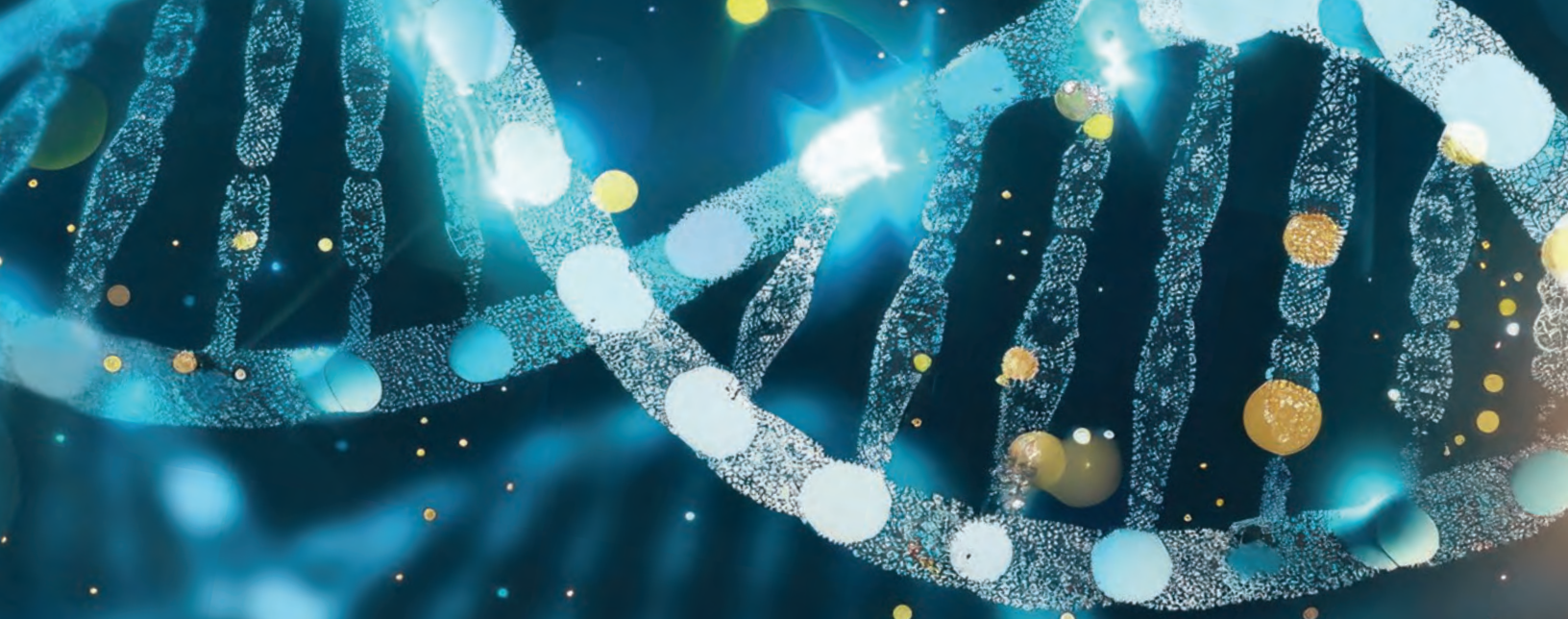


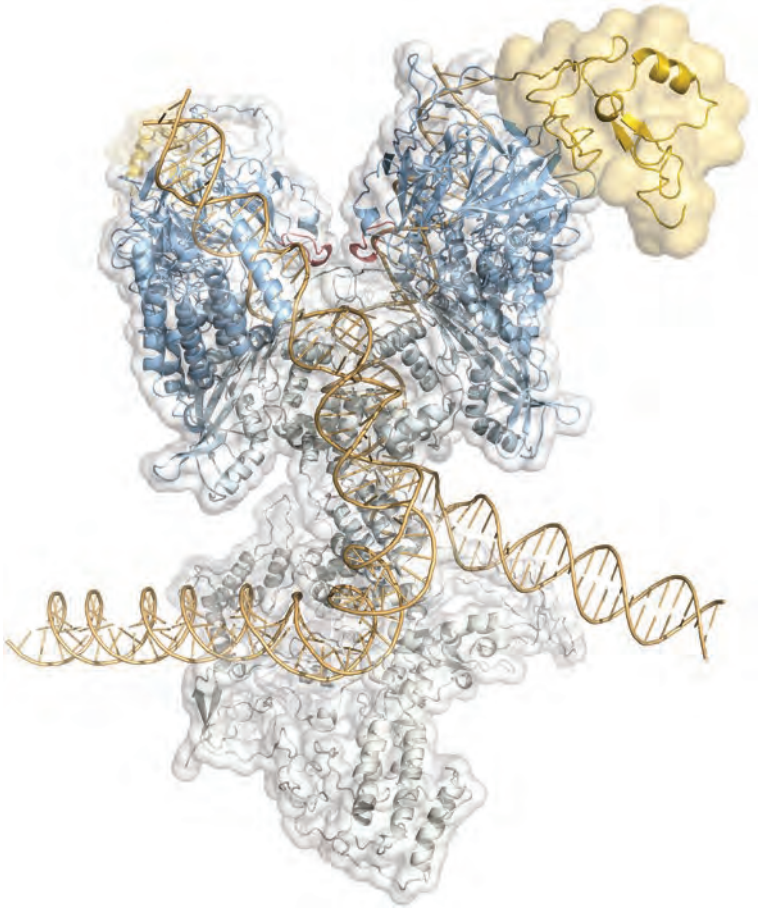
MEDICAL COLLEGE OF WISCONSIN

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

Annual Report, November 2024

BEYOND THE BASE PAIRS

In 2017, the Mellowes Center ushered in a new era of genomics and precision medicine with the slogan "Beyond the Base Pairs." This phrase reflects the understanding that interpreting the genome involves much more than just sequencing it. The genome operates on multiple levels of regulation, and as shown here, the RAG complex plays a critical role in the immune system by modifying specific genome regions to generate antibody diversity. When RAG malfunctions, it can lead to immunodeficiency, autoimmune diseases, and blood cancers. Rather than focusing solely on genes themselves, our work delves into how the genetic code is tagged, packaged, regulated, and transformed into the molecular machinery essential for cellular function. By expanding access to genetic testing, refining experimental design, and enhancing data interpretation, we aim to elevate research and pave new avenues for Precision Medicine, constantly forging the path toward a more advanced future.



Contents

A Message from the Director

I am excited to invite you to learn about the John and Linda Mellowes Center for Genomics Sciences and Precision Medicine: its scientific achievements and its enduring culture of principle-based, mindful professionalism. Indeed, over the years, we have grown into a center of discovery, invention, and innovation, focused on advancing knowledge in rare genomic diseases and cancers. Our work consistently introduces the latest methodologies in modern genomics, providing a comprehensive, system-wide view of diseases and transforming research and patient care. What truly sets us apart is the unique culture we have built, maintained, and allowed to flourish. This culture is grounded in shared principles and mindfulness, creating an environment where professionalism is the essential link binding our community together. This approach drives our commitment to scientific excellence while fostering an atmosphere of respect, integrity, and shared responsibility.

Mindfulness guides every aspect of our work, ensuring our innovations and discoveries are both cutting-edge and compassionate. Education plays a central role in our mission. Our belief in training future precision medicine leaders led us to establish two master's programs and collaborate on a third, all dedicated to this new and rapidly evolving discipline. Our faculty contributes by teaching in these programs and through journal clubs, seminars, and national and international symposia. In every educational endeavor, we uphold the principles of professionalism and mindfulness, shaping a new generation of scholars and practitioners. Beyond education, our center excels in scientific advancement. Our members publish in high-impact journals, contributing to the global understanding of genomics and precision medicine. We work closely with clinician-scientists and many international leaders in their fields to translate our research into practical advancements that improve clinical care. This collaboration between science and practice is central to our mission of making a tangible impact on patient lives.

We also take great pleasure in collaborating with the Office of Research to offer Core Services that provide investigators at the Medical College of Wisconsin (MCW) with advanced 'Omics and Data Science tools.

This partnership is critical to our goal of ensuring that every scientist at MCW has access to the most advanced technologies available, enabling them to push the boundaries of their research and contribute to the collective scientific mission. Moreover, we believe in the importance of community outreach, so we organize narrative medicine sessions that bring the families of affected patients into the conversation. By integrating their experiences with our scientific work, we bridge the gap between the lab and real-world impact, fostering a deeper understanding of the human stories behind the science. The transition of the Mellowes Center into an MCW-wide research hub marks an exciting new chapter in our evolution. This transformation allows us to partner with departments across the institution, bringing together the brightest minds and most innovative talent to shape the future of genomics and precision medicine. Our commitment to mindful care ensures that these partnerships are scientifically groundbreaking and deeply compassionate.

Ultimately, the culture of the Mellowes Center is what has allowed us to thrive. Through this foundation of principles and mindfulness, we have maintained an environment where professionalism, innovation, and community engagement are seamlessly integrated. As we continue to grow, we remain dedicated to advancing the fields of genomics and precision medicine, shaping a future defined by discovery and care.

Raul A. Urrutia, MD

"Act as if what you do makes a difference. It does." – William James

From Genomics to Precision Medicine: The Birth of the Mellowes Center

Mellowes Center is awarded the **Chromatinopathies** grant from AHW to integrate pediatric diagnosis with genetic and epigenetic mechanisms of disease.

2024

2023

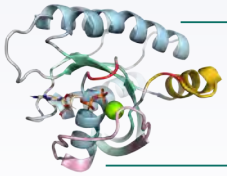
The **NIH UDN** enters phase-III, expanding to include additional clinical and research sites including MCW (MC+CW partnership).

GSPMC renamed to, The Linda T. and John A. **Mellowes Center** for Genomic Sciences and Precision Medicine (Mellowes Center) to honor their $10M Contribution to Innovation.

2022

2021

GSPMC in partnership with CW is named a **National Organization of Rare Disorders** (NORD) Center of Excellence.

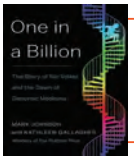


GSPMC establishes the **Precision Medicine Simulation Unit** (PMSU) through a grant with A Healthier Wisconsin (AHW).

2018

2017

MCW launches comprehensive **Genomic Sciences and Precision Medicine Center** (GSPMC).



Working with clinicians from **Children's Wisconsin, MCW is 1st in world** to successfully treat a human by sequencing the patient's genome.

2009

2003

Draft of Human Genome published.

Rat Genome Database established.

2000

1999

MCW founds the **Human and Molecular Genetics Center.**

HMGC Human and Molecular Genetics Center
Leading Personalized Healthcare

The **Human Genome Project** begins.

1990

Narrative Medicine in Partnership with Harmony4Hope

The Mellowes Center has been a strong advocate for Narrative Medicine, emphasizing the importance of patient storytelling in healthcare. By sharing patients' stories and emotions, Narrative Medicine provides holistic care that integrates the role of stories in both understanding and treating illnesses.

Our partnership with Harmony 4 Hope (H4H) reflects this commitment. H4H incorporates music to fuel rare disease research, educate current and future medical professionals, and unite affected communities. Dr. Raul Urrutia, Director of the Mellowes Center, serves as a Scientific Advisor for H4H, recognizing the power of music in raising awareness for rare diseases.

A highlight of our collaboration was the recent Rare Storytellers event, where patient stories, science, and music came together. Featuring Marquette University President Dr. Michael Lovell and his MCW physician, Dr. John Charlson, alongside Musical Ambassador Trapper Schoepp, this event inspired and educated attendees about the realities of rare diseases.

This event exemplified Narrative Medicine, bridging patient experiences, medical education, and research, while fostering empathy and a deeper connection between patients and healthcare providers. Through initiatives like Rare Storytellers and partnerships like H4H, the Mellowes Center continues to advance Narrative Medicine, rare disease research, and compassionate patient care.

Narrative Medicine in Action:

- **March 2022 Rare Storytellers: Meet Peter Frampton** – Celebrated musician Peter Frampton shared his personal story of dealing with Inclusion Body Myositis and his own diagnostic odyssey.
- **September 2022 Rare Storytellers: Remember the Carriers** – Music and conversation with Taylor Kane, founder and executive director of Remember The Girls, a non-profit organization that unites, educates and empowers female carriers of X-linked genetic disorders.
- **April 2023 Rare Storytellers: The Science of Caring, Pediatric Rheumatology** – Advancing education around Narrative Medicine and Pediatric Rheumatology with pediatric physicians and patients.
- **September 2023 Rare Storytellers Meets Milwaukee** – Dr. Michael Lovell, former president of Marquette University, shared his story of diagnosis with a rare form of sarcoma that affects less than 2,000 people each year.
- **September 2024 Rare Storytellers: The Best Songs Start with a Story** – Sharing of Rare Disease experiences at Mayo's Individualized Medicine Conference.
- **November 2024 Rare Storytellers at Mellowes Center's 2nd Annual Rare Diseases and Rare Cancers in the Era of Systems Biology Symposium** – A patient's story of receiving, processing, and managing a Glioblastoma diagnosis.

More than 40 highly specialized researchers and community members came together at the 2023 Harmony for Hope Rare Storytellers meet Milwaukee event. The gathering served as a reminder of the human stories behind each rare disease case, underscoring the need to continue innovating and advancing our research efforts.

Mellowes Center Symposium

The Rare Disease and Rare Cancer in the Era of Systems Biology Symposium brought together a diverse community expected to form small, long-term support groups, which may lead to innovative research opportunities. Investigators have already begun identifying the unique expertise shared by Symposium speakers and are aiming together to advance the understanding of rare diseases and rare cancers. The Mellowes Center supports these collaborations by organizing additional conversations among research teams focused on overcoming complex challenges, emphasizing how data science applications can reveal shared aspects of rare diseases and rare cancers. The ongoing collaborations are anticipated to generate manuscripts, funding grants, and new insights into the clinical applications of 'Omics data in precision medicine.

To raise awareness of Narrative Medicine and Precision Medicine, a short video was produced, using recordings from the Symposium and Rare Storytellers event, tailored for a broad audience. This video illustrates how partnerships between patients, clinicians, and researchers are essential for advancing understanding of diseases that have historically received limited attention. Through narrative medicine and research symposiums, we aim to inspire optimism among patients awaiting diagnosis and encourage the next generation of researchers to focus on rare diseases and cancers.

VIDEO LINK

2023 Symposium Highlights:

- **Hosting over 13 hours of expert seminars on rare diseases and rare cancers describing novel developments in research. Each focus area – Precision Medicine, Mitochondrial Systems, Innovative Technology, Immune Systems, and Systems Biology – engaged expert speakers and featured future focused discussion time.**
- **Critical research collaborations were fostered among investigators (>90 attendees), coming from 5 international locations (Argentina, Guatemala, Japan, Mexico, Spain) and across the USA (>10 medical institutions). Linking these critical teams will ensure expanded access to patient diagnoses and increase the power to discover and understand rare diseases and rare cancers.**
- **Establishing an event that will annually bring together students, faculty and staff to engage in the generation of novel connections and groundbreaking research.**

Expanding the Mellowes Center impact with collaborations at numerous Hospitals, Clinics, and Research Universities worldwide:

- Departamento de Microbiología, Universidad de Buenos Aires, Buenos Aires, Argentina
- Comprehensive Cancer Center, Medical University Vienna, Wien, Austria
- Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
- Molecular Diagnostic Laboratory, Centre Hospitalier Universitaire Sainte-Justine, Montréal, Canada
- Birth Defect Prevention Research Institute, Maternal and Child Health Hospital of Guangxi Zhuang, China
- National Reference Center for Neurogenetic Disorders, Hôpital Armand-Trousseau, Paris, France
- Center of Functional Genomics, Berlin Institute of Health at Charité-Universitäts medizin Berlin, Germany
- Department of Medical Sciences, Ferrara University, Ferrara, Italy
- Department of Clinical Genetics, University Medical Center Rotterdam, Netherlands
- Department of Pediatrics, Umm Al-Qura University, Mecca, Saudi Arabia
- Department of Paediatric Medicine, Mount Elizabeth Hospital, Singapore
- Department of Surgery, Inha University School of Medicine, Incheon, South Korea
- Instituto de Biología Molecular y Celular, Universidad Miguel Hernández, Elche, Spain
- Department of Human Genetics, Bern University Hospital, University of Bern, Bern, Switzerland
- Medway School of Pharmacy, University of Kent and University of Greenwich, United Kingdom

International Collaborations

Since 2017, the Mellowes Center has significantly expanded its national and international collaborations for rare and undiagnosed disease research and clinical care. By partnering with esteemed researchers and clinicians worldwide, the Center leverages cutting-edge technologies and advanced analytical methodologies to understand each patient's genome and what it reveals about their health, wellness, discomfort, or disease. These research collaborations enable the Mellowes Center to bring advanced analytics to a broader network of patients with undiagnosed or rare conditions, ultimately striving to improve patient care and health outcomes. Future projects will continue to build on these efforts by enhancing genomic analysis to diagnose and treat rare diseases with precision and by applying the knowledge gathered from a single patient variant to learn more about the 1000s affected by the disease.

Meeting new people and sharing ideas is at the core of our Team-based approach. We regularly participate in a variety of international conferences including:

Greek KLF: Dawn of the Precision Medicine Era – October 2024 in Delphi, Greece
Bringing together global experts in KLF/SP factor research, this conference focuses on druggable and undruggable targets, ultimately promoting collaborations that lead to advancements in the treatment of human diseases.

Botton-Champalimaud International Pancreatic Cancer Conference – October 2024 in Lisbon, Portugal
Uniting experts from around the world in pancreatic cancer research and treatment, this gathering will showcase new insights, surgical advances, and therapies that improve patient care globally.

Latin American School of Medical and Human Genetics – ELAG Conference 2025
ELAG, a training program for more than 838 students from 17 countries, hosts an international conference that continues to prepare young researchers for the practice of genomic medicine and global collaborations.

– Impacting Health Around the World

2024 Highlights in the Mellowes Center Rare Disease Network

Seattle Children's Hospital – Seattle, WA
To showcase the impactful role of patient narratives in medicine Dr. Urrutia teams up with Dr. Aviya Lanis. These storytelling sessions offer healing to patients and caregivers navigating their diagnostic journey and can lessen the burden of anxiety, depression, and disconnectedness that patients with chronic illnesses often feel. Also, practitioners are reminded of the humanity behind disease and re-invigorated by the primary pursuit, to heal the whole patient.

Nationwide Children's Hospital (NCH) – Columbus, Ohio
The longstanding collaboration with Dr. Roshini Abraham is very effective in investigating inflammatory diseases with inborn errors of immunity. Patient cases are discussed with the intent to understand genetic variants, link these variants to disease diagnosis, and ultimately consider treatment targets in complex clinical cases.

Mayo Clinic – MN, AZ, and FL
Decades of innovative work building a collaborative Network of Precision Medicine research in the Midwest has allowed this team to bilaterally lead the development of computational genomics and 3D Modeling.

INSERM, National Institute of Health and Medical Research – Marseille, France
Dr. Urrutia's collaboration with Dr. Iovanna has led to groundbreaking discoveries in precision medicine, notably the importance of including epigenomic approaches in the classification of pancreatic subtypes (Basal vs. Classical), each requiring unique therapeutic approaches.

Saint Joan de Deu Children's Hospital – Barcelona, Spain
Collaborations with Drs. Francesc Palau & Janet Hoenicka help to treat patients that have symptoms but no diagnosis. Using 3D Genomics, we generate models of protein movement and function as well as conduct experiments in patient-derived cell lines to determine how each unique, potentially one-of-a-kind, genetic change affects physiology.

Casa de Raros – Porto Alegre, Brazil
Dr. Urrutia's collaboration in Brazil offers a unique opportunity to leverage his lab's advanced computational genomics and 3D modeling techniques within their diverse genomic database, establishing an interconnected network of comprehensive care for people with rare diseases. The goal is to provide multidisciplinary care to patients and their families through rapid and accurate diagnosis, advance treatment options, establish research focused on rare genetic diseases, and train the next generation of health professionals.

Four Pillar Programs Emphasized at the Mellowes Center

The Mellowes Center is at the forefront of integrating advanced data science innovations to enhance research capabilities at MCW. By leveraging sophisticated data analytics, machine learning, and artificial intelligence, the Center is transforming raw data into actionable insights. High-performance computing infrastructure allows for efficiently processing large-scale datasets generated by cutting-edge technologies such as single-cell sequencing and spatial transcriptomics. Our long-standing research program in rare diseases and cancers leverages structural bioinformatics, epigenomics, systems biology, functional genomics, and epigenetic therapeutics to define disease and pathobiological mechanisms. The Center also emphasizes data integration, facilitating combining diverse data types to create comprehensive biological models. These innovations enable investigators to uncover hidden patterns, predict biological behaviors, and accelerate the pace of scientific discovery, ultimately leading to more personalized and effective healthcare solutions.

Inherited Diseases of Children and Adults

The Mellowes Center is decoding the genetic mysteries of rare diseases, collaborating worldwide to unlock personalized diagnostics, improve patient outcomes, and develop pathways toward treatments.

We are on a mission to develop the technology and approaches needed to interpret everyone's genetic code. Currently, most genetic differences lack a medical or biological interpretation. Therefore, collaborating with national and international researchers, clinicians, patients, and students, the Mellowes Center seeks to advance multidisciplinary research, leveraging structural and functional genomics, structural bioinformatics, and epigenetics to discover the pivotal role that specific genes have in the pathobiology of rare diseases. Evidenced by an extensive publication record (more than 70), our integrative and holistic approach sets our program apart and shapes the future of genomic data interpretation.

The Mellowes Center, through its partnership with the Children's Wisconsin-MCW Undiagnosed and Rare Disease Program, is a National Organization of Rare Disorders (NORD) Rare Disease Center of Excellence. We connect to Children's Wisconsin Quantitative Health Sciences via our Director of Child Health Bioinformatics. Regionally, this program connects with multiple Midwest institutions to form a rare disease research federation. Finally, our faculty partner with physicians and researchers around the world to explore diverse patient cases and offer 'Omics and Bioinformatics services to researchers through our shared resource units.

Precision Oncology & Cancer Genomics

Mellowes Center is at the forefront of precision oncology, deciphering the genetic code of cancer for more comprehensive and sensitive genetic diagnostics and empowering tools that can be used to tailor treatments and improve outcomes for patients.

We seek to personalize care and improve prevention, diagnosis, and treatment by studying the genetic, epigenetic, and environmental factors influencing cancer. Through its partnership with the MCW Cancer Center, Mellowes Center Precision Oncology faculty harness this power of precision medicine to accelerate innovative research via tumor boards, the adult cancer clinical trials enterprise, and the new Michels Rare Cancers Research Laboratories, which will accelerate novel studies and develop personalized treatments for rare cancers.

Hundreds of genes influence the development, treatment, and outcomes of cancer patients. Mellowes Center researchers investigate the genetic, epigenetic (changes caused by the activation or deactivation of genes), and environmental factors that lead to cancer. These studies show the most promise for personalizing cancer care and establishing novel workflows that improve cancer prevention, diagnosis, and treatment based on each patient's genetic makeup. Our faculty extends this expertise through its partnership with the MCW Cancer Canter, at which they attend tumor boards, facilitate clinical trials, and lead the country in rare cancer research.

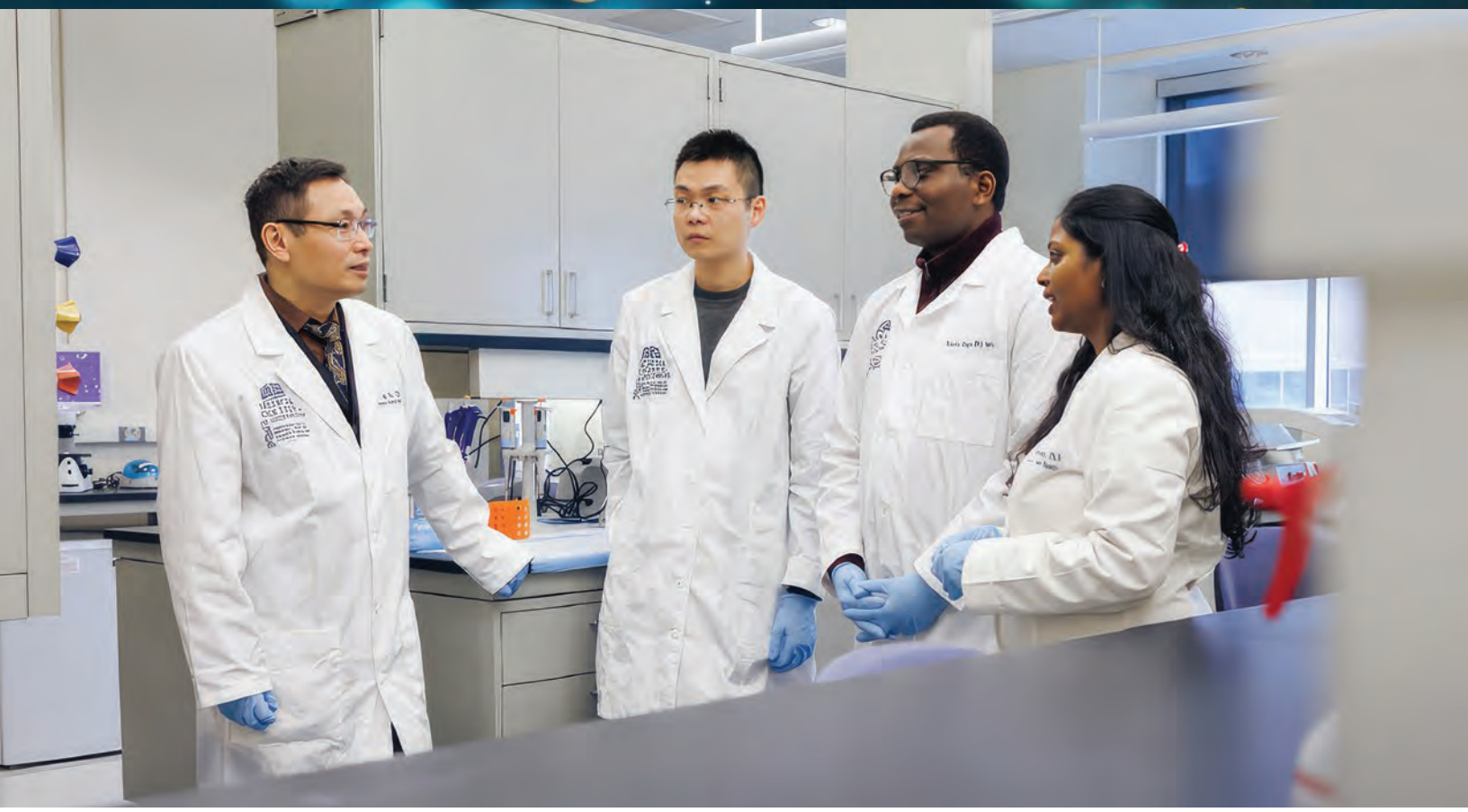
Community & Precision Public Health

The Mellowes Center is leveraging genomics and community partnerships to uncover the unique health risks and opportunities within diverse populations, paving the way for more equitable precision medicine.

Precision Medicine acknowledges the intricate threads of our genetic diversity (that individuals are genetically distinct) woven into the vibrant tapestry of humanity we all share. The Mellowes Center is committed to diversifying the genomic data available for research by facilitating precision medicine studies that go deeper than genetic ancestry. With epigenomics and systems biology at the core of our expertise, integrating ethnic diversity with genome function is particularly interesting. Our commitment to diversifying genomic research focuses on community-based, genomics-informed studies integrating ethnic diversity and environmental impacts.

To explore the intersection of ancestry and historical environmental impacts on our community, which also have implications for genomic regulation, our Center seeks to develop studies informed by our community partners and focus on what matters to them. Listening to our community partners is vital to developing better means to convey the health implications of genomic differences and the epigenomics (or regulatory) modifications due to environmental conditions. This is a promising area of research where we aim to leverage the technologies we have developed to study severe and congenital diseases and reimagine them for application to more common diseases and situations affecting individuals in our community. Yet, we underscore the need for this to be a mutual partnership so that all can benefit in ways that align with their values and with consent.

For this reason, our Center has partnered with the MCW Institute for Health and Equity (IHE) not only to develop the pioneering field of Precision Public Health (PPH), which uses better and more precise data to target disease prevention and control as well as to improve health and health equity worldwide but also to create new careers that will support the practice of precision medicine at a larger scale that reaches more populations. These programs include Masters and certificate programs in Precision Medicine and a Masters program in Genetic Counseling.



Systems Biology Resources in 'Omics and Bioinformatics

Mellowes Center is a powerhouse for Precision Medicine, providing cutting-edge technology and expertise to accelerate genomic research, unlock personalized treatments, and empower multi-'Omic systems biology.

We advance Precision Medicine by developing and adapting novel technologies and methodologies for reliable genetic and epigenetic data analysis. We offer state-of-the-art shared resources in 'Omics and Bioinformatics led by highly experienced teams.

The practice of Precision Medicine depends upon specialized research, developing novel technology, and advancing data interpretation through specialized analysis, leading to discoveries that can inform personalized treatments based on a patient's unique genetic history and makeup. The Mellowes Center onboards, adapts, and develops new methods, allowing researchers to obtain consistent and reliable genetic and epigenetic data that can be analyzed quickly and efficiently. Our advancements in data science, bioinformatics (software tools and approaches specialized for understanding biological data), genomics, molecular modeling, and other fields accelerate research to identify mechanisms by which genetic alterations lead to disease. This panacea of approaches enables more holistic genomic research, also known as systems biology. The practice of systems biology is critical for anchoring computational approaches in biological realities and leveraging high-dimensional information to design and interpret laboratory experiments more optimally.

Because of this specialty program, the Mellowes Center is able to offer researchers state-of-the-art shared resources in both 'Omics and Bioinformatics. We have developed a broad portfolio of supported technologies, with additions made continually via our Research and Development office, and as faculty partner with us to onboard additional infrastructure or methods to support their novel research. These shared resources rapidly adapt and evolve to ensure researchers have access to the most state-of-the-art methodologies and data analysis.

Additionally, the Center partners with the Data Science Institute (DSI) Division of Biostatistics and the Clinical and Translational Science Institute (CTSI) of Southeast Wisconsin to deliver researchers with robust data science support spanning bioinformatics, biostatistics, clinical informatics, and beyond.

Driving Impact Through Generosity and Strategic Funding

We extend our heartfelt gratitude to all the generous donors who have supported the Mellowes Center. Their contributions play a vital role in advancing our mission to lead in precision medicine and innovative research. The generous donations we receive enable us to pursue groundbreaking discoveries, develop novel technologies, and provide cutting-edge clinical care for patients with inherited diseases and rare cancers. Each gift, no matter the size, fuels our efforts to push the boundaries of medical science, foster critical collaborations, and ultimately improve patient outcomes on a global scale.

Linda A and John T Mellowes Endowment

- $10M commitment over 10 years
- Endowed Chairs to facilitate recruitment of key faculty to further drive our mission
- Funds our Center's Innovation and Discovery work

Marcus Corporation Foundation Endowment

- **NEW!** Launching Marcus Corporation Foundation Award in FY25.
- Fostering innovative research in Precision Medicine by providing funding opportunities to MCW clinicians and researchers.
- Data and results generated from these awards can be used as pilot data for subsequent submissions to NIH and other funding sources.

The Marcus Corporation

Additionally, we recognize the meaningful donations from Scott Tilton, Phoebe Lewis, and the Uihlein Foundation
The support of all our donors is invaluable, and we invite others to join us in our journey. Contributions of any size make a profound impact and help us continue our pioneering work. Thank you for being an integral part of our community and for helping us strive towards groundbreaking advancements in precision medicine.

Advancing a Healthier Wisconsin

Supporting Collaborations with local impact

The Mellowes Center is deeply grateful for AHW's continued support in our research and education missions. This past year, we concluded the Precision Medicine Simulation Unit (PMSU) project and launched our next AHW-backed initiative, a Chromatinopathies grant. Building on PMSU-developed tools, we established a Genomics Diagnostics Board to assist clinicians in identifying rare disease cases that benefit from our methods. Using a multidisciplinary approach that combines biophysical validation and in silico molecular modeling, we explore genetic changes in detail – often generating thousands of models for a single alteration. This work aims to reveal new pathways that could lead to innovative treatments, ultimately shortening the diagnostic journey and improving patient care.

MCW MEDICAL SCHOOL | AHW ADVANCING A HEALTHIER WISCONSIN ENDOWMENT

In grateful recognition of Linda T. and John A. Mellowes

In May 2022, the Medical College of Wisconsin dedicated the Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine in recognition of the couple's $10 million investment to advance new research on the human genome.

Lifelong supporters of innovation and discovery, Linda and John moved from Washington, D.C. to Milwaukee in 1970 to continue their family's leadership of Charter Manufacturing, a steel and iron production and manufacturing company founded in the 1930s. Linda joined the MCW Board of Trustees in 1994 and served as board chair from 2008 to 2010. She has also served as a board member of Medical College Physicians, the largest healthcare practice in the state.

The Center is deeply grateful to Linda and John for their generosity and for the trust this investment represents in our work as researchers and clinicians. As we seek to transform how patients are diagnosed and treated, we are proud to have them as partners.

"We truly hope our gift will inspire others to recognize the incredible work being done at MCW and Froedtert Hospital. The research-based healthcare we have access to in our community is world-class and worthy of our support."

– Linda and John Mellowes

Our Commitment to Education and the Community

At the heart of the Mellowes Center's mission lies a steadfast dedication to advancing research while nurturing the next generation of scientists, clinicians, and researchers. As the Thinking Next Generation video shows, our commitment extends beyond the confines of our academic pursuits; it encompasses an active engagement in shaping the future of aspiring minds and fostering a responsible role within our community.

VIDEO LINK

Central to this commitment are our initiatives aimed at empowering budding scientists. For instance, the MCW's Clinical & Translational Science Institute's 500 Stars program passionately provides mentorship and educational avenues to students from diverse backgrounds in middle school, high school, and college. By nurturing their interest in clinical and translational science, we aim to inspire and guide these future leaders.

The Mellowes Center also supports MCW's Summer Program for Undergraduate Research (SPUR). This Program is designed to enrich the academic journey of college students aspiring towards scientific-based graduate studies. Through hands-on research experiences, honing critical thinking skills, and fostering professional networks, we pave the way for their success across various scientific disciplines.

Community Outreach

In addition to these traditional educational activities, we proudly developed and hosted several 'Student Experience Days' welcoming over 100 participants in 2023. These immersive events offered insights into our cutting-edge laboratory facilities, engaged students in a hands-on DNA extraction activity, and facilitated a 'Careers in Science' panel, showcasing diverse career paths within the scientific realm.

Our collaboration with Ronald Reagan High School stands as a testament to our commitment to education. Mellowes Center played a key role in creating and providing these students in science-focused curriculums at a local Milwaukee High School a profound glimpse into the transformative power of genetics in treating rare diseases.

Beyond these educational endeavors, our team members actively seek avenues to contribute meaningfully to our community. Annually, we organize 'Snack Pack' lunches for local youth, conduct sock drives aiding the homeless population, and orchestrate holiday gift drives, bringing joy to over 100 young individuals in our area.

At the Mellowes Center, our dedication goes beyond research; it's about cultivating a generation of passionate scientists while fulfilling our responsibilities as compassionate stewards within our community.

Education Courses

As healthcare continues to shift towards personalized medicine, genetics and genomics are becoming critical components in nearly every branch of medicine. In response to this trend, the Mellowes Center, in partnership with groups like MCW's Institute for Health and Equity and Marquette University, has launched new degree-granting programs to prepare our region for a data-driven healthcare system and modern research. Our vision is to populate the future healthcare delivery system with professionals equipped with knowledge they need to take full advantage of the promise and opportunity that personalized medicine provides. Mellowes Center Faculty have played key roles in the development and continued delivery of the following M.S. programs:

Master of Precision Medicine

Launched in the fall of 2021, the online Precision Medicine Education program trains clinicians to better diagnose, treat, and prevent diseases by accounting for individual variations in genes, environments, and lifestyles. Ultimately, the program improves the ability of healthcare professionals to predict which treatments will work best for specific patients. The program currently has ten students and graduated its first student in the spring of 2023.

Master of Science in Genetic Counseling

This fall, MCW will welcome its fourth class to the program. This program trains genetic counselors who are skilled in providing patients and other members of the care team with information on the complex genetic basis of many diseases, leading to personalized screenings, diagnostic testing, and better treatments. In May 2023, the first class of nine students graduated; 100 percent of them found employment, including five who remained in Wisconsin.

Masters in Bioinformatics

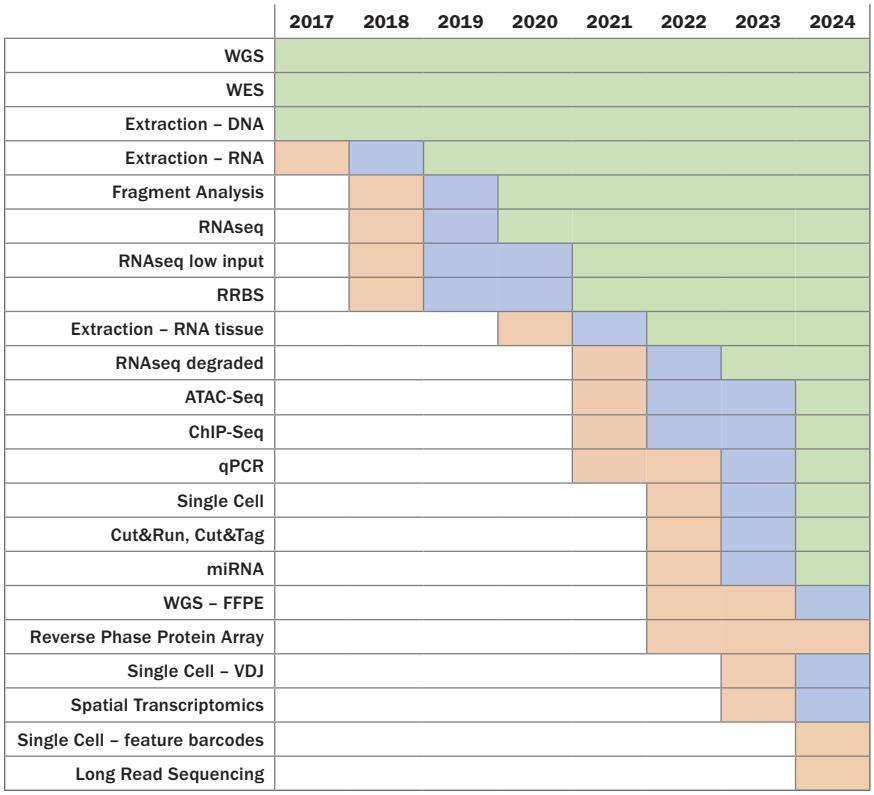
Now in its second year, this program is offered jointly with the Marquette University with an improved, convenient curriculum for students on both campuses. It is designed to equip graduates with a unique blend of theoretical and computational skills and practical experience in the rapidly expanding and evolving field of Bioinformatic analysis.

Technology & Innovation

'Omics Resources

The Mellowes Center is revolutionizing research at MCW by introducing cutting-edge technologies and innovative tools for investigators. Key advancements include the onboarding of the latest single-cell instruments and assays, enabling researchers to analyze cellular heterogeneity with unprecedented precision. We have the capability to not only look at gene expression, but also V(D)J recombination, cell surface antigens, and soon the epigenome as well. Additionally, the implementation of high-definition spatial transcriptomics allow researchers the detailed mapping of gene expression within tissue contexts, offering new insights into spatially resolved biological processes. The Center has also onboarded long-read sequencing methodology through Oxford Nanopore, providing comprehensive genomic data that highlights nucleic acid modifications (5mC, 5hmC, 6mA, 4mC) and surpasses traditional short-read methods. With the ability to map structural variants, phase haplotypes, assess epigenetic modifications, and consider full-length transcript isoforms from native DNA and RNA, we can now fully explore the mechanisms of the genome. These state-of-the-art resources are empowering MCW investigators to push the boundaries of biomedical research and achieve groundbreaking discoveries.

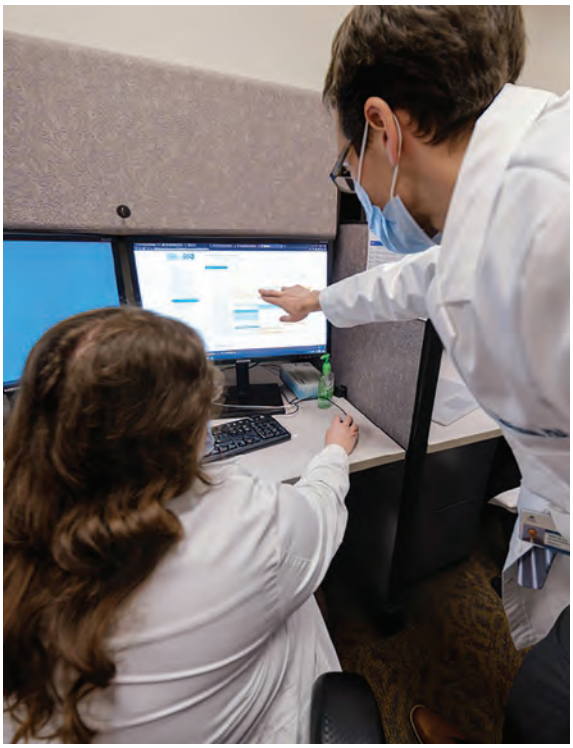
Timeline of Assay and Technology Development



Service Offered
Standardizing
Development

Data Science

The Mellowes Center is at the forefront of integrating advanced data science innovations to enhance research capabilities at MCW. By leveraging sophisticated data analytics, machine learning, and artificial intelligence, the center is transforming raw data into actionable insights. High-performance computing infrastructure allows for the efficient processing of large-scale datasets generated by cutting-edge technologies such as single-cell sequencing and spatial transcriptomics. The Center also emphasizes data integration, facilitating the combination of diverse data types to create comprehensive biological models. These innovations enable investigators to uncover hidden patterns, predict biological behaviors, and accelerate the pace of scientific discovery, ultimately leading to more personalized and effective healthcare solutions.



Donald Basel, MBBCh FACMG

- Division Chief and Professor, Pediatrics (Genetics)
- The Iris and Luis Garcia Chair for Fetal Diagnostics and Therapy
- Program Director, Center of Excellence, National Organization for Rare Disorders
- Program Director, Diagnostic Center of Excellence, Undiagnosed Disease Network
- Associate Director, Undiagnosed & Rare Diseases, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
- Medical Director, Genetics Center, Children's Wisconsin
- Co-program Director, Neurofibromatosis and RASopathy, Children's Wisconsin

Awards, Honors, and Memberships

- Rare Disease Center for Excellence National Organization for Rare Disorders
- Diagnostic Center of Excellence for the NIH Undiagnosed Disease Network
- Association of Professors of Human and Medical Genetics
- International Skeletal Dysplasia Society
- Fellow of the American College of Medical Genetics and Genomics

Research Interests

Dr. Donald Basel, a professor and division chief of Genetics (Dept of Pediatrics) at the MCW, has dedicated his career to the study of rare diseases. As the Associate Director of the Undiagnosed and Rare Disease Program within the Mellowes Center for Genomic Sciences and Precision Medicine, Dr. Basel focuses on identifying and understanding complex genetic disorders. His research interests span a wide range of rare disorders, including skeletal connective tissue disorders, and neurocutaneous syndromes. Dr. Basel's expertise allows him to provide valuable insights into the diagnosis and management of these rare diseases. His work not only contributes to the scientific understanding of rare conditions but also directly impacts patient care by helping to end diagnostic odysseys for those affected by rare genetic disorders.

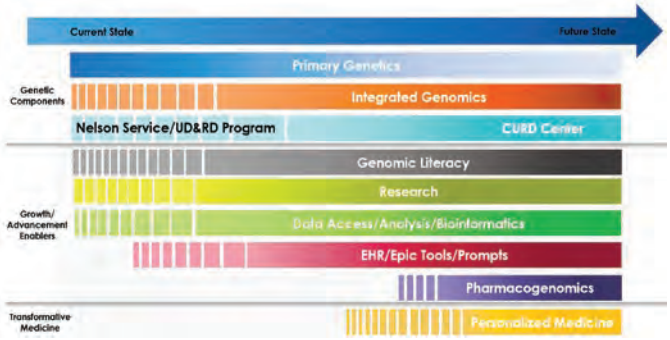
Highlights

Dr. Basel's unwavering commitment to advance research and care for individuals with rare diseases has culminated in the recognition as a designated Center of Excellence for NORD (National Organization for Rare Disorders) and we have joined the prestigious ranks of the NIH Undiagnosed Disease Networkas a Diagnostic Center of Excellence. These achievements further solidify our position as a hub for cutting-edge research and comprehensive diagnostic capabilities. This work has additionally resulted in the establishment of a Rare Disease Treatment Center which together with our robust clinical trial infrastructure will further serve the rare disease community and boost our collaborative research efforts as a leading institution in this field.

Publications

- Kinney, A., et al., *Single center experience developing sustainable genetics clinical care: a model to address workforce challenges in Medical Genetics.* Current Opinion in Pediatrics (in press)
- Thorpe, E., et al., *The impact of clinical genome sequencing in a global population with suspected rare genetic disease.* Am J Hum Genet, 2024. 111(7): p. 1271-1281.
- Singh, E., et al., *Computational structural genomics and clinical evidence suggest BCKDK gain-of-function may cause a potentially asymptomatic maple syrup urine disease phenotype.* JIMD Rep, 2024. 65(3): p. 144-155.

Genetics Strategic Themes



Hui-Zi Chen, PhD

- Assistant Professor, Medicine, Division of Hematology and Oncology

Awards, Honors, and Memberships

- American Association of Cancer Research
- American Society of Clinical Oncology
- International Association for the Study of Lung Cancer
- Society for Immunotherapy of Cancer

Research Interests

Dr. Hui-Zi Chen is a medical oncologist specializing in thoracic and rare cancers and a physician scientist committed to genomics research in advanced solid cancers. As a clinician, she aims to provide compassionate, evidence-based and personalized care to her cancer patients. She has participated in the development of multiple genomics-driven clinical trials and have routinely led discussions at Molecular Tumor Boards to aid oncologists in the interpretation and clinical applicability of results from genomic testing. Dr. Chen is a faculty member in the Discovery and Developmental Therapeutics Research Program at the Medical College of Wisconsin Cancer Center and core faculty member in the Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine. As a physician scientist, she directs a research laboratory that aims to discover new therapeutic vulnerabilities in advanced solid cancers such as small cell lung cancer using high-throughput sequencing technologies and functional genomics.

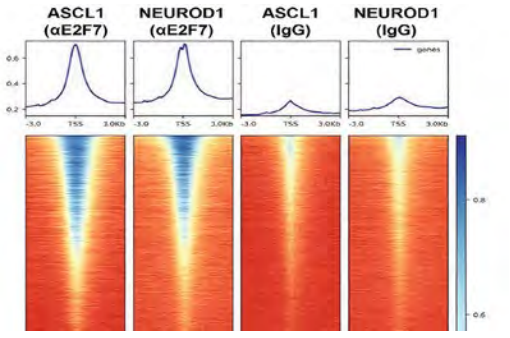
Highlights

– **2024 Grant received:** American Cancer Society IRG entitled “Unraveling the Role of E2F7-Regulated Gene Networks in Small Cell Lung Cancer Development

– **Clinical trial highlights:**

- Daiichi Sankyo Inc. DS3201-324: A study of valemetostat tosylate in combination with DXd ADCs in subjects with solid tumors NCT06244485
- Takeda. TAK280-1501: First in human study of TAK-280 in participants with solid tumors NCT05220098
- Taiho. TAS6417-201: A phase 1/2 trial of CLN-081 in patients with non-small cell lung cancer NCT04036682
- Shanghai Henlius Biotech. SHB-HLX10-005 ASTRIDE: To evaluate efficacy and safety of serplulilmab + chemotherapy in US patients with ES-SCLC NCT05468589
- Amgen. DeLLphi-305: Study comparing tarlatabmab and durvalumab versus durvalumab alone in first-line ES-SCLC following platinum, etoposide and durvalumab NCT06211036

Detecting Actionable Pathways in Small Cell Lung Cancer Subtypes



Publications

- Chen, H., et al., *PD-1 transcriptomic landscape across cancers and implications for immune checkpoint blockade outcome*. npj Genomic Medicine (Accepted)
- Thapa, B., et al., *Successful Targeting of Somatic VHL Alterations With Belzutifan in Two Cases*. J Immunother Precis Oncol 2024, JIPO-24-13
- Karan, D., et al., *Manzamine A reduces androgen receptor transcription and synthesis by blocking E2F8-DNA interactions and effectively inhibits prostate tumor growth in mice*. Mol Oncol, 2024. 18(8): p. 1966-1979
- Shreenivas A., et al., *ALK fusions in the pan-cancer setting: another tumor-agnostic target?* NPJ Precis Oncol 2023 7(1):101

Young-In Chi, PhD

- Research Scientist, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
- Assistant Professor, Department of Surgery, Division of Research

Awards, Honors, and Memberships

- American Society of Human Genetics

Research Interests

Dr. Chi's research focuses on integrating structural biology with computational approaches to study disease-associated genetic variants, particularly in chromatinopathies. His expertise spans from macromolecular structure analysis to molecular dynamics (MD) simulations of proteins involved in epigenetic regulation. At the Medical College of Wisconsin's Mellowes Center for Genomic Sciences and Precision Medicine, Dr. Chi conducts in silico experiments on proteins linked to syndromes like Claes-Jensen, Kabuki, and Kleefstra. His work combines multi-layered structural analyses, MD simulations, and biochemical assays to enhance the annotation of genomic variants. Dr. Chi's collaborative efforts aim to advance the understanding of epigenetics and chromatinopathies, with the ultimate goal of developing more precise, personalized approaches for disease management and treatment.

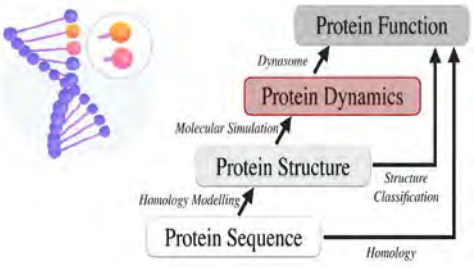
Highlights

The FY2024 marked substantial advances in understanding the structural and molecular dynamics of several research endeavors. Dr. Chi continues to be an integral investigator in the research into undiagnosed pediatric diseases under the broad category of Chromatinopathies, through interpretation of genetic variants that occur in epigenomic regulators. Combining his expertise in three-dimensional interpretation of gene variants with the team's understanding of disease phenotypes, they continue to close the gap in understanding critical components that alter individual gene structure and interactions among proteins in a complex. Additionally, Dr. Chi was instrumental in the development, submission, and acquisition of funding for the multi-PI project to investigate how Kleefstra Syndrome-associated genomic variants within EHMT1 alter structural dynamics and biochemical or biophysical properties to impact domain-specific functions. These achievements underscore his commitment to in silico cutting-edge science that seeks to further clarify the genetic to phenotypic link that may exit in rare epigenetic diseases.

Publications

- Singh, E., et al., *Computational structural genomics and clinical evidence suggest BCKDK gain-of-function may cause a potentially asymptomatic maple syrup urine disease phenotype.* JIMD Rep, 2024. 65(3): p. 144-155.
- Jorge, S.D., et al., *Deep computational phenotyping of genomic variants impacting the SET domain of KMT2C reveal molecular mechanisms for their dysfunction.* Front Genet, 2023. 14: p. 1291307.
- Chi, Y.I., et al., *A multi-layered computational structural genomics approach enhances domain-specific interpretation of Kleefstra syndrome variants in EHMT1.* Comput Struct Biotechnol J, 2023. 21: p. 5249-5258.
- Pollin, G., et al., *Writers and readers of H3K9me2 form distinct protein networks during the cell cycle that include candidates for H3K9 mimicry.* Biosci Rep, 2023. 43(10).

Protein mechanistic-based interpretation of genomic variants



Jing Dong, PhD

- Assistant Professor, Department of Medicine, Division of Hematology and Oncology
- Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
- Cancer Prevention and Outcomes, MCW Cancer Center

Awards, Honors, and Memberships

- DOM Faculty Development Award
- ASH, EHA, ASTCT, AACR, ASHG, TopMed mtDNA working group
- NCI Basic Mechanisms in Cancer Health Disparities Study Section

Research Interests

Dr. Dong's research interests are centered around the integration of high-throughput "omics" data into epidemiological studies, aiming to devise innovative approaches for mitigating the burden of cancer and addressing disparities in cancer outcomes. By leveraging advanced technologies and large-scale data sets, her work seeks to unravel the molecular intricacies underlying cancer development and progression. The overarching goal is to bridge the gap between genomics and epidemiology, providing insights that can inform targeted interventions and public health strategies. Through this integrative approach, she aspires to contribute to the advancement of knowledge in cancer research and play a role in shaping more equitable and effective approaches to cancer prevention and treatment.

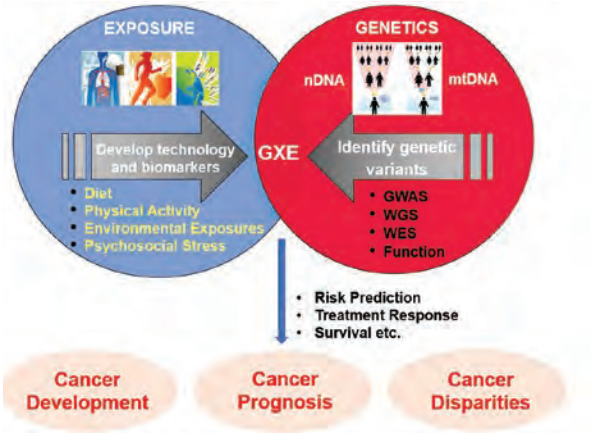
Highlights

In FY2024, Dr. Dong's research endeavors achieved significant milestones and recognition in the field of hematology and oncology, with future implications for improved prognostication and understanding of genetic factors in stem-cell transplantation outcomes and hematological diseases. Experimentally, she is focused on 1- mitochondrial inheritance including genomic and epigenomic factors, which will initiate innovative technology with the Mellowes Center and 2- investigating the landscape of pathogenic germline variants in multiple myeloma, through exome sequencing and DNA methylation analyses.

Publications

- Li, J.R., et al., *Enhancing prognostic power in multiple myeloma using a plasma cell signature derived from single-cell RNA sequencing.* Blood Cancer J, 2024. 14(1): p. 38.
- Auer, P.L., et al., *Donor germ-line variants associate with outcomes of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndromes.* Am J Hematol, 2024. 99(4): p. 770-773.
- Buradagunta, C.S., et al., *Identification of novel loci for multiple myeloma when comparing with its precursor condition monoclonal gammopathy of unknown significance.* Leukemia, 2024. 38(2): p. 383-385.

Dong Lab Overview



Xiaowu Gai, PhD

- Associate Director, Mellowes Center for Genomic and Precision Medicine
- Mellowes Endowed Chair in Systems Biology
- Professor of Pediatrics
- Director of Child Health Bioinformatics
- Division Chief, Bioinformatics and Quantitative Child Health

Awards, Honors, and Memberships

- American Society of Human Genetics
- American Association of Cancer Research

Research Interests

Dr. Xiaowu Gai was recently recruited to the Medical College of Wisconsin to serve as the Director of Child Health Bioinformatics with an endowed chair in Systems Biology at the Mellowes Center and Children's Wisconsin. Dr. Gai's research interests are aimed at understanding human genetic variation at the molecular genetic level and how it is related to human diseases using bioinformatics and genomics methodologies. Dr. Gai shares a common research interest in mitochondrial genomics with multiple investigators at Mellowes Center. Since 2012, Dr. Gai has co-led the International Mitochondrial Disease Sequence Resource (MSeqDR) Consortium. Dr. Gai has also been serving as a multi-PI for two NICHD-funded U24 grants while co-chairing the ClinGen Mitochondrial Disease Variant Curation Expert Panel and the ClinGen Mitochondrial Disease Gene Curation Expert Panel since 2017. He co-led the development of the ACMG guidelines for mitochondrial DNA (mtDNA) variant interpretation.

Highlights

Dr. Gai was the senior or co-senior author of four peer-reviewed publications, and a co-author for another four in FY 2024. The most impactful discovery was that germline ARID1B indels and mtDNA aberrations were oncogenic for pediatric chordoma. This study was published on Molecular Cancer Research and was covered by multiple news outlets, including EurekAlert, MedicalXpress, and News Medical. During FY24, Dr. Gai also received fundings for five grants as a PI, multi-PI and co-Investigator from National Institutes of Health, American Association of Cancer Research, Department of Defense, and Good Ventures foundation.

Publications

- O'Halloran, K., et al., *Pediatric Chordoma: A Tale of Two Genomes.* Mol Cancer Res, 2024. 22(8): p. 721-729.
- Maggo, S., et al., *A method for measuring mitochondrial DNA copy number in pediatric populations.* Front Pediatr, 2024. 12: p. 1401737.
- Shen, L., M.J. Falk, and X. Gai, *MSeqDR Quick-Mitome (QM): Combining Phenotype-Guided Variant Interpretation and Machine Learning Classifiers to Aid Primary Mitochondrial Disease Genetic Diagnosis.* Curr Protoc, 2024. 4(1): p. e955.

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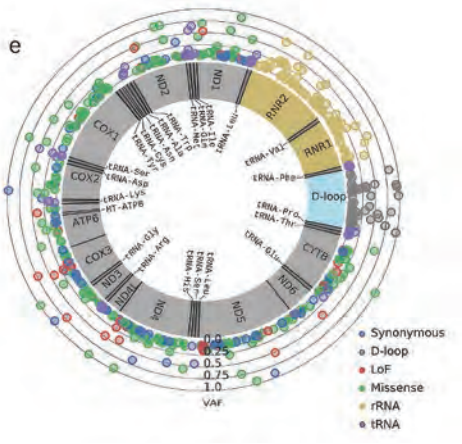
Mitochondrial DNA (mtDNA) Mutations in Pediatric Cancers



William Hogan, PhD

- Mary T. and Ted D. Kellner Chair of Data Science
- Director, Data Science Institute
- Professor, Data Science Institute
- Associate Director for Data Science, Mellowes Center for Genomic Sciences and Precision Medicine

Awards, Honors, and Memberships

- Mary T. and Ted D. Kellner Chair of Data Science

Research Interests

Dr. Hogan is professor and the founding director of the Data Science Institute. He has over 20 years experience in biomedical data science and informatics, including numerous leadership roles and accomplishments in building large-scale infrastructure, creating and implementing public health surveillance systems, developing and disseminating data standards, designing and validating artificial intelligence models, and innovating analysis methods. He has authored over 150 peer-reviewed publications describing this work. His core area of interest is biomedical ontology, or how to represent the types of things that are objects of study in healthcare and biomedical science in order to ensure that data are reusable and that information systems are interoperable. He is the creator and lead curator of three, major ontologies in the Open Biological and Biomedical Ontology (OBO) Foundry: the Drug Ontology, the Ontology of Medically Relevant Social Entities, and the Apollo-SV ontology.

Highlights

In FY2024, Dr. Hogan was part of a U01 proposal to NCI led by a principal investigator at the University College of London. This U01 scored a 29 and was approved by NCI Council. He also received All of Us program funding, serving as MCW site PI on the program's Center for Linkage and Acquisition of Data award. He published 17 articles. He recruited a postdoctoral fellow and established an ongoing collaboration with Dr. Michael Zimmerman on defining the spectrum of BAF related disorders.

Publications

- Wagner, M.M., et al., *Towards Machine-FAIR: Representing software and datasets to facilitate reuse and scientific discovery by machines.* J Biomed Inform, 2024. 154: p. 104647.
- Peng, C., et al., *A study of generative large language model for medical research and healthcare.* NPJ Digit Med, 2023. 6(1): p. 210.
- Dowland, S.C., et al., *Ontology of language, with applications to demographic data.* Applied ontology, 2023. 18(3): p. 239-262.

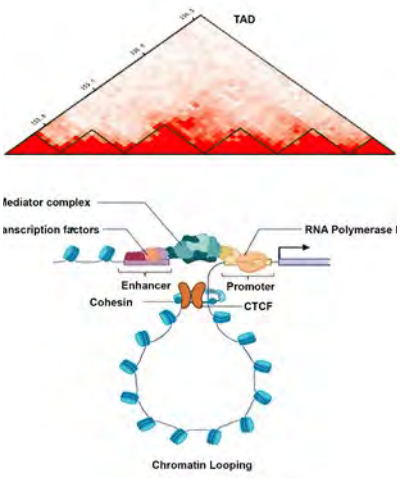
Victor Jin, PhD

- Director, Bioinformatics Shared Resource, Mellowes Center
- Associate Director for Bioinformatics and Systems Biology, Mellowes Center
- Professor, Data Science Institute, Biostatistics
- Mellowes Center Endowed Chair in Bioinformatics and Systems Biology

Awards, Honors, and Memberships

- Member, International Society for Computational Biology
- Editorial Board, BMC Genomics
- Member, American Association for the Advancement of Science (AAAS)

3D Chromatin Dynamics In Cancer



Research Interests

Dr. Jin's research interests revolve around pioneering genomics and computational methodologies aimed at discerning three-dimensional (3D) chromatin interactions from diverse omics-seq datasets. This involves developing innovative approaches to identify and understand the complex regulatory networks within the genome. Another focal point of his work lies in functionally and mechanistically characterizing the roles of epigenetic marks in cancer development and progression. Employing cutting-edge techniques such as 3C/ChIP/RT-qPCR, 3D-FISH, and CRISPR/Cas9, he aims to unravel the intricate epigenetic landscape associated with cancer, providing insights into potential therapeutic avenues. Furthermore, he is dedicated to adapting and applying genome-wide omics-seq techniques directly to patient tissues. This approach enables the identification of epigenetic-driven therapeutic targets and biomarkers, fostering a translational bridge between research findings and clinical applications for more effective and personalized medical interventions

Highlights

In the prolific FY2024, Dr. Jin and his dedicated lab members achieved significant milestones, publishing six peer-reviewed papers, including one in the prestigious Nature Communication. Demonstrating his leadership and expertise, Dr. Jin is currently overseeing the submission of three manuscripts as a co-/corresponding author. Notably, he has been an active participant in advancing scientific research through the submission of approximately 10 grant proposals at the NIH, DOD federal level, and foundation levels, serving as Principal Investigator, Co-Investigator, or Multi-PI. Dr. Jin's commitment to scholarly contributions extends to his role as an Editorial Board Member for BMC Genomics, where he has handled several manuscripts and engaged in reviewing numerous others. Additionally, Dr. Jin's impact is felt beyond his publications, as he was invited to deliver nine talks or seminar presentations at MCW, various meetings, and other esteemed institutions. Furthermore, his expertise was recognized in his participation in a NIH grant review panel and the HK GRC review panel, further solidifying his influential role in shaping and evaluating scientific advancements.

Publications

- Zhou, Y., et al., *Integration of scHi-C and scRNA-seq data defines distinct 3D-regulated and biological-context dependent cell subpopulations.* bioRxiv, 2023.
- Zhou, Y., et al., *3D Chromatin Alteration by Disrupting beta-Catenin/CBP Interaction Is Enriched with Insulin Signaling in Pancreatic Cancer.* Cancers (Basel), 2024. 16(12).
- Pollin, G., et al., *Ehmt2 inactivation in pancreatic epithelial cells shapes the transcriptional landscape and inflammation response of the whole pancreas.* Front Genet, 2024. 15: p. 1412767.

Razelle Kurzrock, MD, FACP

- Professor of Medicine
- Associate Director of Clinical Research
- Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine
- Endowed Chair of Precision Oncology, MCW Cancer Center
- Founding Director, Michels Rare Cancers Research Laboratories, Froedtert and MCW
- Associate Director of Clinical Research, Cancer Center
- Associate Director of Clinical Research, GSPMC

Awards, Honors, and Memberships

- Precision Medicine World Congress Pioneer Award
- Web of Science list of most cited scientists globally

Research Interests

Dr. Kurzrock's research interests encompass a comprehensive exploration of various diseases, with a particular focus on cancer. In the realm of cancer research, her work extends to investigating innovative treatments, specifically emphasizing the evolving field of immunotherapy and precision genomics. She has a particular interest in rare cancers and other rare diseases. Dr. Kurzrock's commitment to advancing precision medicine is evident in her integration of genomic insights into personalized therapeutic strategies. Through a multidimensional approach, her research aims to contribute to the ongoing evolution of medical knowledge and the development of targeted interventions that promise improved outcomes for individuals affected by cancer.

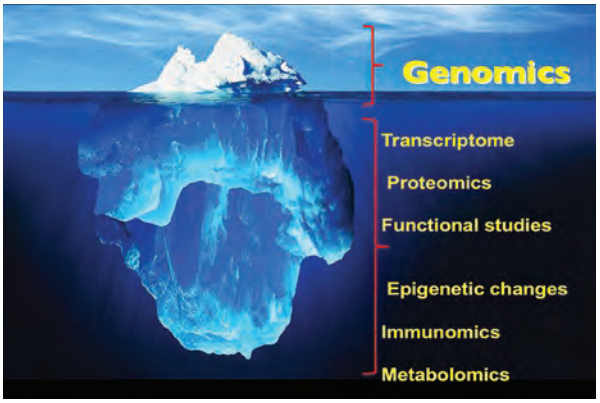
Highlights

In FY2024, Dr. Kurzrock opened new avenues in the field of precision immunotherapy and expanded precision medicine, especially for rare cancers. The goal of these studies is to impact and improve patient care, which led to the founding and expansion of a Precision Medicine and Rare Cancers Clinic at MCW. Dr. Kurzrock has published more than 1,000 peer-reviewed papers. She completed the DART trial, a national immunotherapy trial for rare cancers and the signature trial from the SWOG/NCI committee she chairs. This trial accrued approximately 900 patients and was conducted at over 1,000 sites. Results have already influenced NCCN guidelines for two rare cancers. Dr. Kurzrock has been invited to speak about her research by leading centers around the world, including the Nobel Symposium at Karolinska Institute in Stockholm, Sweden, in September 2023.

Publications

- Adashek, J.J., et al., *Neuregulin-1 and ALS19 (ERBB4): at the crossroads of amyotrophic lateral sclerosis and cancer.* BMC Med, 2024. 22(1): p. 74.
- Patel, S.P., et al., *Phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors (DART) SWOG S1609: adrenocortical carcinoma cohort.* J Immunother Cancer, 2024. 12(7).
- Subbiah, V., et al., *The evolving landscape of tissue-agnostic therapies in precision oncology.* CA Cancer J Clin, 2024. 74(5): p. 433-452

Tip of the Iceberg



Gwen Lomberk, PhD

- Joel and Arlene Lee Chair in Pancreatic Cancer Research
- Professor of Surgery, Pharmacology & Toxicology
- Chief, Division of Research
- Director, Basic Science Research
- Director, Precision Medicine Education Program, Institute of Health & Equity
- Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine

Research Interests

Dr. Lomberk continues to purse epigenomic-based pharmacology as it has the potential to improve pancreatic cancer (PDAC) treatment, the focus of her research. The laboratory aims to contribute to experimental therapeutics by combined inhibition of a genetic-to-epigenetic pathway to treat PDAC, which is crucial for enhancing the use of epigenetic inhibitors and translating similar approaches to other pathways to control cancer growth. Their data demonstrate that combined inhibition of the G2/M regulator, Aurora A, and the H3K9Me pathway synergistically inhibits PDAC growth. By inducing cell cycle arrest through AURKA inhibition, the mitotic machinery is exposed longer to the H3K9Me pathway, triggering a cytotoxic mechanism that ends in mitotic catastrophe, an attractive outcome in oncology. Her long-term research goals focus on studying histone methyltransferase complex regulation, its effects on protein-protein interactions and function, and the dynamics underlying epigenetic targeting consequences. Thus, her team is passionate about discovering molecular interactions and complex dynamics involved in epigenetic mechanisms triggered in response to cellular signals within the context of normal cell biology and pathophysiology to develop better therapeutic strategies for cancer.

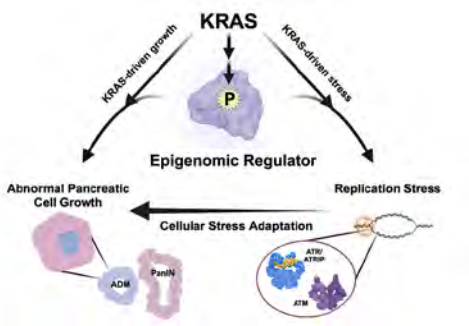
Highlights

In FY2024, Dr. Lomberk's research endeavors achieved notable milestones, marked by the publication of eight manuscripts and several grants submitted, each contributing to or planning for valuable research insights in the field of pancreatic cancer. Beyond publications and grants, our research findings were disseminated through guest lectures at prestigious institutions, including Mayo Clinic Arizona Grand Rounds and the University of Virginia Comprehensive Cancer Center Seminar.

Publications

- Pollin, G., et al., *Ehmt2 inactivation in pancreatic epithelial cells shapes the transcriptional landscape and inflammation response of the whole pancreas.* Front Genet, 2024. 15: p. 1412767.
- Chi, Y.I., et al., *A multi-layered computational structural genomics approach enhances domain-specific interpretation of Kleefstra syndrome variants in EHMT1.* Comput Struct Biotechnol J, 2023. 21: p. 5249-5258.
- Pollin, G., et al., *Writers and readers of H3K9me2 form distinct protein networks during the cell cycle that include candidates for H3K9 mimicry.* Biosci Rep, 2023. 43(10).

Epigenomic Regulation of Adaptation to Oncogene-Driven Stress in PDAC



Angela Mathison, PhD

- Assistant Professor of Surgery, Division of Research
- Director of ‘Omics at Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine

Awards, Honors, and Memberships

- Member Institutional Biosafety Committee, Medical College of Wisconsin, Milwaukee, WI
- Member Association of Biomolecular Resource Facilities (ABRF)

Research Interests

Dr. Mathison’s research interests encompass a multifaceted approach to advancing scientific understanding of disease initiation, establishment, and progression through technological applications. She specializes in 'Omics preparations, focusing on the seamless integration and utilization of cutting-edge assays across many disease disciplines. Her collaborative efforts focus on the intricacies beyond the base pairs, delving into the complex world of pigenetic alterations and gene regulation, particularly in the context of pancreatic cancer development. This research also allows her to consider the functional consequences of specific gene variations that can contribute to altered pathways at the cellular level and provide a comprehensive understanding of how genetic changes influence disease. Through extensive outreach and collaborative conversations, she connects molecular mechanisms with underlying pathological conditions to reveal potential opportunities to reverse or block disease progression.

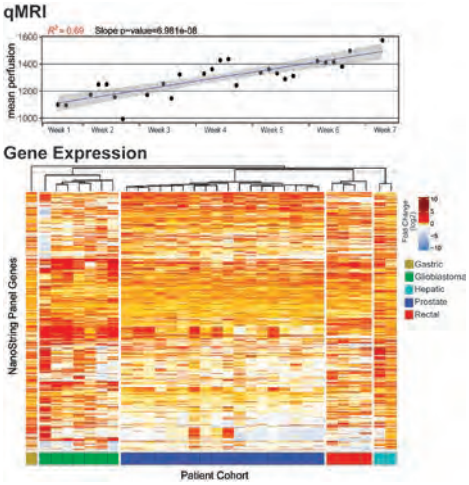
Highlights

In the dynamic landscape of FY2024, Dr. Mathison’s collaborative partnerships have flourished and are marked by several significant achievements. She has been able to serve as co-Investigator on 12 grants and further solidify her role in groundbreaking projects. The establishment, review, and rewarding of RFAs with CTSI have provided valuable resources and support for ongoing initiatives. She is proactively spreading awareness about Mellowes Center Resources for Researchers through seminars, research week posters, flyers, website updates, and more than 47 consultations. Additionally, she has lead the writing of AHW Educational Grants that support the Mellowes Center Symposiums. Her dedication to innovation is evident in the comprehensive approach to onboarding new technology from training, onboarding, protocol establishment, and successful project implementation.

Publications

- Pollin, G., et al., *Ehmt2 inactivation in pancreatic epithelial cells shapes the transcriptional landscape and inflammation response of the whole pancreas.* Front Genet, 2024. 15: p. 1412767.
- Hall, W.A., et al., *Changes in Daily Apparent Diffusion Coefficient on Fully Quantitative Magnetic Resonance Imaging Correlate With Established Genomic Pathways of Radiation Sensitivity and Reveal Novel Biologic Associations.* Int J Radiat Oncol Biol Phys, 2024. 120(2): p. 570-578.
- Kim, J., et al., *Transcriptional Profiling Underscores the Role of Preprocurement Allograft Metabolism and Innate Immune Status on Outcomes in Human Liver Transplantation.* Ann Surg Open, 2024. 5(2): p. e444.
- Zenga, J., et al., *Type I interferon signaling promotes radioresistance in head and neck cancer.* Transl Cancer Res, 2024. 13(5): p. 2535-2543.

Correlating qMRI and Genomic Pathway Changes in Tumors



John Meurer, MD, MBA

- Professor of Community Health and General Pediatrics
- Past Director, Precision Medicine Education Program
- Past Director of the Institute for Health & Equity

Awards, Honors, and Memberships

- MCW Distinguished Service Award, 2022
- AOA National Medical Honor Society, 2022

Research Interests

Dr. Meurer is Co-PI of NIH COVID epidemiology research with a focus on disparities and mortality, impact on vulnerable populations, public health communication and misinformation, vaccination and health outcomes. He is PI of a 2-year evaluation of STRYV365 peak team coaching and Brain Agents video game to improve self and social awareness, coping and relationship skills, and responsible decision-making among youth facing adversity. Dr. Meurer has led Translational Workforce Development for the Clinical and Translational Science Institute for a decade. He mentors 16 students and 6 faculty in research and career and leadership development.

Highlights

Dr. Meurer was founding Director of the MCW Precision Medicine education program including the MS degree, Certificate, CME and CEU program. In July 2024, Gwen Lomberk, PhD, replaced him as program director. He leads development of an online integrated selective course in precision medicine for medical students. Dr. Meurer is Co-Director of MPH courses in population health management and policy.

Publications

- Yuan, A.Y., et al., *Understanding racial/ethnic disparities in COVID-19 mortality using a novel metric: COVID excess mortality percentage.* Am J Epidemiol, 2024. 193(6): p. 853-862.
- Atanasov, V., et al., *Evidence on COVID-19 Mortality and Disparities Using a Novel Measure, COVID excess mortality percentage: Evidence from Indiana, Wisconsin, and Illinois.* PLoS One, 2024. 19(1): p. e0295936.
- Black, B., et al., *COVID-19 Boosters: If The US Had Matched Israel's Speed And Take-Up, An Estimated 29,000 US Lives Would Have Been Saved.* Health Aff (Millwood), 2023. 42(12): p. 1747-1757.
- Atanasov, V., et al., *Selection Effects and COVID-19 Mortality Risk after Pfizer vs. Moderna Vaccination: Evidence from Linked Mortality and Vaccination Records.* Vaccines (Basel), 2023. 11(5).

MCW and STRYV365 Research Team

Brian Smith, PhD

- Associate Professor, Department of Biochemistry
- Associate Director, Program in Chemical Biology
- Associate Director, Structural Genomics Unit, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine

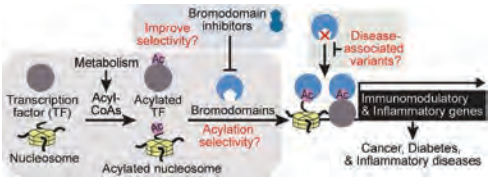
Research Interests

The Smith laboratory studies how epigenetic ‘writer’, ‘reader’, and ‘eraser’ proteins interact with the histone language and cellular metabolism to dynamically regulate gene expression across different cell types and disease states. They employ an impressive array of cutting-edge techniques (ranging from small molecule synthesis and biophysical analyses to cell biology and animal studies) to explore the roles of epigenetic proteins and their downstream cellular impacts in the context of cancer and diabetes.

Highlights

In FY2024, the Smith laboratory achieved significant milestones, reflecting a breadth of accomplishments across various domains. Noteworthy advancements include renewing two premier National Institutes of Health awards, an R35 from the National Institute of General Medical Sciences and an R01 from the National Institute of Diabetes and Digestive and Kidney Diseases. The Smith laboratory also continued its successful continuation of trainee fellowships, with Karina Bursch continuing an F30 from the National Cancer Institute and Dr. Josh Nord continuing a postdoctoral fellowship from Breakthrough T1D. Dr. Smith delivered an invited talk at the FASEB Biology of Acetylation in Health and Disease conference in Rome, Italy, where Dr. Nord also won the First Place Poster Award. Paul Sidlowski was invited to give a talk at the annual Midwest Islet Club at the University of Chicago. The dissemination of knowledge continued through the publication of 12 peer-reviewed articles across esteemed journals, including Computational Structural Biotechnology Journal, Current Opinion in Chemical Biology, Journal of Medicinal Chemistry, ACS Chemical Biology, Molecular Pharmacology, Frontiers in Genetics, and Journal of Biological Chemistry. Finally, Dr. Smith's commitment to institutional service was also displayed through his appointment to the Mentoring Committee for the Medical Scientist Training Program, the Strategic Planning Committee for the Data Science Institute, and Co-Director of the Enrichment Core within the Wisconsin Diabetes Research Center.

Smith Laboratory Overview



Publications

- Bursch, K.L., et al., *Cancer-associated polybromo-1 bromodomain 4 missense variants variably impact bromodomain ligand binding and cell growth suppression.* J Biol Chem, 2024. 300(4): p. 107146.
- Jorge, S.D., et al., *Deep computational phenotyping of genomic variants impacting the SET domain of KMT2C reveal molecular mechanisms for their dysfunction.* Front Genet, 2023. 14: p. 1291307.
- Chi, Y.I., et al., *A multi-layered computational structural genomics approach enhances domain-specific interpretation of Kleefstra syndrome variants in EHMT1.* Comput Struct Biotechnol J, 2023. 21: p. 5249-5258.
- *Ratnasinghe, B.D., et al., Beyond structural bioinformatics for genomics with dynamics characterization of an expanded KRAS mutational landscape.* Comput Struct Biotechnol J, 2023. 21: p. 4790-4803.

Raul Urrutia, PhD

- Warren P. Knowles Chair of Genomics and Precision Medicine
- Director, Mellowes Center for Genomic Sciences and Precision Medicine
- Associate Director, Precision Medicine, CTSI
- Director, Data Science Graduate Program, MCW-MU
- Director, Precision Medicine Discovery and Invention Laboratory
- Professor of Surgery, Biochemistry, and Physiology

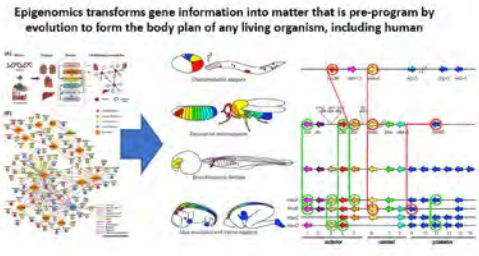
Research Interests

Dr. Raul Urrutia is a distinguished systems biologist exploring epigenomic complexes associated with rare monogenic diseases, rare cancers, and specific cancer subtypes. His research has been instrumental in advancing the understanding of KLF reprogramming factors, the family used to generate iPSC. His laboratory has significantly contributed to basic science, focusing on transcription and chromatin dynamics by integrating methodologies from protein chemistry, molecular biophysics, cell biology, genomics, and epigenomics alongside advanced data science techniques such as gene network modeling and molecular dynamics simulations. Through his investigations into enhancers and super-enhancers, Dr. Urrutia has enhanced knowledge regarding controlling pancreatic ductal adenocarcinoma (PDAC) subtypes, employing an integrative, data-driven approach to multi-omics. Therefore, Dr. Urrutia's research sits at a transformative intersection where his extensive expertise aligns with his innovative work in Genomic Medicine. He is dedicated to improving our understanding of rare and undiagnosed diseases by utilizing a robust foundation in systems biology and computational molecular biophysics. A central aspect of his approach is precision genomics, a field with the potential to revolutionize diagnostic methodologies, thereby expediting the diagnostic process for patients with monogenic and complex conditions and enhancing the accuracy of clinical outcomes. Using both multidimensional methodology and data science. Paradigmatically, Dr. Urrutia has been mapping epigenomic regulator networks that form the body plan (Figure) in an effort to discover molecular mechanisms and their impact on health and disease.

Highlights

In FY2024, Dr. Urrutia's collaborative efforts and partnerships led to significant advances in research and academic achievements. His team achieved the acceptance of 17 papers, showcasing the dedication and expertise of his collaborators and extramural colleagues. Special recognition goes to the Mellowes Center Faculty and Administrative Partners for their invaluable support in submitting three grants. Noteworthy accomplishments include securing an R35 with Dr. Zimmermann, an R21 proposal with Dr. Chi, and an AHW proposal. Dr. Urrutia extends gratitude to those who contributed to Midwest Partnerships, National Collaborations, and the successful launch of the Mellowes Global Program.

Additionally, his efforts have been instrumental in forming the Children's Health Bioinformatics Unit and recruiting Dr. Gai as its Director. His leadership in establishing the Population Sciences Unit, with Dr. Zimmermann and their plans to recruit another Mellowes Chair, further exemplifies Dr. Urrutia's commitment to advancing research and making meaningful contributions to the scientific community.



Epigenomics transforms gene information into matter that is pre-program by evolution to form the body plan of any living organism, including human

Publications

- Santofimia-Castano, P., et al., *Targeting NUPR1-dependent stress granules formation to induce synthetic lethality in Kras(G12D)-driven tumors*. EMBO Mol Med, 2024. 16(3): p. 475-505.
- Jorge, S.D., et al., *Deep computational phenotyping of genomic variants impacting the SET domain of KMT2C reveal molecular mechanisms for their dysfunction.* Front Genet, 2023. 14: p. 1291307.
- Chi, Y.I., et al., *A multi-layered computational structural genomics approach enhances domain-specific interpretation of Kleefstra syndrome variants in EHMT1*. Comput Struct Biotechnol J, 2023. 21: p. 5249-5258.

Brian Volkman, PhD

- Professor of Biochemistry
- Director, Program in Chemical Biology
- Director, Structural Genomics Unit
- Associate Director, Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine

Awards, Honors, and Memberships

- Invited speaker at NIH and VU Amsterdam
- Invited speaker, 4th European Chemokine and Cell Migration Conference, Rega Institute, University of Leuven, Belgium
- Invited speaker, Gordon Research Conference on Chemotactic Cytokines, Portland, Maine

Research Interests

Dr. Volkman's research aims to develop innovative cancer and disease treatments by examining the three-dimensional architecture of proteins involved in disease and synthesizing new drug candidate molecules. This interdisciplinary work combines the expertise of chemists, structural biologists, and clinician-scientists in designing and testing potential therapies. Graduate students in their group have created and patented promising compounds for cancer and psoriasis treatment. They use NMR spectroscopy and many other techniques to (1) understand the transmission of biological signals in terms of molecular structure, recognition and dynamics and (2) exploit this knowledge for the design and discovery of new molecules with practical utility as research tools, bioactive nanomaterials, or new drugs.

Their research explores the intricate relationship between protein structure and function, revealing novel concepts like 'metamorphic' proteins that challenge established folding paradigms. They investigate the thermodynamic and evolutionary origins of these proteins, using human lymphotactin as a model. Additionally, they study how biological signals are controlled by protein interactions, particularly focusing on chemokines implicated in various diseases. By solving the structure of the first chemokine-receptor complex using NMR, they have developed a hybrid in silico/NMR approach to screen for inhibitors. This method targets multiple chemokines, aiming to discover drugs that could potentially treat conditions such as inflammation, cancer, viral infections, autoimmune diseases, and specifically, metastatic cancer and psoriasis.

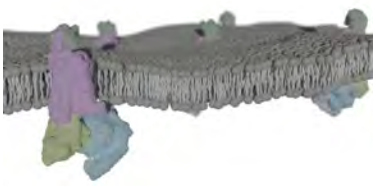
Highlights

The FY2024 marked substantial advances in the team's research endeavors, showcasing the collective achievements of the team members. Jacob significantly contributed to our understanding by generating valuable GLP variant peptide binding data and conducting circular dichroism measurements, elucidating critical aspects of peptide interactions. Meanwhile, Davin emerged as a prolific coauthor, lending expertise to four papers published by the Mellowes Center or Program in Chemical Biology, and notably, collaborating on a paper in PNAS focusing on designed proteins in partnership with David Baker's lab. Furthermore, their research programs saw tangible success with the acquisition of grants. The Program in Chemical Biology secured a new Multi-PI R01 in the spring, led by Dr. Volkman, underscoring the impactful nature of their ongoing investigations. Later in the fall, the Multi-PI DoD grant, spearheaded by Dr. Smith, further highlighted the team's recognition and support for pioneering research in the field. These 2024 achievements underscore their commitment to cutting-edge science, collaborative efforts, and securing external support for innovative research pursuits.

Publications

- Jorge, S.D., et al., *Deep computational phenotyping of genomic variants impacting the SET domain of KMT2C reveal molecular mechanisms for their dysfunction.* Front Genet, 2023. 14: p. 1291307.
- Kerber, P.J., et al., *Fragment-based screening by protein-detected NMR spectroscopy.* Methods Enzymol, 2023. 690: p. 285-310.
- Ratnasinghe, B.D., et al., Beyond structural bioinformatics for genomics with dynamics characterization of an expanded KRAS mutational landscape. Comput Struct Biotechnol J, 2023. 21: p. 4790-4803.

Structural dynamics of chemokine receptor activation and inhibition



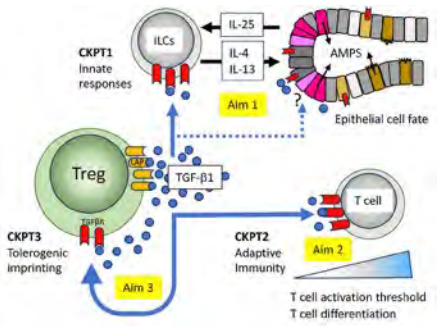
Calvin Williams, PhD

- Professor, Pediatrics and Microbiology & Immunology
- Associate Dean of Research
- Associate Director, Medical Scientist Training Program
- Chief Scientific Officer, Children's Wisconsin Research Institute
- Chief, Pediatric Rheumatology
- Vice Chair, Research, Pediatrics
- Associate Director, Mellowes Center for Genomic Sciences and Precision Medicine

Awards, Honors, and Memberships

- Barri L. Drury Endowed Chair for CRI Chief Scientific Officer
- D.B. and Marjorie Reinhart Chair in Rheumatology, Children's Wisconsin

Essential Role of Treg TGF-b1



Research Interests

The broad, long-term objective of research in Dr. William's laboratory is to establish the mechanisms that promote T cell development in the thymus and maintain T cell tolerance in the periphery. Special emphasis is placed on the role of Foxp3 regulatory T (Treg) cells and they have developed mouse models that are widely used to study Treg cell function. This body of work has contributed to their understanding of T cell receptor antagonism as potent mechanism of peripheral tolerance, the mechanisms of Treg cell-mediated suppression in models of inflammatory autoimmune disease, the role of Foxp3 in Treg cell development, and the identification of "induced" Treg (iTreg) cells as an essential regulatory subset required for mucosal tolerance.

Dr. Williams' lab's current work is focused on the role for Treg cell-produced TGF-b1, which is tightly associated with the generation of this ROR-gt+ Treg subset and with durable mucosal tolerance. The central hypothesis is that the privileged role for Treg cell-produced TGF-b1 arises due to the capacity of Tregs to directly deliver TGF-b1 during a critical developmental window at 3 major checkpoints (CKPTs), making Treg cells the indispensable source of this pleotropic cytokine. They show that a critical reinforcing feedback loop in the gut becomes dysregulated when innate immune populations drive high tissue levels of levels of IFN-g, IL-4, and IL-13. This disturbed cytokine network has broad effects. IL-13 pushes intestinal stem cell differentiation toward tuft and goblet cells and degranulates Paneth cells (CKPT1). IFN-g mediated APC activation combines with a lower T cell activation threshold to both broaden and skew specialized lymphocyte subset maturation (CKPT2). ROR-gt Treg cell development is abrogated in favor of Th2/Th17 effectors. The production and specificity of secreted immunoglobulins changes as the isotypes produced shift from IgA to IgE. The resulting dysbiotic bacterial communities then feedback on the developing immune system to amplify these pathogenic responses (CKTP3).

Publications

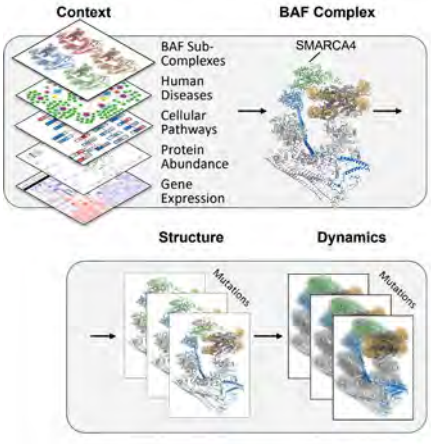
- Sabbagh, S.E., et al., *Patients with juvenile idiopathic arthritis have decreased clonal diversity in the CD8(+) T cell repertoire response to influenza vaccination.* Front Immunol, 2024. 15: p. 1306490.
- Khatun, A., et al., *BATF is Required for Treg Homeostasis and Stability to Prevent Autoimmune Pathology.* Adv Sci (Weinh), 2023. 10(28): p. e2206692.

- Director of Computational Structural Genomics Unit, Mellowes Center
- Inaugural Director, Community-Oriented and Genomics-Informed Precision Medicine Unit, Mellowes Center
- Assistant Professor, Data Science Institute, Medical College of Wisconsin

Awards, Honors, and Memberships

- Rare Disease Center for Excellence National Organization for Rare Disorders
- Diagnostic Center of Excellence for the NIH Undiagnosed Disease Network
- Association of Professors of

Mechanistic studies of the human diseases caused by mutation of the BAF chromatin remodeling complex.



Michael T. Zimmermann, PhD

Research Interests

Dr. Zimmermann focuses on pioneering advancements in genomics interpretation, specifically at the intersection of structural bioinformatics, computational biology, and genomics. Driven by a deep understanding of human biology, biophysics, and disease mechanisms, the lab tackles complex challenges in cancer and rare diseases where much genetic variation remains uninterpreted. We develop novel approaches and enhanced applications of next-gen genomics interpretation. The lab aims to decode the effects of genomic alterations on key oncogenes like KRAS and epigenetic regulatory genes, including SMARCA4, that act within diverse BAF sub-complexes. Modeling the impact of mutations within the proper context is a crucial focus of current developments. Context-specific differences can explain presentation patterns of rare diseases and why tumors arising from each human organ have the profile observed in the clinic. The ultimate goal is to make genomics accessible, practical, and beneficial for individuals by providing valuable insights into the underlying mechanisms of genetic variations.

Highlights

In FY2024, Dr. Zimmermann received his first NIH grant, dedicated to investigating the effects of mutations in RAG2 that underlie immunodeficiency and autoimmunity syndromes. His research aims to uncover how these mutations alter the epigenetic reading capacity, potentially directing the RAG recombinase to different genomic regions. Additionally, he received a grant to establish the Community-Oriented and Genomics-Informed Precision Medicine Unit, which seeks to address gaps in the community's top issue: disparities in mental health-related disorders. Dr. Zimmermann's team also achieved a significant milestone by publishing the first of their large-scale dynamics modeling studies on KRAS. This work validates the relevance of structure-based simulations for genomic variant interpretation and explores "beyond structural bioinformatics" to aid in the mechanistic understanding of 86 distinct mutations. His commitment to advancing scientific knowledge is further demonstrated by the strengthening of national and international collaborations, promoting a global approach to transformative research in his field.

Publications

- Ratnasinghe, B.D., et al., *Beyond structural bioinformatics for genomics with dynamics characterization of an expanded KRAS mutational landscape.* Comput Struct Biotechnol J, 2023. 21: p. 4790-4803.
- Haque, N., et al., *RAG genomic variation causes autoimmune diseases through specific structure-based mechanisms of enzyme dysregulation.* iScience, 2023. 26(10): p. 108040.
- Dsouza, N.R., et al., *Structural and Dynamic Analyses of Pathogenic Variants in PIK3R1 Reveal a Shared Mechanism Associated among Cancer, Undergrowth, and Overgrowth Syndromes.* Life (Basel), 2024. 14(3).
- Chi, Y.I., et al., *A multi-layered computational structural genomics approach enhances domain-specific interpretation of Kleefstra syndrome variants in EHMT1.* Comput Struct Biotechnol J, 2023. 21: p. 5249-5258.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