MICHIGAN INTEGRATIVE MUSCULOSKELETAL HEALTH CORE CENTER
UNIVERSITY OF MICHIGAN

TENTH ANNUAL MUSCULOSKELETAL HEALTH SYMPOSIUM

A celebration of musculoskeletal health research programs at the University of Michigan and affiliated institutions

Keynote Speaker:

Renny T. Franceschi, PhD

Marcus L. Ward Collegiate Professor of Dentistry Emeritus and Professor of Biological Chemistry Emeritus in the Medical School

May 26, 2026
Starting at 9:00 am
North Campus Research Complex, Building 18
Football Rm., 2800 Plymouth Road, Ann Arbor, MI 48109

For further details visit: https://medresearch.umich.edu/labs-departments/cores/MiMHC

Keynote Address

Professor Franceschi received his B.A. from the University of Vermont in 1971, his Ph.D. from Purdue University in 1978 and conducted postdoctoral studies at the University of Wisconsin-Madison from 1978-1980 (mentor, Hector DeLuca). He served on the faculty of Harvard University from 1980-1988 and on the faculty of the University of Texas Medical Center from 1989-1992. Professor Franceschi joined the University of Michigan faculty as an associate professor in 1993 and was promoted to professor in 2000. He served as Research Director at the School of Dentistry from 1998-2000 and Associate Dean for Research from 2002-2005, as well as Associate Director of the Michigan Integrative Musculoskeletal Health Center from 2016-2025. Professor Franceschi's research focused on skeletal development and regeneration with particular emphasis on gene regulatory mechanisms and the influence of extracellular matrix signaling on bone formation. Dr. Franceschi and his colleagues also successfully applied basic discoveries toward the development of tissue engineering and gene therapy approaches for bone regeneration. He coauthored over 170 scholarly publications and was continuously funded by the National Institutes of Health for over 40 years. In 2008, he received the Distinguished Scientist Award for Basic Research in Biological Mineralization from the American Association for Dental and Craniofacial Research. Professor Franceschi taught biochemistry, molecular biology and skeletal biology to generations of dental and graduate students and was primary mentor to 9 PhD students and over 25 postdoctoral fellows. Professor Franceschi is a fellow of the American Association for the Advancement of Science (2020), The American Society for Bone and Mineral Research (2019) and the American Association for Dental and Craniofacial Research (2019).

Front cover Image: "Tendon fibroblasts migrating to close a wound (from the Killian & Abraham Labs)"

Agenda

8:30-9:00 **Poster Setup and Refreshments**

9:00-9:05 **Welcome and MiMHC Update, Megan Killian, PhD**

9:05-10:05 **Faculty Presentations, Megan Killian, PhD, Moderator**

Mario Fabiilli, PhD, *"From Bubbles to Bone: Ultrasound-Responsive Smart Hydrogels for Regeneration"*

Randy Duncan, PhD, *"TRPV4 Channels in Osteoarthritis: Response to a Different Kind of Stress"*

Eri Takematsu, PhD, *"Engineering the Cellular Niche: Biomaterials, ECM Signaling, and Stem Cell Fate"*

10:05-10:15 **Break**

10:15-11:45 **Travel Award Competition, Dave Kohn, PhD, Moderator**

Sydney Markel, *"Role of Proprioception in Orofacial Muscle Control"*

Karin Harumi Uchima Koecklin, *"Proprioceptive Control of Orofacial Functions by Different Neuronal Populations in Mice"*

Mohd Parvez Khan, *"PPARgamma Orchestrates Osteocyte Mitochondrial Metabolism and Oxidative Stress via HIF1a to Preserve Skeletal Integrity During Aging"*

Christophe Merceron, *"Iron-Deficiency Anemia Modulates Erythropoiesis-Bone Crosstalk and Drives Bone Loss"*

Ruchir Sriram, *"Skeletal Implications of Protecting Renal Function via Induced Ketosis in the db/db Murine Model of Early Diabetic Kidney Disease"*

Saumya Bhagat, *"KDM5C-Dependent Control of Osteoclast Pathways: Linking RANKL Signaling, Inflammation, and Sex Differences in Bone homeostasis"*

11:45-12:00 **Group Photo**

12:00-12:30 **Lunch**

12:30-2:00 **Poster Session** ***(First 45min odd numbered posters/Last 45min even numbered)***

2:00-3:00 **Keynote Speaker, Karl Jepsen, PhD, Moderator**

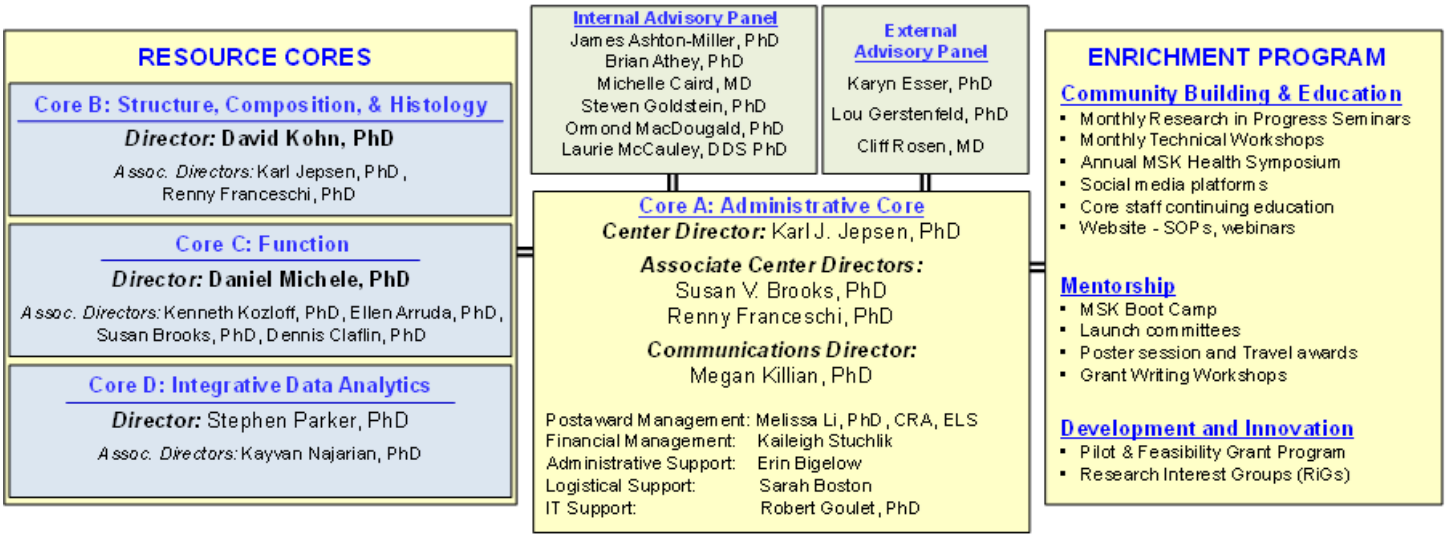
Renny Franceschi, PhD - *"From Then to Now; 30 Years of Bone Biology at Michigan"*

3:00-3:15 **Award Presentations & Conclusion, Megan Killian, PhD, Moderator**

Michigan Integrative Musculoskeletal Health Core Center (MiMHC)

Overview: Since its establishment in 2016, the MiMHC has accelerated science and innovation at UM. Consistent with the mission of NIAMS, **the theme of the MiMHC is understanding mechanisms of musculoskeletal health, injury, and disease across the lifespan**. To continue supporting these goals, we provide centralized resources and expertise to support the diverse research interests of our Research Community and implement an Enrichment Program focused on community building, education, mentorship, communication, and innovation. The MiMHC will enable Center investigators (members) to identify mechanisms of musculoskeletal health, injury and disease through a) an integrative science platform with Resource Cores that are hierarchically structured to facilitate mechanistic studies from the molecular- to organismal-levels with functional and clinically relevant outcomes and b) the promotion of new studies involving interactions among basic scientists and clinicians conducting translational research and emerging inter-disciplinary studies involving new collaborations.

Figure 1. Flowchart showing the organization of the MiMHC.



Contact Information:

Core Leadership

Karl J. Jepsen, PhD	**Center Director**	**kjepsen@med.umich.edu**
Susan Brooks, PhD	**Associate Center Director**	**svbrooks@umich.edu**
Renny Franceschi, PhD	**Associate Center Director**	**rennyf@umich.edu**
Megan Killian, PhD	**Communications Director**	**mlkillia@med.umich.edu**

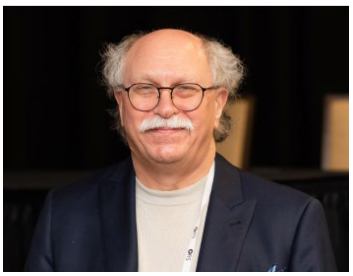
Core Administration and Services

Melissa Li	**Financial Management**	**melilimi@med.umich.edu**
Sarah Boston	**Logistics Support**	**sjayers@med.umich.edu**
Robert Goulet, PhD	**IT support**	**rgoulet@med.umich.edu**
Erin Bigelow	**P30 post-award manager**	**emrob@med.umich.edu**
Kaileigh Stuchlik	**Financial Management**	**klykins@med.umich.edu**

Website: https://medresearch.umich.edu/labs-departments/cores/MiMHC

External Advisory Panel

Karyn Esser, PhD is Professor and Chair of the Department of Physiology and Aging, University of Florida College of Medicine. Dr. Esser and her laboratory pioneered research on the role of circadian rhythms and the molecular clock mechanism in skeletal muscle homeostasis and health. Parallel work includes pursuing the role of physical activity/exercise as a time cue for skeletal muscle and other tissues. Her research goals are to define the transcriptional networks and downstream mechanisms that link the molecular clock with proper skeletal muscle function and phenotype.



Louis C. Gerstenfeld, PhD is Professor of Orthopaedic Surgery at Boston University School of Medicine. Dr. Gerstenfeld has studied skeletal biology for more than 30 years and has broad knowledge across many areas in the field, including metabolic bone disease and orthopedic-related diseases. He was among the first four labs in the United States to develop in vitro osteoblast cultures and helped to establish the standard time dependent sequence of osteogenic differentiation in vitro.

Clifford J. Rosen, MD is Senior Scientist and Director, Center for Clinical & Translational Research, Maine Medical Center Research Institute. Dr. Rosen's laboratory studies the genetic regulation of insulin-like growth factor relative to skeletal metabolism, the relationship between marrow adipogenesis and osteoblastogenesis, and the interactions between whole body and skeletal metabolism.They use age, genetic, environmental, diet and pharmacologic manipulations to understand the complex regulation of bone remodeling. He is interested in understanding the *in vivo* roles of IGF binding proteins (IGFBP) namely IGFBP2 and IGFBP4.

Resource Cores

Structure, Composition and Histology Core (Core B)

Overview: Structure and composition across physiological length-scales (e.g., organ, tissue, cell, matrix, nanoscale-levels) are key intermediate traits that link gene expression with functional outcomes. Genetic and/or environmental perturbations affecting gene expression often lead to measurable changes in these intermediate traits that have mechanical and other functional consequences. Accurately quantifying structure and composition at different length scales is therefore essential to advancing our understanding of the molecular and mechanical mechanisms underlying musculoskeletal health and disease; to develop and evaluate treatment strategies; and to ultimately translate these strategies to the clinic. However, this research requires use of advanced and costly instruments and supporting expertise in cell biology, chemistry, engineering, and biomedical imaging. The Structure, Composition and Histology Core will provide access to the instruments and expertise that will enable Center investigators to quantify these intermediate traits and to accelerate their research programs.

Services include ex-vivo micro-Computed Tomography (μCT) and nano-Computed Tomography (nano-CT), Raman spectroscopy, and histology as the major components. These technologies were chosen for their applicability to all musculoskeletal tissues and based on usage data over the previous 4 years and a 2020 needs-assessment survey from investigators in the MiMHC.

Access to services: Contact David Kohn, PhD when beginning a project and for general assistance with core access. He will provide guidance on experimental design and the appropriate Faculty and Core expert to contact next.

David Kohn, PhD	Director	dhkohn@umich.edu
Renny Franceschi,	Associate	rennyf@umich.edu
PhD Karl Jepsen, PhD	Director	kjepsen@med.umich.edu
	Associate	
	Director	
Carol Whitinger	Histologist	whitinge@med.umich.edu
Emma Snyder-White	Histologist	eparrs@med.umich.edu
Gurjit Mandair, PhD	Raman spectroscopy expert	gmandair@umich.edu
Robert Goulet, PhD	Image acquisition/analysis expert	rgoulet@med.umich.edu
Michelle Lynch	MicroCT expert (Dentistry)	malyn@umich.edu
Andrea Clark	Micro/NanoCT expert (Orthopaedics)	clarkand@med.umich.edu
TBD	Bruker/Skyscan microCT (ex vivo, in vivo)	

Websites:

Dental School microCT core:https://dent.umich.edu/research/core-facilities

ORL nanoCT and microCT corehttps:nanoctcore.med.umich.edu/

Function Core (Core C)

Overview: Discovery of new targets and treatments for musculoskeletal diseases requires a deep understanding of the basic biology of musculoskeletal development and function, rigorous research into the fundamental mechanisms of disease pathogenesis, and robust testing of therapeutic targets and therapies aimed at improving disease outcome. Research using animal models is a cornerstone of these efforts enabling the study of organ and integrative organism function, the impact of environment, age, sex, and genetics on disease, and testing therapies and outcomes with disease-relevant measures. Studying musculoskeletal phenotypes across this wide- ranging scale requires considerable expertise and highly specialized training in physiology, biophysics, and engineering, as well as direct access to costly, high-resolution, state-of-the-art equipment. Rigorous and reproducible basic and preclinical research also requires robust experimental planning that can span multi-modal testing platforms from cellular and organ level function to *in vivo* physiology testing in order to provide a fully comprehensive measure of phenotypic function. *The overall goal of the Function Core of the Michigan Integrative Musculoskeletal Health Core Center (MiMHC) is to provide state-of-the-art animal and tissue level phenotyping resources that can be used by the entire musculoskeletal research community, regardless of individual expertise.*

The Core brings together the leadership and technical proficiency in the physiology and biomechanics of the musculoskeletal system along with specialized laboratory approaches to musculoskeletal biology including state- of-the-art measurements in the following areas:

- bone composition and mechanics
- muscle function and mechanics
- tendon and soft tissue mechanics
- neuromuscular function at the whole animal level
- the adaptations and regeneration of these tissues in response to injury and disease.

Access to services: Contact Dan Michele, PhD (whole animal testing, micro-surgery models), Ken Kozloff, PhD (bone testing, fracture healing/surgical models, in vivo microCT imaging), Ellen Arruda, PhD (tendon testing), or Susan Brooks, PhD (muscle mechanics) when beginning a project.

Daniel Michele, PhD	Director	dmichele@umich.edu
Kenneth Kozloff, PhD	Associate Director	kenkoz@umich.edu
Ellen Arruda, PhD	Associate Director	arruda@umich.edu
Susan Brooks, PhD	Faculty Expert	svbrooks@umich.edu
Steven Whitesall	Core expert	whitesaw@umich.edu
Carol Davis	Core expert	csdav@med.umich.edu
Conor Locke	Core expert	cslocke@med.umich.edu
Andrea (Andy) Poli	Core expert	polia@umich.edu
Alex Donneys	Core expert	alexisd@med.umich.edu
Peter Macpherson	Core expert	petercdm@med.umich.edu

Integrative Data Analytics Core (Core D)

Overview: To maximize discovery and new knowledge generation in the current interdisciplinary and data-rich research environment, it is critical to perform integrative analyses. Such analyses that use diverse data modalities within and across laboratories can contextualize specific findings and are enabled by new computational approaches. Applications of artificial intelligence and data analytics tools are rapidly increasing by advances in big data analysis and machine learning (ML)/deep learning methodologies including both hardware/sensor and software/algorithm design. Musculoskeletal applications benefit from new advancements in imaging technologies and these technologies can achieve high-level performance in tasks such as fracture detection, cartilage defects/osteoarthritis detection, bone age assessment, osteoarthritis grading, adipose tissue segmentation, muscle and soft tissue quality and composition, image-quality improvement, and automatic protocolling. These computational approaches can help place intermediate molecular (omics) and cellular (imaging) traits into context and integrate them in novel ways with one another, as well as with preclinical phenotypic data or clinical data to illuminate mechanisms of musculoskeletal health and disease.

*The **Integrative Data Analytics Core** of the MiMHC will provide Center investigators access to the instruments and expertise to standardize, quantify, and integrate omics, imaging and clinical traits.* We will provide guidance and expertise on *data management* (e.g. data collection protocol, data storage tool usage), *image processing* (e.g. image enhancement, image denoising, image segmentation, imaging feature extraction, image texture analysis), *omics data analysis* (e.g. genome, epigenome, and transcriptome study design, quality control, and normalization), and *integrating omics across modalities and species* (human compared to model organism). Finally, we will assist Center investigators with analyzing all imaging, omics, and preclinical phenotype data or clinical data using integrative approaches, machine learning model training, validation, and interpreting the results. These analytic services were chosen for their applicability to all musculoskeletal tissues and the large number of Center investigators utilizing these computational methods.

The Integrative Data Analytics Core will provide this critical function for the musculoskeletal research community and will enable increased communication and knowledge-sharing among Center investigators as well as growth across UM. The team of Core Directors and Core Staff is composed of experts at analyzing data with different modalities and will provide a unique opportunity for Center investigators to develop and apply data science skills to their problems in a cost-effective and efficient manner.

The Integrative Data Analytics Core will provide expertise in designing and implementing data analytical systems to Center investigators consisting of the following main components:

1) Imaging data analysis
2) Omics data analysis
3) Statistical assessment of biological and biomedical data and integrative machine learning

Access to services: Contact Stephen Parker, PhD when beginning a project and for general assistance with core access. He will provide guidance on experimental design and the appropriate Faculty and Core expert to contact next. Each investigator will also meet with a Faculty Core Expert (Parker: omics analyses and integration; Wittrup / Najarian: image analyses; machine learning) to establish a plan that best supports their research project, and to obtain advice on experimental design, sample size estimates and projected integrative analyses. The amount of support provided to MiMHC members will be determined during this initial meeting. This support could range from providing guidance to ongoing projects, to training of MiMHC staff and trainees to enable them to conduct analyses, to the execution of analyses by core experts.

Stephen Parker, PhD	Director	scjp@umich.edu
Kayvan Najarian, PhD	Associate Director	kayvan@med.umich.edu
Arushi Varshney, PhD	Core expert	arushiv@umich.edu
Emily Wittrup	Core expert	ewittrup@med.umich.edu

Enrichment Program

Overview

The Administrative Core will be responsible for administering an Enrichment Program with guidance from Core Directors, Advisory Panel members, and Core staff on overall direction and impact. The Enrichment Program has three priority areas including *Community Building and Education*, *Mentorship and Career Development*, and *Research Development and Innovation*.

Priority Area 1: Community Building and Education

NEW! This year, we started a **Meet the Authors session** to feature new work by members who have used our cores to share their findings from a recent publication with the community. This session includes a brief presentation by the Principal Investigator of the work, and the majority of the presentation is led by a trainee (postdoctoral fellow, graduate student, or research scholar). This Meet the Authors session promotes trainee and PI engagement and showcases the findings from our P30 core. Both virtual and in-person options on the Ann Arbor campus were included.

Monthly Technical Workshops: Monthly Technical Workshops will be held immediately preceding the MSK RiP seminars. The workshops are open to anyone and provide a venue for educating faculty, staff, and trainees on core services including technologies, study design, and data interpretation.

Annual Musculoskeletal Health Symposium: The Musculoskeletal Health Symposium serves as the annual meeting for the MiMHC. The goals of the symposium are to celebrate the diversity of musculoskeletal research conducted by Center members, promote the Center and core services, build community, and provide career growth opportunities for trainees and junior faculty. This symposium is open to the public and generally held in the Spring in the BSRB.

Priority Area 2: Mentorship and Career Development

Contact: Renny Franceschi, PhD (rennyf@umich.edu)

MSK Boot Camp: The goal of the MSK Boot Camp is to mentor junior faculty on grantsmanship, including writing skills, collecting preliminary data, and understanding the NIH review process. The MSK Boot Camp is modeled after the UM Medical School R01 Boot Camp in that a junior faculty is paired with 3 musculoskeletal experts to provide guidance during the grant development process. Dr. Franceschi forms an expert panel from a group of volunteer musculoskeletal investigators with grant success and reviewing experience as well as a record of mentorship. The program involves monthly meetings with the following schedule: months 1-4 are spent developing the Specific Aims and learning about the NIH extramural grant system including information on relevant study sections; months 5-6 are spent writing the significance and innovation sections; months 7-10 are spent writing the Research Plan. Faculty mentors review the completed grant and will provide guidance on responding to critiques for a resubmission, should that be necessary.

Grant writing support: Grant writing skill development are supported in two additional ways. First, Center investigators who want a grant pre-reviewed prior to submission can contact Dr. Franceschi who will organize a panel of experts willing to review the proposal. Faculty must submit the grant for review at least 2 months before the deadline. The panel reviews the grant using the CSR format within 2 weeks, allowing ample time for the faculty to make meaningful changes to the proposal. Second, Center investigators who need financial support to attend a grant writing workshop (offsite or online) can contact Dr. Franceschi who will provide full or partial funding, depending on the circumstances and availability of funds. This workshop support may include offsetting travel costs or registration fees.

Launch Committees: UM uses Launch Committees to support the career growth of junior faculty and provide advice, information, and encouragement within a confidential and positive atmosphere. Dr. Franceschi will help facilitate these committees by working with new faculty to identify senior investigators with track-records of outstanding mentorship. These committees, which meet bimonthly for a year, will be impactful to junior faculty by providing guidance on major decisions for starting up a lab (hiring process, service decisions, grant submission strategies), navigating UM systems, identifying resources, and connecting junior faculty with other faculty and collaborators throughout UM. These committees have successfully welcomed junior faculty to the musculoskeletal community and have enabled them to begin their careers at UM on a strong foundation.

Trainee Travel Awards: The Annual Symposium includes a Poster Session organized by Dr. Franceschi. Trainees, staff, and junior faculty are invited to submit abstracts 6-8 weeks prior to the symposium. Trainees may elect to compete for one of 3 travel awards. Dr. Franceschi selects 5 judges to review abstracts of trainees, and the 6 highest scoring abstracts are invited to give a podium presentation at the symposium. The same panel of judges scores the presentations based on the quality of science, significance, impact, verbal communication skills, and relevance to musculoskeletal health.

Priority Area 3: Research Development and Innovation

Contact: Susan Brooks, PhD (svbrooks@umich.edu)

Pilot and Feasibility (P&F) grant program: Novel and emerging research will be promoted through a P&F program that will provide support to Center investigators for generating preliminary data for grant submissions within the scope of the NIAMS mission. Two pilot awards of $30,000 each will be funded each year. This pilot grant program will prioritize awards to Assistant Professors and Research Investigators in all tracks, specifically those who have not yet received NIH R01 or equivalent funding. Mid-career faculty (Associate Professors) are also eligible provided they demonstrate that the proposed project represents a significant new direction for their research program. All applicants (regardless of rank) should include a statement of why and how this pilot funding will be useful for them (e.g., career development; establishing independence; pilot data for first R01; new direction for research program; etc.). All applications must align with the NIAMS mission (https://www.niams.nih.gov/about), and all investigators chosen to receive a pilot grant must participate in the MSK Boot Camp program. Prior awardees are not eligible to apply. Those deemed eligible will undergo a full peer-review. Competitive projects expected to have high priority for selection will demonstrate a high likelihood that the award will lead to extramural funding; utilize one or more of the MiMHC services; promote new collaborations; develop novel computational or experimental tools that facilitate the ability of researchers to test for sex-differences or interactions among musculoskeletal tissues; and/or include new bioinformatics tools that promote the use of services offered through the new Integrative Data Analytics core.

For more details on each of the Enrichment Program or any of the Research Cores, please visit the MiMHC website: http://mimhc.med.umich.edu/

Abstracts

(in alphabetical order)

Poster 1

Title: Anemia and Proximal Humerus Fracture Nonunion: A risk factor in younger but not older patients

Alexander Mamonov, BS[1], Erik R. Nakken, MD[1], Blas Garcia-Canga, BS[1], Daniel G. Whitney, PhD[1,2], Annemarie Lang, PhD[1], William R. Aibinder, MD[1]

[1]Department of Orthopaedic Surgery, University of Michigan

[2]Institute for Healthcare Policy and Innovation, University of

Michigan Presenter Name: Alexander Mamonov

Introduction: Proximal humerus fracture (PHF) is the third most common osteoporotic fracture, with incidence rates up to 6%. Rates peak between ages 60 and 90; females over 85 are at highest risk. PHF is primarily treated non-operatively with sling immobilization and physiotherapy. Nonunion is a relatively common complication. Anemia, a deficiency in circulating erythrocytes compromising systemic oxygen transport, presents in nutritional, hemolytic, and aplastic subtypes. Preoperative anemia is a known risk factor for distal femoral nonunion, but current literature lacks investigation into its effect on proximal humeral nonunion.

Methods: This retrospective cohort study harmonized commercial and Medicare fee-for-service claims (01/01/2016–12/31/2023). The cohort included adults ≥19 years old with a PHF and continuous enrollment for ≥6 months post-fracture. Exclusions included cancer in the 1-year pre-fracture baseline, shoulder arthroplasty within 4 weeks post-fracture, and primary outcome (nonunion diagnosis) within the first 6 months post-fracture. Primary exposure was any evidence of anemia in the 1-year pre-fracture period, examined as yes/no, co-occurring condition count (0-14), and groupings (nutritional, hemolytic, aplastic/other). Incidence rate (IR), IR ratio (IRR), and hazard ratio (HR) were estimated for the primary outcome of PHF nonunion from 6 to 18 months post-fracture, before and after adjusting for confounders.

Results: The study included 25,109 adults with anemia (mean age 76.0; 78.2% women; 6.8% commercially insured) and 64,389 without anemia (mean age 68.3; 74.6% women; 26.7% commercially insured). Crude IR and IRR of nonunion were significantly higher for the full anemia cohort (IR=6.0; IRR=1.37) and each sub-cohort (IR [IRR] for 1, 2, and ≥3 anemia conditions was 5.5 [1.25], 6.2 [1.42], and 8.1 [1.85], respectively) compared to the non-anemia cohort. Adjusted HR, however, showed no significant difference for the full anemia cohort (HR=0.97) or sub-cohorts (HR range 0.85-1.00). Age strongly modified these associations ($P \leq 0.001$). Sub-group estimates for ages 40, 50, 60, 70, and 80 showed elevated HRs at younger ages, declining with age to approximately 1.00 by 70 and below 1.00 by 80 for all three anemia exposure types.

Conclusion: Age significantly modified the relationship between anemia and proximal humerus fracture nonunion. While crude rates of nonunion were higher among patients with anemia, adjusted analyses demonstrated that this association was largely attenuated overall, with the effect varying substantially by age. Anemia was associated with increased nonunion risk in younger patients, but this relationship diminished with advancing age and was no longer present by approximately 70 years, suggesting that patient age plays a critical role in the clinical relevance of anemia as a risk factor for nonunion.

Poster 2

Evaluation of Patient-Reported Axial Spine Pain Outcomes After Extracorporeal Shockwave Therapy

Blake T. Marrogy[1]; John Paul A. Atto[2]; Christian T. Stipho[2]; Fadi H. Delly, MD[1]
[1]Wayne State University, Detroit, MI
[2]University of Michigan, Ann Arbor, MI
Presenter: Blake T. Marrogy[1]

Study Goals: Extracorporeal shockwave therapy (ESWT) has emerged as a noninvasive treatment modality for chronic musculoskeletal pain conditions, with increasing application in axial spine and myofascial pain syndromes. Proposed mechanisms of action include modulation of nociceptive signaling, induction of neovascularization, and promotion of tissue repair. Although prior studies have demonstrated the efficacy of ESWT in reducing pain and improving function in select musculoskeletal conditions, patient-reported pain outcomes following ESWT for axial spine-related pain remain variable, partially due to heterogeneity in pain assessment methods and treatment protocols. The objective of this study is to evaluate changes in patient-reported pain outcome measures following ESWT for axial spine-related pain using the visual analog (VAS) pain scale and a validated disability index.

Methods: A retrospective cohort study was conducted. All patients who underwent ESWT for neck, upper back, mid back, lower back, and myofascial pain at a single outpatient clinical setting between 2024 and 2025 were included. Pain severity was assessed using patient-reported pain scores collected at four standardized time points: prior to the first ESWT session (pre-ESWT), immediately following the first treatment session (post-first ESWT), immediately following the midpoint treatment session (post-middle ESWT), and immediately following the final treatment session (post-final ESWT). Changes in pain severity across treatment time points were analyzed. Patient-reported pain disability index scores were compared before and after ESWT. Statistical significance was defined as $p \leq 0.05$.

Results: A total of 85 patients were included in this study. The distribution of presenting complaints was as follows: 61 patients with isolated lower back pain (72%), 11 patients with isolated neck pain (13%), 6 patients with isolated mid back pain (7%), 4 patients with isolated upper back pain (5%), and 3 patients with isolated myofascial pain (3%). Mean patient-reported pain scores (± standard error) demonstrated a progressive decline across treatment time points: pre-ESWT (7.53 ± 0.28), post-first ESWT (5.00 ± 0.25), post-middle ESWT (4.23 ± 0.28), and post-final ESWT (3.51 ± 0.27). Repeated-measures analysis demonstrated that pain scores at the pre-ESWT time point were significantly higher compared with subsequent time points ($p < 0.001$ for all comparisons). Furthermore, the pain disability index score (± standard error) improved following treatment, decreasing from 9.47 ± 2.00 pre-treatment to 6.78 ± 1.62 post-treatment. However, this difference did not achieve statistical significance ($p = 0.103$).

Discussion/Conclusion: ESWT was associated with clinically meaningful reductions in pain severity among patients treated for chronic axial spine-related pain. Patient-reported pain scores demonstrated rapid, sustained improvement across successive treatment sessions. These findings support the utility of ESWT as a noninvasive treatment option for axial spine-related musculoskeletal pain in routine clinical practice. Further prospective, controlled studies are warranted to evaluate long-term outcomes, axial spine-specific response patterns, and standardized pain assessment protocols.

Poster 3

Title: Impact of endurance training on mouse skeletal muscle isoform and RNA binding protein expression

Authors and affiliation: Ahn, A., **DenUyl, B. R.,** Zhang, E. Y., Lloyd, C. J. V., Bauman, C. J., Jaafar, L. A., Stoneback, L., & Ludlow, A. T.

Name of presenter (Only one poster per presenter): DenUyl, B. R.,

Abstract

Regular progressive endurance exercise training induces skeletal muscle adaptations including enhancing mitochondrial function, increased muscle fiber cross sectional area, metabolic flexibility, and aerobic capacity that underlie many cardiometabolic health benefits. Our recent work in acute endurance exercise indicates that, in addition to transcriptional remodeling, post-transcriptional regulation is prominent in recovery, including RNA isoform switching, alternative RNA splicing, and altered expression of splicing regulators. **Study goals:** However, how chronic progressive endurance exercise training impacts RNA isoform expression and RNA binding protein (RBP)/ splicing factor abundance in trained skeletal muscle and how these changes relate to canonical training phenotypes (e.g., skeletal muscle fiber cross sectional area, glycogen content, and mitochondrial content) remains poorly defined. **Methods:** To address this gap, six male HET3 mice completed 12 weeks of progressive uphill treadmill training (13–24 weeks of age), with six age- matched sedentary controls. Forty-eight hours after the final bout, gastrocnemius muscles were collected for fiber CSA, glycogen content, mitochondrial content, and transcriptomic profiling using long-read RNA sequencing (Oxford Nanopore Technologies). Isoform changes were analyzed with IsoformSwitchAnalyzeR. Candidate targets were validated by droplet digital RT-PCR and immunoblotting. **Results:** Training significantly enhanced running capacity, muscle fiber cross sectional area, mitochondrial DNA copy number ratio, and PGC1alpha protein content. Long-read sequencing identified 59 differentially used isoforms representing 15 switching events across 13 genes (FDR < 0.05; switch fraction > 10%). Notably, Rsrp1 exhibited a shift toward a protein-coding isoform (mRsrp1-201; +15.4%) with a reciprocal decrease in a non-coding isoform (mRsrp1-204;
−21.6%; $p < 0.05$). This was accompanied by a 40.0% increase in RSRP1 protein in trained muscle ($p = 0.041$), which strongly correlated with uphill running–induced hypertrophy ($p < 0.001$). Beyond RSRP1, several RBPs/splicing factors were increased in trained muscle, including SF3B4, hnRNPA3, hnRNPA1, and hnRNPM, whereas hnRNPA2B1 and SRSF2 were decreased at the protein level. MBNL1, MBNL2, and RBFOX2 were unchanged. Pearson correlations identified SF3B4, RSRP1, and hnRNPM as significantly associated with muscle fiber CSA. Given these hypertrophy-related associations, we examined *Igf1* isoform expression. IGF1A protein increased
~30% with training, and total Igf1 transcript abundance increased ~50% versus sedentary controls. Isoform-specific PCR showed a ~12% increase in the *Igf1b:Igf1a* ratio post-training. Because SF3B4 is predicted to bind near the alternative exon associated with *Igf1b*, we propose SF3B4 may contribute to increased *Igf1b* expression, pending direct mechanistic validation. Consistent with an anabolic/anti-atrophy shift, trained mice exhibited lower Fbxo32 (atrogin-1/MafBx) mRNA, also observed in the long-read dataset. **Conclusion:** Progressive endurance training induces coordinated changes in skeletal muscle RNA isoform usage and a network of RBPs/splicing factors that correlate with increases in muscle fiber CSA. Future studies are needed to define causality and identify upstream signals that initiate these post-transcriptional adaptations.

Poster 4

Compromised Bone Architecture and Strength in Skeletally Mature Female Mice with Type 2 Diabetes is Associated with Decreased Endosteal Bone Formation and Increased Bone Resorption

Carlos A. Urrego[1], Juan Pablo Raigosa[1], Abigail G. Quint[1], Savannah W. Jomaa[1], Benjamin S. Sexton,[1,2], Ingrid L. Rosko[1], Clifford J. Rosen[3] & David H. Kohn[1,2]

University of Michigan Dept. of Biomedical Engineering[1], Dept of. Biological and Material Sciences[2], Maine Health Institute for Research[3]

Abstract:

Presenter: Carlos A. Urrego

Women with type 2 diabetes (T2D) have a higher risk of fracture compared to diabetic men, but the underlying mechanism by which T2D compromises female bone quality remains unknown. We previously developed a T2D C57BL/6J mouse model and discovered that the effect of T2D on bone quality was driven by reduced cortical total volume (Ct.TV) and bone volume (Ct.BV). This study aimed to determine the role of bone formation and resorption as key determinants in diabetic bone architecture. We recreated our T2D mouse model using a combination of high-fat diet (HFD) and Streptozotocin (STZ). Healthy controls were fed a low-fat diet (LFD) and received sham injections (VEH). Diet-only (HFD+VEH) and STZ-only (LFD+STZ) control groups were also included. T2D was induced at 18 weeks, and all mice were euthanized at 30 weeks of age (n = 18–20). Bone architecture was assessed by micro-computed tomography; mechanical properties by four-point bending; bone formation and resorption by serum assays and dynamic histomorphometry; and bone marrow adiposity by histology with H&E staining. We demonstrated that the combination of HFD and STZ was required to induce diabetes. Only the HFD+STZ group developed and maintained diabetes for 12 weeks (blood glucose >250 mg/dL) **[A]**. The other groups remained euglycemic, proving that HFD or STZ alone were not sufficient to induce T2D in female mice. Consistent with the diabetic state, the combination of HFD and STZ was required to decrease total volume and bone volume. Compared with healthy controls (LFD+VEH), the HFD+STZ group showed a 5.4% reduction in Ct.TV (P=0.0028) and a 7.6% reduction in Ct.BV (P=0.0005) at the mid-diaphysis **[B,C]**. These changes in architecture with T2D led to a 10.7% (P=0.002) decrease in the femoral ultimate load while preserving tissue-level properties **[D,F]**. Furthermore, T2D decreased the mineral apposition rate by 21.1% (P=0.0164) and the bone formation rate (BFR) by 26.2% (P=0.0029) in the endocortical region **[E,G]**. In addition, serum markers indicated a 97.9% (P=0.0002) increase in bone resorption with T2D **[H-J]**. BFR was significantly correlated with Ct.TV (r=0.36) and Ct.BV (r=0.39). Lastly, T2D increased bone marrow adiposity by enlarging the average adipocyte size by 18.5% (P=0.0188), without altering adipocyte number **[K,L]**. In summary, our findings demonstrate that reduced bone volume in T2D is associated with decreased bone formation and increased bone resorption, highlighting impaired bone metabolism as a key driver of the diabetic bone phenotype. This study shows that the combination of HFD and STZ is required to induce T2D in skeletally mature female mice, validates the reproducibility of our T2D animal model, and further supports the hypothesis that T2D's impact on bone quality is structure- driven. Our findings contribute to the understanding of the biomechanical mechanisms by which T2D compromises women's skeletal health.

Poster 5

A Modified Whole-Body Vascular Perfusion Technique for Visualization of Neovascularization in Murine Model Femoral Critical-Sized Defects

Christian T. Stipho[1]; Jennifer E. Ten Eyck[1]; Rohan J. Gupta[1]; Stephanie Taiberg[1]; Noah S. Nelson[1]; Abigail S. Teitelbaum[1]; Noah G. Siegel[1]; Payal F. Sutaria[1]; Adrian Araneo[1]; Steven R. Buchman[1]

[1]Craniofacial Research Laboratory, University of Michigan, Ann Arbor, MI

Presenter: Christian T. Stipho[1]

Study Goals: Robert E. Guldberg's whole-body vascular perfusion techniques are currently the gold standard for visualization of vascular networks and quantification of angiogenesis in murine models of critical-sized bone defects. A critical-sized bone defect is defined as the smallest intraosseous wound that will not heal spontaneously on its own. As successful bone healing is highly dependent on the enhancement of neovascularization, efficient and effective methods for assessing regenerated vascularity within these defects are critical for studying healing outcomes. However, current methods are frequently optimized for overall vascular imaging and may provide incomplete perfusion of osseous defects, particularly in models that involve large segmental bone loss. The goal of this study is to develop and describe a variation of the Guldberg whole-body vascular perfusion technique to further improve visualization of neovascularization within a critical-sized defect of the rat femur.

Methods: Sprague-Dawley rats with either 1-mm or 3-mm critical-sized femoral defects were included in the study. First, experimental animals were anesthetized via inhalation of a 3:1 isoflurane/oxygen mixture. After induction of anesthesia, animals underwent thoracotomy to allow for catheterization of the left ventricle of the heart. Vasculature was first flushed with 100 cc of normal saline (0.9% NaCl) at a pressure of approximately 150 mmHg. Incision of the right atrium was performed to allow for complete evacuation of blood. Specimens were then pressured-fixed with formalin to ensure euthanasia. This was followed by perfusion of an additional 100 cc of normal saline along with a solution of 10-15 cc of Microfil MV-122 (Flow Tech, Carver, MA, USA): a yellow, radiopaque, lead-based, silicone rubber contrast agent. Carcasses were kept at 4℃ for
24 hours to allow complete solidification of Microfil. Rodent femurs were then dissected, harvested, and decalcified to allow for subsequent imaging of defect vascularity using micro-computed tomography (μCT).

Results: Successful perfusion is determined by gross examination of the tongue and eyes for color change to that of Microfil, indicating complete perfusion of distal capillary networks. The figure below represents a 3D microangiography following a successful whole-body perfusion.

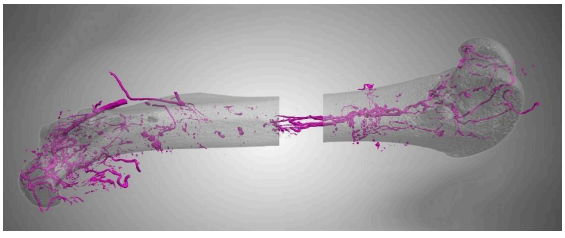


Figure 1. 3D microangiography of blood vessel perfusion of *ex vivo* rat femur with critical-sized defect. Fixated blood vessels are highlighted in magenta. Overlayed femur image with a 3mm defect is provided for anatomical reference.

Discussion/Conclusion: This modified whole-body vascular perfusion technique serves as a reliable method for visualizing neovascularization within rat critical-sized femoral defects. This approach may be utilized in future studies to investigate the effect of regenerative therapies on improving angiogenesis in segmental bone defect models.

Poster 6

Iron-Deficiency Anemia Modulates Erythropoiesis-Bone Crosstalk and Drives Bone Loss

Christophe Merceron[1], Nupur K. Das[2], Prakaimuk Saraithong[1], Gao Xiaohua[1], Andreanna Ulery[1],Sophia Fisher[1], Sia Pradhan[1], Greggory Myers[3], Rami Khoriaty[3], Yatrik Shah[2], Annemarie Lang[1]
[1]Department of Orthopaedic Surgery – University of Michigan, Ann Arbor, MI, [2]Department of Molecular & Integrative Physiology and Internal Medicine – University of Michigan, Ann Arbor, MI, [3]Department of Internal Medicine – University of Michigan, Ann Arbor, MI.

INTRODUCTION: Bone is a dynamic organ that regulates its formation and resorption through bi-directional communication with multiple tissues, organs, and microenvironments via hormonal, inflammatory, and mechanical stimuli. Over a billion people worldwide suffer from disorders of red blood cell formation (erythropoiesis) in the bone marrow, such as iron-deficiency anemia, sickle cell disease, and thalassemia, where skeletal complications are frequent. However, the mechanistic link between altered iron metabolism, erythropoiesis, and bone integrity remains incompletely understood. In this study, we investigated how iron metabolism mediates the crosstalk between erythroid precursors and bone tissue. Specifically, we asked whether iron-deficiency anemia triggers bone loss in skeletally mature mice. To address this, we utilized an inducible, intestine-specific ferroportin (Fpn) knockout mouse model ($Fpn^{\Delta IE}$), which leads to iron-deficiency anemia by blocking dietary iron absorption via targeted deletion of Fpn, the principal iron exporter. Furthermore, we assessed whether pharmacological intervention with a dual kinase inhibitor Saracatinib targeting ALK2, a BMP type I receptor involved in iron-related pathways, could reverse these effects.

METHODS: Transgenic mice expressing a tamoxifen inducible, intestinal epithelium specific Cre recombinase ($Vil^{CreERT2}$) were used in combination with mice homozygous floxed mice for ferroportin ($Fpn^{fl/fl}$) to generate $Vil^{CreERT2}$; $Fpn^{fl/fl}$ mice. Tamoxifen (100 mg/kg IP, 3 days) was administered at 6 weeks of age. Both $Fpn^{\Delta IE}$ and control $Fpn^{fl/fl}$ mice were aged to 24 weeks, then treated with Saracatinib (5 mg/kg) or vehicle by oral gavage for 7 days. Anemia was characterized by automated hematology from peripheral blood. Bone marrow cellularity and erythroid lineage distribution were quantified using multiparametric flow cytometry, with two antibody panels targeting early (c-Kit, Sca-1, CD150, CD41, CD16/32, CD105) and late (CD71, TER119, CD44) erythroid populations. Trabecular and cortical bone parameters were evaluated by nanoCT. Immunofluorescence staining was performed on femora stained for CD31 (endothelial), CD71, and Ter119 (erythroid).

RESULTS: $Fpn^{\Delta IE}$ mice exhibited a pronounced anemic phenotype, with significantly reduced levels of red blood cells (RBC), hemoglobin, hematocrit, and reticulocytes in peripheral blood. Among $Fpn^{\Delta IE}$ animals, two developed mild/moderate anemia (HGB > 9 g/dL), while three were severely anemic (HGB < 9 g/dL); subsequent analyses focused on the latter group. Multiparametric flow cytometry of total bone marrow revealed notable alterations in erythroid lineage populations, with an increase in early progenitors and a marked elevation in the proerythroblast ($Ter119^{lo}$ $CD71^{+}$) subpopulation, accompanied by a reduction in late-stage erythroblasts ($Ter119^{+}$ $CD71^{-}$) in severely anemic mice. Immunofluorescence staining confirmed the increased abundance of $CD71^{+}$ erythroid precursors and revealed pronounced alterations in the vascularized bone marrow niche. NanoCT analysis demonstrated significant trabecular bone loss, as indicated by reductions in bone volume fraction trabecular number and bone mineral density, as well as an increase in trabecular separation. Cortical bone parameters, including cortical thickness and cortical area/total area, were also significantly diminished. These combined findings establish that $Fpn^{\Delta IE}$ mice recapitulate severe iron-deficiency anemia and experience a concomitant deterioration in bone architecture, suggesting a mechanistic link between iron metabolism, erythropoiesis, and bone homeostasis. Remarkably, a one-week course of Saracatinib treatment effectively reversed both the anemic phenotype and skeletal deficits resulting from intestinal ferroportin deletion.

CONCLUSION: Taken together, our results suggest the existence of a link between iron metabolism, erythropoiesis, and bone homeostasis, likely governed by as-yet-undiscovered regulatory pathways. Elucidating these mechanisms and identifying dual-action therapeutic targets has the potential to transform clinical management of disorders affecting both blood and bone. The directionality and causality within this relationship remain unresolved.

Poster 7

Aerobic Exercise Modulates Fibrotic Signaling Without Excess Collagen Accumulation in Skeletal Muscle of Adults With Type 2 Diabetes

Authors: Cory A. Lutz, Jeffrey F. Horowitz, Andrew T. Ludlow, Jacob M. Haus, *Ann Arbor, MI*

Presenter: Cory A. Lutz

Abstract:

Introduction and Objective: Skeletal muscle fibrosis contributes to impaired muscle regeneration, reduced strength, and metabolic dysfunction in type 2 diabetes (T2DM). Transforming growth factor-β1 (TGF-β1) signaling regulates extracellular matrix (ECM) remodeling, but human data linking transcriptional changes to protein-level ECM adaptations following exercise are limited. Our objective was to determine whether exercise-induced transcriptional changes in fibrotic signaling correspond to alterations in collagen and fibrotic pathway protein abundance in skeletal muscle of adults with T2DM. **Methods:** Twenty adults with T2DM underwent vastus lateralis muscle biopsies at baseline and after 12-wks of aerobic exercise training (AE: 60min/d, 5 d/wk, ~70% VO_2max; NCT03021252) or standard of care (CON). Muscle biopsies were taken 48 hrs after the last training session. RNA sequencing (>100M paired-end reads) identified differential expression of fibrosis-related genes and TGF-β1 signaling pathways. Protein abundance of ECM markers was measured by western blot and normalized to total protein. Data were analyzed using a linear mixed-effects model (group, time, group × time). **Results:** RNA-seq identified 27 differentially expressed (AE vs CON) fibrosis-related genes following AE training (padj <0.05, |log2FC|>0.5) including increased SMAD7 expression. AE training also increased expression of structural ECM genes including COL1A1, COL1A2, COL3A1, and COL4A1. Despite these transcriptional changes, mixed-effects analysis revealed no significant main effects of group or time and no group × time interactions for COL1, COL3, SMAD, pSMAD, or TGFB1 protein abundance. **Conclusion:** AE altered transcriptional regulation of fibrotic signaling pathways in skeletal muscle of adults with T2DM without corresponding changes in collagen protein abundance, indicating regulated ECM remodeling rather than fibrotic accumulation. Future work should define ECM remodeling mechanisms with AE.

Supported by: NIH DK109948

Poster 8

Regenerative Potential of Osteoarthritic Chondrocytes for Cartilage Tissue Repair

Di Zu [1], Rhima Coleman [1]
[1]Biomedical Engineering, University of Michigan, Ann Arbor, MI

Presenter: Di Zu

STUDY GOALS: Articular hyaline cartilage has a limited intrinsic capacity for self-repair after injury, which contributes to the development and progression of osteoarthritis (OA), an age-associated degenerative joint disease. The burden of OA increases substantially with age; in the United States, approximately 43% of individuals with OA are aged ≥65 years, and 88% are aged ≥45 years. Despite considerable outcomes of regeneration in young patients, their efficacy is often diminished in older individuals and in joints with established osteoarthritic changes. This reduced regenerative potential is thought to result, at least in part, from impaired extracellular matrix (ECM) production by aged and OA chondrocytes. The objective of this study is to investigate the mechanisms underlying chondrogenic regeneration through phenotypic and genotypic characterization of chondrocytes derived from young healthy, aged healthy, and aged osteoarthritic donors. We hypothesize that, following chondrogenic culture, aged osteoarthritic chondrocytes will exhibit distinct phenotypic and genotypic profiles associated with impaired regenerative capacity compared with young healthy and aged healthy chondrocytes.

METHODS: Human articular chondrocytes (HACs) were isolated from young healthy, aged healthy, and aged osteoarthritic donor knee joints, expanded to passage 4, and cultured in a 3D redifferentiation system. At defined time points, phenotypic outcomes were assessed by extracellular matrix quantification and histological analysis, including sulfated glycosaminoglycan (sGAG) evaluation and cartilage tissue scoring, while genotypic differences were assessed by RT-qPCR and bulk RNA sequencing to compare regeneration capacity among the three chondrocyte groups.

RESULTS: Pellets of HACs were harvested on day 0, 14, and 28 of redifferentiation culture. Extracellular matrix quantification and histological analysis were performed on days 14 and 28. Compared with young healthy HACs, both aged healthy and aged OA HACs exhibited reduced chondrogenic capacity, characterized by lower ECM accumulation and inferior histological morphology; these changes were more severe in aged OA HACs. For genotypic characterization, RT-qPCR and bulk RNA-seq were performed on days 0, 14, and 28. Expression of the chondrogenic marker genes SOX9, COL2A1, and ACAN was reduced in aged healthy and aged OA donor cells, whereas expression of the hypertrophic and catabolic markers RUNX2, COL10A1, and MMP13 was increased relative to young healthy HACs. Transcriptomic profiling further revealed significant enrichment of differentially expressed genes in biological processes associated with cartilage development, chondrocyte differentiation, extracellular matrix organization, and growth factor–mediated signaling, indicating that aging- and OA-associated pathways are strongly linked to chondrogenic regeneration.

DISCUSSION/CONCLUSION: Articular cartilage possesses limited intrinsic self-repair capacity because of its avascular structure and the diminished proliferative and regenerative potential of aged healthy and aged osteoarthritic chondrocytes. Integrated phenotypic and genotypic characterization of chondrocytes from young healthy, aged healthy, and aged OA donors provides a mechanistic framework for understanding cartilage regeneration and identifying pathways associated with age- and OA-related dysfunction. These findings will guide our next studies, which will focus on developing reprogramming strategies to rejuvenate aged OA chondrocytes and shift them toward a more youthful, healthy phenotype. Overall, this study demonstrates that an integrated phenotypic and transcriptomic approach reveals distinct molecular and functional signatures associated with regenerative capacity in aged and osteoarthritic chondrocytes.

Poster 9

TITLE: Incidence and Timing of Periprosthetic Joint Infection After Primary Total Hip and Knee Arthroplasty

AUTHORS: Nakken ER, Surapaneni M, Arhewoh ER, Wang Z, Jandzinski M, Kheir MM.
AFFILIATION: University of Michigan, Department of Orthopaedic Surgery
PRESENTER: Erik R. Nakken, MD

STUDY GOALS: Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are among the most commonly performed orthopaedic procedures, with annual volumes steadily increasing. Periprosthetic joint infection (PJI) complicates approximately 1–2% of these cases, with 39–58% reported to occur within the first postoperative year. We aim to describe the temporal incidence of PJI after THA and TKA to improve treatment planning and patient counseling.

METHODS: A retrospective review was conducted using institutional records and the Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI) database, identifying patients who underwent primary THA or TKA between 2000 and 2023, and were subsequently treated for PJI. Cases were verified through manual chart review. PJI was defined according to the 2018 Musculoskeletal Infection Society (MSIS) criteria. Demographics, treatment details, and time to infection were analyzed. Minimum follow-up was one year.

RESULTS: Among 14,610 primary arthroplasties performed, 152 cases of PJI were identified, an overall infection rate of 1.04%. Temporal distribution of PJI diagnoses was as follows: 49% within 3 months, 56% within 6 months, 66% within 1 year, 78% within 2 years, 90% within 5 years, and 98% within 10 years postoperatively.

CONCLUSION: The observed PJI rate aligns with national estimates. The majority of infections occurred early, with over half diagnosed within 6 months and less than 25% occurring beyond 2 years. These findings underscore the critical importance of early postoperative vigilance for PJI detection and intervention.

Months After Surgery	Infections (N)	Infection Percentage
1	50	36.3%
2	64	45.0%
3	70	48.8%
4	74	51.3%
5	76	52.5%
6	81	55.6%
12	97	65.6%
24	117	78.1%
36	126	83.8%
48	129	85.6%
60	136	90.0%
120	148	97.5%

Table 1: Timing of periprosthetic joint infection after surgery

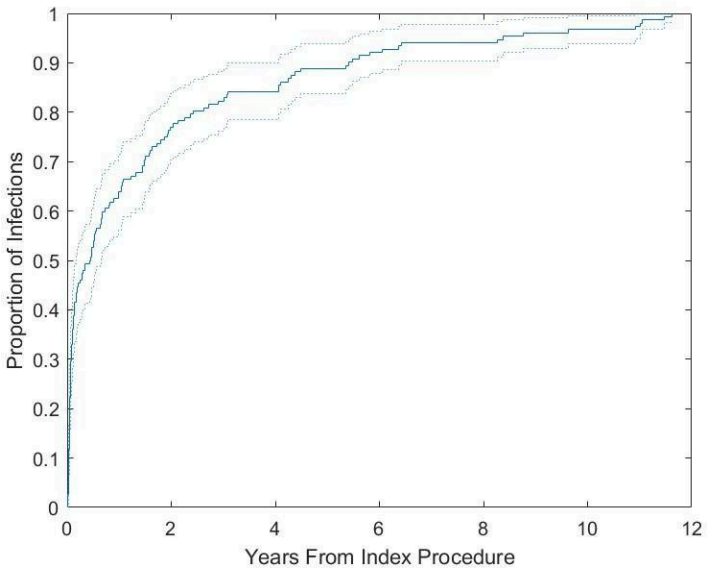


Figure 1: The proportion of periprosthetic joint infection by time after surgery

Poster 10

Regeneration of Intervertebral Disc in a Rat Tail Model of Degenerative Disc Disease

Authors and Affiliation:
Syed Faizan Ali Rizvi[12], Ali Alamri[12], G. Rasul Chaudhry[12]
[1]Oakland University, Rochester, Michigan, USA, and [2] OU-WB Institute for Stem Cell and Regenerative Medicine, Oakland University, Rochester, Michigan

Presenter:
Syed Faizan Ali, Rizvi

Abstract:

Background and Study Goal
Primitive mesenchymal stem cells (pMSCs) derived from umbilical cord tissue show greater proliferation and differentiation ability than MSCs from other sources. These cells exhibit a fibroblast-like morphology and express mesenchymal markers, although they are smaller than MSCs from other tissues. pMSCs grow rapidly, with a doubling time of about 15 hours, which stays consistent even after passage 30. This study aimed to evaluate the differentiation of these primitive MSCs into nucleus pulposus-like cells (NPCs) and to assess the regenerative potential of a scaffold-NPC combination in a rat model of intervertebral disc degeneration (DDD).

Methods
pMSCs were isolated from human umbilical cord tissue and induced to differentiate into NPCs using a specialized differentiation medium. To assess their regenerative potential, a rat tail model of DDD was established by puncturing the tail intervertebral disc (IVD) with a 20-gauge needle. The animals with degenerated discs were divided into eight groups (n=6 each) for the injection of PKH26-labeled cells: healthy control, diseased, diseased with vehicle (PBS), polyethylene glycol polymers (PEG), pMSCs, PEG+pMSCs, NPCs, and PEG+NPCs. The IVDs of the animal tails were evaluated using magnetic resonance imaging (MRI). After 4 and 8 weeks post-injection, the animals were sacrificed, and the IVDs were extracted for histological and molecular analysis.

Results
MRI analysis showed a progressive decrease in NP signal intensity 2 weeks after disc puncture. Degenerated discs treated with cells and PEG exhibited higher NP signal intensity than untreated degenerated discs. The highest signal intensity was observed in animals treated with NPCs and PEG, with more noticeable results at eight weeks than at four weeks after transplantation. Tracking of PKH26-labeled cells confirmed the presence of transplanted cells within the injected discs. Histological analysis using hematoxylin and eosin (H&E) staining revealed structural improvements in both the NP and the annulus fibrosus (AF) in the discs treated with cells and PEG. Additionally, collagen type II antibody staining of the NP in IVDs treated with cells further supported these findings. Overall, these results indicate that combining the scaffold with NPCs effectively promotes NP regeneration and helps repair or reorganize collagen lamellae in the AF.

Conclusion
These findings demonstrate that pMSCs have the potential to differentiate into NPCs. When combined with a PEG scaffold, these NPCs not only support NP regeneration but also help reorganize collagen fibers within the AF. This innovative approach highlights the ability of cell-based therapies to address DDD. Overall, the results suggest a promising strategy for improving spinal health and recovery through advanced regenerative techniques.musculoskeletalmusculoskeletal

Poster 11

Abstract for Annual Musculoskeletal Health Symposium 2026

Title: Analyzing metabolic dysregulation in skeletal cells to manage chronic kidney disease bone loss

Authors and affiliation: Jie Ren Gerald Har[1], Akshdeep Singh[1], Ruchir Sriram[1], Maciek R. Antoniewicz[2], Lauren E. Surface[1]
[1]Department of Biologic and Material Sciences and Prosthodontics, University of Michigan School of Dentistry; [2]Department of Chemical Engineering, University of Michigan

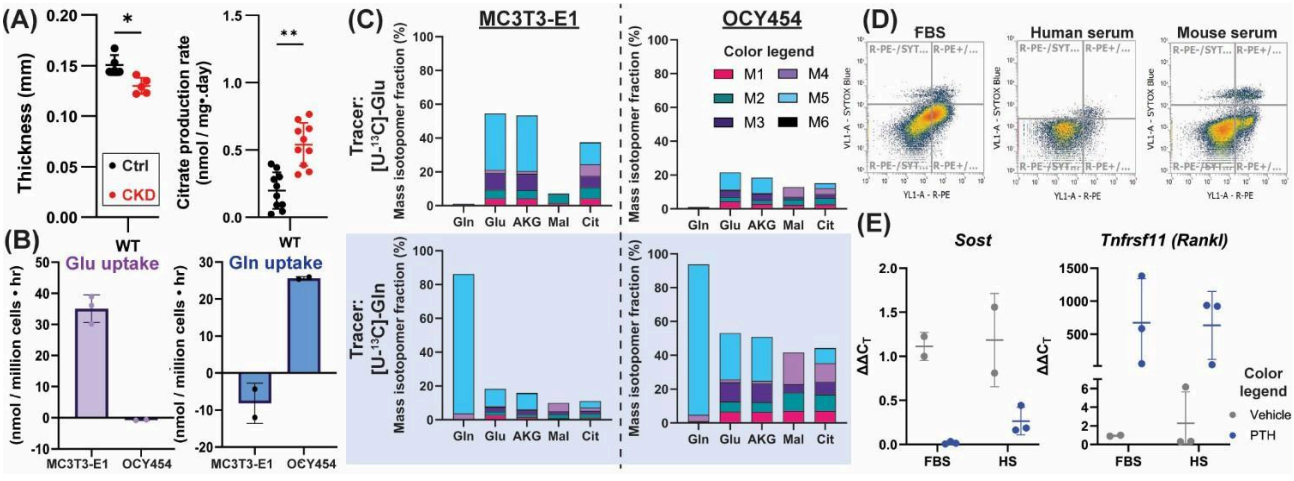
Name of presenter (Only one poster per presenter): Jie Ren Gerald Har
Is this abstract to be judged in the competition? **YES**/NO

Study goals: Clinical studies reveal that patients with chronic kidney disease (CKD) suffer from an elevated incidence of fractures, but the clinical targets to manage this bone loss remain inadequately understood. Our earlier work demonstrated that accelerated skeletal citrate production is coincident with adenine-induced CKD bone loss (Fig. A). To target this metabolic dysregulation, we sought to identify how distinct skeletal cell types are metabolically rewired in CKD, ultimately driving greater citrate production. This knowledge would form a basis for identifying and modulating metabolic activity within specific skeletal cell types to improve bone outcomes. To this end, this study characterizes how CKD derangements metabolically rewire distinct skeletal cell types *in vitro*.

Methods and Results: ^{13}C-metabolic flux analysis (^{13}C-MFA) was performed on MC3T3-E1 and OCY454 – established models of osteoblasts and osteocytes respectively. Both cell lines were cultured in media supplemented with additional inorganic phosphate (Pi) or parathyroid hormone (PTH), to simulate CKD-related hyperphosphatemia or hyperparathyroidism. OCY454 was also cultured under the uremic toxin, indoxyl sulfate (IS). ^{13}C-MFA showed that differentiated MC3T3-E1 and OCY454 demonstrate distinct metabolic demands to fuel the TCA cycle, with MC3T3-E1 primarily utilizing glutamate while OCY454 utilized glutamine without net consumption of glutamate (Fig. B-C). While addition of PTH (500ng/mL) into culture media increases glucose-to-citrate conversion in both cell types, high-resolution ^{13}C-MFA revealed that PTH and Pi distinctly influenced metabolism in both cell types (shown in poster). These results reveal skeletal cell type-specific metabolic rewiring due to CKD derangements, providing further basis for cell type-specific targeting of metabolic dysregulation.

To establish the feasibility of analyzing metabolic dysregulation due to CKD using serum from patients with CKD or mouse models of CKD, we cultured OCY454 cells in human serum (HS) and mouse serum (MS). Flow cytometry analysis of apoptosis and necrosis via Annexin / Sytox Blue staining confirms that cells remain viable under HS and MS (Fig. D). OCY454 continue to express osteocytic gene markers in human serum (HS). Additionally, osteocyte *Sost* and *Tnfrsf11* (*Rankl*) expression and response to PTH remained robust under both FBS and HS (Fig. E). These assays confirm that cells remain active under non-FBS sources of serum, complementing studies using animal models of CKD.

Discussion/conclusion: ^{13}C-MFA data on osteoblast and osteocyte metabolism will be utilized within our group's recently-funded endeavor to resolve skeletal metabolic fluxes disrupted by CKD or other diseases, to identify actionable metabolic targets in future therapies. In addition, use of serum obtained from human patients may form a new approach methodology to investigate systemic effects of CKD.



Poster 12

Title: Development of an ISS-Compatible Tissue-Engineered Neuromuscular Co-Culture Platform

Authors and affiliation: Hayleigh Kahn[1], Eileen Y. Su[1], Derek H. Hwang[1], Lisa M. Larkin[1,2]
[1]Department of Molecular and Integrative Physiology, [2]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI

Name of presenter: Hayleigh Kahn

Study Goals: Sarcopenia is the age-related loss of skeletal muscle mass and function. There is limited understanding of and a lack of intervention to address sarcopenia, despite societal costs. Astronauts have shown similar muscle atrophy after just 17 days in microgravity. Thus, microgravity may provide an accelerated environment to study the underlying mechanisms of sarcopenia. Microgravity and aging appear to disrupt the neuromuscular junction (NMJ) structure and reactive oxidative species (ROS) activity, altering muscle function. We plan to investigate these disruptions in microgravity aboard the International Space Station (ISS) using a nerve-muscle co-culture system, evaluating NMJ structure and function. Our goals in preparing a co-culture system: (1) fabricate viable co-cultures of skeletal muscle units (hSMUs), engineered neural conduits (hENCs), and motor neurons (MNs) and (2) develop a protocol adjusting for obstacles faced on the ISS.

Methods: Human skeletal muscle myoblasts (Lonza) and human bone marrow mesenchymal stromal cells (RoosterBio) were used to construct hSMUs and hENCs. Applied StemCell's human induced pluripotent stem cells were used to proliferate and network MNs within hENCs. Co-culture viability was determined by assessing force production. We developed one media suitable for all three tissue types and adjusted protocols for limitations that occur in microgravity, including limited media storage, storage temperature, and lack of mixing or 100% media exchange capabilities. We devised a protocol that would work on the ISS given these limitations.

Results: Co-cultures were optimal when hSMUs and hENCs were fabricated separately on 60 mm plates and fused 5 days after co-culturing, before transfer to the ISS tissue bioreactor. The media best suited for the three tissue types (3D media) included 91% DMEM, 7% HS, 1% ABAM, 1% Dex, 1uL/mL ITSX, 0.72 uL/mL Ascorbic Acid, 1% N2, with 2.8 mL per well, stored at 4 degrees. Optimal frequency with partial media exchanges was every 2 days.

Discussion/Conclusion: We are able to fabricate viable co-cultures made of hSMUs, hENCs, and MNs with functional NMJs, and developed a protocol adjusting for differences between our typical "terrestrial" protocol and adjusting for the limitations on the ISS. The co-cultures are prepared for launch into the microgravity environment on the ISS and ready to examine the underlying mechanisms of ROS on the development of sarcopenia.

Poster 13

Title: Anionic Tags Enable Stable Antibody Capture by Bone's Inorganic Matrix

Authors: Javier Cabello-Villegas, Colin Greineder

Affiliation: University of Michigan Emergency Medicine Research

Abstract:

Study Goals

The goal of this study is to target antibodies to bone and determine the effectiveness of different anionic peptide tags for this purpose. The broader objective is to optimize antibody binding for therapeutic applications, enabling site-specific delivery of antibody-based therapies to bone tissue.

Methods

IgG antibodies bearing anionic peptide tags were produced *in vitro*, and their ability to bind to bone *in vivo* and to hydroxyapatite -the inorganic matrix of bone- *in vitro* was tested. The antibody tags consisted of anionic poly-aspartic acid or poly-glutamic acid chains of varying lengths attached to the C-terminus of the heavy chains. To detect binding, antibodies were radiolabeled with I-125, and radioactivity bound to the target was measured. Untagged antibodies served as controls. For the *in vivo* analysis, radiolabeled antibodies were injected into mice, and pharmacokinetics in blood as well as biodistribution to bone and other organs were quantified over seven days.

Results

The results show that a ten-aspartic-acid tag on each IgG heavy chain (D10 divalent) is sufficient to stably target antibodies to hydroxyapatite and bone both *in vitro* and *in vivo*. *In vitro*, a D10 tag on only one of the two heavy chains (D10 monovalent) also exhibited stable binding, though at a lower level, suggesting a potential two-step process: the monovalent D10 may have lower initial affinity than the divalent D10, but once bound, it remains stably associated. *In vivo*, the D10 divalent antibody accumulated in bone but not in other tissues, and this accumulation persisted for seven days even after circulating antibody levels markedly declined. *In vitro*, the D10 divalent IgG exhibited stable binding for days, and it was released by high phosphate concentrations, consistent with calcium carboxylate chelation.

Discussion/Conclusion

The *in vitro* and *in vivo* data show that antibodies can be stably targeted to bone through anionic tags. This strategy may enable bone-specific therapeutic antibody delivery. The finding that capture by the bone matrix is stable yet reversible suggests that the antibodies remain structurally intact. We envision that the antigen affinity of such antibodies could be modulated to function either as high-affinity scavengers for bone-associated ligands or, for lower-affinity antibodies, as local concentrators that enhance ligand targeting.

Poster 14

Title: Long-Lived Mouse Models Show Increased Early BCAA Catabolism and Glycolytic Enzymes in Gastrocnemius Muscle

Authors: Jiexian Chen[1], Estella Gan[2], Justin Xhelilaj[3], Richard A. Miller[1,4], Gonzalo G. Garcia[1]

Affiliation: 1. Department of Pathology 2. Department of Molecular Cellular and Developmental Biology 3. College of Literature, Science and the Arts 4. University of Michigan Geriatrics Center

Name of presenter: Jiexian Chen

Abstract to include study goals, methods, results, and discussion/conclusion:

Lifespan-extending interventions improve systemic metabolism, but their effects on skeletal muscle metabolic pathways remain unclear. Because skeletal muscle is essential for mobility, energy use, and healthy aging, we asked whether mouse models associated with extended lifespan share common metabolic changes in gastrocnemius muscle. Previous work from our group suggested that these models show reduced glycolytic enzymes and increased amino acid catabolic enzymes in liver, but it is unknown whether skeletal muscle shows a similar or distinct pattern.

We reanalyzed published proteomic datasets from gastrocnemius muscle of acarbose-, canagliflozin-, and caloric-restriction-treated mice, as well as Snell dwarf and GHRKO mice, with males and females analyzed separately. Key findings were further evaluated by western blot and qRT-PCR, and two-way ANOVA was used to test treatment/genotype, sex, and interaction effects. Proteomics suggested a modest increase in enzymes involved in the early steps of branched-chain amino acid catabolism, including Bcat2, Bckdhb, and Dbt. Dbt, the lipoamide acyltransferase component of the branched-chain α-keto acid dehydrogenase complex, was further examined by western blot and qRT-PCR. For enzymes with both protein and mRNA validation, including Dbt, Pgk1, and Pfkfb1, protein and transcript results were generally consistent in most long-lived models.

Sex-specific patterns were also examined. Among the drug-treated groups, canagliflozin showed the clearest sex-specific pattern: canagliflozin-treated females had a weaker or absent increase in early BCAA markers, including Dbt, Bcat2, and Bckdhb, and a weaker response in some glycolytic markers, including Pfkfb1. In contrast, downstream BCAA catabolic enzymes and alanine-glutamine-asparagine catabolic enzymes did not show a common increase in gastrocnemius muscle. Gastrocnemius muscle also showed increased glycolytic enzymes, including Pgk1 (phosphoglycerate kinase 1) and Pfkfb1 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1), which were further evaluated by western blot and qRT-PCR.

Together, these data suggest that long-lived mouse models share a distinct gastrocnemius muscle metabolic signature: early BCAA catabolic enzymes tend to increase, glycolytic enzymes increase, and AGA catabolism is not broadly upregulated. These findings provide a hypothesis-generating model for skeletal muscle metabolic remodeling during lifespan extension.

Poster 15

Intra-Articular Oxygen Dynamics as an Early Biomarker of Post Traumatic Osteoarthritis After ACL Rupture

Jinha Kwon[1](Presenter), Xiaohua Gao[1], Michael Newton[1], Tristan Maerz[1,2], Annemarie Lang[1]
[1]Department of Orthopaedic Surgery - University of Michigan, Ann Arbor, MI
[2]Institute for Biomechanics, ETH Zürich, Zürich, Switzerland

Post traumatic osteoarthritis (PTOA) is a common and progressive degenerative condition that frequently develops after anterior cruciate ligament (ACL) rupture [1,2]. Because articular cartilage is avascular, its oxygen supply depends primarily on diffusion from synovial fluid. Oxygen tension is a critical regulator of chondrocyte metabolism, and disruption of intra-articular oxygen homeostasis after joint trauma may therefore contribute to disease initiation and progression. However, the early oxygen tension after ACL rupture, and their relationship to long term joint degeneration, remain unclear. Here, we hypothesized that ACL rupture induces early spatial and temporal alterations in intra-articular oxygen tension that are associated with vascular remodeling and may predict subsequent cartilage degeneration.

To test this hypothesis, PTOA was induced by noninvasive ACL rupture in 14-week-old female C57BL/6J mice under IACUC approved procedures [3,4]. Intra-articular oxygen tension was measured using the phosphorescent probe Oxyphor PtG4 following 5 µL intra-articular injection of 50 µM/mL Oxyphor. Oxygen measurements were performed at baseline and at days 3, 7, and 28 after injury (sample sizes: n = 4 for days 3 and 7, n = 2 for days 0 and 28). Knee joints were subsequently collected for histological and immunofluorescence analysis including endomucin staining for vascular structures and H&E staining for synovial inflammation. Functional outcomes were evaluated using the Blackbox 2.0 gait analysis system to quantify limb loading (n=8 for days 3, 7, and 14; and n=4 for day 28).

Oxyphor-based phosphorescence lifetime measurements revealed dynamic changes in intra-articular partial oxygen pressure (pO_2) following ACL rupture. Baseline oxygen tension in uninjured joints was 52.26 ± 10.93 mmHg. Oxygen levels increased at day 3 to 61.55 ± 11.83 mmHg, indicating an early hyperoxic phase, followed by a gradual decline to 54.93 ± 5.57 mmHg at day 7 and 39.52 ± 17.69 mmHg at day 28, suggesting progression toward hypoxia during joint degeneration. Endomucin staining demonstrated increased vascular structures within the joint cavity after injury, consistent with early vascular remodeling. Gait analysis revealed a significant reduction in limb pressure at day 3 followed by gradual recovery, indicating transient functional impairment. Together, these findings demonstrate a temporal association between oxygen imbalance, vascular remodeling, and functional changes after ACL rupture.

These preliminary findings suggest that intra-articular oxygen tension undergoes dynamic changes during early PTOA development after ACL rupture. Early hyperoxia likely indicates acute inflammatory and vascular responses, while the subsequent shift toward hypoxia suggests impaired oxygen delivery and ongoing tissue stress as remodeling progresses. The association between vascular remodeling and oxygen imbalance supports a mechanistic link between metabolic disruption and early joint pathology. These findings suggest that noninvasive oxygen monitoring may serve as a functional biomarker of early PTOA progression and may facilitate earlier diagnosis and intervention before irreversible joint degeneration develops.

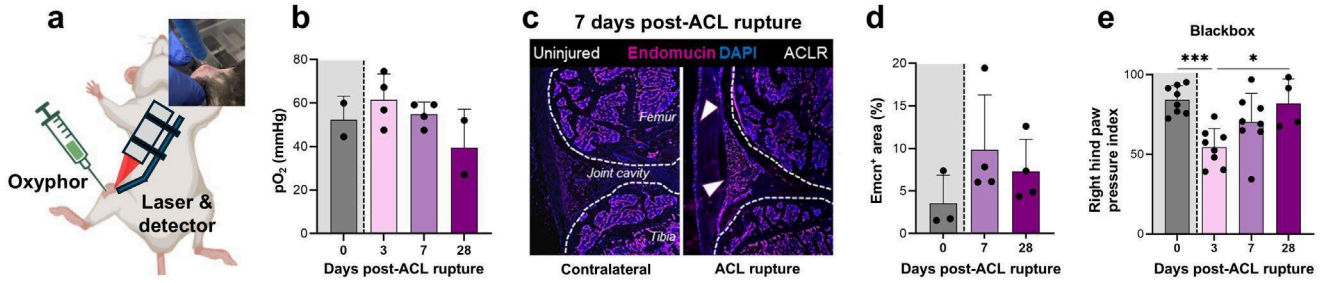


Fig. Intra-articular oxygen dynamics, vascular remodeling, and functional recovery after ACL rupture. *(a)* Oxyphor-based oxygen measurement setup. *(b)* pO_2 increases early then declines by day 28. *(c–d)* Endomucin staining and quantification show vascular expansion (days 7). *(e)* Blackbox analysis reveals early pressure loss and gradual recovery (mean ± SD, $p < 0.05$).

REFERENCES: [**1**] Herzog, M. M. *et al. Sports Health* (2018), [**2**] Lyman, S. *et al. JBJS* 91, 2321 (2009), [**3**] Bergman, R. F. *et al. Osteoarthritis Cartilage* 32, 1060–1073 (2024), [**4**] Newton, M. D. *et al.* 2025.03.11.642661 (2025)

Poster 16

Evaluating Patient-Reported Joint Pain Outcomes After Extracorporeal Shockwave Therapy

John Paul A. Atto[1]; Blake T. Marrogy[2]; Christian T. Stipho[1]; Fadi H. Delly, MD[2]
[1]University of Michigan, Ann Arbor, MI
[2]Wayne State University, Detroit, MI
Presenter: John Paul A. Atto[1]

Study Goals: Chronic joint pain is a prevalent source of disability in the United States, contributing substantially to decreased quality of life and increased health care utilization. Extracorporeal shockwave therapy (ESWT) has emerged as a noninvasive treatment modality for a variety of chronic musculoskeletal pain conditions. Proposed mechanisms of action include modulation of nociceptive pathways, induction of neovascularization, and promotion of tissue repair. Although prior studies have demonstrated the efficacy of ESWT in reducing pain and improving function in various musculoskeletal conditions, patient-reported pain outcomes following ESWT for joint pain remain variable due to heterogeneity in pain assessment and treatment protocols. The objective of this study is to evaluate changes in patient-reported pain outcome measures following ESWT for joint-specific pain utilizing the visual analog (VAS) pain scale and a validated disability index.

Methods: A retrospective cohort study was designed. All patients who underwent ESWT for joint- related pain involving the knee, shoulder, hip, elbow, hand, or foot at a single outpatient clinical setting between 2024 and 2025 were included. Pain severity was assessed using patient-reported pain scores collected at four standardized time points: prior to the first ESWT session (pre-ESWT), immediately following the first session (post-first ESWT), immediately following the midpoint treatment session (post-middle ESWT), and immediately following the final treatment session (post-final ESWT). Changes in pain severity across treatment time points were analyzed. Patient- reported pain disability index scores were compared before and after ESWT. Statistical significance was defined as $p \leq 0.05$.

Results: A total of 83 patients were included in this study. The distribution of presenting complaints was as follows: 38 patients with isolated knee pain (45%), 24 patients with isolated shoulder pain (29%), 10 patients with isolated foot pain (12%), 5 patients with isolated hand pain (6%), 3 patients with isolated hip pain (4%), and 3 patients with isolated elbow pain (4%). Mean patient-reported pain scores (± standard error) demonstrated a progressive decline across treatment time points: pre-ESWT (8.02 ± 0.28), post-first ESWT (5.23 ± 0.32), post-middle ESWT (4.28 ± 0.27), and post-final ESWT (4.10 ± 0.30). Repeated-measures analysis demonstrated that pain scores at the pre-ESWT time point were significantly higher compared with each subsequent time point ($p < 0.001$ for all comparisons). Furthermore, the pain disability index score (± standard error) significantly improved following treatment, decreasing from 12.36 ± 2.44 pre-treatment to
7.45 ± 1.89 ($p = 0.001$).

Discussion/Conclusion: ESWT was associated with significant reductions in pain severity and disability among patients treated for chronic joint pain. Pain scores demonstrated a rapid and sustained improvement across successive treatment sessions. These findings support the clinical utility of ESWT as a noninvasive treatment option for joint-related musculoskeletal pain in routine practice. Further prospective, controlled studies are warranted to evaluate long-term outcomes, joint-specific response patterns, and standardized pain assessment protocols.

Poster 17

Title: Metal Hypersensitivity in Spinal Instrumentation: Clinical Features and Outcomes

Authors and Affiliations: Joseph Abbo [1], Jacob Thomas [2], Christian Stipho [3], Ilyas S Aleem [1]

[1] Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, MI, USA [2] Oakland University William Beaumont School of Medicine, Rochester, MI, USA [3] Department of Plastic Surgery, University of Michigan, Ann Arbor, MI, USA

Presenter: Joseph Abbo

Introduction: Metal hypersensitivity is a rare but clinically significant complication following implantation of spinal instrumentation. The presentation of metal hypersensitivity can mimic infection or mechanical failure which makes it difficult to diagnose. Evidence to guide diagnosis and management is largely limited to short case series and case reports.
Purpose: To systematically evaluate the clinical presentation, diagnostic methods, and outcomes of metal hypersensitivity associated with spinal instrumentation
Methods: A systematic review was conducted of PubMed, Embase, and Scopus from inception through February 19th in accordance with PRISMA guidelines. Title and abstract screening, full text review, and data extraction were performed independently by two reviewers with conflicts resolved by a third reviewer. Eligible studies included adult patients with suspected or confirmed metal hypersensitivity following spinal instrumentation that reported patient level clinical outcomes.
Results: 13 studies met inclusion criteria comprising 17 patients (11 case reports, one 2 patient series, and one 4 patient series). The median patient age was 49 years old with a range of 19-69. Common presentations included persistent pain and dermatologic manifestations near the operative site. Metal hypersensitivity was confirmed by patch testing or lymphocyte transfusion testing in 11 patients (65%). Onset of symptoms ranged from immediate postoperatively to 15 years after implantation. 16 patients underwent removal or revision with clinical improvement in 13 of those cases (88%).
Conclusion: Metal hypersensitivity following spinal instrumentation is uncommon but may present in a delayed manner with symptoms that are very hard to distinguish from the more common postoperative complications. In reported cases where infection and mechanical causes were ruled out, hardware removal was frequently associated with clinically significant improvement. This supports hypersensitivity as a plausible contributing factor.

Poster 18

Proprioceptive control of orofacial functions by different neuronal populations in mice

Karin Harumi Uchima Koecklin[1]*, Sydney Markel[1], Peng Li[1]
[1]University of Michigan, Ann Arbor, MI, USA. *Presenter

Study goals: Musculoskeletal function depends on precisely coordinated muscle activity guided by proprioception, the body's ability to sense its own position and movement. While this sensory feedback is essential for stable posture and accurate movements, the neural mechanisms that transform mechanosensory input into appropriate motor output remain incompletely understood. This gap is especially evident in the orofacial system, where orofacial muscles must execute exceptionally precise, rapid, and continuously adaptable movements to support essential behaviors such as chewing, swallowing, breathing, and speech. A key hub for this control is the mesencephalic nucleus of the trigeminal nerve (Vmes), a unique population of primary sensory neurons whose cell bodies reside within the brain, which relays proprioceptive input from orofacial tissues including jaw muscle spindles and periodontal receptors. However, the molecular mechanisms underlying these pathways and the heterogeneity of proprioceptive neuron populations involved remain poorly defined. Our aim is to determine the role of different subsets of Vmes neurons in the control of the jaw muscles during orofacial function and their underlying molecular receptors.

Methods: Using mouse genetic tools, we first define the projection patterns of two Vmes populations labeled by Vglut1-Cre (vesicular glutamate transporter 1) and Pv-Cre (parvalbumin) in orofacial tissues. We then conditionally deleted Piezo2, which encodes a mechanosensitive ion channel protein essential for mechanosensation and proprioception, in each population, as well as in a muscle-specific manner, to determine its functional contribution.

Results: First, we mapped the innervation pattern of two Vmes populations labeled by Vglut1-Cre and Pv-Cre. We found that Vglut1 neurons robustly innervate muscle spindles in the masseter (jaw-closing) muscle, but not Pv-Cre neurons. To determine the functional consequences of these distinct innervation patterns, we examined muscle performance in two conditional knockout (cKO) models in which Piezo2 was deleted in either Vglut1-Cre or Pv-Cre neurons. Vglut1-Cre mutants displayed a dramatic reduction in biting force in a biting force assay, and decreased firing frequency and overall activity in masseter electromyography (EMG) recordings during chewing. In contrast, Pv-Cre mutants showed no detectable deficits in either biting force or EMG activity. We next assessed fine motor control of the jaw by measuring the duration mice could hold a small object between their incisors. Interestingly, both Vglut1-Cre and Pv-Cre mutants exhibited impaired performance in this task, suggesting that additional Vmes innervations likely contribute to fine oral motor control. To test whether the deficits in biting force and muscle activity arise specifically from Vmes neurons that innervate masseter muscle spindles, we generated a muscle-specific cKO model that deletes Piezo2 in Vmes neurons projecting selectively to the masseter. These mice exhibited reduced biting force and decreased masseter EMG activity during chewing, phenocopying the Vglut1-Cre mutants, but their fine motor control remained intact. **(Fig. 1A,B)**

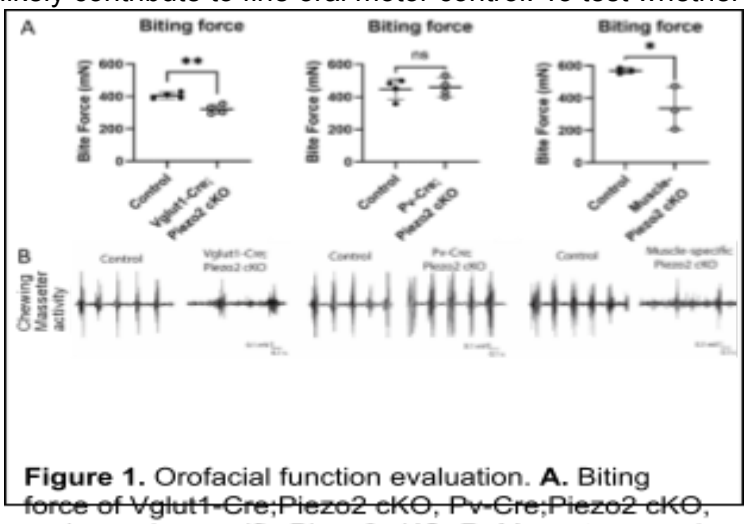


Figure 1. Orofacial function evaluation. **A.** Biting force of Vglut1-Cre;Piezo2 cKO, Pv-Cre;Piezo2 cKO, and muscle-specific Piezo2 cKO. **B.** Masseter muscle activity (EMG) during chewing, comparing all three cKO models.

Discussion/Conclusions: Together, these results identify distinct populations of Vmes neurons defined by different genetic markers, innervation patterns, and functional roles. Specifically, the loss of biting force and chewing-related muscle activity is mediated by spindle-innervating Vmes neurons, whereas fine oral motor control likely depends on additional Vmes subpopulations. Further investigation of other orofacial behaviors, particularly those involving proprioceptive inputs from non-muscle receptors, will help clarify the distinct contributions of Vmes neuron subpopulations.

Poster 19

TITLE

Uncovering the role of actin nucleation by the Arp2/3 complex during membrane injury

AUTHORS & AFFILIATIONS

Kristen D. Turner[1] and Daniel E. Michele[1,2]

[1]Department of Molecular & Integrative Physiology, University of Michigan, Ann Arbor, MI, USA
[2]Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, USA

NAME OF PRESENTER

Kristen D. Turner, PhD

ABSTRACT

Muscular dystrophies are genetic disorders leading to profound muscle weakness, loss of ambulation and often cardiomyopathy. Patients and mouse models of these disorders have increased sensitivity to membrane injury due to mutations in dystrophin, a large structural protein linking the actin cytoskeleton to the plasma membrane dystrophin-glycoprotein complex. We previously showed that membrane repair protein, dysferlin, fails to be recruited to laser-induced membrane wounds in skeletal muscle during inhibition of actin polymerization using cytochalasin D. However, mechanisms of actin assembly and organization during membrane injury are unknown. The Arp2/3 complex is the earliest identified regulator of branched actin polymerization. The purpose of this study was to determine the role of Arp2/3 in skeletal muscle during membrane wounding. Single fibers were excised from flexor digitorum brevis (FDB) muscles from the mouse hind paws. Fibers were maintained at 37°C in matrigel-coated plates and pre- loaded with fluorescent indicators of membrane resealing (Fluo-4 AM) and F-actin recruitment (SiR- Actin). Upstream inhibition of Arp2/3 was carried out using 25μM Wiskostatin treatment and compared to vehicle controls. Fibers were injured using a confocal microscope equipped with a high-powered laser at 2x2 ROIs. Real-time pre- and post-injury images were obtained and quantified. Fluo-4 area was increased in Wiskostatin-treated fibers after injury (P=0.003). These data were consistent with direct Arp2/3 inhibition using 100μM CK666 (P=0.028). Furthermore, CK666 treatment also decreased SiR- Actin at membrane wounds (P=0.035). Together, these data suggest pharmacological inhibition of the Arp2/3 complex impairs membrane resealing and F-actin recruitment at skeletal muscle membrane wounds.

Poster 20

Early diagnosis and treatment of knee osteoarthritis with a novel microRNA

Authors: Madhu Baghel PhD[1,2], Thomas G. Wilson BS[1,2], Trevor Banka MD[2], Jason Davis MD[3,4], Vasilios Moutzouros MD[2], Shabana Amanda Ali PhD[1,2,5,6]

Affiliations: 1. Bone and Joint Center, Henry Ford Health + Michigan State University Health Sciences, Detroit, MI, USA; 2. Department of Orthopedic Surgery, Henry Ford Health, Detroit, MI, USA; 3. Michigan Orthopaedic Surgeons, West Bloomfield, MI, USA; 4. Department of Orthopaedic Surgery, Corewell Health William Beaumont University Hospital, Royal Oak, MI, USA; 5. Department of Physiology, Michigan State University, East Lansing, MI, USA; 6. Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA

Study goals: Osteoarthritis (OA) is a debilitating joint disease with no disease-modifying therapies, highlighting the critical need for effective diagnostic and therapeutic strategies. MicroRNAs are epigenetic factors that can serve as minimally-invasive biomarkers, mechanistic drivers, and therapeutic targets in disease. Novel miRNAs, which are predicted from sequencing data, are particularly promising due to their unique association with specific biological contexts. Here we characterize a novel microRNA, referred to as novel_miRNA_2, in knee OA.

Methods: To assess its role as a biomarker, we measured novel_miRNA_2 levels in plasma of individuals with early knee OA, late knee OA, and non-OA controls by real-time qPCR. We then performed area under the receiver operating characteristic curve analysis. To characterize novel_miRNA_2, we assessed its biogenesis by measuring transcripts of its predicted host gene *ZNF773*, primary (pri-) novel_miRNA_2, and mature novel_miRNA_2 across multiple knee OA tissues from patients. To validate predicted targets, we treated tissue explants with novel_miRNA_2 mimic and measured gene expression. We examined therapeutic effects in a surgical mouse model of knee OA, with
systemic delivery of novel_miRNA_2 mimic starting at early and late timepoints (**Fig.1A**). Finally, we investigated potential upstream regulators of novel_miRNA_2 in knee OA tissue.

Results: Circulating novel_miRNA_2 levels accurately distinguished early OA from both non-OA and late OA. In knee OA tissues, *ZNF773*, pri-novel_miRNA_2, and mature-novel_miRNA_2 were consistently elevated in early versus late OA. Novel_miRNA_2 repressed genes such as *RUNX2*, which regulate bone formation. In mice, early novel_miRNA_2 mimic treatment significantly reduced OA severity, including osteophyte (bone spur) formation (**Fig. 1B**). Upstream of novel_miRNA_2, the Hedgehog (Hh) signaling pathway appears to suppress novel_miRNA_2 biogenesis in late OA while increasing *RUNX2* to exacerbate the severity of OA.

Conclusions: Using human and mouse models, we present the first comprehensive characterization of a novel microRNA in OA. We show novel_miRNA_2 is a promising diagnostic biomarker and therapeutic target for early knee OA, with a mechanistic role in regulating bone formation to impact disease severity.

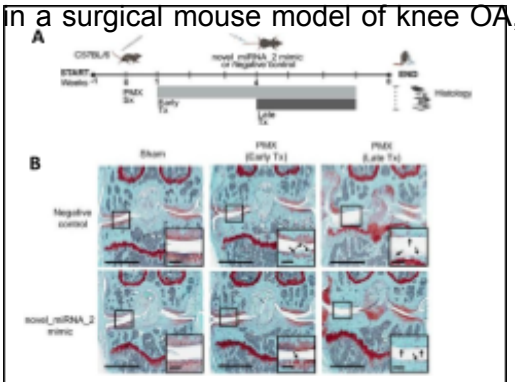


Figure 1. A novel microRNA candidate for early knee osteoarthritis diagnosis and treatment. (A) Experimental design. PMX = partial medial meniscectomy, treatments, and endpoints. (B) Representative coronal sections of operated mouse knee joint stained with Safranin-
O. Scale bars = 1 mm. Insets show magnified regions (scale bars = 100 μm). Black arrow indicates cartilage damage. C) OARSI scoring of PMX and sham mice following treatments (n=5). Bars = mean maximal quadrant score ±95% CI. *p<0.05. D) Osteophyte area in PMX and sham mice following treatments (n=5). Datapoints represents mean of the medial tibial and medial femoral osteophyte area for each mouse. Bars = mean osteophyte area ± 95% ±95% CI. *p<0.05.

Poster 21

Title: Linking Chondrocyte Activity to Cartilage Deformation by Pseudo-Cell Tracking

Authors and affiliation:
Meng-Jia Lian[1], Mou-Chi Cheng[2], Celia Flory[1], Maggie Wang[3], Dana Akkal[3], Jonathan Wong[3], Lydia Glowney[1], Haichun Pan[1], KristinaZheng[1], Yuji Mishina[1], Dawen Cai[2], Tomer Stern[1]
[1]University of Michigan School of Dentistry,
[2]University of Michigan Medical School,
[3]University of Michigan College of Literature, Science, and the Arts

Name of presenter: Meng-Jia Lian

ABSTRACT

Study Goal: The epiphyseal cartilage prefigures the developing bone and drives its elongation, yet the quantitative relationship between chondrocyte activity and tissue morphogenesis remains unresolved. While cell division, hypertrophy, and matrix deposition are recognized contributors, the growth plate is a spatially heterogeneous structure where distinct zones deform through unique combinations of cellular processes. Because live-imaging deep 3D cartilage is technically challenging, these dynamics have not been directly reconstructed at a tissue scale. This gap limits our fundamental understanding of bone elongation and 3D shape formation, constraining mechanistic insight into skeletal dysplasias. To bridge this, we developed a computational framework for pseudo-cell tracking that reconstructs growth plate dynamics from sequential fixed 3D images at cellular resolution. This enables tissue-wide quantification of cell activities, extraction of deformation tensors, and direct association of cellular processes with local morphogenesis.

Methods: We utilized optical clearing and light-sheet fluorescence microscopy to image intact embryonic mouse growth plates expressing a membrane-localized reporter at high resolution. Deep-learning segmentation was used to map the 3D shape and position of up to 140,000 chondrocytes per tissue. To reconstruct cell movements across developmental time points, we adapted a statistical geometry framework for matching cells in sequential fixed samples while accounting for cell division and loss. This strategy enabled tissue-wide quantification of chondrocyte behaviors—including changes in cell volume, cell shape, and extracellular matrix deposition—alongside spatially resolved measurement of the direction and magnitude of local tissue deformation.

Results: Focusing on axial elongation, our tissue-wide analysis identified the transition from the prehypertrophic to the hypertrophic zone as the principal region of elongation, exhibiting substantially higher local longitudinal strain than elsewhere. In this region, increases in cell volume and changes in cell aspect ratio emerged as the strongest candidate cellular contributors to local tissue deformation. Other regions displayed distinct deformation profiles and differing combinations of cell behaviors, highlighting the spatial complexity of the growth plate.

Conclusions: Pseudo-cell tracking enables the quantification of cellular activities and tissue deformations across scales using sequential fixed samples. This opens new opportunities for studying cartilage morphogenesis in both normal and pathological bone development. Furthermore, because it relies on minimal tissue-specific assumptions, pseudo-cell tracking offers a versatile strategy for reconstructing developmental dynamics in various other organ systems.

Poster 22

Title: Preliminary evaluation of full volume strain measurement in patellar cartilage following osteochondral allograft transplantation using magnetic resonance imaging

Authors and affiliation: Michael A. Hernández Lamberty[1], Carla Nathaly Villacís Núñez[1], Ulrich Sheven[1], John A. Grant[4], Ellen M. Arruda[1,2,3], Rhima M. Coleman[1,2,4]

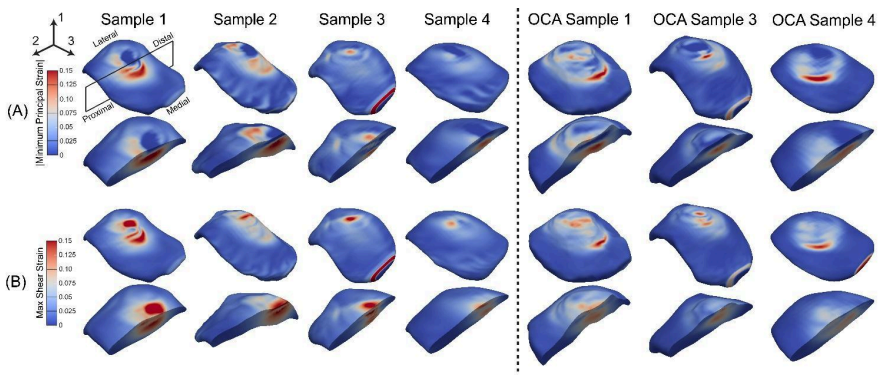
[1]Department of Mechanical Engineering, [2]Department of Biomedical Engineering, [3]Program in Macromolecular Science and Engineering ,[4]Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, Michigan

Articular cartilage defects of the patellofemoral joint are clinically challenging and mechanically demanding. Osteochondral allograft (OCA) transplantation is the standard treatment for large cartilage injuries; however, little is known about intra-tissue mechanics after transplantation. Computational models suggest that cartilage thickness mismatch concentrates stresses at donor–recipient interfaces in OCA-treated patella, but direct experimental evidence is scarce. The goal of this work was to provide a full-volume assessment of patellar cartilage mechanics before and after OCA transplantation and compare results to finite element (FE) models.

A displacement-encoded MRI sequence was used to quantify full-volume displacement and strain fields in human patellar AC before and after OCA transplantation under controlled indentation. Intact cadaveric patellae (n=4) were prepared, with three serving as recipients and one as donor. Samples were cyclically compressed in a custom-built rig using nominal displacements of 1 and 2 mm. The complex phase data were unwrapped and converted to displacements; the Green–Lagrange strain tensor was computed using a finite element framework in FEniCS. Minimum principal strain (E_{min}) and maximum shear strain ($E_{maxshear}$) were analyzed. FE models were developed for all cartilage samples. Cartilage was modeled using a linear elastic functionally graded material model.

Global displacement fields were similar between intact and OCA samples, with spherical indentation exhibiting through-thickness compression and lateral displacement in the longitudinal and transverse directions. E_{min} localized beneath the indenter, while $E_{maxshear}$ concentrated near the articular surface. OCA-transplanted samples exhibited localized changes in strain distribution near portions of the graft rim, though these features varied across samples (Fig.1). Top-view percentile maps highlighted redistributed high-strain regions in some OCA samples. FE models demonstrated similar displacement and strain fields through the thickness of the cartilage to those obtained from experimental methods; however, rim effects were absent in the FE models.

This study provides the first experimental full-volume displacement and strain distributions in patellar cartilage after OCA transplantation and demonstrates their utility for validating and improving FE models. Comparison of measured and predicted strain fields reveals where current models succeed and where interface mechanics remain under-represented, guiding future work toward developing material models of cartilage and simulations of OCA mechanics.



Poster 23

PPARgamma Orchestrates Osteocyte Mitochondrial Metabolism and Oxidative Stress via HIF1a to Preserve Skeletal Integrity During Aging

Mohd Parvez Khan, Beata Lecka-Czernik
University of Toledo, Department of Orthopaedic Surgery, Toledo, Ohio

Is this abstract to be judged in competition? Yes (Mohd Parvez Khan, junior faculty)

Peroxisome Proliferator Activated Receptor gamma (PPARγ) is a nuclear receptor well characterized for its roles in adipogenesis, insulin sensitization, and systemic metabolism. Our recent work revealed unexpectedly high levels of PPARγ in osteocytes (OTs), the most abundant and long-lived cells comprising ~95% of all bone cells. Due to high volume and more than 30 years of lifespan OTs are uniquely positioned to coordinate skeletal mass and systemic bioenergetics, and hence even subtle metabolic alterations in these cells can profoundly influence bone homeostasis. The role of OTs' PPARy in regulation of systemic and bone metabolism is just emerging (Baroi 2021, Kim 2023, Baroi 2024).
To comprehensively investigate the role of OTs' PPARy in regulation of bone homeostasis during aging, we employed OT specific PPARγ loss-of-function mouse models. Conditional OT specific knockout (Dmp1Cre;Pparγ$^{fl/fl}$; γOT^{KO}) and control ((Dmp1Cre; γOT^{Ctrl}) mice were analyzed longitudinally to determine age-dependent systemic and skeletal outcomes. Metabolic profiling with Comprehensive Lab Animal Monitoring System (CLAMS) of adult (5 mo old) γOT^{KO} mice exhibited increased systemic energy expenditure characterized by elevated respiration (VO_2 and VCO_2), thermogenesis, locomotor activity, and food intake, independent of circulating sclerostin. Paradoxically, aged (24 mo old) γOT^{KO} mice displayed reduced respiration and accelerated bone loss, which was not associated with increased OTs apoptosis measured with TUNEL assay, suggesting an age-dependent metabolic shift towards enhanced cellular senescence as a prime effector of the observed phenotype. Transcriptomic profiling of OTs from adult γOT^{KO} mice demonstrated significant enrichment of mitochondrial OxPhos and electron transport chain (ETC) pathways, with elevated expression of genes coding for ETC subunits COX5A, COX5B and COX6a1, oxidative stress markers (e.g., *Cyba*, *Pura*, *Cct6a*), senescence regulator *Cdkn1a/p21*, and calcium channel genes implicated in ROS accumulation. Consistent with the in vivo findings, CRISPR/Cas9 edited osteocytic cells (MLO-Y4) in vitro data corroborated increased ATP production, elevated ROS accumulation, and induction of cellular senescence with upregulated p21 level, accompanied by reduced *Hif1a* expression and decreased expression of HIF1a target genes including *Vegf* and *Bnip3*. Proteomic analyses further revealed that PPARγ physically sequesters crucial mitochondrial proteins such as NADH dehydrogenase 1a subcomplex subunit 9 (NDUFA9), mitochondrial import membrane translocase subunit (TIM44) and mitochondrial aminotransferase (GOT2), suggesting its direct regulation of ETC activity and OxPhos. Moreover, PPARγ-deficient OTs secreted increased levels of senescence-associated secretory phenotype (SASP) factors including IL-6, TNF-α, and matrix metalloproteinases.
Furthermore, using mouse construct with tamoxifen-induced specific deletion of PPARγ in OTs (Dmp1Cre-ERT2;Pparγ$^{fl/fl}$; herein γOT^{TKO}), we evaluated the effect of an acute loss of PPARγ on OTs phenotype in 12-month-old γOT^{TKO} mice. The results support our earlier demonstration using γOT^{KO} mice indicating increased oxidative stress, decreased defenses against it, and decreased hypoxia signaling. OTs freshly isolated from γOT^{TKO} mice exhibited significantly reduced expression of *Hif1a*, *Vegf*, Heme Oxygenase 1 (*Hmox1*), Kelch-Like ECH-Associated Protein 1 (*Keap1*), and Parkinsonism Associated Deglycase (*Park7*) genes compared to tamoxifen treated age and sex matched control mice (γOT^{TCtrl}). HMOX1 is known sentinel against oxidative stress. KEAP1 sustains redox balance with Nuclear Factor Erythroid 2–Related Factor 2 (NRF2) whereas PARK7 is a redox-sensitive protective protein that helps cells survive oxidative stress and maintain mitochondrial health. These factors collectively regulate hypoxia adaptation, mitochondrial homeostasis, and antioxidant defense pathways that regulate ROS accumulation and thus oxidative stress. Their coordinated reduction in PPARγ-deficient OTs suggests impaired cellular potential to counteract mitochondrial ROS and maintain redox balance. Reduced expression levels of these genes in OTs isolated from γOT^{TKO} mice supports our notion that osteocytic PPARγ maintains hypoxia signaling, redox homeostasis and protects against oxidative stress driven senescence. These findings open a possibility for development of pharmacologic means to modulate PPARγ activity in OTs to preserve skeletal health during aging.

Poster 24

Title: Spatial organization of osteoclast and osteoblast populations in craniofacial and long bones

Authors and affiliation: Mylene Monteiro Pighini[1], Elaheh Vahab[1], Uday Parom[1], Aria Myers[1], Kiera McConnell[1], Yuji Mishina[1]

[1] Department of Biologic and Materials Sciences, The University of Michigan, Ann Arbor, MI 48109, United States

Name of presenter (Only one poster per presenter): Mylene Pighini

Bone remodeling is a regulated process that depends on the coordinated activities of osteoblast-driven bone formation and osteoclast-mediated bone resorption. Although osteoblasts are known to regulate osteoclast differentiation through factors such as RANKL and inflammatory cytokines, increasing evidence indicates that osteoclasts also influence osteoblast behavior through direct interaction mechanisms. Importantly, bone remodeling dynamics vary across skeletal sites, with craniofacial bones such as the alveolar bone and mandibular condyle exhibiting higher turnover characteristics compared to long bones like the tibia. However, quantitative comparisons of osteoblast and osteoclast populations across these sites under physiological conditions remain limited. To address this gap, we quantified osteoblast and osteoclast lineage cells in the alveolar bone, mandibular condyle and tibia using Col1a1-GFP; LysMCre; Rosa26-tdTomato reporter mice, in which osteoblast-lineage cells express GFP (green) and osteoclast-lineage cells are genetically labeled with Tomato expression (red). Analyses were performed at defined developmental and postnatal time points selected to capture active bone formation and remodeling: alveolar bone at postnatal day 10 to 12 (P10-12) (first molar eruption), P20 (second molar eruption), and 2 months (third molar and mature alveolus); tibia at P23 and 2 months; and mandibular condyle at P20 and 1.5 months, corresponding to periods of active endochondral bone formation and postnatal maturation. Confocal imaging will be used to define site-specific distributions of osteoblast and osteoclast populations across developmental stages and skeletal locations. These analyses are expected to establish normative reference values across age, sex, and skeletal site, providing a foundation for future studies of bone degeneration and growth adaptation examining osteoclast–osteoblast signaling during craniofacial growth and bone remodeling.

Poster 25

Histopathology-guided spatial transcriptomics reveals context-dependent divergence of type IIx myofibers in mTORC1-driven myopathy

Jer-En Hsu[1], Qingyang Zhao[1], Weiqiu Cheng[2], Hyun-Min Kang[2*], Susan V. Brooks[1*], Myungjin Kim[1*] & Jun Hee Lee[1*]

[1]Department of Molecular & Integrative Physiology, University of Michigan, Ann Arbor, MI, USA
[2]Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA

Name of presenter: Qingyang Zhao

Skeletal muscle myopathies are often defined by classic histopathological features, yet the molecular programs underlying these abnormalities remain poorly understood because conventional approaches cannot resolve transcriptional states at the level of individual myofibers. To address this limitation, we combined histopathology with high-resolution Seq-Scope spatial transcriptomics in a rodent model of constitutive mTORC1 hyperactivation. We profiled cross-sections from soleus (SOL) and extensor digitorum longus (EDL), two muscles with distinct fiber-type composition, and assigned whole-transcriptome profiles to individual myofibers through histology-guided segmentation.

Among all myofiber populations, type IIx fibers (MF2X) emerged as the most pathology-prone shared fiber type and displayed striking context-dependent divergence between the two muscles. In SOL, MF2X fibers predominantly underwent pathological enlargement, accompanied by gene programs linked to sustained growth signaling, cytoskeletal remodeling, and impaired proteostasis with defective autophagy. In contrast, in EDL, MF2X fibers developed a basophilic phenotype marked by elevated RNA density and activation of lipid handling, oxidative respiration, and ribonucleotide synthesis pathways. These contrasting outcomes were not observed in type I and IIa fibers, which showed relative resistance to pathological remodeling.

These findings demonstrate that sustained mTORC1 signaling does not impose a uniform pathological program even within a single shared fiber type. Instead, MF2X fibers adopt distinct molecular and histological trajectories depending on muscle context. More broadly, this work highlights the utility of histopathology-guided spatial transcriptomics for linking morphology to molecular state at single-fiber resolution and identifies MF2X divergence as a key feature of mTORC1-driven myopathy.

Poster 26

Presenter: Rana Dabaja, Postdoctoral Research Fellow (Decker Lab)

Authors & Affiliates: Rana Dabaja*, Kelsey Martin, Victoria Maglaras, Pablo Galindo-Fernandez, Ann M. Decker, Joseph T. Decker

Title: Mertk Inhibition Protects Alveolar Bone in Peri-Implantitis

Abstract

Introduction: Peri-implantitis, a highly prevalent inflammatory condition affecting the connective tissue surrounding dental implants, leads to progressive bone loss and remains a major clinical challenge, especially in patients with systemic inflammatory diseases. Oftentimes, management involves invasive surgical procedures, with retreatment increasing the risk of failure. Recent studies have identified the TAM family of receptor tyrosine kinases (Tyro3, Axl, and Mertk) as regulators of bone homeostasis, affecting osteoblastic bone formation and osteoclastic bone resorption. Specifically, Mertk signaling mediates inflammatory responses in systemic inflammatory conditions and negatively regulates bone mass by inhibiting osteoblastic function. The deletion of Mertk in models of periodontitis has been associated with enhanced bone formation, with studies finding that the osteoblastic function is no longer inhibited. The **goal of this study** was to determine if Mertk inhibition protected against bone loss during peri-implantitis.

Methods: A dental implant murine model was used for this research. Dental implants were placed in the left primary maxillary molar of 6-wk-old C57BL/6 (wild-type) and Mertk$^{-/-}$ mice, followed by a 4-week healing period for osseointegration. Following healing, peri-implantitis was induced by placing a 6-0 silk ligature around the implant and leaving it in place for seven days. The maxillae were then collected for evaluation of bone regeneration using micro-computed tomography (volumetric and linear analyses), flow cytometry analysis, and histological analysis. Volumetric bone loss was defined as BV/TV and calculated by defining a cylindrical region beginning 10 slices below the implant head, extending 50 μm radially from the implant, and extending 0.44 mm axially into the alveolar bone to assess local bone changes. Linear bone loss was measured as a 2D distance from the base of the implant head to the integrated alveolar bone at four sites (mesial, distal, buccal, and lingual) and then averaged.

Results: The volumetric analysis, BV/TV, showed that Mertk$^{-/-}$ mice at day 7 ligated had significantly less bone loss than WT day 7 ligated mice (*p<0.05). There is a significant reduction in bone volume in Mertk$^{-/-}$ ligated mice when compared to their healthy controls (*p<0.05), whereas WT day 7 ligated mice showed a highly significant reduction in bone volume compared to WT controls (****p<0.0001). Measurements showed significantly less bone loss in Mertk$^{-/-}$ mice compared to that of WT mice at day 7 (**p<0.01). There was no significant difference in bone loss between healthy Mertk-/- and day 7, whereas WT ligated mice had a highly significant amount of bone loss compared to healthy WT controls (***p<0.001). Flow cytometry analysis is currently underway to characterize immune cell populations, and maxillary samples have been submitted for histological processing.

Discussion/Conclusion: Peri-implant bone loss was evaluated using both linear and volumetric microCT analyses to capture changes in vertical bone height and three-dimensional bone volume. Linear measurements quantify vertical bone loss along the implant surface, whereas volumetric analysis evaluates three-dimensional changes in bone volume within a defined region of interest. MicroCT analysis showed that Mertk deletion protects against bone loss in ligature-induced peri-implantitis, although it does not identify the cellular mechanisms that drive this effect. Ongoing flow cytometry will characterize immune cell populations involved in the inflammatory response, while histological analysis will evaluate bone formation within the peri-implant region. These findings suggest that targeting Mertk signaling may be a promising therapeutic strategy for preventing inflammation-driven bone loss in peri- implantitis.

Poster 27

Abstract for Annual Musculoskeletal Health Symposium 2026

Title: Skeletal implications of protecting renal function via induced ketosis in the *db/db* murine model of early diabetic kidney disease

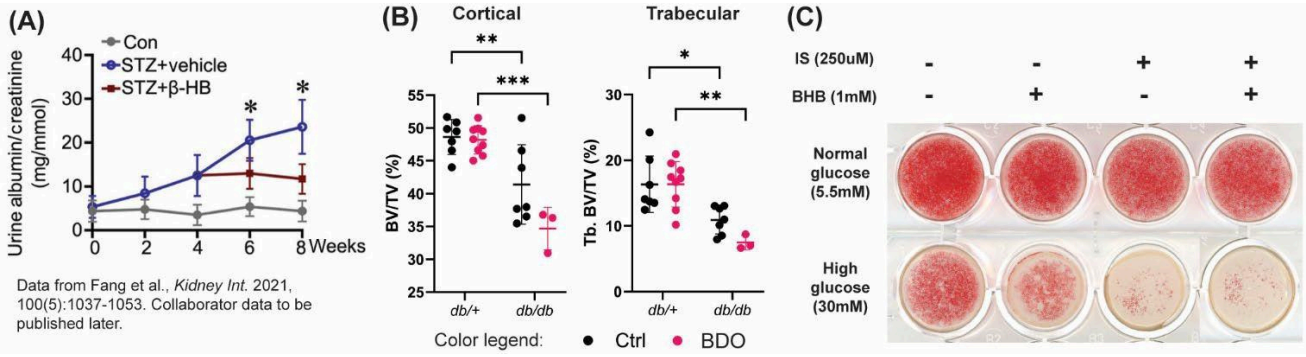
Authors and affiliation: Ruchir Sriram[1,#], Akshdeep Singh[1,#], Jie Ren Gerald Har[1,#], Saroj Chakraborty[2], Dylan Kuennen[1], Subramaniam Pennathur[2], Lauren Surface[1]
[1]Department of Biologic and Material Sciences and Prosthodontics, University of Michigan School of Dentistry; [2]Department of Internal Medicine, Division of Nephrology, University of Michigan Medical School; [#]Equal contribution

Name of presenter (Only one poster per presenter): Co-presenters: Ruchir Sriram, Akshdeep Singh
Is this abstract to be judged in the competition? **YES**/NO

Study goals: This study aims to determine the skeletal effects of protecting renal function via induced ketosis in the context of diabetic nephropathy (DN). Diabetes and renal failure are independent and interacting factors fueling bone loss and managing these chronic conditions is part of preserving skeletal and overall health. Recent studies show that induction of ketosis either via fasting, caloric restriction, or dietary supplementation of ketone bodies or precursors alleviates symptoms of both diabetes and kidney disease. For example, direct delivery of β-hydroxybutyrate (BHB) lowers fasting blood glucose in human subjects, and protects kidney function in various animal models of kidney diseases. Since ketosis protects against DN symptoms, it is possible that ketosis may also alleviate bone loss in this disease context. However, current knowledge on the skeletal impact of ketosis remains varied. Some clinical and animal model studies have reported a potential decline in bone properties in the context of ketosis. As such, to investigate whether ketosis benefits or adversely impacts the skeleton in DN, the skeletal impact of supplementing 1,3-butanediol (BDO), a ketone precursor, in the *db/db* mouse model of early diabetic kidney disease (DKD) is analyzed.

Methods and Results: The *db/db* mouse model is employed as symptoms of early DKD develop in these mice at 8 weeks of age. Ketosis is induced by supplementing drinking water with 5% (w/v) BDO when mice are at 8 weeks of age. Mice were then sacrificed at ~25 weeks of age. Urinary albumin-creatinine ratio analyzed over the course of BDO induction confirmed that ketosis protects kidney function in early DKD mice, as reported before (Fig. A). μCT of tibiae revealed a loss of cortical and trabecular bone in the *db/db* mice, and BDO treatment led to slightly lowered cortical and trabecular bone volume fraction, though not statistically significant (Fig. B). *In vitro* assays with differentiated MC3T3-E1 osteoblasts (Fig. C) confirm that hyperglycemia reduces osteoblast mineralization, which is further diminished by application of 250uM indoxyl sulfate (IS) to simulate systemic derangements in DKD. Mineralization of osteoblasts was not rescued by addition of 1mM BHB to the culture media.

Discussion/conclusion: Induction of ketosis via oral BDO reduces DN progression in the *db/db* mouse model, but impact on bone microarchitecture was not significant. Results thus suggest that ketosis protects kidney function without severe detrimental effects on the skeleton in this context of early DKD. Further analysis is ongoing to understand the lack of skeletal response to BDO treatment e.g. lack of senotherapeutic effects by BDO on the skeleton. Future investigations would involve establishing the efficacy and safety of ketogenic induction in other models of kidney disease, and to investigate how bone loss in DN may be managed through the induction of ketosis in combination with other therapies (e.g. low carb diet with supplements to protect the bone, or ketosis with anti-resorptives).



Poster 28

Title: **CD47 Knockout Induces Hemolytic Anemia and Disrupts Fracture Healing**

Authors and Affiliation: Salem Wang[1], Christina Capobianco[1], Prakaimuk Saraithong[1], Annemarie Lang[1], Kurt Hankenson[1]

[1]University of Michigan, Ann Arbor, MI

Name of Presenter: Salem Wang

Study Goal: CD47 is a ubiquitously expressed cell surface receptor known to act as 'don't eat me' signal by binding to SIRPα, inhibiting macrophage-mediated phagocytosis of healthy cells. A deletion of CD47 is not lethal because immune clearance of cells lacking CD47 also requires expression of an 'eat me' signal, such as foreign antigens or mutagens not present in most healthy cells. However, for mature red blood cells (RBCs), the lack of nuclei may be perceived as abnormal and induce clearance in the absence of CD47. Interestingly, global knockout of CD47 has been shown to hinder long bone fracture healing with delayed fracture callus formation and decreased chondrogenesis. We hypothesize that CD47 knockout induces RBC clearance, impairing nutrient and oxygen delivery and thereby disrupts long bone fracture healing.

Methods: To investigate this hypothesis, femoral fractures were performed on WT and CD47-null mice, and mice were harvested at 3 and 7 days post fracture. Body and spleen weights were recorded at the time of harvest for mice 3 days post fracture, and complete blood counts and reticulocyte (immature RBC) analyses were conducted. Fractured femurs were fixed in 10% neutral buffered formalin, paraffin processed and sectioned at 5um. Tissues were stained with Prussian Blue to assess deposited iron in the form of hemosiderin in the callus at 7 days post fracture. Fractured tibia were also sectioned and analyzed for Prussian Blue staining at 4 days post fracture. Single cell RNAseq was performed on tibial fracture calluses at 7 days post fracture, and stromal cells were isolated for GSEA hallmark analysis from WT and CD47-null mice at 7 days post tibial fracture.

Results: CD47-null mice were found to have enlarged spleens compared to WT and displayed a phenotype consistent with hemolytic anemia of decreased mature RBCs, decreased hemoglobin, and decreased hematocrit. We additionally observed increased reticulocytes in CD47-null mice. This supports that CD47-null mice have increased clearance of mature RBCs with increased production of progenitors. CD47-null histology stains showed an increase in iron deposits compared to WT at 4 and 7 days post- fracture. Via GSEA analysis, CD47-null stromal cells displayed increased stress response signals at 7 days post fracture.

Discussion/Conclusion: Our findings demonstrate that global CD47 deletion leads to hemolytic anemia and stromal stress, which may contribute to delayed fracture healing. This study poses implications for the use of CD47 antibodies in clinical trials to clear cancer cells, which overexpress CD47 for immune evasion. Developing novel antibodies that have a higher specificity for CD47 found on cancer cells relative to healthy cells could serve to improve clinical outcomes.

Poster 29

KDM5C-Dependent Control of Osteoclast Pathways: Linking RANKL Signaling, Inflammation, and Sex Differences in Bone homeostasis

Saumya Bhagat[1], Ye Liu[1], Di Lu[1], Matt Weiland[2], Connie Krawczyk[2], Tao Yang[1]

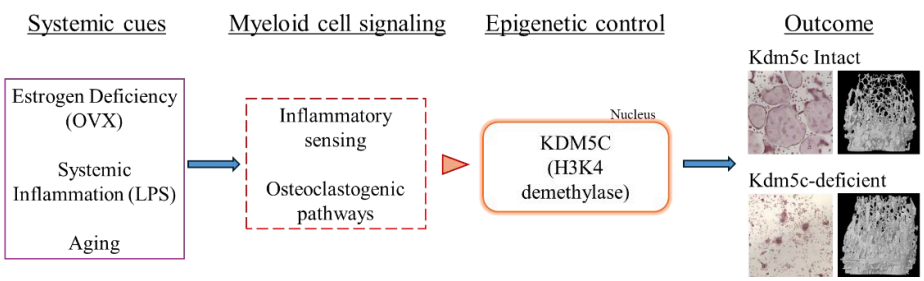
[1]Dept of Cell Biology and [2]Dept of Metabolism & Nutritional Programming, VAI-Grand Rapids, MI
Presenter: Saumya Bhagat

Study Goals: Osteoclasts are central regulators of bone remodeling and respond to both endocrine and inflammatory cues; dysregulation of their activity contributes to osteoporosis and inflammatory bone loss. Bone homeostasis is maintained through tightly regulated osteoclast–osteoblast crosstalk, which coordinates bone resorption and formation. Increasing evidence indicates that epigenetic mechanisms influence osteoclast differentiation and may underlie sex-specific differences in skeletal disease susceptibility. Here, we investigated KDM5C, an X-linked H3K4 demethylase, in regulating osteoclastogenesis under inflammatory conditions. We hypothesized that KDM5C epigenetically regulates inflammatory and RANKL-mediated signaling, thereby modulating key transcriptional checkpoints during osteoclast differentiation.

Methods: Myeloid-specific *Kdm5c* KO mice (LysM-Cre) were used to investigate the role of KDM5C in osteoclast differentiation. Bone marrow–derived macrophages (BMMs) were stimulated with RANKL ± LPS and collected across osteoclast differentiation time points. Osteoclastogenic gene expression (*c-Fos, Nfatc1, Itpr2, Ppp3r1, Ctsk, Calcr*) was quantified by qPCR, and activation of NF-κB, AKT, and ERK signaling was assessed by immunoblotting. To examine osteoclast–osteoblast crosstalk, osteoblast cultures were stimulated with mature OC culture supernatant to assess how OC-secreted factors influence osteogenesis *in vitro*. *In vivo* relevance was evaluated using models of estrogen deficiency (OVX), systemic inflammation (LPS), and aging, and bone microarchitecture parameters were analyzed by μCT.

Results: Loss of *Kdm5c* enhances early inflammatory sensing and perturbs TRAF6–AKT/NF-κB signaling, altering the progression of RANKL-mediated osteoclastogenesis. *Kdm5c*-deficient OCs show reduced expression of calcium signaling components (*Itpr2, Ppp3r1*) and blunted induction of the master regulator *Nfatc1*, resulting in decreased expression of mature osteoclast markers (*Ctsk, Calcr*). Western blot analyses reveal that female BMMs are more sensitive to KDM5C loss, exhibiting greater reductions in NF-κB activation and downstream signaling, whereas male BMMs maintain comparatively robust AKT and ERK pathway activity throughout osteoclastogenesis. Consequently, signaling differences between control and cKO conditions are more pronounced in females, suggesting sex-specific compensatory mechanisms that allow males to partially preserve osteoclast differentiation. OC-OB coculture experiments revealed that OC-derived factors from *Kdm5c*-deficient cells promote osteoblast mineralization *in vitro*. Together, these results indicate that myeloid-specific Kdm5c deficiency delayed osteoclast commitment, impaired maturation, and produced a secretome that enhanced delayed osteoclast commitment and impaired maturation, osteogenesis in female mice.

Conclusion: KDM5C acts as an epigenetic regulator that integrates inflammatory signaling with osteoclastogenic pathways. Deletion of *Kdm5c* in myeloid cells impairs osteoclast maturation and may confer protection against bone loss under inflammatory and estrogen-deficient conditions. These findings indicate that KDM5C-dependent regulatory networks contribute to sex-specific control of bone remodeling and represent a potential therapeutic target for inflammatory bone diseases.



Poster 30

Title: Chondroprogenitor maturation arrest in spatially distinct tracheal mesenchymal populations underlies cartilage ring defects in *Evc2* mutant mice

Authors and affiliation: Sher Khehra[1], Hiroki Ueharu[1], Yuji Mishina[1]
[1]Department of Biologic and Material Sciences & Prosthodontics, University of Michigan School of Dentistry, Ann Arbor, MI
Name of presenter: Sher Khehra

Objectives: C-shaped cartilage rings provide the trachea with essential structural support during respiration. Damage or developmental failure may result in tracheomalacia, which is fatal in severe congenital cases. However, the molecular and cellular mechanisms underlying C-shaped cartilage formation, particularly why cartilage forms the C-shape at the ventral side of the trachea, are poorly understood. Our preliminary data showed that mice with homozygous global loss-of-function of *Evc2* (*Evc2* mutant), which encodes a ciliary protein that facilitates Hedgehog signaling transduction and is causative for Ellis-van Creveld syndrome, develop incomplete tracheal cartilage rings and perinatal lethality through abnormal Hedgehog signaling and mesenchymal condensation. Elucidating how EVC2 leads to abnormal mesenchymal condensation will provide insight into how the C-shaped structure is formed in a spatially specific manner under normal physiological conditions. Given the spatial nature of mesenchymal condensation patterning, we applied spatial transcriptomics to resolve the progenitor state transitions underlying tracheal mesenchymal condensation.

Methods: We performed 10x Visium HD spatial transcriptomics on transverse cryosections from *Evc2* mutant and littermate control mouse embryo tracheas at embryonic day 12.5 (n = 2 per genotype). Cell segmentation was performed using the 10x Genomics spatial pipeline, followed by clustering and differential expression analysis in Seurat and pseudotime trajectory reconstruction in Monocle3.

Results: Cell clustering identified five tracheal cell populations. Notably, there were two spatially and transcriptionally distinct *Sox9*-expressing chondroprogenitors: an inner population and an outer population (Figure 1A). In *Evc2* mutants, the inner population expanded approximately two-fold compared to controls while the outer population was proportionally reduced (Figure 1B). Pseudotime trajectory analysis placed the inner population at an earlier progenitor state and the outer population at a more advanced state. *Evc2* mutant chondroprogenitors accumulated at the earlier state and failed to progress, suggesting that the condensation defect arises from a progenitor maturation failure (Wilcoxon $p < 2.2 \times 10^{-16}$; Figure 2A-B). Differential expression within the chondroprogenitor compartment identified upregulation of 24 genes, including WNT signaling-related genes such as *Wnt5a*, suggesting involvement of non-canonical Wnt signaling in the arrested state.

Conclusions: These findings reveal previously uncharacterized spatial heterogeneity within the tracheal chondroprogenitor pool and identify a maturation failure as the cellular basis of the condensation defect in *Evc2* mutant tracheas. Current efforts focus on validating spatial transcriptomic findings and defining the signaling mechanisms that maintain the arrested progenitor state.

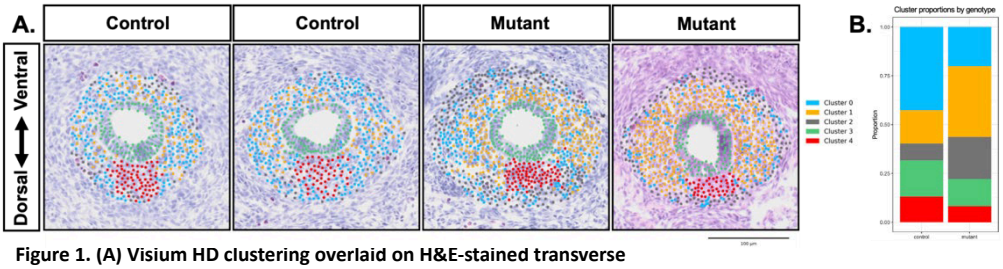


Figure 1. (A) Visium HD clustering overlaid on H&E-stained transverse trachea sections from E12.5 control and *Evc2* mutant embryos, with cluster colors indicated on the right. Scale bar = 100 µm. (B) Proportion of cell clusters by genotype.

Figure 2. Pseudotime trajectory of chondroprogenitor populations (clusters 0 and 1) in (A) control and (B) *Evc2* mutant tracheas at E12.5. Color indicates pseudotime value (purple = early, yellow = late).

Poster 31

Activation of Mechanotransduction in Redifferentiating Human Articular Chondrocytes in response to Short-Term Mechanical Stimulation

Sriranjani Seshadri[1], Ruxin Yang[1], Weiping Li[4], Kiera Downey[1], Cheri X. Deng4, Rhima M. Coleman[1,2,3]

[1]Department of Biomedical Engineering, University of Michigan, Ann Arbor

[2]Department of Orthopaedic Surgery, University of Michigan Medical School, Ann Arbor

[3]Department of Mechanical Engineering, University of Michigan, Ann Arbor

[4]Department of Biomedical Engineering, Michigan State University, East Lansing, MI

Name of Presenter: Sriranjani Seshadri

Introduction

Autologous chondrocyte implantation (ACI) is less effective in patients over 45 because expanded cells dedifferentiate and lose redifferentiation capacity. Mechanical loading may help restore chondrocyte function, but the response of early OA cells remains to be elucidated. The objective of this study was to compare the early response of early OA human articular chondrocytes (HACs) to young HACs.

Methods

HACs from young or OA donors were encapsulated (20 million cells/mL) in hydrogels composed of 5% polyethylene glycol (PEG), type I collagen, and hyaluronic acid. Cyclic mechanical loading was applied using tensile acoustic rheometry (TAR) at 10% strain and 1 Hz for 30 minutes per session, repeated over five days with a two-day rest period. Free-swelling hydrogels served as controls. Mechanotransduction and chondrocyte-specific gene expression was evaluated using RT-qPCR, protein levels were assessed by immunofluorescence (not shown).

Results

Mechanical loading enhanced ACAN, COL2A1, and hypertrophic gene expression in young HACs, (Figure 1), consistent with increased matrix synthesis and chondrocyte maturation. In OA HACs, loading did not increase chondrogenic gene expression; however, aggrecan and collagen protein levels were higher than young HACs as confirmed by immunofluorescence, suggesting that post-transcriptional mechanisms contribute to matrix deposition; protein expression in young HACs remained largely unchanged. TGF-β signaling was generally similar between cell types, though OA HACs exhibited slightly reduced SMAD1/5/9 activation and increased SMAD2/3 activation compared to young HACs, consistent with a phenotype favoring tissue remodeling processes. Hypertrophic protein markers decreased in OA HACs after loading but remained unchanged in young HACs, indicating that loading may selectively suppress pathological hypertrophy in OA HACs. Loading induced variable YAP1 and increased CCN1 expression in OA HACs (not shown), similar to young HACs but to a lesser extent, suggesting that mechanotransduction pathways remain partially responsive in disease-altered cells.

Discussion

Short-term mechanical stimulation modulated behavior in both young and early OA HACs, but with different magnitudes. Overall, brief loading benefited OA HACs by enhancing matrix deposition and reducing hypertrophy.

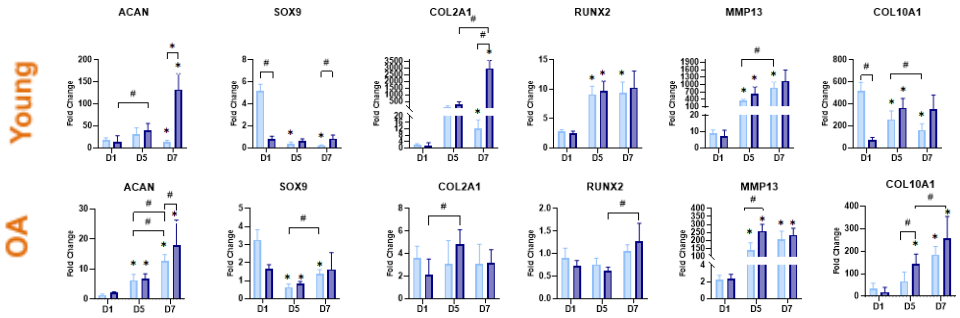


Figure 1: Expression of chondrogenic (ACAN/SOX9/COL2) genes in (A) young and (B) OA HACs in soft hydrogels. The data is normalized to D0. * indicates statistical significance of the specified condition compared to D1. # indicates statistical significance between specified groups.

Poster 32

Role of proprioception in orofacial muscle control

Markel, S, Uchima Koecklin, KH, and Li, P

Authors: Sydney Markel[1], Karin Uchima[1,2], and Peng Li[1,2,3]

1. Life Sciences Institute, University of Michigan 2. Department of Biologic and Materials Sciences & Prosthodontics, University of Michigan 3. Department of Molecular and Integrative Physiology, University of Michigan

Name of presenter: Sydney Markel

Study goals: Musculoskeletal function is regulated by sensory inputs, primarily proprioception, the body's sense of position and movement. Despite the well-recognized health consequences of orofacial disturbances, the neural mechanisms underlying proprioceptive control of orofacial motor functions in both normal and pathological conditions are not yet fully understood. Orofacial muscles must execute highly precise, rapid, and continuously adaptable movements to support essential behaviors. The mesencephalic nucleus of the trigeminal nerve (Vmes) is a unique sensory nucleus that processes proprioceptive input from the orofacial muscles. These neurons express the *Piezo2* gene, which encodes a mechanosensitive ion channel protein crucial for proprioception and mechanosensation. Vmes neurons innervate muscle spindles, which are specialized proprioceptors in skeletal muscle that detect changes in muscle length and the speed at which the change occurs. Muscle spindles are composed of three fiber types: bag 1, bag 2, and chain type. In the orofacial region, they are most densely concentrated in the masseter muscles, which are responsible for jaw closing. The aim of our study is to elucidate the innervation patterns and functional roles of distinct Vmes populations in orofacial proprioception and motor function. **Methods:** We utilized two loss-of-function conditional knockout (cKO) mouse models to delete the *Piezo2* gene in Vmes subpopulations*:* Vglut1-Cre cKO (*Slc17a7*) and Pv-Cre cKO (*Pvalb*) and examined their effects on the muscle spindle structure and masseter muscle function. For structural analysis, masseter muscles from both cKO mice and their littermate controls were cryosectioned, immunostained, and imaged by confocal microscopy. Muscle spindle lengths were quantified from the images using ImageJ and statistical comparisons were performed using a t-test. For functional assessment, jaw-closing force was measured using a bite force transducer. **Results:** We observed distinct innervation patterns of Vglut1-Cre and Pv-Cre Vmes neurons across muscle spindle types. Vglut1-Cre neurons robustly innervate all three muscle spindle types, while Pv-Cre neurons innervate only the chain type muscle spindle fibers. Consistent with these innervation patterns, Vglut1-Cre cKO mice showed disrupted muscle spindle morphology across all three muscle spindle types, including shortened, partially degenerated spindles and spindles lacking a defined annulospiral ending, whereas Pv-Cre cKO mice showed disruptions restricted to the chain type. Furthermore, muscle functional examinations revealed that the Vglut1-Cre cKO mice showed reduced bite force and bite frequency compared with the Pv-Cre cKO mice. **Discussion:** Our findings demonstrate that different Vmes neuronal population exhibit differential innervation patterns in muscle spindles. Piezo2 is critical for the structural integrity of the muscle spindles they innervate. Furthermore, orofacial proprioception plays a key role in regulating bite force and bite frequency, a function specifically mediated by Piezo2 in Vglut1-Cre neurons. Vglut1 neurons are therefore essential for muscle spindle function and orofacial proprioception, whereas the role of Pv neurons remains incompletely understood. Overall, these results highlight the functional specialization of Vmes subpopulations in controlling muscle spindle structure and orofacial motor performance. Our research on orofacial proprioception will advance our understanding of the neural mechanisms underlying orofacial disturbances.

Poster 33

Beyond the knee: Investigating multi-joint osteoarthritis in human and animal models

Thomas G. Wilson[1,2], Madhu Baghel[1,2], Christopher Little[3], T. Sean Lynch[2], Vasilios Moutzouros[2], Jonathan Braman[2], Jason Davis[4], Shabana Amanda Ali[1,2,5]

1. Bone and Joint Center, Henry Ford Health + Michigan State University Health Sciences, Detroit, MI
2. Department of Orthopedic Surgery, Henry Ford Health, Detroit, MI
3. Kolling Institute, University of Sydney, Sydney, Australia
4. Michigan Orthopedic Surgeons, West Bloomfield, MI
5. Center for Molecular Medicine and Genetics, Wayne State University,

Detroit, MI Presenting author: Thomas G. Wilson

Study aims: Osteoarthritis (OA) is a complex, heterogeneous disease that can affect multiple joints such as the knee, hip and shoulder, often within the same individual. Although multi-joint OA is common, most research has focused on the knee due to its high prevalence and robust animal models. This leaves OA in other joints comparatively underexplored, limiting understanding of joint-specific mechanisms. Developing experimental models in these underrepresented joints is crucial to identifying common and distinct factors to guide more precise therapeutic strategies. We aim to characterize OA from both a single- and multi-joint perspective, leveraging new and existing human and animal models.

Methods: To compare human knee, hip and shoulder OA, we have established the Henry Ford Health (HFH) OA biorepository, a collection of tissues and biofluids from consented individuals undergoing joint surgery. Biospecimens include plasma, synovial fluid, subchondral bone, articular cartilage, synovium, and periarticular fat across all joints. Joint-specific tissues include meniscus, anterior cruciate ligament, vastus medialis oblique muscle, and infrapatellar fat pat from knee; acetabular labrum, quadratus femoris muscle, and ligamentum teres from hip; and glenoid labrum, rotator cuff muscle, and biceps tendon from shoulder (**Figure 1**). Clinical data include demographics, comorbidities, radiographic OA staging and diagnosis, and patient-reported outcomes. In parallel, we are developing a surgical mouse model of hip OA to complement existing knee models. Hip instability will be induced via ligamentum teres transection and OA progression assessed by behavioral testing, microCT imaging, and histology.

Results: To date, the HFH OA biorepository comprises 668 participants contributing biospecimens from N=772 surgical procedures. The biorepository currently stores more than 17,700 aliquots spanning 16 tissue and biofluid types encompassing approximately 11,900 from knee, 5,300 from hip, and 500 from shoulder. A subset of participants has contributed samples from multiple joint sites, including N=66 bilateral knee, N=24 bilateral hip, and N=14 contributing both knee and hip biospecimens. Ligamentum teres transection has been successfully performed in live animals, with model characterization ongoing.

Conclusions: We are establishing resources to investigate OA across joint types, providing a foundation for exploring joint-specific disease mechanisms. This is expected to provide insight into a fundamental question in the field - is OA the same or different across joints?

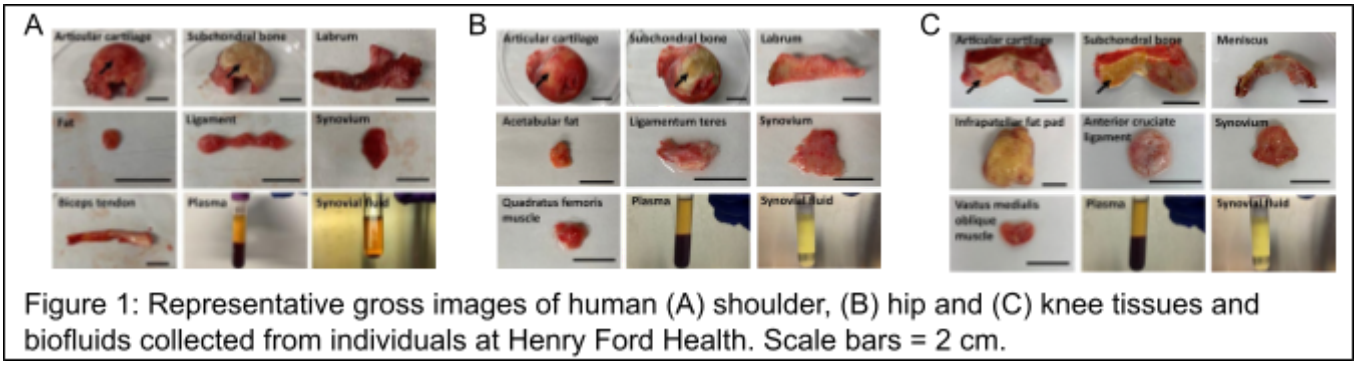


Figure 1: Representative gross images of human (A) shoulder, (B) hip and (C) knee tissues and biofluids collected from individuals at Henry Ford Health. Scale bars = 2 cm.

Poster 34

Title: Chronic Stress Induces Body Weight Reduction Driven by Lean Mass Loss in Diet-Induced Obese Mice

Authors and affiliation: Tiange Bu[1], Cecelia Occhipinti[2], Zhe Wu[3], Nathan Qi[3], Kristen Schuh[4], Natalie Tronson[4], Dave Bridges[1]
[1]Department of Nutritional Sciences, University of Michigan School of Public Health, Ann Arbor, MI
[2]College of Literature, Science, and the Arts, University of Michigan, Ann Arbor, MI
[3]Michigan Mouse Metabolic Phenotyping Center, University of Michigan, Ann Arbor, MI
[4]Department of Psychology, University of Michigan, Ann Arbor, MI

Name of presenter: Tiange Bu

Background Obesity and chronic stress share a bidirectional relationship and both contribute to adverse metabolic and psychological outcomes. The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in stress responses and may influence energy balance and tissue metabolism. However, how body composition, especially lean mass, is regulated under chronic stress in diet-induced obesity remains poorly understood.

Methods Male C57BL/6J mice were fed either a high-fat diet (HFD) for 12 weeks to establish diet-induced obesity, or remain on a normal chow diet (NCD). Mice were then randomized to a 21-day chronic unpredictable stress (CUS) protocol or left unstressed as controls. Body weight, food intake, and body composition were monitored throughout the study. Anxiety-like behaviors were assessed using the Open Field Test (OFT) and Elevated Plus Maze (EPM), and quadriceps muscle were prepared for mRNA and protein assessment.

Results HFD-fed mice gained significantly more body weight and fat mass compared with NCD-fed controls during the diet-induction period. Following initiation of the CUS protocol, as expected, stressed mice exhibited increased anxiety-like behavior in OFT, confirming the effectiveness of the protocol. Throughout the stress-induction period, body weight declined significantly in stressed mice, with stressed HFD mice losing weight at a rate of 0.12 ± 0.04 g/day compared with 0.06 ± 0.03 g/day in stressed NCD mice. Body composition analysis indicated that this decrease in body weight was primarily associated with reductions in lean mass, with stressed HFD mice losing lean mass at a rate of 0.11 ± 0.02 g/day compared with 0.04 ± 0.01 g/day in NCD mice (diet-time interaction $p < 0.001$), while changes in fat mass were comparatively modest and not statistically significant. Importantly, caloric intake remained higher in HFD-fed mice throughout the study, suggesting that reduced food intake did not account for the observed body weight loss.

Conclusion These findings indicate that chronic stress causes body weight reductions in diet-induced obese mice that are driven by lean mass loss rather than decreased caloric intake. Ongoing analyses of quadriceps muscle samples will evaluate whether chronic stress activates skeletal muscle catabolic pathways, including FOXO transcription factors and atrogenes such as Atrogin-1 and MuRF1.

Poster 35

Integration of DDR2-Binding Peptides into ECM-mimic 3D Nanofibrous Scaffolds for Synergistic Bone Regenerations

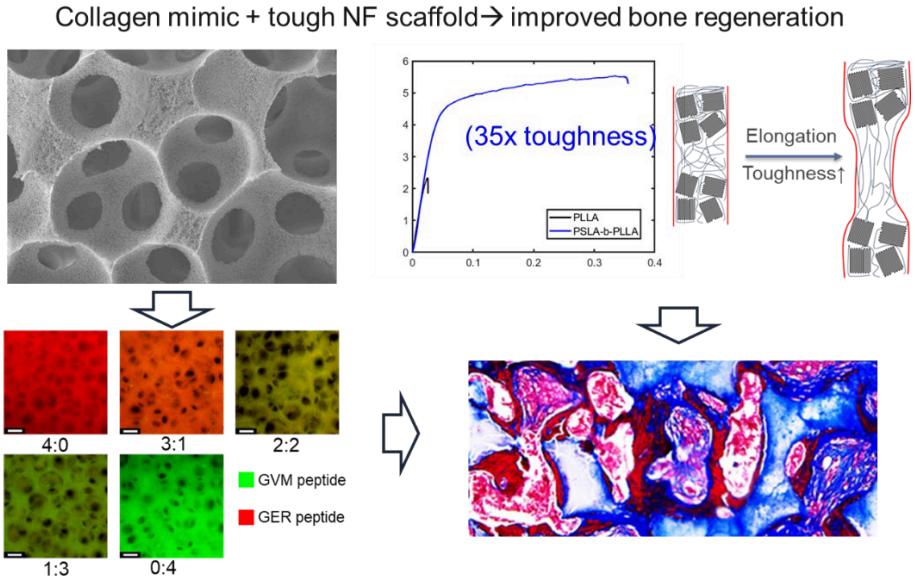
Tongqing Zhou (presenter), Rafael C. Cavalcante, Chunxi Ge, Renny T. Franceschi, Peter X. Ma
Department of Biologic and Materials Sciences and Prosthodontics, Macromolecular Science & Engineering Center, The University of Michigan, Ann Arbor, MI 48109, USA

Study goals: Bone grafting remains a high-demand clinical procedure, with over 500,000 cases performed annually in the United States. Poly(L-lactic acid) (PLLA) is a widely used biodegradable polymer for bone tissue engineering. We have developed a thermally induced phase separation (TIPS) method to fabricate nanofibrous (NF) PLLA scaffolds that mimic collagen geometry and enhance osteogenesis. However, conventional polymer scaffolds lack molecular cues of the native extracellular matrix (ECM). Therefore, we report two functional PLLA-based graft/block copolymers incorporating methacrylate or norbornene groups, enabling covalent conjugation of bioactive peptides to 3D NF scaffolds via click chemistry, an important upgrade to existing porous 3D NF scaffolds.

Methods: We synthesized and characterized copolymer compositions to preserve the characteristic nanofibrous morphology during TIPS while increasing peptide conjugation density and mechanical strength. To recapitulate both structural and receptor-specific ECM signaling, peptides targeting the two principal collagen receptors — discoidin domain receptor 2 (DDR2) and β1 integrins—were conjugated to the scaffolds and evaluated in a critical-sized bone defect model.

Results: These studies integrate DDR2-binding peptides into 3D scaffolds for bone regeneration. Dual-peptide functionalization produced synergistic effects, yielding enhanced vascularization, accelerated bone maturation, and a 7.8-fold increase in mineralized bone formation compared to non-functionalized controls after 8 weeks in vivo. Furthermore, improved mechanical integrity of the copolymer scaffolds further augmented regenerative outcomes, underscoring the importance of structural stability in porous biomaterials.

Conclusions: Collectively, these results establish a biomimetic scaffold platform that recreates ECM cues at both the nanoscale and the molecular level to direct receptor-mediated bone regeneration. The increase in regenerated bone volume suggests a potent bone tissue engineering strategy, promising for future clinical applications.



Poster 36

Abstract for Annual Musculoskeletal Health Symposium 2026

Title: Investigating the impact of CKD on bone health and Osteocyte function

Authors and affiliation: Varnika Jakka[1], Lauren E. Surface[1], Jie Ren Gerald Har[1]

Name of Presenter: Varnika Jakka

Study Goals: Patients with chronic kidney disease (CKD) have increased bone loss and are more prone to fractures, however, the mechanisms by which CKD changes osteocyte function and bone regulation are not fully understood. Osteocytes play an important role in regulating bone remodeling and signaling to osteoblasts and osteoclasts, making them a critical cell type to study in CKD-related bone disease. This study investigates how CKD-related conditions affect osteocyte behavior using both mouse models and osteocyte cell culture experiments.

Methods and Results: Based on an earlier metabolic assay, OCY454 cells consume a high amount of glutamine compared to asparagine. To further examine the role of glutamine and asparagine in osteocyte behavior, differentiated cells were cultured without asparagine, glutamine, or both amino acids. Removal of glutamine led to a significant reduction in total protein production, while removal of asparagine showed a smaller effect. These results suggest that osteocytes may require glutamine for biological processes such as protein synthesis and cell metabolism.

To analyze osteocyte regulation under CKD-related conditions, differentiated OCY454 osteocyte cells were treated with parathyroid hormone (PTH), indoxyl sulfate (IS), or a combination of both. PTH and IS are two factors that are elevated in CKD and contribute to bone and mineral disorders, and were applied to examine how CKD-associated hormonal and metabolic changes affect osteocyte protein production. In osteocyte cultures, PTH treatment reduced the visible collagen layer compared to control wells, while overall protein levels remained similar between control and IS-treated groups. The combined PTH + IS group showed greater variability in protein levels, suggesting a possible interaction effect on osteocyte protein regulation.

To further examine how amino acid deprivation affects osteocyte signaling, preliminary qPCR analysis is currently ongoing to look at the expression of eight genes involved in osteocyte signaling and bone regulation: RPLP0, Sost, Dkk1, RankL, OPG, Phex, Slc3a5, and Dmp1, with additional analysis being conducted to better understand gene expression changes under a lack of amino acids. The genes selected are osteocyte gene expression markers.

Discussion/Conclusion: Together, these findings provide insight into how CKD-related conditions and amino acid changes may influence osteocyte behavior and protein production. Further analysis of these gene expression patterns will help identify metabolic pathways disrupted in osteocytes during CKD. Understanding these disruptions may guide future strategies to improve bone health in CKD patients, including potential metabolic therapies or treatments that restore osteocyte function.

Poster 37

Engineered Fiber Constructs to Investigate Tension-Mediated Skeletal Muscle Differentiation

Vivian T. Wong[1,2], Maggie E. Jewett[1], Anan Ghrayeb[3], Brendon M. Baker[1], Carlos A. Aguilar[1,2]

[1]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI

[2]Biointerfaces Institute, University of Michigan, Ann Arbor, MI

[3]Department of Mechanical Engineering, University of Michigan, Ann Arbor, MI

Abstract:

Following injury, skeletal muscle has a remarkable ability for regeneration driven by quiescent muscle stem cells that activate, proliferate, and differentiate into mature myotubes to restore tissue homeostasis. In vivo, these cells reside on the basal lamina in between myofibers and respond to both biochemical and biophysical cues that regulate their maturation. While signaling during myogenesis has been widely studied, how mechanical cues influence skeletal muscle differentiation remains less understood. Here, we engineer fiber constructs to investigate how myoblasts respond to mechanical tension in a controlled ex vivo environment. We hypothesize that these engineered fibers can function as an artificial niche that promotes myotube maturation.

To test this, microchannel device molds were 3D printed and cast with polydimethylsiloxane (PDMS), then mounted onto glass coverslips for cell seeding. Our engineered fiber constructs (termed "EHTugs") consist of a hydrogel composite containing 10 mg mL^{-1} fibrin, 2 mg mL^{-1} rat tail collagen type I, and 4% dextran-vinyl sulfone (DVS) electrospun fibers functionalized with cRGD, seeded with 20 M cells mL^{-1}. Following gelation at 37ºC for 30 min, constructs were cultured for 7 days. This platform was previously established using cardiomyocytes and cardiomyofibers.

First, we demonstrate that C2C12 myoblasts seeded onto EHTugs self-assemble into uniform constructs that express myosin heavy chain (MyHC), indicating myogenic differentiation. Confocal imaging shows that cells align along the engineered fibers, suggesting that myoblast organization responds to the imposed mechanical architecture and tension. To investigate niche interactions, we will co-culture primary murine $PDGFRa^{+}$ fibro-adipogenic progenitors (FAPs) with C2C12 myoblasts and compare these constructs to C2C12-only constructs. We hypothesize that co-cultured constructs under tension will exhibit enhanced skeletal muscle differentiation, measured by increased fusion index and myotube width, potentially mediated by paracrine signaling from FAPs.

Next, to examine how pathological niche states influence differentiation, we will induce cellular senescence in FAPs by treating them with 10 μM etoposide for 24 h prior to seeding and assess their impact on myotube maturation under tension. Finally, as a proof of concept, we will integrate flexible robotic actuators to mechanically "exercise" the engineered constructs. We hypothesize that dynamic actuation will further enhance myotube maturation and establish a new platform for in vitro skeletal muscle biology studies. Together, this work establishes an engineered fiber platform that enables controlled investigation of mechanical and cellular cues during skeletal muscle differentiation for regenerative muscle applications.

Poster 38

Title: The Role of Myeloid Specific Thrombospondin 1 in Fracture Healing
Authors: Zaynah Saraya, Christina Capobianco, Salem Wang, Luke Schroeder, Kurt Hankenson
Affiliations: Orthopaedic Research Laboratories, Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, MI
Name of presenter: Zaynah Saraya

Study Goals: Fracture healing is a complex event that involves the coordination of many processes including inflammation, blood vessel ingrowth, matrix organization, and remodeling. Impaired fracture healing is debilitating, thus a goal of our lab is to better understand potential therapeutic targets. Thrombospondin 1 (TSP1) is a protein secreted by macrophages during the inflammatory phase of bone healing. Previous studies have shown that its absence, in complete knockout mice, impairs fracture healing and creates a larger, more fibrotic callus. We hypothesize that macrophage produced TSP1 acts in a paracrine manner to limit the production of fibrosis by fracture fibroblasts.
Methods: To target myeloid-specific TSP1 in fracture repair, we validated a mouse model with TSP1 disrupted in macrophages Lysm-Cre (TSP1floxed). We assessed recombination and loss of TSP1 using quantitative-PCR in the fracture callus and spleen 4 days post fracture (DPF). Fractures were performed by first stabilizing the tibia with a hypodermic needle followed by a guillotine weight drop. We then performed Micro-CT analysis and histological staining using Fast Green/Safranin-O at 15 DPF. We also analyzed blood vessels at 15 DPF using CD31 staining and ImageJ.
Results: In the conditional knockout mice, there was an 80% decrease in TSP1 expression in the myeloid population and no difference in the stromal population (Fig 1A). Via Micro-CT (Fig 1B) and histology (not shown) we found that there is no change in bone volume but increased callus size indicative of excessive matrix deposition. We found at 15 DPF the TSP1-LysM-Cre + and Cre- had a comparable blood vessel quantity in the callus (Fig D).
Discussion/Conclusion: Overall, there is dysregulated matrix formation when myeloid TSP1 is knocked out, consistent with the complete TSP1 deletion that was previously observed; this is suggestive that myeloid specific TSP1 expression is necessary to regulate normal fracture repair.

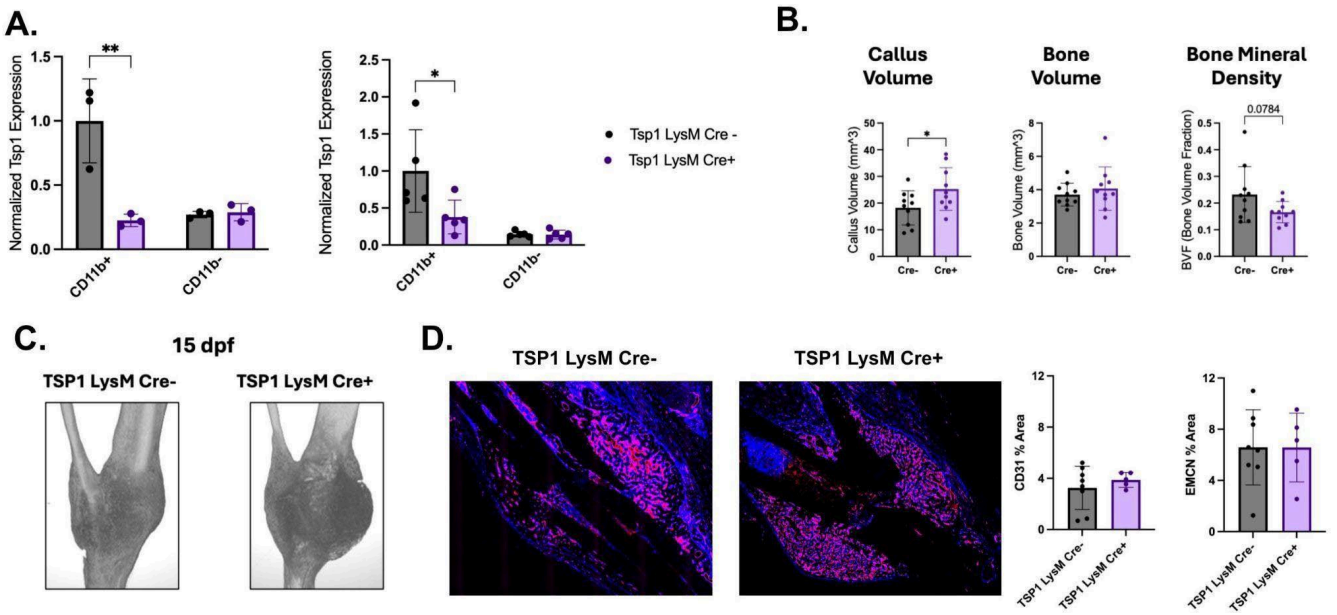


Figure 1: **(A)** Comparison of TSP1 Expression in fracture callus and spleen 4 DPF. **(B)** Micro Ct analysis of TSP1 Lsym-Cre -/+ fracture calluses at 15 DPF **(C)** Representative images of features at 15 DPF. Analysis was performed using two sided T-testTwo-way ANOVA was performed,
*p<0.05, **p<0.01. **(D)** 10X stitched images of TSP1 LysM Cre- and Cre+ fracture calluses and quantification of percent area made up by blood vessels. Two-sided T test was performed.