.O., Edward Via College of Osteopathic Medicine

Katie Butera, P.T., D.P.T., Ph.D., University of Delaware

Gert Bronfort, D.C., Ph.D., University of Minnesota

Christine Goertz, D.C., Ph.D., Duke University School of Medicine

Brian Noehren, P.T., Ph.D., University of Kentucky

11:18 a.m.	Panel Discussion
11:50 p.m.	Questions and Answers From the Zoom and VideoCast Audiences
Noon	LUNCH
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	Chair: Qi Duan, Ph.D., National Institute of Biomedical Imaging and Bioengineering
	Co-Chair: Julia Bachman, Ph.D., NINDS
	External Co-Chair: Riccardo Lattanzi, Ph.D., New York University
1:05 p.m.	**Riccardo Lattanzi, Ph.D.,** New York University. *Quantitative magnetic resonance imaging to characterize joint diseases*
1:17 p.m.	**Valentina Pedoia, Ph.D.,** University of California, San Francisco. *Uncovering associations between data-driven learned quantitative magnetic resonance imaging biomarkers and chronic pain*
1:29 p.m.	**Kevin Koch, Ph.D.,** Medical College of Wisconsin. *Methodology and analysis of dynamic carpal bone measures derived from 4-dimensional magnetic resonance imaging*
1:41 p.m.	**Ziying Yin, Ph.D.,** Mayo Clinic. *Magnetic resonance elastography-based slip interface imaging to assess the mobility of the myofascial interface: a feasibility study*
1:53 p.m.	Panelist Comments for Additional Perspectives
	Scott Banks, Ph.D., University of Florida
	Feliks Kogan, Ph.D., Stanford University
	Lucia Cevidanes, D.D.S., M.S., Ph.D., University of Michigan
	Siddhartha Sikdar, Ph.D., George Mason University
2:03 p.m.	Panel Discussion
2:35 p.m.	Questions and Answers From the Zoom and VideoCast Audiences
2:45 p.m.	BREAK
3:15 p.m.	*Session Six: General Discussion*
	Chair: Helene M. Langevin, M.D., NCCIH
	Co-Chair: Gayle Lester, Ph.D., NIAMS
3:20 p.m.	Open Discussion of Challenges and Opportunities
4:05 p.m.	Chair Summary
4:20 p.m.	Co-Chair Summary

4:35 p.m. **Summary and Concluding Remarks:** **Alex Tuttle, Ph.D.,** Program Director and Workshop Lead, NCCIH

4:45 p.m. **ADJOURN**

Welcome and Opening Remarks

Rebecca Baker, Ph.D., Director, National Institutes of Health Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®

Dr. Baker is the director of the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, in the Office of the Director, National Institutes of Health (NIH). Dr. Baker helped develop the NIH HEAL Initiative and leads coordination of initiative programmatic activities between the NIH Office of the Director and relevant Institutes and Centers. She also provides expert advice to and represents the NIH director on Initiative-related activities, including interagency efforts in pain and opioid research and policy. Prior to this position, Dr. Baker served as special assistant to the NIH director and the principal deputy director working directly with NIH leadership to analyze complex biomedical research policy issues and assist in the development of new science and policy initiatives. She earned her Ph.D. from the University of Pennsylvania and her bachelor's degree from Cornell University.

Helene M. Langevin, M.D., Director, National Center for Complementary and Integrative Health

Dr. Langevin was sworn in as director of the National Center for Complementary and Integrative Health on November 26, 2018. Previously, she was the director of the Osher Center for Integrative Medicine in Boston, jointly based at Brigham and Women's Hospital and Harvard Medical School, and a professor in residence of medicine at Harvard Medical School. She was a professor of neurological sciences at the University of Vermont Larner College of Medicine in Burlington until 2012. Her research has centered around the role of connective tissue in chronic musculoskeletal pain and the mechanisms of acupuncture, manual, and movement-based therapies. Her more recent work has focused on the effects of stretching on inflammation resolution mechanisms within connective tissue. Dr. Langevin received her medical degree from McGill University in Montreal, Canada. She completed a postdoctoral research fellowship in neurochemistry in the Medical Research Council Neurochemical Pharmacology Unit at the University of Cambridge, England, and a residency in internal medicine and postdoctoral fellowship in endocrinology and metabolism at the Johns Hopkins Hospital in Baltimore.

Lindsey A. Criswell, M.D., M.P.H., D.Sc., Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Criswell became the director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) in February 2021. As NIAMS director, Dr. Criswell oversees the Institute's annual budget of nearly $625 million, which supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. Prior to joining NIAMS, Dr. Criswell was vice chancellor of research at the University of California, San Francisco (UCSF). A board-certified rheumatologist, Dr. Criswell was also a professor of rheumatology and a professor of orofacial sciences at UCSF. Dr. Criswell was a principal investigator on multiple National Institutes of Health grants and published more than 250 peer-reviewed journal papers. Her research focused on the genetics and epidemiology of human autoimmune disease, particularly rheumatoid arthritis and systemic lupus erythematosus. Dr. Criswell has a bachelor's degree in genetics and a master's degree in public health from the University of California, Berkeley, and an M.D. from UCSF. She earned a D.Sc. in genetic epidemiology from the Netherlands Institute for Health Sciences, Rotterdam. She completed a residency in internal medicine and a fellowship in rheumatology.

Session One: Structural and Mechanical Factors in Joint Pain

Chair: Rebecca Lenzi, Ph.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Lenzi, program director, Division of Extramural Research, National Institute of Arthritis and Musculoskeletal and Skin Diseases at the National Institutes of Health (NIH), also serves as co-lead of the Back Pain Consortium Research Program and the Restoring Joint Health and Function to Reduce Pain Consortium for the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®. Dr. Lenzi served in the Office of Strategic Coordination at NIH where she worked in evaluation, outreach, and strategic planning for NIH Common Fund programs in several areas related to cellular and molecular biology, pain, bioinformatics, genomics, physical activity, and workforce development. She received her bachelor's degree from the University of Notre Dame and her doctorate in biology from Georgetown University. She pursued postdoctoral work with the U.S. Military HIV Research Program, where she studied immunogenetic factors that influence HIV infection and the course of clinical diseases.

Co-Chair: Melissa Ghim, Ph.D., National Institute of Dental and Craniofacial Research

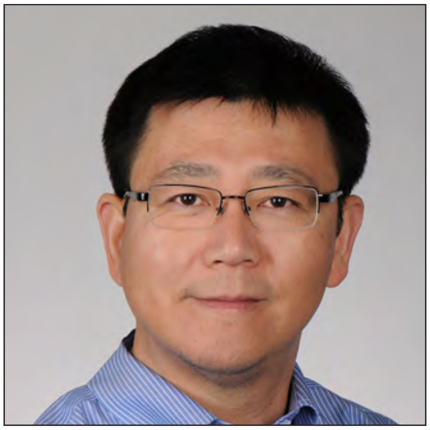
Dr. Ghim is the director of the Neuroscience of Orofacial Pain and Temporomandibular Disorders program at the National Institute of Dental and Craniofacial Research (NIDCR). Dr. Ghim received her Ph.D. at the University of Maryland, College Park, in the Integrative Neuroscience Program and was a postdoctoral associate at State University of New York Upstate Medical University in the Department of Neurosurgery. Prior to joining NIDCR, Dr. Ghim served as a senior program director at the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) on content related to gender diversity and the underrepresentation of women in the biomedical research workforce. Dr. Ghim led and coordinated various programs and projects, including the NIH Prize for Enhancing Faculty Gender Diversity, the career development goal of the Trans-NIH Strategic Plan for Research on Women's Health, and the early development of the NIH Sex as a Biological Variable Primer course. She was the NIH task lead on the National Academies of Sciences, Engineering, and Medicine consensus study and report "Promising Practices for Addressing the Underrepresentation of Women in Science, Engineering, and Medicine." Prior to joining ORWH, Dr. Ghim served as the training director at the National Institute on Drug Abuse.

External Co-Chair: Richard F. Loeser, M.D., University of North Carolina School of Medicine

Dr. Loeser is the Joseph P. Archie, Jr. Eminent Professor of Medicine in the Division of Rheumatology, Allergy, and Immunology at the University of North Carolina (UNC) School of Medicine. He also serves as director of the Thurston Arthritis Research Center and associate director of the UNC Core Center for Clinical Research, which is funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Dr. Loeser received his medical degree from West Virginia University School of Medicine and completed his residency and fellowship training in internal medicine, rheumatology, and geriatrics at Wake Forest School of Medicine. His research interests include the basic mechanisms relevant to the development of osteoarthritis, including the role of aging. His laboratory studies human joint tissue cells and mouse models of osteoarthritis, as well as biological samples from human clinical osteoarthritis studies. He serves as co-editor of *Arthritis and Rheumatology*.

Osteoarthritis Pathobiology

Osteoarthritis (OA) is a multifactorial condition characterized by progressive degradation and loss of articular cartilage, subchondral bone thickening, osteophyte formation, and varying degrees of synovial hyperplasia and synovitis. Additional intra-articular tissues are often affected, including the meniscus in the knee, ligaments, and local fat pads. Because the articular cartilage is not directly innervated, pain in OA originates from other joint tissues. Joint tissues remodel in response to mechanical loading to adapt to the loads. Excessive or abnormal loading that exceeds the capacity of the joint to adapt results in pathologic remodeling that leads to OA. Failure to adapt to loading can occur due to genetic factors and changes related to aging. OA has been characterized as a nonhealing chronic wound with activation of the innate immune system, resulting in increased production of proinflammatory mediators and matrix-degrading enzymes. Senescent cells have been identified in joint tissues affected by OA. Senescent cells can assume the senescence-associated secretory phenotype (SASP), characterized by production of the same proinflammatory factors and matrix-degrading enzymes seen in OA joints, suggesting an important role for senescent cells in OA. The excessive remodeling and chronic wound environment of the joint results in a positive feed-forward loop facilitated in part by the ability of matrix breakdown products (matrikines) to stimulate further production of proinflammatory mediators and matrix-degrading enzymes. Although it is well established that OA is a complex pathobiological process and not simply “wear and tear,” interventions proven to stop or reverse the disease process are lacking.



Hai Yao, Ph.D., Clemson University/Medical University of South Carolina

Dr. Yao is the Ernest R. Norville Endowed Chair in Biomedical Engineering and professor of bioengineering at Clemson University. He is also a professor of oral health sciences at the Medical University of South Carolina (MUSC) and serves as associate chair for the Clemson–MUSC joint bioengineering program. He is director of the Centers of Biomedical Research Excellence for the National Institute of General Medical Sciences and leads the South Carolina Translational Research Improving Musculoskeletal Health initiative at Clemson and a National Institute of Dental and Craniofacial Research training program at MUSC. His research focuses on the biomechanical function, degeneration, and regeneration of musculoskeletal systems, especially the temporomandibular joint. His research will facilitate earlier diagnosis, novel treatment development, and outcomes assessment of temporomandibular disorders. He served on a committee for a recent temporomandibular disorder study report for the National Academies of Sciences, Engineering, and Medicine. Dr. Yao received his doctorate in biomedical engineering from the University of Miami and his postdoctoral training in musculoskeletal bioengineering at the Georgia Institute of Technology.

Deciphering Relationships Between Joint Structure, Function, and Pain Through Whole Joint Biomechanical Modeling

Musculoskeletal systems feature intimate relationships between form and function, with a gracefully efficient physical order that manifests itself on the organ, tissue, cell, and molecular levels. The existence of such a hierarchy of structural and functional harmony is closely regulated by mechanical forces. Breakdown of this harmony leads to pathological changes, eventually resulting in dysfunction and pain. Therefore, deciphering the relationship between joint structure, function, and pain is key to the fundamental mechanisms of joint disorders and developing therapeutic approaches, whether structural, functional, neurological, or behavioral, to restore joint function and alleviate pain. Computational biomechanical modeling at the whole joint level has emerged as an essential tool for joint research and clinics, offering numerous advantages that make it indispensable for unraveling the complex nature of joint structure-function-pain relationships. These advanced models provide a detailed representation of the joint's intricate anatomy, biomechanics, and mechanobiology, empowering researchers and clinicians to effectively identify the factors contributing to joint pain and dysfunction. By facilitating the exploration of diverse scenarios, computational models enable the examination of complex relationships among various factors, including those difficult to investigate simultaneously with conventional experimental methods (such as strain, neural distribution, and pain). Our team has been implementing this multifaceted approach to comprehend the interplay among elements contributing to temporomandibular joint (TMJ) pain, including mechanical loading, strain distribution, and nerve activation. Integrating these factors into a cohesive model allows researchers to gain a deeper understanding of the complex pain mechanisms associated with TMJ disorders.

Ali Guermazi, M.D., Ph.D., Boston University Chobanian and Avedisian School of Medicine

Dr. Guermazi is professor of radiology and medicine, director of the quantitative imaging center, and assistant dean of diversity and inclusion at Boston University Chobanian and Avedisian School of Medicine. He is also chair of radiology for the VA Boston Healthcare System. Dr. Guermazi researches musculoskeletal diseases and has made scientific contributions to the use of magnetic resonance imaging for assessing the diagnostics, incidence, and disease progression of osteoarthritis. His work has focused on identifying structural risk factors for developing and worsening osteoarthritis. Before joining Boston University, he was director of osteoporosis and arthritis research at the University of California, San Francisco, and director of clinical research at Synarc in San Francisco. He is editor in chief of *Skeletal Radiology* and has been president of the International Society of Osteoarthritis Imaging since 2019. Dr. Guermazi spent 12 years in Paris and worked at the prestigious Saint-Louis Hospital. He obtained his medical degree from the University of Sfax, his medical specialty from René Descartes University, and his doctorate from Jikei University. He is a visiting professor in Japan at Jikei University and Kyoto Prefectorial University.

Structural Damage in Osteoarthritis and Relationship With Pain

Osteoarthritis (OA) is assessed radiographically either by semiquantitative scoring systems such as the Kellgren-Lawrence (KL) grading scale or the Osteoarthritis Research Society International (OARSI) atlas, which grades tibiofemoral joint space narrowing and osteophytes separately for each compartment. Magnetic resonance imaging (MRI) is very sensitive to early changes that cannot be seen on radiographs. Its role for elucidating associations with pain incidence, progression, or fluctuation has been previously shown. In population-based studies, a significant discordance between radiographically diagnosed OA and knee pain has been reported. The underlying pathologies leading to pain cannot be readily discerned from radiography alone and may require consideration of other factors. Utilizing imaging modalities such as MRI, several structural alterations such as meniscal tears, subchondral bone marrow lesions, subarticular bone attrition, synovitis, and effusion have been related to knee pain. Furthermore, changes in bone marrow lesions and inflammatory markers on MRI are associated with fluctuations in pain in patients with knee OA. How much of the variance in pain is accounted for by structural change is not fully understood. One reason for this difficulty is that most studies focused on late disease stages when numerous pathologic changes are already commonly present. Evidence suggests that large bone marrow lesions are strongly associated with knee pain, followed by synovitis and effusion, and potentially also cartilage volume and thickness. Interpretation of these relationships is challenging, as it is not clear whether the associations are causal or are markers of the severity of other structural pathology that may contribute to pain.

David Walsh, Ph.D., University of Nottingham

Dr. Walsh, professor of rheumatology, University of Nottingham, is also a consulting rheumatologist at Sherwood Forest Hospitals National Health Service Foundation Trust. For 21 years he has delivered multidisciplinary pain-management programs for people with low-back pain. In 2010, he established the university's Pain Centre Versus Arthritis with a multidisciplinary team that includes researchers in the fields of preclinical neuroscience, psychology, neuroimaging, orthopedics, genetics, epidemiology, and evidence synthesis. Through translational research on mechanisms within the joints and the nervous system that interact with psychosocial factors to produce arthritis pain, the center develops new and improved treatments. To improve the lives of people with chronic pain, Dr. Walsh develops targeted treatment approaches based on mechanistic pain phenotypes. His randomized controlled trials employ pharmacologic and nonpharmacologic interventions. Since 2020, he has been the inaugural program director leading the creation of the U.K. Research and Innovation/Versus Arthritis Advanced Pain Discovery Platform. He was a member of the guideline development group for the National Institute for Health and Care Excellence guidelines for the management of low-back pain and sciatica and continues to combine research with clinical practice in rheumatology.

Subchondral Bone as a Source of Pain

Pain is the cardinal symptom of most forms of arthritis and a major source of distress, disability, and health care utilization. Subchondral bone is a key structure leading to arthritis pain. Bone marrow lesions (BMLs) on magnetic resonance imaging are associated with current and progressive osteoarthritis pain. Pain is associated with histological correlates of BMLs, including fibrovascular and inflammatory infiltration of subchondral bone spaces, breaching of the osteochondral junction, and vascular and neuronal ingrowth into articular cartilage. Neurotrophic and sensitizing factors are expressed within osteoarthritic subchondral bone. Similar associations have been noted but less fully investigated in rheumatoid arthritis and in spondylosis. Pain is a complex experience underpinned by multiple interacting mechanisms. Osteoarthritis pain may be either constant or intermittent, and pain on weight-bearing is particularly associated with subchondral pathology. Effective interventions for advanced osteoarthritis include total joint replacement surgery and osteotomy, each of which alters biomechanical stresses through subchondral bone, as well as subchondral innervation. Subchondral bone might be not the only mediator of all arthritis pain, with contributions from synovitis, neuronal sensitization, central nervous system pain processing, and psychological and social factors. However, better understanding and detection of mechanisms within subchondral bone have huge potential to improve management and relieve the burden of arthritis.

Additional Panelist Biographies

Farshid Guilak, Ph.D., Washington University School of Medicine in St. Louis

Dr. Guilak is the Mildred B. Simon Research Professor of Orthopaedic Surgery at Washington University School of Medicine in St. Louis. He is also director of research for St. Louis Shriners Hospitals for Children and codirector of the Washington University Center of Regenerative Medicine. His laboratory focuses on multidisciplinary approaches that combine biology and bioengineering to develop new stem cell therapies or pharmacologic treatments for osteoarthritis and rheumatoid arthritis, with a particular emphasis on pain and functional outcomes. He is the past president of the Orthopaedic Research Society and has served as editor in chief of the *Journal of Biomechanics* for the past 20 years. He has won numerous national and international awards for his research, and in 2022, he became a fellow at the National Academy of Engineering, National Academy of Medicine, and National Academy of Inventors for his work in the fields of regenerative medicine and mechanobiology and his applications of synthetic biology in those fields.

Joel A. Block, M.D., Rush University Medical Center

Dr. Block is the Willard L. Wood, M.D., Professor of Rheumatology, professor of medicine, and chief of the Division of Rheumatology at Rush University Medical Center. His early research focused on cartilage biology and the chondrocytic proteoglycans, and several of his human chondrocyte cell models remain in use in laboratories on four continents. His interests subsequently broadened to include the role of aberrant biomechanical loading in lower extremity osteoarthritis. He leads a large multidisciplinary group that studies osteoarthritis from a broad perspective, including joint tissue biology, physiology of pain, and mechanical mediators of osteoarthritis progression, all with a focus on identifying novel therapeutic strategies. Dr. Block is a member of the editorial board of *Osteoarthritis and Cartilage* and served as editor in chief from 2016 to 2022. In addition, he is a member of the editorial boards of the *Journal of Orthopaedic Research* and *Journal of Clinical Rheumatology* and is the president-elect of the United States Bone and Joint Initiative. He has served on and chaired numerous grant review panels at the National Institutes of Health, Arthritis Foundation, U.S. Department of Defense, and several overseas granting authorities.

Thomas L. Clemens, Ph.D., University of Maryland School of Medicine

Dr. Clemens, professor of orthopaedic surgery, University of Maryland School of Medicine, has held faculty positions at Columbia University, Cedars-Sinai Medical Center, the University of Cincinnati, and the University of Alabama at Birmingham, where he established a doctoral program sponsored by Howard Hughes. Dr. Clemens received a doctorate in biochemistry from the University of London and completed postdoctoral training as a research fellow in medicine at Massachusetts General Hospital. Dr. Clemens was the Lewis Cass Spencer Professor and vice chair for research in the Department of Orthopaedic Surgery at the Johns Hopkins School of Medicine from 2009 to 2022. His research has been funded by the National Institutes of Health and the U.S. Department of Veterans Affairs and focuses on cellular and molecular mechanisms that control the development and repair of skeletal muscle and bone. He has authored more than 170 publications, served as editor in chief of the *Journal of Bone and Mineral Research*, and received the prestigious Louis V. Avioli Founders Award from the American Society of Bone and Mineral Research in 2013.

Laura Stone, Ph.D., University of Minnesota

Dr. Stone, professor of anesthesiology, University of Minnesota, has used preclinical models and patient populations to investigate the mechanisms underlying low-back and musculoskeletal pain, optimization of pharmacologic and nonpharmacologic treatments, and the epigenetic regulation of chronic pain. She received her doctorate in neuroscience from the University of Minnesota in 1999. As a postdoctoral trainee at Oregon Health and Science University, she was the first recipient of the postdoctoral John J. Bonica Training Fellowship from the International Association for the Study of Pain. After working in both biotechnology and academia, she joined the faculty at McGill University in 2007, where she cofounded and directed the Quebec Back Pain Consortium. Dr. Stone has been an inventor on seven patents, has received funding from the National Institutes of Health and the Canadian Institutes of Health Research, and has co-authored more than 80 manuscripts.

Tristan Maerz, Ph.D., University of Michigan

Dr. Maerz, assistant professor of orthopaedic surgery and biomedical engineering, University of Michigan, was born and raised in southern Germany and moved to Michigan as a teenager. He completed his doctoral degree in biomedical engineering at Wayne State University in 2015 and joined the Department of Orthopaedic Surgery at Michigan Medicine in 2017 after an 8-year tenure as an orthopaedic research engineer at Beaumont Hospital. Through the study of immunological events that occur following traumatic joint injury, Dr. Maerz's laboratory identifies novel therapeutic strategies for the treatment of post-traumatic osteoarthritis. He serves on Federal and international study sections and is active in the Orthopaedic Research Society, his primary academic community. With a highly trainee-oriented and collaborative philosophy, the Maerz lab is home to a diverse group of scientists spanning the fields of engineering, physiology, computational biology, and immunology.

Session Two: Mechanisms of Whole Joint Pathology

Chair: John Williams, Ph.D., National Institute on Aging

Dr. Williams, physiologist, bone cell biologist, Division of Aging Biology, National Institute on Aging, is a program officer in the Aging Physiology Branch and oversees the Kidney and Urogenital Program, the Bone and Cartilage Program, and the Reproductive and Endocrine Program. He covers grants investigating the basic biology of muscle, bone, cartilage, and wound healing. In 1993, Dr. Williams switched from insulin signal transduction to osteoclast biology and did research primarily on bone metabolism until 2007. Dr. Williams was previously an associate professor in nephrology with a joint appointment in the Department of Physiology at the University of Kentucky College of Medicine. Dr. Williams received his doctorate from Oklahoma State University and postdoctoral training at Washington University in St. Louis.

Co-Chair: Wen Chen, Ph.D., National Center for Complementary and Integrative Health

Dr. Chen, branch chief of Basic and Mechanistic Research, Division of Extramural Research, National Center for Complementary and Integrative Health (NCCIH), oversees fundamental science research, translational research, and intervention optimization research, as well as methodology and technology development related to all complementary and integrative health approaches. Dr. Chen received her doctorate in biological chemistry and molecular pharmacology from Harvard University. She also earned a master's degree in medical sciences as part of the Harvard-Markey Medical Scientist training program at Harvard Medical School. Dr. Chen did her postdoctoral training in proteomics at the Massachusetts Institute of Technology. Before joining NCCIH, she worked as a scientific editor at *Neuron*, program coordinator at the National Institute of Mental Health, and program director at the National Institute on Aging overseeing a research portfolio on sensory and motor disorders of aging.

External Co-Chair: Martin Lotz, M.D., Scripps Research

Dr. Lotz, professor, Department of Molecular Medicine, Scripps Research, has performed research on joint biology and arthritis pathogenesis since 1983. His research has identified aging-related changes in joint tissues that determine risk for osteoarthritis, and his studies have discovered that cellular homeostasis mechanisms that are compromised in aging represent an early event leading to tissue damage. The Joint Omics project uses next generation sequencing, single-cell, and spatial technologies to uncover aging- and disease-associated changes in the transcriptomes in joint tissues. Data from this project are being used to identify key regulators of the abnormal phenotypes of cells, with a focus on transcription factors. Dr. Lotz's current investigations address the role of transcription factors and the circadian rhythm pathway in cartilage homeostasis and osteoarthritis pathogenesis. These transcription factors are also being investigated in intervertebral disc degeneration. Efforts to discover small molecules and genetic approaches to target transcription factors in the treatment of joint and spine diseases are ongoing.

Carla Stecco, M.D., University of Padua

Dr. Stecco, orthopedic surgeon, professor of anatomy and movement sciences, University of Padua, is a founding member of the Fascial Manipulation Association and the Fascial Research Society. She is also a member of the Italian Society of Anatomy and Histology and the European Association of Clinical Anatomy. Her scientific activity is devoted to the study of anatomy of human fasciae from the macroscopic, histologic, and pathologic perspectives. She organizes and conducts courses in Italy and in other countries about the theory of fascial anatomy and the practice of fascial manipulation technique. Dr. Stecco is the author of more than 180 papers, the first photographic atlas of the human fasciae, and various books translated into 11 languages. She received her medical degree in 2002 and her specialization in orthopaedic surgery in 2008 from the University of Padua.

Myofascial Component of Joint Pain

The "motor unit" or the "muscle" has long been considered the quantal element in the control of movement. However, in recent years, new research has proved the strong interaction between muscle fibers and intramuscular connective tissue and between muscles and fasciae, suggesting that the muscles can no longer be considered the only elements that organize movement. In addition, innervation and vascularization of muscle are strongly connected with intramuscular connective tissue. In this presentation, the concept of "myofascial unit" will be discussed, focusing on the bilateral dependent relationship, both anatomical and functional, that occurs between fascia, muscle, joints, nerves, and vessels. Consequently, new studies about the possible role of fasciae in pain will be presented, with particular attention to the microscopic anatomy of the fasciae, their layer conformation, their innervation, and the hyaluronan amount that defines the tissue hydration and the ability to glide. Finally, the presence of various receptors for hormones, such as estrogen, relaxin, the endocannabinoid system, and angiotensin, will be discussed in this presentation, showing that the hormonal inputs are able to modify the microscopic aspects of the fasciae. This knowledge could contribute to understanding of the biomechanical behavior of the fasciae and their role in acute and chronic myofascial pain.

Anne-Marie Malfait, M.D., Ph.D., Rush University Medical Center

Dr. Malfait is a professor in the Department of Internal Medicine, Division of Rheumatology, and the George W. Stuppy, M.D., Chair of Arthritis at Rush University Medical Center. Her early training at Ghent University was in rheumatology, and her basic research training focused on cartilage biology. During her postdoctoral training at the Kennedy Institute of Rheumatology, she was involved in early inflammatory arthritis experiments that targeted the tumor necrosis factor. In 2001, she joined the pharmaceutical industry as part of a team that developed disease-modifying osteoarthritis drugs. In 2009, Dr. Malfait established a research group at Rush University that focused on the relationship between joint damage and the neurobiological processes that underlie pain associated with rheumatic diseases. She is the director of the Chicago Center on Musculoskeletal Pain for the National Institute of Arthritis and Musculoskeletal and Skin Diseases and is the principal investigator of Restoring Joint Health and Function to Reduce Pain, a consortium funded by the National Institutes of Health aimed at mapping the joint-nerve interactome of the knee. She is the co-editor in chief of *Osteoarthritis and Cartilage* and serves on the scientific advisory board of the Arthritis National Research Foundation.

Structural Neuroplasticity in Joint Innervation

A critical gap that hinders the development of novel, effective pain therapeutics for osteoarthritis (OA) is our incomplete understanding of the nociceptive innervation of the joint. Innervation patterns of normal musculoskeletal structures underpin nociception, and all joint tissues, including synovium, subchondral bone, muscles, ligaments, tendons, and periosteum, are densely innervated. Articular cartilage is aneural. Importantly, the sensory innervation of the joint is not static but shows tremendous plasticity in the course of joint disease. For example, in human osteoarthritic knee joints and in rodent models of knee OA, osteochondral channels are present in the sclerotic subchondral bone, and they can breach the tidemark. These osteochondral channels contain blood vessels and nociceptive C-fibers. In the OA knee, sprouting C-fibers have also been observed in the menisci and in osteophytes. Evidence from experimental models suggests that neo-innervation also occurs in the synovium in very early stages of OA. Synovial inflammation may, however, also be associated with reduced sensory innervation of the synovium, both in rheumatoid arthritis and in rodent or human OA. Alterations in joint innervation may contribute to pain in joint disease. A detailed description of joint innervation, including the anatomical distribution of nociceptors and nociceptor subsets (e.g., specific mechanosensitive subsets) in healthy and diseased knees, as well as the relationship with vascularization, will be necessary to fully understand joint pain. Drivers of neuroplasticity need to be identified.

Kelsey H. Collins, Ph.D., University of California, San Francisco

Dr. Collins is an assistant professor of orthopaedic surgery and director of the Laboratory for Musculoskeletal Crosstalk at the University of California, San Francisco. She received her doctorate in biomedical engineering from the University of Calgary. During her postdoctoral studies under the guidance of Farshid Guilak, Ph.D., at Washington University School of Medicine in St. Louis, she created a tissue engineering and regenerative medicine platform to determine the crosstalk signaling mechanisms between adipose and musculoskeletal tissues. For this work, she received the New Investigator Recognition Award from the Orthopaedic Research Society, was named among the inaugural class of rising stars in engineering in health by Columbia University, and received the Orthoregeneration Award from the Orthoregeneration Network Foundation. Her transition to independence has been supported by an award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases to investigate the role of adipokines in osteoarthritis susceptibility and pain and to generate a new class of osteoarthritis therapies.

The Role of Adipose Tissue Crosstalk and Systemic Factors in Knee Joint Damage and Pain

Obesity-induced osteoarthritis (OA) involves both metabolic and biomechanical factors, and a key link is excess adipose tissue. To separate the mechanistic contributions of adiposity, we used a mouse model of lipodystrophy (LD), in which the animals completely lack fat but maintain normal body mass. Unexpectedly, we observed that LD mice are protected from cartilage damage. When fat was transplanted into LD mice, protection from OA was reversed, implicating that adipose tissue and factors it secretes called adipokines—but not body weight—are critical mediators of joint degeneration. To determine which adipokines are involved in OA, we have developed a tissue engineering and regenerative medicine approach to generate designer fat pads that do not produce leptin, an adipokine associated with OA. By applying a multiomic approach that considers both the transcriptional landscape and the secretome of leptin knockout fat pads, we can objectively determine which pathways and fat-secreted targets are involved in the reintroduction of cartilage damage and pain in LD mice. We will discuss how cartilage injury may induce changes in systemic adipose external to the knee joint, illustrating a bidirectional crosstalk mechanism that can be harnessed for therapeutic development, strengthening the understanding of fat-cartilage crosstalk in OA. Finally, using parabiosis OA superimposition studies, we will share insights into the potential role of adipose cell migration compared to adipose cell signaling in response to injury. The spatial context of knee joint tissue changes and crosstalk in these studies will be presented using novel spatial transcriptomics approaches in mice.

Martin Lotz, M.D., Scripps Research (see biography on page 20)

Intertissue Communication

The intra-articular space represents a unique environment where direct tissue-tissue contact and mechanotransduction or exchange of soluble messengers maintain joint homeostasis and generate a whole joint response to injury and in disease. Intertissue communication is most evident by the involvement of all joint tissues in response to a primary insult to a single tissue such as cartilage, meniscus, or tendons and ligaments. In osteoarthritis, substantial progress has been accomplished in understanding changes and mechanisms in the individual joint tissues. But mechanisms that are shared between all tissues are poorly characterized and have not been pursued as targets for therapeutic intervention. Mediators of intertissue communication that promote spreading and chronicity of pathogenic signaling are potentially more promising therapeutic targets. This presentation will review mechanisms and mediators of intertissue communication within the joint, between articular cartilage, subchondral bone, meniscus, synovium, intra-articular adipose tissue, sensory nerves, and the vasculature. Approaches will illustrate how a whole joint cross-communication map can be generated; how dysregulation of these pathways in disease promotes inflammation, tissue damage, and pain; and how targeting these communication pathways holds promise for developing new therapeutic interventions.

Additional Panelist Biographies

Dana Orange, M.D., M.Sc., Rockefeller University

Dr. Orange is an assistant professor at Rockefeller University and an assistant attending rheumatologist at the Hospital for Special Surgery. Her research focuses on understanding the molecular underpinnings of rheumatoid arthritis symptoms, such as pain, morning stiffness, and flares. Dr. Orange received her medical degree from Weill Cornell Medicine at Cornell University and her master's degree from Rockefeller University. She completed her internal medicine residency at NewYork-Presbyterian Hospital and her fellowship in rheumatology at the Hospital for Special Surgery.

Nick J. Willett, Ph.D., University of Oregon

Dr. Willett, associate professor, Department of Bioengineering, Phil and Penny Knight Campus for Accelerating Scientific Impact, University of Oregon, has co-appointments in the orthopaedics department at Oregon Health and Science University and at the Portland VA Medical Center. Dr. Willett is also associate director for the Wu Tsai Human Performance Alliance at the University of Oregon, where he runs the Regenerative Rehabilitation Moonshot project. Dr. Willett received his doctorate in biomedical engineering from a joint Georgia Institute of Technology and Emory University program. His research focuses on developing novel technologies and therapies to create new tissues and repair different musculoskeletal tissues after loss from disease, trauma, or age. Dr. Willett's team works primarily with bone, muscle, and cartilage in the hopes of treating ailments ranging from degenerative diseases to sports injuries, including meniscal and tendon tears, traumatic injuries from blast wounds, and injuries due to car accidents. His research sits at the interface of engineering and clinical disciplines.

Marcas Bamman, Ph.D., Florida Institute for Human and Machine Cognition

Dr. Bamman is a senior research scientist and director of healthspan, resilience, and performance research at the Florida Institute for Human and Machine Cognition (IHMC). He leads translational human research on chronic disease, elite performers, biological underpinnings, and clinical outcomes. His research has been supported by Federal funding since the 1990s. Before joining IHMC in 2020, during a 25-year career at the University of Alabama at Birmingham, he was a professor in the school of medicine, founding director of the Center for Exercise Medicine, and a professor of regenerative and translational medicine. For the National Institutes of Health, Dr. Bamman served as director of the Rehabilitation Research Resource to Enhance Clinical Trials and the Medical Rehabilitation Research Resource Network coordinating center. He is an executive committee member for the Molecular Transducers of Physical Activity Consortium, is a fellow of the American College of Sports Medicine (ACSM), and was chair of the 2021 ACSM World Congress on the Basic Science of Exercise in Regenerative Medicine. Dr. Bamman has published more than 170 research papers, served on more than 90 grant review panels, and served as associate editor for three peer-reviewed journals.

Alisa J. Johnson, L.M.T., Ph.D., University of Florida

Dr. Johnson, research assistant professor, Pain Research and Intervention Center of Excellence, University of Florida, conducts clinical translational research to identify targetable factors driving variability in knee osteoarthritis pain and pain-related disability to guide the development of tailored, mechanism-based therapeutics. Dr. Johnson received her doctorate in experimental psychology from Baylor University and her postdoctoral training at the University of Florida under the mentorship of Roger Fillingim, Ph.D. She has also served as a visiting scholar for the Clinical and Translational Science Institute at the University of Florida. She is currently the principal investigator for a Resource Center for Minority Aging Research grant and is examining the contribution of myofascial tissue alterations in older adults with knee osteoarthritis pain. She is an active member of the U.S. Association for the Study of Pain and the Gerontological Society of America. Dr. Johnson's dedication to improving health outcomes in adults living with chronic pain stems from her 20-year clinical career as a massage therapist and is evidenced by her commitment to developing targeted interventions for improved pain management.

Tuhina Neogi, M.D., Ph.D., Boston University Chobanian and Avedisian School of Medicine

Dr. Neogi is professor of medicine and the Alan S. Cohen Professor of Rheumatology at Boston University Chobanian and Avedisian School of Medicine, professor of epidemiology at Boston University School of Public Health, and chief of rheumatology at Boston Medical Center. Her research focuses on osteoarthritis and gout, with particular focus on pain mechanisms. She is a past chair of the arthritis advisory committee for the U.S. Food and Drug Administration, has served on the boards of international societies, and has served on committees for the American College of Rheumatology (ACR) and the International Association for the Study of Pain, among others. Her work was recognized with the 2014 ACR Henry Kunkel Early Career Investigator Award for outstanding and promising independent contributions to rheumatology research, the 2022 Osteoarthritis Research Society International Clinical Research Award for her contributions to osteoarthritis research, and an honorary doctorate from Lund University in Sweden. She also received the 2016 Robert Dawson Evans Research Mentoring Award in recognition of her mentoring excellence. She has led or engaged in the development of new classification criteria for a number of rheumatic diseases and led ACR's national treatment guidelines for gout and osteoarthritis.

Session Three: Differences Among Joint Types and Joint Pain Populations

Chair: Melissa Ghim, Ph.D., National Institute of Dental and Craniofacial Research (see biography on page 11)

Co-Chair: Miguel R. Ossandon, Ph.D., National Cancer Institute

Dr. Ossandon, program director, Diagnostic Biomarkers and Technology Branch, National Cancer Institute, has a dual background in clinical laboratory and computer science. He began his work in cancer research in the Lombardi Comprehensive Cancer Center at Georgetown University, where he also trained in computer science as an undergraduate. Dr. Ossandon has worked at the National Cancer Institute since 2007 and manages a diverse grant portfolio that includes research on technologies for circulating tumor DNA, exosomes, and circulating tumor cells. He received his master's degree from The George Washington University and his doctorate in computer science from the University of Maryland, Baltimore County.

External Co-Chair: Clair A. Francomano, M.D., Indiana University School of Medicine

Dr. Francomano, professor of medical and molecular genetics, Indiana University School of Medicine, is an internist and medical geneticist who has focused throughout her career on the heritable disorders of connective tissue. She was the first clinical director for the National Human Genome Research Institute. She serves as chair of the Medical and Science Board for the Ehlers-Danlos Society and as a member of the steering committee for the International Consortium on Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders. In 2022, she served on a committee for the National Academies of Sciences, Engineering, and Medicine that reviewed the issue of disability in people with heritable disorders of connective tissue. Dr. Francomano has published more than 150 articles in peer-reviewed literature and has authored or edited four books.

Heritable Disorders of Connective Tissue as Models for Human Joint Disease

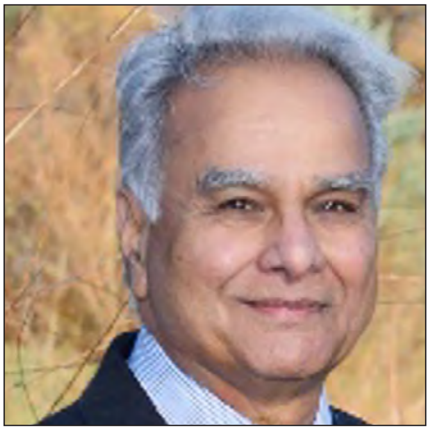
The heritable disorders of connective tissue (HDCT) are a widely diverse group of over 500 distinct inherited disorders, affecting the connective tissue in myriad ways. Many, if not most, of these conditions manifest joint involvement, and in many cases, the affected joints mirror those seen in common joint diseases, such as osteoarthritis and the inflammatory arthritides, causing joint pain in the general population. Knowledge about the specific genes and variants that underlie the HDCT can help inform our understanding of the effects of specific proteins and metabolic pathways that contribute to human joint disease. Moreover, understanding the precise effects of specific genes on the human skeleton can theoretically help in the formulation of rational therapeutic strategies to address joint pain in the general population. This talk will present an overview of the heritable disorders of connective tissue, the genes and gene families that underlie them, and some of the differences in the skeletal manifestations observed among them. These differences include the specific joints and types of connective tissue affected by the many HDCT, as well as differences in joint manifestations between women and men who live with these conditions.

Beth A. Winkelstein, Ph.D., University of Pennsylvania

Dr. Winkelstein is the Eduardo D. Glandt President's Distinguished Professor of Bioengineering and Neurosurgery at the University of Pennsylvania. Her laboratory studies the biomechanical mechanisms of painful spine and joint injuries and is defining the pathophysiological cellular mechanisms that drive chronic pain, the mechanotransduction of pain, and the potential diagnostic and therapeutic approaches for these disorders. She has pioneered several preclinical models of painful tissue injuries, including whiplash models, which are the first injury models with clinically relevant symptoms. Dr. Winkelstein's group implements rigorous engineering analyses to define biomechanical metrics and relate them to complicated neuronal plasticity responses throughout the nervous system. Her group also uses integrated imaging approaches to understand subfailure micro- and macroscale biomechanical tissue responses and uses functional imaging to identify cellular activation networks in the brain and spinal cord. Dr. Winkelstein received her bachelor's degree in bioengineering from the University of Pennsylvania and her doctorate in biomechanical engineering with a focus on neck injury biomechanics from Duke University. In 2002, she joined the faculty at the University of Pennsylvania after completing a postdoctoral fellowship at Dartmouth College on the neuroimmunology of pain.

Temporomandibular Joint and Spinal Facet Joint Pain: Lessons Learned From Their Similarities and Differences

Chronic joint pain is a widespread problem that frequently occurs with aging and trauma. Painful conditions in two such joints provide helpful platforms to elucidate the mechanical and molecular mechanisms contributing to synovial joint pain: the cervical spinal facet joints and the temporomandibular joint. Indeed, collectively, studies have revealed the combined influence of tissue mechanics, molecular processes, and nociception in joint pain and similarities across these anatomical sites. Both can involve trauma and disease progression, but there are also important differences within an individual and across demographic groups. For example, there are important differences in anatomic shape, loading, and innervation in normal conditions. In the injured, degenerated, and/or unhealthy joint, structural and biochemical changes can be induced, altering their microenvironment and modifying the biomechanics of their constitutive tissues, which themselves are innervated. Further, despite similarities in the joint, central nervous system, and supraspinal circuitry related to painful joints, their presentation, diagnoses, and interventions vary by sex and other important clinical and biomedical factors. Platforms such as in vitro and in vivo models provide complementary approaches to clinical data to better develop relevant and effective clinical treatments and care tailored to individual patients.



Vijay Goel, Ph.D., University of Toledo

Dr. Goel is a Distinguished University Professor, McMaster-Gardner Professor, endowed chair of bioengineering, and co-director of the Engineering Center for Orthopedic Research Excellence at the University of Toledo. He is known worldwide for his pioneering research in the field of spinal disorders, has multiple peer recognitions, including four lifetime achievement awards from four professional societies, and has authored multiple publications. He is also a very experienced life-science business strategist and entrepreneur and has licensed four of his concepts to companies. He conducts U.S. Food and Drug Administration (FDA)-required testing for multinational and startup companies and consults for various spine companies. Dr. Goel is involved in the design and development of several spinal devices, a novel-type calcium phosphate cement, a biosensor for detecting infection, and a procedure for nanocoating spinal implants. Collectively with Anand Agarwal, M.D., Sarit Bhaduri, Ph.D., and others, he has filed several patents. He was the founding co-chair of the American National Standards Institute committee on spinal implants and laid the foundation for developing the guidelines for implant evaluation, which led to the document that was adopted by the FDA.

Structure and Function: Spine and Sacroiliac Joint

As part of the axial skeleton, the spine provides flexibility, transmits load to the sacroiliac joint (SIJ), and protects the nerve roots. In comparison, the SIJ is rigid and thus primarily transmits load to the pelvic girdle and then to the legs. The range of motion across the SIJ is only a few degrees, compared to the spine, where each segment may have more than 10 degrees of rotation. Discs, facets, and ligaments transmit loads in the spine, while the SIJ is the primary structure for load transmission. Shear loads contribute to disc damage leading to pain. Shear loads are very high across the SIJ. During pregnancy, ligaments and pubic symphysis become loose and thus place more burden on the SIJ. This leads to larger motions and higher stresses across the SIJ, bone structure, and ligaments. These can lead to higher incidences of bone fracture and pain. We need to develop more models to look into SIJ mechanics in males and females with and without pain across different age groups. Magnetic resonance imaging and computed tomographic scans can help achieve these objectives. Finally, mechanics can be related to biology to understand the interactions in this regard. We have hundreds of magnetic resonance imaging scans under the National Institutes of Health–funded Back Pain Consortium Research Program at the University of California, San Francisco.

Amanda Nelson, M.D., M.S.C.R., Rh.M.S.U.S., University of North Carolina School of Medicine

Dr. Nelson, associate professor, Thurston Arthritis Research Center, University of North Carolina (UNC) School of Medicine, is a board-certified internist and rheumatologist. Her research program focuses on a variety of aspects of osteoarthritis, including the contribution of bone shape to osteoarthritis risk, novel methodologies for analysis of large and complex datasets, sex and race/ethnicity differences, ultrasound imaging, and assessment of whole-body burden. She has received funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the Centers for Disease Control and Prevention, and the Rheumatology Research Foundation, and she is on the board of directors of the Osteoarthritis Research Society International. Dr. Nelson is the director of the Phenotyping and Precision Medicine Resource Core within UNC's Core Center for Clinical Research and is co-principal investigator of the Johnston County Osteoarthritis Project, a community-based prospective cohort of osteoarthritis, multiple chronic conditions, pain, and disability that has continued for 30 years. She is also co-principal investigator of the Johnston County Health Study. Dr. Nelson received her medical degree from the Vanderbilt School of Medicine and completed her rheumatology fellowship and M.S.C.R. degree at UNC.

Differences by Sex and Race in Multiple Joint Osteoarthritis

This workshop highlights that osteoarthritis (OA) is a disease of the whole joint (Sessions 1 and 2) and of the whole person (Session 4). OA is a serious disease that often affects multiple joints in a single person, and this burden of disease contributes to pain, functional decline, morbidity, and excess mortality. Women and individuals from groups historically underrepresented in medical research bear a higher burden of many chronic medical conditions, including OA. Disparities in joint replacement for OA are widely recognized, persistent, and multifactorial, although they are not related to lesser disease burden. The Johnston County Osteoarthritis Project followed a diverse cohort of Black and White men and women for 30 years to obtain insights on patterns of OA across multiple joint sites by race and sex. This unique population-based study included assessments of pain, radiographic OA, physical function, comorbid conditions, medications, biomarkers, genetics, and mortality. The Johnston County Health Study is building on this infrastructure to enroll a new cohort inclusive of Black, White, and Hispanic men and women age 35 to 70 years to further inform understanding of the disease of OA in the general population. Findings of these studies to be discussed include a high burden of large-joint OA in Black participants, a greater burden of pain and loss of function in women and minority groups, and increased mortality among individuals with joint pain. Consideration of the whole joint and the whole person is needed in designing pain management strategies suited to diverse populations.

Additional Panelist Biographies

Leslie Russek, P.T., D.P.T., Ph.D., Clarkson University

Dr. Russek, professor emeritus of physical therapy, Clarkson University, is a certified orthopaedic clinical specialist in physical therapy with more than 32 years of clinical practice experience and 27 years of experience working with patients with headaches, temporomandibular pain, hypermobility, and cervical instability. She has published widely on hypermobility, fibromyalgia, and chronic pain. She recently led an international team of clinical and research experts to develop consensus recommendations for conservative care of upper cervical instability in patients with hypermobility-related disorders. Dr. Russek presents nationally and internationally on hypermobility, headaches, temporomandibular dysfunction, and chronic pain management. She recently participated in a committee on selected heritable connective tissue disorders and disability for the National Academies of Sciences, Engineering, and Medicine.

Anna Shmagel, M.D., M.Sc., AbbVie

Dr. Shmagel is the medical director of immunology clinical development at AbbVie and a rheumatologist at the Hines VA Medical Center. She is a clinical development physician with expertise in rheumatology, clinical trials, medical monitoring, and epidemiology. Currently, she conducts clinical trials that evaluate pain outcomes in adults and children with rheumatologic conditions. Her research focuses on chronic low-back pain and osteoarthritis. She concentrates on these conditions because of their high societal burden and the lack of effective strategies for prevention and treatment. Dr. Shmagel has also investigated the effects of environmental risk factors in the development of chronic musculoskeletal pain. This work involved the use of data from the National Health and Nutrition Examination Survey to study the association between viral pathogen exposures and arthritis. She has also used data from the Osteoarthritis Initiative cohort at the National Institutes of Health to investigate the role of dietary magnesium intake in the development and progression of knee osteoarthritis pain. For the American College of Rheumatology, she served on a team that developed clinical practice guidelines for osteoarthritis. She received her medical degree from the I.M. Sechenov First Moscow State Medical University in 2008.

Kendi Hensel, D.O., Ph.D., Texas College of Osteopathic Medicine

Dr. Hensel is an associate professor of family medicine and osteopathic manipulative medicine for the Texas College of Osteopathic Medicine at the University of North Texas Health Science Center at Fort Worth. She has worked as an investigator and treatment provider for multiple clinical research studies on osteopathic manipulative medicine, including a study funded by the National Institutes of Health on the effects of osteopathic manipulative medicine on pregnant women. Dr. Hensel is currently involved in clinical, educational, and research activities at the Texas College of Osteopathic Medicine and in national efforts to improve the evidence base and utilization of osteopathic manipulation treatment in patient care. Her research interests center around mechanistic and clinical effectiveness studies of osteopathic manipulative medicine. She served as the 2019–2020 president of the American Academy of Osteopathy. She received her doctorate in osteopathic medicine from the Oklahoma State University College of Osteopathic Medicine, completed a combined family practice and neuromusculoskeletal medicine residency at the University of New England, and achieved board certification in both specialties.

Laura C. Cappelli, M.D., M.H.S., Johns Hopkins University School of Medicine

Dr. Cappelli, associate professor of medicine and oncology, Division of Rheumatology, Johns Hopkins University School of Medicine, is also a faculty member at the Johns Hopkins Arthritis Center. Her primary research focus is the rheumatologic adverse effects of cancer immunotherapy, including their clinical characteristics, epidemiology, impact on patients, and biologic mechanisms. Dr. Cappelli co-chairs the immune-related toxicity team and leads a rheumatic immune-related adverse events program at Johns Hopkins. In addition, she studies rheumatoid arthritis, focusing on patients with seronegative disease and on the use of autoantibodies as biomarkers. She earned her medical degree from the Johns Hopkins University School of Medicine and completed her residency in internal medicine and fellowship in rheumatology at the Johns Hopkins Hospital. Dr. Cappelli obtained her M.H.S. in clinical investigation at the Johns Hopkins Bloomberg School of Public Health.

Gary F. Bouloux, D.D.S., M.D., Emory University School of Medicine

Dr. Bouloux is the J. David Allen Family Professor and interim chief of the Division of Oral and Maxillofacial Surgery at Emory University School of Medicine. He leads the division in the diagnosis and surgical management of trigeminal nerve injuries. Dr. Bouloux's research evolves from his interest in temporomandibular joint dysfunction and includes surgical outcomes, psychological predictors of outcomes, laser-assisted surgical arthroscopy, the use of hyaluronic acid, and metal hypersensitivity following total joint replacement. His multicenter studies into the efficiency of various surgical treatments for temporomandibular disorders have advanced the science and practice of oral and maxillofacial surgery. Dr. Bouloux is the chair of the special committee of temporomandibular joint care for the American Association of Oral and Maxillofacial Surgeons and was appointed president of the American Society of Temporomandibular Joint Surgeons in 2020. Dr. Bouloux received the Oral and Maxillofacial Surgery Foundation Research Recognition Award in 2017 and the 2018 Daniel M. Laskin Award for the most outstanding publications in the *Journal of Oral and Maxillofacial Surgery*.

Concluding Remarks

Emmeline Edwards, Ph.D., Director of the Division of Extramural Research, National Center for Complementary and Integrative Health

Dr. Edwards is director of the Division of Extramural Research of the National Center for Complementary and Integrative Health (NCCIH). In that capacity, she is responsible for development of scientific programs or areas of science that fulfill NCCIH's mission as well as planning, implementation, and policy. Prior to joining NCCIH, Dr. Edwards served as deputy director of the Extramural Program at the National Institute of Neurological Disorders and Stroke. Before coming to the National Institutes of Health, Dr. Edwards earned her Ph.D. in neurochemistry from Fordham University, did postdoctoral research in behavioral pharmacology and neuroscience at the State University of New York, and was a tenured associate professor in the Department of Pharmacology at the University of Maryland. Her research there focused on the neural mechanisms of complex behaviors and characterization of a genetic model of affective disorders. She also served as chair of the Graduate Studies and Research Committee and as a member of the Dean's Executive Council at the University of Maryland.

Welcome Back

Walter Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke

Dr. Koroshetz is the director of the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Koroshetz joined NINDS in 2007 as deputy director, and he served as acting director from October 2014 through June 2015. As NINDS director, Dr. Koroshetz directs program planning and budgeting and oversees the scientific and administrative functions of the Institute. He has held leadership roles in many National Institutes of Health (NIH) and NINDS programs, including NIH's Brain Research through Advancing Innovative Neurotechnologies Initiative, the NIH Blueprint for Neuroscience Research, the Traumatic Brain Injury Center collaborative effort between the NIH intramural program and the Uniformed Services University of the Health Sciences, and the establishment of the NIH Office of Emergency Care Research. Dr. Koroshetz serves as chair of the Interagency Pain Research Coordinating Committee and the Executive Committee for the NIH Pain Consortium. Before joining NINDS, Dr. Koroshetz served as vice chair of the neurology service and director of stroke and neurointensive care services at Massachusetts General Hospital (MGH). He was a professor of neurology at Harvard Medical School and led neurology resident training at MGH between 1990 and 2007. Dr. Koroshetz received his medical degree from the University of Chicago.

Session Four: Interventions To Address Joint Pain and Disease

Chair: Alex Tuttle, Ph.D., National Center for Complementary and Integrative Health

Dr. Tuttle, program director in the Basic and Mechanistic Research Branch at the National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH), oversees the manual therapy and force-based manipulation portfolios as well as NCCIH's pain preclinical and translational research portfolios. Dr. Tuttle currently leads several NIH-wide initiatives, including the Helping to End Addiction Long-Term® (HEAL) Initiative, or NIH HEAL Initiative®, myofascial pain biomarkers program and the joint NCCIH/National Institute of Neurological Disorders and Stroke (NINDS) Force-Based Manipulation Research Networks program. He serves as a representative on the NIH HEAL Initiative Preclinical and Translational Working Group and as NCCIH's primary scientific contact for numerous preclinical and translational programs within the NIH HEAL Initiative. Dr. Tuttle is the NCCIH representative for the Trans-NIH Medical Rehabilitation Coordinating Committee. Prior to joining NCCIH, Dr. Tuttle served as the acting chief of staff for NINDS, where he worked with the Institute director and senior leadership to set guidance and interpret regulations and funding policies. Dr. Tuttle completed his undergraduate education at Haverford College. He obtained his doctorate degree in experimental psychology at McGill University in Montreal.

Co-Chair: Michael L. Oshinsky, Ph.D., National Institute of Neurological Disorders and Stroke

Dr. Oshinsky is director of the Office of Preclinical Pain Research for the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH). He is responsible for coordinating research and administrative issues related to pain and headache research across NINDS's neuroscience, translational research, and clinical research divisions. Dr. Oshinsky is also a co-chair for the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®. A major goal of the NIH HEAL Initiative is to accelerate the discovery and preclinical development of pain treatments with little or no addiction liability. From 2001 to 2014, Dr. Oshinsky was on the faculty at Thomas Jefferson University, where he was the director of preclinical research at the Jefferson Headache Center and led an NIH-funded research program aimed at developing and characterizing animal models of headache. In 2011, the American Headache Society awarded Dr. Oshinsky the Harold G. Wolff Lecture Award for headache research. Dr. Oshinsky received his doctorate in neurobiology and behavior from Cornell University.

External Co-Chair: Kathleen Sluka, P.T., Ph.D., University of Iowa

Dr. Sluka is a professor in the Department of Physical Therapy and Rehabilitation Science at the University of Iowa. Dr. Sluka's translational research program focuses on the neurobiology of musculoskeletal pain as well as the mechanisms and effectiveness of nonpharmacologic pain treatments. She has published over 250 peer-reviewed manuscripts, numerous book chapters, and a textbook on pain mechanisms and management for the physical therapist. Dr. Sluka is actively involved in the International Association for the Study of Pain and the American Physical Therapy Association, serving on committees, task forces, and society boards. Dr. Sluka received her Ph.D. in anatomy from the University of Texas Medical Branch.

Does Transcutaneous Electrical Nerve Stimulation Work for Pain Control?

Transcutaneous electrical nerve stimulation (TENS), the application of current through the skin for pain control, is a safe and inexpensive nonpharmacologic treatment for pain. Animal models show that TENS produces analgesia through activation of opioid and serotonin receptors in the central nervous system, which subsequently reduces release of excitatory neurotransmitters and sensitization of dorsal horn neurons. However, the clinical literature on TENS is mixed, with some studies showing effectiveness while others do not. This has led to systematic reviews and clinical practice guidelines, particularly for osteoarthritis and low-back pain, concluding that TENS is ineffective and not recommended. Although many of the trials were designed with the highest of standards, recent evidence suggests that factors related to TENS application need to be considered in an assessment of efficacy. These factors include dosing of TENS, negative interactions with opioid use, the population and outcome assessed, and the timing of the outcome measurement. Considering these factors, we will highlight effectiveness using data from a recent randomized controlled trial, the Fibromyalgia Activity Study with TENS, examining TENS in fibromyalgia. This talk will provide an overview of mechanisms and clinical trial design factors to help improve future clinical trials and systematic reviews of the literature for TENS.

Dan Rhon, P.T., D.P.T., D.Sc., Ph.D., Uniformed Services University of the Health Sciences

Dr. Rhon retired from active Federal service as a medical officer in the U.S. Army after 20 years. Dr. Rhon is a professor in the Department of Rehabilitation Medicine, Uniformed Services University of the Health Sciences. He is also the director of the Musculoskeletal Research in Primary Care Program at Brooke Army Medical Center. Dr. Rhon received his master's degree in physical therapy and doctor of science degree from Baylor University. He received his doctor of physical therapy degree from Temple University and his Ph.D. from the University of Newcastle. Dr. Rhon completed a manual therapy fellowship at Brooke Army Medical Center and a research postdoctoral fellowship at the University of Utah. Dr. Rhon is the recipient of a Lifetime Research Award from the U.S. Army Medical Specialist Corps, a two-time Rose Award recipient for Excellence in Research from the American Physical Therapy Association (APTA), and a recipient of the Eugene Michaels New Investigator Award from the APTA. He has over 130 publications and has received over $20 million in competitive research grant funding. Dr. Rhon's research interests revolve around the identification and implementation of optimal care pathways for musculoskeletal pain disorders.

Manual Therapy for Treating Lower Extremity Osteoarthritis-Related Joint Pain: Effectiveness and Proposed Therapeutic Mechanisms

Osteoarthritis (OA) is the most common painful joint disorder of the lower extremities, with the highest prevalence in the knee joint. Manual therapy has been shown to have efficacy for knee OA in placebo-controlled trials and comparative effectiveness against other common OA treatments such as exercise and corticosteroid injections. It is also shown to be a cost-effective intervention. Despite this, its utilization in the management of this patient population in the United States is quite low, especially when compared to the use of pharmacologic therapies. This presentation will provide a brief summary of the evidence to support the use of manual therapy for knee OA, proposed mechanisms of pain modulation, and barriers related to its poor uptake within U.S. health systems.

Stephen Messier, Ph.D., Wake Forest University

Dr. Messier, professor and director of the J.B. Snow Biomechanics Laboratory at Wake Forest University, has 32 years of experience in clinical trials research specifically related to knee osteoarthritis (OA). Dr. Messier is the principal investigator of the Weight Loss and Exercise for Communities with Arthritis in North Carolina (WE-CAN) trial and The Osteoarthritis Prevention Study (TOPS). WE-CAN is a pragmatic randomized clinical trial of 823 older adults with knee OA and overweight and obesity and is designed to determine if the diet and exercise intervention implemented in a highly controlled efficacy trial could be successfully implemented in diverse community settings. TOPS is a randomized clinical trial of diet and exercise designed to prevent incident knee OA in 1,230 at-risk females. These studies are funded by the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, other National Institutes of Health Institutes and Offices, and the Arthritis Foundation. Dr. Messier received the lifetime achievement award from the Osteoarthritis Research Society International (2022), the Borelli Award from the American Society of Biomechanics (2020) for outstanding career accomplishment through exemplary research in biomechanics, and the career achievement award from the American College of Sports Medicine Biomechanics Group (2009).

Diet and Exercise Interventions: Effects on Pain

Clinical guidelines strongly encourage the use of nonpharmacologic interventions to relieve pain and improve function in people with knee osteoarthritis (OA). Diet and exercise have proven effective with level 1 evidence of efficacy in reducing knee pain and improving other clinical outcomes in both short-term and long-term randomized clinical trials. This presentation will discuss the clinical effects of diet and exercise interventions in people with obesity and/or knee OA. Abnormal knee joint loading and systemic low-grade inflammation are underlying mechanisms responsible for OA progression. Dietary weight loss, with or without exercise, impacts both the biomechanical and inflammatory disease pathways by decreasing joint loading and inflammatory cytokine activity, resulting in less subchondral tissue damage, less synovitis, and less cartilage loss. The resulting outcomes are less knee pain, improved function and mobility, and enhanced health-related quality of life. While the empirical evidence supports exercise to relieve pain and improve function, questions regarding whether a significant proportion of this improvement is a function of the attention provided to the participants remain unresolved. Similarly, questions remain regarding the amount of weight loss that is most effective and can be reasonably attained. Finally, in people at high risk for knee OA, there is evidence that diet and exercise may reduce the incidence of knee OA.

Preeti Raghavan, M.B.B.S., Johns Hopkins Medicine

Dr. Raghavan is the Sheikh Khalifa Stroke Institute Endowed Chair and director of the Center of Excellence for Stroke Treatment, Recovery and Rehabilitation at Johns Hopkins Medicine. Dr. Raghavan is an associate professor of physical medicine and rehabilitation and neurology and serves as the vice chair for research in physical medicine and rehabilitation. Her research interests include recovery of motor control after brain injury by understanding the mechanisms of and barriers to recovery and improving access to rehabilitation through innovative treatments and advances in systems of care. She completed her physical medicine and rehabilitation residency at the Albert Einstein College of Medicine in New York and then completed a National Institutes of Health–funded research fellowship in motor control and learning at Columbia University, New York. Prior to joining Johns Hopkins, Dr. Raghavan served as faculty at Teachers College, Columbia University; Mount Sinai School of Medicine in New York; and New York University Grossman School of Medicine.

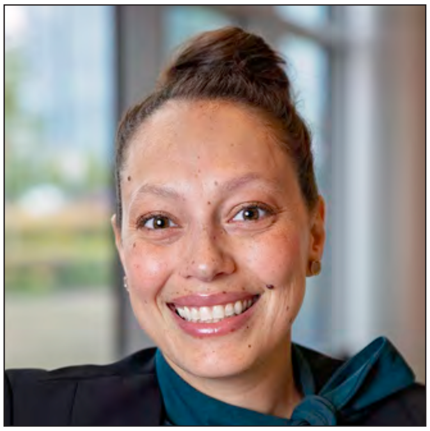
Mechanisms Underlying a Novel Pharmacologic Approach to Restoring Whole Joint Health

The whole joint includes not only the bones, articular structures, and periarticular tissues, but also the muscles that cross the joints to generate movement. The muscles consist of both myofibers and the extracellular matrix (ECM). This talk will briefly review the pathophysiology of the ECM in myofascial pain and whole joint pain in the context of post-stroke shoulder pain (PSSP) and its potential treatment. Shoulder pain is extremely common after stroke and occurs in 30 to 70 percent of patients. PSSP is thought to be caused mainly by damage to the myofascial tissues around the shoulder joint; however, magnetic resonance imaging studies show that the degree of structural damage to the muscles does not correlate with the degree of pain. The accumulation of hyaluronic acid (HA) in muscle and its fascia can cause myofascial dysfunction. HA is a glycosaminoglycan consisting of long-chain polymers of disaccharide units of glucuronic acid and N-acetylglucosamine and is a chief constituent of the ECM of muscle. In physiologic quantities, HA functions as a lubricant and a viscoelastic shock absorber, enabling force transmission during contraction and stretch. Reduced joint mobility and spasticity result in focal accumulation and alteration of HA in muscle. This can lead to the development of stiff areas and taut bands, dysfunctional gliding of deep fascia and muscle layers, reduced range of motion, and pain. A novel pharmacologic approach, using the enzyme hyaluronidase to target excessive accumulation of HA in the ECM, may potentially preserve and restore whole joint health in PSSP.

Additional Panelist Biographies

Gunnar Brolinson, D.O., Edward Via College of Osteopathic Medicine

Dr. Brolinson is vice provost for research, professor of family and sports medicine, and discipline chair for sports medicine at the Edward Via College of Osteopathic Medicine. He is board certified in family practice with a subspecialty certification in sports medicine. He is a team physician and adjunct professor at Virginia Polytechnic Institute and State University, volunteers as a physician for the United States National Olympic Committee, and is a team physician for the U.S. ski team. Previously, he was co-director of a primary care sports medicine fellowship training program at Toledo Hospital and a team physician for the University of Toledo. His research interests have included exercise and immune function, exercise and bone mineral density, mild traumatic brain injury in sports, impact biomechanics, human factors in auto safety, sports performance, and manipulation. Dr. Brolinson is a frequent speaker at national sports medicine meetings and teaches didactic laboratory sessions on the use of osteopathic manipulative therapy for athletic injuries. He is a past president of the American Osteopathic Academy of Sports Medicine and has published several scholarly articles and book chapters on sport and exercise medicine. He received his D.O. degree from Kirksville College of Osteopathic Medicine.



Katie Butera, P.T., D.P.T., Ph.D., University of Delaware

Dr. Butera, assistant professor, University of Delaware, is a physical therapist and clinician scientist. Dr. Butera completed her D.P.T. at the University of Florida in 2011. Her clinical expertise is in neurorehabilitation, serving patients with spinal cord injuries, stroke, neurodegenerative diseases, acute/chronic pain, and orthopedic multitrauma. After several years of full-time clinical practice, Dr. Butera completed her research doctoral training (Ph.D.; University of Florida; 2020) with a focus in pain and movement science and a postdoctoral fellowship in implementation science and pragmatic clinical research (University of Colorado; 2020–2022). As an early-stage investigator at the University of Delaware, Dr. Butera is building a clinical pain research program to optimize health and functional outcomes for individuals with chronic pain and disability. Goals of her work include understanding neural mechanisms underlying pain and movement interactions, evaluating movement-evoked pain and performance-based measures for use in pain populations, developing and testing movement-based interventions to reduce pain and improve function, and implementing effective pain rehabilitation approaches in real-world clinical settings.

Gert Bronfort, D.C., Ph.D., University of Minnesota

Dr. Bronfort has been a leader for more than 25 years in research investigating conservative and integrative care for disabling and costly musculoskeletal pain conditions. Long a proponent of interdisciplinary collaboration, Dr. Bronfort has formed numerous regional, national, and international partnerships to conduct innovative, high-impact patient-oriented research. He has led numerous federally funded randomized clinical trials investigating manual therapies, exercise, and self-care and has authored several high-profile systematic reviews. Dr. Bronfort is a long-standing and active member of the Cochrane Collaboration's Low Back Pain Editorial Group, as well as the Cervical Overview Group. He has served on several national and international committees, including the Advisory Council for the National Center for Complementary and Alternative Medicine, the World Health Organization, and the U.S. Health Resources and Services Administration Advisory Committee on Interdisciplinary, Community-Based Linkages. Dr. Bronfort completed his Ph.D. at Vrije University in Amsterdam, Netherlands.

Christine Goertz, D.C., Ph.D., Duke University School of Medicine

Dr. Goertz is a professor of musculoskeletal research and vice chair for Implementation of Spine Health Innovations in the Department of Orthopaedic Surgery at Duke University School of Medicine. Dr. Goertz received her doctor of chiropractic degree from Northwestern Health Sciences University and her Ph.D. from the University of Minnesota School of Public Health. Her 30-year research career has been devoted to working with multidisciplinary teams to design and implement clinical and health services research studies that increase knowledge regarding the effectiveness and cost of complementary and integrative health practices, with a focus on patient-centered, nonpharmacologic treatments for spine-related disorders. She has received more than $40 million in federal funding as a principal investigator and has co-authored over 130 peer-reviewed papers. Dr. Goertz has served on the Interagency Pain Research Coordinating Committee and was chairperson of the Board of Governors for the Patient-Centered Outcomes Research Institute.

Brian Noehren, P.T., Ph.D., University of Kentucky

Dr. Noehren is associate dean of research in the College of Health Sciences at the University of Kentucky and professor in the Department of Physical Therapy. Dr. Noehren received his master's degree in physical therapy from the University of Connecticut in 2001. Following a number of years of clinical practice, he completed his Ph.D. in biomechanics and movement science at the University of Delaware, graduating in 2009. Dr. Noehren is a translational scientist with a focused research program dedicated to understanding how pain, muscle function, and biomechanics are affected in common orthopedic conditions. His work ranges from defining cellular adaptations within muscle to whole muscle imaging, as well as employing inverse kinematics and kinetics to observe the impact of muscle dysfunction on movement mechanics. Dr. Noehren is funded by the National Institutes of Health and the U.S. Department of Defense to study recovery after common injuries such as anterior cruciate ligament injuries and lower extremity fractures. He has also been funded through the National Science Foundation and several other foundations. Dr. Noehren has published 70 papers in high-impact journals and has given numerous national and international presentations.

Session Five: Emerging Technologies and Models

Chair: Qi Duan, Ph.D., National Institute of Biomedical Imaging and Bioengineering

Dr. Duan is a program director for the National Institute of Biomedical Imaging and Bioengineering (NIBIB) Division of Health Informatics Technologies. Dr. Duan received his Ph.D. in biomedical engineering from Columbia University in 2008, majoring in medical imaging. Before joining NIBIB in 2018, he worked at the New York University School of Medicine, National Institutes of Health, and U.S. Food and Drug Administration in the field of medical imaging and image analysis, as well as medical device regulation. Dr. Duan's research and development experience spans a wide variety of medical imaging modalities, such as ultrasound, magnetic resonance imaging, X-ray, and computed tomography, as well as areas of bioengineering. His work has included many aspects of the total product life cycle of medical imaging and image analysis. Dr. Duan is currently a senior member of the Engineering in Medicine and Biology Society of the Institute of Electrical and Electronics Engineers.

Co-Chair: Julia Bachman, Ph.D., National Institute of Neurological Disorders and Stroke

Dr. Bachman serves as a scientific program manager within the Systems and Cognitive Neuroscience cluster in the Division of Neuroscience at the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Bachman's portfolio consists of early-stage translational projects for small-molecule and biologic drug development as part of the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®. Dr. Bachman received a Ph.D. in molecular and cellular neuroscience from the Johns Hopkins University School of Medicine, investigating molecular mechanisms of glutamate receptor trafficking and synaptic plasticity in the context of learning and memory. Dr. Bachman did her postdoctoral training in electrophysiology and circuit mapping at Howard Hughes Medical Institute's Janelia Research Campus, followed by an Intramural Research Training Award postdoctoral fellowship at the National Institute on Deafness and Other Communication Disorders. Dr. Bachman joined NINDS in 2019 as a health program specialist in the Division of Translational Research, where she supported several translational programs, including the Innovation Grants to Nurture Initial Translational Efforts program, the NINDS and NIH HEAL Initiative biomarker programs, and the Blueprint Neurotherapeutics Network for Biologics.

External Co-Chair: Riccardo Lattanzi, Ph.D., New York University

Dr. Lattanzi is a professor of radiology, electrical and computer engineering, and biomedical engineering at New York University (NYU). Dr. Lattanzi serves as the director of the Center for Biomedical Imaging at the NYU Grossman School of Medicine, overseeing the translational research mission of the Department of Radiology. He also leads the training subaward of the Center for Advanced Imaging Innovation and Research through the National Institute for Biomedical Imaging and Bioengineering and serves as the director of the Ph.D. program in biomedical imaging and technology. Dr. Lattanzi's research lies at the boundary between physics, engineering, and medicine. He investigates fundamental principles involving the interactions of radiofrequency electromagnetic fields with biological tissue in order to develop new techniques and technologies that are aimed at improving the diagnostic power of magnetic resonance imaging. He won the International Society for Magnetic Resonance in Medicine I.I. Rabi Young Investigator Award, received a National Science Foundation CAREER award and Fulbright scholarship, and was selected as an Aspen Junior Fellow of the Aspen Institute Italia, a Young Leader of the Council for the United States and Italy, and a European Young Leader. Dr. Lattanzi received his Ph.D. from the Massachusetts Institute of Technology.

Quantitative Magnetic Resonance Imaging To Characterize Joint Diseases

In quantitative magnetic resonance imaging (MRI), rather than producing clinical images to evaluate tissue morphology, the acquired magnetic resonance (MR) data are used to reconstruct quantitative maps of physical parameters, such as relaxation times, to assess underlying biological and biochemical changes in tissue. Various quantitative MR parameters have been proposed to detect early changes in the biochemical components of the articular cartilage, namely proteoglycans, water, and collagen, which occur before morphologic changes. Deep-learning and novel MRI techniques are paving the way for the clinical translation of quantitative MRI for the characterization of joint diseases. Model-based techniques such as MR fingerprinting have enabled rapid and reliable acquisitions of multiple complementary quantitative MR parameters that reflect the biochemical composition of cartilage. Automatic processing pipelines based on deep learning make clinical translation of quantitative compositional MRI a more tangible goal, bringing the reality of characterizing and staging early cartilage changes closer to the point of patient management.

Valentina Pedoia, Ph.D., University of California, San Francisco

Dr. Pedoia holds a double appointment as associate professor in the radiology and biomedical imaging department at the University of California, San Francisco, and as leader of image analysis at Altos Labs. Dr. Pedoia is a computer scientist by training, with more than 15 years of experience in biomedical imaging. Her primary interest is in developing computer-vision and machine-learning algorithms to transform biomedical imaging into knowledge. Her research spans imaging scale and modalities, from understanding fundamental mechanistic phenomena with microscopy to in vivo magnetic resonance imaging, with the common aim of exploring imaging biomarkers of aging. Dr. Pedoia has great interest in the clinical translation of novel technology and is invested in making all imaging modalities more efficient and effective by boosting speed in acquisition and processing.

Uncovering Associations Between Data-Driven Learned Quantitative Magnetic Resonance Imaging Biomarkers and Chronic Pain

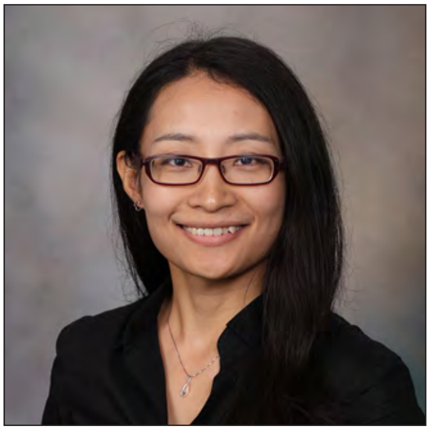
Knee pain is the most common and debilitating symptom of knee osteoarthritis (OA). While there is a perceived association between OA imaging biomarkers and pain, there are weak or conflicting findings for this relationship. This study uses deep-learning (DL) models to elucidate associations between bone shape, cartilage thickness, and T2 relaxation times extracted from magnetic resonance images (MRI) and chronic knee pain. Class activation maps (Grad-CAM) applied on the trained chronic pain DL models are used to evaluate the locations of features associated with presence and absence of pain. For the cartilage thickness biomarker, features sensitive for pain presence were generally located on the medial side, while features specific for pain absence were generally located on the anterior lateral side. This suggests that the association of cartilage thickness and pain varies, requiring a more personalized averaging strategy. We propose a novel DL-guided definition for cartilage thickness spatial averaging based on Grad-CAM weights. We showed a significant improvement in modeling chronic knee pain with the inclusion of the novel biomarker definition.

Kevin Koch, Ph.D., Medical College of Wisconsin

Dr. Koch, Medical College of Wisconsin, is a physicist who focuses on the development and clinical translation of diagnostic imaging technologies. Dr. Koch's research interests are diverse but primarily focus on magnetic resonance imaging (MRI) artifact reduction, MRI-based tissue magnetism measurements, and dynamic imaging of moving joints.
For much of Dr. Koch's career, he has been involved in the invention, development, and clinical testing of an MRI metal artifact reduction technique known as 3D multispectral imaging (3D-MSI). Although 3D-MSI is now clinically used across various MRI vendors, Dr. Koch and his team remain dedicated to its continual improvement through support from Federal grants and industry partnerships. Using his background in magnetostatics, Dr. Koch and his team have also developed deep-learning methods for tissue susceptibility quantification, which they have successfully applied to mild traumatic brain injury cases. Most recently, Dr. Koch's group has begun exploring kinematic imaging within orthopedics, where, with support from the National Institutes of Health, they have developed mechanisms to profile carpal bones during unconstrained wrist motion. Their aim with the overall program is to provide tools that may help surgeons and therapists manage chronic wrist instability.

Methodology and Analysis of Dynamic Carpal Bone Measures Derived From 4-Dimensional Magnetic Resonance Imaging

Although magnetic resonance imaging (MRI) and computed tomographic (CT) arthrography can be utilized to assess carpal ligament damage, the functional impact of such damage remains elusive within current diagnostic mechanisms. To address this gap, our team has developed MRI technology for dynamic profiling of carpal bones. We hypothesize that appropriately curated dynamic carpal bone metrics could improve specificity in diagnosing damaged carpal ligaments. We will present our construction and analysis of dynamic carpal data elements derived from 4-dimensional (4D)-MRI of the moving wrist. Using a novel dynamic MRI acquisition and custom-developed automated post-processing algorithms, we demonstrate the feasibility of quantifiable carpal bone tracking during radial-ulnar deviation and flexion-extension movements. Across a clinically asymptomatic cohort of 31 subjects and a symptomatic cohort of 20 subjects, dynamic data elements were constructed from capitate-normalized profiles of the scaphoid and lunate bones in a subject-specific, radius-based coordinate system. The stability of these measures across the symptomatic and asymptomatic cohorts is presented and discussed. In addition, preliminary analysis of dynamic metrics as a function of wrist pathology is presented. The results of these preliminary analyses suggest that the derived data elements have promising capabilities for characterizing carpal pathology and abnormalities.



Ziying Yin, Ph.D., Mayo Clinic

Dr. Yin is an assistant professor of medical physics in the Department of Radiology at the Mayo Clinic. Dr. Yin earned her Ph.D. in bioengineering from the University of Illinois at Chicago in 2014. Specializing in magnetic resonance elastography, her research primarily centers on exploring the mechanical characteristics of biological tissues, including the study of tissue adherence, stiffness, and viscosity. Specifically, Dr. Yin is drawn to researching tumor consistency and adherence, investigating the brain's reaction to repeated head impacts, and evaluating the mobility of myofascial interfaces. Dr. Yin is a principal investigator for two National Institutes of Health grants and is a Junior Fellow of the International Society of Magnetic Resonance in Medicine.

Magnetic Resonance Elastography-Based Slip Interface Imaging To Assess the Mobility of the Myofascial Interface: A Feasibility Study

Myofascial pain syndrome (MPS) is a common health concern characterized by pain originating from muscles and surrounding fascia. Recent efforts to understand MPS pathology have focused on myofascial connective tissue and the function of fascial plane mobility. Magnetic resonance elastography (MRE)-based slip interface imaging (SII) presents a unique, noninvasive methodology for evaluating this fascial plane mobility. In this study, we explored the SII's feasibility to visualize the mobility of myofascial interfaces in several regions—the forearm, upper leg, and lower back—in healthy volunteers. Our approach involved inducing mechanical vibrations into the muscles through specialized MRE drivers that interact with the targeted muscle groups. The resulting motion data was encoded, enabling us to compute a metric known as normalized octahedral shear strain (NOSS), a metric assessing the adherence or slipperiness between two adjacent layers. The outcome of this feasibility study revealed high NOSS values at functional intramuscular or intermuscular myofascial interfaces. This result suggested unrestricted mobility of the fascial planes among healthy volunteers. Moreover, we noted that SII demonstrated sensitivity to varying muscular loading states. A key insight from this study was that specific MRE driving mechanisms are required for each body location, and these mechanisms are still undergoing refinement. In summary, our investigation has established the potential of MRE-based SII for assessing the mobility of myofascial interfaces across multiple body locations. This study lays a solid foundation for future research utilizing MRE/SII to distinguish healthy fascial planes from those that are dysfunctional in MPS patients.

Additional Panelist Biographies

Scott Banks, Ph.D., University of Florida

Dr. Banks is a professor in the University of Florida Department of Mechanical and Aerospace Engineering, with appointments in Biomedical Engineering and Orthopaedics and Sports Medicine. He received an M.S. degree in biomedical engineering from Case Western Reserve University and a Ph.D. in mechanical engineering from the Massachusetts Institute of Technology. Dr. Banks has been active in orthopedics and joint mechanics research his entire career. Dr. Banks served as president and conference host for the International Society for Technology in Arthroplasty. He has co-authored 200 peer-reviewed journal papers, which have been cited 8,000 times. Dr. Banks holds numerous medical device patents, resulting in over $2 million in royalties to the University of Florida. In addition to mentoring engineering students, Dr. Banks has mentored 40 orthopedic surgeons as long-term research fellows. He continues to work with several start-ups, has established medical device companies, and has designed joint-replacement implants that have been used in over 200,000 patients. Dr. Banks loves sharing his excitement for engineering in the classroom and has been named the Mechanical and Aerospace Engineering and College of Engineering Teacher of the Year, as well as the student-selected faculty lecturer twice.

Feliks Kogan, Ph.D., Stanford University

Dr. Kogan is an assistant professor of radiology at Stanford University and has a research focus on imaging of musculoskeletal function and disease. Dr. Kogan earned his Ph.D. in bioengineering at the University of Pennsylvania, during which he received a Howard Hughes Medical Institute Interfaces Fellowship and completed the preclinical academic curriculum at the University of Pennsylvania School of Medicine. Afterward, Dr. Kogan did his postdoctoral fellowship in the radiology department at Stanford University. Dr. Kogan's group is focused on the development of early markers of disease with novel imaging methods and the translation of these methods to produce actionable information to impact patient outcomes. Dr. Kogan has extensive experience with cutting-edge imaging technologies, including multimodal positron emission tomography–magnetic resonance imaging systems, novel quantitative imaging biomarkers, and ultrahigh magnetic field (7 Tesla). He is a junior fellow of the International Society for Magnetic Resonance in Medicine and a member of the Council of Early Investigators in Imaging of the Academy for Radiology and Biomedical Imaging Research.

Lucia Cevidanes, D.D.S., M.S., Ph.D., University of Michigan

Dr. Cevidanes is the Thomas and Doris Graber Professor of Dentistry and a professor in the Department of Orthodontics at the University of Michigan and is a Diplomate of the American Board of Orthodontics. Dr. Cevidanes is a practicing clinician who has published over 200 manuscripts on 3D imaging and artificial intelligence (AI), for which she has received research grants from the American Association of Orthodontics Foundation and the National Institute of Dental and Craniofacial Research. Her work has been recognized by the American Association of Orthodontists Thomas M. Graber Award, B.F. Dewel Award, Milo Hellman Award, and Wuehrmann Award from the American Academy of Oral and Maxillofacial Radiology. Her interests include 3D imaging and AI to solve difficult clinical problems in orthodontics, studying current and new treatment approaches and technical procedures, and understanding treatment outcomes for craniofacial anomalies and dentofacial deformities. Dr. Cevidanes received her Ph.D. from the University of North Carolina, Chapel Hill.

Siddhartha Sikdar, Ph.D., George Mason University

Dr. Sikdar, professor, George Mason University Department of Bioengineering, is the director of the Center for Adaptive Systems of Brain-Body Interactions (CASBBI), which pursues transdisciplinary research to enable all individuals to fully participate in needed and desired life roles and activities. Dr. Sikdar's research group within CASBBI conducts translational research using imaging to investigate brain-body interactions in a number of clinical conditions of major public health significance, such as chronic pain, stroke, spinal cord injury, and amputation. Dr. Sikdar's group uses state-of-the-art ultrasound and laser instrumentation for developing new ultrasound, optical, and hybrid imaging techniques, as well as assistive technologies. Dr. Sikdar obtained his Ph.D. in electrical engineering from the University of Washington, Seattle, in 2005. He was a recipient of the National Science Foundation (NSF) CAREER Award, Volgenau School of Engineering Rising Star Award, and George Mason's Emerging Researcher/Scholar/Creator Award. Dr. Sikdar's current research is funded by the National Institutes of Health (NIH), NSF, U.S. Department of Defense, and U.S. Department of Veterans Affairs. He is a principal investigator in the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, to develop imaging biomarkers for myofascial pain.

Session Six: General Discussion

Chair: Helene M. Langevin, M.D., National Center for Complementary and Integrative Health (see biography on page 9)

Co-Chair: Gayle Lester, Ph.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Lester is the director of the Division of Extramural Research at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). In addition to her programmatic management of grants, Dr. Lester serves as the project officer for the public-private partnership Osteoarthritis Initiative, a group of NIAMS contracts that supports a longitudinal cohort study on knee osteoarthritis and the discovery of biomarkers. Dr. Lester led NIAMS's efforts focused on bone quality and biomarkers for osteoporosis and osteoarthritis and continues to serve as project director for the Foundation for the National Institutes of Health (NIH) Biomarker Consortium Bone Quality Project. Dr. Lester has received numerous National Institutes of Health Director's Awards for her work related to discovery of diagnostic imaging biomarkers and diagnostic biomarker development based on the Osteoarthritis Initiative. Dr. Lester joined NIAMS in January 2001. Prior to Dr. Lester's arrival at NIH, she was a professor in the Department of Orthopedics at the University of North Carolina, Chapel Hill. Her research interests included ligament healing, hormonal control of bone metabolism, measurement and regulation of bone mineral density, biochemical markers of bone turnover, and articular cartilage biochemistry. Dr. Lester has authored more than 60 peer-reviewed publications and several book chapters.

Summary and Concluding Remarks

Alex Tuttle, Ph.D., Program Director and Workshop Lead, National Center for Complementary and Integrative Health (see biography on page 35)

NIH Planning Committee

National Center for Complementary and Integrative Health

Wen Chen, Ph.D. (see biography on page 19)

Helene M. Langevin, M.D. (see biography on page 9)

Alex Tuttle, Ph.D. (see biography on page 35)

National Cancer Institute

Miguel R. Ossandon, Ph.D. (see biography on page 26)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Rebecca Lenzi, Ph.D. (see biography on page 11)

Gayle Lester, Ph.D. (see biography on page 48)

National Institute of Biomedical Imaging and Bioengineering

Qi Duan, Ph.D. (see biography on page 42)

National Institute of Dental and Craniofacial Research

Melissa Ghim, Ph.D. (see biography on page 11)

National Institute of Neurological Disorders and Stroke

Michael L. Oshinsky, Ph.D. (see biography on page 35)

Julia Bachman, Ph.D. (see biography on page 42)

National Institute on Aging

Devon Oskvig, Ph.D., National Institute on Aging

Dr. Oskvig is the program director of the Neurobiology of Pain Program in the Behavioral and Systems Neuroscience Branch of the Division of Neuroscience at the National Institute on Aging (NIA). Dr. Oskvig currently represents NIA on a number of efforts across the National Institutes of Health (NIH), including the NIH Pain Consortium; the Helping to End Addiction Long-Term® Initiative, or NIH HEAL Initiative®, Preclinical and Translational Scientific Team; the Common Fund Acute to Chronic Pain Signatures Working Group; and the VA Pain Research Working Group. Prior to joining NIA in 2020, Dr. Oskvig was a scientific review officer at NIH's Center for Scientific Review, managing the review of developmental, aging, and lifespan grant applications from a broad range of cognitive and perceptual domains, including attention, learning, memory, cognition, decision-making, executive function, social cognition, spatial navigation, and interactions between functional systems (e.g., emotion and cognition). Prior to that, Dr. Oskvig was a military medical research consultant with a large government consulting firm. Dr. Oskvig received a Ph.D. in lifespan cognitive neuroscience from Georgetown University and completed her postdoctoral training in the National Institute of Mental Health Intramural Research Program.

John Williams, Ph.D. (see biography on page 19)