3rd Annual Symposium on Rare Diseases and Rare Cancers in the Era of Systems Biology

November 12-13, 2025 (Hybrid)
Sonesta Hotel, Milwaukee, WI

MEDICAL COLLEGE OF WISCONSIN

Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine

Message from the Director!

Colleagues and Friends,

Three years ago, we launched, for the first time at MCW, our stellar Symposium of Genomics Sciences and Precision Medicine, which has been attended by prestigious National and International experts in the field as well as a large diversity of learners. Thus, it is now my pleasure to invite you to the 3rd Annual Mellowes Center Symposium on November 12-13, a transformative two-day hybrid event that promises to push the boundaries of genomic science and precision medicine.

This year's symposium brings together leading researchers, clinicians, and innovators for groundbreaking discussions on the latest advances in our field. Beyond the science, we are honored to present Rare Storytellers—a powerful session featuring the voices and journeys of rare disease patients. These remarkable individuals remind us of the profound purpose behind every experiment, every discovery, and every sleepless night in the lab. Their courage and resilience are the beating heart of our mission.

I strongly encourage you to join us for this extraordinary gathering. Whether you attend in person or virtually, you will have the opportunity to engage with cutting-edge research, forge meaningful connections with peers, and draw inspiration from the very people whose lives we strive to transform.

At the Mellowes Center, we believe that advancing genomic sciences and precision medicine requires more than breakthrough research—it demands a commitment to education, community engagement, and the cultivation of future leaders. Together, we are not simply studying the genome; we are rewriting the future of medicine, empowering the next generation of scientists and healthcare professionals to tackle humanity's most pressing health challenges.

Thank you for your continued partnership in this vital work. Your dedication, collaboration, and shared vision make our mission possible. Let us continue to innovate together, inspire one another, and create a lasting legacy in genomic science that will echo through generations to come.

I look forward to seeing you at the symposium.

With warmest regards and deepest appreciation,

Raul A. Urrutia, MD
Director, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
Warren P. Knowles Chair of Genomics and Precision Medicine
Professor of Surgery, Biochemistry, and Physiology
Associate Director, Precision Medicine, CTSI
Co-Director, Data Science, CTSI
Chief Scientific Officer, Cancer Epigenetic Society
Emeritus Professor, Mayo Clinic, Rochester

Day 1: Wednesday, November 12, 2025

8:00 a.m. - 8:45 a.m.

Registration, Light Breakfast, and Networking

8:45 a.m. - 9:15 a.m.

Introduction and Welcome

- **Raul Urrutia, MD**
  Director, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
  Medical College of Wisconsin

- **Amy Sordahl**
  Program Coordinator for Advancing a Healthier Wisconsin (AHW)

9:15 a.m. - 12:00 p.m.

Panel Session 1: Mechanisms to Medicine in Mitochondrial Diseases

- **Jing Dong, PhD**
  Medical College of Wisconsin
  “Mitochondrial DNA variation and stem-cell transplantation outcomes”

- **Andreas Beyer, PhD**
  Medical College of Wisconsin
  "Is Coronary Artery Disease "just" a metabolic problem, Lessens from the micro-circulation"

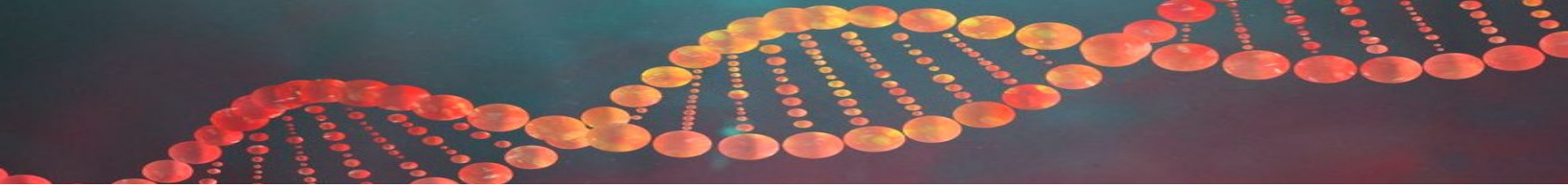
- **Francesc Palau, MD, PhD**
  Barcelona Children’s Hospital
  "Mitochondrial contact sites in genetic disease"

- **Gyorgy Hajnoczky, MD**
  Thomas Jefferson University
  "Mitochondrial Signaling in Health and Disease"

- **Group Q & A Session**
  Panel Moderator: Xiaowu Gai, PhD

12:00 p.m. - 1:00 p.m.

Lunch, Posters, and Networking



1:00 p.m. - 2:00 p.m.

KEYNOTE SPEAKER

- **Marni J. Falk, MD**
  Executive Director, Mitochondrial Medicine Frontier Program
  Distinguished Endowed Chair in the Department of Pediatrics
  Professor, Division of Human Genetics, Department of Pediatrics, University of Pennsylvania Perelman School of Medicine

  "Scaling Precision Therapeutic Development for Rare Disease: Building bridges from preclinical modeling to clinical stage development"

2:00 p.m. - 2:30 p.m.

Lightning Talks

- **Akorfa Adobor (Medical Student)**
  "Racial and Ethnic Disparities in Melanoma Stage at Diagnosis: A Real-World Data Analysis"
- **Kimani Njoya (Graduate Student)**
  "Natural history of SPP1 Signaling in NF1 Tumor Progression"
- **Neshatul Haque, PhD (Postdoctoral Fellow)**
  "Unraveling Genetic and Epigenetic Dynamics: Molecular Insights into SMARCA4-Mediated Chromatin Remodeling in Disease"
- **Shahram Arsang-Jang, PhD (Postdoctoral Fellow)**
  "Effects of Donor and Recipient Mitochondrial DNA Variants on Graft-Versus-Host Disease Onset in MDS Patients After Allogeneic hematopoietic stem cell transplantation"

2:30 p.m. - 5:15 p.m.

Panel Session 2: Diagnostic Discovery of Diseases

- **Donald Basel, MD**
  Children's Wisconsin
  "Integrated Genomics in Pediatric care"
- **Filippo Pinto e Vairo, MD, PhD**
  Mayo Clinic
  "From n=1 to n=1000s"
- **Bryn Webb, MD, FACMG**
  University of Wisconsin-Madison
  "Advancing Rare Disease Diagnosis: The University of Wisconsin Undiagnosed Diseases Program Experience"
- **Aoy Tomita Mitchell, PhD**
  Medical College of Wisconsin
  "From Genotype to Phenotype: The Role of MYH6 in Congenital Heart Malformations"
- **Group Q & A Session**
  Panel Moderator: **Michael T. Zimmermann, PhD**

5:00 p.m. - 6:00 p.m.

Social Hour, Posters, and Networking

Day 2: Thursday, November 13, 2025

7:00 a.m. - 8:00 a.m.

Registration, Light Breakfast, and Networking

8:00 a.m. - 10:15 a.m.

Panel Session 3: Human Diseases of the Epigenome

- **Jill Fahrner, MD, PhD**
  Johns Hopkins School of Medicine
  "Mendelian Disorders of the Epigenetic Machinery: Novel Insights from the Bedside and the Bench"
- **Rosanna Weksberg, MD, PhD**
  University of Toronto-Sick Kids Hospital
  "Epigenomic Analysis: Impact on Precision Medicine for Rare Disease"
- **Christopher Pin, PhD**
  Purdue University
  "Epigenetic programs affecting progression and resistance in pancreatic cancer"
- **Group Q & A Session**
  Panel Moderator: **Raul Urrutia, MD**

10:15 a.m. - 11:15 a.m.

KEYNOTE SPEAKER

- **Danny E. Miller, MD, PhD**
  Assistant Professor
  University of Washington and Seattle Children's Hospital

  "Streamlining clinical and research genetic testing: the promise of long-read sequencing"

11:15 a.m. - 11:45 a.m.

Posters and Networking

11:45 a.m. - 1:30 a.m.

Rare Storytellers®: Navigating from Pediatric to Adult Care

- **Kerry Hughes, M.Ed -** Harmony 4 Hope, Founder and President
- **Claire Bevec -** Rare Storyteller diagnosed with Autosomal Recessive Polycystic Kidney Disease (ARPKD/CHF)
- **Taylor Schalk -** Rare Storyteller diagnosed with Superior Mesenteric Artery Syndrome
- **Michael Muriello, MD -** Medical Guest; Associate Professor of Pediatrics-Medical College of Wisconsin
- **Trapper Schoepp -** Harmony4Hope Musical Ambassador; Milwaukee Songwriter & Performer
- **Steve Scaffidi –** Special Guest Moderator; Radio Host for 620WTMJ

1:30 p.m. – 2:00 p.m.

Posters and Networking

2:00 p.m. – 2:30 p.m.

Lightning Talks

- **Justin Freestone (Graduate Research Assistant)**
  "Evaluation of MAB21L1 variants associated with human ocular disorders"
- **Gareth Pollin, PhD (Postdoctoral Fellow)**
  "Decoding KRAS Mutation-Specific Nuclear Reorganization in PDAC Through Chromatin Disruption and DNA Damage Signaling That Drive Variant-Specific Malignancy"
- **Megan Fischer (Graduate Student)**
  "Modeling and functional dissection of the human 8q21.11 deletion syndrome in zebrafish"
- **Miracle Emosivbe (Graduate Student)**
  "New insights into functional responses of CXCR4 WHIM mutants"

2:30 p.m. – 5:15 p.m.

Panel Session 4: Functional Modeling and Validation of Disease Variants

- **Joy Lincoln, PhD**
  Medical College of Wisconsin
  "Marfan Syndrome: Genotype-Phenotype in Mitral Valve Prolapse"
- **Lihsia Chen, PhD**
  University of Minnesota
  "Modeling the KCNK9 Imprinting Syndrome in C. elegans"
- **Audrey Gasch, PhD**
  University of Wisconsin-Madison
  "Systems biology in rare diseases: from model organisms to humans"
- **Laura Lambert, PhD**
  Mayo Clinic
  "Functional Omics for N=1 Disease Diagnostics"
- **Group Q & A Session**
  Panel Moderator: **Gwen Lomberk, PhD**

5:15 p.m. - 6:00 p.m.

Closing Remarks, Social Hour, Posters, and Networking

KEYNOTE SPEAKER

Marni J. Falk, MD

Executive Director, Mitochondrial Medicine Frontier Program
Distinguished Endowed Chair in the Dept. of Pediatrics
Professor, Division of Human Genetics, Dept. of Pediatrics,
University of Pennsylvania Perelman School of Medicine
The Children's Hospital of Philadelphia

A board-certified Clinical Geneticist and Pediatrician, Dr. Falk advances precision care, diagnostics, and therapeutics for rare disorders, focusing on primary mitochondrial disease. She co-leads the global Mitochondrial Disease Sequence Data Resource (MSeqDR) and ClinGen Mitochondrial Disease Expert Panels, and founded the CHOP/UPENN Mitochondria Research Affinity Group.

At CHOP, Dr. Falk directs a translational research lab investigating mitochondrial disease mechanisms, global metabolic consequences, and the preclinical development of targeted therapies and nanosensors in multiple model systems. She co-founded CHOP's Mitochondria-Cancer Connections program to explore mechanistic and therapeutic intersections of mitochondrial disease and osteosarcoma. She also partners with industry to integrate data-driven approaches into rare disease clinical research and co-founded Rarefy Therapeutics LLC in 2023 to advance precision, low-cost therapies for rare diseases.

She has authored more than 175 peer-reviewed papers and edited Mitochondrial Disease Genes Compendium: From Genes to Clinical Manifestations. She serves on the Scientific and Medical Advisory Board of the United Mitochondrial Disease Foundation, is a founding member of CHOP's Center for Mitochondrial and Epigenomic Medicine and holds leadership roles in multiple national and international scientific societies.

KEYNOTE SPEAKER

Danny Miller, MD, PhD

Assistant Professor
University of Washington and Seattle Children's Hospital

Danny Miller is an Assistant Professor in the Department of Pediatrics, Division of Genetic Medicine, and the Department of Laboratory Medicine and Pathology at the University of Washington and is an attending physician at Seattle Children's Hospital. His lab is developing long-read sequencing-based clinical genetic tests with a goal of increasing the rate of genetic diagnoses, reducing the time required to make a genetic diagnosis, and lowering barriers to obtaining comprehensive clinical testing. Clinically, he cares for patients in both general genetics and skeletal dysplasia clinics.

OUR SPEAKERS

Donald Basel, MD

Professor and Division Chief of Genetics, Department of Pediatrics
Medical College of Wisconsin

Donald Basel is a Professor of Pediatrics and Division Chief of Genetics at MCW. He serves as the Medical Director for Genetics and the Undiagnosed Center of Excellence at Children's Wisconsin. He has been a practicing geneticist for 25 years, 7 years in bench research developing proof of concept therapies for targeted down regulation of collagen in a osteogenesis imperfect mouse model. He has grown the genome program at CW/MCW and implemented an integrated genomics approach to diagnosis and care at CW. He is the PI on several studies for inborn errors of metabolism and has a strong track record of research collaboration. He is a keen advocate for healthy kids in Wisconsin and strives to improve quality of care and equitable access to tertiary care for all.

Session: Diagnostic Discovery of Diseases

Andreas Beyer, PhD

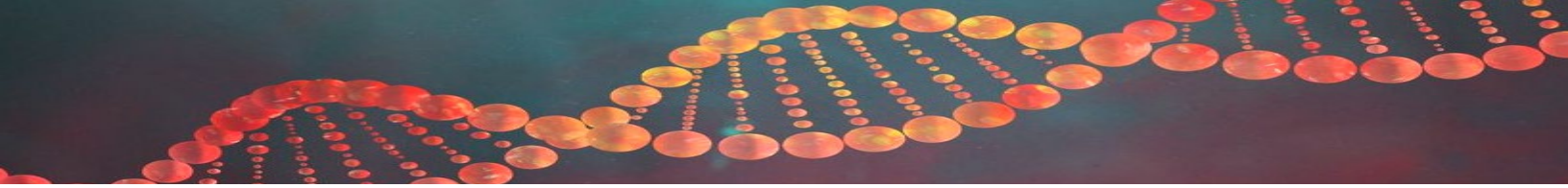
Professor, Department of Medicine & Physiology
Medical College of Wisconsin

Dr. Beyer's research focuses on the translational aspects of vascular pathophysiology, with an emphasis on microvascular endothelial (dys)function. The mechanisms underlying disease-induced microvascular dysfunction remain poorly defined and represent a critical gap in knowledge. The Beyer Laboratory employs innovative approaches to understand the clinical relevance of mitochondrial stress responses in the human microcirculation.

Ongoing studies from the lab implicate changes in mitochondrial integrity as a cause of endothelial dysfunction in patients with coronary artery disease (CAD), or atherosclerosis. These findings have led to a new line of investigation aimed at understanding how cancer and anti-cancer therapies—including chemotherapy and molecular therapies—damage the microcirculation and increase the risk of major adverse cardiovascular events (MACE) in cancer survivors.

As part of an integrated group of investigators, the Beyer Lab is a recognized leader in the study of the human microcirculation. Using translational approaches, the team defines physiological and molecular mechanisms that contribute to the development and progression of cardiovascular disease (CVD). Their groundbreaking discoveries have prompted a re-evaluation of how microvascular tone is regulated in patients. The lab is well-positioned, with the necessary expertise and infrastructure, to investigate how microvascular dysfunction contributes to the intersection between cancer and cardiovascular disease. Dr. Beyer brings scientific curiosity, motivation, preparation, and leadership experience to achieve the objectives of this research program.

Session: Mechanisms to Medicine in Mitochondrial Diseases



Lihsia Chen, PhD

Associate Professor of Genetics, Cell Biology & Development
University of Minnesota

Lihsia Chen received her B.A. in Biology at the Johns Hopkins University She earned her PhD in Developmental Biology at The Johns Hopkins University, conducting her PhD thesis work in the Dept. of Embryology at the Carnegie Institute of Washington. She then completed her postdoctoral training at the Howard Hughes Medical Institute at the Duke University School of Medicine before joining the University of Minnesota faculty in the Dept. of Genetics, Cell Biology & Development. Her research program uses C. elegans as a genetic model organism to dissect the functions and mechanisms of action of diverse genes underlying diverse neurodevelopmental disorders, including L1 Syndrome, the Autism and Schizophrenia Spectrum Disorders, and the KCNK9-Imprinting Syndrome.

Session: Functional Modeling and Validation of Disease Variants

---

Jing Dong, PhD

Assistant Professor, Dept of Medicine, Hematology and Oncology
Medical College of Wisconsin

Dr. Jing Dong is an Assistant Professor in the Division of Hematology and Oncology in the Department of Medicine. Trained in molecular epidemiology, Dr. Dong's research focuses on identifying genomic alterations in both nuclear and mitochondrial genomes that contribute to cancer risk and prognosis. She is also deeply engaged in investigating the determinants of cancer disparities and aims to integrate genetic and non-genetic factors to improve cancer risk prediction models.

Session: Mechanisms to Medicine in Mitochondrial Diseases

Jill Fahrner, MD, PhD

Associate Professor, Genetic Medicine & Pediatrics
Director, Epigenetics and Chromatin Clinic
Johns Hopkins School of Medicine

Dr. Jill Fahrner is an Associate Professor in the Departments of Genetic Medicine and Pediatrics at Johns Hopkins University School of Medicine. She is a physician-scientist with a long-standing interest in epigenetic mechanisms of disease and serves as Director of the multidisciplinary Epigenetics and Chromatin Clinic, where her clinical focus is on caring for individuals with epigenetic and chromatin disorders. She has helped to delineate Mendelian disorders of the epigenetic machinery (chromatinopathies) as a distinct group characterized by intellectual disability and abnormal growth. Her laboratory research aims to elucidate disease mechanisms and develop therapies for a subset of these disorders. She has led the field in defining mechanisms of abnormal growth and identified a potential epigenetic therapy for Weaver syndrome. She led an international collaboration to delineate the first neurodevelopmental disorder of the DNA demethylation machinery, Beck-Fahrner Syndrome, and identified a diagnostic genome-wide DNA methylation profile for the disorder. She earned her PhD in Cellular and Molecular Medicine from Johns Hopkins and her MD from the University of North Carolina before completing Pediatrics residency training at Duke. She completed Clinical Genetics residency training and served as Chief Resident in the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins before joining the faculty. She is a long-standing member of the American Society of Human Genetics and serves on the ASHG Program Committee, the editorial board of the American Journal of Medical Genetics Part A, a National Organization for Rare Disorders (NORD) working group, and multiple rare disease medical and scientific advisory boards. She has received numerous awards, including a Johns Hopkins Clinician Scientist Award, a William and Ella Owens Medical Research Foundation Award, the Margaret Ellen Nielsen Award, and a Hartwell Foundation Individual Biomedical Research Award. Her research is supported by the National Institutes of Health, the Maryland Stem Cell Research Fund, and Johns Hopkins University Catalyst and Discovery Awards.

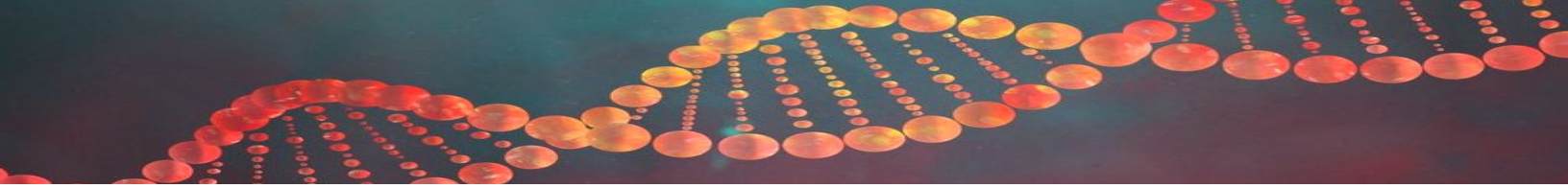
Session: Human Diseases of the Epigenome

Audrey Gasch, PhD

Professor of Medical Genetics & Director, Center for Genomic Science Innovation
University of Wisconsin - Madison

Dr. Gasch's research merges comparative and functional genomics with systems biology and data science to understand fundamental principles in genotype-phenotype relationships. She has a longstanding interest in genetic variation in stress defense systems, in model organisms and across evolution. As Director of the UW-Madison Center for Genomic Science Innovation, she is bringing perspectives and approaches from model-organism systems biology to human genetics and rare diseases.

Session: Functional Modeling and Validation of Disease Variants



György Hajnóczky, MD

Raphael Rubin Endowed Professor
Thomas Jefferson University

Dr. György Hajnóczky is the founding director of the MitoCare Center for Mitochondrial Imaging Research and Diagnostics at Thomas Jefferson University. His group was among the first to visualize mitochondrial energy and ion metabolism in single live cells, has studied the interactions between mitochondria and other organelles, and has initiated or contributed to the development of several novel concepts in mitochondrial biology.

Session: Diagnostic Discovery of Diseases

Laura Lambert, PhD

Associate Consultant, Clinical Genomics
Director, Functional Omics Resource
Mayo Clinic

Laura Lambert Ph.D. is an Associate Consultant I in Physiology and Biomedical Engineering with joint appointments in Clinical Genomics and Biochemistry and Molecular Biology. Dr. Lambert is Director of the Mayo Clinic Functional Omics Resource, a laboratory which designs and executes functional genomic studies across the institution, and co-investigator of the Minnesota Functional Omics Resource. She has extensive experience in the development of precision cell and animal models for the study of rare genetic diseases from her previous roles as Director of the UAB Transgenic and Genetically Engineered Model Systems Core, Co-Lead of the Disease Modeling Unit in the UAB Center for Precision Animal Modeling, and Director of Models and Therapeutics in the UAB Precision Medicine Institute. This includes the application of these models to determine both pathogenicity of genetic changes as well as the investigation of novel therapeutic strategies for addressing patient needs in these ultra-rare conditions. Her research focuses on the use of gene therapy and other n=1 therapeutic approaches (e.g., exon skipping, ribozymes, CRISPRa/CRISPRi, prime editing, base editing) for rare genetic conditions, with a focus on nanoparticle-based delivery platforms. Her research has been funded by multiple NIH grants as well as many foundation-based grants examining personalized medicine approaches, including her current work in n=1 nanoparticle mRNA delivery for the Wolverine Foundation in conjunction with Moderna.

Session: Functional Modeling and Validation of Disease Variants

Joy Lincoln, PhD

Professor, Pediatrics
Director, Cardiovascular Research, Herma Heart Institute
Chief Scientific Officer, Children's WI
Medical College of Wisconsin

Joy Lincoln PhD, FAHA, is a Professor of Pediatrics at the Medical College of Wisconsin (MCW) and Associate Section Chief within the division of Pediatric Cardiology. In addition, Dr. Lincoln holds the positions of Associate Chief Scientific Officer within the Children's Research Institute, and Director of Cardiovascular Research at the Herma Heart Institute at Children's Wisconsin (CW). Dr. Lincoln obtained her BS and PhD in molecular biology at The University of Durham in the UK, and relocated to the US in 2002 as a postdoctoral fellow at Cincinnati Children's Hospital under the mentorship of Dr. Katherine Yutzey, which is where her research interests in congenital heart disease began, and in particular heart valve biology and disease. After her training, Dr. Lincoln joined faculty at The University of Miami, Miller School of Medicine as an Assistant Professor and in parallel with research, led The Office of Post Doctoral Programs. In 2011, Dr. Lincoln was recruited as an Associate Professor to Nationwide Children's Hospital affiliated with The Ohio State University where her work in heart valve disease advanced to the translational level and her interest in mentoring and training continued as she as appointed Associate Director of Faculty Development. In 2019, Dr. Lincoln was recruited to MCW and CW where she now holds administrative research leadership positions while pursuing her passion for research. Dr. Lincoln's program has been continuously funded for 18 years and she has mentored over 130 trainees; many of which have secured positions in biomedical research and academia.

Session: Functional Modeling and Validation of Disease Variants

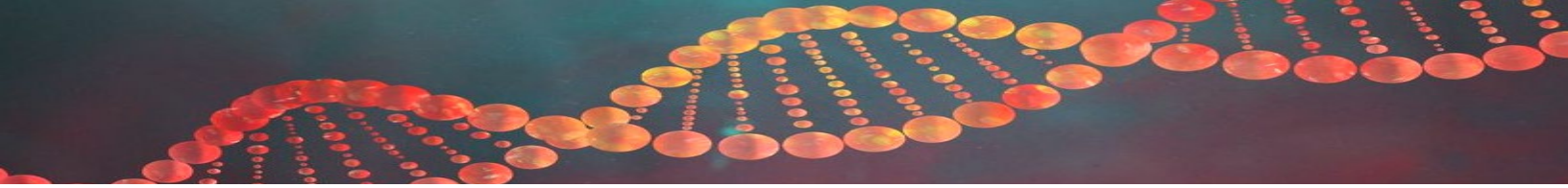
---

Francesc Palau, MD, PhD

CSIC Research Professor St. Joan de Deu
Distinguished Investigator St. Joan de Deu Barcelona Children's Hospital

Dr. Palau is a pediatrician and medical geneticist by training. I am a Research Professor at the Spanish National Research Council and currently a Distinguished Investigator at the Sant Joan de Déu Research Institute, where I co-direct the Neurogenetics and Molecular Medicine research group. I am Chair of the Scientific Advisory Board of the SJD Únicas Center at Barcelona Children's Hospital, where I served as head of the Department of Genetic Medicine. The interests of my research group focus on the study of genetics, pathophysiology, and therapies for rare diseases, especially neuromuscular diseases and genetic neurodevelopmental syndromes.

Session: Mechanisms to Medicine in Mitochondrial Disease



Filippo Pinto e Vairo, MD, PhD

Associate Professor of Medical Genetics
Medical Director, Program for Rare and Undiagnosed Diseases (PRaUD)
Mayo Clinic

Dr. Pinto e Vairo is the Medical Director of the Program for Rare and Undiagnosed Diseases (PRaUD) in the Center for Individualized Medicine, which aims to transform clinical practice for patients. The program is establishing genomic clinical services for patients with rare diseases in close collaboration with divisions and departments throughout Mayo Clinic, improving the triaging of patients with undiagnosed diseases to facilitate better clinical care, and promoting translational research by enhancing discovery opportunities. This work will ultimately increase the number of patients who receive a genetic diagnosis and improve their clinical management and treatment.

Session: Diagnostic Discovery of Diseases

Christopher Pin, PhD

Professor, Department. of Physiology & Pharmacology
Distinguished Scientist, Verspeeten Family Cancer Centre, London Health Sciences
Purdue University

Dr. Christopher Pin's laboratory investigates the events that promote differentiation and function of exocrine pancreatic cells (acinar cells) and how alterations in these processes may initiate or drive the progression of pancreatitis and pancreatic ductal adenocarcinoma (PDAC) using preclinical models and patient samples. His laboratory has generated and characterized numerous genetically altered mouse lines to examine the biological and pathological significance of transcriptional and epigenetic mediators involved in the reprogramming of acinar cells in response to chronic stress.

Dr. Pin's team identified targeted silencing of genes essential for pancreatic cell maturation following injury and recently established a living biobank of organoids derived from pancreatic cancer patients. His laboratory has published more than 60 research articles, including seminal studies identifying new roles for ATF3, EZH2, and ATRX in promoting acinar cell de-differentiation and the early stages of pancreatic cancer.

His research has been funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council, the Cancer Research Society, and the Canadian Cancer Society. Over the past 25 years, Dr. Pin has directly supervised more than 100 trainees. He is currently a Professor at the University of Western Ontario in the Departments of Physiology and Pharmacology, Pediatrics, and Oncology, and a Distinguished Scientist at the Verspeeten Family Cancer Center within the London Health Sciences Centre. He also serves on the executive committee as the lead translational scientist for the Baker Centre for Pancreatic Cancer Research.

Session: Human Diseases of the Epigenome

Aoy Tomita-Mitchell, PhD

Professor, Department of Surgery and Biomedical Engineering
Medical College of Wisconsin

Aoy Tomita-Mitchell, PhD, is a Professor at the Medical College of Wisconsin (MCW) in the Department of Surgery, Division of Congenital Heart Surgery and Department of Biomedical Engineering (BME). Aoy received her B.S. (Mechanical Engineering) and her Ph.D. (Biological Engineering) from the Massachusetts Institute of Technology and completed a post-doctoral fellowship at the Children's Hospital of Philadelphia in Dr. Elizabeth Goldmuntz' lab. She oversees a translational research laboratory focused on investigations of human genetic variation in congenital heart disease (CHD). Her lab demonstrated that rare, predicted damaging genetic variants in the alpha myosin heavy chain (MYH6) gene are associated with hypoplastic left heart syndrome (HLHS), a complex and severe single ventricle malformation. The Mitchell research team has also been working in the arena of cell-free DNA (cfDNA) for many years. After leading scientific development of a non-invasive test to identify fetal cfDNA abnormalities through maternal plasma analysis, the team became interested in the use of cfDNA technology to monitor both heart transplant patients and lung transplant patients for rejection. More recently the team has been measuring cfDNA levels in a range of diseases including in patients undergoing pediatric cardiac surgery.

Session: Diagnostic Discovery of Diseases

Bryn Webb, MD, FACMG

Associate Professor in the Division of Genetics and Metabolism
University of Wisconsin-Madison

Dr. Bryn Webb is an Associate Professor in the Department of Pediatrics, Division of Genetics and Metabolism, at the University of Wisconsin School of Medicine and Public Health. She is a board-certified clinical geneticist, clinical molecular geneticist, and pediatrician, and currently serves as Director of the University of Wisconsin Undiagnosed Disease Program. Dr. Webb has extensive experience in the analysis of short-read and long-read genome sequencing, transcriptomics, metabolomics, and optical genome mapping. She has led investigations identifying novel ultra-rare genetic conditions and has collaborated on numerous additional gene discoveries. Her research laboratory uses stem cell-derived neuronal models and mouse models to investigate the pathophysiology of rare genetic disorders. In addition to her research and clinical work, Dr. Webb is a dedicated advocate for individuals with rare diseases, regularly meeting with Wisconsin's U.S. Senators and Representatives to advance rare disease policy. She also serves as a Section Editor for Genetics in Medicine and is on the Board of Directors of the Moebius Syndrome Foundation.

Session: Diagnostic Discovery of Diseases

Rosanna Weksberg, MD, PhD
Professor of Genetics
Hospital for Sick Children & University of Toronto

Dr. Rosanna Weksberg is a Professor of Pediatrics and Genetics at the Hospital for Sick Children and the University of Toronto. Research in her laboratory focuses on elucidating the role of epigenetics in human disease. In particular, her team explores the impact of genetic and environmental factors on genome-wide epigenetic variation and its role in a variety of human genetic disorders, including neurodevelopmental syndromes, autism, and epilepsy.

In recent years, Dr. Weksberg's group has dedicated considerable effort to defining optimal experimental systems for identifying epigenetic alterations associated with human disease. Their work has included evaluations of multiple cell types, genome-wide microarray platforms, bioinformatics tools, and, most recently, long-read sequencing technologies.

Session: Human Diseases of the Epigenome

Rare Storytellers®

Claire Bevec

Rare Storyteller

Claire was born with Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis (ARPKD/CHF), underdeveloped lungs, a hole in her heart, and a cleft lip and palate. Doctors said she wouldn't survive. Nineteen years later, she is still here. Over the years, her lungs grew stronger and the hole in her heart closed. Her kidneys continued to fail with hundreds of cysts growing, and at nine years old she received a lifesaving kidney transplant. She grew up going to doctors' appointments instead of the park and camping out in the ER instead of in her backyard. However, she wouldn't change it for the world. It's made her who she is. Instead of harboring anger, she has learned to tell her story. As a Rare Storyteller for Harmony 4 Hope, she advocates for others like her by talking to medical professionals and students about recognizing the effects of rare disease on individuals and their families. Claire also meets with legislators to advocate for the healthcare needs of children and hopes to inspire others to not let their suffering define their personhood.

In addition to being a Rare Storyteller, Claire also writes a regular column for Harmony 4 Hope called Claire 4 Rare, featuring people with rare diseases and sharing their stories with you. She hopes to bring positivity and inspiration into your lives through her words and through these stories of pain, suffering, resilience, and ultimately, triumph.

Taylor Schalk

Rare Storyteller

Taylor Schalk lives with several chronic health conditions, including Superior Mesenteric Artery (SMA) compression syndrome, Postural Orthostatic Tachycardia Syndrome (POTS), and Cyclic Vomiting Syndrome, among others. Her rare disease journey began at age 12 in pediatric care, and now at 26, she continues to navigate the complexities of adult medicine and rare disease.

Inspired by her personal experiences, Taylor became a nurse and is passionate about bringing compassion and understanding to her work in healthcare. She is grateful for the opportunity to share her story—both as a patient and a healthcare professional—and to advocate for others living with rare and chronic illnesses. Taylor credits her advocacy journey with connecting her to incredible people, including her friend and fellow storyteller, Claire.

Kerry Morgan Hughes, M.Ed.

Harmony 4 Hope, Founder and President,
Rare Disease Ambassador, Mellowes Center at Medical College of Wisconsin

Kerry combines her passion for working with children and love for music to shine the spotlight on Rare Diseases. The goal is twofold: to fuel research for countless orphan diseases from which patients suffer due to the lack of funding and to use the power of music and storytelling to educate on this lesser-known cause which impacts millions of people worldwide.

Kerry is an alumnus of Marquette University where her philanthropic work had its beginnings. An accomplished educator holding a master's degree in reading instruction, Kerry continues to pursue her love of educating through Rare Storytellers®, the flagship program of Harmony 4 Hope that she created.

Kerry and her 5-year-old Golden Retriever, Walter, are members of the Animal Assisted Therapy Team at their local hospital, visiting patients and staff on a regular basis. They also volunteer together at a local elementary school where Kerry and Walter have created a close bond with many special needs students. Walter is a registered therapy dog through the nationally recognized Alliance of Therapy Dogs. When Kerry is not working, she enjoys spending quality time with her family, traveling, walking, live music, Pilates, and gardening.

Michael Muriello, MD

Assistant Professor of Pediatrics, Division of Genetics,
Medical College of Wisconsin
Medical Guest

Michael Muriello, MD, is an Assistant Professor at the Medical College of Wisconsin in clinical genetics within the Department of Pediatrics. He completed his medical training at Rush Medical College and a residency in Internal Medicine and Pediatrics at Rush University Medical Center, followed by a fellowship in Medical Genetics at Johns Hopkins University. His research focused on investigation of genomic data to find the molecular etiology of rare disorders focusing on complex inheritance patterns and specific diseases such as cardiomyopathies, aortopathies, connective tissue disorders and Tarlov Cysts. He joined the Medical College of Wisconsin in 2018 where he has continued to expand his interest in rare and undiagnosed diseases, connective tissue disorders, adult genetics, general dysmorphology and metabolism. He has particular interest in the role of genomics in the future of medicine including precision medicine, individualized management, and therapies.

Trapper Schoepp

Harmony4Hope Musical Ambassador
Milwaukee Songwriter and Performer

"What's most important to me is to be a link in the chain of folk singers before and after my time," Trapper Schoepp says in light of his fifth album, *Siren Songs.* Recorded at Johnny Cash's Cash Cabin in Hendersonville, TN, Trapper continues down the trail trod by his musical heroes. In 2019, the Milwaukee singer-songwriter published a long-lost song with Bob Dylan called "On, Wisconsin" – making him the youngest musician to share a co-writing credit with the Nobel Prize laureate. The song led to a #1 trending article in Rolling Stone and over a hundred tour dates worldwide.

In fall 2025, Trapper will release his rawest work yet titled *Osborne,* which traces his path through addiction, recovery and chronic pain brought on by BMX accidents in his youth. *Osborne* lends its name from the unit Trapper was in at a Minnesota rehab facility and is also a nod to the songwriter's muse Ozzy, who attended the same facility.

Steve Scaffidi

Radio Host for 620WTMJ
Moderator

Steve Scaffidi is a recognized media personality and community leader deeply rooted in Milwaukee. As the host of WTMJ620's "Point Taken," Steve blends his strong communication skills and interview experience to connect with a wide range of listeners. Throughout his radio career, he has cultivated an inclusive atmosphere, welcoming divergent viewpoints and engaging guests from across the spectrum, making his show a mainstay for meaningful conversation within the community.

Steve's career demonstrates a longstanding dedication to communication, with 17 years at The Nielsen Company and ownership of Marketpoint Media, a Milwaukee-based marketing firm. His experiences outside broadcasting are equally notable; he has initiated and led impactful community projects such as Oak Creek Cares and the Mayor's Fitness & Weight Loss Challenge, both aimed at improving wellbeing and city engagement. His local ties are evident in his deep involvement and advocacy for Milwaukee and Oak Creek, and his passion for building connections remains a hallmark of his work. Steve embodies the spirit of community involvement and civic pride. His ability to foster open dialogue and connect with people from diverse backgrounds underscores his success as a leader and communicator.

Drawing on his wealth of experience, compassion, and readiness to engage with every story shared, Steve joins us as the Rare Storyteller discussion moderator for his third consecutive year.

PANEL MODERATORS

Xiaowu Gai, PhD

Linda T. and John A. Mellowes Endowed Chair in Systems Biology
Professor, Pediatrics; Division Chief, Bioinformatics and Quantitative Child Health
Director, Child Health Bioinformatics
Associate Director, Mellowes Center for Genomic Sciences and Precision Medicine
Medical College of Wisconsin

Dr. Xiaowu Gai is a genomicist and bioinformatician whose research focuses on human genetic variation in congenital disorders and pediatric cancers. He has contributed to the discovery of many disease genes including *NMNAT1* for Leber congenital amaurosis and *FBXL4* for mitochondrial encephalomyopathy. Since 2012, he has co-led the International Mitochondrial Disease Sequence Resource (MSeqDR) Consortium and serves as co-chair of the ClinGen Mitochondrial Disease Variant and Gene Curation Expert Panels. Before joining the Medical College of Wisconsin in 2024 as Professor of Pediatrics, Division Chief of Bioinformatics and Quantitative Child Health, and Director of Child Health Bioinformatics, Dr. Gai was Director of Bioinformatics at the Center for Personalized Medicine, Children's Hospital Los Angeles. There, he led and co-led the development of many genomics-based diagnostic tests, including OncoKids® for pediatric cancers, a pan-cancer liquid biopsy assay LB4Kids, and clinical whole genome/exome sequencing for rare genetic disorders. He is a strong advocate for advancing genomic medicine in clinical care.

Session: Mechanisms to Medicine in Mitochondrial Diseases

Gwen Lomberk, PhD

Joel and Arlene Lee Chair in Pancreatic Cancer Research
Chief, Division of Research, Dept. of Surgery
Professor of Surgery and Pharmacology & Toxicology
Director, Precision Medicine Education (PM ED) Program, Institute of Health & Humanity
Medical College of Wisconsin

Gwen Lomberk, PhD is Professor and the Joel and Arlene Lee Chair in Pancreatic Cancer Research in the Department of Surgery with a joint appointment in the Department of Pharmacology and Toxicology at the Medical College of Wisconsin (MCW). She also serves as the Chief of the Division of Research for the Department of Surgery and Director of the Precision Medicine Education (PM Ed) Program for the Institute for Health & Humanity. She received her undergraduate degree in Biochemistry from Boston College and her PhD in Tumor Biology at Mayo Clinic Graduate School of Biomedical Sciences. Prior to joining MCW in 2017, she was on faculty at the Mayo Clinic in the Division of Gastroenterology and Hepatology, Department of Medicine. Her research focuses on epigenomics and nuclear structure in pancreatic cancer, as well as developing novel therapeutic strategies that can help fight this dismal disease.

Session: Functional Modeling and Validation of Disease Variants

Raul Urrutia, MD

Director, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
Warren P. Knowles Chair of Genomics and Precision Medicine
Professor of Surgery, Biochemistry, and Physiology
Medical College of Wisconsin

Dr. Raúl Urrutia is an internationally recognized leader in epigenomics whose research has transformed understanding of how the epigenome regulates gene expression and contributes to human disease. His pioneering work has revealed how histone modification, DNA methylation, and chromatin remodeling drive cancer development and influence precision medicine.

Dr. Urrutia founded and led one of the nation's first cancer epigenetics programs at the Mayo Clinic, where his studies defined how histone deacetylases (HDACs) silence gene promoters through sequence-specific recruitment of SIN3A-containing complexes. His discoveries further demonstrated how histone acetyltransferases and methyltransferases coordinate to shape chromatin structure, establishing fundamental principles of epigenetic regulation in cancer.

Through his extensive publications, Dr. Urrutia has advanced understanding of the "epigenetic code" and its role in pancreatic cancer, diabetes, and gastrointestinal disease. His research on Krüppel-like transcription factors (KLFs) and HP1-mediated chromatin subcodes continues to guide the field's exploration of gene control. Active in national and international scientific societies, he remains a leading voice in efforts to translate epigenomic discovery into new insights for precision medicine.

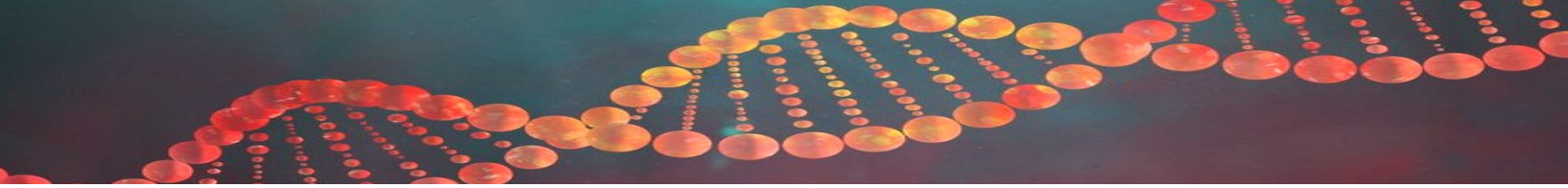
Session: Human Diseases of the Epigenome

Michael T. Zimmermann, PhD

Director, Computational Structural Genomics Unit, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
Associate Professor, Data Science Institute
Medical College of Wisconsin

Dr. Zimmermann and his collaborative team is transforming genomic medicine by pioneering a shift from static, sequence-based annotation to dynamic, mechanistic interpretation of genetic variation. His primary research focus applies structural bioinformatics and computational biology to power next-generation genomic data interpretation, a crucial step because most genetic variants, particularly in cancer and rare diseases, are medically uninterpreted. This lack of interpretation often prolongs the lengthy, costly, and emotionally taxing diagnostic odyssey for patients and families. To address this gap, his work reveals how DNA changes affect proteins, complexes, and thereby how they cause disease, bridging atomic-level insights with clinical genetics. This approach, termed Computational Structural Genomics (CSG), is grounded in a paradigm of mechanism-based computational modeling at atomic resolution. Evaluating how individual variants alter protein structure, dynamics, and function, linked with higher-order modeling of protein complexes, the team simulates how local changes reverberate to cellular machinery. Integrative modeling drives innovative genomic solutions, enhancing diagnostic clarity and empower development towards targeted treatments.

Session: Diagnostic Discovery of Diseases



Poster Sessions: Day 1

Last Name	First Name	Title / Role	Abstract Title
Adobor	Akorfa	Medical Student	Racial and Ethnic Disparities in Melanoma Stage at Diagnosis: A Real-World Data Analysis
Arneson	Ashlyn	Genetic Counseling Student	Genetic Testing Uptake in Monogenic Familial Hypercholesterolemia and its Implications on Clinical Outcomes
Arsang-Jang	Shahram	Postdoctoral Fellow	Effects of Donor and Recipient Mitochondrial DNA Variants on Graft-Versus-Host Disease Onset in MDS Patients After Allogeneic hematopoietic stem cell transplantation
Dong	Xiaowei	PhD Student	Tissue-Specific Co-Expression Patterns of BAF Complex Genes Across Human Endocrine and Non-Endocrine Tissues
Fogarty	Rebekah	Bioinformatics Analyst I	AVATAR – Advancing Variant Analysis through Translational Assessment and Representation
Haque	Neshatul	Postdoctoral Fellow	Unraveling Genetic and Epigenetic Dynamics: Molecular Insights into SMARCA4-Mediated Chromatin Remodeling in Disease
Hughes	Kerry	Rare Disease Ambassador	Improving the Sense of Healing In Genomic Diseases and Cancer Through Narrative Medicine and Music
Mathison	Angela	Associate Professor	Mapping Epigenetic and Transcriptomic Changes in Gender-Affirming Testosterone-Treated Breast Tissue
Njoya	Kimani	Graduate student	Natural history of SPP1 Signaling in NF1 Tumor Progression
Reis	Linda	Program Manager II	Exploring the role of CDH2 in human disease through phenotypic and variant analyses
Tschannen	Mike	R&D Scientist	Leveraging Oxford Nanopore Technologies for Diverse Sequencing Applications at the Mellowes Center ‘Omics Core
Wagenknecht	Jessica	Bioinformatics Analyst II	Structural Dynamics of KRAS Walker B Variants Reveal Diverse Mechanisms of Oncogenic and RASopathy-Associated Mutations
Wendt Andrae	Jaime	Project Manager	Advancing Tissue and Immune Profiling with 10x Genomics Visium HD, Single-Cell RNA Sequencing, and CITE-seq at the Mellowes Center ‘Omics Core
Zimmermann	Michael	Associate Professor	Unlocking Disease Mechanisms: Systems and Structural Genomics in Epigenetic Disorders

Poster Sessions: Day 2

Last Name	First Name	Title / Role	Abstract Title
Arneson	Ashlyn	Genetic Counseling Student	Genetic Testing Uptake in Monogenic Familial Hypercholesterolemia and its Implications on Clinical Outcomes
Bursch	Karina	MD/PhD Graduate Student	Polybromo-1 bromodomain missense variants associated with clear cell renal cell carcinoma exhibit variable biochemical fitness
Butler	Shawna	Post Baccalaureate Research Fellow	Epigenetic Regulation of DNA Damage Response Domains in Pancreatic Cancer
Dzikowski	Madeline	Graduate Student	Dual Inhibition of PRMT5 and CHK1 Drives Cell Cycle Arrest, Transcriptional Reprogramming, and Apoptosis in Pancreatic Ductal Adenocarcinoma
Emosivbe	**Miracle**	**PhD Graduate Student**	**New insights into functional responses of CXCR4 WHIM mutants**
Enkhtuul	Byamba	Graduate Student	The Ankyrin Domain of G9a/GLP as a Mechanistic Hub in Rare Disease and Cancer
Fischer	**Megan**	**Graduate Student**	**Modeling and functional dissection of the human 8q21.11 deletion syndrome in zebrafish**
Freestone	**Justin**	**Graduate Research Assistant**	**Evaluation of MAB21L1 variants associated with human ocular disorders**
LeClaire	Michael	Graduate Student	BRD4 Missense Variants in Cornelia de Lange Syndrome Negatively Impact the Stability and Functionality of Bromodomains in a Disproportionate Manner
Parveen	Sana	Postdoctoral Fellow	Exploring epigenetic control of immunogenicity in small cell lung cancer through multi-omics analyses
Pollin	**Gareth**	**Postdoctoral Fellow**	**Decoding KRAS Mutation-Specific Nuclear Reorganization in PDAC Through Chromatin Disruption and DNA Damage Signaling That Drive Variant-Specific Malignancy**
Tanwar	Riya	PURE Student	PRMT5 Highlights Noncanonical Functions of Chromatin-Modifying Enzymes in Cytoplasmic Stress Responses
Urrutia	Raul	Director	Evolutionary Constraints, Isoform Conservation, and Cancer-Associated Mutations in MEP50
VanderPloeg	Emily	Research Technician I	Zebrafish Avatars of Human Sorsby Fundus Dystrophy
Wu	Jiawei	Postdoctoral Fellow	Leveraging Vector Embeddings for Rapid and Accurate Pathogenicity Prediction of Genetic Variants
Yu	**Duo**	**Assistant Professor**	**Bayesian Counterfactual Machine Learning Individualizes Radiation Modality Selection to Mitigate Immunosuppression**

SPECIAL THANKS TO OUR SPONSOR!

MCW MEDICAL SCHOOL

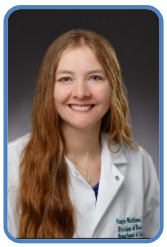
ADVANCING A HEALTHIER WISCONSIN ENDOWMENT

2025 SYMPOSIUM PLANNING COMMITTEE

Jenni Koch, MBA
Center Administrative Manager
Mellowes Center for Genomic Sciences and Precision Medicine

Chris Bauer, MS
Research Grants Coordinator II
Mellowes Center for Genomic Sciences and Precision Medicine

Joe Camp, MBA
Business Manager Sr.
Mellowes Center for Genomic Sciences and Precision Medicine



Angela J. Mathison, PhD
Associate Director for Operations and Academic Relationships
Director of 'Omics Research & Development, Mellowes Center for Genomic Sciences & Precision Medicine
Associate Prof., Department of Surgery | Division of Research

Full Abstract List

Day 1	
First Author	Akorfa Adobor
Co-Author(s)	Natalie Norton; Ankit Choudhury; Karolyn Wanat
Title	Racial and Ethnic Disparities in Melanoma Stage at Diagnosis: A Real-World Data Analysis
Abstract	Background Black, Hispanic, and Asian populations have a lower incidence of cutaneous melanoma (CM), a potentially lethal skin cancer, compared to non-Hispanic White populations, a difference attributed primarily to the photoprotective properties of melanin. This lower perceived risk can decrease the clinical index of suspicion among both patients and clinicians, creating a concerning paradox. Despite the lower incidence of CM, patients from marginalized groups who develop melanoma are often diagnosed at a more advanced stage. This disparity in staging contributes significantly to increased mortality rates. However, large-scale, multi-institutional data are needed to thoroughly characterize this problem, representing a critical gap in the literature. Objective To evaluate the feasibility of using a large, federated health research network (TriNetX) to compare the stage at diagnosis for cutaneous melanoma between non-Hispanic White patients and patients from historically marginalized racial and ethnic groups. Methods A feasibility study will be conducted using aggregate, de-identified patient data. The study will identify cohorts of patients with a new diagnosis of cutaneous melanoma (ICD-10 C43.x) between 2010–2025, stratified by race and ethnicity. The primary metric for comparison will be the stage at initial diagnosis, analyzing variables such as Breslow depth, ulceration status, and the presence of nodal or distant metastasis. Feasibility will be determined by the ability to identify a sufficient number of melanoma cases within marginalized population cohorts and the completeness of associated pathologic staging data. Conclusion This research will assess whether real-world data is a viable tool for understanding the drivers of disparate outcomes in cutaneous melanoma. A successful feasibility analysis will provide a strong foundation for future studies aimed at identifying barriers to early detection and will underscore the urgent need for tailored public awareness campaigns and clinician education to help close the survival gap for this deadly cancer.

Day 1	
First Author	Ashlyn Arneson
Co-Author(s)	Mayya Safarova, MD, PhD; Rachel Sundstrom, MS, CGC; Alison La Pean Kirschner, MS, CGC
Title	Genetic Testing Uptake in Monogenic Familial Hypercholesterolemia and its Implications on Clinical Outcomes
Abstract	Background and Significance: Familial hypercholesterolemia (FH) is a prevalent (1:250-1:310) yet underdiagnosed (~10%) inherited disorder that causes significant risk for premature cardiovascular disease due to lifelong elevation of plasma low-density lipoprotein cholesterol (LDL-C). Molecular testing for FH, often facilitated by a genetic counselor, is considered the gold standard to initiate targeted lipid lowering therapy and cascade testing of at-risk relatives. At present, it is unknown how current policies and procedures within the Froedtert Healthcare System impact the uptake of genetic counseling and testing, medical management, and health outcomes for patients with FH. The present study aims to identify influences on diagnosis and management of patients with FH to guide interventions to address underdiagnosis and burden of disease for patients with FH in the Froedtert Health System. Purpose: We aim to identify appropriateness of genetic counseling referrals, estimate the uptake of appointment scheduling and genetic testing, and define influences on patient uptake or refusal of genetic counseling and testing. In the formed cohort, we will assess the impact of a genetic diagnosis of FH on medical management and health outcomes, comparing these outcomes with individuals diagnosed with clinical FH who did not undergo genetic testing or who tested negative. Methods: Leveraging electronic health records (EHR) data and cohort collection tools – including EMERSE, Epic Reporting Workbench, and i2b2 – we will explore trends in referrals, scheduled appointments, and genetic test orders/results to identify facilitators and barriers for patients to access genetic testing. For patients with available genetic test results, we will compare longitudinal management and outcomes to evaluate impact of a genetic test result. Additionally, we will identify patients with potential clinical FH – defined as two occurrences of LDL-C ≥190mg/dL – to compare to the referral cohort to identify influences on access to genetic counseling for FH. Results: We queried a database of 1.4 million patients with available lab results and identified 5,522 adult patients with potential clinical FH (prevalence 0.4%, 1:250). Our initial analyses suggest a total of 292 appointments in the Adult Genetics Clinic from January 2011 to September 2025, indicating only 5.3% of potential clinical FH patients have had a genetics consultation. Ongoing evaluation of the appointment cohort and review of genetics referrals will aim to describe trends within these cohorts influencing this low uptake of genetic counseling. Conclusions: This work will further increase awareness and identify gaps and barriers to the adoption and use of genetic testing for patients with FH, affecting patients, clinicians, and healthcare systems. Existing barriers result in underdiagnosis and undertreatment of FH, despite expert consensus supporting testing for definitive diagnosis, risk stratification, and effective cascade screening.

Day 1	
First Author	Shahram Arsang-Jang
Co-Author(s)	Paul Auer; Wael Saber; Raul Urrutia; Jing Dong
Title	Effects of Donor and Recipient Mitochondrial DNA Variants on Graft-Versus-Host Disease Onset in MDS Patients After Allogeneic hematopoietic stem cell transplantation
Abstract	Background: Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a potentially curative therapy for hematologic malignancies and immune disorders, yet its success is limited by graft-versus-host disease (GvHD). Despite therapeutic advances, nearly half of patients still develop GvHD, and robust biomarkers for risk prediction and early diagnosis are lacking. Mitochondrial dysfunction and the release of mitochondrial DNA (mtDNA) have been implicated in immune activation. We previously showed that mtDNA variants in genes such as MT-CYB and MT-ND5 were prognostic for post-transplant outcomes in myelodysplastic syndromes (MDS), but the role of mtDNA variation in GvHD pathogenesis remains largely unexamined. Here, we investigated whether donor and recipient mtDNA variants influence GvHD risk and outcomes. Methods: We analyzed 494 European ancestry donor–recipient pairs with MDS who underwent first allo-HCT between 2014 and 2018 through the CIBMTR repository. Whole-genome sequencing of pre-transplant blood samples was performed, achieving high-depth mtDNA coverage (mean 14,596×), and variants were identified with the MToolBox pipeline. Associations between mtDNA variants and acute or chronic GvHD were assessed using Fine-Gray competing risk models, adjusted for clinical covariates and 10 principal components derived from genomic data. Gene-level effects were tested with SKAT-O. Bonferroni correction was applied for multiple testing. Results: The mean age of MDS recipients was 66 years, 63.9% were male, 71.4% had 8/8 HLA-matched unrelated donors, and median follow-up time was 14.2 months (IQR 6.9–35.3). Adjusted analyses showed associations of MT-ND5 (m.13965T>C, m.13830T>C) with aGvHD24, MT-tRNA (m.14010T>C) and MT-ATP8 (m.8473T>C) with aGvHD34, and MT-ND5 (m.12810A>G) with cGvHD. Gene-based analyses showed significant associations after Bonferroni correction: MT-NDL4 in MDS patients with aGvHD24 (HR = 0.65; 95% CI = 0.46–0.93), and donor MT-CYB (HR = 1.18; 95% CI = 1.02–1.36) and MT-rRNA (HR = 1.14; 95% CI = 1.05–1.25). No mtDNA genes were significantly associated with aGvHD34. For chronic GvHD, donor MT-CO2 (HR = 1.30; 95% CI = 1.02–1.65) and MT-CO3 (HR = 0.75; 95% CI = 0.58–0.96) were significant predictors, while associations in MDS patients were not. Interaction analyses showed reduced risk with concurrent tRNA mutations in both MDS and donors (HR = 0.59; 95% CI = 0.36–0.99), whereas mutations restricted to the MDS group were not significant. Conclusions: Donor and recipient mtDNA variants are significantly associated with acute and chronic GvHD after allo-HCT. Variants in MT-ND4, MT-CYB, MT-CO2, MT-CO3, as well as mt-tRNA and rRNA, were significant predictors of GvHD. Importantly, gene-based interaction analyses showed that evaluating mtDNA variation in both MDS patients and donors provides a more precise view of GvHD risk. These findings highlight the role of mtDNA as a driver of alloimmune activation and support its potential as a biomarker for donor–recipient compatibility and GvHD risk stratification.

Day 2	
First Author	Karina L Bursch
Co-Author(s)	Salomão Dória Jorge; Audrey E. Catlin; Jacob Licklider; Raul A. Urrutia; Brian C. Smith
Title	Polybromo-1 bromodomain missense variants associated with clear cell renal cell carcinoma exhibit variable biochemical fitness
Abstract	The tumor suppressor Polybromo-1 (PBRM1) modulates chromatin accessibility and gene transcription in health and disease. PBRM1 contains six bromodomains that bind acetylated lysine residues on histones and other nuclear proteins. PBRM1 mutations, which often ablate protein expression and tumor suppressor activity, exist in ~40% of clear cell renal cell carcinoma (ccRCC) cases. Loss-of-function PBRM1 mutations correlate with improved patient response to anti-angiogenic agents, a mainstay of ccRCC therapy. However, missense mutations cluster in PBRM1 bromodomains and exist in ~15% of ccRCC cases. These missense mutations generate full-length protein variants with unknown structural and functional features that may impact patient response to anti-angiogenics. In-depth biophysical and cellular studies of all known PBRM1 missense variants are intractable due to the >900 PBRM1 missense variants reported across all cancer types in the Catalogue of Missense Mutations in Cancer database; we hypothesize that computational approaches can fill this void to provide actionable assessments of PBRM1 missense variant impacts in ccRCC and other cancers. Here, we computationally predicted and experimentally tested the impacts of ccRCC-associated missense variants in the second (BD2) and fourth bromodomains (BD4) of PBRM1 on bromodomain biochemical fitness, as assessed by stability, structural integrity, and ligand binding. These impacts were predicted with a multi-tiered genomics analysis pipeline at the levels of protein sequence (2D), structure (3D), and molecular dynamics (4D). Combined predictions from all pipeline levels were used to assign missense variants a fitness score between 0-1, with scores closer to 1 identifying biochemically deleterious missense variants predicted to decrease stability, structural integrity, and ligand binding. We predicted that many ccRCC-associated PBRM1-BD2 and -BD4 missense variants are biochemically deleterious and cluster in the structurally and functionally significant bromodomain core and ligand binding loops. In contrast, PBRM1-BD2- and BD4 missense variants from the general population with no known disease association are predicted to be biochemically neutral and cluster in regions of lower functional importance. We recombinantly purified all reported ccRCC-associated PBRM1-BD2 and -BD4 missense variants to evaluate the concordance between missense variant fitness predictions and specific biophysical parameters. Bromodomain stability and structural integrity were assessed with differential scanning fluorimetry, circular dichroism, and 1H-NMR spectroscopy. Bromodomain ligand binding was quantified with AlphaScreen and electrophoretic mobility shift assays. PBRM1 missense variant 2D/3D/4D integrated fitness scores correlated with measures of acetylated lysine ligand binding, while missense variant 3D and integrated fitness scores correlated with measures of protein thermal stability. Our results demonstrate that computational prediction of PBRM1 missense variant fitness accelerates mechanistic understanding of PBRM1 missense variant function. This knowledge supports future studies correlating specific PBRM1 missense variants with PBRM1 tumor-suppressive functions to inform future ccRCC personalized medicine approaches.

Day 2	
First Author	Shawna Butler
Co-Author(s)	Madeline Dzikowski; Gwen Lomberk
Title	Epigenetic Regulation of DNA Damage Response Domains in Pancreatic Cancer
Abstract	Introduction: Pancreatic cancer, one of the deadliest cancers in the United States, progresses from low-grade Pancreatic Intraepithelial Neoplasia (PanINs) to aggressive Pancreatic Ductal Adenocarcinoma (PDAC) due to genetic and epigenetic changes (1). Among these, the dysregulation of G9a (EHMT2), a lysine methyltransferase that regulates transcription through histone lysine 9 (H3K9) mono- and di-methylation, plays a key role, impacting crucial cellular processes such as proliferation, differentiation, and DNA replication and repair (2). While evidence supports a role for G9a in the ATM DNA damage repair pathway (3), the interaction between G9a and ATM in pancreatic cancer remains unknown. Hypothesis/Objective: My goal is to define how ATM affects G9a function during DNA damage response and repair in pancreatic cancer. I hypothesize that ATM-mediated phosphorylation of G9a is essential for its role in these processes, contributing to chemoresistance. Methods: We used varying cell models to activate the ATM pathway via DNA double-strand break (DSB) induction:U2OS DIvA, a cancer cell line genetically engineered to express a modified AsiSI restriction enzyme molecule to generate a tamoxifen inducible system that creates specific controlled DBS's within the genome, and the pancreatic cell line MIA PaCa-2 and modified G9a and ATM K.O models, which were treated with doxorubicin, a chemotherapeutic agent that induces DSBs. DSBs were induced in the MIA PaCa-2 ATM KO cells for 0-3 hours, and cell lysates were collected to evaluate the ATM DNA damage pathway and its downstream effects. MIA PaCa-2 G9a K.O model were transduced with adenovirus expressing WT (rWT), non-phosphorylatable S525A, or phosphomimetic S525D of G9a for rescue experiments. Treated cells received 3 hours of doxorubicin. Western blots were performed to measure protein levels of the phosphorylated and total forms of ATM, CHK2, and G9a. Results: Upon induction of DSBs, we detected activation of the ATM pathway, evidenced by CHK2 phosphorylation. We also found concurrent phosphorylation of G9a at serine 525, 569, and 579. Cells without ATM (MIA-PaCa-2 ATM KO) showed delayed activation of P-CHK2 and significant reduction in G9a phosphorylation at S525 in response to doxorubicin treatment compared to the same cells with intact ATM (ATM WT). This supports ATM-mediated phosphorylation of S525 of G9a. Initial rescue experiments with WT or S525 mutant G9a in cells without G9a (MIA-PaCa-2 G9a KO) show potential alterations in doxo-induced ATM pathway signaling with the phosphomimetic S525D mutant. These preliminary findings suggest that G9a phosphorylated at S525 may function as a negative feedback regulator of the ATM pathway. Conclusion: Given that many cancers develop resistance through enhanced DNA repair capabilities, understanding the interplay between epigenetic regulation and DNA repair can lead to strategies that prevent or overcome this resistance, enhancing long-term treatment outcomes.

Day 1	
First Author	Xiaowei Dong
Co-Author(s)	Neshatul Haque; Jessica Wagenknecht; Michael T. Zimmermann
Title	Tissue-Specific Co-Expression Patterns of BAF Complex Genes Across Human Endocrine and Non-Endocrine Tissues
Abstract	BRG1/BRM-associated factor (BAF) chromatin remodeling complexes are essential for normal endocrine function and are implicated in various metabolic and developmental disorders. However, the full range of chromatin-based regulatory programs and their molecular configurations in endocrine development remains unclear. In this study, we developed a computational pipeline to analyze bulk RNA-seq data from 45 human tissues and constructed tissue-specific co-expression networks for 30 core BAF complex genes. Using co-expression network analysis and Louvain clustering, we identified co-expression patterns that formed coherent gene communities for each tissue, comprising different combinations of 46 curated BAF subcomplex genes. In metabolically active non-endocrine tissues (kidney, skeletal muscle, vasculature, fibroblasts), we observed strong co-expression with canonical BAF (cBAF) and polybromo-associated BAF (pBAF) gene communities. Central nervous system tissues were dominated by the neuron-specific BAF (nBAF) complex. Endocrine tissues (e.g., thyroid, adrenal) and gastrointestinal epithelia displayed co-expression profiles resembling smooth muscle–like BAF and pBAF complexes, suggesting chromatin programs that integrate hormone secretion with contractile and barrier functions. These patterns show that each tissue exhibits a distinct, non-random combination of BAF subcomplexes, potentially reflecting its functional chromatin state. Our results demonstrate that latent patterns in tissue-specific gene expression profiles may reveal differences in protein complex regulation. The modular deployment of BAF chromatin remodeling complexes appears tailored to the functional demands of each organ. This study lays a foundation for further investigation of epigenetic regulation in endocrine development and pathobiological mechanisms and provides a framework for identifying tissue-specific chromatin remodeling strategies.

Day 2	
First Author	Madeline Dzikowski
Co-Author(s)	Veda Gunia; Guillermo Urrutia; Shawna Butler; Gareth Pollin; Angela Mathison; Raul Urrutia; Gwen Lomberk
Title	Dual Inhibition of PRMT5 and CHK1 Drives Cell Cycle Arrest, Transcriptional Reprogramming, and Apoptosis in Pancreatic Ductal Adenocarcinoma
Abstract	Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related deaths in the United States, with a dismal 5-year survival rate of only 13%. Despite advances in cancer therapies, survival outcomes for PDAC patients have seen only marginal improvements, highlighting an urgent need for innovative therapies. Protein arginine methyltransferase 5 (PRMT5) has emerged as a promising therapeutic target, with ongoing clinical trials for PDAC treatment. Here, we aimed to define the impact of PRMT5 inhibition on DDR signaling and related processes in PDAC, highlighting vulnerabilities to inform novel combination therapies. To achieve this, we employed a comprehensive set of techniques, including immunofluorescence, western blotting, and qPCR for molecular characterization; Incucyte live-cell analysis and clonogenic assays to assess cell growth dynamics in vitro; tumorigenesis assays using xenografts and immunohistochemistry to evaluate in vivo effects; and RNA-seq and ATAC-seq to investigate transcriptomic and chromatin accessibility changes. We found that PRMT5 inhibition in PDAC cells leads to drastically reduced levels of a key mediator of DDR signaling, ATM, suggesting that this effect may impair the ability of PDAC cells to manage genomic stress, exposing potential vulnerabilities. Thus, we hypothesized that combined inhibition of PRMT5 with EPZ015938 and the ATR effector protein, CHK1, with prexasertib, will synergize to inhibit PDAC growth. We tested this combination treatment in vitro in PDAC cells and in vivo via the treatment of xenograft tumors in mice. Using proliferation and clonogenic assays, we found a synergistic decrease in cell growth with a combined inhibition of PRMT5 and CHK1 in L3.6 PDAC cells. This reduced cell growth with the combination treatment was accompanied by increased Caspase 3/7, Annexin V, and overall cell death compared to individual or vehicle control treatment, indicating apoptosis as a cellular mechanism underlying this effect. In subcutaneous xenografts, we found that mice receiving the combined inhibition of PRMT5 and CHK1 had substantial reductions in tumor volume without notable changes in body weight and extended survival compared to those with individual treatments or vehicle control. Lastly, RNA-seq and ATAC-seq analyses in L3.6 cells revealed that the combination treatment disrupts cancer cell survival through coordinated changes in gene expression and chromatin accessibility, targeting pathways involved in DNA integrity and cellular adaptation, thus providing mechanistic insights into its therapeutic efficacy. In conclusion, our findings underscore the role of PRMT5 as a key modulator of DDR via the ATM pathway in PDAC cells and its potential targeting with the ATR-CHK1 pathway in combination as a promising therapeutic strategy for this dismal disease.

Day 2	
First Author	Miracle Emosivbe
Co-Author(s)	Aaren Manz; Joseph Crecelius; Ya Zhou; Adriano Marchese
Title	New insights into functional responses of CXCR4 WHIM mutants
Abstract	WHIM (Warts, Hypogammaglobulinemia, Infections and Myelokathexis) syndrome is a rare congenital combined immunodeficiency disease caused by an autosomal dominant mutation in the encoding region of CXCR4 gene. CXCR4 is a G protein-coupled receptor, and most of the known WHIM mutations disrupt the carboxyl-terminal region of CXCR4 (C-tail). The C-tail is essential for the regulation of CXCR4 signaling, and the disruption of the C-tail in WHIM mutants leads to impaired regulation, which typical requires β-arrestin recruitment and receptor endocytosis. WHIM mutants display reduced β-arrestin recruitment and receptor endocytosis, which leads to impaired receptor desensitization and culminates in enhanced signaling. Although this is the generally accepted mechanistic explanation for WHIM syndrome, recent studies have identified WHIM mutants that do not show impaired canonical receptor regulation. In addition, recent studies have revealed new functions for the C-tail of CXCR4 that remain uncharacterized in WHIM mutants. Therefore, the mechanistic basis for WHIM remains poorly understood, and functional profiling of WHIM mutants is incomplete. The goal of this research is to provide a complete functional profile of WHIM mutants, including a single amino acid substitution mutant (E343K), truncation mutant (R334X) and a frameshift mutant (E345Vfs*12). We first began by studying the ability of these mutants to recruit β-arrestin1 (β-arr1). We observed that recruitment of β-arr1 was impaired with the R334X and E345Vfs*12 mutants, but was preserved by E343K. The preserved recruitment of β-arr1 to E343K deviates from the existing paradigm; therefore, we explored G protein-dependent signaling of these variants by examining agonist-stimulated inhibition of cAMP production. We observed no significant difference in cAMP inhibition by these WHIM mutants when compared with WT CXCR4, which is in contrast to published reports indicating enhanced inhibition of cAMP production of WHIM mutants. To explore this further, we examined direct activation of the heterotrimeric G protein using the PRESTO-Tango BRET assay and found that E345Vfs*12, but not E343K or R334X, showed enhanced G protein coupling. In addition, we examined agonist-stimulated endocytosis of the WHIM mutants since previous studies correlated prolonged residence time of the receptor on the membrane as a hallmark of WHIM mutants. We observed that only E343K undergoes normal endocytosis, but that endocytosis of R334X and E345Vfs*12 was impaired. Our study reveals that β-arrestin recruitment, G protein signaling and/or endocytosis do not fully align with previous reports of the functional responses of WHIM mutants, which suggests that the current paradigm for the mechanistic basis of WHIM syndrome needs revision. A comprehensive functional profiling of WHIM mutants is important to understand the underlying basis of WHIM syndrome.

Day 2	
First Author	Byamba Enkhtuul
Co-Author(s)	Davin Jensen; Young-In Chi; Michael T Zimmermann; Brian Volkman; Brian Smith; Raul Urrutia; Gwen Lomberk
Title	The Ankyrin Domain of G9a/GLP as a Mechanistic Hub in Rare Disease and Cancer
Abstract	Mutations in EHMT1 (GLP), a histone methyltransferase that forms a heterodimeric complex with EHMT2 (G9a), cause Kleefstra syndrome, a rare neurodevelopmental disorder. Many pathogenic variants cluster in the ankyrin domain, a region specialized for protein–protein interactions and recognition of methylated histones. The ankyrin domain is therefore a critical regulatory hub with direct disease relevance. Beyond rare disease, G9a/GLP are dysregulated in cancer, where they mediate H3K9 mono- and di-methylation (H3K9me1/2), transcriptional repression, heterochromatin remodeling, therapeutic resistance, and have been implicated in replication stress. While the G9a/GLP complex relies on multiple accessory proteins for chromatin targeting, one notable partner is LRWD1/ORCA, a chromatin 'reader' that recognizes H3K9me3 and also contributes to DNA replication origin licensing. Through these functions, LRWD1 may coordinate G9a/GLP activity at the interface of chromatin regulation and replication control. While the ankyrin domains of G9a and GLP are known to mediate binding to LRWD1, it remains unclear whether this interaction drives the role of the G9a/GLP complex in replication stress and related disease-associated processes. To address this, we used computational modeling approaches, including molecular docking and dynamics, to examine ankyrin-ORCA interactions and identified candidate binding interfaces. We complemented these studies with in vitro binding assays between recombinant ankyrin domain and full-length LRWD1, confirming direct interaction. To assess functional relevance, we reintroduced ankyrin-domain mutants into G9a-KO cells via adenoviral transduction and evaluated histone methylation (H3K9me1/2/3), total histone H3, and protein levels of ORCA, WIZ, GLP, Cyclin D, SUV39H1, and G9a by Western blot. By integrating computational, biochemical, and functional approaches, we aim to define how ankyrin-LRWD1 interactions shape G9a/GLP activity. Our findings highlight the ankyrin domain as a hub through which these enzymes influence disease-related processes, from rare chromatinopathies to cancer, and establish the ankyrin-LRWD1 interface as a novel therapeutic target.

Day 2	
First Author	Megan Fischer
Co-Author(s)	Samuel Thompson; Ross F Collery; Elena V. Semina
Title	Modeling and functional dissection of the human 8q21.11 deletion syndrome in zebrafish
Abstract	Heterozygous 8q21.11 microdeletions involving ZFHX4 and PEX2 cause variable phenotypes including intellectual disability, facial dysmorphism, skeletal and ocular anomalies. Recessive variants in PEX2 cause Zellweger syndrome with no known carrier phenotype, while intragenic dominant alleles in ZFHX4 have been recently associated with a syndromic neurodevelopmental disorder as well as isolated Peters anomaly. We developed and/or characterized germline zebrafish models of zfhx4- and/or pex2- deficiency with a goal to further dissect their roles in 8q21.11 deletion syndrome. A ZIRC zebrafish line carrying a c.919A>T (p.K307*) nonsense variant in zfhx4 showed no gross embryonic phenotype and no major defects in the facial cartilage. Genotyping of adults showed near-complete lethality of homozygous fish (n=121 [1 -/-, 75 +/-, 45 +/+]; p-value<0.0001); further analysis revealed most homozygous larvae die before 1 month of age (n=30 [2, 17, 11]; p-value=0.0515). Closer examination of embryonic stages revealed a subtle, but consistent, shallow anterior segment at 5 days-post-fertilization that correlated with homozygous genotype. Embryos were sorted and raised by phenotype which allowed for an increase in homozygous survival (n=42 [6, 28, 8]; p-value=0.0882). The 1-month homozygotes showed delayed development while the adult mutants presented with abnormal pigmentation, irregular head shape, and atypical swimming behaviors. Examination of the eyes using optical coherence tomography (n=7) revealed a spectrum of ocular anomalies including a shallow anterior segment and irregularities in the central cornea, and histology (n=1) showed a thin corneal epithelium and stroma. The c.919A>T variant is predicted to lead to loss-of-function (LOF) via nonsense-mediated decay, however semi-quantitative PCR analysis showed stable transcript. The resultant protein is likely to be misfolded due to the early truncation but, if stable, it will produce a short protein with 2 zinc finger domains; alternatively, a downstream methionine may be utilized to encode a protein with 20 zinc fingers and 4 homeodomains. Thus, the c.919A>T variant may lead to a partial or complete LOF or produce a protein with a new deleterious effect. To further investigate zfhx4 LOF as well as a possible phenotypic contribution from pex2, guide RNAs targeting zfhx4 (exon 6/10) and pex2 (exon 2/2) were co-injected. Adult F0 fish displayed abnormal pigmentation similar to the p.K307* adults. Analysis of F1 fish identified gene-specific frameshift alleles as well as a larger genomic deletion affecting both genes. Further characterization of these mutants is underway. Decreased survival of zfhx4 mutants shows an essential role in development, and initial characterization suggests a role of the gene in pigment patterning as well as craniofacial, neuromuscular, and ocular development.

Day 1	
First Author	Rebekah J. Fogarty
Co-Author(s)	Jessica Wagenknecht; Neshatul Haque; Xiaowei Dong; Young-In Chi; Raul Urrutia; Michael T. Zimmermann
Title	AVATAR – Advancing Variant Analysis through Translational Assessment and Representation
Abstract	Minimizing the diagnostic odyssey, a protracted journey through the medical system, for patients with rare diseases remains a critical goal for both researchers and clinicians. Despite advances in genomic technologies, 50-70% of rare disease patients remain genetically undiagnosed after genetic testing. In our experience, this diagnostic gap is often due to difficulties inherent with ultra-rare genetic variation and the emphasis on population-genetics to help guide inference. Most ultra-rare and one-of-a-kind (n=1) variants remain poorly characterized and lacking clinical interpretation. Incredibly, one-of-a-kind variants are 48% of those observed in medically relevant genes from population-genetics screening. This demonstrates the pressing emergent need for improved interpretative tools to further characterize variant impacts. Herein, we present a multi-tier evaluation process of generating an AVATAR, which serves as an embodiment of the individual patient's biochemical and cellular physiology, focused on a specific gene or gene product. Through our efforts, we have developed a standardizable framework for obtaining diverse, multi-disciplinary information to project biological context and mechanistic insights onto the variant of interest. In essence, it is prerequisite and typically cryptic to identify what needs to be modeled and with context-dependent interpretation, using biophysics and biochemistry to interpret a human genetic variation. To generate the AVATAR, we collect a wide array of data to develop a model at gene, protein, complex, cell, and tissue levels. Our goal is to make this an automated and intelligent integration process. We then apply Deep Variant Phenotyping (DVP) leveraging computational structural genomics to generate new data within the most appropriate context. AVATAR assembly serves as a systems biology-based approach toward hypothesis generation, which informs our structural genomics workflow and experimental design. The AVATAR provides a system-wide context for us to infer the mechanistic details of downstream impact by genetic variants, both on a biochemical and cellular level. Through employing this approach, we enable reclassification of genetic variants according to the most likely underlying and pathobiologically relevant molecular mechanism. Once variant impacts are mechanistically characterized, the findings may be applied towards informing individualized treatment and precision medicine approaches to improve patient outcomes. Thus, we anticipate that application of AVATAR processes will shorten diagnostic odysseys for rare disease patients.

Day 2	
First Author	Justin Freestone
Co-Author(s)	Elena V. Semina
Title	Evaluation of MAB21L1 variants associated with human ocular disorders
Abstract	MAB21L1 and MAB21l2 genes encode proteins of unknown function and have been implicated in congenital ocular disorders in humans. Autosomal dominant variants in MAB21L1 (missense alleles affecting Arginine51 or Phenylalanine52) have been linked to variable phenotypes including aniridia and microphthalmia. Autosomal recessive variants in MAB21L1 are associated with another ocular phenotype, Cerebello-oculo-craniofacial-genital syndrome (COFG syndrome) in which the primary ocular findings include corneal opacity. These variants are primarily premature truncating variants with one missense variant affecting Glutamine233 also reported. Due to the two different inheritance patterns observed between the phenotypes, it is hypothesized that the AD missense variants have a gain-of-function effect on the protein, whereas the AR mutations cause a loss-of-function. To investigate the effects of these variants on MAB21L1, FLAG-tagged MAB21L1 wild-type and variant expression constructs, MAB21L1 p.Cys246Leu fs*18, MAB21L1 p.Glu233Pro, MAB21L1 p.Tyr280*, and MAB21L2 p.Tyr280*, were transfected into human lens epithelial B3 (HLE-B3) cells to evaluate their subcellular localization. While wild-type MAB21L1 demonstrated primarily nuclear localization, each of the 4 AR variant proteins displayed mislocalization to the peri-nuclear region of the cell. Co-staining with additional cellular markers is being performed and will be presented. The mislocalization of these mutant proteins suggests that autosomal recessive variants in MAB21L1 are unable to perform their wildtype function within the nucleus consistent with their predicted loss-of-function effects. Additionally, studies of endogenous MAB21L1/MAB21L2 distribution in untransfected HLE-B3 cells utilizing a MAB21L1/MAB21L2 specific antibody detected nucleolar staining of these proteins. An in-silico prediction tool was utilized to identify a potential MAB21L1 nuclear localization signal and we are in the process of creating a construct that is missing this portion of the protein and testing its cellular localization.

Day 1	
First Author	Neshatul Haque
Co-Author(s)	Jessica Wagenknecht; Raul Urrutia; Michael T. Zimmermann
Title	Unraveling Genetic and Epigenetic Dynamics: Molecular Insights into SMARCA4-Mediated Chromatin Remodeling in Disease
Abstract	The BAF (BRG1/BRM-associated factor) complex, a pivotal chromatin remodeler, regulates gene expression by altering nucleosome positioning, playing a critical role in cellular differentiation and development. Mutations in BAF complex genes, particularly SMARCA4, are implicated in various diseases, including intellectual disability syndromes like Coffin-Siris syndrome and cancers such as rhabdoid tumors. Understanding the molecular mechanisms underlying these genetic variations is essential for elucidating disease pathogenesis and developing targeted therapies. To gain insights into the functional dynamics of SMARCA4, a key ATPase subunit of the BAF complex, we performed all-atom molecular dynamics simulations (MDS) of the SMARCA4 helicase domain in complex with a nucleosome in three states: ATP-bound, ADP-bound, and APO (nucleotide-free) forms. Simulations were conducted for 400 ns in triplicate, providing robust statistical analysis of conformational dynamics. Our results reveal significant conformational differences, with the ATP-bound state differing from the ADP-bound state by 40% and from the APO state by 60%, as quantified by root mean square inner product (RMSIP) analysis. Principal component analysis (PCA) of the trajectories indicates that the ADP-bound state exhibits a hybrid conformational profile, partially resembling both ATP-bound and APO states, suggesting it acts as a transitory intermediate during the ATP hydrolysis cycle. This cycle involves ATP hydrolysis, transitory stabilization in the ADP-bound state, and subsequent ADP ejection to transition to the APO state. Notably, we observed substantial rearrangements in residues critical for nucleotide binding and DNA interaction, which are essential for the mechanical function of SMARCA4 as a chromatin remodeling motor. These findings highlight key residues and interactions governing helicase activity, providing a molecular framework for understanding BAF complex function, illuminating a clearer path for the interpretation of human disease-associated genetic variants' mechanisms. This study thus represents a trailblazing step toward deconvoluting the impact of genetic variants in SMARCA4 and other genes whose products encode BAF components. By identifying specific residues involved in helicase function, our work paves the way for variant-specific drug discovery, advancing precision medicine for BAF-related diseases.

Day 1	
First Author	Kerry Hughes
Co-Author(s)	Christopher Bauer; Jennifer Koch; Joseph Camp; Angela Mathison; Michael Zimmermann; Raul Urrutia
Title	Improving the Sense of Healing In Genomic Diseases and Cancer Through Narrative Medicine and Music
Abstract	The Mellowes Center, in partnership with Harmony 4 Hope (H4H), has pioneered an innovative approach combining narrative medicine and musical storytelling to address rare diseases and cancers. Through their signature program, Rare Storytellers®, patients share personal narratives alongside medical professionals and musicians, synthesizing stories, songs, and scientific discovery to educate and empower the rare disease community. The program features a structured format where rare disease patients, medical experts, and musical ambassadors come together to share experiences through both narrative and musical expression. This approach aligns with emerging research in narrative medicine showing that storytelling interventions can significantly impact patient well-being, reduce disease-related pain, and improve treatment outcomes. Incorporating music, Rare Storytellers® further enhances the therapeutic potential of narrative medicine, using it as a tool to fuel scientific discoveries while uniting the rare disease community.

Day 2	
First Author	Michael LeClaire
Co-Author(s)	Karina Bursch; Fanny Boulet; Pradeep Madapura, PhD; Brian Smith, PhD
Title	BRD4 Missense Variants in Cornelia de Lange Syndrome Negatively Impact the Stability and Functionality of Bromodomains in a Disproportionate Manner
Abstract	Cornelia de Lange Syndrome (CdLS) is a genetic neurodevelopmental disorder estimated to impact every 1 in 10,000 to 1 in 30,000 births, manifesting as distinct facial features and malformation of the patient's hands. CdLS is canonically attributed to loss of function mutations in cohesin-related genes, thereby leading to loss of higher order chromatin structure and improper gene transcription. Genotyping CdLS patients has led to identifying de novo missense mutations in the BRD4 gene. BRD4 is a bromodomain and extra-terminal (BET) protein family member and contains two tandem bromodomains. Bromodomains bind, or "read", lysine acetylation (Kac) on chromatin and other nuclear proteins, which profoundly impacts gene expression regulation, cell growth, and chromatin structure. Genetic BRD4 CdLS mutations lead to missense protein variants, yet the structural and functional effects of these mutations are unknown and could be tied to disease manifestation. To streamline our understanding of how these missense variants contribute to CdLS development, we hypothesize that computational approaches can assess the impacts of BRD4 missense variants in CdLS and other rare diseases. In this study, we computationally predicted and experimentally evaluated the stability and functionality of CdLS missense variants in the first and second bromodomains (BD1 and BD2) of BRD4. Computational predictions were generated via a genomics analysis pipeline at protein sequence, structure, and molecular dynamics levels. Most CdLS-linked BRD4 bromodomain variants were located in the bromodomain binding loops and predicted to negatively impact bromodomain stability and ligand binding. Three recently reported CdLS-linked BRD4-BD1 and BRD4-BD2 variants were recombinantly expressed and purified to assess the accuracy of the computationally predicted effects on protein stability and ligand binding. Bromodomain stability was assessed with differential scanning fluorimetry, and bromodomain ligand affinity was assessed using AlphaScreen assays. Compared to the wild-type protein, CdLS-linked BRD4 missense variants exhibited imbalanced loss in protein stability and affinity for acetylated histone peptides, validating the predictions made by our computational pipeline. These results illustrate that our computational pipeline accelerates genotype-to-phenotype correlation between disrupted BRD4 function and CdLS development.

Day 1	
First Author	Angela Mathison, PhD
Co-Author(s)	Jaime Wendt Andrae, MB(ASCP)CM; Michael Tschannen, MB(ASCP)CM; Gwen Lomberk, PhD; Raul Urrutia, MD; Chandler Cortina, MD
Title	Mapping Epigenetic and Transcriptomic Changes in Gender-Affirming Testosterone-Treated Breast Tissue
Abstract	Over 2.5 million American adults identify as transgender and gender diverse (TGD), and many assigned female at birth use gender-affirming testosterone (GAT). While GAT provides psychosocial benefits, its transcriptional and epigenetic effects on breast tissue remain largely unknown, underscoring the need for high-quality single-cell Multiome data to understand its molecular impact. The first step in the process, nuclei isolation from human breast tissue, is technically challenging due to high fat content and patient tissue heterogeneity, which can limit yield and nuclear integrity. To address this, we compared nuclei isolation methods using the 10x Genomics Chromium Nuclei Isolation Kit and the Miltenyi Biotec gentleMACS method with bead-based cleanup across mouse liver tissue as well as human breast tissue. The 10x kit produced low yields of intact nuclei with frequent blebbing and fat contamination, whereas the Miltenyi method with bead cleanup generated higher-quality nuclei with fewer artifacts. Building on this optimized approach, we look to isolate breast tissue from TGD-AFB individuals using GAT with matched cisgender controls undergoing breast reduction surgery. Comparing the single cell Multiome of these samples will allow us to investigate the influence of GAT on cellular composition, gene expression, and chromatin accessibility. Ultimately, we aim to reveal new cellular mechanisms that underlie breast tissue restructuring, clarifying changing risks for breast cancer in TGD individuals.

Day 1	
First Author	Kimani Njoya
Co-Author(s)	Li Sun; Huda Zayed; Donia Alson; Oluwatosin Aina; Sajjad Khan; Ximei Veneklasen; Daochun Sun
Title	Natural history of SPP1 Signaling in NF1 Tumor Progression
Abstract	Neurofibromatosis type 1 (NF1) is a genetic tumor predisposition disorder that affects approximately 1 in 3000 individuals globally. About 20%-50% of NF1 patients develop plexiform neurofibromas (pNF), benign peripheral nerve sheath tumors associated with significant morbidity, including severe pain, vision, and hearing loss. Importantly, pNFs carry a lifelong risk of malignant transformation into malignant peripheral nerve sheath tumors (MPNST), highly aggressive sarcomas with a 5-year survival rate of 20%-50%. Selumetenib, the only FDA-approved targeted therapy for pNF, provides only modest tumor reduction, and no approved therapies exist for MPNST, underscoring the urgent need for novel therapeutic strategies. pNF and MPNST originate from neural crest-derived Schwann cell precursors (SCP), stem-like cells regulated by cell-intrinsic and extrinsic factors in the tumor microenvironment. Through analysis of human single-cell RNA sequencing (scRNA-seq) data, we found that SPP1 is highly expressed by SCP-like tumor cells in pNF and signals via its receptor, CD44, in an autocrine manner to support tumor cell stemness. In MPNST, a distinct population of SPP1-expressing macrophages emerges, contributing to an immunosuppressive microenvironment. The functional role of SPP1 in tumor progression was confirmed by significantly prolonged survival in the MPNST mouse model cisNf1+/-;Trp53+/-;Spp1-/-. Furthermore, scRNA-seq analysis of pre-tumor nerves in the pNF mouse model DhhCreNf1fl/fl revealed upregulation of SPP1 in NES+ Schwann lineage cells compared to normal nerves. Spatial transcriptomics of human pNF and MPNST confirmed colocalization of SPP1+ SCP-like cells and macrophages, supporting the autocrine and paracrine signaling model. These findings establish SPP1 as a novel prognostic marker for NF1-associated tumors, and position the SPP1-CD44 axis as a potential therapeutic target to disrupt tumor-initiating programs in pNF and reprogram the immunosuppressive tumor microenvironment in MPNST.

Day 2	
First Author	Sana Parveen
Co-Author(s)	Ramesh Adhinaveni; Neshatul Haque; Kun Fang; Raul Urrutia; Victor Jin; Hui-Zi Chen
Title	Exploring epigenetic control of immunogenicity in small cell lung cancer through multi-omics analyses
Abstract	Background: Small Cell Lung Cancer (SCLC) is an aggressive neuroendocrine malignancy characterized by epigenetic dysregulation. EZH2, a key component of the Polycomb Repressive Complex 2 (PRC2), is overexpressed in SCLC and correlates with poor prognosis. Recent studies show that EZH2 inhibition enhances SCLC cell immunogenicity, though the underlying mechanisms remain unclear. Aim: This study investigates how EZH2 function alters the epigenetic landscape in SCLC using an integrated multi-omics approach. In SCLC cell lines treated with EZH1/2 dual inhibitor Valemetostat, we examine changes in chromatin accessibility (ATAC-seq), three-dimensional chromatin organization (micro-C profile), and gene expression (RNA-seq). Key Findings: Gene set enrichment analysis of RNA-seq data revealed upregulation of genes involved in antigen processing, presentation, and inflammatory response pathways following EZH1/2 inhibition in SCLC cell line H146. ATAC-seq analysis showed increased chromatin accessibility of genes with increased expression, primarily in distal regulatory regions. Crucially, we addressed the limitation of ATAC-seq in providing only one-dimensional accessibility information by performing Micro-C profiling. This approach confirmed that EZH1/2 dual inhibition led to the formation of neo-loops between accessible promoters and their enhancers. Specifically, we observed gained loops leading to increased HLA-B and HLA-C expression with Valemetostat treatment. Validating these findings at the transcriptional and protein levels, qRT-PCR and flow cytometry analyses confirmed increased surface expression of pan-HLA molecules following Valemetostat treatment. Functional inhibition of EZH1/2 was confirmed by Western blot analyses showing decreased H3K27me3 levels. These results collectively demonstrate that EZH1/2 controls gene expression in SCLC by establishing long-range interactions between promoter and enhancer elements through modulation of chromatin accessibility, ultimately impacting the expression of key immunogenic factors. Conclusion: Our integrative multi-omics approach reveals a comprehensive model of EZH1/2 contribution to SCLC pathogenesis, highlighting its role in chromatin reorganization and gene expression regulation. Future work will focus on identifying additional therapeutically relevant genes within the EZH1/2-regulated network for potential intervention strategies.

Day 2	
First Author	Gareth Pollin
Co-Author(s)	Michael Zimmermann; Angela Mathison; Chi Young-In; Juan Iovanna; Gwen Lomberk; Rail Urrutia
Title	Decoding KRAS Mutation-Specific Nuclear Reorganization in PDAC Through Chromatin Disruption and DNA Damage Signaling That Drive Variant-Specific Malignancy
Abstract	Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer characterized by activating KRAS mutations in over 90% of cases. The most common variants G12D, G12V, and G12R, differ in signaling and clinical outcomes, with G12R tumors showing better survival than G12D or G12V, highlighting KRAS-driven heterogeneity. Early PDAC development features nuclear remodeling such as enlargement and disorganization, which we hypothesized to be influenced by heterogeneity. To test this, we performed RNA-seq (log_2FC) 24 hours after inducing KRAS G12D, G12V, or G12R in HPNE cells and found that genes involved in chromatin remodeling and nuclear structure showed mutation-specific regulation. HDAC5 was downregulated in G12D (–0.73) and G12V (–0.61), but unchanged in G12R (+0.16). TP53 and CBX7 followed a similar pattern, with stronger repression in G12D (–0.89 and –0.86, respectively) and G12V (–0.92 and –0.97), compared to minimal changes in G12R (–0.10 and –0.04). HIST1H2AC, a replication-dependent histone, was decreased in G12D (–0.22) but modestly upregulated in G12R (+0.36) and G12V (+0.13). Next, we performed phosphorylation profiling (log_2FC) to assess variant-specific regulation of epigenomic regulators. HDAC1 (Ser421) and HDAC2 (Ser394), key chromatin compaction enzymes, showed highest phosphorylation in G12D (+1.88 and +1.53), followed by G12V (+1.23 and +0.76), and lowest in G12R (+0.03 and -0.17). The DNA damage markers p53 (Ser15) and H2A.X (Ser139) were also activated in G12D (+2.12 and +0.53) and G12V (+0.56 and +1.33), compared to G12R (0.00 and -0.44). Phosphorylation of BRCA1 (Ser1457) was highest in G12D (+1.42), moderate in G12V (+1.01), and lowest in G12R (-0.07). Similarly, Chk1 (Ser317) and Chk2 (Thr68), which coordinate cell cycle arrest in response to DNA stress, showed the strongest activation in G12D (+2.05 and +1.07), followed by G12V (+0.87 and +0.32), and G12R (+0.55 and +0.11). To confirm the impact on nuclear architecture, we used super-resolution immunofluorescence and found, heterogeneous reorganization of nuclear domains in KRAS-mutant cells, supporting mutation-specific effects on nuclear structure. This study uncovers how KRAS mutation heterogeneity drives distinct nuclear remodeling programs in early PDAC, highlighting nuclear architecture disruption as a key feature of malignant transformation and a potential therapeutic target.

Day 1	
First Author	Linda M. Reis
Co-Author(s)	Jenina Capasso; Smith Ann Chisholm; Mathilde Becmeur-Lefebvre; Amy E. Roberts; Helen Livesey; Oliver Murch; Vardha Ismail; Fabiola Ceroni; Sébastien Moutton; Emanuela Argilli; Bernd Auber; Vykuntaraju K Gowda; Varunvenkat M Srinivasan; Maria Rasmussen; Arthur Sorlin; Gabriella Gazdagh; Sarah Wedderburn; Claire Beneteau; Marie Denis-Musquer; P. Christian Remmelzwaal; Samuel Thompson; Isabelle Banke; Gavin Arno; Yuri V. Sergeev; Elliott H. Sherr; Nicolas Chassaing; Nicola Ragge; Alex V. Levin; Elena V. Semina
Title	Exploring the role of CDH2 in human disease through phenotypic and variant analyses
Abstract	CDH2 encodes N-cadherin which is important in cell adhesion. Variants in CDH2 cause agenesis of the corpus callosum (ACC), cardiac, ocular, and genital syndrome (ACOGS). The most consistent features are ACC, congenital heart defects, Peters anomaly or other developmental ocular anomalies, and micropenis/cryptorchidism in males. Cognitive impairment, neuropsychiatric disorders, and mild craniofacial features are common but not fully penetrant. Here we present 14 new individuals with ACOGS with likely pathogenic/pathogenic (L/P) CDH2 alleles and 8 individuals with other developmental phenotypes (1 L/P and 7 variants of uncertain significance (VUS)). Together with prior reports, 29 individuals (26 families) with 21 unique L/P alleles (5 alleles seen in two families each) and features of ACOGS have now been identified. While having multiple affected systems is typical, five individuals have only a single structural anomaly consistent with ACOGS. Analysis of clinical data also revealed new associations, including umbilical or inguinal hernia and spine, gastrointestinal, or chest wall anomalies. The majority of ACOGS variants are missense alleles (86%) clustered in the EC4-EC5 transition region (48%) or within the EC1 domain (29%). The EC1 domain is known to be important in trans adhesion between cadherin molecules. Protein modeling revealed that 62% of L/P missense alleles within EC2-5 affect a residue directly involved in calcium binding, known to be important in maintaining stable protein conformation, with an additional 15% in neighboring regions. The 4 ACOGS non-missense alleles (19%) consist of 3 truncating variants in the cytoplasmic domain expected to escape nonsense-mediated decay (NMD) and a splice site variant that was shown to result in exon-skipping causing an in-frame deletion in EC1 by nanopore sequencing of blood-derived patient RNA. For variants associated with other developmental phenotypes, three missense (1 EC2 and 2 cytoplasmic), one frameshift (NMD), and 3 gene deletion alleles were identified; NMD/deletion alleles are considered VUS since haploinsufficiency is not a proven mechanism of disease. Combined with prior reports, there are seven alleles expected to lead to haploinsufficiency via gene deletion or NMD. Most individuals in this group do not have typical features of ACOGS; however, mild cognitive impairment, umbilical and/or inguinal hernia, and kidney anomalies are common, suggesting a novel clinical association for CDH2.

Day 2	
First Author	Riya Tanwar
Co-Author(s)	Gareth Pollin; Gwen Lomberk; Raul Urrutia
Title	PRMT5 Highlights Noncanonical Functions of Chromatin-Modifying Enzymes in Cytoplasmic Stress Responses
Abstract	Stress granules (SGs) are dynamic, membrane-less organelles that form in response to cellular stress and influence translation, resource allocation, and cell fate. SG formation and resolution are increasingly recognized as critical processes in disease progression, particularly in cancer, inflammation, and neurodegenerative disorders. Their assembly is tightly regulated by post-translational modifications, including phosphorylation, ubiquitination, and methylation. Many enzymes responsible for these modifications are traditionally associated with epigenetic and chromatin regulation, prompting investigation into their potential roles in SGs. To explore this, we conducted a bioinformatic curation integrating stress granule proteomic datasets with interaction data from the MSGP database. Gene ontology enrichment analysis revealed a significant overrepresentation of the term Chromatin Organization (GO:0006325, adjusted p=0.0034), suggesting broader roles for chromatin-associated proteins in SGs. Furthermore, we identified 45 chromatin regulators linked to SGs, including methyltransferases (PRMT5, PRMT1, TRDMT1), acetylation-related factors (SMARCA1, SMARCD2, ATAD2), chromatin readers (ARID2, RBBP4, CBX1, CBX3), and erasers (HDAC6, KDM2A, SIRT6). Among these, PRMT5 emerged as a key candidate due to its established role in RNA processing. Interactome analysis revealed significant enrichment in SG-associated proteins (adjusted p=1.16e-12). Loss of PRMT5 catalytic activity reduced symmetric dimethylarginine (SDMA) on 27 SG-associated proteins. Disruption of its adaptor-binding site (ABS) led to additional SDMA loss on a subset of these, including SERBP1, CIRBP, TAF15, HNRNPA3, and G3BP1, indicating that both catalytic and adaptor functions are required for SG-specific methylation. Functionally, inhibition of PRMT5 using either a catalytic inhibitor (EPZ015938) or ABS inhibitor (BRD0639) significantly reduced the number of arsenite-induced SGs per cell (EPZ p=0.0002; BRD p=0.0014). EPZ treatment also reduced SG-localized SDMA levels (p=0.002), whereas BRD did not (p=0.10), suggesting a methylation-independent role for the ABS in regulating SG assembly. Together, these findings reveal a novel mechanism by which PRMT5 regulates SG dynamics through distinct catalytic and adaptor-mediated activities. This work expands the known functions of chromatin-associated proteins and identifies new regulatory pathways that govern disease-relevant cellular adaptation to stress.

Day 1	
First Author	Michael Tschannen MB(ASCP)cm,
Co-Author(s)	Jaime Wendt Andrae MB(ASCP)cm; Xiaowu Gai PhD; Donald Basel MD; Jiawei Wu PhD; Angela Mathison PhD; Raul Urrutia MD
Title	Leveraging Oxford Nanopore Technologies for Diverse Sequencing Applications at the Mellowes Center 'Omics Core
Abstract	Introduction: Advances in sequencing technology have revolutionized genomics research, with Oxford Nanopore Technologies (ONT) emerging as a leader in long-read sequencing. ONT offers unique capabilities, including real-time DNA and RNA sequencing, generation of ultra-long reads, and direct detection of base pair modifications on native molecules. These features enable diverse applications such as genome assembly, transcriptomics, epigenomics, and pathogen detection. Methods: The Mellowes Center 'Omics Resource provides a suite of ONT services, delivering cutting-edge solutions tailored to individual research needs. Here we highlight key ONT applications, including de novo assembly of complex genomes, full-length transcript characterization, detection of epigenetic modifications, and mitochondrial variant analysis. The Center's workflows incorporate Rapid, Long, and Ultra-Long DNA Sequencing, Direct RNA Sequencing, PCR-cDNA Sequencing, and 10x Genomics cDNA Sequencing, offering flexibility based on project requirements. Each application provides specific advantages, such as optimized preparation time, read quality, and read length for DNA sequencing, and minimal bias, input requirements, and sample type for RNA sequencing. Results: Research studies, workflows, and quality metrics are presented to demonstrate the successful implementation of ONT applications in a diverse set of investigator projects. Examples include human whole-genome sequencing with automated methylation detection, full-length transcript interrogation, and structural variant analysis in cancer genomics using 10x Genomics single-cell cDNA products. Additionally, we continue to refine and develop strategies to optimize sequencing yield, reduce turnaround times, and provide comprehensive education and support to clients new to ONT platforms. Conclusions: By incorporating ONT technology into its service portfolio, the Mellowes Center 'Omics Resource addresses emerging research challenges, expands access to long-read sequencing, and fosters collaboration and collegiality within the MCW scientific community. This client-focused, flexible approach ensures the Center remains a leader in delivering innovative sequencing solutions to advance scientific discovery.

Day 1	
First Author	Raul Urrutia
Co-Author(s)	Gareth Pollin; Chi Young-In; Gwen Lomberk
Title	Evolutionary Constraints, Isoform Conservation, and Cancer-Associated Mutations in MEP50
Abstract	MEP50, an essential cofactor for PRMT5 (arginine methyltransferase), acts as a cofactor of steroid endocrine receptors in reproductive organs through its WD40 domain architecture, in particular the first 140 amino acids. Here, we apply a multi-tier approach for understanding the genomic conservation, variation, and disease-associated mutations that span sequence-to-structure-tomolecular dynamic studies. Sequence-to-Structure analyses was gathered through paralogs annotation analyses (PAA) and ortholog annotation analyses (OAA). For PAA, we analyzed 95 human WD40 paralogs and identified conserved residues within MEP50's six WD40 repeats, including conserved motifs such as WD and LS. Conservation peaked in the last eight residues of each repeat, supporting β-propeller stability. For OAA, we analyzed 200 orthologs and found most sequence variation occurs outside the WD40 domains, demonstrating that structured repeats experience strong evolutionary constraint while more flexible regions tolerate greater divergence. Among the repeats, WD40_1 showed the highest conservation at 89%, followed by WD40_6 (75%), WD40_2 (71%), and WD40_3 (70%), whereas WD40_4 and WD40_5 exhibited lower conservation at 46% and 40%, respectively. Moreover, we also discovered a conserved alternatively spliced MEP50 isoform that lacks WD40 repeat 2 but retains the PRMT5-binding domain and phosphorylation sites. Both canonical and short isoforms maintain over 90% conservation across mammals, underscoring their essential roles in regulating PRMT5. Next, we investigated the impact of cancer-associated mutations on MEP50 function in endocrine tissues. We analyzed variants present in both isoforms, including W152K, W59R, Y163N, S98Y, A97T, G76R, V182M, T79M, L86P, and A303V, as well as mutations unique to the canonical isoform, D146H and E107K. Structural modeling revealed that these substitutions disrupt key hydrogen bonds, salt bridges, and π-interactions, leading to changes in predicted folding energy ranging from –1.06 to 6.20 kcal/mol. We further showed that these mutations can cause disfunction by increasing residue flexibility "dynamic hotspot" by up to 0.6 Å in distal regions, reflecting long-range allosteric effects that propagate dynamic strain. This study identified conserved residues critical for MEP50's structure and function as well as discovered a conserved alternatively spliced isoform retaining key domains, suggesting functional modulation that requires further study.

Day 2	
First Author	Emily VanderPloeg
Co-Author(s)	Ross F. Collery
Title	Zebrafish Avatars of Human Sorsby Fundus Dystrophy
Abstract	Sorsby fundus dystrophy (SFD) is an autosomal dominant macular degenerating disease affecting nearly 1-in-220,000 individuals. SFD is caused by mutations in the gene coding for tissue inhibitor of metalloproteinase-3 (TIMP3). There are 22 known TIMP3 mutations that are associated with SFD. With SFD, visual acuity begins to decline during the third to fifth decade of life – depending on the mutation variant – leading to progressive central vision loss. Symptoms include, night blindness, lipid deposition, neovascularization, and macular degeneration. Currently, there is no cure for SFD other than delivering anti-VEGF treatments to control abnormal blood vessel growth in the eye, which is the major cause of vision loss. TIMP3 is a protein located primarily in the extracellular matrix (ECM) between the retinal pigment epithelium (RPE) and the choroid. TIMP3 regulates restructuring of the ECM environment by interacting with matrix metalloproteinases (MMPs). MMPs degrade components of the ECM such as collagens, fibronectins, and elastins. TIMP3 also plays important roles in differentiation, inflammatory response, angiogenesis and more. This study aims to better understand TIMP3's role in SFD progression by creating transgenic zebrafish lines that express pathological mutant human TIMP3 variants under the control of the rpe65a promoter. This is the first instance of an animal model expressing mutant human TIMP3 to study the onset and progression of this blinding disease. TIMP3 and its variants Y151C, W198C, S204C, TIMP3 3xCys (which contains all three cysteine amino acid changes) were PCR amplified and cloned into donor plasmids via the Tol2 gateway system to make pTol2:rpe65a: hs TIMP3 (mutant)-mCherry expression constructs. Each plasmid construct along with Tol2 transposase were injected into zebrafish eggs. The injected zebrafish were raised to adulthood and were bred to identify transgenic offspring. Transgenic offspring were raised to the appropriate ages and sacrificed for histology. Zebrafish heads were collected, fixed, cryoprotected and frozen. Sections were stained with mouse primary antibody zpr-1 (recognizes cone arrestin 3a; red-green cones), then stained with goat anti-mouse secondary antibody AlexaFluor-488, and counterstained with ToPro3 to label nuclei. Results showed that mutant variants of TIMP3 appear to have different persistence profiles. TIMP3W198C and TIMP33xCys fluorescence was visible at 7 days post-fertilization (dpf) and is visible into adulthood. Fluorescence was observed in the RPE cells and exported from the basal side to accumulate in the ECM adjacent to the choroid and sclera, as well as along the RPE microvilli interdigitating the photoreceptors. TIMP3Y151C was visible during development, but subsequently is difficult to observe until 6 months. TIMP3S204C is only visible during development and is not visible in juvenile or adult fish. TIMP3WT and wild-type zebrafish sections are being collected as controls for comparison with pathological mutant TIMP3 transgenic lines. Our data suggests that TIMP3 aggregation and/or turnover patterns differ between variants. We will continue to study the effects on the retina of expression of mutant versions of human TIMP3, and will profile photoreceptor morphology, health, and function, as well as overall retinal health to better understand Sorsby fundus dystrophy phenotypes observed in human patients carrying these mutations.

Day 1	
First Author	Jessica Wagenknecht
Co-Author(s)	Michael T. Zimmermann; Davin R. Jensen; Neshatul Haque; Angela J. Mathison; Jacob Licklider; Guadalupe K. Valdivia Esparza; Gwen A. Lomberk; Brian C. Smith; Raul A. Urrutia; Brian F. Volkman
Title	Structural Dynamics of KRAS Walker B Variants Reveal Diverse Mechanisms of Oncogenic and RASopathy-Associated Mutations
Abstract	The KRAS GTPase is the most frequently mutated oncogene in human cancer and causes multiple germline diseases, named RASopathies. We uniformly studied 14 KRAS variants in the canonical Walker motifs, which we hypothesize alter nucleotide binding by distinct structural and dynamic mechanisms. Performing 1H–15N NMR spectroscopy and thermal stability, we measured nucleotide-dependent biophysical characteristics of these KRAS mutant proteins. In addition, we conducted molecular dynamics (MD) simulations to discover the underlying details of position, variant, and ligand-specific effects. Both approaches revealed mutational propensities to change KRAS conformations, destabilize the nucleotide pocket, and alter coupling to the cellular signaling cascade. Indeed, we find that KRAS variants form 4 groups, namely those with: 1) loss of characteristic GDP-bound conformations with alterations of GTP-bound ones, 2) loss of characteristic GTP-bound conformations with simultaneous distortions of GDP-bound conformations, 3) propensity towards GDP-bound conformations regardless of nucleotide state, and 4) few changes, to the resolution assessed. The results from NMR and MD analyses are congruent and complementary. Our data reveal shared characteristics between somatic and germline pathobiological mechanisms. This new knowledge advances our understanding of KRAS mutations at an atomic resolution level with significant implications for multiple biomedical fields.

Day 1	
First Author	Jaime Wendt Andrae, MB(ASCP)CM
Co-Author(s)	Michael Tschannen, MB(ASCP)CM; Angela Mathison, PhD; Raul Urrutia, MD
Title	Advancing Tissue and Immune Profiling with 10x Genomics Visium HD, Single-Cell RNA Sequencing, and CITE-seq at the Mellowes Center 'Omics Core
Abstract	The Mellowes Center 'Omics Core plays a critical role in advancing high-throughput genomic research by providing access to cutting-edge technologies to MCW investigators. The integration of 10x Genomics Visium spatial transcriptomics, single-cell RNA sequencing, CITE-seq (Cellular Indexing of Transcriptomes and Epitopes by Sequencing), and the Visium High Definition (HD) platform offers a powerful combination for detailed molecular analysis at unprecedented resolution. The Visium platform enables the simultaneous examination of gene expression across tissue sections while preserving spatial context, allowing researchers to explore complex tissue architecture and cellular heterogeneity. The Visium HD capabilities further enhance spatial resolution, providing even finer mapping of transcriptomic activity at single-cell resolution within tissue samples. This advancement enables more precise dissection of cellular organization and molecular gradients within tissues, offering a deeper understanding of tissue-specific biology. Coupled with 10x Genomics single-cell RNA sequencing (Next-GEM, GEM-X, Flex), these technologies enhance the ability to investigate gene expression at the resolution of individual cells, facilitating insights into cellular interactions, microenvironments, and disease mechanisms. Additionally, CITE-seq enables the concurrent profiling of cell surface proteins and transcriptomes, offering a more comprehensive approach to immune cell phenotyping, activation states, and signaling pathways in diverse biological contexts. In particular, the combination of spatial transcriptomics, single-cell sequencing, and immune profiling enables comprehensive immune landscape analysis within tissues, advancing our understanding of immune cell subsets, their interactions, and their roles in diseases such as cancer, autoimmune disorders, and infections. By adopting 10x Genomics technologies, including the high-resolution capabilities of Visium HD, The Mellowes Center 'Omics Core can generate high-dimensional data that facilitate the characterization of cellular diversity, immune profiling, and tissue microenvironments. This integrated multi-omics approach accelerates discovery, enabling reproducible, data-driven insights across a wide range of biological and disease contexts, particularly in immunology and cancer immunotherapy.

Day 1	
First Author	Jiawei Wu
Co-Author(s)	Michael Muriello; Donald G. Basel; Xiaowu Gai
Title	Leveraging Vector Embeddings for Rapid and Accurate Pathogenicity Prediction of Genetic Variants
Abstract	Background: Interpreting the pathogenicity of genetic variants remains a critical bottleneck in genomic medicine. Millions of variants of uncertain significance (VUS) hinder the clinical application of genetic findings. Traditional computational approaches often rely on hand-engineered features and fail to fully capture the complexity of multidimensional genomic annotations. Methods: We developed a novel semantic embedding framework, VUS.Life, that transforms variant annotations into natural language descriptions and leverages pre-trained language models to capture pathogenicity-relevant relationships in high-dimensional vector space. This approach enables direct pathogenicity prediction through representation learning rather than traditional feature-based methods. Results: We evaluated the framework using curated variants from three disease-associated genes: BRCA1 (n=3,311) and BRCA2 (n=4,074) from BRCA Exchange, and FBN1 (n=1,532) from ClinVar. Variant annotations from the Variant Effect Predictor (VEP) were converted into natural language while excluding fields linked to known pathogenicity assertions to prevent data leakage. We then embedded these descriptions using three models: MPNet (all-mpnet-base-v2), Google's text-embedding-004, and MedEmbed-large-v0.1. A k-nearest neighbor (k-NN) approach (up to 20 neighbors) was used to predict pathogenicity for new or unreviewed variants. Dimensionality reduction techniques (PCA, t-SNE, UMAP) enabled visualization of the embedding spaces. k-NN classification showed exceptional performance across all genes and embedding models. For BRCA1, overall accuracy ranged from 97.3% (Google) to 97.9% (MPNet), with benign/likely benign accuracy of 95.1–97.2% and pathogenic/likely pathogenic accuracy of 97.9–98.4%. For BRCA2, overall accuracy ranged from 97.9% (Google) to 99.1% (MedEmbed), with benign/likely benign accuracy of 96.6–99.2% and pathogenic/likely pathogenic accuracy of 98.6–99.4%. FBN1 validation confirmed the method's generalizability, with accuracy exceeding 96% across all embeddings. Application to not-yet-reviewed BRCA1/2 variants demonstrated the framework's practicality and scalability, with unknown variants aligning closely to known benign or pathogenic clusters. Conclusions: This semantic embedding framework, VUS.Life, accurately captures pathogenicity-relevant features from complex variant annotations, enabling high-accuracy (>96%) automated classification across multiple genes and models. The approach generalizes beyond well-curated genes and supports scalable, interpretable, and representation-based classification of VUS. It holds significant promise for alleviating the variant interpretation bottleneck in clinical genomics.

Day 2	
First Author	Duo Yu, PhD
Co-Author(s)	Michael J. Kane, PhD; Yiqing Cheng, PhD; Steven H. Lin, MD, PhD; Radhe Mohan, PhD, FAAPM, FASTRO; Brian P. Hobbs, PhD
Title	Bayesian Counterfactual Machine Learning Individualizes Radiation Modality Selection to Mitigate Immunosuppression
Abstract	PURPOSE: Lymphocytes play critical roles in cancer immunity and tumor surveillance. Radiation-induced lymphopenia (RIL) is a common side effect observed in cancer patients undergoing chemoradiation therapy (CRT), leading to impaired immunity and worse clinical outcomes. While proton beam therapy (PBT) has been suggested to reduce RIL risk compared to intensity-modulated radiation therapy (IMRT), this study utilized Bayesian counterfactual machine learning to identify distinct patient profiles and inform personalized radiation modality choice. METHODS: A novel Bayesian causal inferential technique is introduced and applied to a matched retrospective cohort of 510 esophageal cancer patients undergoing chemoradiation therapy to identify patient profiles for which immunosuppression could have been mitigated from radiation modality selection. RESULTS: Body mass index (BMI), age, baseline absolute lymphocyte count (ALC), and planning target volume (PTV) determined the extent to which reductions in ALCs varied by radiation modality. Five patient profiles were identified. Significant variation in ALC nadir between PBT and IMRT was observed in three of the patient subtypes. Notably, older patients (age > 69) with normal weight experienced a two-fold reduction in mean ALC nadir when treated with IMRT versus PBT. Mean ALC nadir was reduced significantly for IMRT patients with lower ALC at baseline (< 1.6 k/μL) who were overweight or obese when compared to PBT, whereas overweight patients with higher baseline ALC showed clinical equipoise between modalities. CONCLUSION: Individualized radiation therapy selection can be an important tool to minimize immunosuppression for high-risk patients. The Bayesian counterfactual modeling techniques presented in this article are flexible enough to capture complex, nonlinear patterns while estimating interpretable patient profiles for translation into clinical protocols.

Day 1	
First Author	Michael Zimmermann
Co-Author(s)	Neshatul Haque; Jessica Wagenknecht; Rebekah Fogarty; Xiaowei Dong; Angela Mathison; Janet Hoenicka; Francesc Palau; Gwen Lomberk; Raul Urrutia
Title	Unlocking Disease Mechanisms: Systems and Structural Genomics in Epigenetic Disorders
Abstract	We present a novel paradigm for better understanding and treating cancer and rare diseases caused by epigenetic dysregulation, transforming diagnostics with mechanistic and systems biology insights using computational structural genomics. Our premise is that studying multi-protein complexes, rather than individual genes, will provide better mechanistic understanding, improve diagnostics, define disease spectra, and build trajectories towards therapeutics. This paradigm emerged from our work in Genomic Odyssey Boards, where clinical and research teams integrate findings from classical genomics approaches with our calculations that leverage three-dimensional and time-dynamic modeling of gene products. This is important since current guidelines and data science methods for genetic diagnosis are primarily based on single genes, linear sequences, evolutionary conservation, and population-level empirical observations, rather than 3D features and calculations derived from gene products. We can therefore add to the field, mutation-specific structural, dynamic, and systems-level information, for a more powerful interpretive toolset across diverse clinical and research domains. Our goal is to accurately predict which mutations cause human disease by developing context-dependent and mechanistic interpretations of genetic information. We will provide examples of this paradigm through studies of the BAF complex from the SWI/SNF family of chromatin remodeling enzymes, and the COMPASS complex from the histone methyltransferase family. These enzymes regulate genome accessibility and whose activity changes influence episignatures, or the patterns of genomic accessibility that define cellular states. They are critical to study because 1) they are required for normal physiology and tissue development, 2) germline mutations define rare diseases like Coffin-Siris syndrome that affect people of all genetic ancestries, and 3) somatic mutations frequently underly cancer development from many body tissues. Both complexes are composed of multiple proteins, for which a mutation causes different diseases. The information we derive feeds back to our translational program to empower a positive cycle where we are discovering mechanisms of genetic diseases, expanding the numbers of patients that can be diagnosed, and identifying potential therapeutic paths. Therefore, this talk will demonstrate the power of leveraging computational structural genomics to interpret human genetic variation for epigenetic regulatory complexes.