

MOLECULAR AND HUMAN GENETICS



2026

ACCREDITATION

Baylor College of Medicine is accredited by the Southern Association of Colleges and Schools Commission on Colleges to award masters and doctorate degrees. Contact the Commission on Colleges at 1866 Southern Lane, Decatur, GA 30033-4097 or call (404) 679-4500 for questions about the accreditation of Baylor College of Medicine. The Commission should be contacted only if there is evidence that appears to support Baylor's significant non-compliance with a requirement or standard.

NOTICE OF NONDISCRIMINATION

Baylor College of Medicine is committed to a safe and supportive learning and working environment for its learners, faculty and staff. College policy prohibits discrimination on the basis of race, color, age, religion, gender, gender identity or expression, sexual orientation, national origin, veteran status, disability or genetic information. Harassment based on any of these classifications is a form of discrimination and also violates College policy (02.2.25, 02.2.26) and will not be tolerated. In some circumstances, such discriminatory harassment also may violate federal, state or local law.

MOLECULAR AND HUMAN GENETICS

The logo for Baylor College of Medicine, featuring the text "Baylor College of Medicine" in a white serif font, centered within a dark blue square.

Baylor
College of
Medicine

BCM.EDU/GENETICS

MESSAGE FROM THE CHAIR

I am pleased to introduce you to the Department of Molecular and Human Genetics at Baylor College of Medicine. Our mission is to transform medicine with the science and practice of genetics and genomics. The integrated research, clinical and diagnostic activities housed within our department have made us a leader in basic science discover, translation, and the implementation of genomic medicine.

The Department remains a top-ranked genetics program, ranking first among other U.S. genetic departments in total awarded funding and number of grants from the National Institutes of Health for fourteen consecutive years.

We continue to lead in the diagnostic testing arena with Baylor Genetics, our joint venture first established with H.U. Group Holdings, Inc., over ten years ago. This jointly governed laboratory continues to support the academic mission and innovation of the department while promising to extend the impact of genetic diagnostic testing worldwide.

Our faculty continue to deliver on our clinical, training and research missions at home and abroad through our regional, national and global partnerships.

In addition, new and continuing consortia with the NIH and industry are leading to new gene discoveries and advancements in the implementation of genetics and genomics in medicine. These consortia include the Genomic Research to Elucidate the Genetics of Rare diseases (GREGoR), the Knockout Mouse Phenotyping Program (KOMP), the Center for Precision Medicine Models (CPMM), Clinical Genome Resource (CLINGEN), the Somatic Mutations across Human Tissues (SMaHT), and multiple consortia in the Rare Diseases Clinical Research Network (RDCRN).

The Baylor College of Medicine Undiagnosed Diseases Center (UDC) houses our NIH



Undiagnosed Diseases Network (UDN) clinical site and continues to provide clinical services and genetic testing and analysis to assess patients who have not received a diagnosis for their condition. The NIH-supported Project TEXOME, GIVE and MAGNET studies address access to genomic care expertise for underserved families and healthcare providers in Texas. These three genomic medicine projects utilize the Consultagene platform to provide access to genetic evaluation, peer-to-peer consultation and genetic counseling.

Baylor's *All of Us* Evenings with Genetics Research Scholar Program is now in its fifth year and has completed three successful Biomedical Researcher Faculty Summits.

The future holds much promise due to the talent and dedication of our renowned faculty, trainees and staff. I consider myself privileged to be a part of this exciting and vital effort.

Best regards,

A handwritten signature in black ink, appearing to read 'B. Lee' with a stylized flourish at the end.

Brendan Lee, M.D., Ph.D.
Robert and Janice McNair Endowed Chair
in Molecular and Human Genetics

CONTENTS

About the Department **6**

Graduate and Medical Education **8**

Clinical Affairs **13**

Diagnostic Laboratory Affairs **14**

Community Outreach **19**

Research Faculty **20**

Primary Appointments **21**

Secondary Appointments **87**

Baylor College of Medicine **96**

Texas Medical Center **97**

Houston **98**

Baylor College of Medicine Affiliated
Hospitals, Institutions and Facilities Map **99**

ABOUT THE DEPARTMENT



Huda Zoghbi, M.D.



Richard Gibbs, Ph.D.

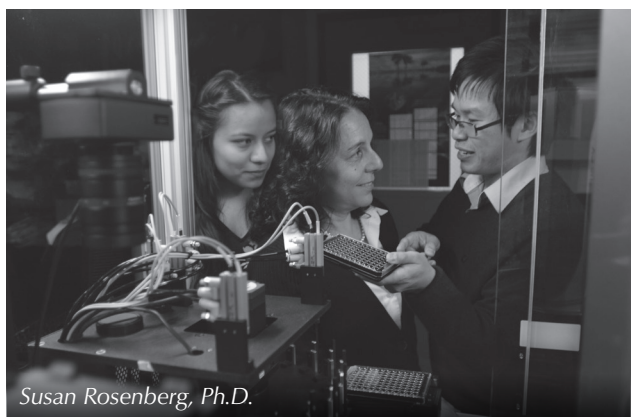
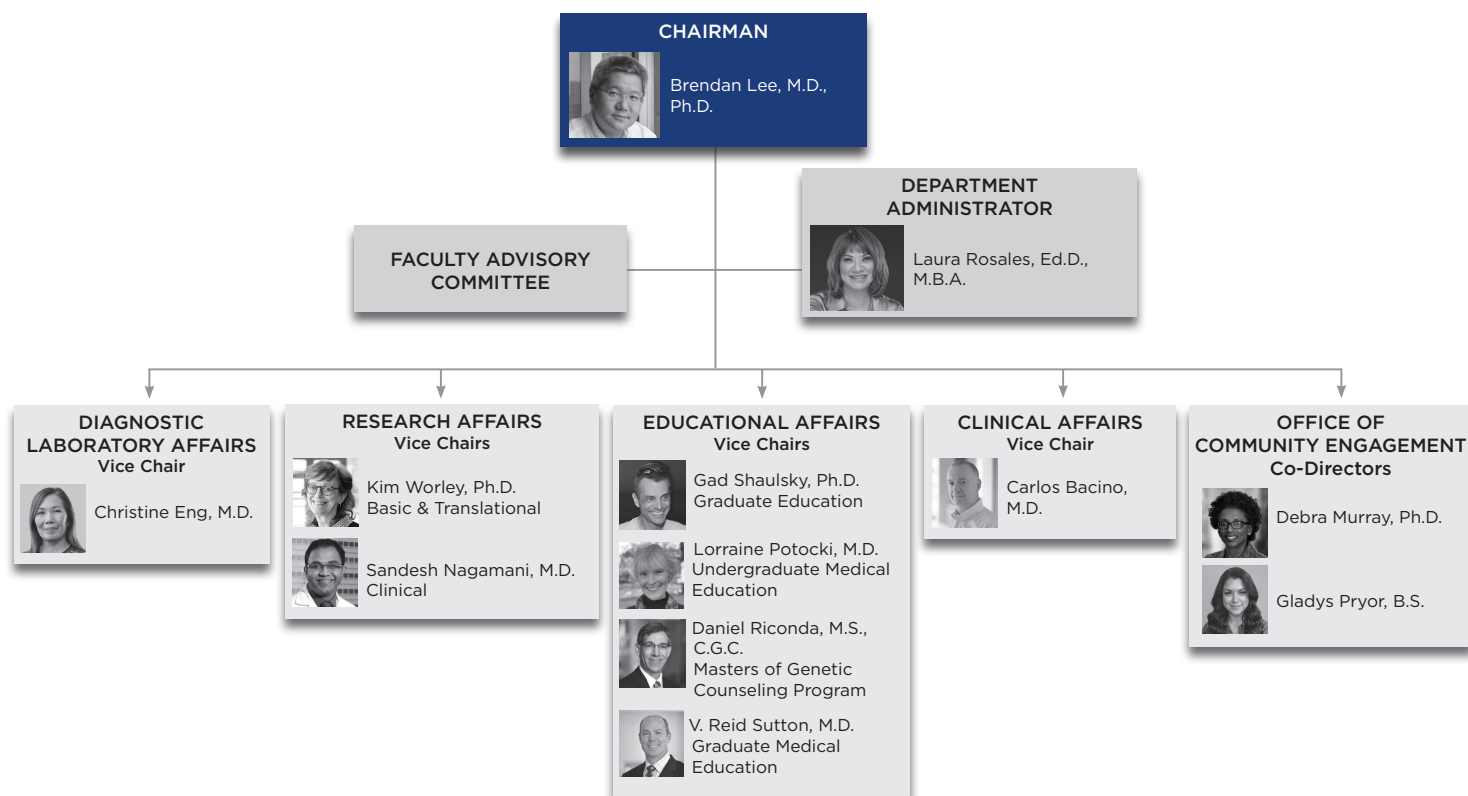
The Institute for Molecular Genetics was created in 1985, and the Department of Molecular and Human Genetics was established in 1994. The Department embodies more than five decades of organized genetics activity at Baylor College of Medicine. Beginning in the 1970's with the arrival of Drs. C. Thomas Caskey and Arthur Beaudet, it has become the leading genetics program in the world. The Department is currently chaired by Dr. Brendan Lee, the Robert and Janice McNair Endowed Chair and professor of molecular and human genetics at Baylor, and offers a variety of research, clinical and training programs in genetics and genomics to graduate students, medical students, postdoctoral research fellows and medical genetics residents. The Department integrates basic research in genetic and genomic mechanisms; translational research in disease models; observational and therapeutic clinical trials in rare and common genetic diseases; reproductive, pediatric and adult medical genetics care; and cutting-edge genetic diagnostic services.

We have more than 540 faculty, trainees and staff in the Department. Our research faculty are joined by clinical, genetic counseling and diagnostic laboratory faculty in our mission to transform medicine with the science and practice of genetics and genomics. Our faculty include elected members of the National Academy of Sciences, the National Academy of Medicine, the Academy of Arts and Sciences and the American Association for the Advancement of Science.

The Human Genome Sequencing Center at Baylor College of Medicine, led by Dr. Richard Gibbs, the Wofford Cain Chair and professor of molecular and human genetics at Baylor, is a major strength of the research environment. Other important academic centers and units led by genetics faculty include the Duncan Neurological Research Institute, led by Dr. Huda Zoghbi, distinguished service professor at Baylor and Howard Hughes Medical Institute investigator, and the Huffington Center on Aging, led by Dr. Hui Zheng, Huffington Foundation Endowed Chair in Aging and professor of molecular and human genetics and neuroscience at Baylor.

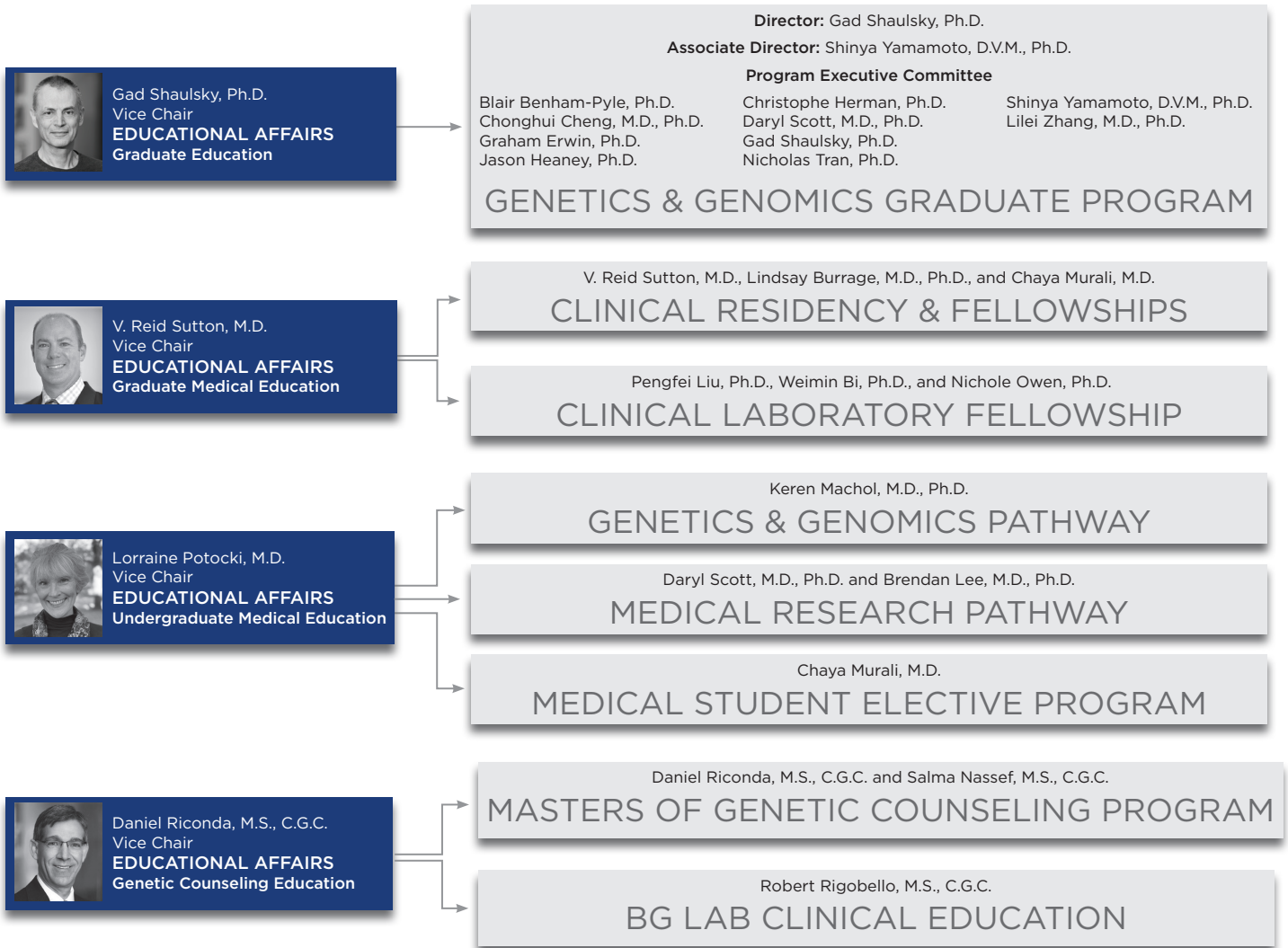
Among genetics departments at U.S. medical schools, we continue to rank highest in both the number of grants and total funding from the National Institutes of Health for 14 consecutive years. Our facilities are equipped with state-of-the-art instrumentation for research in molecular, cellular and biochemical genetics. There are several specialized research centers that galvanize collaboration among faculty at Baylor, as well. We have also extended our mission globally with a center for medical genetics at the Chinese University of Hong Kong and the joint venture diagnostic laboratory, Baylor Genetics, with H.U. Group Holdings, Inc. The Department's various research, clinical and administrative activities currently occupy over 110,000 square feet of space. Because of this rich environment, the Department continues to be a magnet for trainees interested in genetics while continuing to grow in breadth, depth and accomplishments.

DEPARTMENT LEADERSHIP



GRADUATE AND MEDICAL EDUCATION

DIVISION OF EDUCATIONAL AFFAIRS



GRADUATE PROGRAM IN GENETICS & GENOMICS

The Graduate Program in Genetics & Genomics provides outstanding educational opportunities for students who wish to pursue a career in research, education and service in this field. Students in the program obtain rigorous training in modern biology with a special emphasis on genetics and genomics and participate in cutting-edge research on a variety of topics. Our students have received prestigious awards and have published their work in some of the best peer-reviewed journals in the world. The unique environment of a large medical center provides our students with an opportunity to obtain education and practical experience in both basic and applied research.

The program requires a full-time commitment to graduate studies and research. To encourage our students to fulfill their potential and excel in their work, we provide a competitive stipend, which stretches further in Houston where the cost of living is lower than in other large U.S. cities. Students who enroll in 2025-2026 will receive \$40,000 per year. Tuition, medical and dental insurance also are provided. Students who obtain funding through personal fellowships receive an additional \$3,000 bonus from the Dean of the Graduate School.

The requirements for graduation include the successful completion of 30 credit hours of required courses and electives, the successful completion of the Qualifying

Examination, the conduct of an original research project and the submission and defense of a doctoral dissertation.

The research interests of the program faculty span a broad range, from the study of the basic principles of DNA replication and repair to DNA recombination, cell cycle control, aging and differentiation and development in a variety of model organisms. Studies in model organisms, such as *E. coli*, yeast, *Dictyostelium*, flies, worms and mice, are tightly integrated with studies on the genetic basis of the human condition.



Gad Shaulsky, Ph.D.

For the didactic phase of graduate training, students participate in a set of foundational courses during the first two terms, followed by field-specific courses and a variety of electives. Through these courses, students will obtain a broad, coherent background in advanced aspects of genetics, molecular biology, bioinformatics, biochemistry and cell biology. This material is supplemented with journal clubs and seminars. Students interested in bioinformatics, genomics and systems biology can join a special track that offers flexible training in mathematics, statistics and computational biology.

The concentration of the coursework in the first year enables the student to progress relatively quickly to full-time laboratory research efforts. During the first year, students also participate in a minimum of three laboratory rotations. Through these rotations, students obtain valuable hands-on experience in laboratory techniques and become acquainted with a variety of research topics before selecting a major thesis adviser.

Students may also take relevant elective courses offered by other programs at Baylor College of Medicine, Rice University, the University of Texas Health Science Center-Houston, University of Texas Medical Branch, Texas A&M Institute of Biosciences and Technology or the University of Houston at any time during their graduate school tenure.

In the first two terms of the second year of study, the students write a detailed research proposal on a topic in the

field of their planned dissertation research. They defend the proposal to a qualifying examination committee composed of faculty from the Graduate Program in Genetics & Genomics. Upon successful completion of the examination and course work, the student is admitted to candidacy to pursue a thesis research project under the direction of the major adviser and a thesis advisory committee.

The final step to the completion of the Ph.D. is the preparation of a thesis and presentation of the thesis research work at a formal seminar, followed by a dissertation defense to the thesis committee.

Throughout the duration of this program, graduate students are required to attend seminars. Several excellent seminar programs exist within the Department of Molecular and Human Genetics, as well as in other departments at Baylor College of Medicine. The Department of Molecular and Human Genetics also sponsors an annual two-day research retreat where department faculty, graduate students and postdoctoral trainees present and discuss their research in an informal, interactive atmosphere.

Program Leadership

Gad Shaulsky, Ph.D., Director

Shinya Yamamoto, D.V.M., Ph.D., Associate Director

Graduate Program Administrator

Judi Coleman

MEDICAL STUDENT EDUCATION

The **Genetics & Genomics Pathway** at Baylor College of Medicine was established in 2011 and was the first of its type in the nation, providing a unique and valuable opportunity for medical students to integrate genetics early on in their medical careers. Advances in medical genetics, molecular biology and biomedical technology have applications to the treatment of disease, determination of disease risk, use of pharmacologic agents, reproductive counseling and interpretation of clinical laboratory data. In addition, ethical and public policy concerns related to the application of these technologies to promote health and wellness have emerged.

The goals of the Genetics & Genomics Pathway include building upon the foundation of basic genetic principles with additional educational experiences in medical genetics; enhancing the medical student experience to

include a broad range of patients with genetic conditions; developing the student's appreciation for the nuances inherent in performing and interpreting clinical diagnostic analyses in biochemical genetics, molecular genetics and cytogenetics; providing an interface with the community and patient advocacy organizations to enhance the student's awareness of the social concerns faced by patients and families affected with genetic disorders; preparing students to author a scholarly publication and/or presentation; and providing students the means to network and discuss various topics and career paths in medical genetics.

Pathway Director

Keren Machol, M.D., Ph.D.

Pathway Associate Director for the Temple Campus:

Maria Blazo, M.D.

POSTDOCTORAL RESEARCH TRAINING

The faculty of the Department of Molecular and Human Genetics have broad expertise and have mentored hundreds of postdoctoral trainees. Faculty research projects range from seeking answers to basic science questions to ones that

are immediately clinically applicable. Specific research interests are outlined in the profile of each faculty member. Applications for and inquiries regarding research postdoctoral training should be addressed to the specific faculty member.

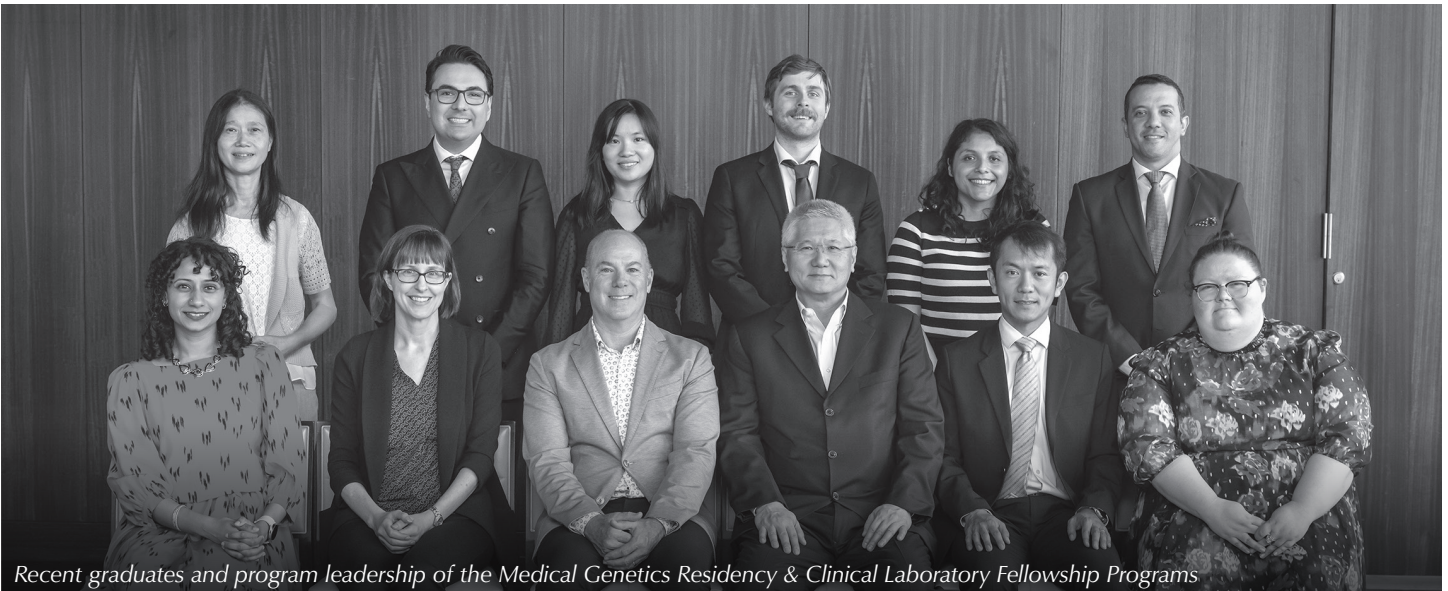
RESIDENCY AND FELLOWSHIP TRAINING PROGRAMS

The **Medical Genetics & Genomics Residency Programs** are accredited by the Accreditation Council for Graduate Medical Education (ACGME). The programs are currently approved for a total of 12 residents. Available training pathways include a two-year residency in medical genetics and genomics (individuals enter this program after at least two years of other residency training) and four-year combined programs in pediatrics/medical genetics and genomics, internal medicine/medical genetics and genomics, and maternal-fetal medicine and medical genetics and genomics. In all pathways, genetics clinical time is divided between rotations on the inpatient consultation service, outpatient general adult and pediatric clinics, prenatal clinics, subspecialty clinics and the diagnostic laboratory, as well as attending conferences and didactic teaching sessions.

The clinical experience is both thorough and extensive because of the availability of the department's clinical

services and clinical faculty; the comprehensive diagnostic laboratory, which includes areas of cytogenetics, biochemical genetics and molecular genetics; the active prenatal diagnosis program; and several medically-relevant research projects. A variety of lectures and conferences on clinical and research topics is provided to residents. Most graduates of the program stay additional years in a mentored faculty position developing independent research programs. Trainees are strongly encouraged to seek individual fellowships and NIH K awards for salary and research funding beyond the second year of training.

Medical Biochemical Genetics is a fellowship that is accredited by the ACGME for Medical Genetics. This one-year training program is meant to provide additional training in the diagnosis and management of inborn errors of metabolism. Board certification is available through the American Board of Medical Genetics and Genomics (ABMGG).



Recent graduates and program leadership of the Medical Genetics Residency & Clinical Laboratory Fellowship Programs

Our **Clinical Biochemical Genetics** and **Laboratory Genetics and Genomics (LGG)** fellowships are also accredited by the ACGME. Baylor offers two-year fellowship training in both programs. LGG is a specialty of the ABMGG that incorporates training in molecular and cytogenetic techniques, clinical interpretation and laboratory management in a single 24-month program.

Training takes place at our diagnostic laboratory, Baylor Genetics, and our affiliated hospital, Texas Children's Hospital, where more than 20 laboratory directors and more than 30 physicians and genetic counselors support the program through direct supervision of fellows as well as through the didactic curriculum.

Fellows have the opportunity to participate in clinical test validations, take part in the ongoing assay developments and improvements and develop research projects that are often translational in scope. The integrated training provided by the fellowship programs prepare those who

wish to become laboratory directors in academic or commercial diagnostic centers as well as those who wish to lead projects focusing on clinical genetic and genomic diagnostics.

Program Leadership

V. Reid Sutton, M.D., Director of Clinical Residency and Fellowship Programs

Lindsay Burrage, M.D., Ph.D., Associate Program Director of Residency Programs

Chaya Murali, M.D., Assistant Program Director of Residency Programs

Pengfei Liu, Ph.D., LGG Program Director

Weimin Bi, Ph.D., LGG Associate Program Director

Nichole Owen, Ph.D., LGG Associate Program Director

ABMGG Residency & Fellowship Program Coordinator

Kara Mitchell

BAYLOR COLLEGE OF MEDICINE AND THE CHINESE UNIVERSITY OF HONG KONG JOINT CENTER FOR MEDICAL GENETICS

In 2016, Baylor College of Medicine and the Chinese University of Hong Kong signed a memorandum of understanding to establish the Baylor College of Medicine and Chinese University of Hong Kong Joint Center for Medical Genetics in Hong Kong with a vision to create a platform for training in clinical genetics and expert services for genetic disorders.

The aims of the Center are to design, establish and conduct professional development activities and training

in medical genetics and genetic counseling to fit the increasing need in Asia; establish a leading referral center in Asia for prenatal and postnatal diagnosis and treatment for patients and families affected by genetic disorders; and host an annual pan-Asian symposium on state-of-the-art clinical genetics care and research.

Center Director: Fernando Scaglia, M.D.



Genetic Counseling Program class of 2025

GENETIC COUNSELING PROGRAM

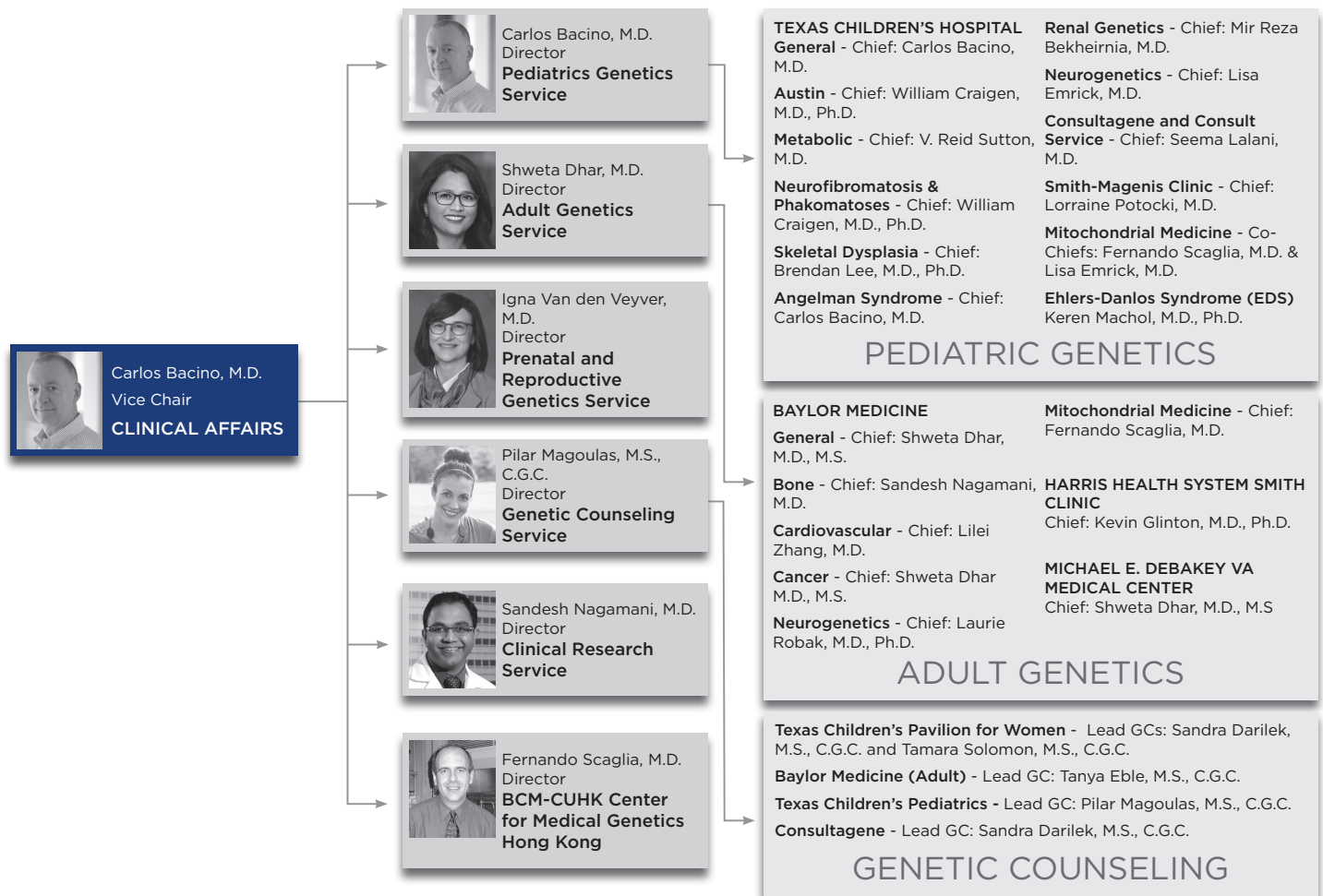
The Baylor College of Medicine Genetic Counseling Program was accredited in February 2018 and graduated its first class of eight students in June 2020. The program now admits 10 students each year. The 21-month Master of Science degree program is housed under the School of Health Professions and was founded with the financial and logistical support of the Department of Molecular and Human Genetics. The program provides students a transformative education in genomic medicine and the practice of genetic counseling. The outstanding clinical, laboratory and research faculty empower graduates to be empathic professionals with effective critical thinking skills. Clinical rotations include a variety of clinics offered both in-person and via telehealth with the following services: pediatric genetics at Texas Children's Hospital,

adult genetics at the Michael E. DeBakey VA Medical Center, Harris Health System and Baylor Medicine at McNair Campus, and prenatal and reproductive genetics at Texas Children's Pavilion for Women and Consultagene Clinic, among others. Program differentiators include the variant interpretation and counseling course developed in collaboration with the diagnostic laboratory, Baylor Genetics, and the diverse research opportunities available within the department and across the Texas Medical Center.

Program Leadership:

Daniel Riconda, M.S., C.G.C., Director
Salma Nassef, M.S., C.G.C., Associate Director
Rachel Franciskovich, M.S., C.G.C., Research Coordinator

DIVISION OF CLINICAL AFFAIRS



GENETICS CLINICS

Baylor College of Medicine's Clinical Genetics Program is the largest in the country, with 14 clinics spanning multiple genetics-based disciplines from prenatal/reproductive health to pediatric and adult genetics care. The clinical program takes a collaborative approach that provides patients with the highest quality of individualized care.

Our pediatric genetics clinic service provides inpatient care to complex and/or critically ill patients at Texas Children's Hospital and several other hospitals within the Texas Medical Center and just outside Houston (Texas Children's Hospital West Campus and Texas Children's Hospital The Woodlands). The outpatient pediatric genetics clinics are among the largest genetics clinics in the U.S. and see more than 5,000 patients annually.

Recently, the Department of Molecular and Human Genetics has partnered with Texas Children's Hospital to establish inpatient and outpatient clinical genetics services at the new Texas Children's Hospital North Austin Campus.

Specialty clinics within the Texas Children's Genetics Clinic include the metabolic clinic, neurofibromatosis clinic and the skeletal dysplasia clinic. There are many multidisciplinary team clinics like the Angelman Syndrome Clinic, and the Mitochondrial Medicine Clinic. The department's clinical and genetic counseling faculty also staff joint clinics with other departments such as oncology (cancer genetics), otolaryngology (otogenetics) and neurology (neurogenetics/tuberous sclerosis).

The Adult Genetics Clinic is one of the largest genetics clinics of it's kind, providing inpatient and outpatient care

exclusively for adult patients in four different healthcare settings (Baylor Medicine, Harris Health, the Michael E. DeBakey VA Medical Center and through the virtual Consultagene Clinic). Patients are seen for a wide variety of indications including, but not limited to, intellectual disability, neurological conditions, cardiovascular conditions, connective tissue disorders and for a personal or family history of cancer. In addition to our general genetics clinic, we have specialty clinics such as the Metabolic and Genetic Disorders of the Bone Clinic, Cancer Genetics Clinic, Neurogenetics Clinic, Cardiovascular Genetics Clinic and Mitochondrial Medicine Clinic.



Sandesh Nagamani, M.D. and Shweta Dhar, M.D., M.S.

CLINIC LOCATIONS

Adult Genetics

Harris Health System Smith Clinic
2525-A Holly Hall St.
Houston, TX 77054

Michael E. DeBakey VA Medical Center
1st Floor, Specialty Clinic
2002 Holcombe Blvd.
Houston, TX 77030

Baylor Medicine at McNair Campus
7200 Cambridge St., 9th Floor
Suite 9A, Houston, TX 77030

Telegenetic Counseling

Consultagene Clinic
www.consultagene.org

Pediatric Genetics

Texas Children's Hospital Wallace Tower
6701 Fannin St., 16th Floor
Houston, TX 77030

Prenatal & Reproductive Genetics

Texas Children's Pavilion for Women
6651 Main Street
Houston, TX 77030

Ben Taub Tower Specialty Clinics
1502 Ben Taub Loop
Houston, Texas 77030

The physicians and genetic counselors of the Baylor Prenatal and Reproductive Genetic Counseling Service specialize in prenatal and reproductive genetic risk assessment and the latest genetic testing technologies. Through partnership with the Department and the Texas Children's Fetal Center, they offer world-renowned clinical and research expertise in prenatal and preconception genetic screening, diagnostic testing and counseling. Services are offered at TCH through in-person and virtual visits at the Pavilion for Women, seven Houston community maternal-fetal medicine clinics, and the Austin campus maternal fetal medicine clinic. We also offer genetic counseling at the Ben Taub Tower Specialty Clinics, and virtually through the Baylor Consultagene Clinic.

By having a strong foundation of physicians and other team members, including genetic counselors, metabolic nurses and dietitians, we provide optimal inpatient care to advance our practice of medicine through genetics. Collectively, our goal is to improve the lives of patients by providing valuable information from which they can make the best possible decisions.

Clinical Faculty

April Adams, M.D.
Carlos A. Bacino, M.D.
Mir Reza Bekheirnia, M.D.
Lindsay Burrage, M.D., Ph.D.
Sanmati Cuddapah, M.D.
William J. Craigen, M.D., Ph.D.
Shweta Dhar, M.D., M.S.
Christine M. Eng, M.D.
Kevin Glington, M.D., Ph.D.

Seema Lalani, M.D.
 Brendan Lee, M.D., Ph.D.
 James R. Lupski, M.D., Ph.D.
 Keren Machol, M.D., Ph.D.
 Ronit Marom, M.D., Ph.D.
 Yishay Ben Moshe, M.D.
 Chaya Murali, M.D.
 Sandesh Nagamani, M.D.
 Sharon E. Plon, M.D., Ph.D.
 Lorraine Potocki, M.D.
 Laurie Robak, M.D., Ph.D.
 Fernando Scaglia, M.D.
 Daryl A. Scott, M.D., Ph.D.
 V. Reid Sutton, M.D.

Ignatia B. Van den Veyver, M.D.
 Michael Francis Wangler, M.D.
 Monika Weisz Hubshman, M.D., Ph.D.
 Lilei Zhang, M.D., Ph.D.

Nursing Faculty

Saima Ali, M.S.N., R.N., FNP-C
 Dianne Bauri, M.S., R.N., FNP-C
 Alexandra Grace, CPNP-PC
 Alicia Turner, M.S.N., R.N., FNP-C
 Julie Mathew, M.S.N., R.N., FNP-C

Nursing Staff

Wanda Dosal, B.S.N.

GENETIC COUNSELING

The Department of Molecular and Human Genetics is home to over 60 genetic counselors that cover a wide range of clinical subspecialties, as well as research and laboratory positions. Genetic counselors communicate complex genetics information to families in a way that is understandable and practical to them, while supporting patients and their family members throughout the genetics evaluation and testing process.

Prenatal and reproductive genetic counselors provide compassionate genetic counseling for pregnant women and partners or those considering a future pregnancy. They counsel individuals with personal or family histories of birth defects or genetic conditions, recurrent miscarriages, parental age concerns, high-risk carrier or prenatal screening results, and for fetal anomalies detected by ultrasound. The team also offers preconception counseling for preimplantation genetic testing options and to assist with interpretation of results of these tests. Services are available to individuals located throughout Texas via virtual appointments through the Texas Children's Maternal Fetal Clinics and Consultagene Clinic as well as in person at our Houston and Austin locations.

Pediatric genetic counselors often work as part of a team and evaluate children in the inpatient and outpatient setting at the Texas Children's Hospital main campus and The Woodlands

campus. They evaluate children in the general genetics clinics for a variety of indications, such as developmental delay, autism spectrum disorders, intellectual disability, inborn errors of metabolism, skeletal dysplasias, hearing loss and birth defects. They see patients in many other subspecialty and multidisciplinary clinics for obesity, cystic fibrosis, hematology, cardiology, neurology, allergy and immunology and pediatric oncology.

Adult and cancer genetic counselors evaluate and offer genetic counseling services to patients at the McNair campus, Michael E. DeBakey VA Medical Center, Harris Health System and the Lester and Sue Smith Breast Center.



Tanya Eble, M.S., C.G.C.

Common indications for referral to an adult genetics clinic or genetic counselor include increased risk of hereditary cancer syndromes, such as breast and ovarian cancer, colon cancer and thyroid cancer, and adults with intellectual disability or mitochondrial disorders.

In addition to the clinical genetic counselors, the department has laboratory genetic counselors at Baylor Genetics who sign-out genetic test results, communicate results to physicians, genetic counselors and other providers and assist with genetic variant interpretation for complex genetic and genomic data. Genetic counselors who have a primary focus in research participate in clinical research activities and work closely with Baylor Genetics and clinical geneticists for new gene identification. Collaboration on various projects and sharing of genomic data is routinely performed with researchers, physicians and other genetic specialists around the world.

Genetic Counseling Faculty

Katie Chan, M.S., C.G.C.
 Sandra Darilek, M.S., C.G.C.
 Tanya N. Eble, M.S., C.G.C.
 Stacey Edwards, M.S., C.G.C.
 Laura I. Ellis, M.S., C.G.C.
 Jamie Fong, M.S., C.G.C.
 Rachel Franciskovich, M.S., C.G.C.
 Georgiann Garza, M.S., C.G.C.
 Amanda Gerard, M.S., C.G.C.
 Farah Ladha, M.S., C.G.C.
 Rebecca Littlejohn, M.S., C.G.C.
 Emily Magness Bland, M.S., C.G.C.
 Pilar Magoulas, M.S., C.G.C.
 Veena S. Mathur, M.S., C.G.C.
 Liz Mizerik, M.S., C.G.C.
 Jill Anne Mokry, M.S., C.G.C.
 Andrea Moon, M.S., C.G.C.
 Salma A. Nassef, M.S., C.G.C.
 Daniel Riconda, M.S., C.G.C.
 Patricia Robbins-Furman, M.P.H., B.S., C.G.C.
 Sarah R. Scollon, M.S., C.G.C.
 Tamara Solomon, M.S., C.G.C.
 Ashley Spector, M.S., C.G.C.
 Melissa Stuebben, M.S., C.G.C.
 Cathy Sullivan, M.S., C.G.C.
 Lauren Westerfield, M.S., C.G.C.

Genetic Counseling Staff

Benjamin Akman, M.S., C.G.C.
 Darwin Argueta, M.S., C.G.C.
 Erin Atkinson, M.S., C.G.C.
 Miavonna Craig, M.S., C.G.C.
 Lauren Desrosiers-Battu, M.S., C.G.C.
 Wanda Dosal, RN
 Dina El Achi, M.S., C.G.C.
 Serena Fleming, M.S.
 Melyssa Garner, M.S., C.G.C.
 Laura George, M.S.
 Hailey Hein, M.S., C.G.C.
 Nhi Ho, M.S., C.G.C.
 Shontiara Johnson, M.S.
 Kari Johnston, M.S., C.G.C.
 Alexandra (Lexi) McKeown, M.S., C.G.C.
 Josephine Minick, M.S., C.G.C.
 Bailey Mitchell, M.S.
 Morgan Nutter, M.S.
 Lisa Saba, M.S., C.G.C.
 McKay Shumway, M.S., C.G.C.
 Meagan Siehr, M.S., C.G.C.
 Emily Soludczyk, M.S., C.G.C.
 Mikaela Thurmond, M.S., C.G.C.
 Blake Vuocolo, M.S., C.G.C.
 Arden Wheeler, M.S.
 Abigail Yesso, M.S., C.G.C.

DIAGNOSTIC LABORATORY AFFAIRS

DIVISION OF DIAGNOSTIC LABORATORY AFFAIRS



BAYLOR GENETICS

Established in February 2015, Baylor Genetics, a joint venture between Baylor College of Medicine and H.U. Group Holdings, Inc., strives to continue the tradition of genetic testing innovation and operational excellence. By building on the Department of Molecular and Human Genetics' strengths in research and discovery, Baylor Genetics' mission is to provide quality genetic testing services for 21st-century precision medicine. Over the last 40 years, the laboratory has been at the forefront of introducing novel genetic testing modalities that have provided more tools to diagnose patients with genetic disorders. The innovative testing approaches developed at the laboratory include whole exome sequencing, Chromosomal Microarray Analysis (CMA), universal carrier screening, non-invasive prenatal testing for single gene disorders, metabolomics, and most recently, whole transcriptome RNA sequencing. Baylor Genetics continues to offer high-

quality comprehensive diagnostic services in all areas of genetic testing including cytogenetics, biochemical genetics, cancer genetics, mitochondrial genetic testing and next-generation sequencing panels. The laboratory, located within Houston's Texas Medical Center, is staffed with more than 200 employees, has a library of over 3,000 tests, and serves clients in all 50 states and 16 countries. Baylor Genetics is well-equipped with cutting-edge diagnostic equipment, allowing it to generate the most accurate clinical genetic data. In collaboration with the Department's newly established, Medical Genetics Multi-omic Laboratory (MGML), it strives to make available both standard of care genetic testing and cutting-edge innovative tests at the leading edge of research.

Baylor Genetics is committed to its academic foundation through publications and grants to participate in federally-funded large-scale sequencing projects. In addition, we



are committed to the education and training of the next generation of clinical and laboratory diagnosticians through our participation in the American Board of Medical Genetics and Genomics fellowship programs.

Diagnostic Laboratory Faculty

Carlos Bacino, M.D.
Weimin Bi, Ph.D.
Jun Chen, Ph.D.
Hongzheng Dai, Ph.D.
Sarah Elsea, Ph.D.
Christine Eng, M.D.
Xiaoyan Ge, Ph.D.
Natalia Golardi, Ph.D.
Eric Kao, Ph.D.
Ning Liu, Ph.D.
Pengfei Liu, Ph.D.
Xi Luo, Ph.D.
Linyan Meng, Ph.D.
Nichole Owen, Ph.D.

Katharina Schulze, Ph.D.
Yue "Cindy" Si, Ph.D.
Teresa Santiago Sim, Ph.D.
Janice Smith, Ph.D.
Qin Sun, Ph.D.
V. Reid Sutton, M.D.
Pawel Stankiewicz, Ph.D.
Casey Thornton, Ph.D.
Liesbeth Vossaert, Ph.D.
Yue Wang, Ph.D.
Chung Wah Wu, Ph.D.
Fan Xia, Ph.D.
Bo Yuan, Ph.D.
Xiaonan Zhao, Ph.D.

COMMUNITY ENGAGEMENT

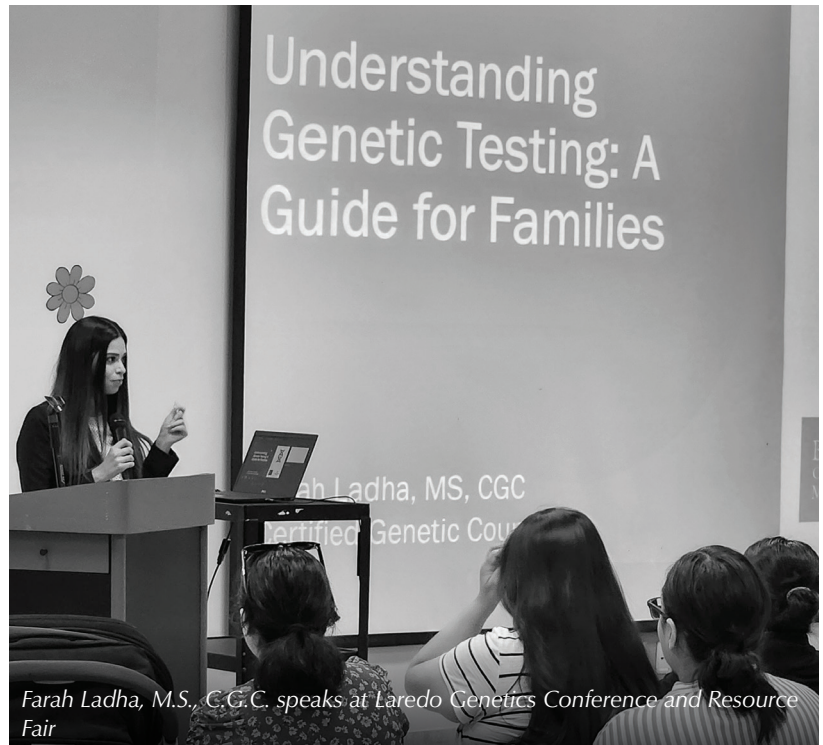
The Office of Community Engagement in the Department of Molecular and Human Genetics works to provide education and resources regarding genetics services to the community-at-large.

The **Evenings with Genetics series** has served the community for 19 years. The department partners with Texas Children's Hospital to offer this free seminar series to the public. A genetics faculty member paired with faculty from another specialty area, plus a parent speaker, are highlighted at each seminar. The goals of the series are to provide current genetic and genomic information in a clear, plain-language manner offer support and resources to families impacted by a genetic disorder; and foster interdepartmental collaborations. Seminars are translated to Spanish. During this past year, we celebrated our 19th anniversary with the fifth annual "Race and Genetics: Perspectives of Precision Medicine" webinar series during Black History Month.

The **All of Us Evenings with Genetics Research Program** provides data science training to senior postdoctoral trainees and early career faculty.

Through a collaboration with the UT Texas Center for Disability Studies, the Texas Department of State Health Services and Texas Children's Hospital, the office provides **statewide genetics outreach** in the form of in-person events and webinars for the community as well as those for health professionals.

The **Careers in Genetics and Genomics series** is an annual virtual series that presents the genetics and genomics career path to high school and undergraduate students. Another virtual program, **A White Coat and Genes: The Life of a Medical Geneticist**, offers third and fourth-year medical students the opportunity to learn about careers in medical genetics from department faculty and students.



Farah Ladha, M.S., C.G.C. speaks at Laredo Genetics Conference and Resource Fair

In 2021, the office developed the **Clinical Research Education Training Program (CRETP)**, a short-term summer training program that allows first and second-year medical students the opportunity to gain clinical research experience in the field of medical genetics. In 2022, the **Medical Genetics Visiting Students Program** was created to provide fourth-year medical students a four-week clinical rotation with faculty in the Department of Molecular and Human Genetics.

The office also offers "Understanding Genetic Variations" sessions at national student research meetings to introduce genetics and genomics careers and biomedical researchers conducting genetics/genomics research to encourage participation in the field.

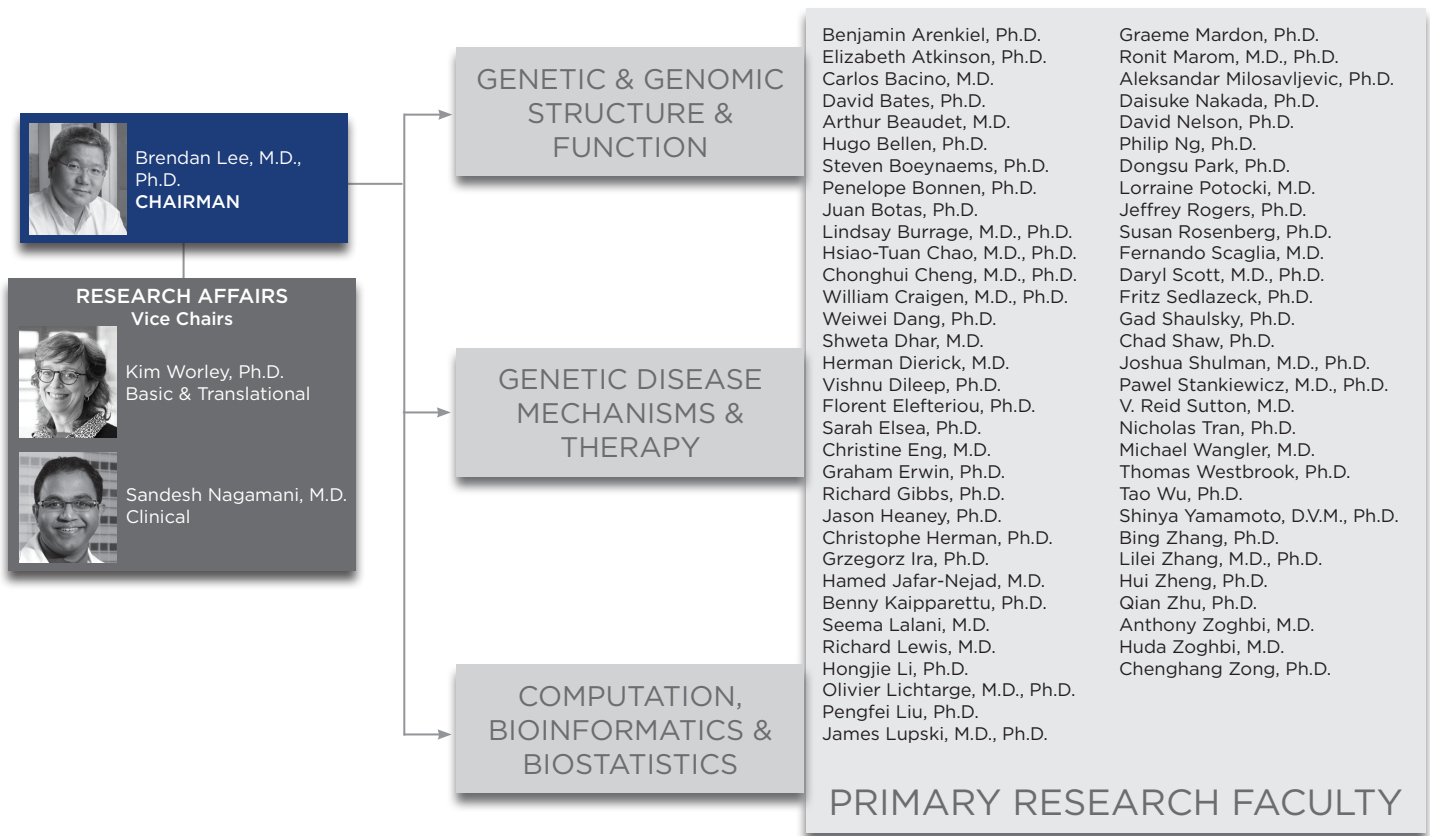
Co-Directors

Debra Murray, Ph.D.

Gladys Pryor, B.S.

RESEARCH FACULTY

Division of Research Affairs



The research interests of the more than 70 primary research faculty members span important areas, such as:

Bioinformatics
Bacterial genetics
Cancer genetics
Cytogenetics
DNA recombination
Drosophila genetics
Functional genomics
Gene therapy
Gene structure and expression

Genome sequencing
Genomic stability, replication and repair
Mammalian development
Metabolic basis for inherited human disease
Mouse molecular genetics
Neurogenetics
Somatic cell genetics
Yeast genetics

BENJAMIN R. ARENKIEL, PH.D.**McNair Scholar**

Professor, Departments of Molecular and Human Genetics and Neuroscience
Faculty Member, Graduate Programs in Development, Disease Models & Therapeutics; Genetics & Genomics; Neuroscience; and Developmental Biology

Ph.D., University of Utah School of Medicine
Howard Hughes Medical Institute Postdoctoral Fellow, Duke University

RESEARCH INTERESTS

The main focus of our research is to elucidate the basic mechanisms that guide the formation and maintenance of neural circuits in the mammalian brain. Using the mouse, we apply multifaceted experimental approaches that combine genetic engineering, optical imaging, and electrophysiological recording techniques to better understand synapse and circuit function.

The blueprints for most neural circuits are specified by innate, genetic mechanisms. However, circuit architecture and function can be strongly influenced by neural activity and sensory experience. Towards better understanding the interplay between experience, synaptic connectivity, and circuit function, we are currently pursuing three main projects in our laboratory: 1) Identifying activity dependent- and neuropeptide signaling mechanisms that underlie synaptogenesis and circuit formation of adult-born neurons. 2) Mapping functional connectivity of brain circuits, with emphasis on the olfactory system, basal forebrain, and hypothalamus. 3) Elucidating signaling and circuit mechanisms that govern feeding behavior.

The long-term goal of our research is to form a deeper understanding of the mechanisms that guide synapse and circuit formation, with the ultimate hope of gaining insight towards repairing or replacing damaged or diseased nervous tissue. At the heart of this experimentation is the continued effort to develop novel tools and techniques to mark and manipulate neurons and their associated circuits.

**SELECTED PUBLICATIONS**

Lyons-Warren AM, Tantry EK, Moss EH, Kochukov MY, Belfort BDW, Ortiz-Guzman J, Freyberg Z, **Arenkiel BR** (2023). Co-transmitting interneurons in the mouse olfactory bulb regulate olfactory detection and discrimination. **Cell Rep.** 42: 113471.

Pekarek BT, Kochukov M, Lozzi B, Wu T, Hunt PJ, Tepe B, Hanson Moss E, Tantry EK, Swanson JL, Dooling SW, Patel M, Belfort BDW, Romero JM, Bao S, Hill MC, **Arenkiel BR** (2022). Oxytocin signaling is necessary for synaptic maturation of adult-born neurons. **Genes Dev.** 36: 1100-1118.

Ung K, Huang TW, Lozzi B, Woo J, Hanson E, Pekarek B, Tepe B, Sardar D, Cheng YT, Liu G, Deneen B, **Arenkiel BR** (2021). Olfactory bulb astrocytes mediate sensory circuit processing through Sox9 in the mouse brain. **Nat Commun.** 12: 5230.

Liu G, Froudarakis E, Patel JM, Kochukov MY, Pekarek B, Hunt PJ, Patel M, Ung K, Fu CH, Jo J, Lee HK, Tolias AS, **Arenkiel BR** (2019). Target specific functions of EPL interneurons in olfactory circuits. **Nat Commun.** 10: 3369.

Patel JM, Swanson J, Ung K, Herman A, Hanson E, Ortiz-Guzman J, Selever J, Tong Q, **Arenkiel BR** (2019). Sensory perception drives food avoidance through excitatory basal forebrain circuits. **ELife.** 8. pii: e44548.

Tepe B, Hill MC, Pekarek BT, Hunt PJ, Martin TJ, Martin JF, **Arenkiel BR** (2018). Single-Cell RNA-Seq of Mouse Olfactory Bulb Reveals Cellular Heterogeneity and Activity-Dependent Molecular Census of Adult-Born Neurons. **Cell Rep.** 25: 2689-2703.e3.

McClard CK, Kochukov MY, Herman I, Liu Z, Eblimit A, Moayedi Y, Ortiz-Guzman J, Colchado D, Pekarek B, Panneerselvam S, Mardon G, **Arenkiel BR** (2018). POU6f1 Mediates Neuropeptide-Dependent Plasticity in the Adult Brain. **J Neurosci.** 38: 1443-1461.

Herman AM, Ortiz-Guzman J, Kochukov M, Herman I, Quast KB, Patel JM, Tepe B, Carlson JC, Ung K, Selever J, Tong Q, **Arenkiel BR** (2016). A Cholinergic basal forebrain feeding circuit modulates appetite suppression. **Nature.** 538: 253-256.

Huang L, Ung K, Garcia I, Quast KB, Cordiner K, Saggau P, **Arenkiel BR** (2016). Task Learning Promotes Plasticity of Interneuron Connectivity Maps in the Olfactory Bulb. **J Neurosci.** 36: 8856-71.

Garcia I, Quast KB, Huang L, Herman AM, Selever J, Deussing JM, Justice NJ, **Arenkiel BR** (2014). Local CRH Signaling Promotes Synaptogenesis and Circuit Integration of Adult-Born Neurons. **Dev Cell.** 30: 645-59.

ELIZABETH ATKINSON, PH.D.**Assistant Professor**, Department of Molecular and Human Genetics*Ph.D., Washington University in St. Louis**Postdoc, IRACDA fellow; Harvard Medical School – Massachusetts General Hospital & Broad Institute***RESEARCH INTERESTS**

The primary goal of the Atkinson Lab is to reduce disparities in genomics research across ancestries. We accomplish this by leveraging global genomic datasets and cutting-edge computational techniques to build and apply resources for the improved statistical genetic study of diverse human populations that genomics has so far underserved. Our work is centered around neuropsychiatric traits with a particular focus on admixed American populations, though many of the tools we build are broadly applicable across phenotypes and populations, giving them the potential for widespread impact on human health.

A necessary precursor to accounting for global diversity in genomics research is a thorough understanding of population history and evolution, which shapes the naturally occurring patterns of genetic variation. Therefore, the second line of inquiry explores characterizing key aspects of human evolution with ancestrally tuned evolutionary statistics using global DNA collections. Elucidating the forces shaping the genetic variation of modern populations is not only of significant academic interest but is vital for determining the appropriate methods for statistical and medical genomic analyses of diverse datasets.

We are in the leadership of multiple international consortia working to generate diverse datasets, including the Psychiatric Genomics Consortium Post-Traumatic Stress Disorder working group, Latin American Trans-Ancestry Initiative for Obsessive Compulsive Disorder, the *All of Us Research Evenings with Genetics* Program, and the Latin American Genomics Consortium.

**SELECTED PUBLICATIONS**

Atkinson EG, Maihofer AX, Kanai M, Martin AR, Karczewski KJ, (...), Neale BM (2021). Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power. **Nat Genet.** 53: 195-204.

Atkinson EG, Dalvie S, Pichkar Y, Kalungi A, Majara L, Injera WE, et al (2022). Genetic structure correlates with ethnolinguistic diversity in eastern and southern Africa. **Am J Hum Genet.** 109: 1667-1679.

Atkinson EG, Audesse AJ, Palacios JA, Bobo DM, Webb AE, Ramachandran S, Henn BM (2018). No Evidence for Recent Selection at FOXP2 among Diverse Human Populations. **Cell.** 174: 1424-1435.e15.

Majara L, Kalungi A, Koen N, (...), Stein DJ, Kinyanda E., **Atkinson EG**, Martin AR (2023). Low and differential polygenic score generalizability among African populations due largely to genetic diversity. **HGG Adv.** 4: 100184.

Ragsdale AP, Weaver TD, **Atkinson EG**, Hoal E, Möller M, Henn BM, Gravel S (2023). A weakly structured stem for human origins in Africa. **Nature.** 617: 755-763.

Atkinson EG, Artomov M, Karczewski KJ, Loboda AA, Rehm HL, MacArthur DG, Neale BM, Daly MJ (2023). Discordant calls across genotype discovery approaches elucidate variants with systematic errors. **Genome Res.** 33: 999-1005.

Atkinson EG, Bianchi SB, Ye GY, Martínez-Magaña JJ, Tietz GE, Montalvo-Ortiz JL, Giusti-Rodríguez P, Palmer AA, Sanchez-Roige S (2022). Cross-ancestry genomic research: time to close the gap. **Neuropsychopharmacology.** 47: 1737-1738.

Tan T, **Atkinson EG** (2023). Strategies for the Genomic Analysis of Admixed Populations. **Annu Rev Biomed Data Sci.** 6: 105-127.

Atkinson EG. (2023). Estimation of cross-ancestry genetic correlations within ancestry tracts of admixed samples. **Nat Genet.** 55: 527-529.

Nievergelt CM, Maihofer AX, **Atkinson EG**, (...), Koenen KC (2024). Genome-wide association analyses identify 95 risk loci and provide insights into the neurobiology of post-traumatic stress disorder. **Nat Genet.** 56: 792-808.

CARLOS A. BACINO, M.D., FACMG

Professor and Vice Chair for Clinical Affairs, Department of Molecular and Human Genetics

Director, Pediatric Genetics Clinic

Medical Director, Cytogenetics Laboratory, Baylor Genetics

Chief, Genetics Service, Texas Children's Hospital

M.D., University of Buenos Aires, Argentina

Intern and Resident, Pediatrics, Beth Israel Medical Center

Fellow, Clinical Genetics and Cytogenetics, Cedars-Sinai Medical Center, Los Angeles

RESEARCH INTERESTS

I am primarily devoted to clinical activities in the Department of Molecular and Human Genetics. I am involved in the diagnosis and management of pediatric patients with birth defects and rare genetic disorders. I am also interested in bone disorders and participate in the Skeletal Dysplasia Clinic at TCH (Texas Children's Hospital). I am directly involved in the supervision and training of medical students, residents and fellows. I am in addition the Medical Director of the Cytogenetics Laboratory at Baylor Genetics, and I have a particular interest in structural chromosomes abnormalities and genomic disorders (contiguous gene deletion/duplication syndromes), as well as the mechanism of origin of these chromosome anomalies.

Epigenetics and Disorders of Imprinting: I have worked in Angelman syndrome clinical research for 20 years and have been involved early on in two different clinical trials aimed to revert the silencing of the paternal allele. Our group is participating in a phase II clinical research trial using an antisense oligonucleotide sponsored by IONIS Pharmaceutical (ION582) administered intrathecally. This antisense drug attempts to activate the paternal *UBE3A* gene and ameliorate the symptoms of Angelman syndrome by altering patterns of imprinting. We currently run a multidisciplinary clinic at Texas Children's Hospital for patients with Angelman syndrome that started with the support of the Angelman Syndrome Foundation.

Skeletal dysplasias: Through the sponsorship of several pharmaceutical companies, I am involved in different studies offering treatments in achondroplasia. This includes a phase III clinical research trial using a recombinant cartilage natriuretic peptide (CNP) also known as vosoritide (BMN-111), a drug that promotes linear and AGV skeletal growth in these patients. This drug was recently approved by the FDA in children after birth. We are part of another trial sponsored by Ascendis Pharma also using a long-acting recombinant CNP injected weekly. We are completing Phase IIb and moving into a Phase III trial.

Undiagnosed Disease Network (UDN): Our group is currently recruiting and studying patients with rare disorders under the auspices of the UDN consortium. This effort has been made possible by a grant awarded by the NIH under the leadership of Dr. Brendan Lee and will give us a unique ability to characterize rare disorders, make new discoveries, and gain insight into novel genes and disease mechanisms. I am currently the co-PI of this effort.



SELECTED PUBLICATIONS

Murdock DR, Dai H, Burrage LC, Rosenfeld JA, Ketkar S, (...), **Bacino CA**, (...); Undiagnosed Diseases Network, Lee B (2021). Transcriptome-directed analysis for Mendelian disease diagnosis overcomes limitations of conventional genomic testing. **J Clin Invest.** 131: e141500.

Chung HL, Mao X, Wang H, Park YJ, Marcogliese PC, (...), **Bacino CA**, Bellen HJ, Xiao B (2020). De Novo Variants in CDK19 Are Associated with a Syndrome Involving Intellectual Disability and Epileptic Encephalopathy. **Am J Hum Genet.** 106: 717-725.

Savarirayan R, Tofts L, Irving M, Wilcox W, **Bacino CA**, (...), Day J (2020). Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. **Lancet.** 396: 684-692.

Tokita MJ, Braxton AA, Shao Y, Lewis AM, Vincent M, (...), **Bacino CA**, (...), Walkiewicz MA (2016). De Novo Truncating Variants in SON Cause Intellectual Disability, Congenital Malformations, and Failure to Thrive. **Am J Hum Genet.** 99: 720-7.

Boone PM, Chan YM, Hunter JV, Pottkotter LE, Davino NA, Yang Y, Beuten J, **Bacino CA** (2016). Increased bone turnover, osteoporosis, progressive tibial bowing, fractures, and scoliosis in a patient with a final-exon SATB2 frameshift mutation. **Am J Med Genet A.** 170: 3028-3032.

Bi W, Cheung SW, Breman AM, **Bacino CA** (2016). 4p16.3 microdeletions and microduplications detected by chromosomal microarray analysis: New insights into mechanisms and critical regions. **Am J Med Genet A.** 170: 2540-50.

Ilari R, Agosta G, **Bacino C** (2016). 5q14.3 deletion neurocutaneous syndrome: Contiguous gene syndrome caused by simultaneous deletion of *RASA1* and *MEF2C*: A progressive disease. **Am J Med Genet A.** 170: 688-93.

Bacino C, Chao YH, Seto E, Lotze T, Xia F, Jones RO, Moser A, Wangler MF (2015). A homozygous mutation in *PEX16* identified by whole-exome sequencing ending a diagnostic odyssey. **Mol Genet Metab Rep.** 5: 15-18.

Brunetti-Pierri N, Torrado M, Fernandez Mdel C, Tello AM, Arberas CL, Cardinale A, Piccolo P, **Bacino CA** (2014). Terminal osseous dysplasia with pigmentary defects (TODPD) due to a recurrent filamin A (FLNA) mutation. **Mol Genet Genomic Med.** 2: 467-71.

Bacino CA, Dhar SU, Brunetti-Pierri N, Lee B, Bonnen PE (2012). *WDR35* mutation in siblings with Sensenbrenner syndrome: A ciliopathy with variable phenotype. **Am J Med Genet A.** 158A: 2917-24.

DAVID BATES, PH.D.

Associate Professor, Departments of Molecular and Human Genetics and Molecular Virology & Microbiology; Dan L Duncan Comprehensive Cancer Center
Faculty Member, Graduate Programs in Genetics & Genomics; Immunology & Microbiology; and Integrative Molecular and Biomedical Sciences

Ph.D., University of New Mexico

Postdoc, University of New Mexico School of Medicine

Postdoc, Harvard University

RESEARCH INTERESTS

Chromosome Dynamics: Although genetic information is encoded in a one-dimensional array of DNA bases, all major DNA processes (replication, transcription and recombination) are controlled by changes in the three-dimensional structure of DNA. Large-scale structural features of chromosomes including the arrangement of important chromosomal sites (origins, termini and centromeres) and overall chromosome compactness change dramatically and predictably during the cell cycle. However, these features are difficult to measure using standard microscopy methods. Our lab is developing a novel chromosome painting technology to image individual domains within the entire chromosome in single bacterial cells. This method, inspired by in situ hybridization-based human karyotyping techniques, utilizes multi-color combinatorial labeling and high-resolution three-dimensional photography to generate whole genome maps of the chromosome. Our goal is to define the cell cycle program of chromosome movement in *E. coli* using a cell cycle synchronization apparatus we designed called the “baby cell machine.”

Chromosome Cohesion: In eukaryotes, replicated chromosomes are held together by linkages (cohesion) until they are separated by the mitotic spindle apparatus. Our lab showed that an analogous cohesion process occurs in bacteria, in which replicated DNA is linked together as it exits the replication fork, remaining stably attached for 10-20 minutes before segregating apart. Evidence suggests that bacterial cohesion is not protein (glue) based, but rather results from entanglement of sister chromosomes in a topological structure called a precatenane. Interestingly, cohesion occurs much more strongly in some regions of the *E. coli* chromosome, which we refer to as “snaps”. We are currently exploring models of how these centromere-like snaps are generated and what role they play in faithful chromosome replication, repair and segregation.

DNA Replication: *In vitro*, precatenanes form along DNA segments that are under positive helical tension (overwound). The presence of precatenanes behind replication forks *in vivo* implies that replicative helicases generate tension that outpaces the relaxing ability of topoisomerases (forks can travel at an astounding 1000 bp/sec!). Theoretically, this tension rapidly spins the replication fork causing the two replicated DNAs to wrap around each other. Our lab is investigating whether DNA-bound proteins act as topological barriers during replication, driving the formation of precatenanes. The basic enzymology of DNA replication is well conserved among all life, and it has recently been shown that eukaryotic chromosomes are also highly catenated along their lengths.

We expect that our work will lead to a better understanding of the factors that limit replication fork speed, cause replication fork stalling (quickly leading to double-strand breaks) and inhibit chromosome segregation. These events in humans are a major source of genomic instability and diseases including cancer.



SELECTED PUBLICATIONS

Visser BJ, Joshi MC, **Bates D** (2017). Multi-Locus imaging of the *E. coli* chromosome by Fluorescent *In Situ* Hybridization. **Methods Mol Biol.** 1624: 213-226.

Bates D, Pettitt BM, Buck GR, Zechiedrich L (2016) Importance of entanglement and disentanglement during DNA replication and segregation. **Phys Life.** 18: 160-4.

Xia J, Chen L, Mei Q, Ma CH, Halliday JA, Lin HY, Magnan D, Pribis JP, Fitzgerald DM, Hamilton HM, Richters M, Nehring R, Shen X, Li L, **Bates D**, Hastings PJ, Herman C, Jayaram M, Rosenberg SM (2016). Holliday-junction trap shows how cells use recombination and a junction-guardian role of RecQ helicase. **Sci Adv.** 2: e1601605.

Magnan D, **Bates D** (2015). Regulation of DNA Replication Initiation by Chromosome Structure. **J Bacteriol.** 197: 3370-7.

Magnan D, Joshi MC, Barker AK, Visser BJ, **Bates D** (2015). DNA Replication Initiation Is Blocked by a Distant Chromosome-Membrane Attachment. **Curr Biol.** 25: 2143-9.

Moore JM, Magnan D, Mojica AK, **Bates D**, Rosenberg SM, Hastings PJ (2015). Roles of nucleoid-associated proteins in stress-induced mutagenic break repair in starving *Escherichia coli*. **Genetics.** 201: 1349-62.

Lies M, Visser BJ, Joshi MC, Magnan D, **Bates D** (2015). MioC and GidA proteins promote cell division in *E. coli*. **Front Microbiol.** 6: 516.

Kleckner N, Fisher JK, Stouf M, White MA, **Bates D**, Witz G (2014). The bacterial nucleoid: nature, dynamics and sister segregation. **Curr Opin Microbiol.** 22: 127-37.

Cambridge J, Blinkova A, Magnan D, **Bates D**, Walker JR (2014). A replication-inhibited unsegregated nucleoid at mid-cell blocks Z-ring formation and cell division independently of SOS and the SlmA nucleoid occlusion protein in *Escherichia coli*. **J Bacteriol.** 196: 36-49.

Joshi MC, Magnan D, Montminy TP, Lies M, Stepankiw N, **Bates D** (2013). Regulation of sister chromosome cohesion by the replication fork tracking protein SeqA. **PLoS Genet.** 9: e1003673.

Shee C, Cox BD, Gu F, Luengas EM, Joshi MC, (...), **Bates D**, Harris RS, Miller KM, Rosenberg SM (2013). Engineered proteins detect spontaneous DNA breakage in human and bacterial cells. **ELife.** 2: e01222.

ARTHUR BEAUDET, M.D.

Professor, Department of Molecular and Human Genetics

*M.D., Yale University School of Medicine
Resident, Pediatrics, John Hopkins Hospital
Postdoc, National Institutes of Health*

RESEARCH INTERESTS

Dr. Arthur Beaudet was a professor of molecular and human genetics at Baylor College of Medicine and previous chairman of the Department of Molecular and Human Genetics. He left BCM in 2020 to serve as founder and CEO of Luna Genetics but returned as a voluntary Professor in 2024.

Beaudet was inducted into the Institute of Medicine in 1995, the Society of Scholars in 2008, and into the National Academy of Sciences in 2011. He was previously the president of the American Society of Human Genetics.

Beaudet began his research in the 1960s with studies on protein synthesis. In the 1970s, Beaudet et al. demonstrated mutations in cultured somatic cells; he has also conducted much research on inborn errors of metabolism, particularly urea cycle disorders. In 1988, Beaudet's laboratory published a paper describing the first recognition of uniparental disomy (UPD) in humans. This paper proposed four mechanisms for UPD, each of which has since been shown to occur. His group co-discovered that the *UBE3A* gene was inactivated as the cause of Angelman syndrome, and that deletion of the snoRNAs likely contributes to the Prader-Willi phenotype. In collaboration with Isis (now Ionis) Pharmaceuticals he demonstrated that oligonucleotides could be used to activate the paternal allele of *Ube3a* in the mouse as a possible therapeutic correction in Angelman syndrome. This has led to clinical trials for Angelman syndrome.

Beaudet has published research on the possible association between the deficiency of a carnitine biosynthesis gene and risk of autism in boys and has contended that some of these cases of autism may be preventable through carnitine supplementation. Beaudet has also developed a test which enables doctors to detect whether a child was conceived because of incest without testing either parent. During his 48 years at Baylor, Beaudet mentored over 80 postdoctoral trainees and was the primary thesis advisor for 10 Ph.D. graduate students. Beaudet worked for over a decade at BCM and for four years at Luna Genetics on developing a commercial form of cell based noninvasive prenatal testing using fetal cells in the mother's blood during the first trimester. There is still a need for better forms of prenatal testing.

Beaudet was a principal investigator at the Howard Hughes Medical Institute.



SELECTED PUBLICATIONS

Bellair M, Amaral E, Ouren M, Roark C, Kim J, O'Connor A, Soriano A, Schindler ML, Wapner RJ, Stone JL, Tavella N, Merriam A, Perley L, Breman AM, **Beaudet AL** (2024). Noninvasive single-cell-based prenatal genetic testing: A proof-of-concept clinical study. *Prenat Diagn*. 44: 304-316.

Vossaert L, Wang Q, Salman R, Zhuo X, Qu C, Henke D, Seubert R, Chow J, U'ren L, Enright B, Stilwell J, Kaldjian E, Yang Y, Shaw C, Levy B, Wapner R, Breman A, Van den Veyver I, **Beaudet A** (2018). Reliable detection of subchromosomal deletions and duplications using cell-based noninvasive prenatal testing. *Prenat Diagn*. 38: 1069-1078.

Beaudet AL (2017). Brain carnitine deficiency causes non-syndromic autism with an extreme male bias: A hypothesis. *BioEssays*. 39(8). doi: 10.1002/bies.201700012.

Kølvraa S, Singh R, Normand EA, Qdaisat S, van den Veyver IB, Jackson L, Hatt L, Schelde P, Uldbjerg N, Vestergaard EM, Zhao L, Chen R, Shaw CA, Breman AM, **Beaudet AL** (2016). Genome-wide copy number analysis on DNA from fetal cells isolated from the blood of pregnant women. *Prenat Diagn*. 36: 1127-1134.

Breman AM, Chow JC, U'ren L, Normand EA, Qdaisat S, Zhao L, Henke DM, Chen R, Shaw CA, Jackson L, Yang Y, Vossaert L, Needham RH, Chang EJ, Campton D, Werbin JL, Seubert RC, Van den Veyver IB, Stilwell JL, Kaldjian EP, **Beaudet AL** (2016). Evidence for feasibility of fetal trophoblastic cell-based noninvasive prenatal testing. *Prenat Diagn*. 36: 1-11.

Meng L, Ward AJ, Chun S, Bennett CF, **Beaudet AL**, Rigo F (2015). Towards a therapy for Angelman syndrome by reduction of a long non-coding RNA. *Nature*. 518: 409-12.

HUGO J. BELLEN, D.V.M., PH.D.

Chair in Neurogenetics at the Jan and Dan Duncan Neurological Research Institute

March of Dimes Chair in Developmental Biology

Distinguished Service Professor, Departments of Molecular and Human Genetics and Neuroscience

Faculty Member, Graduate Programs in Development, Disease Models & Therapeutics; Genetics & Genomics; and Neuroscience

Business Engineer, Solvay, University of Brussels, Belgium

D.V.M., Ghent University, Belgium

Ph.D., Genetics, University of California, Davis

Postdoc, Cell Biology, Biozentrum, University of Basel, Switzerland

RESEARCH INTERESTS

One of the main aims of the research in my lab is to elucidate the molecular basis of neurodegeneration. Since no unbiased genetic screens in model organisms were performed to sample genes that cause neurodegenerative phenotypes, we embarked on such a screen in fly photoreceptors and isolated 700 mutations corresponding to 165 complementation groups. This screen has provided a very rich resource of novel mutants for the fly community and has permitted us to dissect mechanisms for a variety of diseases, including Charcot-Marie-Tooth disease, Leigh Syndrome, and Friedreich's ataxia. This screen has also led to the identification of mutations in 32 genes that encode proteins that are targeted to mitochondria. By exploring the molecular mechanisms of these rare diseases, we were able to determine biochemical pathways that also play a role in Parkinson's disease, Amyotrophic Lateral Sclerosis, and Alzheimer's Disease. These pathways are now being studied intensely in the lab.

My lab as well as the laboratories of Michael Wangler and Shinya Yamamoto here at BCM were selected by the Undiagnosed Diseases Network (UDN) as the *Drosophila* Model Organism Screening Center (MOSC). Through close collaborations with human geneticists and physicians, we have identified variants in numerous human genes that are associated with neurological diseases in children. We have participated in the discovery of the genetic causes of 60 human diseases in the past ten years. We are also studying some of these genes in depth to determine the molecular events that underlie these diseases to identify targets to develop drugs and have been successful in identifying FDA approved drugs for four diseases.

My lab also plays an important role in developing new tools to manipulate flies and to generate reagents for the fly community. I have been the PI of the Gene Disruption Project for more than 20 years. The reagents that we have produced include more than 25,000 single transposable element insertion stocks in more than 70 percent of all fly genes. These stocks are currently distributed by the Bloomington *Drosophila* Stock Center (BDSC). Most recently we created a novel transposable element named MiMIC that allows a staggering array of manipulations of the fly genome *in vivo*. So far more than 17,000 lines have been created, of which 7,500 have been deposited in the BDSC. We have used these lines to tag 1,000 genes with a multifunctional tag that allows us to determine gene expression patterns *in vivo*, immunoprecipitations, ChIP, and *in vivo* protein inactivation. Finally, in collaboration with Norbert Perrimon at Harvard, we have developed the CRIMIC technology. This allows us to insert a small multifunctional cassette in almost any gene using CRISPR. We are in the process of inserting these very versatile tags in thousands of genes and have generated more than 3,500 tagged genes so far. We have excellent resources via NIH and private foundations.

WEBSITE: FLYPUSH.RESEARCH.BCM.EDU

**SELECTED PUBLICATIONS**

Goodman LD, Ralhan I, Li X, Lu S, Moulton MJ, (...), **Bellen HJ** (2024). Tau is required for glial lipid droplet formation and resistance to neuronal oxidative stress. **Nat Neurosci.** 27: 1918-1933.

Yamamoto S, Kanca O, Wangler MF, **Bellen HJ** (2024). Integrating non-mammalian model organism in the diagnosis of rare genetic human disease. **Nat Rev Genet.** 25: 46-60.

Dutta D, Kanca O, Byeon SK, Marcogliese PC, Zuo Z, (...), **Bellen HJ** (2023). A defect in mitochondrial fatty acid synthesis impairs iron metabolism and causes elevated ceramide levels. **Nat Metab.** 5: 1595-1614.

Chung HL, Ye Q, Park YJ, Zuo Z, Kanca O, Mok J-W, Tatikota SG, Lu S, Perrimon N, Lee HK, **Bellen HJ** (2023). Very long-chain fatty acids induce glial-derived Sphingosine-1-Phosphate synthesis, secretion, and neuroinflammation. **Cell Metab.** 35: 855-874.

Wang L, Lin G, Zuo Z, Li Y, Byeon SK, Pandey A, **Bellen HJ** (2022). Neuronal activity induces Glucosylceramide that is secreted via exosomes for lysosomal degradation in glia. **Sci Adv.** 8: ebn3326.

Moulton MJ, Barish S, Ralhan I, Chang J, Goodman LD, Harland J, Marcogliese PC, Johansson JO, Ioannou M, **Bellen HJ** (2021). Neuronal ROS-induced glial lipid droplet formation is altered by loss of Alzheimer's disease-associated genes. **Proc Natl Acad Sci USA.** 118: e2112095118.

Chung HL, Wangler MF, (...), Herndon MJ, Chen S; Members of Undiagnosed Diseases Network, (...), Bucelli RC, Yamamoto S, Lee HK, Prada CE, Chae JH, Vogel TP, **Bellen HJ** (2020). Loss- or gain-of-function mutations in *ACOX1* cause axonal loss via different mechanisms. **Neuron.** 106: 589-606.

Lin G, Lee PT, Chen K, Mao D, Tan KL, Zuo Z, Lin WW, Wang L, **Bellen HJ** (2018). Phospholipase *PLA2G6*, a Parkinsonism-associated gene, affects Vps26 and Vps35, retromer function, and ceramide levels, similar to α -synuclein gain. **Cell Metab.** 28: 605-618.

Liu L, MacKenzie KR, Putluri N, Maletić-Savatić M, **Bellen HJ** (2017). The glia-neuron lactate shuttle and elevated ROS promote lipid synthesis in neurons and lipid droplet accumulation in glia via APOE/D. **Cell Metab.** 26: 719-737.

Liu L, Zhang K, Sandoval H, Yamamoto S, Jaiswal M, Sanz E, Li Z, Hui J, Graham BH, Quintana A, **Bellen HJ** (2015). Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration. **Cell.** 160: 177-790.

Yamamoto S, Jaiswal M, Charrng W-L, (...), **Bellen HJ** (2014). A *Drosophila* genetic resource to study human disease genes and its use for gene discovery in human exome data. **Cell.** 159: 200-214.

STEVEN BOEYNAEMS, PH.D.

Assistant Professor, Department of Molecular and Human Genetics
Investigator, Jan and Dan Duncan Neurological Research Institute
Faculty Member, Center for Alzheimer's and Neurodegenerative Disease,
 Therapeutic Innovation Center, Dan L Duncan Comprehensive Cancer Center
CPRIT Scholar in Cancer Research
Departmental Commercialization Officer

B.Sc., M.Sc., Ph.D., KU Leuven, Belgium
EMBO Postdoctoral Fellow, Stanford University

RESEARCH INTERESTS

The overall focus of our lab is to understand one of the most basic questions in biology: how do cells perceive and deal with stress? Stress is a universal feature of all cellular life. Whether it concerns abiotic (e.g., temperature) or biotic (e.g., viral infection) stress, cells/organisms need to adapt to their ever-changing environment. Protein aggregation is a hallmark of a stressed cell, so how do cells protect themselves? It is becoming increasingly clear that cells undergo broad (reversible) spatial and biophysical rearrangements of their entire proteome in times of stress, yet the regulatory and organizational principles remain almost completely unresolved. Biomolecular condensates (BMCs) have emerged as key stress-responsive compartments, and our work has indeed shown that such assemblies allow cells to sense and respond to stress.

Protein aggregation and the stress response are intimately tied to human disease—whether it concerns age-related stresses or exposure to environmental/physical stresses in neurodegenerative disease, the cellular stress caused by hypoxia and chemotherapy in the tumor microenvironment, or the corruption of the host proteostatic machinery in infectious disease. Stress and the associated responses modulate the onset and progression of virtually every human disease. It therefore may come as no surprise that defects in BMCs are associated with several human diseases and the aging process. Yet, we still have a very limited understanding of whether such BMC alterations are adaptive or actually driving dysfunction and whether we can drug them. Our lab addresses this open question by using a multidisciplinary approach—spanning biophysics to *in vivo* modeling and drug screening—combined with orthogonal model systems and a synthetic biology tool kit to (A) untangle how the cellular stress response is regulated and (B) engineer new tools to therapeutically target it in aging and human disease.

We mostly focus on neurodegenerative diseases and brain cancer but understand that the same molecular processes underlying these conditions are not exclusively limited to humans. Indeed, evolution has already found solutions to many of the problems we face in human medicine today. For example, while the aging human brain is incredibly susceptible to protein aggregation, other organisms seem to defy the biological limits of life and are able to maintain proteostasis in the harshest of environments. It is therefore that we are teaming up with collaborators from around the world to study stress-tolerant organisms to understand the molecular underpinnings of their resilience. Figuring out how these organisms prevent proteins from aggregating will highlight new strategies to boost proteostasis in protein-aggregation diseases. In all, a multi-model and evolution-inspired approach forms the backbone of our lab. By repurposing nature's ingenuity, we develop innovative bio-synthetic and -mimetic tools and drugs to combat disease.

WEBSITE: WWW.BOEYNAEMSLAB.ORG



SELECTED PUBLICATIONS

Boeynaems S, Ma XR, Yeong V, Ginell GM, Chen JH, (...), Gitler AD. Aberrant phase separation is a common killing strategy of positively charged peptides in biology and human disease. **bioRxiv** [Preprint]. 2023 Mar 9: 2023.03.09.531820. doi: 10.1101/2023.03.09.531820.

Boeynaems S, Dorone Y, Zhuang Y, Shabardina V, Huang G, Marian A, Kim G, Sanyal A, Şen NE, Griffith D, Docampo R, Lasker K, Ruiz-Trillo I, Auburger G, Holehouse AS, Kabashi E, Lin Y, Gitler AD (2023). Poly(A)-binding protein is an ataxin-2 chaperone that regulates biomolecular condensates. **Mol Cell**. 83: 2020-2034.e6.

Lasker K, **Boeynaems S**, Lam V, Scholl D, Stainton E, Briner A, Jacquemyn M, Daelemans D, Deniz A, Villa E, Holehouse AS, Gitler AD, Shapiro L (2022). The material properties of a bacterial-derived biomolecular condensate tune biological function in natural and synthetic systems. **Nat Commun**. 13: 5643.

Dorone Y*, **Boeynaems S***, Flores E, Jin B, Hateley S, Bossi F, Lazarus E, Pennington JG, Michiels E, De Decker M, Vints K, Baatsen P, Bassel GW, Otegui MS, Holehouse AS, Exposito-Alonso M, Sukenik S, Gitler AD, Rhee SY (2021). A prion-like protein regulator of seed germination undergoes hydration-dependent phase separation. **Cell** 184: 4284-4298. *co-first authors

Hasting RL, **Boeynaems S** (2021). Designer condensates: a toolkit for the biomolecular architect. **J Mol Biol**. 433: 166837.

Fumagalli F*, Young FL*, **Boeynaems S***, De Decker M, Mehta A, (...), Van Damme P (2021). C9orf72-derived arginine-containing dipeptide repeats associate with axonal transport machinery and impede microtubule-based motility. **Sci Adv**. 7: eabg3013. *co-first authors

Boeynaems S, Holehouse AS, Weinhardt V, Kovacs D, Van Lindt J, Larabell C, Van Den Bosch L, Das R, Tompa P, Pappu RV, Gitler AD (2019). Spontaneous driving forces give rise to protein-RNA condensates with coexisting phases and complex material properties. **PNAS** 116: 7889-7898.

Bogaert E*, **Boeynaems S***, Kato M, Guo L, Caulfield TR, (...), Van Den Bosch L# (2018). Molecular dissection of FUS points at synergistic effect of low-complexity domains in toxicity. **Cell Rep**. 24: 529-537. *co-first authors

Boeynaems S, Alberti S, Fawzi NL, Mittag T, Polymenidou M, Rousseau F, Schymkowitz J, Shorter J, Wolozin B, Van Den Bosch L, Tompa T, Fuxreiter M (2018). Protein phase separation: a new phase in cell biology. **Trends Cell Biol**. 28: 420-435.

Boeynaems S, Bogaert E, Kovacs D, Konijnenberg A, Timmerman E, (...), Van Den Bosch L (2017). Phase Separation of C9orf72 Dipeptide Repeats Perturbs Stress Granule Dynamics. **Mol Cell**. 65: 1044-1055.

PENELOPE E. BONNEN, PH.D.

Associate Professor, Departments of Molecular and Human Genetics and Molecular Physiology & Biophysics

Faculty Member, Computational and Integrative Biomedical Research Center; Graduate Programs in Quantitative & Computational Biosciences; Development, Disease Models & Therapeutics; and Genetics & Genomics

Ph.D., Baylor College of Medicine

Postdoc, Rockefeller University

RESEARCH INTERESTS

Personalized genomics to identify genes causing Mitochondrial Disease

Mitochondrial disease has an incidence of 1/5000 and can affect every organ system. Childhood-onset mitochondrial disease most often results from recessive mutations in the nuclear genome; however, the vast majority of cases remain without a molecular diagnosis and no effective treatments thus underscoring the critical need to identify the genetic aberrations driving these disorders. We are leveraging a personalized functional genomics approach combining genome-wide sequencing, mitochondrial functional profiling in patient cells, and functional genomics to identify validated novel mitochondrial disease genes. This project will significantly advance the diagnosis and treatment of mitochondrial disease, as well as provide new insights into the mechanisms underlying the pathology of mitochondrial respiratory chain disorders and commonly occurring conditions associated with mitochondrial dysfunction such as cancer, diabetes and neurodegeneration.



SELECTED PUBLICATIONS

Besse A, Wu P, Bruni F, Donti T, Graham BH, Craigen WJ, McFarland R, Moretti P, Lalani S, Scott KL, Taylor RW, **Bonnen PE** (2015). The GABA transaminase, ABAT, is essential for mitochondrial nucleoside metabolism. *Cell Metab.* 21: 417-27.

Bonnen PE, Yarham JW, Besse A, Wu P, Faqeih EA, Al-Asmari AM, Saleh MA, Eyaid W, Hadeel A, He L, Smith F, Yau S, Simcox EM, Miwa S, Donti T, Abu-Amero KK, Wong LJ, Craigen WJ, Graham BH, Scott KL, McFarland R, Taylor RW (2013). Mutations in *FBXL4* Cause Mitochondrial Encephalopathy and a Disorder of Mitochondrial DNA Maintenance. *Am J Hum Genet.* 93: 471-81.

Craigen WJ, Graham BH, Wong LJ, Scaglia F, Lewis RA, **Bonnen PE** (2013). Exome sequencing of a patient with suspected mitochondrial disease reveals a likely multigenic etiology. *BMC Med Genet.* 14: 83.

Bacino CA, Dhar SU, Brunetti-Pierri N, Lee B, **Bonnen PE** (2012). *WDR35* mutation in siblings with Sensenbrenner syndrome: a ciliopathy with variable phenotype. *Am J Med Genet A.* 158A: 2917-24.

Bacino CA, Arriola LA, Wiszniewska J, **Bonnen PE** (2012). *WDR62* missense mutation in a consanguineous family with primary microcephaly. *Am J Med Genet A.* 158A: 622-5.

International HapMap 3 Consortium, et al. (2010). Integrating common and rare genetic variation in diverse human populations. *Nature.* 467: 52-8.

Bonnen PE, Lowe JK, Altshuler DM, Breslow JL, Stoffel M, Friedman JM, Pe'er I (2010). European admixture on the Micronesian island of Kosrae: lessons from complete genetic information. *Eur J Hum Genet.* 18: 309-16.

Bonnen PE, Pe'er I, Plenge RM, Salit J, Lowe JK, Shapero MH, Lifton RP, Breslow JL, Daly MJ, Reich DE, Jones KW, Stoffel M, Altshuler D, Friedman JM (2006). Evaluating potential for whole-genome studies in Kosrae, an isolated population in Micronesia. *Nat Genet.* 38: 214-7.

Bonnen PE, Wang PJ, Kimmel M, Chakraborty R, Nelson DL (2002). Haplotype and linkage disequilibrium architecture for human cancer-associated genes. *Genome Res.* 12: 1846-53.

Bonnen PE, Story MD, Ashorn CL, Buchholz TA, Weil MM, Nelson DL (2000). Haplotypes at ATM identify coding-sequence variation and indicate a region of extensive linkage disequilibrium. *Am J Hum Genet.* 67: 1437-51.

JUAN BOTAS, PH.D.**Huffington Endowed Chair For Neurodegenerative Disease****Professor**, Departments of Molecular and Human Genetics**Investigator**, Jan and Dan Duncan Neurological Research Institute**Faculty Member**, Graduate Programs in Genetics & Genomics and Quantitative & Computational Biosciences**Director**, High-Throughput Behavioral Screening Facility

Ph.D., University of Madrid

Postdoc, Stanford University Medical Center

RESEARCH INTERESTS

During the past two decades many genes triggering neurological diseases have been identified. Some of these diseases are caused by gain of function mutations and/or impaired proteolysis of the respective proteins. Among these proteins are huntingtin (Huntington's disease, HD), alpha-synuclein (Parkinson's disease, PD) and the tau and amyloid precursor proteins (in Alzheimer's AD). On the other hand, diseases like Rett Syndrome are caused by loss of function mechanisms.

Despite many significant advances, we still have a poor understanding of what happens between the triggering of the disease by the faulty protein and the ultimate death of the neuron. What are the molecular mechanisms and gene networks driving pathogenesis? What mechanisms are deployed by neuron and glia to compensate CNS dysfunction? Can we identify therapeutic targets common to more than one disease?

To address these questions, we integrate computational and wet-lab approaches using a combination of experimental model systems including *Drosophila* and mice, as well as neuronal primary cultures and iPSC-derived human neurons. Importantly, we have generated fruit fly (*Drosophila*) models for many neurological and neuromuscular disorders that recapitulate key neuropathological phenotypes observed in patients. For example, *Drosophila* models of the neurodegenerative diseases spinocerebellar ataxia type 1 (SCA1), Huntington's, Parkinson's and Alzheimer's show late onset, progressive neuronal degeneration and disease-specific neuropathology. We use these *Drosophila* models as a discovery tool: together with state-of-the-art robotic instrumentation they allow us to carry out high-throughput, genome-wide genetic screens to identify genetic modifiers and therapeutic targets. Genome-scale screens *in vivo* are possible in *Drosophila* but not feasible using mouse models. These genetic approaches are integrated with human and model system -omic datasets. Network analyses allow us to nominate highly validated targets for in-depth studies using mice and human neurons.

In sum, we use a multidisciplinary, cross-species approach for comparative analysis of modifier genes and pathogenic mechanisms. Our goal is to identify therapeutic opportunities that may be applied to more than one neurological disorder.

**SELECTED PUBLICATIONS**

J Li, BK Amoh, E McCormick, A Tarkunde, KF Zhu, A Perez, (...), **J Botas** (2023). Integration of Transcriptome-Wide Association Study with Neuronal Dysfunction Assays Provides Functional Genomics Evidence for Parkinson Disease Genes. **Hum Mol Genet.** 32: 685-695.

Stephens MC, Brandt V, **Botas J** (2022). The developmental roots of neurodegeneration. **Neuron.** 110: 1-3.

Onur TS, Laitman A, Zhao H, Keyho R, Kim H, Wang J, Mair M, Wang H, Li L, de Haro M, Wan Y-W, Allen C, Lu B, Al-Ramahi I, Liu Z, **Botas J** (2021). Downregulation of glial genes involved in synaptic function mitigates Huntington's disease pathogenesis. **Elife.** 10: e64564.

Kim YW, Al-Ramahi I, Koire A, Wilson SJ, Konecki DM, Mota S, Soleimani S, Botas J, Lichtarge O (2020). Harnessing the paradoxical phenotypes of APOE ε2 and APOE ε4 to identify genetic modifiers in Alzheimer's disease. **Alzheimers Dement.** 17: 831-846.

Al-Ramahi I, Lu B, Di Paola S, Pang K, de Haro M, (...), Liu Z, Medina DL, **Botas J** (2018). High-Throughput Functional Analysis Distinguishes Pathogenic, Nonpathogenic, and Compensatory Transcriptional Changes in Neurodegeneration. **Cell Syst.** 7: 28-40.e4.

Rousseaux MWC, Vázquez-Vélez GE, Al-Ramahi I, (...), Elledge SJ, Liu Z, **Botas J**, Zoghbi HY (2018). A Druggable Genome Screen Identifies Modifiers of α-Synuclein Levels via a Tiered Cross-Species Validation Approach. **J Neurosci.** 38: 9286-9301.

Bouché V, Espinosa AP, Leone L, Sardiello M, Ballabio A, **Botas J** (2016). *Drosophila* Mitf regulates the V-ATPase and the lysosomal-autophagic pathway. **Autophagy.** 12: 484-98.

Park J, Al-Ramahi I, Tan Q, (...), Westbrook TF, **Botas J**, Zoghbi HY (2013). RAS-MAPK-MSK1 pathway modulates ataxin 1 protein levels and toxicity in SCA1. **Nature.** 498: 325-31.

Romero E, Cha GH, Verstreken P, Ly CV, Hughes RE, Bellen HJ, **Botas J** (2008). Suppression of neurodegeneration and increased neurotransmission caused by expanded full-length huntingtin accumulating in the cytoplasm. **Neuron.** 57: 27-40.

Sofola OA, Jin P, Qin Y, Duan R, Liu H, de Haro M, Nelson DL, **Botas J** (2007). RNA-binding proteins hnRNP A2/B1 and CUGBP1 suppress fragile X CCG premutation repeat-induced neurodegeneration in a *Drosophila* model of FXTAS. **Neuron.** 55: 565-71.

Fernandez-Funez P, Rosales MLN, de Gouyon B, She WC, Luchack J, Turiegano E, Benito J, Capovilla M, Skinner PJ, McCall A, Canal I, Orr HT, Zoghbi HY, **Botas J** (2000). Identification of genes that modify ataxin-1 induced neurodegeneration. **Nature.** 408: 101-6.

LINDSAY C. BURRAGE, M.D., PH.D.

Associate Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Programs in Genetics & Genomics and Development,
 Disease Models & Therapeutics

M.D., Ph.D., Case Western Reserve University
Pediatrics Residency, University Hospitals of Cleveland
Medical Genetics Residency, Baylor College of Medicine
Biochemical Genetics Fellowship, Baylor College of Medicine

RESEARCH INTERESTS

As a physician-scientist and clinical biochemical geneticist, I have a long-standing interest in the pathophysiology of inborn errors of metabolism and their utility as models for more common disorders. Our group uses laboratory-based approaches in murine models and clinical studies to gain greater understanding of the etiology of long-term complications of inborn errors of metabolism with a special focus on urea cycle disorders in order to optimize management strategies for our patients.

One main focus of my research program is to gain a greater understanding of chronic liver dysfunction in individuals with urea cycle disorders. As an investigator in the Urea Cycle Disorders Consortium (UCDC) of the Rare Diseases Clinical Research Network, I have pursued a variety of data-mining projects using data from the UCDC Longitudinal Study of Urea Cycle Disorders. Using this data, we discovered an increased prevalence of chronic hepatocellular injury in two distal urea cycle disorders (argininosuccinate lyase deficiency and arginase deficiency) compared to disorders impacting enzymes that are more proximal in the cycle. To follow-up this work, we are performing a more comprehensive assessment of liver disease using serum biomarkers and novel imaging techniques in individuals with urea cycle disorders.

Our clinical study of hepatic complications complements our laboratory-based work in the murine models of urea cycle disorders. First, we are investigating the underlying mechanisms for liver disease in mouse models of argininosuccinate lyase (ASL) deficiency. The ASL-deficient mice model the human disorder with urea cycle dysfunction, nitric oxide (NO) deficiency, and chronic hepatocellular injury with hepatomegaly. In addition, as in human patients with the disorder, we have recently discovered hepatic glycogen accumulation and impaired hepatic glycogenolysis in these mice. Second, we are using *in vitro* and *in vivo* models to investigate the underlying mechanisms of Lysinuric Protein Intolerance, a secondary urea cycle disorder, that is associated with osteoporosis, failure to thrive, and immune dysregulation.

To complement my independent research program, I am also involved in a variety of large interdisciplinary research teams focusing on various aspects of rare disease research. As an investigator in the Urea Cycle Disorders Consortium, I am involved in a wide variety of multi-center clinical research initiatives focused on urea cycle disorders. Locally, at Baylor, I have a leadership role in the sequence analysis team (e.g. exome and whole genome) for the Baylor College of Medicine site for the Undiagnosed Diseases Network (UDN). The work of our team has led to discovery of multiple potential new disease genes and phenotypic expansion in the setting of a wide variety of phenotypes. In addition, I am one of the principal investigators for the Baylor Center for Precision Medicine Models. This large collaborative project focuses on the generation and use of precision medicine models to support gene discovery in rare undiagnosed diseases and to facilitate pre-clinical studies to investigate therapies for these disorders.

**SELECTED PUBLICATIONS**

Ali S, Nisar A, Zhang A, Nagamani S, Aceves-Ewing NM, Rawls B, Quan T, Enns G, Goss J, Leung DH, Shneider BL, Jain S, Hazard FK, Schady D, **Burrage LC** (2025). Prevalence of fibrosis in hepatic explants and biopsies from individuals with urea cycle disorders. **Mol Genet Metab.** 145: 109175.

Brooks D, Burke E, Lee S, Eble TN, O'Leary M, (...); Undiagnosed Diseases Network; Lalani S, Rosenfeld JA, **Burrage LC** (2024). Heterozygous MAP3K20 variants cause ectodermal dysplasia, craniosynostosis, sensorineural hearing loss, and limb anomalies. **Hum Genet.** 143: 279-291.

Stroup BM, Li X, Ho S, Zhouyao H, Chen Y, Ani S, Dawson B, Jin Z, Marom R, Jiang MM, Lorenzo I, Rosen D, Lanza D, Aceves N, Koh S, Seavitt JR, Heaney JD, Lee B, **Burrage LC** (2023). Delayed skeletal development and IGF-1 deficiency in a mouse model of lysinuric protein intolerance. **Dis Model Mech.** 16: dmm050118.

Nagamani SCS, Ali S, Izem R, Schady D, Masand P, Shneider BL, Leung DH, **Burrage LC** (2021). Biomarkers for liver disease in urea cycle disorders. **Mol Genet Metab.** 133: 148-156.

Stroup BM, Marom R, Li X, Hsu CW, Chang CY, (...), Heaney JD, Lee B, **Burrage LC** (2020). A global *Slc7a7* knockout mouse model demonstrates characteristic phenotypes of human lysinuric protein intolerance. **Hum Mol Genet.** 29: 2171-2184.

Burrage LC, Madan S, Li X, Ali S, Mohammad M, (...), Leung DH, Bali D, Lee B (2020). Chronic liver disease and impaired hepatic glycogen metabolism in argininosuccinate lyase deficiency. **JCI Insight.** 5: e132342.

Burrage LC, Reynolds JJ, Baratang NV, Phillips JB, Wegner J, (...), Bacino CA, Campeau PM, Lee B (2019). Bi-allelic Variants in *TONSL* Cause SPONASTRIME Dysplasia and a Spectrum of Skeletal Dysplasia Phenotypes. **Am J Hum Genet.** 104: 422-438.

Burrage LC, Thistlethwaite L, Stroup BM, Sun Q, Miller MJ, (...), Milosavljevic A, Lee BH, Elsea SH (2019). Untargeted metabolomic profiling reveals multiple pathway perturbations and new clinical biomarkers in urea cycle disorders. **Genet Med.** 21: 1977-1986.

Santiago-Sim T*, **Burrage LC***, Ebstein F, Tokita MJ, Miller M, (...), Heaney JD, Walkiewicz MA (2017). Biallelic Loss-of-Function Mutations in *OTUD6B* Cause an Intellectual Disability Syndrome Associated with Seizures, Microcephaly, Absent Speech, Hypotonia, Growth Retardation with Prenatal Onset, and Dysmorphic Features. **Am J Hum Genet.** 100: 676-688. *contributed equally.

Burrage LC, Sun Q, Elsea SH, Jiang M, Nagamani SCS, (...), Members of the Urea Cycle Disorders Consortium, Lee BH (2015). Human Recombinant Arginase Enzyme Reduces Plasma Arginine in Mouse Models of Arginase Deficiency. **Hum Mol Genet.** 24: 6417-27.

HSIAO-TUAN CHAO, M.D., PH.D.**McNair Scholar**

Assistant Professor, Departments of Molecular and Human Genetics, Pediatrics-Neurology and Neuroscience

Associate Program Director, Child Neurology Residency-Basic Neuroscience Track

Investigator, The Cain Foundation Laboratories, Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital

M.D., Baylor College of Medicine

Ph.D., Baylor College of Medicine

Intern, Pediatrics, Texas Children's Hospital

Resident, Pediatric Neurology, Texas Children's Hospital

RESEARCH INTERESTS

As a physician-scientist, my efforts are primarily focused on understanding the genetic and neural circuit basis of neurodevelopmental disorders such as intellectual disability, epilepsy, autism, schizophrenia and other neuropsychiatric conditions. One emerging theme in the field is that disrupted inhibitory neuronal signaling and cerebellar dysfunction has been found in association with many neurologic and psychiatric disorders. This would be consistent with the growing body of knowledge that inhibitory neurons are highly diverse and key for virtually all aspects of neurobiology from neural circuit development to information processing. Therefore, elucidating the genetic etiologies of inhibitory neuronal development and function has great potential to advance our understanding of neurodevelopmental and neuropsychiatric disorders. However, determining the genetic cause is only the first step. The critical advance needed for translation of human genetic studies into clinical applications is to identify the consequences of genetic alterations at the molecular, cellular, neural network and whole-organism levels. This mechanistic dissection bridges molecular function to disease pathogenesis, which is crucial for the development of effective targeted therapeutics. Types of genetic alterations we study in the lab impact transcriptional regulation, protein translation, cell-type specific specification, synapse formation and neurotransmitter release.

Our goal is to determine the role of cerebro-cerebellar inhibitory neuronal dysfunction in the pathogenesis of neurodevelopmental and neuropsychiatric disorders by deciphering how genetic alterations perturb neurotransmission in the brain, impact neural development and lead to abnormal neurologic output. In the Chao Lab, we integrate cross-species approaches in humans to uncover the genetic etiologies of neurodevelopmental disorders, fruit flies to elucidate the molecular pathways and mice to explore the cascade of events in the mammalian brain and develop pre-clinical studies. A variety of approaches and techniques are employed in our laboratory including comprehensive human phenotyping and multiomics studies, genetically engineered mouse and fruit fly models, functional analyses with electrophysiology, imaging, transcriptomics, molecular and cellular assays, and behavioral profiling. We use these approaches to understand the pathogenesis of autism and cerebellar ataxia disorders due to loss of the transcription factor EBF3 and the pathogenesis of developmental epileptic encephalopathies due to loss of scaffolding proteins like PPFIA3 or disrupted regulation of protein translation by EIF2AK2.

In addition to the laboratory research activities, our team leads an Undiagnosed Epilepsy Genetics Initiative at the Cain Foundation Laboratories in the Duncan NRI to identify genetic determinants of undiagnosed developmental epileptic encephalopathies and discover new disease gene relationships. Finally, we are leading a Phase 0 natural history study for *STXBP1*-related epileptic encephalopathy with the goal of continuing to Phase 1/2 gene therapy studies. The findings from the clinical studies inform our laboratory research efforts to understand how gene disruptions alter neuronal development, perturb neural network activity and lead to cognitive and behavioral abnormalities in neurodevelopmental and psychiatric disorders. Together, our approaches in translational neuroscience, developmental biology, and genetics directly integrates human studies with model organisms to accelerate diagnosis, prognosis, and potential therapeutic interventions for neurologic disorders.

**SELECTED PUBLICATIONS**

Paul MS, Michener SL, Pan H, Pfliger JM, Rosenfeld JA, (...), Undiagnosed Diseases Network, Bacino CA, Lee BH, **Chao HT** (2024). A syndromic neurodevelopmental disorder caused by rare variants in *PPFIA3*. **Am J Hum Genet**. 111: 96-118.

Corriveau M*, Amaya S*, Koebel MC*, (...), **Chao HT** (2023). *PAK1* c.1409T>A (p.Leu470Gln) *de novo* variant disrupts the protein kinase domain, leading to epilepsy, macrocephaly, spastic quadriplegia, and hydrocephalus: Case report and review of the literature. **Am J Med Genet A**. 191: 1619-1625. *equal contribution.

Paul MS*, Duncan AR*, Genetti C, Grant PE, Shi J, (...), **Chao HT***, Agrawal PA** (2023). Rare *EIF4A2* variants are associated with a neurodevelopmental disorder characterized by intellectual disability, hypotonia, and epilepsy. **Am J Hum Genet**. 110: 120-145. *equal contribution. ^co-corresponding authors.

Deisseroth CA, Lerma VC, Magyar CL, Pfliger JM, Nayak A, (...), **Chao HT** (2022). An Integrated Phenotypic and Genotypic Approach Reveals a High-Risk Subtype Association for *EBF3* Missense Variants Affecting the Zinc Finger Domain. **Ann Neurol**. 92: 138-153.

Magyar CL, Murdock DR, Burrage LC, Dai H, Lalani SR, (...), **Chao HT** (2022). *PRUNE1* c.933G>A synonymous variant induces exon 7 skipping, disrupts the DHHA2 domain, and leads to an atypical NMIHBA syndrome presentation: Case report and review of the literature. **Am J Med Genet A**. 188: 1868-1874.

Calame D, Hainlen M, Takacs D, Ferrante L, Pence K, Erick LT, **Chao HT** (2020). *EIF2AK2*-related neurodevelopmental disorder with leukoencephalopathy mimics Pelizaeus-Merzbacher disease. **Neurol Genet**. 7: e539.

Mao D, Reuter CM, Ruzhnikov MRV, Beck AE, Farrow EG, (...), Agrawal PB*, Bernstein JA*, Bellen HJ*, **Chao HT*** (2020). *De novo EIF2AK1* and *EIF2AK2* variants are associated with developmental delay, leukoencephalopathy, and neurologic decompensation. *equal contribution. **Am J Hum Genet**. 106: 570-583.

Chao HT*, Davids M*, Burke E, Pappas JG, Rosenfeld JA, (...), Bellen HJ, Wangler MF, Malicdan MCV (2017). A syndromic neurodevelopmental disorder caused by *de novo* variants in *EBF3*. **Am J Hum Genet**. 100: 128-137. *equal contribution

Chao HT, Chen H, Samaco RC, Xue M, Chahrour M, (...), Zoghbi HY (2010). Dysfunction in GABA signaling mediates autism-like stereotypies and Rett syndrome phenotypes. **Nature**. 468: 263-9.

Chao HT, Zoghbi HY, Rosenmund C (2007). MeCP2 controls excitatory synaptic strength by regulating glutamatergic synapse number. **Neuron**. 56: 58-65.

CHONGHUI CHENG, PH.D.

Professor, Departments of Molecular and Human Genetics and Molecular and Cellular Biology; Lester and Sue Smith Breast Center

Faculty Member, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

CPRIT Scholar in Cancer Research

M.D., Peking University Health Science Center

Ph.D., Sloan-Kettering Institute/Cornell University Weill Graduate School of Medical Sciences

Postdoc, Massachusetts Institute of Technology

RESEARCH INTERESTS

In the Cheng lab, we strive to understand the fundamental questions of how RNA regulation controls cellular processes in normal biology and in the context of cancer. Working at the interface of RNA splicing and breast cancer biology, our current focus is on the regulation of breast cancer metastasis driven by alternative splicing. We use molecular biology, genomics and bioinformatics approaches in conjunction with genetic models and patient samples to discover rules and networks that regulate metastasis and associated processes. We work closely with physician-scientists and aim to apply our findings from basic research to the development of prognostic markers and therapeutics for the treatment of breast cancer.

The developmental program, Epithelial-Mesenchymal Transition (EMT), is frequently re-activated in metastatic and recurrent tumors. Our work provided a conceptual understanding depicting a causal role for RNA alternative splicing in EMT and breast cancer recurrence. We found that splice isoform switching of the *CD44* gene must take place in order for cells to undergo EMT. We also discovered a novel splicing-mediated pathway that drives cancer metastasis. We demonstrated that the RNA binding protein hnRNPM reprograms alternative splicing including *CD44* and promotes a breast cancer metastatic phenotype. By competitive binding on cis-regulatory RNA elements, hnRNPM activates a mesenchymal splicing program in a cell-type restricted manner, emphasizing a tightly regulated splicing program during tumor metastasis. We are combining patient data biocomputing analysis with cell-based and animal experiments to determine the networks of RNA regulation that govern the phenotype of breast cancer metastasis.

In collaboration with nano-technology engineers, we developed the “NanoFlare” method that enables the detection and isolation of live circulating tumor cells (CTC), establishing a platform to study splicing-mediated cancer cell plasticity and phenotypes in patient-derived samples. We are continuing this collaboration to develop novel tools for the prognosis and diagnosis of breast cancer.

We have been intrigued by the fact that nearly all human genes are detected to undergo alternative splicing, vastly expanding the human proteomes. Therapeutic resistance of promising anti-tumor drugs, such as the anti-HER2 antibody Trastuzumab and the B-RAF(V600E) inhibitor Vemurafenib, is now known to be caused by aberrantly spliced HER2 and B-RAF. Despite these important observations, alternative splicing in cancer has remained largely an untargeted territory. We are actively looking for dedicated research fellows to join us to understand the contribution of RNA regulation in breast cancer metastasis and to apply it to clinical settings.

**SELECTED PUBLICATIONS**

Zheng R, Dunlap M, Bobkov GOM, Gonzalez-Figueroa C, Patel KJ, Lyu J, Harvey SE, Chan TW, Quinones-Valdez G, Choudhury M, Le Roux CA, Bartels MD, Vuong A, Flynn RA, Chang HY, Van Nostrand EL, Xiao X*, **Cheng C*** (2024). hnRNPM protects against the dsRNA-mediated interferon response by repressing LINE-associated cryptic splicing. *Mol Cell*. 84: 2087-2103.e8.

Hu X*, Harvey SE*, Zheng R, Lyu J, Grzeskowiak CL, Powell E, Piwnica-Worms H, Scott KL, **Cheng C** (2020). The RNA-binding protein AKAP8 suppresses tumor metastasis by antagonizing EMT-associated alternative splicing. *Nat Commun*. 11: 486.

Qiu Y, Lyu J, Dunlap M, Harvey SE, **Cheng C** (2020). A combinatorially regulated RNA splicing signature predicts breast cancer EMT states and patient survival. *RNA*. 11: 486.

Zhang W, Bado IL, Hu J, Wan YW, Wu L, Wang H, Gao Y, Jeong HH, Xu Z, Hao X, Lege BM, Al-Ouran R, Li L, L J, Yu L, Singh S, Lo H-C, Niu M, Liu L, Jiang W, Li Y, Wong STC, **Cheng C**, Liu Z, Zhang XHF (2021). The bone microenvironment invigorates metastatic seeds for further dissemination. *Cell* 184: 2471-2486.

Zhang H, Brown RL, Wei Y, Zhao P, Liu S, Liu X, Deng Y, Hu X, Zhang J, Gao XD, Kang Y, Mercurio AM, Goel HL, **Cheng C** (2019). CD44 splice isoform switching determines breast cancer stem cell state. *Genes Dev*. 33: 166-179.

Harvey SE, Xu Y, Lin X, Gao XD, Qiu Y, Ahn J, Xiao X, **Cheng C** (2018). Coregulation of alternative splicing by hnRNPM and ESRP1 during EMT. *RNA*. 24: 1326-1338.

Huang H, Zhang J, Harvey SE, Hu X, **Cheng C** (2017). RNA G-quadruplex secondary structure promotes alternative splicing via the RNA-binding protein hnRNPF. *Genes Dev*. 31: 2296-2309.

Xu Y, Gao XC, Lee JH, Huang H, Tan H, Ahn J, Reinke L, Peter ME, Feng Y, Gius D, Siziopikou KP, Peng J, Xiao X, **Cheng C** (2014). Cell type-restricted activity of hnRNPM promotes breast cancer metastasis via regulating alternative splicing. *Genes Dev*. 28: 1191-1203.

Halo T, McMahon KM, Angeloni NL, Wang W, Xu Y, Malin D, Strekalova E, Cryns VL, **Cheng C***, Mirkin CA*, Thaxton CS* (2014). NanoFlares for the detection, isolation, and culture of live tumor cells from human blood. *PNAS* 111: 17104-17109.

Brown RL, Reinke LM, Damerow MS, Perez D, Chodosh LA, Yang J, **Cheng C** (2011). CD44 splice isoform switching in human and mouse epithelium is essential for epithelial-mesenchymal transition and breast cancer progression. *J Clin Invest*. 121: 1064-1074.

WILLIAM J. CRAIGEN, M.D., PH.D.

Professor, Departments of Molecular and Human Genetics, Molecular Physiology and Biophysics, and Pediatrics

Faculty Member, Graduate Programs in Genetics & Genomics; Development, Disease Models & Therapeutics; and the Clinical Translational Research Certificate of Added Qualification (CTR-CAQ) program

Director, Neurofibromatosis Clinic, Texas Children's Hospital

M.D., Ph.D., Baylor College of Medicine

Fellow, Medical Genetics, Baylor College of Medicine

Resident, Pediatrics, Baylor College of Medicine

RESEARCH INTERESTS

Mitochondrial Function: Mitochondria are now recognized to play a variety of important physiologic roles in various processes beyond ATP synthesis, including programmed cell death (apoptosis), retrograde signaling, cellular proliferation and the regulation of intermediary metabolism. I have a longstanding interest in the molecular basis of these processes, both at a basic research level and as they apply to diagnostics and clinical practice.

Human Genetic Disorders: Despite advances in identifying human metabolic diseases, pathophysiologic mechanisms are poorly understood and specific treatment strategies lacking. I continue to be involved in both the clinical and molecular characterization of inborn errors of metabolism. As a clinical biochemical geneticist, I participate in the Undiagnosed Diseases Network (UDN) in discovering novel disease genes. I also serve as the co-chair of the Metabolism Working Group of the ClinGen consortium, where we strive to curate disease-causing variants in genes that cause metabolic disorders.



SELECTED PUBLICATIONS

Wong LC, Chen T, Schmitt ES, Wang J, Tang S, Landsverk M, Li F, Zhang S, Wang Y, Zhang VW, **Craigen WJ** (2020). Clinical and laboratory interpretation of mitochondrial mRNA variants. **Hum Mutat.** 41: 1783-1796.

Craigen WJ (2012). Mitochondrial DNA mutations: an overview of clinical and molecular aspects. **Methods Mol Biol.** 837: 3-15.

Raghavan A, Sheiko T, Graham BH, **Craigen WJ** (2012). Voltage-dependant anion channels: novel insights into isoform function through genetic models. **Biochim Biophys Acta.** 1818: 1477-85.

Akman HO, Sheiko T, Tay SK, Finegold MJ, Dimauro S, **Craigen WJ** (2011). Generation of a novel mouse model that recapitulates early and adult onset glycogenosis type IV. **Hum Mol Genet.** 20: 4430-9.

Akman HO, Raghavan A, **Craigen WJ** (2011). Animal models of glycogen storage disorders. **Prog Mol Biol Transl Sci.** 100: 369-88.

Wong LJ, Scaglia F, Graham BH, **Craigen WJ** (2010). Current molecular diagnostic algorithm for mitochondrial disorders. **Mol Genet Metab.** 100: 111-7.

Roy SS, Ehrlich AM, **Craigen WJ**, Hajnóczky G (2009). VDAC2 is required for truncated BID-induced mitochondrial apoptosis by recruiting BAK to the mitochondria. **EMBO Rep.** 10: 1341-7.

Baines CP, Kaiser RA, Sheiko T, **Craigen WJ**, Molkenin JD (2007). Voltage-dependent anion channels are dispensable for mitochondrial-dependent cell death. **Nat Cell Biol.** 9: 550-5.

Anflous-Pharayra K, Cai ZJ, **Craigen WJ** (2007). VDAC1 serves as a mitochondrial binding site for hexokinase in oxidative muscles. **Biochim Biophys Acta.** 1767: 136-42.

Sabirov RZ, Sheiko T, Liu H, Deng D, Okada Y, **Craigen WJ** (2006). Genetic demonstration that the plasma membrane maxianion channel and voltage-dependent anion channels are unrelated proteins. **J Biol Chem.** 281: 1897-904.

Cheng EH, Sheiko TV, Fisher JK, **Craigen WJ**, Korsmeyer SJ (2003). VDAC2 inhibits BAK activation and mitochondrial apoptosis. **Science.** 301: 513-7.

Weeber EJ, Levy M, Sampson MJ, Anflous K, Armstrong D, Brown SE, Sweatt JD, **Craigen WJ** (2002). The role of mitochondrial porins and the permeability transition pore in learning and synaptic plasticity. **J Biol Chem.** 277: 18891-7.

WEIWEI DANG, PH.D.

Associate Professor, Department of Molecular and Human Genetics and Huffington Center on Aging

Faculty Member, Graduate Programs in Cancer & Cell Biology, Development, Disease Models & Therapeutics, and Genetics & Genomics

CPRIT Scholar in Cancer Research

Ph.D., Southern Illinois University

Postdoc, University of Pennsylvania

RESEARCH INTERESTS

Our laboratory is studying epigenetic regulation for aging and oncogenesis. Aging is the single greatest risk factor for diseases that are principal causes of mortality, including cardiovascular diseases, diabetes, neurodegenerative diseases and infectious diseases. A breakthrough in aging research resulting in even moderate retardation of aging and a delay in the onset of age-associated diseases, such as cancer, would have a tremendous impact on the quality of life for the public. However, aging and how it contributes to the development of age-associated diseases remain poorly understood. Epigenetic changes, including histone modifications and proteomes, are critical regulatory mechanisms, involved in all developmental processes including aging and age-associated diseases. The goal of our research is to discover novel chromatin and proteomics regulation pathways that modulate longevity and regulate the development of age-associated diseases, such as cancer. These mechanistic studies will form the basis for the future development of therapeutic targets for treating age-associated diseases and improving human health span.

Replicative aging of budding yeast has been a powerful system for aging studies, providing fundamental genetic and molecular insights into both cellular and organismal aging. Studies of chromatin biology have also immensely benefited from the yeast model since it provides a uniquely tractable system for such studies and because many molecular mechanisms of chromatin are highly conserved from yeast to complex eukaryotes. We use budding yeast replicative aging as a model to study how epigenetic regulations can modulate longevity. Our earlier work was among the first to demonstrate that changes in epigenetic markings can causatively alter lifespan in the budding yeast. We later discovered age-associated cryptic transcription and showed that suppressing it through epigenetic mechanisms can promote yeast lifespan. We have now extended these findings to worms and mammalian stem cells. Better stress response has been associated with longevity in many experimental models. In another study, we revealed that a highly conserved chromatin remodeling enzyme regulates aging through stress response pathways in yeast and that this mechanism is also likely conserved in other eukaryotes. More recently, our team discovered a novel form of stress response called Chromatin Architectural Defect (CAD) response that becomes activated when nucleosomes are lost from chromatin, a phenomenon found in aged cells and tissues. Strikingly, moderately activating CAD response promotes longevity in yeast and the nematode *C. elegans*. These studies not only discovered novel molecular mechanisms regulating the aging process but also provide new possibilities for intervention through epigenetic pathways. Furthermore, through a series of unbiased lifespan screens and other high throughput systems biology approaches, we have identified more chromatin regulation pathways that seem to also alter lifespan. Such pathways include those involved in transcription regulation, DNA damage response, cellular stress response, chromatin compaction and heterochromatin formation, etc. Further studies are currently carried out in our lab to elucidate the molecular mechanisms and their causal relationship to aging.

Stem cell aging and cellular senescence are important processes that contribute to the aging pathology and development of cancer. As a complement to our yeast replicative aging model, we are using mammalian primary cell lines and adult stem cells to study whether and how chromatin and epigenetic regulation pathways identified in yeast are involved in stem cell aging and cellular senescence. Our recently published study demonstrates that age-associated cryptic transcription that we initially discovered in yeast is also a hallmark of aged mammalian stem cells, as well as a broad range of tissues, providing valuable insights into the aging processes in mammals.

**SELECTED PUBLICATIONS**

Zhang Q, **Dang W**, Wang MC (2025). Lysosomes Signal through Epigenome to Regulate Longevity across Generations. **Science**. 389: 1353-1360.

Yu A, Yu R, Liu H, Ge C, **Dang W** (2023). SIRT1 safeguards adipogenic differentiation by orchestrating anti-oxidative responses and suppressing cellular senescence. **GeroScience**. 46: 1107.

McCauley BS*, Sun L*, Yu R, Lee M, Liu H, Leeman DS, Huang Y, Webb AE, **Dang W** (2021). Altered chromatin states drive cryptic transcription in aging mammalian stem cells. **Nature Aging**. 1: 684. *equal contribution

Sun Y*, Yu R*, Guo H-B, Qin H, **Dang W** (2021). A Quantitative Yeast Aging Proteomics Analysis Reveals Novel Aging Regulators. **GeroScience**. 43: 2573. *equal contribution

Yu R*, Cao X*, Sun L, Zhu J, Wasko B, Liu W, Crutcher E, Liu H, Jo MC, Qin L, Kaeberlein M, Han Z, **Dang W** (2021). Inactivating histone deacetylase HDA promotes longevity by mobilizing trehalose metabolism. **Nat Commun**. 12: 1981. *equal contribution

Liu L, Yan Z, Osia BA, Twarowski J, Sun L, Kramara J, Lee R, Kumar S, **Dang W**, Ira G, Malkova A (2021). Tracking break-induced replication shows that it stalls at roadblocks. **Nature**. 590: 655-659.

Yu R, Sun L, Sun Y, Han X, Qin L, **Dang W** (2019). Cellular Response to Moderate Chromatin Architectural Defects Promotes Longevity. **Sci Adv**. 5: eaav1165.

Jo MC, Liu W, **Dang W***, Qin L# (2015). High-throughput analysis of yeast replicative aging using a novel microfluidic system. **Proc Natl Acad Sci U S A**. 112: 9364-9. #co-corresponding authors.

Sen P*, **Dang W***#, Donahue G, Dai J, Dorsey J, Cao X, Liu W, Cao K, Perry R, Lee JY, Wagner J, Gregory BD, Kaeberlein M, Kennedy BK, Boeke J, Berger SL# (2015). H3K36 methylation promotes longevity by enhancing transcription fidelity. **Genes Dev**. 29: 1362-76. *equal contribution; #co-corresponding authors.

Dang W, Sutphin GL, Dorsey J, Otte GL, Cao K, Perry R, Wanat JJ, Saviolaki D, Murakami CJ, Tsuchiyama S, Robinson B, Gregory BD, Vermeulen M, Shiekhattar R, Johnson FB, Kennedy BK, Kaeberlein M, Berger SL (2014). Inactivation of yeast Isw2 chromatin remodeling enzyme mimics longevity effect of calorie restriction via induction of genotoxic stress response. **Cell Metab**. 19: 952-66.

Dang W, Steffen KK, Perry R, Dorsey J, Johnson FB, Shitafard A, Kaeberlein M, Kennedy BK, and Berger SL (2009). Histone H4 lysine-16 acetylation regulates cellular lifespan. **Nature**. 459: 802-7.

SHWETA DHAR, M.D., M.S.

Professor, Department of Molecular and Human Genetics
Medical Director, Adult Genetics Service
National Program Executive Director, Genomics, Veterans Health Administration
Section Chief, Internal Medicine – Genetics, Michael E. DeBakey Veteran Affairs Medical Center

MBBS, NHL Municipal Medical College
Resident, Pathology & Microbiology, The Gujarat Cancer and Research Institute
M.S., Stephen F. Austin University
Resident, Internal Medicine, New York INF Beekman Downtown Hospital
Fellow, Medical Genetics, Baylor College of Medicine

RESEARCH INTERESTS

The Adult Genetics Service at Baylor College of Medicine is one of the largest in the country, allowing us to start our own combined internal medicine/medical genetics residency program. My primary clinical focus lies in the diagnosis and management of adults with known and suspected genetic conditions. These include diagnosis and management of single gene disorders, chromosomal disorders, familial cancer syndromes, risk assessment for cancer, as well as testing for known genetic disorders in the family.

I also work at the Michael E. DeBakey Department of Veterans Affairs Medical Center where I see Veterans with genetic disorders and develop regulations and policies around the practice of clinical genomics in my role as the National Program Director for Genomics. Extending this role at the national level, I serve as a clinical director for the Board of Directors for the American College of Medical Genetics & Genomics (ACMG).

I am also involved in the education of medical students at BCM in the field of adult genetics. As founding director of the Genetics & Genomics Pathway and recent past course director for the genetics course for BCM medical students, I am always looking for opportunities to enhance the genetic education of our medical students and residents. I serve as elective director for the adult genetics electives. I continue this commitment to education in genomics through my recent appointment as Vice President of Education for ACMG.



SELECTED PUBLICATIONS

Handbook of Clinical Adult Genetics and Genomics – A Practice-Based Approach. **Dhar SU**, Nagamani SC, Eble TN, eds. Elsevier. 2020

McDonald MF, Prather LL, Helfer CR, Ludmir EB, Echeverria AE, Yust-Katz S, Patel AJ, Deneen B, Rao G, Jalali A, **Dhar SU**, Amos CI, Mandel JJ (2023). Prevalence of pathogenic germline variants in adult-type diffuse glioma. *Neurooncol Pract.* 10: 482-490.

Glinton KE, Potocki L, **Dhar SU** (2021). An innovative medical school curriculum to enhance exposure to genetics and genomics: Updates and outcomes. *Genet Med.* 30: S1098-3600

Zhao S, Chen WJ, **Dhar SU**, Eble TN, Kwok OM, Chen LS (2021). Pursuing genetic testing for children with autism spectrum disorders: What do parents think? *J Genet Couns.* 30: 370-382

Chen WJ, Zhao S, Stelzig D, Nimmons KM, **Dhar SU**, Eble TN, Martinez D, Yeh YL, Chen LS (2021). Family Health History-Based Cancer Prevention Training for Community Health Workers. *Am J Prev Med.* 60: e159-e167

Yang Y, **Dhar SU**, Taylor J, Krishnan B (2021). Papillary renal cell carcinoma in Lynch/Muir Torre syndrome with germline pathogenic variant in MSH6 and molecular analysis: report of a case and review of the literature. *J Kidney Cancer VHL* 8: 8-19.

Assia Batzir N, Bhagwat PK, Eble TN, Liu P, Eng CM, (...), **Dhar SU**, Wangler MF (2019). De novo missense variant in the GTPase effector domain (GED) of DNMT1 leads to static encephalopathy and seizures. *Cold Spring Harb Mol Case Stud.* 5(3). pii: a003673.

Prakash P, Eble TN, **Dhar SU** (2018). Quality improvement of clinic flow for complex genetic conditions: Using Ehlers-Danlos syndrome as a model. *Mol Genet Genomic Med.* 6: 993-1000.

Machol K, Jankovic J, Vijayakumar D, Burrage LC, Jain M, (...); Undiagnosed Diseases Network, **Dhar SU** (2018). Atypical Alexander disease with dystonia, retinopathy, and a brain mass mimicking astrocytoma. *Neurol Genet.* 4: e248.

Eble TN, Nagamani SC, Franco LM, Plon SE, Blazo M, **Dhar SU** (2013). The practice of adult genetics: A 7-year experience from a single center. *Am J Med Genet A.* 161: 89-93.

Dhar SU, Alford RL, Nelson EA, Potocki L (2012). Enhancing exposure to genetics and genomics through an innovative medical school curriculum. *Genet Med.* 14: 163-7.

Chen LS, Xu L, Huang TY, **Dhar SU** (2013). Autism genetic testing: a qualitative study of awareness, attitudes, and experiences among parents of children with autism spectrum disorders. *Genet Med.* 15: 274-81.

HERMAN A. DIERICK, M.D.

Associate Professor, Departments of Molecular and Human Genetics and Neuroscience

Faculty Member, Graduate Programs in Genetics & Genomics and Neuroscience

M.D., Catholic University of Leuven

Postdoc, University of Michigan

Postdoc, Northwestern University

Research Fellow, The Neurosciences Institute

RESEARCH INTERESTS

Aggression is a complex social behavior that is influenced by numerous genetic and environmental factors. Neither the genes underlying this behavior nor its neurobiological mechanism(s) are very well worked out. Much of the aggressive behavior observed in nature is directed towards animals of the same species, so-called intraspecific aggression, and revolves around competition for limited resources in the environment, food and mating partners. Most if not all animals show some form of aggression which suggests that the fundamental aspects of aggressive behavior may well be conserved throughout the animal kingdom. Even though aggression is a normal behavior necessary for animals to successfully compete and contribute to the survival of the animal and the species, aggression can also take on pathological forms. Numerous human diseases are characterized by an aggression component.

In the past, we have pursued two angles to start to understand the neurobiological basis of aggression in *Drosophila melanogaster*. In a first set of experiments, we performed selection on a wild-type strain using a very specific selective pressure in a population-based environment. We picked animals for further breeding that performed a rare but highly aggressive behavioral element known as escalated fighting in which males reciprocally lunge at each other and box and tussle in order to gain control over a territory. After the selected lines showed reliably different levels of aggression from control strains, we performed microarray expression experiments to look for changes in gene expression in the heads of the high and low aggression strains. This resulted in a list of candidate genes, some of which as individual mutations partially recapitulated the phenotype. In a set of follow-up experiments, we analyzed the effect of two neuromodulators, known to affect aggression in mammals. Both these modulators, serotonin (5-HT) and neuropeptide F (npf) strongly affect aggression in the fly, albeit not exactly in the same way.

Our research goal is to continue to dissect the genetics and neurobiological mechanisms of aggressive behavior in *Drosophila melanogaster*, using the many sophisticated genetic, cell biological and neurobiological tools that are available in this species. Eventually, we want to investigate whether the mechanisms and genes identified in the vinegar fly are conserved in vertebrate species including mammals.

**SELECTED PUBLICATIONS**

Huang G, **Dierick HA** (2022). The need for unbiased genetic screens to dissect aggression in *Drosophila melanogaster*. **Front Behav Neurosci**. 16: 901453.

Dierick HA, Ben-Shahar Y, Raman B, Gabbiani F (2021). Genetic and viral approaches to record or manipulate neurons in insects. **Curr Opin Insect Sci**. 48: 79-88.

Matinyan N, Karkhanis MS, Gonzalez Y, Jain A, Saltzman A, Malovannaya A, Sarrion-Perdigones A, **Dierick HA**, Venken KJT (2021). Multiplexed drug-based selection and counterselection genetic manipulations in *Drosophila*. **Cell Rep**. 36: 109700.

Chowdhury B, Wang M, Gnerer JP, **Dierick HA** (2021). The Divider Assay is a high-throughput pipeline for aggression analysis in *Drosophila*. **Commun Biol**. 4: 85.

Davis SM, Thomas AL, Liu L, Campbell IM, **Dierick HA** (2018). Isolation of Aggressive Behavior Mutants in *Drosophila* Using a Screen for Wing Damage. **Genetics**. 208: 273-282.

Thomas AL, Davis SM, **Dierick HA** (2015). Of fighting flies, mice and men: are some of the molecular and neuronal mechanisms of aggression universal in the animal kingdom? **PLoS Genet**. 11: e1005416.

Gnerer JP, Venken KJ, **Dierick HA** (2015). Gene-specific cell labeling using MiMIC transposons. **Nucleic Acids Res**. 43: e56.

Davis SM, Thomas A, Nomie KJ, Huang L, **Dierick HA** (2014). Tailless and Atrophin control *Drosophila* aggression by regulating neuropeptide signalling in the pars intercerebralis. **Nat Commun**. 5: 3177.

Thomas A, Lee PJ, Dalton J, Nomie KJ, Stoica L, Costa-Mattioli M, Chang P, Nuzhdin S, Arbeitman M, **Dierick HA** (2012). A versatile method for cell specific profiling of translated mRNAs in *Drosophila*. **PLoS One**. 7: e40276.

Dierick HA, Greenspan RJ (2007). Serotonin and neuropeptide F have opposite modulatory effects on fly aggression. **Nat Genet**. 39: 678-82.

VISHNU DILEEP, PH.D.

Assistant Professor, Department of Molecular and Human Genetic and Huffington Center on Aging
CPRIT Scholar in Cancer Research

Ph.D., Florida State University
Postdoctoral Training, Massachusetts Institute of Technology

RESEARCH INTERESTS

The main focus of our research is to elucidate the genomic and epigenomic basis of brain aging and neurodegeneration. We investigate how chromatin organization and epigenetic modifications influence normal brain function and how their dysregulation contributes to neurodegenerative diseases, particularly Alzheimer's disease. Our work also explores DNA damage as a critical genomic phenomenon in brain aging, examining various DNA lesions as disruptors of chromatin features in brain cell types and drivers of neurological disorders.

Our current projects include: 1) Mapping DNA damage at single-cell resolution and its impact on genome organization across brain cell types in Alzheimer's disease, 2) Understanding the role of 3D genome organization in microglia activation and its implications for neuroinflammation, and 3) Investigating the impact of DNA-damaging chemotherapeutic agents on genome organization and integrity in brain cells.

The long-term vision for our lab is to develop precision medicine approaches for neurodegeneration, cognitive dysfunction, and other age-related brain diseases. This goal is informed by our pursuit of a clearer understanding of the underlying genomic and epigenomic disruptions. To achieve this, we utilize in vitro models, mouse models, and human post-mortem tissue, while integrating diverse disciplines including chromatin biology, innovative tool development, and computational biology. By combining these approaches, we aim to unravel the complex interplay between genomic factors and brain health.



SELECTED PUBLICATIONS

Dileep V, Boix CA, Mathys H, Marco A, Welch GM, Meharena HS, Loon A, Jeloka R, Peng Z, Bennett DA, Kellis M, Tsai LH (2023). Neuronal DNA double-strand breaks lead to genome structural variations and 3D genome disruption in neurodegeneration. **Cell**. 186: 4404-4421.e20.

Meharena HS, Marco A, **Dileep V**, Lockshin ER, Akatsu GY, Mullahoo J, Watson LA, Ko T, Guerin LN, Abdurrob F, Rengarajan S, Papanastasiou M, Jaffe JD, Tsai LH (2022). Down-syndrome-induced senescence disrupts the nuclear architecture of neural progenitors. **Cell Stem Cell**. 29: 116-130.e7.

Bartlett DA, **Dileep V**, Handa T, Ohkawa Y, Kimura H, Henikoff S, Gilbert DM (2021). High-throughput single-cell epigenomic profiling by targeted insertion of promoters (TIP-seq). **J Cell Biol**. 220: e202103078.

Marco A, Meharena HS, **Dileep V**, Raju RM, Davila-Velderrain J, Zhang AL, Adaikkan C, Young JZ, Gao F, Kellis M, Tsai LH (2020). Mapping the epigenomic and transcriptional interplay during memory formation and recall in the hippocampal engram ensemble. **Nat Neurosci**. 23: 1606-1617.

Dileep V, Wilson KA, Marchal C, Lyu X, Zhao PA, Li B, Poulet A, Bartlett DA, Rivera-Mulia JC, Qin ZS, Robins AJ, Schulz TC, Kulik MJ, McCord RP, Dekker J, Dalton S, Corces VG, Gilbert DM (2019). Rapid Irreversible Transcriptional Reprogramming in Human Stem Cells Accompanied by Discordance between Replication Timing and Chromatin Compartment. **Stem Cell Reports**. 13: 193-206.

Sima J, Chakraborty A, **Dileep V**, Michalski M, Klein KN, Holcomb NP, Turner JL, Paulsen MT, Rivera-Mulia JC, Trevilla-Garcia C, Bartlett DA, Zhao PA, Washburn BK, Nora EP, Kraft K, Mundlos S, Bruneau BG, Ljungman M, Fraser P, Ay F, Gilbert DM (2019). Identifying cis Elements for Spatiotemporal Control of Mammalian DNA Replication. **Cell**. 176: 816-830.e18.

Dileep V, Gilbert DM (2018). Single-cell replication profiling to measure stochastic variation in mammalian replication timing. **Nat Commun**. 9: 427.

Dixon JR, Xu J, **Dileep V**, Zhan Y, Song F, Le VT, (...), Yue F (2018). Integrative detection and analysis of structural variation in cancer genomes. **Nat Genet**. 50: 1388-1398.

Dileep V, Ay F, Sima J, Vera DL, Noble WS, Gilbert DM (2015). Topologically associating domains and their long-range contacts are established during early G1 coincident with the establishment of the replication-timing program. **Genome Res**. 25: 1104-13.

Pope BD, Ryba T, **Dileep V**, Yue F, Wu W, (...), Gilbert DM (2014). Topologically associating domains are stable units of replication-timing regulation. **Nature**. 515: 402-5.

FLORENT ELEFTERIOU, PH.D.

Professor, Departments of Molecular and Human Genetics and Orthopedic Surgery

Associate Director, Center for Skeletal Medicine and Biology

Ph.D., Claude Bernard University
Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

Our research aims at understanding how the skeleton forms, grows, mineralizes, ages, repairs and communicates with other tissues in health and diseases.

One main focus of the laboratory is on the etiology of the skeletal maladies observed in individuals with neurofibromatosis type I (NF1). We are particularly interested in the fracture non-union and dystrophic scoliosis observed in some of these patients. We use genetic strategies to identify both cells of origin and molecular abnormalities causing these orthopedic conditions, with the goal of designing and testing novel targeted therapeutic strategies to improve bone mass, bone strength and bone repair in children with NF1. These studies also provide critical insights into the role of neurofibromin, the RAS-GAP protein encoded by the *NF1* gene, in endochondral bone formation, remodeling, repair and mineralization.

A second focus area of the laboratory is related to the interaction between the autonomic nervous system and bone cells. Our current emphasis is on determining the role of the endogenous sympathetic and parasympathetic nervous systems in the regulation of bone homeostasis, and on addressing the biological and clinical relevance of our preclinical findings. This leads us to study the role of the norepinephrine transporter and conditions including bone aging, depression and Alzheimer's disease and their impact on bone remodeling.

A third active line of research in the laboratory revolves around the biology of chondrocytes, the cells of cartilaginous tissues that allow bone elongation during the development and protection of joint articular surfaces in adults. Through our focus on the transcription factor *TonEBP/Nfat5*, we investigate how chondrocytes survive and function in their hyperosmotic, avascular and low nutrient environment.



SELECTED PUBLICATIONS

Couasnay G, Madel MB, Lim J, Lee B, **Elefteriou F** (2021). Sites of Cre-recombinase activity in mouse lines targeting skeletal cells. **J Bone Miner Res.** doi: 10.1002/jbmr.4415. Online ahead of print.

Ma Y, Gross AM, Dombi E, (...), Widemann BC, Rios JJ, **Elefteriou F** (2020). A molecular basis for neurofibroma-associated skeletal manifestations in NF1. **Genet Med.** 22: 1786-1793.

Ma Y, **Elefteriou F** (2020). Brain-Derived Acetylcholine Maintains Peak Bone Mass in Adult Female Mice. **J Bone Miner Res.** 35: 1562-1571.

Zhu Y, Ma Y, **Elefteriou F** (2018). Cortical bone is an extra-neuronal site of norepinephrine uptake in adult mice. **Bone Rep.** 9: 188-198.

Elefteriou F (2018). Impact of the Autonomic Nervous System on the Skeleton. **Physiol Rev.** 98: 1083-1112.

Mulcrone PL, Campbell JP, Clément-Demange L, Anbinder AL, (...), **Elefteriou F** (2017). Skeletal Colonization by Breast Cancer Cells Is Stimulated by an Osteoblast and b2AR-Dependent Neo-Angiogenic Switch. **J Bone Miner Res.** 32: 1442-1454.

Karolak MR, Yang X, **Elefteriou F** (2015). FGFR1 signaling in hypertrophic chondrocytes is attenuated by the Ras-GAP neurofibromin during endochondral bone formation. **Hum Mol Genet.** 24: 2552-64.

de la Croix Ndong J, Makowski AJ, Uppuganti S, Vignaux G, Ono K, (...), **Elefteriou F** (2014). Asfotase- α improves bone growth, mineralization and strength in mouse models of neurofibromatosis type-1. **Nat Med.** 20: 904-10.

Ono K, Karolak MR, Ndong Jde L, Wang W, Yang X, **Elefteriou F** (2013). The ras-GTPase activity of neurofibromin restrains ERK-dependent FGFR signaling during endochondral bone formation. **Hum Mol Genet.** 22: 3048-62.

Stevenson DA, Little D, Armstrong L, (...), Viskochil DH, Yang FC, **Elefteriou F** (2013). Approaches to treating NF1 tibial pseudarthrosis: consensus from the Children's Tumor Foundation NF1 Bone Abnormalities Consortium. **J Pediatr Orthop.** 33: 269-75.

Campbell JP, Karolak MR, Ma Y, (...), Yang X, Sterling JA, **Elefteriou F** (2012). Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. **PLoS Biol.** 10: e1001363.

SARAH H. ELSEA, PH.D.

Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Program in Development, Disease Models & Therapeutics
Member, Dan L Duncan Comprehensive Cancer Center
Director, Clinical Genomics, Human Genome Sequencing Center - Clinical Laboratory

Ph.D., Vanderbilt University
Postdoc, Baylor College of Medicine
Fellow, Clinical Biochemical Genetics, Baylor College of Medicine

RESEARCH INTERESTS

Despite many advances in the diagnosis of rare diseases, individual genetic variation and the pathophysiological mechanisms underlying these complex disorders are often poorly understood. Our research goals are to define the biochemical mechanisms and molecular pathways impacted by rare disease, particularly neurodevelopmental, neurodegenerative and neurometabolic disorders complicated by obesity and circadian rhythm defects, including autism, intellectual disability, seizures and behavioral phenotypes. Clinical and molecular analysis of neurometabolic conditions, such as NAXD and NAXE deficiency, AADC deficiency, and SSADH deficiency and multiple genomic disorders, wherein deletion or duplication of a portion of the genome is the primary underlying etiology leading to altered gene dosage, are the primary areas of investigation in the Elsea Lab.

We are developing and translating into clinical practice personalized medicine approaches for neurodevelopmental, neurodegenerative, and metabolically-driven conditions utilizing genomic, metabolomic, and transcriptomic approaches to improve diagnosis, disease management, and quality of life for individuals with rare disease. To improve diagnosis and genomic variant interpretation and to address the need for a broad-based functional metabolic screen that goes beyond traditional testing, we developed at Baylor Genetics a clinical untargeted metabolomics pipeline for diagnosis and management of inborn errors of metabolism. Global MAPS offers a functional genomics approach to clinical genomic variant interpretation and has facilitated biomarker discovery and development of metabolomic profiles for diagnosis and therapeutic management for multiple metabolic conditions. Further supporting efforts in personalized medicine, large-scale projects in the BCM-Human Genome Sequencing Center, such as *All of Us*, provide insight into genomic variation in diverse populations, and ClinGen genomic variant curation projects facilitate personalized medicine approaches to medical care. Together with this efforts, we are developing an expanded newborn screening disorder panel to improve early screening for treatable genetic conditions, reducing health disparities associated with delayed diagnosis of these rare but treatable disorders.

We incorporate multi-omics technologies to interrogate mouse, cellular, and other rare disease models. Integrating genomics, expression profiling, metabolomics, epigenetic profiling and other functional data to define the biochemical and molecular pathways that may be amenable to therapeutic targeting provides a comprehensive approach to improve diagnosis, enhance understanding of phenotypes and define the molecular and metabolic pathways altered in the disease state. Defining molecular relationships among subsets of neurodevelopmental disorders toward developing common, targeted therapeutics is a key outcome of these efforts. For example, a hallmark feature of the genomic disorder Smith-Magenis syndrome (SMS) is a circadian rhythm defect, with significant sleep disturbance and obesity. Our work has shown that *RAI1* directly regulates expression of *BDNF*, a key player in development and metabolism, and *CLOCK*, a master regulator of circadian rhythm, providing strong evidence for molecular and cellular etiology behind the sleep phenotype—these data from the base knowledge for therapeutic targeting in SMS. To further support these efforts, we designed and maintain the SMS Patient Registry to collect natural history data across the lifespan. Other patient registries are also in development to further our knowledge of rare conditions and to support ongoing research efforts to bring basic research closer to the patient.



SELECTED PUBLICATIONS

Elatrash C, Shi J, Wilson T, **Elsea SH**, Sisley S (2024). Blind to the perils of pursuing food: Behaviors of individuals with Smith-Magenis Syndrome. **Genet Med Open**. 2: 101857.

Glinton KE, Gijavanekar C, Rajagopal A, Mackay LP, Martin KA, Pearl PL, Gibson KM, Wilson TA, Sutton VR, **Elsea SH** (2024). Succinic semialdehyde dehydrogenase deficiency: a metabolic and genomic approach to diagnosis. **Front Genet**. 15: 1405468.

Gijavanekar C, **Elsea SH** (2023). Clinical Untargeted Metabolomics as a Functional Screen to Improve Variant Classification. **Curr Protoc**. 3: e720.

Elsea SH, Razjouyan J, Lee KM, Lynch JA, Martini S, Pandit LM (2023). Association of Glucose-6-Phosphate Dehydrogenase Deficiency With Outcomes in US Veterans With COVID-19. **JAMA Netw Open**. 6: e235626.

Manor J, Calame D, Gijavanekar C, Fisher K, Hunter J, Mizerik E, Bacino C, Scaglia F, **Elsea SH** (2022). NAXE deficiency: A neurometabolic disorder of NAD(P)HX repair amenable for metabolic correction. **Mol Genet Metab**. 136: 101-110.

Manor J, Calame DG, Gijavanekar C, Tran A, Fatih JM, Lalani SR, Mizerik E, Parnes M, Mehta VP, Adesina AM, Lupski JR, Scaglia F, **Elsea SH** (2022). Niacin therapy improves outcome and normalizes metabolic abnormalities in an NAXD-deficient patient. **Brain**. 145: e36-e40.

Milosavljevic S, Glinton KE, Li X, Medeiros C, Gillespie P, Seavitt JR, Graham BH, **Elsea SH** (2022). Untargeted Metabolomics of Slc13a5 Deficiency Reveal Critical Liver-Brain Axis for Lipid Homeostasis. **Metabolites**. 12: 351.

Gandhi AA, Wilson TA, Sisley S, **Elsea SH**, Foster RH (2022). Relationships between food-related behaviors, obesity, and medication use in individuals with Smith-Magenis syndrome. **Res Dev Disabil**. 127: 104257.

Thistlethwaite LR, Li X, Burrage LC, Riehle K, Hacia JG, Braverman N, Wangler MF, Miller MJ, **Elsea SH**, Milosavljevic A (2022). Clinical diagnosis of metabolic disorders using untargeted metabolomic profiling and disease-specific networks learned from profiling data. **Sci Rep**. 12: 6556.

Liu N, Xiao J, Gijavanekar C, Pappan KL, Glinton KE, Shayota BJ, Kennedy AD, Sun Q, Sutton VR, **Elsea SH** (2021). Comparison of Untargeted Metabolomic Profiling vs Traditional Metabolic Screening to Identify Inborn Errors of Metabolism. **JAMA Netw Open**. 4: e2114155.

CHRISTINE M. ENG, M.D.

Professor and Vice Chair for Diagnostic Laboratory Affairs, Department of Molecular and Human Genetics
Chief Quality Officer and Chief Medical Officer, Baylor Genetics
Director, Storage Disorders Clinic

M.D., Tulane University School of Medicine

RESEARCH INTERESTS

My research interests are directed toward translational medicine, specifically the application of molecular genetics to the diagnosis and treatment of genetic diseases. Recently, my efforts have been focused on laboratory and clinical aspects of genetic testing and clinical research in lysosomal storage diseases.

My main area of interest is the development, implementation, and evaluation of novel molecular approaches to the diagnosis of genetic disorders. As Senior Director of the Medical Genetics Laboratories and Medical Director of the Whole Genome Laboratory, our primary mission is to provide state-of-the-art genetic testing for common and rare conditions in a CAP and CLIA-certified clinical laboratory. To this end, we are very active in the development of new disease tests and testing strategies, refinement of testing methods for improved sensitivity and specificity, and extension of these activities beyond the usual scope of a molecular diagnostic lab. In collaboration with the Human Genome Sequencing Center at Baylor, we have recently developed, validated, and implemented whole exome sequencing as a clinical diagnostic test for individuals with apparent genetic disorders that have been a challenge to diagnose. The whole exome sequencing test is a highly complex test that identifies changes in a patient's DNA that are causative or related to their medical concerns. In contrast to current sequencing tests that analyze one gene or small groups of related genes at a time, the whole exome sequencing test analyzes the exons or coding regions of thousands of genes simultaneously using next-generation sequencing techniques. Identification of the underlying diagnosis can improve medical management and offer information to the family regarding prognosis. Another area of development in the area of personalized medicine is based on determining an individual's genomic profile. We recently developed and validated a highly multiplexed, beadchip assay that is designed to detect single nucleotide changes in disease genes and genetic loci that are causative or predictive of specific single gene disorders, increase the risk of developing certain common multifactorial conditions such as diabetes, or are associated with the altered metabolism and response to certain drugs. In addition to the development of tests for clinical application, we also have an active interest in determining molecular mechanisms for novel mutations detected through routine testing as well as identifying potential novel disease genes.

My major clinical research interest is in lysosomal storage diseases, particularly Fabry disease, Gaucher disease, and Mucopolysaccharidosis type 2, with emphasis on both clinical and laboratory approaches to the elucidation of the natural history, molecular genetics, and evaluation of treatments in clinical trials. Previous accomplishments in my laboratory include the further characterization of the natural history of the classical and cardiac variant forms of the disease, the study of genotype-phenotype correlations, and the development of rapid mutation assays for prenatal diagnosis and identification of carrier females. Currently, my efforts have been directed toward the evaluation in clinical trials of novel treatment approaches for Fabry disease, Gaucher disease, and other lysosomal storage disorders in the form of recombinant enzyme replacement therapy and chaperone therapy.



SELECTED PUBLICATIONS

Zimran A, Pastores GM, Tytki-Szymanska A, Hughes DA, Elstein D, Mardach R, **Eng C**, Smith L, Heisel-Kurth M, Charrow J, Harmatz P, Fernhoff P, Rhead W, Longo N, Giraldo P, Ruiz JA, Zahrieh D, Crombez E, Grabowski GA (2013). Safety and efficacy of velaglycerase alfa in Gaucher disease type 1 patients previously treated with imiglycerase. **Am J Hematol.** 88: 172-8.

Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, **Eng CM** (2013). Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders. **N Engl J Med.** 369: 1502-11.

Berryer MH, Hamdan FF, Klitten LL, Møller RS, Carmant L, Schwartzentruber J, Patry L, Dobrzaniecka S, Rochefort D, Neugnot-Ceroli M, Lacaille JC, Niu Z, **Eng CM**, Yang Y, Palardy S, Belhumeur C, Rouleau GA, Tommerup N, Immken L, Beauchamp MH, Patel GS, Majewski J, Tarnopolsky MA, Scheffek K, Hjalgrim H, Michaud JL, Di Cristo G. (2013). Mutations in SYNGAP1 cause intellectual disability, autism, and a specific form of epilepsy by inducing haploinsufficiency. **Hum Mutat.** 34: 385-94.

Wapner RJ, Martin CL, Levy B, Ballif BC, **Eng CM**, Zachary JM, Savage M, Platt LD, Saltzman D, Grobman WA, Klugman S, Scholl T, Simpson JL, McCall K, Aggarwal VS, Bunke B, Nahum O, Patel A, Lamb AN, Thom EA, Beaudet AL, Ledbetter DH, Shaffer LG, Jackson L (2012). Chromosomal microarray versus karyotyping for prenatal diagnosis. **N Engl J Med.** 367: 2175-84.

Darilek S, Ward P, Pursley A, Plunkett K, Furman P, Magoulas P, Patel A, Cheung SW, **Eng CM** (2008). Pre- and postnatal genetic testing by array-comparative genomic hybridization: genetic counseling perspectives. **Genet Med.** 10: 13-8.

Sahoo T, Cheung SW, Ward P, Darilek S, Patel A, (...), **Eng CM** (2006). Prenatal diagnosis of chromosomal abnormalities using array-based comparative genomic hybridization. **Genet Med.** 8: 719-27.

Eng CM, et al. (2006). Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. **Genet Med.** 8: 539-48.

Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, **Eng CM**, et al. (2006). A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). **Genet Med.** 8: 465-73.

GRAHAM ERWIN, PH.D.

Assistant Professor, Department of Molecular and Human Genetics
Faculty Member, Dan L Duncan Comprehensive Cancer Center

Ph.D. in Biochemistry, University of Wisconsin–Madison
Postdoctoral Fellowship in Genetics, Stanford University

RESEARCH INTERESTS

The Erwin Lab investigates the functional role of repetitive DNA with a focus on translating these discoveries into diagnostics and therapies for human health. Repeat expansions cause more than 40 rare neurodegenerative and neurological diseases, and these diseases are devastating, each in their own way. Spinocerebellar ataxias rob patients—often children—of their ability to control their movements, permanently relegating many to a wheelchair. Other diseases, such as Friedrich's ataxia, lead to severe cardiomyopathies and heart failure. However, variations in tandem repeats (TRs) are often not explored because they are not captured well by conventional bioinformatic tools. The overarching goal of our research is to identify TR variation in the human genome, characterize its function, and generate new chemical tools that can serve as the starting point for first-in-class therapies to treat devastating neurodegenerative diseases. Our lab is motivated by two discoveries that we made:

1. Development of a therapeutic framework for synthetic transcriptional regulators. Gene expression is highly regulated, and defects in this process lead to a host of diseases. We previously showed that programmable DNA-binding polyamides target repetitive DNA sequences with high affinity and specificity (Erwin et al, *Angewandte Chemie* 2014, Erwin et al, *PNAS* 2016). Based on these findings, we designed and synthesized a new class of sequence-specific, synthetic transcription elongation factors (Syn-TEFs). These molecules are composed of programmable DNA-binding polyamides flexibly tethered to a small molecule (JQ1) that engages the transcription elongation machinery. This work culminated in Syn-TEF1, a molecule that actively enables transcription across repressive GAA repeats that silence frataxin expression in Friedrich's ataxia, a terminal neurodegenerative disease with no effective therapy (Erwin et al, *Science* 2017). Syn-TEF1 defines a modular framework for developing a class of molecules that promote transcription at targeted genomic loci. An analog of Syn-TEF1 is currently being tested in Phase 1 clinical trials.

2. Discovery of recurrent repeat expansions (rREs) in human cancer genomes. Repeat expansions are often not explored beyond neurological and neurodegenerative disorders. However, in some cancers, mutations accumulate in short tracts of TRs (STRs), a phenomenon termed microsatellite instability. At Stanford University, we identified TR expansions in 2,622 human cancer genomes, spanning 29 cancer types. In 7 cancer types, we found 160 recurrent repeat expansions (rREs); most of these (155/160) were subtype specific (Erwin et al, *Nature* 2023). We found that rREs were non-uniformly distributed in the genome with an enrichment near candidate cis-regulatory elements, suggesting a role in gene regulation. Furthermore, we found that targeting cells harboring this rRE with a rationally designed, sequence-specific Syn-TEF led to a dose-dependent decrease in cell proliferation. Overall, our results demonstrate that rREs are an important but unexplored source of genetic variation in human cancers.



SELECTED PUBLICATIONS

Erwin GS, Gürsoy G, Al-Abri R, Suriyaprakash A, Dolzhenko E, Zhu K, Hoerner CR, White SM, Ramirez L, Vadlakonda A, Vadlakonda A, von Kraut K, Park J, Brannon CM, Sumano DA, Kirtikar RA, Erwin AA, Metzner TJ, Yuen RKC, Fan AC, Leppert JT, Eberle MA, Gerstein M, Snyder MP (2023). Recurrent repeat expansions in human cancer genomes. *Nature*. 613: 96-102.

Erwin GS, Grieshop MP, Ali A, Qi J, Lawlor M, Kumar D, Ahmad I, McNally A, Teider N, Worringer K, Sivasankaran R, Syed DN, Eguchi A, Ashraf M, Jeffery J, Xu M, Park PMC, Mukhtar H, Srivastava AK, Faruq M, Bradner JE, Ansari AZ (2017). Synthetic transcription elongation factors license transcription across repressive chromatin. *Science*. 358: 1617-1622.

Xiong K, **Erwin GS**, Ansari AZ, Blainey PC (2016). Sliding on DNA: From Peptides to Small Molecules. *Angew Chem Int Ed Engl*. 55: 15110-15114.

Erwin GS, Grieshop MP, Bhimsaria D, Eguchi A, Rodríguez-Martínez JA, Ansari AZ (2016). Genome-wide Mapping of Drug-DNA Interactions in Cells with COSMIC (Crosslinking of Small Molecules to Isolate Chromatin). *J Vis Exp*. 107: e53510.

Erwin GS, Bhimsaria D, Eguchi A, Ansari AZ (2014). Mapping polyamide-DNA interactions in human cells reveals a new design strategy for effective targeting of genomic sites. *Angew Chem Int Ed Engl*. 53: 10124-8.

Eguchi A, Lee GO, Wan F, **Erwin GS**, Ansari AZ (2014). Controlling gene networks and cell fate with precision-targeted DNA-binding proteins and small-molecule-based genome readers. *Biochem J*. 462: 397-413.

Erwin GS, Grieshop MP, Bhimsaria D, Do TJ, Rodríguez-Martínez JA, Mehta C, Khanna K, Swanson SA, Stewart R, Thomson JA, Ramanathan P, Ansari AZ (2016). Synthetic genome readers target clustered binding sites across diverse chromatin states. *Proc Natl Acad Sci U S A*. 113: E7418-E7427.

RICHARD A. GIBBS, PH.D.**Wofford Cain Chair in Molecular and Human Genetics****Professor**, Department of Molecular and Human Genetics**Faculty Member**, Graduate Programs in Genetics & Genomics; Quantitative & Computational Biosciences; Integrative Molecular and Biomedical Sciences; and Translational Biology & Molecular Medicine**Director**, Human Genome Sequencing Center*Ph.D., University of Melbourne**Postdoc, Baylor College of Medicine***RESEARCH INTERESTS**

Richard Gibbs is the Founder and Director of the Human Genome Sequencing Center (HGSC), established at Baylor in 1996. The HGSC has a core mission of advancing medical care through research and translation of genomics. The group was one of the five worldwide sites to undertake and complete the Human Genome Project, culminating in the contribution of approximately 10% of the sequence in 2003. The group subsequently collaborated to sequence many key species (*Drosophila melanogaster*, Brown Norway rat, rhesus macaque, bovine, *Dictyostelium discoideum*, sea urchin and honey bee genomes), to generate the first comprehensive map of human genetic variation (the HapMap project) and to generate the Cancer Genome Atlas. The HGSC next pioneered whole exome capture methods and published the first whole genome diploid sequence of a human (James Watson). Next, we demonstrated the utility of whole genome sequencing for genetic disease discovery and for guiding effective clinical treatments, enabling deployment of these methods into routine clinical practice.

The HGSC is now focused on three areas including: technical development of genomics methods in the laboratory and via bioinformatics; clinical translation of genomics to large patient populations; and the discovery of the genetic basis of disease. The latter includes programs for the systematic discovery of the cause of human single gene (mendelian) defects. We also are investigating the role of somatic variation as a driver of non-malignant human disease as part of the NIH Somatic Mutation across Human Tissues (SMAHT) program. Additional efforts are in the role of genetics on the effects of space and other extreme environments and the role of family groups in advancing research and the care of children with rare disease.

**SELECTED PUBLICATIONS**

Krishnavajhala A, Gingras MC, Urquieta E, Chao H, Bandaranaike D, Chen Y, Bhamidipati S, Korchina V, Griffin SM, Masternak MM, Moreno H, Mohammed J, Murugan M, Posey JE, Wu JH, Muzny D, **Gibbs RA**, Doddapaneni H (2025). The GENESTAR manual for biospecimen collection biobanking and omics data generation from commercial space missions. **NPJ Microgravity**. 11: 16.

Murdock DR, Venner E, Muzny DM, Metcalf GA, Murugan M, (...), Wehrens XHT, Ballantyne CM, **Gibbs RA** (2021). Genetic testing in ambulatory cardiology clinics reveals high rate of findings with clinical management implications. **Genet Med**. 23: 2404-2414

Gibbs RA (2020). The Human Genome Project changed everything. **Nat. Rev. Genet**. 21: 575-6.

Jiang Y, Wangler MF, McGuire AL, Lupski JR, Posey JE, Khayat MM, Murdock DR, Sanchez-Pulido L, Ponting CP, Xia F, Hunter JV, Meng Q, Murugan M, **Gibbs RA** (2018). The phenotypic spectrum of Xia-Gibbs syndrome. **Am J Med Genet A**. 176: 1315-1326.

Xia F, Bainbridge MN, Tan TY, Wangler MF, Scheuerle AE, (...), **Gibbs RA** (2014). *De novo* truncating mutations in AHDC1 in individuals with syndromic expressive language delay, hypotonia, and sleep apnea. **Am J Hum Genet**. 94: 784-9.

Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, **Gibbs RA**, Eng CM (2013). Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders. **N Engl J Med**. 369: 1502-11.

Bainbridge MN, Wisniewski W, Murdock DR, Friedman J, Gonzaga-Jauregui C, Newsham I, Reid JG, Fink JK, Morgan MB, Gingras MC, Muzny DM, Hoang LD, Yousaf S, Lupski JR, **Gibbs RA** (2011). Whole-genome sequencing for optimized patient management. **Sci Transl Med**. 3: 87re3.

Lupski JR, Reid JG, Gonzaga-Jauregui C, Rio Deiros D, Chen DC, (...), **Gibbs RA** (2010). Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. **N Engl J Med**. 362: 1181-91.

Wheeler DA, Srinivasan M, Egholm M, Shen Y, Chen L, McGuire A, He W, Chen YJ, Makhijani V, Roth GT, Gomes X, Tartaro K, Niazi F, Turcotte CL, Irzyk GP, Lupski JR, Chinault C, Song XZ, Liu Y, Yuan Y, Nazareth L, Qin X, Muzny DM, Margulies M, Weinstock GM, **Gibbs RA**, Rothberg JM (2008). The complete genome of an individual by massively parallel DNA sequencing. **Nature**. 452: 872-6.

Albert TJ, Molla MN, Muzny DM, Nazareth L, Wheeler D, Song X, Richmond TA, Middle CM, Rodesch MJ, Packard CJ, Weinstock GM, **Gibbs RA** (2007). Direct selection of human genomic loci by microarray hybridization. **Nat Methods**. 4: 903-5.

JASON HEANEY, PH.D.

Associate Professor, Department of Molecular and Human Genetics
Research Member, Dan L Duncan Comprehensive Cancer Center and Center for Reproductive Medicine
Academic Director, Genetically Engineered Rodent Models Core
Faculty Member, Graduate Programs in Genetics & Genomics and Development, Disease Models & Therapeutics

Ph.D., Pennsylvania State University

Postdoc, Case Western Reserve University

RESEARCH INTERESTS

In my laboratory we use mouse genetics, genomics, and genome editing technologies to catalog gene function and contribution to human disease. Ongoing research includes:

Characterizing genes and developmental pathways that contribute to testicular germ cell tumors (TGCTs). Germ cells arise during embryogenesis as pluripotent-like primordial germ cells (PGCs) that differentiate into mature gametes and ultimately the cells and tissues of an adult organism. Defects during male germ cell development can lead to the formation of TGCTs. In 129 mice, TGCTs arise during embryogenesis as foci of pluripotent embryonal carcinoma cells (EC cells), which differentiate to form teratomas. During embryogenesis, male germ cells normally enter mitotic arrest until after birth and female germ cells initiate the meiotic program, both of which are accompanied by down-regulation of pluripotency. We have identified a defect in this developmental switch as the cause of TGCT initiation. In TGCT susceptible gonads, XY germ cells do not enter mitotic arrest, delay expression of male germ cell differentiation genes, and continue to express core pluripotency factors. Ongoing studies are using genome editing in mice, developmental biology approaches, and single-cell RNA sequencing to (1) characterize mechanisms by which male germ cell sex specification is delayed, (2) test the contribution of a shift in pluripotent states to germ cell transformation into EC cells, (3) functionalize TGCT susceptibility loci identify in human genome-wide association studies, and (4) explore environmental contributions to TGCT risk.

Determining the mechanisms by which gene loss-of-function contributes to infertility. The Knockout Mouse Phenotyping Program (KOMP2), as a part of the International Mouse Phenotyping Consortium (IMPC) has established an infrastructure for high-throughput generation of null alleles and broad-based, adult and embryo phenotyping of knockout mouse lines. To date, 6.5% of the mouse lines characterized by the IMPC demonstrate male and/or female infertility with many novel infertility genes being identified. Ongoing studies are focused on these novel infertility genes with the goals of (1) understanding the cellular and molecular mechanisms by which loss-of-function mutations in these genes contribute to infertility and (2) determining whether these genes are potential targets for novel birth control options.

Characterizing gene and variant contribution to Mendelian diseases. Up to 70% of patients with suspected genetic disease remain undiagnosed likely because their disease-causing variant(s) has yet to be discovered or the clinical significance of identified variants remains unclear. Precision model organisms are important tools aiding in the interpretation of these variants and are critical for testing therapeutic paradigms. The **BCM Center for Precision Medicine Models** supports local, national, and international programs and individual researchers in the development of precision fly and mouse that will end the diagnostic odyssey of patients with undiagnosed, rare, and Mendelian diseases and serve as resources for pre-clinical studies investigating personalized medicine approaches to their care. The Center uses a variety of genome editing approaches to build mouse models of human disease with the goals of (1) validating new gene-disease relationships, (2) confirming phenotype expansion for known disease genes, and (3) testing new treatment approaches. The **Baylor/Rice Genome Editing Testing Center** assists researchers with pre-clinical testing of novel genome editing delivery systems and approaches in mouse models. The Center is using novel genome editing reporter mouse models made at Baylor to test the efficacy of new delivery systems and mouse models of human disease to test novel genome editing approaches that may ameliorate or cure disease.



SELECTED PUBLICATIONS

Elrick H, Peterson KA, Wood JA, Lanza DG, Acar EF, Teboul L, (...) International Mouse Phenotyping Consortium, Murray SA, **Heaney JD**, Nutter LM (2024). Impact of Essential Genes on the Success of Genome Editing Experiments Generating 3,313 New Genetically Engineered Mouse Lines. **Sci Rep.** 14: 22626.

Lanza DG, Mao J, Lorenzo I, Liao L, Seavitt JR, Ljungberg MC, Simpson EM, DeMayo FJ, **Heaney JD** (2024). An oocyte-specific Cas9-expressing mouse for germline CRISPR/Cas9-mediated genome editing. **Genesis.** 62: e23589.

Yang L, Leynes C, Pawelka A, Lorenzo I, Chou A, Lee B, **Heaney JD** (2024). Machine learning in time-lapse imaging to differentiate embryos from young vs old mice†. **Biol Reprod.** 110: 1115-1124.

Ahmed AA, Salas E, Lanza DG, **Heaney JD**, Pangas SA (2023). Generation of a novel Stra8-driven Cre recombinase strain for use in pre-meiotic germ cells in mice†. **Biol Reprod.** 109: 184-191.

Peterson KA, Khalouei S, Hanafi N, Wood JA, Lanza DG, (...), **Heaney JD**, Murray SA, Ramani A, Nutter LMJ (2023). Whole genome analysis for 163 gRNAs in Cas9-edited mice reveals minimal off-target activity. **Commun Biol.** 6: 626.

Rana N, Privitera C, Kondolf HC, Bulek K, Lechuga S, (...), **Heaney JD**, Ivanov AI, Pizarro TT (2022). GSDMB is increased in IBD and regulates epithelial restitution/repair independent of pyroptosis. **Cell.** 185: 283-298.e17.

Liang SQ, Walkey CJ, Martinez AE, Su Q, Dickinson ME, Wang D, Lagor WR, **Heaney JD**, Gao G, Xue W (2022). AAV5 delivery of CRISPR-Cas9 supports effective genome editing in mouse lung airway. **Mol Ther.** 30: 238-243.

Webster NJ, Maywald RL, Benton SM, Dawson EP, Murillo OD, LaPlante EL, Milosavljevic A, Lanza DG, **Heaney JD** (2021). Testicular germ cell tumors arise in the absence of sex-specific differentiation. **Development** 148: dev197111.

Lanza DG, Gaspero A, Lorenzo I, Liao L, Zheng P, (...), **Heaney JD** (2018). Comparative analysis of single-stranded DNA donors to generate conditional null mouse alleles. **BMC Biol.** 16: 69.

Dawson EP, Lanza DG, Webster NJ, Benton SM, Suetake I, **Heaney JD** (2018). Delayed male germ cell sex-specification permits transition into embryonal carcinoma cells with features of primed pluripotency. **Development.** 145. pii: dev156612.

Santiago-Sim T, Burrage LC, Ebstein F, Tokita MJ, Miller M, (...), **Heaney JD**, Walkiewicz M (2017). Biallelic loss-of-function variants in OTUD6B cause an intellectual disability syndrome associated with seizures, microcephaly, absent speech, hypotonia, prenatal onset growth retardation, and dysmorphic features. **Am J Hum Genet.** 100: 676-88.

CHRISTOPHE HERMAN, PH.D.

Professor, Departments of Molecular and Human Genetics and Molecular Virology and Microbiology

Faculty Member, Graduate Programs in Genetics & Genomics; Immunology & Microbiology; and Integrative Molecular and Biomedical Sciences

Ph.D., Université libre de Bruxelles

Postdoc, Massachusetts Institute of Technology

Postdoc, University of California, San Francisco

RESEARCH INTERESTS

Transcription errors and Epigenetic Inheritance

Phenotypic inheritance relies on the correct transfer of genetic (DNA) and epigenetic (heritable expression state) information. It is well established that DNA alteration can heritably change the phenotype of a cell, but what is less clear is what triggers heritable epigenetic change. Seminal work in bacteria has highlighted the importance of genetic networks in epigenetic inheritance. To generate stable phenotypic diversity in a population, cells with identical genomes can be differently programmed by transcription factors connected in a positive feedback loop, allowing the stable expression of two alternative phenotypes. Regulatory proteins associated with these molecular switches are often present in low numbers and therefore, subject to fluctuation or "molecular noise." Therefore, the strategy used by a genetic network to control levels of its key regulators is fundamental to the understanding of the potential sources of dysregulation. Molecular noise in gene expression is universal and arises as a result of the stochastic nature of transcription and translation and can directly perturb the behavior of genetic-regulatory-networks generating phenotypic diversity.

My lab is investigating the role of transient errors in information transfer (transcription, translation, or post-translational modification errors) in the dysregulation of bistable genetic networks leading to heritable change in phenotype. To study the contribution of information transfer errors to the generation of heritable phenotypic diversity, we are using classical bistable switches in the bacterium *Escherichia coli*, the bacteriophage lambda genetic switch, and the Lac operon.

With the exception of Prion inheritance, the idea that transient errors in information transfer from RNA to protein can have heritable consequences without any alteration of the DNA sequence has not been considered before. Our work challenges this idea by showing that transient alteration of autocatalytic systems can have profound heritable consequences. Thus, our work suggests that transient errors in information transfer may be an important mechanism of epigenetic change and should be considered as the causative agent for many human diseases ranging from the progression of AIDS to devastating neurodegenerative diseases.



SELECTED PUBLICATIONS

Sivaramakrishnan P, Sepúlveda L, Halliday JA, Núñez MA, Liu J, Golding I, Rosenberg SM, **Herman C** (2017). The transcription fidelity factor GreA impedes DNA break repair. **Nature**. 550: 214-218.

Han B, Sivaramakrishnan P, Lin CJ, Neve IAA, He J, Tay LWR, Sowa JN, Sizovs A, Du G, Wang J, **Herman C**, Wang MC (2017). Microbial Genetic Composition Tunes Host Longevity. **Cell**. 169: 1249-1262.

Satory D, Gordon AJ, Wang M, Halliday JA, Golding I, **Herman C** (2015). DksA involvement in transcription fidelity buffers stochastic epigenetic change. **Nucleic Acids Res**. 43: 10190-9.

Gordon AJ, Satory D, Halliday JA, **Herman C** (2013). Heritable change caused by transient transcription errors. **PLoS Genet**. 9: e1003595.

Satory D, Gordon AJ, Halliday JA, **Herman C** (2011). Epigenetic switches: can infidelity govern fate in microbes? **Curr Opin Microbiol**. 14: 212-7.

Tehranchi AK, Blankschien MD, Zhang Y, Halliday JA, Srivatsan A, Peng J, **Herman C**, Wang JD (2010). The transcription factor DksA prevents conflicts between DNA replication and transcription machinery. **Cell**. 141: 595-605.

Koodathingal P, Jaffe NE, Kraut DA, Prakash S, Fishbain S, **Herman C**, Matouschek A (2009). ATP-dependent proteases differ substantially in their ability to unfold globular proteins. **J Biol Chem**. 284: 18674-84.

Blankschien MD, Lee JH, Grace ED, Lennon CW, Halliday JA, Ross W, Gourse RL, **Herman C** (2009). Super DksAs: substitutions in DksA enhancing its effects on transcription initiation. **EMBO J**. 28: 1720-31.

Gordon AJ, Halliday JA, Blankschien MD, Burns PA, Yatagai F, **Herman C** (2009). Transcriptional infidelity promotes heritable phenotypic change in a bistable gene network. **PLoS Biol**. 7: e44.

Blankschien MD, Potrykus K, Grace E, Choudhary A, Vinella D, Cashel M, **Herman C** (2009). TraR, a homolog of a RNAP secondary channel interactor, modulates transcription. **PLoS Genet**. 5: e1000345.

GREGORY IRA, PH.D.

Professor, Department of Molecular and Human Genetics

Faculty Member, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

Ph.D., Copernicus University

Postdoc, Brandeis University

RESEARCH INTERESTS

DNA recombination is ubiquitous and essential for DNA-based life. Recombination repairs DNA gaps and breaks that occur during replication or are induced in meiosis. Mutation in human genes involved in homologous recombination results in genome instability and diseases including a large fraction of inherited breast and ovarian cancers, Nijmegen breakage syndrome, ataxia telangiectasia, Bloom syndrome, Fanconi Anemia, Rothmund-Thomson syndrome, and others. Eukaryotes show a very high degree of conservation of mechanisms and protein components of recombination. This offers great potential for using model organisms to study DNA recombination processes. We use budding yeast, given the extensive genetic and molecular approaches available.

Our research goal is to understand the molecular mechanisms of homologous recombination and the role different proteins play during recombination. More specifically we are focusing on the function of DNA helicases and newly identified genetic screen proteins in DNA repair. The main experimental model is recombination induced by a single double-strand-break. This assay allows us to follow the kinetics of all steps in recombination at the level of DNA strand exchange and protein-DNA interaction. The results from our projects will constitute the foundation for studying DNA recombination in human cells and will provide insight into the molecular basis of genetic instability observed in cancer.



SELECTED PUBLICATIONS

Yu Y, Pham N, Xia B, Papusha A, Wang G, Yan Z, Peng G, Chen K, **Ira G** (2018). Dna2 nuclease deficiency results in large and complex DNA insertions at chromosomal breaks. **Nature**. 564: 287–290.

Mayle R, Campbell IM, Beck CR, Yu Y, Wilson M, Shaw CA, Bjergbaek L, Lupski JR, **Ira G** (2015). DNA REPAIR. Mus81 and converging forks limit the mutagenicity of replication fork breakage. **Science**. 349: 742-7.

Wilson MA, Kwon Y, Xu Y, Chung WH, Chi P, Niu H, Mayle R, Chen X, Malkova A, Sung P, **Ira G** (2013). Pif1 helicase and Polδ promote recombination-coupled DNA synthesis via bubble migration. **Nature**. 502: 393-6.

Chen X, Cui D, Papusha A, Zhang X, Chu C-D, Tang J, Chen K, Pan X, **Ira G** (2012). The Fun30 nucleosome remodeler promotes resection of DNA double-strand break ends. **Nature**. 489: 576-80.

Chen X, Niu H, Chung WH, Zhu Z, Papusha A, Shim EY, Lee SE, Sung P, **Ira G** (2011). Cell cycle regulation of DNA double-strand break end resection by Cdk1-dependent Dna2 phosphorylation. **Nat Struct Mol Biol**. 18: 1015-9.

Niu H, Chung WH, Zhu Z, Kwon Y, Zhao W, Chi P, Prakash R, Seong C, Liu D, Lu L, **Ira G***, Sung P* (2010). Mechanism of the ATP-dependent DNA end-resection machinery from *Saccharomyces cerevisiae*. **Nature**. 467: 108-11. *Corresponding authors

Prakash R, Satory D, Dray E, Papusha A, Scheller J, Kramer W, Krejci L, Klein H, Haber JE, Sung P, **Ira G** (2009). Yeast Mph1 helicase dissociates Rad51-made D-loops; implications for crossover control in mitotic recombination. **Genes Dev**. 23: 67–79.

Zhu Z, Chung WH, Shim EY, Lee SE, **Ira G** (2008). Sgs1 helicase and two nucleases Dna2 and Exo1 resect DNA double strand break ends. **Cell**. 134: 981-94.

HAMED JAFAR-NEJAD, M.D.

Professor, Department of Molecular and Human Genetics

Faculty Member, Graduate Programs in Genetics & Genomics and Development, Disease Models, & Therapeutics

M.D., Tehran University of Medical Sciences, Iran

Postdoc, University of Ottawa, Canada

Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

The long-term goals of our research are (1) to understand the roles of glycosylation and deglycosylation in the regulation of developmental signaling pathways, animal development, and human disease pathophysiology, and (2) to identify and characterize dosage-sensitive genetic modifiers of select human rare diseases in animal models, followed by establishing the most promising candidates as potential therapeutic targets for those diseases. A long-term area of interest has been the role of O-linked glycosylation in animal development and human disease. Our efforts in this area have led to the identification of the glycosyltransferase *POGLUT1*, which adds O-glucose glycans to epidermal growth factor-like (EGF) repeats of the receptors and ligands of the Notch signaling pathway, and characterization of this enzyme and its downstream glycosyltransferases in Notch signaling. More recently, we and our collaborators have identified a new form of limb-girdle muscular dystrophy caused by recessive mutations in *POGLUT1* and have elucidated the roles that this enzyme plays in the generation and maintenance of muscle stem cells.

A major focus of our group over the last decade has been the development of the biliary system in the context of Alagille syndrome (ALGS), a multisystem disorder characterized by bile duct paucity and primarily caused by mutations in the Notch pathway ligand *JAG1*. Alarming, only 24-40% of patients with ALGS with early cholestasis reach their 18th birthday without a liver transplant. Coexisting cardiovascular and renal anomalies often preclude liver transplantation in ALGS, and even among transplant recipients, complications are common. Currently, no FDA-approved therapies exist to promote biliary development in ALGS or other diseases with bile duct paucity. To address this unmet need, we have developed mouse models that span the spectrum of ALGS liver disease severity. Through genetic studies, we identified two dosage-sensitive suppressors of the liver phenotypes in these models: the glycosyltransferase *Poglut1* and the transcription factor *Sox4*. We have reported that postnatal knockdown of these genes—via antisense oligonucleotides for *Poglut1* and adeno-associated virus for *Sox4*—dramatically improves liver phenotypes in ALGS models. Ongoing work includes mechanistic and preclinical studies aimed at advancing these candidates toward clinical trials, as well as exploring their relevance to other cholestatic diseases.

We are also investigating the role of N-linked glycosylation and deglycosylation in animal development, with a focus on intestinal development, innate immunity, and metabolism. Using *Drosophila* as a model, we found that loss of the deglycosylating enzyme NGLY1 disrupts gut barrier integrity, triggers innate immune activation, and induces severe lipid catabolism. Our data suggest that altered gut microbiome contributes to the developmental delay in *Ngly1*-mutant *Drosophila* larvae. Current efforts focus on determining the molecular basis and the physiological consequences of altered gut microbiome in *Ngly1*-deficient *Drosophila* and in mutants for select N-glycosylation pathway components. We are also examining the consequences of loss of these genes in the intestine on other organs, including the fat body (equivalent to mammalian liver and immune system) and the nervous system. These studies aim to uncover shared and distinct roles of glycosylation-related genes in shaping the gut microbiome and modulating the host's response to it, as well as inter-organ communication. Ultimately, this work may provide novel insight into the pathophysiology of congenital disorders of glycosylation and deglycosylation.



SELECTED PUBLICATIONS

Fox D, Xie J, Burwinkel JL, Adams JM, Chetal K, Keivandarian M, Faingelert Y, Subramanian S, Lopez MF, Peters AL, Salomonis N, Zarrin-Khameh N, Gao G, Huppert SS, **Jafar-Nejad H** (2025). Adeno-associated Virus-mediated Silencing of *Sox4* Leads to Long-Term Amelioration of Liver Phenotypes in Mouse Models of Alagille Syndrome. **Gastroenterology**. 169: 1000-1016.

Cho S, Servián-Morilla E, Navarro V, Rodriguez-Gonzalez B, Yuan Y, Cano R, Rambhiya AA, Darabi R, Haltiwanger RS, Paradas C, **Jafar-Nejad H** (2025). The glycosyltransferase *POGLUT1* regulates muscle stem cell development and maintenance in mice. **PLoS Genet**. 21: e1011806.

Pandey A, Galeone A, Han SY, Story BA, Consonni G, Mueller WF, Steinmetz LM, Vaccari T, **Jafar-Nejad H** (2023). Gut barrier defects, intestinal immune hyperactivation, and enhanced lipid catabolism drive lethality in NGLY1-deficient *Drosophila*. **Nat Commun**. 14: 5667.

Niknejad N, Fox D, Burwinkel JL, Zarrin-Khameh N, Cho S, Soriano A, Cast AE, Lopez MF, Huppert KA, Rigo F, Huppert SS, **Jafar-Nejad P, Jafar-Nejad H** (2023). ASO silencing of a glycosyltransferase, *Poglut1*, improves the liver phenotypes in mouse models of Alagille syndrome. **Hepatology**. 78: 1337-1351.

Han SY, Pandey A, Moore T, Galeone A, Duraine L, Cowan TM, **Jafar-Nejad H** (2020). A conserved role for AMP-activated protein kinase in NGLY1 deficiency. **PLoS Genet**. 16: e1009258.

Galeone A, Adams JM, Matsuda S, Presa MF, Pandey A, Han SY, Tachida Y, Hirayama H, Vaccari T, Suzuki T, Lutz CM, Affolter M, Zuberi A, **Jafar-Nejad H** (2020). Regulation of BMP4/Dpp retrotranslocation and signaling by deglycosylation. **ELife**. 9: e55596.

Adams JM, Huppert KA, Castro EC, Lopez MF, Niknejad N, Subramanian S, Zarrin-Khameh N, Finegold MJ, Huppert SS, **Jafar-Nejad H** (2020). *Sox9* is a modifier of the liver disease severity in a mouse model of Alagille syndrome. **Hepatology**. 71: 1331-1349.

Servián-Morilla E, Cabrera-Serrano M, Johnson K, (...), **Jafar-Nejad H**, Straub V, Paradas C (2020). *POGLUT1* biallelic mutations cause myopathy with reduced satellite cells, α -dystroglycan hypoglycosylation and a distinctive radiological pattern. **Acta Neuropathol**. 139: 565-582.

Galeone A, Han SY, Huang C, Hosomi A, Suzuki T, **Jafar-Nejad H** (2017). Tissue-specific regulation of BMP signaling by *Drosophila* N-glycanase 1. **ELife**. 6: e27612.

Thakurdas SM, Lopez MF, Kakuda S, Fernandez-Valdivia R, Zarrin-Khameh N, Haltiwanger RS, **Jafar-Nejad H** (2016). *Jagged1* heterozygosity in mice results in a congenital cholangiopathy which is reversed by concomitant deletion of one copy of *Poglut1* (*Rumi*). **Hepatology**. 63: 550-65.

BENNY ABRAHAM KAIPARETTU, PH.D.

Associate Professor, Department of Molecular and Human Genetics

Ph.D., JIPMER, Pondicherry, India

Postdoc, Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Germany & Lester and Sue Smith Breast Center at Baylor College of Medicine

RESEARCH INTERESTS

Abnormal metabolism is an emerging hallmark of cancer progression and metastasis. Metabolic plasticity that occurs by rewiring cellular metabolic status allows cancer cells to dissociate from the primary tumor, overcome the nutrient and energy limitations in the microenvironment, and eventually survive to form metastasis in hostile environments. Although aerobic glycolysis (Warburg effect) is generally regarded as a dominant metabolic program in cancer, recent evidence suggests that mitochondrial oxidative phosphorylation (OXPHOS) significantly contributes to cancer progression and metastasis. Nevertheless, it is still unclear how these metabolic modes are regulated in cancer and the particular advantages each of these modes confers to metastasizing tumors. My lab seeks to understand the mechanism of mitochondrial energy reprogramming and mitochondria-nuclear crosstalk in cancer progression and metastasis of aggressive tumors. Most lab projects have a translational focus to evaluate our findings' therapeutic potential using preclinical studies.

Hybrid metabolic status of aggressive cancer cells: To address the interplay between glycolysis and OXPHOS in metastatic cancer, we use mathematical modeling and experimental validation to simulate the metabolic regulatory network dynamics and couple gene regulation with metabolic pathways. We have recently shown that metastatic cancer cells can acquire a hybrid (glycolysis & OXPHOS) metabolic phenotype in which both glycolysis and OXPHOS can be utilized for energy production and biomass synthesis. This hybrid state enables cancer cells to achieve metabolic plasticity for robust survival under hostile environments.

Mitochondria-nuclear crosstalk in cancer: Mitochondrial signaling can regulate several oncopathways. To understand the genetic and metabolic factors involved in the crosstalk between mitochondria and nucleus, my lab uses transmitochondrial cybrid (cybrid) models as a discovery tool. In cybrid models, we compare mitochondria from different cells under a commonly defined nuclear background. Thus, cybrids are an excellent tool to decipher the inter-organellar communication between mitochondria and the nucleus systematically. We utilize cybrid models coupled with multiple-OMICs approaches to identify genes and pathways regulated by mitochondria-nuclear communication. Discoveries from cybrids are then validated using cell lines, mouse models, patient-derived xenografts (PDXs) and clinical data.

Metabolic reprogramming and drug resistance: Compared to other breast cancer subtypes, triple-negative breast cancer (TNBC) is associated with a worse overall outcome owing to the lack of targeted therapies. We have published the pioneering report on the clinical significance of mitochondrial energy reprogramming to fatty acid β -oxidation (FAO) in metastatic TNBC as a prerequisite to attain aggressive metastatic potential. We have shown that FAO is critical for the Src family kinases (SFKs) in TNBC. We are now evaluating how FAO-SFK crosstalk sustains a feed-forward loop that permits TNBC metastasis. Additionally, we also focus on the mechanisms of drug resistance to SFK inhibitors in TNBC.

Bioimaging and Multimodal Nanomaterials: In collaboration with material scientists, we have developed several nano-based compounds for bioimaging. We are currently focusing on materials that can be altered by cellular metabolic or biochemical modulations



SELECTED PUBLICATIONS

Jia D, Lu M, Jung KH, Park JH, Yu L, Onuchic JN*, **Kaiparettu BA***, Levine H* (2019). Elucidating cancer metabolic plasticity by coupling gene regulation with metabolic pathways. *Proc Natl Acad Sci U S A*. 116: 3909-3918. *corresponding authors

Mukhopadhyay UK, Oturkar CC, Adams C, Wickramasekera N, Bansal S, (...), Bshara W, **Kaiparettu BA**, Das GM (2019). TP53 Status as a Determinant of Pro- vs Anti-Tumorigenic Effects of Estrogen Receptor-Beta in Breast Cancer. *J Natl Cancer Inst*. 111: 1202-1215.

Jia D, Park JH, Jung KH, Levine H, **Kaiparettu BA*** (2018). Elucidating the Metabolic Plasticity of Cancer: Mitochondrial Reprogramming and Hybrid Metabolic States. *Cells*. 7: 21. *corresponding author

Yu L, Lu M*, Jia D, Ma J, Ben-Jacob E, Levine H, **Kaiparettu BA***, Onuchic JN* (2017). Modeling the Genetic Regulation of Cancer Metabolism: Interplay between Glycolysis and Oxidative Phosphorylation. *Cancer Res*. 77: 1564-1574. *corresponding authors

Park JH, Vithayathil S, Kumar S, Sung PL, Dobrolecki LE, (...), Creighton CJ, Wong LC*, **Kaiparettu BA*** (2016). Fatty Acid Oxidation-Driven Src Links Mitochondrial Energy Reprogramming and Oncogenic Properties in Triple-Negative Breast Cancer. *Cell Rep*. 14: 2154-2165. *corresponding authors

Davis CF, Ricketts CJ, Wang M, Yang L, Cherniack AD, (...), **Kaiparettu BA**, (...), The Cancer Genome Atlas Research Network, Creighton CJ (2014). The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell*. 26: 319-330.

Gupta BK*, Singh S, Kumar P, Lee Y, Kedawat G, (...), **Kaiparettu BA*** (2016). Bifunctional Luminomagnetic Rare-Earth Nanorods for High-Contrast Bioimaging Nanoprobes. *Sci Rep*. 6: 32401. *corresponding author

Narayanan TN, Gupta BK, Vithayathil SA, Aburto RR, Mani SA, Taha-Tijerina J, Xie B, **Kaiparettu BA**, Torti SV, Ajayan PM (2012). Hybrid 2D nanomaterials as dual-mode contrast agents in cellular imaging. *Adv Mater*. 24: 2992-8.

Vithayathil SA, Ma Y, **Kaiparettu BA*** (2012). Transmitochondrial cybrids: tools for functional studies of mutant mitochondria. *Methods Mol Biol*. 837: 219-30. *corresponding author

Abraham BK, et. al. (2005). Prevalence of CD44+/CD24-/low cells in breast cancer may not be associated with clinical outcome but may favor distant metastasis. *Clin Cancer Res*. 11: 1154-9.

SEEMA R. LALANI, M.D.

Professor, Department of Molecular and Human Genetics

M.D., Aga Khan University

Resident, Pediatrics, Hershey Medical Center

Fellow, Medical Genetics, Baylor College of Medicine

Fellow, Clinical Cytogenetics, Baylor College of Medicine

Fellow, Clinical Molecular Genetics, Baylor College of Medicine

RESEARCH INTERESTS

My work has focused on understanding the molecular basis of neurodevelopmental disorders in the pediatric population. We have used diagnostic tools such as exome and genome sequencing in understanding the genetic basis of birth defects. I have been involved with the Undiagnosed Diseases Network (UDN) study at Baylor College of Medicine for several years and helped characterize diagnoses in multiple undiagnosed children with rare diseases. In 2016, we described the first cohort of patients with TANGO2 deficiency disorder (TDD) and are leading the international natural history study. In 2022, we started Project GIVE, an NIH study to reduce genomic health disparities in the Hispanic children living in the Rio Grande Valley and El Paso in Texas. We are using an academic web-based virtual platform called Consultagene to combine virtual health delivery with genome sequencing in this pediatric population living along the Texas-Mexico border. In 2024, we were funded by the NHGRI to provide rapid genome sequencing to critically ill newborns in Texas, using Consultagene to improve access to genomic care.



SELECTED PUBLICATIONS

Miyake CY, Lay EJ, Soler-Alfonso C, Ginton KE, Houck KM, Tosur M, Moran NE, Stephens SB, Scaglia F, Howard TS, Kim JJ, Pham TD, Valdes SO, Li N, Murali CN, Zhang L, Kava M, Yim D, Beach C, Webster G, Liberman L, Janson CM, Kannankeril PJ, Baxter S, Singer-Berk M, Wood J, Mackenzie SJ, Sacher M, Ghaloul-Gonzalez L, Pedroza C, Morris SA, Ehsan SA, Azamian MS, **Lalani SR** (2023). Natural history of TANGO2 deficiency disorder: Baseline assessment of 73 patients. **Genet Med.** 25: 100352.

Vuocolo B, Sierra R, Brooks D, Holder C, Urbanski L, Rodriguez K, Gamez JD, Mulukutla SN, Hernandez A, Allegre A, Hidalgo H, Rodriguez S, Magallan S, Gibson J, Bernini JC, Watson M, Nelson R, Mellin-Sanchez L, Garcia N, Berry L, Dai H, Soler-Alfonso C, Carter K, Lee B, **Lalani SR** (2024). Project GIVE: using a virtual genetics service platform to reduce health inequities and improve access to genomic care in an underserved region of Texas. **J Neurodev Disord.** 16: 52.

Lalani SR (2020). Other genomic disorders and congenital heart disease. **Am J Med Genet C Semin Med Genet.** 184: 107-115.

Lalani SR, Graham B, Burrage L, Lai YC, Scaglia F, Soler-Alfonso C, Miyake CY, Yang Y (2018). TANGO2-Related Metabolic Encephalopathy and Arrhythmias. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. **GeneReviews® [Internet]**. Seattle (WA): University of Washington, Seattle; 1993–2020.

Meng L, Pammi M, Saronwala A, Magoulas P, (...), Shaw C, Walkiewicz M, Bi W, Xia F, Lee B, Eng CM, Yang Y, **Lalani SR** (2017). Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. **JAMA Pediatr.** 171: e173438.

Lalani SR, Liu P, Rosenfeld JA, Watkin LB, (...), Yang Y (2016). Recurrent Muscle Weakness with Rhabdomyolysis, Metabolic Crises, and Cardiac Arrhythmia Due to Bi-allelic TANGO2 Mutations. **Am J Hum Genet.** 98: 347-57.

Lalani SR, Zhang J, Schaaf CP, Brown CW, Magoulas P, Tsai AC, (...), Xia F (2014). Mutations in PURA cause profound neonatal hypotonia, seizures, and encephalopathy in 5q31.3 microdeletion syndrome. **Am J Hum Genet.** 95: 579-83.

Szafranski P, Von Allmen GK, Graham BH, Wilfong AA, (...), **Lalani SR** (2015). 6q22.1 microdeletion and susceptibility to pediatric epilepsy. **Eur J Hum Genet.** 23: 173-9.

Wiszniewski W, Hunter JV, Hanchard NA, Willer JR, Shaw C, Tian Q, Illner A, Wang X, (...), **Lalani SR** (2013). TM4SF20 Ancestral Deletion and Susceptibility to a Pediatric Disorder of Early Language Delay and Cerebral White Matter Hyperintensities. **Am J Hum Genet.** 93: 197-210.

BRENDAN LEE, M.D., PH.D.

Robert and Janice McNair Endowed Chair in Molecular and Human Genetics

Professor and Chair, Department of Molecular and Human Genetics
Faculty Member, Graduate Programs in Genetics & Genomics; Development, Disease Models & Therapeutics

Director, Center for Skeletal Medicine and Biology

Associate Director, Medical Research Pathway, School of Medicine, Baylor College of Medicine

Director, Texas Children's Hospital Skeletal Dysplasia Clinic

Director, The Lawrence Family Bone Disease Program of Texas

Ph.D., State University of New York Downstate Medical Center

M.D., State University of New York Downstate Medical Center

Research Fellow, Mount Sinai School of Medicine

Resident, Pediatrics, Baylor College of Medicine

Clinical Fellow, Medical Genetics, Baylor College of Medicine

Clinical Fellow, Clinical Biochemical Genetics, Baylor College of Medicine

RESEARCH INTERESTS

Developmental, translational and clinical studies of skeletal dysplasias and inborn errors of metabolism

As a pediatrician and geneticist, the overall mission of my research program is to translate the study of structural birth defects and inborn errors of metabolism into a basic understanding of development, disease and novel therapeutic approaches. In the area of metabolism, we have applied genetic approaches to the study of biochemical genetic disorders (specifically urea cycle disorders) as models of complex diseases (those involving nitric oxide dysregulation). This has led us to study the consequences of metabolic derangements broadly in the endocrine, cardiovascular, skeletal, renal and neurological systems. In the area of structural birth defects, we have studied paracrine and endocrine signaling pathways that regulate skeletal development including morphogens (TGF β , Wnt and Notch), and extracellular matrix proteins and their modifications (e.g., collagen prolyl-hydroxylation and lysyl-hydroxylation) that contribute to human skeletal dysplasias including brittle bone diseases and connective tissue diseases like Ehlers-Danlos syndrome. These developmental pathways have led us to ask how their dysregulation contributes to common diseases such as osteoporosis, osteoarthritis and bone cancer.

Our mechanistic discoveries are translated via clinical research that is performed as part of the Skeletal Dysplasia Clinic and the Metabolic Disorders Clinic at Texas Children's Hospital, respectively, and as part of the NIH Rare Diseases Clinical Research Network (RDCRN) Brittle Bone Disorders Consortium. My clinical research program began with stable isotopic measurements in urea cycle disorder patients to better assess new treatments. I have led investigator-initiated studies testing combined phenylbutyrate/arginine treatment and nitric oxide supplementation in patients with argininosuccinic aciduria and phenylbutyrate in maple syrup urine disease and industry-sponsored Phase II and III studies of the now FDA-approved ammonia scavenger glyceryl-triphenylbutyrate in urea cycle patients. In the area of skeletal dysplasias, I have studied the utility of zoledronic acid, teriparatide and anti-TGF β treatments in pediatric and adult osteogenesis imperfecta. Our preclinical gene therapy studies have led to a clinical trial of high-capacity adenoviral gene therapy in osteoarthritis. As an extension of these studies, I lead the RE-JOIN consortium of the NIH HEAL initiative mapping the neuronal pain mediators into the osteoarthritis joint. As part of my genomic medicine studies, I have focused on advancing the diagnosis of genetic diseases via gene discovery, multi-omic approaches to phenotyping and mechanistic studies in the NIH Undiagnosed Diseases Network. Finally, I am committed to developing a scientific workforce as part of the *All of Us* Evenings with Genetics Scholars Program.

**SELECTED PUBLICATIONS**

Ketkar S Dai H Burrage L Murdock D Dawson B, (...), **Lee B** (2025). Integrative exome sequencing and machine learning identify MICB and interferon pathway genes as contributors to SSC risk. *Ann Rheum Dis*. 84: 1363-1374.

Chen YT Jiang MM Leynes C Adeyeye M Majano CF, (...), **Lee B** (2025). ATRX silences Cartpt expression in osteoblastic cells during skeletal development. *J Clin Invest*. 135: e163587.

Marom R, Song IW, Busse EC, Washington ME, Berrier AS, (...), **Lee BH** (2024). The IFITM5 mutation in osteogenesis imperfecta type V is associated with an ERK/SOX9-dependent osteoprogenitor differentiation defect. *J Clin Invest*. 134: e170369.

Song IW, Nagamani SC, Nguyen D, Grafe I, Sutton VR, (...), **Lee B** (2022). Targeting TGF- β for treatment of osteogenesis imperfecta. *J Clin Invest*. 132: e152571.

Jin Z, Kho J, Dawson B, Jiang MM, Chen Y, (...), **Lee B** (2021). Nitric oxide modulates bone anabolism through regulation of osteoblast glycolysis and differentiation. *J Clin Invest*. 131 (5): e138935.

Murdock DR, Dai H, Burrage LC, Rosenfeld JA, Ketkar S, (...), **Lee B** (2021). Transcriptome-directed analysis for Mendelian disease diagnosis overcomes limitations of conventional genomic testing. *J Clin Invest*. 131 (1): e141500.

Joeng KS, Lee YC, Lim J, Chen Y, Jiang MM, Munivez E, Ambrose C, **Lee BH** (2017). Osteocyte-specific *WNT1* regulates osteoblast function during bone homeostasis. *J Clin Invest*. 127: 2678-2688.

Grafe I, Yang T, Alexander S, Homan EP, Lietman C, Jiang MM, (...), **Lee B** (2014). Excessive transforming growth factor- β signaling is a common mechanism in osteogenesis imperfecta. *Nat Med*. 20: 670-5.

Laine CM, Joeng KS, Campeau PM, Kiviranta R, (...), Cohn DH, Gibbs RA, **Lee B**, Mäkitie O (2013). *WNT1* mutations in early-onset osteoporosis and osteogenesis imperfecta. *N Engl J Med*. 368: 1809-16.

Erez A, Nagamani SC, Shchelochkov OA, Premkumar MH, (...), Aschner JL, Bryan NS, **Lee B** (2011). Requirement of argininosuccinate lyase for systemic nitric oxide production. *Nat Med*. 17: 1619-26.

Engin F, Yao Z, Yang T, Zhou G, Bertin T, Jiang MM, Chen Y, Wang L, Zheng H, Sutton R, Boyce BF, **Lee B** (2008). Dimorphic effects of Notch signaling in bone homeostasis. *Nat Med*. 14: 299-305.

Morello R, Bertin TK, Chen Y, Hicks J, (...), Eyre DR, Yao Z, Boyce BF, **Lee B** (2006). CRTAP is required for 3-prolyl-hydroxylation and loss of its function causes recessive Osteogenesis Imperfecta. *Cell*. 127: 291-304.

RICHARD A. LEWIS, M.D., M.S.

Professor, Departments of Molecular and Human Genetics, Ophthalmology, Pediatrics, and Medicine

Member, National School of Tropical Medicine and the Steering Committee of the Undiagnosed Disease Network at Baylor College of Medicine

M.D., University of Michigan Medical School

M.S., University of Michigan

Residency in Ophthalmology, University of Michigan Hospitals, Ann Arbor, Michigan

Fellowship, Montefiore Hospital, Einstein School of Medicine, Bronx, New York

Fellowship, Bascom Palmer Eye Institute, University of Miami, Miami, Florida

RESEARCH INTERESTS

Dr. Lewis, an ophthalmologist historically affiliated with the Cullen Eye Institute, joined the Department of Molecular and Human Genetics to provide in-depth consultations and research in genetic eye disorders and ocular manifestations of systemic hereditary disorders for Texas Children's Hospital and the adult genetics services at the Baylor-affiliated hospitals. His clinical practice includes genetic eye disease and their constitutional associations. With numerous members of the Department, he and his colleagues pioneered the mapping and isolation of many X-linked ocular disorders, including X-linked Retinitis Pigmentosa, Chorioideremia, the Oculo-Cerebro-Renal Syndrome of Lowe, Blue Cone Monochromacy, X-linked Nettleship-Falls Ocular Albinism, and the Nance-Horan X-linked Cataract-Dental Syndrome.

Dr. Lewis and Dr. David Nelson collaborated and isolated the gene for Incontinentia Pigmenti (IP2) at Xq28, an X-dominant disorder with multisystem complications in the eye, skin, brain, and teeth, and embryonic lethality in males. Studies with Dr. Ignatia Van den Veyver and Dr. Reid Sutton continue the search for the genetic construct for Aicardi Syndrome, another distinctive phenotype in females only with extreme retinal and optic nerve malformations and profound brain and developmental consequences.

For many years, he has collaborated with Dr. Lupski on studies of Mendelian ocular disorders, including Stargardt Disease/Fundus Flavimaculatus (the most common genetic juvenile macular degeneration), the Laurence-Moon-Bardet-Biedl Syndromes (LMBBS: progressive retinal dystrophy with obesity, polydactylia, developmental disability, and various renal anomalies), the Usher Syndromes (retinitis pigmentosa and neurosensory deafness), and Leber Congenital Amaurosis (genetically heterogeneous disorders that share profound visual impairment from birth and other systemic features from neurosensory hearing impairment to progressive renal failure). The first human examples of digenic triallelic inheritance in man were defined from their extensive studies of his LMBBS cohort. The role of the Stargardt Disease gene in Age-Related Macular Degeneration and autosomal recessive forms of retinitis pigmentosa were explored here first as well.

Ongoing collaborations with Dr. Lupski and Dr. Jennifer Posey include the discovery of the gene for the "Hutterite-type" juvenile-onset cataract and the recognition that this gene may also cause subsequent sudden death of these individuals in their third and fourth decades of life; the study of an unusual autosomal dominant form of progressive retinal dystrophy uniquely associated with mitral valve prolapse and other cardiac malformations; the genetic evaluation of a multigenerational Texas family with autosomal dominant optic atrophy preceding nearly uncontrollable grand mal seizures, first identified by Dr. Arthur Beaudet; the search for the underlying genetic mechanism(s) of the Hallermann-Streiff Syndrome, a rare ectodermal dysplasia with a distinctive face, beaked nose, natal teeth, thin hair, congenital and often spontaneously resorbing cataracts, and proportionate short stature; and the investigations of the spectrum of Septo-Optic Dysplasia, optic nerve hypoplasia, and cerebral visual impairment, the Goldenhar Syndromes, and molecular investigations of yet-defined forms of ectodermal dysplasia.

Dr. Lewis also serves on the Steering Committee of Baylor's Undiagnosed Disease Network. He has been a member of the Steering Committee of the National Eye Institute's National Ophthalmic Disease Genotyping Network (eyeGENE) Program since its inception in 2003 and its chair since 2009. He was the principal investigator for Baylor of the Studies of the Ocular Complications of AIDS (SOCA) for its entire 25-year history, the longest single NIH-funded research protocol in the history of the Department of Ophthalmology, and its sole Principal Investigator for the Age-Related Eye Disease Study 2 (AREDS2), that demonstrated that neither lutein nor fish oil (nor both) reduces the risk of progression of macular degeneration in older Americans and that supplemental micronutrients do not protect against cognitive decline.



SELECTED PUBLICATIONS

Akula SK, Marciano JH, Lim Y, Exposito-Alonso D, Hylton NK, (...), **Lewis RA**, Segal RA, Bazan JF, Smith KA, Golden JA, Cho G, Walsh CA (2023). TMEM161B regulates cerebral cortical gyration, Sonic Hedgehog signaling, and ciliary structure in the developing central nervous system. *Proc Natl Acad Sci U S A*. 120: e2209964120.

Chong SC, Cao Y, Fung ELW, Kleppe S, Gripp KW, Herte-cant J, El-Hattab AW, Suleiman J, Clark G, von Allmen G, Rodziyevska O, **Lewis RA**, Rosenfeld JA, Dong J; Undiagnosed Diseases Network; Wang X, Miller MJ, Bi W, Liu P, Scaglia F (2023). Expansion of the clinical and molecular spectrum of WWOX-related epileptic encephalopathy. *Am J Med Genet A*. 191: 776-785.

Mao K, Borel C, Ansar M, Jolly A, Makrythanasis P, (...), **Lewis RA**, (...), Zhang Q, Zhang YB, Antonarakis SE (2023). *FOXP3* pathogenic variants cause one form of craniofacial microsomia. *Nat Commun*. 14: 2026.

Keehan L, Haviland I, Gofin Y, Swanson LC, El Achkar CM, Schreiber J, (...), **Lewis RA**, (...), Olson HE, Burrage LC; Undiagnosed Diseases Network (2022). Wide range of phenotypic severity in individuals with late truncations unique to the predominant *CDKL5* transcript in the brain. *Am J Med Genet A*. 188: 3516-3524.

Keehan LA, Jiang M-M, Marom R, (...), **Lewis RA**, (...), Craigden WJ, Rosenfeld JA, Lee B, Burrage LC (2021). A novel *de novo* intronic variant in *ITPR1* causes Gillespie Syndrome. *Am J Med Genet Part A*. 185: 2315-2324.

Lewis RA, Nussbaum RL, Brewer ED. Lowe Syndrome. 2001 Jul 24 [updated 2019 Apr 18]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.

Poli MC, Ebstein F, Nicholas SK, de Guzman MM, Forbes LR, (...), **Lewis RA**, Lee B; Undiagnosed Diseases Network members, (...), Orange JS (2018). Heterozygous Truncating Variants in *POMP* Escape Nonsense-Mediated Decay and Cause a Unique Immune Dysregulatory Syndrome. *Am J Hum Genet*. 102: 1126-1142.

Chambers TM, Agopian AJ, **Lewis RA**, Langlois PH, Danysh HE, Weber KA, Shaw GM, Mitchell LE, Lupo PJ (2018). Epidemiology of anophthalmia and microphthalmia: Prevalence and patterns in Texas, 1999-2009. *Am J Med Genet A*. 176: 1810-1818.

Boone PM, Yuan B, Gu S, Ma Z, (...), **Lewis RA** (2015). Hutterite-type Cataract Maps to Chromosome 6p21.32-p21.31, Cosegregates with a Homozygous Mutation in *LEMD2*, and is Associated with Sudden Cardiac Death. *Mol Genet Genomic Med*. 4: 77-94.

HONGJIE LI, PH.D.

Assistant Professor, Department of Molecular and Human Genetics and
Huffington Center for Aging
CPRIT Scholar in Cancer Research

Ph.D., University of Rochester, Rochester, New York
Postdoctoral fellow, Stanford University

RESEARCH INTERESTS

Technology development of multi-omics: We have developed the first single-cell RNA sequencing platform in *Drosophila* neurons and glia for studying neural development (*Cell* 2017; *Curr Biol.* 2020). Recently, we developed a single-nucleus RNA-seq method in flies (*eLife* 2021) and applied it to the Fly Cell Atlas (*Science* 2022) and Aging Fly Cell Atlas (*Science* 2023), a large collaborative project aiming to get the transcriptomic map of the entire fly. We will continue developing and applying multi-omics technologies (transcriptomics, epigenomics and proteomics) and combine them with powerful fly genetic tools to study development, aging and diseases.

Anti-brain aging to increase healthy lifespan: Our long-term goal is to identify molecular and cellular mechanisms that contribute to brain aging, including glia-neuron interactions, systemic inflammatory signals and gut-brain interactions. We will apply single-cell sequencing and cell surface proteomics (Li J, Han S, Li H, et al. *Cell* 2020) to study glia-neuron interactions and inter-organ communications to understand brain aging. We will employ single-bacterium genomics to explore gut microbiota changes during aging and study how they contribute to brain aging.

Limiting age-triggered tumor initiation and growth: Age is the biggest risk factor for many types of cancers, including breast, prostate, lung and colorectal cancers (*Dis Model Mech.* 2016). A central goal of this project is to discover how aging triggers tumor onset in the regenerating intestine. We will use fly intestine as a discovery model to generate hypotheses that we will then test in mouse cancer models and human colon cancers, aiming to develop effective strategies for limiting age-related tumor initiation and growth.



SELECTED PUBLICATIONS

Park YJ, Lu TC, Jackson T, Goodman LD, Ran L, Chen J, Liang CY, Harrison E, Ko C, Chen X, Wang B, Hsu AL, Ochoa E, Bieniek KF, Yamamoto S, Zhu Y, Zheng H, Qi Y, Bellen HJ, **Li H** (2025). Distinct systemic impacts of A β 42 and Tau revealed by whole-organism snRNA-seq. **Neuron**. 113: 2065-2082.e8.

Gao SM, Qi Y, Zhang Q, Guan Y, Lee YT, Ding L, Wang L, Mohammed AS, **Li H**, Fu Y, Wang MC (2024). Aging atlas reveals cell-type-specific effects of pro-longevity strategies. **Nat Aging**. 4(7): 998-1013.

Lu TC, Brbić M, Park YJ, Jackson T, Chen J, Kolluru SS, Qi Y, Katheder NS, Cai XT, Lee S, Chen YC, Auld N, Liang CY, Ding SH, Welsch D, D'Souza S, Pisco AO, Jones RC, Leskovec J, Lai EC, Bellen HJ, Luo L, Jasper H, Quake SR, **Li H** (2023). Aging Fly Cell Atlas Identifies Exhaustive Aging Features at Cellular Resolution. **Science**. 380: eadg0934.

Li H, et al. Among authors: Li T, Li JSS, Li J, Li K, Li L (2022). Fly Cell Atlas: a single-nucleus transcriptomic atlas of the adult fruit fly. **Science** 375: eabk2432.

McLaughlin CN, Brbić M, Xie Q, Li T, Horns F, Kolluru SS, Keschull JM, Vacek D, Xie A, Li J, Jones RC, Leskovec J, Quake SR, Luo L, **Li H** (2021). Single-cell transcriptomes of developing and adult olfactory receptor neurons in *Drosophila*. **eLife**. 10: e63856

Xie Q, Brbic M, Horns F, Kolluru SS, Jones RJ, Li J, Reddy A, Xie A, Kohani S, Li Z, McLaughlin CN, Li T, Xu C, Vacek D, Luginbuhl DJ, Leskovec J, Quake SR, Luo L, **Li H** (2021). Temporal evolution of single-cell transcriptomes of *Drosophila* olfactory projection neurons. **eLife**. 10: e63450

Li H (2020). Single-cell RNA sequencing in *Drosophila*: Technologies and applications. **Wiley Interdiscip Rev Dev Biol**. 16: e396.

Li H, Li T, Horns F, Li J, Xie Q, Xu C, Wu B, Keschull JM, McLaughlin CN, Kolluru SS, Jones RC, Vacek D, Xie A, Luginbuhl DJ, Quake SR, Luo L (2020). Single-Cell Transcriptomes Reveal Diverse Regulatory Strategies for Olfactory Receptor Expression and Axon Targeting. **Curr Biol**. 30: 1189-1198.e5.

Li H, Shuster SA, Li J, Luo L (2018). Linking neuronal lineage and wiring specificity. **Neural Dev**. 13: 5.

Li H, Horns F, Wu B, Xie Q, Li J, Li T, Luginbuhl DJ, Quake SR, Luo L (2017). Classifying *Drosophila* Olfactory Projection Neuron Subtypes by Single-Cell RNA Sequencing. **Cell**. 171: 1206-1220.e22.

OLIVIER LICHTARGE, M.D., PH.D.**The Cullen Foundation Endowed Chair**

Professor, Departments of Molecular and Human Genetics, Biochemistry & Molecular Biology, and Pharmacology

Faculty Member, Graduate Programs in Genetics & Genomics; Quantitative and Computational Biosciences; Developmental Biology; and Integrative Molecular and Biomedical Sciences

Director, Computational and Integrative Biomedical Research Center (CIBR)

Ph.D., Stanford University

M.D., Stanford University

Residency, Internal Medicine, University of California, San Francisco

Fellowship, Endocrinology, University of California, San Francisco

Postdoc, University of California, San Francisco

RESEARCH INTERESTS

Our lab marries computation with experiments to understand the molecular evolution of genes and pathways—how their functions may become corrupted by genetic mistakes or how they may be re-engineered to new designs. Technically, we draw upon a wide range of disciplines to address fundamental questions in structural biology, clinical genomics and precision medicine. Over the long-term, we hope to discover new therapeutic paths and improve screening and early detection to preserve health and also to harness the synthetic potential of organisms for biotechnology. In the short-term we seek to interpret the mutational action of human genome variations and pinpoint the genes that drive complex diseases.

Starting from structural bioinformatics, our algorithms broadly merge mathematical and evolutionary principles. They enable multi-scale data integration and, in favorable conditions, precise control of molecular functions. This has led to discoveries across diverse systems, including G protein signaling, malaria, cancer, and neurological disorders. Newer interests include network theory, text-mining and cognitive computing. Specific examples include a network compression scheme that made tractable the diffusion of information across nearly 400 species. This approach uncovered a possible mechanism for the best drug against malaria. Other network studies, reasoned over the entire PubMed literature to discover new kinases and protein interactions for p53.

A recent promising line of research quantifies the evolutionary action (EA) of mutations on fitness to make a bridge between molecular biology and population genetics. EA correlates with experimental loss of function in proteins; with morbidity and mortality in people; and with purifying gene selection in populations. In head and neck cancer patients, EA stratifies outcomes and suggests alternate therapy for some patients. In autism, the mutational EA burden correlated with the depth of cognitive harm (IQ). In the future, we hope to unite these different approaches into a coherent path to compute precision therapy and personalized risk based on each patient's unique profile of genome variations.

**SELECTED PUBLICATIONS**

Bourquard T, Lee K, Al-Ramahi I, Pham M, Shapiro D, (...), **Lichtarge O** (2023). Functional variants identify sex-specific genes and pathways in Alzheimer's Disease. **Nat Commun.** 14: 2765.

Lagisetty Y, Bourquard T, Al-Ramahi I, Mangleburg CG, Mota S, (...), **Lichtarge O** (2022). Identification of risk genes for Alzheimer's disease by gene embedding. **Cell Genom.** 2: 100162.

Marciano DC, Wang C, Hsu TK, Bourquard T, Atri B, Nehring RB, Abel NS, Bowling EA, Chen TJ, Lurie PD, Katsonis P, Rosenberg SM, Herman C, **Lichtarge O** (2022). Evolutionary action of mutations reveals antimicrobial resistance genes in *Escherichia coli*. **Nat Commun.** 13: 3189.

Hsu TK, Asmussen J, Koire A, Choi BK, Gadhiar MA, Huh E, Lin CH, Konecki DM, Kim YW, Pickering CR, Kimmel M, Donehower LA, Frederick MJ, Myers JN, Katsonis P, **Lichtarge O** (2022). A general calculus of fitness landscapes finds genes under selection in cancers. **Genome Res.** 32: 916-929.

Koire A, Katsonis P, Kim YW, Buchovecky C, Wilson SJ, **Lichtarge O** (2021). A method to delineate *de novo* missense variants across pathways prioritizes genes linked to autism. **Sci Transl Med.** 13: eabc1739.

Kim YW, Al-Ramahi I, Koire A, Wilson SJ, Konecki DM, Mota S, Soleimani S, Botas J, **Lichtarge O** (2021). Harnessing the paradoxical phenotypes of APOE ε2 and APOE ε4 to identify genetic modifiers in Alzheimer's disease. **Alzheimers Dement.** 17: 831-846.

Choi BK, Dayaram T, Parikh N, Wilkins A, Nagarajan M, (...), **Lichtarge O** (2021). Literature-Based Automated Discovery of Tumor Suppressor p53 Phosphorylation and Inhibition by NEK2. **PNAS** 115: 10666-10671.

Cancer Genome Atlas Research Network (2017). Comprehensive and Integrative Genomics Characterization of Hepatocellular Carcinoma. **Cell.** 169: 1327-41.

Spangler S, Wilkins AD, Bachman BJ, Nagarajan M, Dayaram T, Haas P, (...), **Lichtarge O** (2014). Automated hypothesis generation based on mining scientific literature. **Proceedings of the 20th ACM SIGKDD international conference on Knowledge discovery and data mining** (New York, NY)

Katsonis P, **Lichtarge O** (2014). A formal perturbation equation between genotype and phenotype determines the Evolutionary Action of protein-coding variations on fitness. **Genome Res.** 24: 2050-8.

Lisewski AM, Quiros JP, Ng CL, Adikesavan AK, Miura K, Putluri N, (...), **Lichtarge O** (2014). Supergenomic network compression and the discovery of EXP1 as a glutathione transferase inhibited by artesunate. **Cell.** 158: 916-28.

PENGFEI LIU, PH.D., FACMGG

Associate Professor, Department of Molecular and Human Genetics
Director, Medical Genetics and Multiomics Laboratory (MGML)
Director, ACGME/ABMGG Laboratory Genetics and Genomics Fellowship Program
Associate Director of Clinical Research, Baylor Genetics

Ph.D., Baylor College of Medicine

RESEARCH INTERESTS

Dr. Liu is a board-certified Ph.D. clinical geneticist with a primary research interest in translating new technologies into clinical testing to advance the diagnostics and therapy of rare diseases. His clinical work has provided key evidence to recognize the necessity and importance of clinical reanalysis of diagnostic exome data. Dr. Liu has led the launch of clinical whole genome sequencing at Baylor Genetics as well as the clinical RNA-seq for the Undiagnosed Diseases Network (UDN). He has received multiple honors and awards, including the Michael Watson's Genome Medicine Innovation Award from the American College of Medical Genetics, the Genomic Innovator Award from the National Human Genome Research Institute, and the Cotterman Award from the American Society of Human Genetics.



SELECTED PUBLICATIONS

Li S, Zhao S, Sinson JC, (...), **Liu P** (2024). The clinical utility and diagnostic implementation of human subject cell transdifferentiation followed by RNA sequencing. **Am J Hum Genet.** 111: 841-862.

Zhao S, Macakova K, Sinson J, (...), **Liu P** (2024). Clinical validation of RNA sequencing for Mendelian disorder diagnostics. **medRxiv.** doi.org/10.1101/2024.08.15.24312057

Mao D, Liu C, Wang L, (...), **Liu P**, Liu Z (2024). AI-MARVEL - A Knowledge-Driven AI System for Diagnosing Mendelian Disorders. **NEJM AI.** 1: 10.1056/aioa2300009.

Du H, Jolly A, Grochowski CM, (...), **Liu P** (2022). The multiple *de novo* copy number variant (MdnCNV) phenomenon presents with peri-zygotic DNA mutational signatures and multilocus pathogenic variation. **Genome Med.** 14: 122.

Yuan B, Schulze K, (...), **Liu P** (2022). Sequencing individual genomes with recurrent deletions reveals allelic architecture and disease loci for autosomal recessive traits. **Genome Med.** 14: 113.

Liu P, Meng L, Normand EA, (...), Lupski JR, Yang Y (2019). Reanalysis of Clinical Exome Sequencing Data. **N Engl J Med.** 380: 2478.

Yuan B, Neira J, Pehlivan D, (...), Xiao R, **Liu P** (2019). Clinical exome sequencing reveals locus heterogeneity and phenotypic variability of cohesinopathies. **Genet Med.** 21: 663-675.

Vetrini F, McKee S, Rosenfeld JA, (...), Lupski JR, **Liu P** (2019). *De novo* and inherited TCF20 pathogenic variants are associated with intellectual disability, dysmorphic features, hypotonia, and neurological impairments with similarities to Smith-Magenis syndrome. **Genome Med.** 11: 12.

Liu P, Yuan B, Carvalho CM, (...), Hurles ME, Lupski JR (2017). An Organismal CNV Mutator Phenotype Restricted to Early Human Development. **Cell.** 168: 830.

Liu P, Erez A, Nagamani SC, (...), Lupski JR, Bi W (2011). Chromosome catastrophes involve replication mechanisms generating complex genomic rearrangements. **Cell.** 146: 889.

JAMES R. LUPSKI, M.D., PH.D., D.S.C. (HON)**The Cullen Foundation Endowed Chair in Molecular and Human Genetics**

Professor, Departments of Molecular and Human Genetics and Pediatrics
Faculty Member, Graduate Programs in Genetics & Genomics; Integrative Molecular and Biomedical Sciences; and Translational Biology & Molecular Medicine

Ph.D., New York University

M.D., New York University School of Medicine

Postdoc, New York University

Resident, Pediatrics, Baylor College of Medicine

Fellow, Medical Genetics, Baylor College of Medicine

Sabbatical, Wellcome Trust Sanger Institute

D.Sc., Watson School of Biological Sciences, Cold Spring Harbor Laboratory (CSHL)

RESEARCH INTERESTS

To what extent are *de novo* DNA rearrangements in the human genome responsible for sporadic human disease traits? How many human Mendelian and complex traits, as well as sporadic genomic disorders, developmental disabilities and birth defects, are due to structural changes and/or gene copy number variants (CNV)? To what extent is secondary structure mutagenesis, rather than W-C base pair changes, underlying variant alleles and human disease traits? What are the molecular mechanisms for human genomic rearrangements and structural variant (SV) mutagenesis? The answers to these questions will impact both prenatal and postnatal molecular diagnostics, as well as patient and family management and therapeutics. Moreover, the answers have profound implications for organismal developmental biology, biological homeostasis, and human gene and human genome evolution.

My lab focuses on four major related areas of human genetics and genomics research: i) Mechanisms of Structural Variant (SV/CNV) mutagenesis, ii) the use of rare variant, family-based genomics to glean insights into gene variant alleles contributing to disease traits, iii) understanding disease biology as perturbations from homeostasis caused by mutation, and iv) molecular pathways to disease and therapeutics.

In 2011, the Clan Genomics Hypothesis was posited, and the complex allelic architecture of human disease was summarized formally. The implication of Clan Genomics was that recent mutation may have a greater influence on susceptibility to, or protection from, disease than is conferred by variations that arose in distant ancestors. This was conceptually illustrated by a 'heat map' in the color shades of the rainbow with the 'hotter colors' (red/orange) overlying the siblings in a nuclear family, yellow the parents, and the 'cooler colors', e.g., green, showing more distant ancestors in the clan. The rare variants (copy number variant, CNV; single nucleotide variant, SNV; indels) with large effects have arisen recently in the family/clan/population history. Therefore, new mutations in you and your recent ancestors, and novel combinations aggregated in your personal genome from your parents, account for many medically actionable variant loci.

Clan Genomics provided a framework for a rare variant parsing of genome-wide variant allele data from the assayable portion of individual personal genomes and examining for Mendelian expectations. The hypotheses being tested, rare variant alleles and Mendelian expectations, explores pathogenic variation that might contribute to disease trait manifestations in the family. During the last 10 years, the Clan Genomics hypothesis has been tested worldwide in hundreds of thousands of personal genomes – to date, no data have emerged that warrant rejection of the hypothesis.

**SELECTED PUBLICATIONS**

Lupski JR (2022). Biology in balance: human diploid genome integrity, gene dosage, and genomic medicine. **Trends Genet.** 38: 554-571.

Duan R, Hijazi H, Gulec EY, (...), **Lupski JR** (2022). Developmental genomics of limb malformations: Allelic series in association with gene dosage effects contribute to the clinical variability. **HGG Adv.** 3: 100132.

Lupski JR (2021). Clan genomics: From OMIM phenotypic traits to genes and biology. **Am J Med Genet A.** 185: 3294-3313.

Gonzaga-Jauregui C, Yesil G, Nistala H, (...) **Lupski JR** (2020). Functional biology of Steel syndrome founder allele and evidence for clan genomics derivation of *COL27A1* pathogenic alleles worldwide. **European J Hum Genet.** 28: 1243-1264.

Beck CR, Carvalho CMB, Coban Akdemir Z, (...) **Lupski JR** (2019). Megabase length hypermutation accompanies human structural variation at 17p11.2. **Cell** 176: 1310-1324.

Bahrambeigi V, Song X, Sperle K, (...) **Lupski JR** (2019). Distinct patterns of complex rearrangements and a mutational signature of microhomeology are frequently observed in *PLP1* copy number gain structural variants. **Genome Med.** 11:80.

Song X, Beck CR, Du R, (...) **Lupski JR** (2018). Predicting human genes susceptible to genomic instability associated with *Alu/Alu*-mediated rearrangements. **Genome Res.** 28:1228-1242.

Posey JE, Harel T, Liu P, (...) **Lupski JR** (2017). Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation. **N Engl J Med** 376:21-31.

Gonzaga-Jauregui C, Harel T, (...) **Lupski JR** (2015). Exome sequence analysis suggests genetic burden contributes to phenotypic variability and complex neuropathy. **Cell Rep.** 12: 1169-1183.

Liu P, Erez A, Nagamani SC, (...), **Lupski JR**, Bi W (2011). Chromosome catastrophes can involve replication mechanisms generating complex genomic rearrangements. **Cell.** 146: 889-903.

Lupski JR, Reid JG, Gonzaga-Jauregui C, Rio Deiros D, Chen DC, Nazareth L, (...), Muzny DM, Gibbs RA (2010). Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. **N Engl J Med.** 362: 1181-91.

Lee JA, Carvalho CMB, **Lupski JR** (2007). A DNA replication mechanism for generating non-recurrent rearrangements associated with genomic disorders. **Cell.** 131: 1235-47.

GRAEME MARDON, PH.D.**James R. Davis Chair in Pathology**

Professor, Departments of Molecular and Human Genetics, Neuroscience, Ophthalmology and Pathology & Immunology

Faculty Member, Graduate Programs in Genetics & Genomics; Development, Disease Models & Therapeutics

Ph.D., Massachusetts Institute of Technology

Postdoc, University of California, Berkeley

RESEARCH INTERESTS

The primary goal of our research is to understand the molecular mechanisms of retinal development with the ultimate goal of improving our ability to prevent, diagnose, and treat human retinal disease. To this end, we are using the fruit fly *Drosophila melanogaster* as a model system to identify and determine the function of conserved genes required for normal retinal development. In spite of substantial differences between vertebrate and insect retinal morphology, genetic mechanisms of retinal development have been conserved for more than 500 million years. Thus, study of the molecular and genetic pathways controlling *Drosophila* eye development has provided a valuable set of tools with which to decipher the development and function of the vertebrate retina.

Our current research is focused on the highly conserved family of Onecut transcription factors. *oncut* genes are required for normal eye development in mammals but their mechanism of action is not understood. The *Drosophila* Onecut DNA binding domains are 90% identical to their human counterparts and we are using the fly as a model to decipher the mechanisms of *oncut* function. To this end, we have generated extensive genetic tools as well as single cell RNA-sequencing (scRNA-seq) data on multiple stages of the developing and adult *Drosophila* eye, single cell chromatin accessibility data (ATAC-seq) on larval eyes, scRNA-seq for *oncut* mutant eye discs, and chromatin immunoprecipitation sequencing (ChIP-seq) for Onecut. These data have revealed many new insights into *Drosophila* eye development with unprecedented resolution and form the basis for many studies of *oncut* function.

**SELECTED PUBLICATIONS**

Raja K, Yeung K, Shim YK, Li Y, Chen R, **Mardon G** (2023). A single cell genomics atlas of the *Drosophila* larval eye reveals distinct photoreceptor developmental timelines. **Nat Commun.** 14: 7205.

Raja KKB, Yeung K, Li Y, Chen R, **Mardon G** (2024). A single cell RNA sequence atlas of the early *Drosophila* larval eye (2024). **BMC Genomics.** 25: 616.

Bollepogu Raja KK, Yeung K, Shim YK, **Mardon G** (2024). Integrative Genomic Analyses Reveal Putative Cell Type-specific Targets of the *Drosophila* Ets Transcription Factor Pointed. **BMC Genomics** 25: 103.

Yeung K, Raja K, Shim Y-K, Li Y, Chen R, **Mardon G** (2022). Single Cell RNA Sequencing of the Adult *Drosophila* Eye Reveals Distinct Clusters and Novel Marker Genes for All Major Cell Types. **Commun Biol.** 5: 1370.

Yeung K, Wang F, Li Y, Wang K, **Mardon G**, Chen R (2018). Integrative genomic analysis reveals novel regulatory mechanisms of eyeless during *Drosophila* eye development. **Nucleic Acids Res.** 46: 11743-11758.

Jin M, **Mardon G** (2016). Distinct Biochemical Activities of Eyes absent During *Drosophila* Eye Development. **Sci Rep.** 6: 23228.

Jin M, Eblimit A, Pulikkathara M, Corr S, Chen R, **Mardon G** (2016). Conditional knockout of retinal determination genes in differentiating cells in *Drosophila*. **FEBS J.** 283: 2754-66.

Jin M, Aibar S, Ge Z, Chen R, Aerts S, **Mardon G** (2016). Identification of novel direct targets of *Drosophila* *Sine oculis* and *Eyes absent* by integration of genome-wide data sets. **Dev Biol.** 415: 157-67.

RONIT MAROM, M.D., PH.D.

Assistant Professor, Department of Molecular and Human Genetics
Caroline Wiess Law Scholar

M.D./Ph.D., Tel Aviv University, Tel Aviv, Israel

Pediatric Residency, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Medical Genetics Residency, Baylor College of Medicine

Medical Biochemical Genetics Fellowship, Baylor College of Medicine

Postdoctoral Research Fellowship, Baylor College of Medicine

RESEARCH INTERESTS

Our research is focused on elucidating the role of ER-Golgi trafficking in skeletal development and understanding the mechanisms of secretory pathway defects in inherited bone fragility. Secretory pathway defects are a group of childhood-onset, multisystem disorders that are growing in number and present with diverse phenotypes, including intellectual and developmental disabilities (IDD), immunodeficiency and skeletal abnormalities. They are caused by pathogenic variants in genes encoding subunits of coat protein complexes (coatomers), Golgi proteins, motor proteins and accessory molecules that are collectively involved in the sorting and transport of proteins, nucleic acids and lipids between subcellular organelles. Whereas many organ systems can be affected, the skeletal system seems particularly vulnerable as normal skeletal development is dependent on the appropriate transport and processing of abundant extracellular matrix proteins through the secretory pathway. Using mouse models, we apply skeletal phenotyping, cell biology and molecular biology approaches to study the physiological, cellular and molecular changes that are induced by secretory pathway defects in bone. We are currently pursuing two projects in the lab:

1. Elucidating the mechanism of *COPB2* haploinsufficiency in juvenile osteoporosis. We have identified heterozygous, loss-of-function variants in *COPB2*, encoding a subunit of the coatomer complex I (COPI), in individuals presenting with a clinical spectrum of osteopenia, recurrent fractures and IDD. We have shown that *Copb2*^{+/-} mice recapitulated the low bone mass phenotype observed in this disorder and that secretion of procollagen is abnormal in *COPB2*-deficient cells and zebrafish embryos. The goals of this study are (1) to understand at which stage in skeletal development *COPB2* may be critical, and what are the cellular and physiological alterations induced by *COPB2* haploinsufficiency during bone development; and (2) to determine if protein glycosylation, endoplasmic reticulum (ER) stress and autophagy pathways are altered in *COPB2*-deficient cells, and whether these pathways can be targeted for future therapy in patients with *COPB2*-related disorder.

2. Understanding the mechanism of *KIF5B*-related osteogenesis imperfecta (OI). Kinesin motor proteins facilitate the transport of intracellular cargo, including mRNA, proteins and organelles. Pathogenic variants in kinesin-related genes have been implicated in neurodevelopmental disorders and skeletal dysplasias. We have identified dominant-negative variants in *KIF5B* as a novel cause of OI. The *KIF5B* variants were modeled in cells and in *C. elegans* and our data support an intracellular trafficking defect and down regulation of the mTOR signaling pathway. Interestingly, the mTOR pathway plays a critical role in skeletal homeostasis, and reduced mTOR signaling has been previously implicated in mouse models of OI. We are currently generating a knock-in mouse model that will allow to study *in vivo* the consequences of tissue and stage-specific expression of the mutant *Kif5b*.

The long-term goals of our research are to identify new genetic causes of skeletal dysplasia and to advance the knowledge on the role of protein secretion and the bone glycome (glycans and glycosylated molecules secreted to the extracellular matrix) during health and disease. The mechanistic insights obtained from this study will facilitate the development of diagnostic and treatment strategies for disorders of intracellular trafficking.



SELECTED PUBLICATIONS

Marom R, Song IW, Busse EC, Washington ME, Berrier AS, Rossi VC, Ortinau L, Jeong Y, Jiang MM, Dawson BC, Adeyeye M, Leynes C, Lietman CD, Stroup BM, Batkovskyte D, Jain M, Chen Y, Cela R, Castellon A, Tran AA, Lorenzo I, Meyers DN, Huang S, Turner A, Shenava V, Wallace M, Orwoll E, Park D, Ambrose CG, Nagamani SC, Heaney JD, Lee BH (2024). The IFITM5 mutation in osteogenesis imperfecta type V is associated with an ERK/SOX9-dependent osteoprogenitor differentiation defect. *J Clin Invest.* 134: e170369.

Marom R, Zhang B, Washington ME, Song IW, Burrage LC, Rossi VC, Berrier AS, Nonet M, Chen J, Baldrige D, Silverman G, Sutton VR, Rosenfeld JA, Tran AA, Hicks MJ, Murdock D, Dai H, Weis M, Caswell R, Stals K, Undiagnosed Diseases Network, Eyre D, Krakow D, Pak S, Schedl T, Lee BH (2023). Dominant negative variants in *KIF5B* cause osteogenesis imperfecta via down regulation of mTOR signaling. *PLOS Genet.* 19: e1011005.

Marcogliese PC, Deal SL, Andrews J, Harnish JM, Bhavana VH, (...), **Marom R**, Wangler MF, Yamamoto S (2022). *Drosophila* functional screening of *de novo* variants in autism uncovers damaging variants and facilitates discovery of rare neurodevelopmental diseases. *Cell Rep.* 38: 110517.

Marom R, Burrage LC, Venditti R, Clément A, Blanco-Sánchez B, Jain M, Scott DA, Rosenfeld JA, Sutton VR, Shinawi M, Mirzaa G, DeVile C, Roberts R, Calder AD, Allgrove J, Grafe I, Lanza DG, Li X, Joeng KS, Lee YC, Song IW, Sliepka JM, Batkovskyte D, Washington M, Dawson BC, Jin Z, Jiang MM, Chen S, Chen Y, Tran AA, Emrick LT, Murdock DR, Hanchard NA, Zapata GE, Mehta NR, Weis MA, Scott AA, Tremp BA, Phillips JB, Wegner J, Taylor-Miller T, Gibbs RA, Muzny DM, Jhangiani SN, Hicks J, Stottmann RW, Dickinson ME, Seavitt JR, Heaney JD, Eyre DR, Westerfield M, De Matteis MA, Lee B (2021). *COPB2* loss of function causes a coatopathy with osteoporosis and developmental delay. *Am J Hum Genet.* 108: 1710-1724.

Marom R, Jain M, Burrage LC, Song IW, Graham BH, Brown CW, Stevens SJC, Stegmann APA, Gunter AT, Kaplan JD, Gavrilova RH, Shinawi M, Rosenfeld JA, Bae Y, Tran AA, Chen Y, Lu JT, Gibbs RA, Eng C, Yang Y, Rousseau J, de Vries BBA, Campeau PM, Lee B (2017). Heterozygous variants in *ACTL6A*, encoding a component of the BAF complex, are associated with intellectual disability. *Hum Mutat.* 38: 1365-1371.

Lietman CD*, **Marom R***, Munivez E, Bertin TK, Jiang MM, Chen Y, Dawson B, Weis MA, Eyre D, Lee B (2015). A transgenic mouse model of OI type V supports a neomorphic mechanism of the IFITM5 mutation. *J Bone Miner Res.* 30: 489-98. *Equally contributing first author.

ALEKSANDAR MILOSAVLJEVIC, PH.D.

Professor, Department of Molecular and Human Genetics

Director, Graduate Program in Quantitative and Computational Biosciences

Faculty Member, Graduate Program in Genetics & Genomics

Co-Director, Computational and Integrative Biomedical Research Center (CIBR)

Ph.D., University of California, Santa Cruz

RESEARCH INTERESTS

The **Bioinformatics Research Laboratory (BRL)**, directed by Dr. Milosavljevic, develops new data intensive methods and advanced computational approaches to advance understanding of biological systems and improve human health. The laboratory is engaged in collaborative projects with over a dozen current collaborators in the areas of genomics, epigenomics, extracellular RNA (exRNA) communication, and tumor biology. The laboratory serves as the data coordination and analysis center for consortia, including NIH Common Fund projects that are modeled after the Human Genome project and aim to transform biomedical research by creating maps and atlases of previously unexplored yet promising domains of biology.

As part of the **NIH Roadmap Epigenomics Initiative**, the laboratory constructed the Human Epigenome Atlas that maps cell-type specific epigenetic programs and identifies markers of cellular identity. This information is currently being applied to better understand the biology of human tumors, specifically the diversity of cell types within tumors and their interactions during cancer progression.

As part of the **NIH Extracellular RNA Communication Consortium**, the laboratory is half-way through a 10-year project to construct the exRNA Atlas that catalogs extracellular RNAs found in human body fluids that are involved in physiological or pathological intercellular communication of endocrine and paracrine type. One specific area of interest is paracrine signaling between epithelial, stromal and immune cells within tumors that are mediated by microRNAs and that may serve as "liquid biopsy" markers to guide cancer therapy.

The laboratory is involved in analysis of genome variation in human health and disease. As part of the **Clinical Genome Resource project**, the laboratory has developed the ClinGen Pathogenicity Calculator, Evidence Repository, Linked Data Hub, Allele Registry and other core components of the emerging ecosystem of data and computable knowledge to aid the interpretation of human genome variation in clinical contexts.

One particular challenge in interpreting genetic variation from whole genome sequencing is the understanding of the impact of genetic variation in regulatory loci. To address this question, we mapped the "epigenomic footprints" of genetic variation by constructing an extremely high-resolution map of sequence-dependent allelic imbalances in DNA methylation and other epigenomic marks. Surprisingly, the regulatory loci showed stochastic switching, which is defined as random transitions between fully methylated and unmethylated states of DNA between cells and even between the two chromosomes within the same cell. The methylation imbalances at thousands of loci are explainable by different relative frequencies of the methylated and unmethylated states for the two alleles at heterozygous loci. Further analyses provided a unifying model that links sequence-dependent allelic imbalances of the epigenome, stochastic switching at gene regulatory loci, and disease-associated genetic variation.



SELECTED PUBLICATIONS

Onuchic V, Lurie E, Carrero I, Pawliczek P, Patel RY, Rozowsky J, Galeev T, Huang Z, Altshuler RC, Zhang Z, Harris RA, Coarfa C, Ashmore L, Bertol JW, Fakhouri WD, Yu F, Kellis M, Gerstein M, **Milosavljevic A** (2018). Allele-specific epigenome maps reveal sequence-dependent stochastic switching at regulatory loci. **Science**. 361: eaar3146. doi: 10.1126/science.aar3146.

Pawliczek P, Patel RY, Ashmore LR, Jackson AR, Bizon C, Nelson T, Powell B, Freimuth RR, Strande N, Shah N, Paithankar S, Wright MW, Dwight S, Zhen J, Landrum M, McGarvey P, Babb L, Plon SE, **Milosavljevic A** (2018). Clinical Genome (ClinGen) Resource. ClinGen Allele Registry links information about genetic variants. **Hum Mutat**. 39: 1690-1701.

Patel RY, Shah N, Jackson AR, Ghosh R, Pawliczek P, Paithankar S, Baker A, Riehle K, Chen H, Milosavljevic S, Bizon C, Rynearson S, Nelson T, Jarvik GP, Rehm HL, Harrison SM, Azzariti D, Powell B, Babb L, Plon SE, **Milosavljevic A** (2017). ClinGen Resource. ClinGen Pathogenicity Calculator: a configurable system for assessing pathogenicity of genetic variants. **Genome Med**. 9: 3.

Onuchic V, Hartmaier RJ, Boone DN, Samuels ML, Patel RY, White WM, Garovic VD, Oesterreich S, Roth ME, Lee AV, **Milosavljevic A** (2016). Epigenomic Deconvolution of Breast Tumors Reveals Metabolic Coupling between Constituent Cell Types. **Cell Rep**. 17: 2075-2086.

Amin V, Harris RA, Onuchic V, Jackson AR, Charnecki T, Paithankar S, Lakshmi Subramanian S, Riehle K, Coarfa C, **Milosavljevic A** (2015). Epigenomic footprints across 111 reference epigenomes reveal tissue-specific epigenetic regulation of lincRNAs. **Nat Commun**. 6: 6370.

Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, (...), **Milosavljevic A**, Ren B, Stamatoyanopoulos JA, Wang T, Kellis M (2015). Integrative analysis of 111 reference human epigenomes. **Nature**. 518: 317-30.

Li J, Harris RA, Cheung SW, Coarfa C, Jeong M, Goodell MA, White LD, Patel A, Kang SH, Shaw C, Chinault AC, Gambin T, Gambin A, Lupski JR, **Milosavljevic A** (2012). Genomic hypomethylation in the human germline associates with selective structural mutability in the human genome. **PLoS Genet**. 8: e1002692.

Miller CA, Settle SH, Sulman EP, Aldape KD, **Milosavljevic A** (2011). Discovering functional modules by identifying recurrent and mutually exclusive mutational patterns in tumors. **BMC Med Genomics**. 4: 34.

SANDESH C. S. NAGAMANI, M.B.B.S., M.D.

Professor and Vice Chair for Research Affairs - Clinical, Department of Molecular and Human Genetics

Director, Baylor Intellectual and Developmental Disabilities Research Center (IDDRC)

M.B.B.S., University of Mysore

M.D., Gandhi Medical College

Internship, Internal Medicine, Fairview Hospital

Residency, Clinical Genetics, Baylor College of Medicine

Residency, Internal Medicine, Baylor College of Medicine

Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

I am an internist and a clinical geneticist who is focused on improving clinical care in individuals with genetic disorders. The focus of my research program is clinical investigation including conducting natural history studies, proof-of-concept pilot studies, and interventional clinical trials in individuals with inborn errors of metabolism and skeletal dysplasias.

Inborn Errors of Metabolism: I served as Multiple Principal Investigator (MPI) for the NIH Rare Diseases Clinical Research Network's Urea Cycle Disorders Consortium (UCDC) and contact PI for the Pilot/Feasibility core and the career enhancement core of the consortium. The UCDC has implemented 19 studies that have collectively enrolled a more than 1600 participants, trained nearly 30 early career investigators, and facilitated the development of novel biomarkers, clinical endpoints, and therapies for urea cycle disorders.

Skeletal dysplasia: As a lead investigator of the NIH Rare Diseases Clinical Research Network's Brittle Bone Disorders Consortium, I am involved in conducting natural history studies and interventional clinical trials in individuals with osteogenesis imperfecta, the most common osteodysplasia in humans. I have developed clinical endpoints and biomarkers to assess disease burden from the perspective of clinical trial readiness and had lead roles in clinical trials evaluating novel therapies for OI including the first disease-specific therapy with anti-transforming growth factor beta antibody.

Clinical Interests: As an internist and clinical geneticist, I provide care to adults with a wide variety of heritable conditions including osteogenesis imperfecta, genetic skeletal disorders, intellectual and developmental disabilities, Mendelian forms of cancer, and heritable connective tissue disorders.

Intellectual and Developmental Disabilities Research Center: I serve as MPI and Director for the NICHD-funded Intellectual and Developmental Disabilities Research Center at BCM. Our center supports translational research activities of more than 80 investigators engaged in advancing research and clinical care for individuals with intellectual and developmental disabilities.

Educational Activities: On the educational front, I have been heavily involved in patient-outreach activities and education of early career investigators. I have assisted in developing resources for education of families and physicians across our country about specific rare disorders. I have worked with the TeleECHO program to implement and deliver virtual training materials to patients and providers. The latter project has used guided-practice model to reduce health disparities in underserved and remote areas through innovative tele-mentoring.

**SELECTED PUBLICATIONS**

Song IW, **Nagamani SC**, Nguyen D, Grafe I, Sutton VR, (...), Lee B (2022). Targeting TGF- β for treatment of osteogenesis imperfecta. **J Clin Invest.** 132: e152571.

Nagamani SCS, Ali S, Izem R, Schady D, Masand P, Shneider BL, Leung DH, Burrage LC (2021). Biomarkers for liver disease in urea cycle disorders. **Mol Genet Metab.** 133: 148-156.

Murali CN, Cuthbertson D, Slater B, Nguyen D, Turner A, (...), Members of the BBDC, **Nagamani SCS** (2020). Pediatric Outcomes Data Collection Instrument is a Useful Patient-Reported Outcome Measure for Physical Function in Children with Osteogenesis Imperfecta. **Genet Med.** 22: 581-589.

Lee JS, Adler L, Karathia H, Carmel N, Rabinovich S, (...), **Nagamani SCS**, Unda M, Wilson DM 3rd, Elhasid R, Caracado A, Samuels Y, Hannenhalli S, Ruppin E, Erez A (2018). Urea Cycle Dysregulation Generates Clinically Relevant Genomic and Biochemical Signatures. **Cell.** 174: 1559-1570.e22.

Kho J, Tian X, Wong WT, Bertin T, Jiang MM, Chen S, (...), **Nagamani SCS**, Lee BH (2018). Argininosuccinate Lyase Deficiency Causes an Endothelial-Dependent Form of Hypertension. **Am J Hum Genet.** 103: 276-287.

Nagamani SCS, Agarwal U, Tam A, Azamian M, McMeans A, Didelija IC, Mohammad MA, Marini JC (2018). A randomized trial to study the comparative efficacy of phenylbutyrate and benzoate on nitrogen excretion and ureagenesis in healthy volunteers. **Genet Med.** 20: 708-716.

Jain M, Tam A, Shapiro JR, Steiner RD, Smith PA, (...), Members of the Brittle Bone Disorders Consortium*, **Nagamani SCS** (2019). Growth characteristics in individuals with osteogenesis imperfecta in North America: results from a multicenter study. **Genet Med.** 21: 275-283.

Marini JC, Agarwal U, Didelija IC, Azamian M, Stoll B, **Nagamani SC** (2017). Plasma Glutamine Is a Minor Precursor for the Synthesis of Citrulline: A Multispecies Study. **J Nutr.** 147: 549-555.

Orwoll ES, Shapiro J, Veith S, Wang Y, Lapidus J, (...), **Nagamani SC**, Lee B (2014). Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. **J Clin Invest.** 124: 491-8.

Nagamani SC, Campeau PM, Shchelochkov OA, Premkumar MH, Guse K, et al. (2012). Nitric-oxide supplementation for treatment of long-term complications in argininosuccinic aciduria. **Am J Hum Genet.** 90: 836-46.

DAISUKE NAKADA, PH.D.

Professor, Department of Molecular and Human Genetics

Faculty Member, Graduate Programs in Cancer & Cell Biology; Development, Disease Models & Therapeutics; Developmental Biology; Translational Biology and Molecular Medicine; and Integrative Molecular & Biomedical Sciences

CPRIT Scholar in Cancer Research

Leukemia and Lymphoma Society Scholar

Ph.D., Nagoya University, Japan

Postdoc, University of Michigan

RESEARCH INTERESTS

Hematopoietic stem cells (HSCs) are immature progenitor cells that are responsible for replenishing blood cells that are lost during homeostasis and become activated upon inflammation or injury to promote regeneration. HSCs are multipotent and have the full developmental potential to differentiate into all blood cells types and persist throughout life through a cell division mechanism called self-renewal. Differentiation and self-renewal often go awry in blood cancer, or leukemia, to enable unlimited proliferation of malignant blood cells.

The focus of our lab is to study the molecular and cellular mechanisms that regulate self-renewal and differentiation in HSCs and leukemia. We use mouse genetics, genome-editing tools and epigenome profiling to understand how physiological changes and stress conditions stimulate HSCs. We recently developed a lineage-tracing mouse model to trace the fate of HSCs and to study their behavior *in vivo*. This model is being used to investigate how HSCs respond to hematopoietic insults and the mechanisms by which they regenerate the blood system after stress. We also study how mechanisms that regulate HSCs go awry to cause leukemia. Our recent study indicates that leukemia cells rely on particular metabolic and epigenetic master regulators to support their unlimited proliferative capacity and to block differentiation. Our ongoing studies aim to identify and characterize novel metabolic processes that are essential for leukemia progression that can be targeted for intervention. By studying differentiation and self-renewal mechanisms in normal stem cells and cancer cells, we seek to identify key differences that could be targeted to promote regeneration by normal stem cells and suppress cancer by disabling the aberrant stem cell mechanisms.



SELECTED PUBLICATIONS

Tseng YJ, Kageyama Y, Murdaugh RL, Kitano A, Kim JH, Hoegenauer KA, Tiessen J, Smith MH, Uryu H, Takahashi K, Martin JF, Samee MAH, **Nakada D** (2024). Increased iron uptake by splenic hematopoietic stem cells promotes TET2-dependent erythroid regeneration. **Nat Commun.** 15: 538.

Eagle K, Jiang Y, Shi X, Li M, Obholzer NP, Hu T, Perez MW, Koren JV, Kitano A, Yi JS, Lin CY, **Nakada D** (2022). An oncogenic enhancer encodes selective selenium dependency in AML. **Cell Stem Cell.** 29: 386-399.

Shi X, Jiang Y, Kitano A, Hu T, Murdaugh RL, Li Y, Hoegenauer KA, Chen R, Takahashi K, **Nakada D** (2021). Nuclear NAD⁺ homeostasis governed by NMNAT1 prevents apoptosis of acute myeloid leukemia stem cells. **Sci Adv.** 7: eabf3895.

Murdaugh RL, Hoegenauer KA, Kitano A, Holt MV, Hill MC, Shi X, Tiessen JF, Chapple R, Hu T, Tseng YJ, Lin A, Martin JF, Young NL, **Nakada D** (2021). The histone H3.3 chaperone HIRA restrains erythroid-biased differentiation of adult hematopoietic stem cells. **Stem Cell Reports.** 16: 2014-2028.

Jiang Y, Hu T, Wang T, Shi X, Kitano A, Eagle K, Hoegenauer KA, Konopleva MY, Lin CY, Young NL, **Nakada D** (2019). AMP-activated protein kinase links acetyl-CoA homeostasis to BRD4 recruitment in acute myeloid leukemia. **Blood.** 134: 2183-2194.

Hu T, Morita K, Hill MC, Jiang Y, Kitano A, Saito Y, Wang F, Mao X, Hoegenauer KA, Morishita K, Martin JF, Futreal PA, Takahashi K, **Nakada D** (2019). PRDM16s transforms megakaryocyte-erythroid progenitors into myeloid leukemia-initiating cells. **Blood.** 134: 614-625.

Hu T, Kitano A, Luu V, Dawson B, Hoegenauer KA, Lee BH, **Nakada D** (2019). Bmi1 Suppresses Adipogenesis in the Hematopoietic Stem Cell Niche. **Stem Cell Reports.** 13: 545-558.

Chapple RH, Tseng YJ, Hu T, Kitano A, Takeichi M, Hoegenauer KA, **Nakada D** (2018). Lineage tracing of murine adult hematopoietic stem cells reveals active contribution to steady-state hematopoiesis. **Blood Adv.** 2: 1220-1228.

Shi X, Kitano A, Jiang Y, Luu V, Hoegenauer KA, **Nakada D** (2018). Clonal expansion and myeloid leukemia progression modeled by multiplex gene editing of murine hematopoietic progenitor cells. **Exp Hematol.** 64: 33-44. e5.

Chapple RH, Hu T, Tseng YJ, Liu L, Kitano A, Luu V, Hoegenauer KA, Iwakaki T, Li Q, **Nakada D** (2018). ERa promotes murine hematopoietic regeneration through the Ire1a-mediated unfolded protein response. **ELife.** 7: e31159. doi: 10.7554/eLife.31159.

DAVID L. NELSON, PH.D.**The Cullen Foundation Professorship in Molecular Genetics****Professor**, Department of Molecular and Human Genetics**Director**, BCM-Michigan-Emory Fragile X Research Center**Faculty Member**, Graduate Programs in Neuroscience and Genetics & Genomics**Program Director**, Graduate Programs in Cancer and Cell Biology and Integrative Molecular and Biomedical Sciences*Ph.D., Massachusetts Institute of Technology**Postdoc, National Institute for Neurological, Communicative Disorders & Stroke, NIH**Postdoc, Baylor College of Medicine***RESEARCH INTERESTS**

One of the most exciting findings in human genetics has been the recognition that unstable trinucleotide repeats contribute to more than four dozen genetic disorders, including myotonic muscular dystrophy, amyotrophic lateral sclerosis (Lou Gehrig's disease) and Huntington's disease. With collaborators, Nelson described the first of these unstable DNA sequences, a polymorphic CGG trinucleotide repeat in the *FMR1* gene found to be enlarged in people with Fragile X syndrome, the most common form of inherited intellectual disability and autism. The mechanism by which this mutation leads to disease is through loss of function of *FMR1* due to diminished expression accompanied by aberrant methylation of the gene. The *FMR1* gene product is an RNA-binding protein that interacts with complexes of RNA and ribosomes. It regulates the translation of hundreds of mRNAs. The Nelson group focuses on dissecting the function(s) of *FMR1* and its paralogs *FXR1* and *FXR2*. Understanding factors that lead to DNA instability of this sequence is also a key interest.

The Nelson group also studies disorders found in people with smaller expansions of the *FMR1* CGG repeat, known as premutation carriers (55-200 repeats). Males with CGG repeat lengths in this range are at risk for a late-onset neurodegenerative disorder termed FXTAS. FXTAS is distinct from fragile X syndrome; individuals are cognitively unaffected until their 6th or 7th decade, but then show neuronal degeneration accompanied by neuronal nuclear inclusions that stain with ubiquitin on autopsy. The Nelson group has utilized models in flies and mice to investigate the hypothesis that a gain of function through RNA toxicity is responsible for neuronal dysfunction and death. Fly models allowed identification and characterization of modifiers, and mouse models showed definitively that the CGG repeat was both necessary and sufficient to affect mammalian neurons. The group is also studying Fragile X-associated primary ovarian insufficiency, (FXPOI) a disorder resulting in early menopause found in some female carriers of the premutation. Using mouse models, the group has improved its understanding of the mechanism of ovarian insufficiency. Identifying genetic modifiers in both FXTAS and FXPOI is a goal for potential therapies. The group has demonstrated roles for several RNA-binding proteins including TDP-43 and alterations in 5-hydroxymethylcytosine, suggesting widespread dysregulation of gene expression.

**SELECTED PUBLICATIONS**

Kang JY, Wen Z, Pan D, Zhang Y, Li Q, (...), **Nelson DL**, Guo X, Zhou Y, Gou LT, Huang Y, Liu MF (2022). LLPS of FXR1 drives spermiogenesis by activating translation of stored mRNAs. **Science**. 377: eabj6647.

Yildirim Z, Baboo S, Hamid SM, Dogan AE, Tufanli O, (...), **Nelson DL**, Yates JR 3rd, Walter P, Erbay E (2022). Intercepting IRE1 kinase-FMRP signaling prevents atherosclerosis progression. **EMBO Mol Med**. 14: e15344.

Kong HE, Lim J, Linsalata A, Kang Y, Malik I, (...), **Nelson DL**, Epstein MP, Cutler DJ, Todd PK, Sherman SL, Warren ST, Jin P (2022). Identification of *PSMB5* as a genetic modifier of fragile X-associated tremor/ataxia syndrome. **Proc Natl Acad Sci U S A**. 119: e2118124119.

Shelly KE, Candelaria NR, Li Z, Allen EG, Jin P, **Nelson DL** (2021). Ectopic expression of CGG-repeats alters ovarian response to gonadotropins and leads to infertility in a murine *FMR1* premutation model. **Hum Mol Genet**. 30: 923-938.

Kong HE, Lim J, Zhang F, Huang L, Gu Y, **Nelson DL**, Allen EG, Jin P (2019). Metabolic pathways modulate the neuronal toxicity associated with fragile X-associated tremor/ataxia syndrome. **Hum Mol Genet**. 28: 980-991.

Estañ MC, Fernández-Núñez E, Zaki MS, Esteban MI, Donkersvoort S, Hawkins C, (...), **Nelson DL**, Otaify GA, Temtamy S, Aglan M, Issa M, Bönnemann CG, Lapunzina P, Yoon G, Ruiz-Perez VL (2019). Recessive mutations in muscle-specific isoforms of FXR1 cause congenital multi-minicore myopathy. **Nat Commun**. 10: 797.

Higashimori H, Schin CS, Chiang MS, Morel L, Shoneye TA, **Nelson DL**, Yang Y. (2016) Selective Deletion of Astroglial FMRP Dysregulates Glutamate Transporter GLT1 and Contributes to Fragile X Syndrome Phenotypes In Vivo. **J Neurosci**. 36: 7079-94.

Lumaban JG, **Nelson DL** (2015). The Fragile X proteins Fmrp and Fxr2p cooperate to regulate glucose metabolism in mice. **Hum Mol Genet**. 24: 2175-84.

Galloway JN, Shaw C, Yu P, Parghi D, Poidevin M, Jin P, **Nelson DL** (2014). CGG repeats in RNA modulate expression of TDP-43 in mouse and fly models of fragile X tremor/ataxia syndrome. **Hum Mol Genet**. 23: 5906-15.

Yao B, Lin L, Street RC, Zalewski ZA, Galloway JN, Wu H, **Nelson DL**, Jin P (2014). Genome-wide alteration of 5-hydroxymethylcytosine in a mouse model of fragile X-associated tremor/ataxia syndrome. **Hum Mol Genet**. 23: 1095-107.

PHILIP NG, PH.D.

Associate Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Programs in Genetics & Genomics and Translational Biology & Molecular Medicine

Ph.D., University of Guelph
Postdoc, McMaster University

RESEARCH INTERESTS

My laboratory is interested in developing gene therapies using helper-dependent adenoviral vectors (HDA_v). HDA_v (also called gutless or gutted adenovirus) do not contain any viral genes and thus represent a major improvement over early generation adenoviral vectors with respect to safety and efficacy. These vectors can transduce target cells with high efficiency to provide high level long-term transgene expression without chronic toxicity. Studies into improving the production of HDA_v as well as their characterization are ongoing in my laboratory including manufacturing the vector under current Good Manufacturing Practices (cGMP) for clinical applications in humans.

A focus of my laboratory is liver-directed gene therapy using HDA_v to treat a wide variety of genetic and acquired disease such as hemophilia, Crigler-Najjar syndrome, cardiovascular disease, alpha 1-antitrypsin deficiency and many others. We are investigating novel methods of delivering HDA_v preferentially into the liver of mice, dogs and nonhuman primates. We have developed a minimally invasive, balloon occlusion catheter-based method to deliver HDA_v preferentially into the liver of large animals which results in negligible toxicity and long-term, high level transgene expression. This technology may pave the way towards human clinical application for a wide variety of genetic and acquired diseases. We are also investigating ways of modifying the capsid of the vector to achieve preferential transduction of hepatocytes.

Another major focus of my laboratory is lung-directed gene therapy using HDA_v with the primary goal of treating cystic fibrosis. We have developed a novel method of aerosolizing HDA_v into the lungs of nonhuman primates which has resulted in very high efficiency gene transfer to the airway epithelium with negligible toxicity. These encouraging and compelling results may pave the way to treat patients with cystic fibrosis in the future.

We are also interested in investigating the innate and adaptive immune responses to HDA_v. These important studies will provide information regarding the host-vector interactions which will be very useful for further improving the safety and efficacy of HDA_v-mediated gene therapy.

Another active area of research in my lab is gene editing of human induced pluripotent stem cells (iPSCs) by HDA_vs. Gene editing of iPSCs has emerged as a powerful tool in research and has great potential in medicine. The major appeal of HDA_v-mediated gene editing is that induction of an artificial double stranded break at the chromosomal target locus by a designer endonuclease is not required to achieve high targeting efficiency, thereby eliminating the potential for off-target cleavage. We are interesting in understanding the mechanism of gene editing by HDA_v so that we may further improve its efficiency to ultimately permit direct and efficient in vivo gene editing in the future.



SELECTED PUBLICATIONS

Palmer DJ, Grove NC, Ing J, Crane AM, Venken K, Davis BR, **Ng P** (2016). Homology requirements for efficient, footprintless gene editing at the CFTR locus in human iPSCs with helper-dependent adenoviral vectors. **Mol Ther Nucleic Acids**. 5: e372.

Palmer DJ, Grove NC, **Ng P** (2016). Helper virus-mediated downregulation of transgene expression permits production of recalcitrant helper-dependent adenoviral vector. **Mol Ther Methods Clin Dev**. 3: 16039.

Brunetti-Pierri N, Ng T, Iannitti D, Cioffi W, Stapleton G, Law M, Breinholt J, Palmer D, Grove N, Rice K, Bauer C, Finegold M, Beaudet A, Mullins C, **Ng P** (2013). Transgene Expression up to 7 Years in Nonhuman Primates Following Hepatic Transduction with Helper-Dependent Adenoviral Vectors. **Hum Gene Ther**. 24: 761-5.

Brunetti-Pierri N, Liou A, Patel P, Palmer D, Grove N, Finegold M, Piccolo P, Donnachie E, Rice K, Beaudet A, Mullins C, **Ng P** (2012). Balloon catheter delivery of helper-dependent adenoviral vector results in sustained, therapeutic hFIX expression in rhesus macaques. **Mol Ther**. 20: 1863-70.

Brunetti-Pierri N, **Ng P** (2011). Helper-dependent adenoviral vectors for liver-directed gene therapy. **Hum Mol Genet**. 20: R7-13.

Dimmock D, Brunetti-Pierri N, Palmer DJ, Beaudet AL, **Ng P** (2011). Correction of hyperbilirubinemia in Gunn rats using clinically relevant low doses of helper-dependent adenoviral vectors. **Hum Gene Ther**. 22: 483-8.

Vetrini F, Brunetti-Pierri N, Palmer DJ, Bertin T, Grove NC, Finegold MJ, **Ng P** (2010). Vasoactive Intestinal Peptide Increases Hepatic Transduction and Reduces Innate Immune Response Following Administration of Helper-dependent Ad. **Mol Ther**. 18: 1339-45.

Brunetti-Pierri N, **Ng P** (2010). Helper-dependent adenoviral vectors. In Parham, M and Bruinvels, J (Eds.) **Gene Therapy for Autoimmune and Inflammatory Diseases**. Birkhauser Publishing, Basel, Switzerland.

Brunetti-Pierri N, **Ng P** (2009). Progress towards liver and lung-directed gene therapy with helper-dependent adenoviral vectors. **Curr Gene Ther**. 9: 329-40.

Brunetti-Pierri N, **Ng P** (2009). Helper-dependent adenoviral vectors for gene therapy. In Templeton, NS (Ed.) **Gene Therapy: Therapeutic Mechanisms and Strategies, 3rd Edition**. Marcel Dekker, Inc., New York, NY.

DONGSU PARK, PH.D.

Assistant Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Program in Genetics & Genomics; Development, Diseases Models & Therapeutics; Center for Skeletal Medicine and Biology

Ph.D., Baylor College of Medicine

Postdoc, Massachusetts General Hospital & Harvard Stem Cell Institute

RESEARCH INTERESTS

The main interest of my lab is to understand the *in vivo* identity and pathophysiological function of stem/progenitor cells in bone regeneration and repair and to develop better treatment methods for devastating bone and connective tissue disorders. While adult skeletal stem cells (SSCs) are critical for life-long maintenance and regeneration of bone and bone marrow (BM), the *in vivo* characteristics and function of SSCs in different bones and compartments remain unanswered questions. To address these questions, we have developed a new strategy utilizing single cell analysis, genetic pulse-chase models, and advanced intravital imaging technology and defined the lifespan and unexpectedly short-term recycling of osteoblasts *in vivo*. Further, long-term maintenance of osteogenic cells comes from lineage-restricted skeletal stem/progenitor cells (Park et al, *Cell Stem Cell* 2012). More recently, we discovered adult SSC heterogeneity and a long-term repopulating SSC subset present in periosteum (outer layer of bone) *in vivo*. These periosteal SSCs are critical for periosteal (outer) bone maintenance, specifically express CCL5 receptors, CCR5, and have a unique CCL5-dependent migratory mechanism required for bone injury repair (Ortinou et al, *Cell Stem Cell*, 2019). We now aim to address functional heterogeneity and epigenetic regulation of human and mouse SSCs in the context of skeletal aging and to explore the clinical relevance of these cells in bone disorders, injuries and cancer bone metastasis.

Further, we aim to define mechanisms to regulate the BM medullary cavity and stroma cell function. We recently identified that a subset of Cxcl12+ stroma cells appear in tibial and femoral diaphysis, coinciding with the development of the medullary cavity. Surprisingly, upon bone injury, these cells readily respond and proliferate within the internal fracture callus and suppress bone forming cells with the recovery of BM cavity. Bone marrow also provides a specialized microenvironment (niche) for HSC function. To understand how stress signals control endogenous HSCs and their niche interaction, we generated novel animal models to selectively label endogenous HSCs and SSCs and found a clear displacement of HSCs away from CXCL12-expressing niche cells upon interferon treatment. We are now elucidating the identity of unique stroma progenitor cells with anti-osteogenic function and their regulation mechanism for BM medullary cavity maintenance and normal bone repair.

My laboratory is also interested in the identity and function of stem cell populations in non-skeletal tissues such as muscle and tendon. Our recent studies demonstrated that the adult muscles and tendons contain a discrete population of stem cells that appear postnatally and undergo clonal expansion under mechanical stress and injury. By using a variety of genetic, immunologic, and microscopic technologies, we are investigating their stem cell heterogeneity and mechanisms that govern tendon and connective tissue regeneration and repair. These studies will elucidate fundamental aspects of skeletal tissue regeneration and may lead to the development of new regenerative medicine strategies.

**SELECTED PUBLICATIONS**

Solidum JGN, Jeong Y, Heralde F 3rd, **Park D*** (2023). Differential regulation of skeletal stem/progenitor cells in distinct skeletal compartments. **Front Physiol** 14: 1137063.

Grol MW, Haelterman NA, Lim J, Munivez EM, Archer M, Hudson DM, Tufa SF, Keene DR, Lei K, **Park D**, Kuzawa CD, Ambrose CG, Eyre DR, Lee BH (2021). Tendon and motor phenotypes in the *Crtap*^{-/-} mouse model of recessive osteogenesis imperfecta. **Elife** 10: e63488.

Florez MA, Matatall KA, Jeong Y, Ortinau L, Shafer PW, Lynch AM, Jaksik R, Kimmel M, **Park D***, King KY* (2020). Interferon Gamma Mediates Hematopoietic Stem Cell Activation and Niche Relocalization through BST2. **Cell Reports**. 33: 108530. *co-corresponding authors

Ortinou LC, Wang H, Lei K, Deveza L, Jeong Y, Hara Y, Grafe I, Rosenfeld SB, Lee D, Lee B, Scadden DT, **Park D*** (2019). Identification of Functionally Distinct Mx1+αSMA+ Periosteal Skeletal Stem Cells. **Cell Stem Cell**. 25: 784-796. e5.

Scaramozza A, **Park D**, Kollu S, Beerman I, Sun X, Rossi DJ, Lin CP, Scadden DT, Crist C, Brack AS (2019). Lineage Tracing Reveals a Subset of Reserve Muscle Stem Cells Capable of Clonal Expansion under Stress. **Cell Stem Cell**. 24: 944-957.e5.

Deveza L, Ortinau L, Lei K, **Park D*** (2018). Comparative analysis of gene expression identifies distinct molecular signatures of bone marrow- and periosteal-skeletal stem/progenitor cells. **PLoS One**. 13: e0190909.

Park D, Spencer JA, Koh BI, Kobayashi T, Fujisaki J, Clemens TL, Lin CP, Kronenberg HM, Scadden DT (2012). Endogenous bone marrow MSCs are dynamic, fate-restricted participants in bone maintenance and regeneration. **Cell Stem Cell**. 10: 259-72.

Park D, Lapteva N, Seethamagari M, Slawin KM, Spencer DM (2006). An essential role for Akt1 in dendritic cell function and tumor immunotherapy. **Nat. Biotech.** 24: 1581-90.

LORRAINE POTOCKI, M.D., FACMG

Professor and Vice Chair for Undergraduate Medical Education, Department of Molecular and Human Genetics

Director, Genetics & Genomics Pathway, School of Medicine, Baylor College of Medicine

M.D., Boston University School of Medicine

Resident, Pathology, University of Massachusetts

Fellow, Fetal and Perinatal Pathology, Brown University

Fellow, Medical Genetics, Baylor College of Medicine

RESEARCH INTERESTS

As a clinical geneticist I strive to provide the most comprehensive and compassionate care to individuals with developmental and genetic disorders. As a medical educator I strive to engender curiosity in all learners and help foster an environment that is conducive to collaborative learning and discovery.

My clinical research interest stems from experience in the characterization of Potocki-Shaffer syndrome (PSS), Smith-Magenis syndrome (SMS; deletion 17p11.2), and Potocki-Lupski syndrome (PTLS; duplication 17p11.2).

PSS is a contiguous gene deletion syndrome due to an interstitial deletion within the short arm of chromosome 11 [del(11)(p11.2p12)]. Clinical findings of PSS include intellectual disability, multiple exostoses, biparietal foramina, and genital anomalies in males. The presence of multiple exostoses is associated with deletion of *EXT2*, the presence of biparietal foramina is associated with the deletion of *ALX4*, and haploinsufficiency of *PHF21A* is associated with intellectual disability and craniofacial anomalies. Individuals with duplication of this region have also been identified.

SMS is associated with a heterozygous deletion within 17p11.2 or point mutation of *RAI1* that maps within 17p11.2. While the phenotype is variable among patients with the same sized deletion, most patients have cognitive impairment, neurobehavioral abnormalities, and severe sleep disturbances including an inversion of the circadian rhythm of melatonin. Cardiovascular anomalies—observed in less than 50%—include septal defects, and in more severe cases, obstruction of the right ventricular outflow tract as seen in tetralogy of Fallot. While not thoroughly investigated, growth hormone deficiency may play a role in the short stature and obesity phenotype observed in SMS.

Duplication 17p11.2 represents the reciprocal recombination of the common SMS deletion. The clinical phenotype of persons with dup17p11.2 is distinct from that of SMS and consists of infantile hypotonia and failure to thrive, mildly dysmorphic facial features, cognitive impairment, and autism spectrum. Although sleep disturbances are less of a concern for individuals with PTLS, many have sleep disordered breathing. Cardiovascular anomalies are seen in approximately 50 percent of patients and include left ventricular outflow tract anomalies such as hypoplastic left heart and bicuspid aortic valve. Growth hormone deficiency is observed in a subset of our PTLS cohort.

Clinical comparisons of PTLS and SMS, in conjunction with molecular analyses, will provide insight as to dosage sensitivity and the roles of the genes within this region.



SELECTED PUBLICATIONS

Franciskovich R, Soler-Alfonso C, Neira-Fresneda J, Lupski JR, McCann-Crosby B, **Potocki L** (2020). Short stature and growth hormone deficiency in a subset of patients with Potocki-Lupski syndrome: Expanding the phenotype of PTLS. *Am J Med Genet A*. 182: 2077-2084.

Kaplan KA, Elsea SH, **Potocki L** (2020). Management of sleep disturbances associated with Smith-Magenis syndrome. *CNS Drugs*. 34: 723-730.

Markovitz R, Ghosh R, Kuo ME, Hong W, Lim J, Bernes S, Manberg S, Crosby K, Tanpaiboon P, Bharucha-Goebel D, Bonnemann C, Mohila CA, Mizerik E, Woodbury S, Bi W, Lotze T, Antonellis A, Xiao R, **Potocki L** (2020). GARS-related disease in infantile spinal muscular atrophy: Implications for diagnosis and treatment. *Am J Med Genet A*. 182:1167-1176.

Dhar SU, Alford RL, Nelson E, **Potocki L** (2012). Enhancing exposure to genetics and genomics through an innovative medical school curriculum. *Genet Med*. 14: 163-7.

Glinton KE, **Potocki L**, Dhar SU (2022). An innovative medical school curriculum to enhance exposure to genetics and genomics: Updates and outcomes. *Genet Med*. 24: 722-728.

Soler-Alfonso C, Motil KJ, Robbins-Furman P, Friedman EJ, Eifret A, Fraley K, **Potocki L** (2011). Potocki-Lupski syndrome — A microduplication syndrome associated with oral pharyngeal dysphasia and failure to thrive. *J Pediatr*. 158: 655-659.

Potocki L, Bi W, Treadwell-Deering D, Carvalho CM, Eifert A, (...), Lupski JR (2007). Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. *Am J Hum Genet*. 80: 633-49.

Potocki L, Chen KS, Park SS, Osterholm DE, Withers MA, (...), Lupski JR (2000). Molecular mechanism for duplication 17p11.2- the homologous recombination reciprocal of the Smith-Magenis microdeletion. *Nat Genet*. 24: 84-7.

JEFFREY ROGERS, PH.D.

Associate Professor, Department of Molecular and Human Genetics and Human Genome Sequencing Center

Core Scientist, Wisconsin National Primate Research Center, Madison, WI

Faculty Member, Graduate Programs in Genetics & Genomics and Development, Disease Models & Therapeutics

Ph.D., Anthropology, Yale University

RESEARCH INTERESTS

My research is focused on the genetics and genomics of nonhuman primates. These species are widely used as animal models of disease because they are so similar genetically and physiologically to humans. For studies of neurobiology and behavior, infectious diseases, metabolic diseases and other common health problems, nonhuman primates provide unique and valuable experimental models. As the analysis of genetic mechanisms has become central to so much of both biomedical and basic biological research, detailed information about the genomics of nonhuman primates has become more important and more useful.

My laboratory is working on various aspects of primate genomics, including both basic comparative analyses and targeted research using primate models of human disease. I am one of the three co-leaders of the Primate Conservation and Sequencing Initiative. This is an international consortium of primatologists, evolutionary biologists, geneticists, and experts in genome analysis including computational biologists and bioinformaticians. Our team includes people from 17 countries and is growing. Together we are conducting the largest survey to date of genomic diversity across primates. In Phase One of this project (Kuderna et al. 2023; Gao et al. 2023) we published analyses of deep whole genome sequences from 809 individuals representing 233 primate species, most of which are threatened with extinction. We are now continuing with Phase Two, expanding our studies to more species. This work has documented an unexpectedly high level of genetic variation within primate species, higher than the levels found in human populations. We are also investigating various other aspects of primate genetics and evolutionary biology (Kuderna et al. 2023). The same comparative data have also been shown to provide new insights into the genetics of disease in humans. Gao et al. (2023) showed that information about the composition of genetic variation in nonhuman primates is remarkably valuable in predicting which mutations in the human genome will cause disease and which are benign. Our program also includes a broad survey of population genomics across six species of *Papio* baboons in which we identified several new locations of between-species hybridization and gene flow (Sorensen et al. 2023). These studies add to our understanding of primate speciation as well as providing a model of gene flow between humans and Neanderthals.

In a separate project, we are conducting an extensive survey of genomic variation in the most widely studied nonhuman primate in biomedical research, the rhesus macaque (*Macaca mulatta*). By sequencing the genomes or exomes of >2,000 rhesus macaques from various US research colonies we found hundreds of thousands of functionally significant genetic variants that can be used to examine the effects of specific genes on various disease-related phenotypes (Warren et al. 2020). Information regarding genetic variation, including changes in protein-coding sequences and putative regulatory sequences, in combination with other genomic data, makes all these primate species more useful for future biomedical research projects.

The third major line of research in my laboratory is the targeted analysis of specific nonhuman primate models of human genetic diseases. In collaboration with psychiatrists and neurobiologists, we have studied individual variation in behavior and neurophysiology among macaques and baboons (Rogers 2018; Fox et al. 2021). The complex social behavior displayed by primates makes them outstanding subjects for neurobiological investigation (Oler et al. 2010; Rogers et al. 2013; Fawcett et al. 2014; Gunter et al. 2022), pointing to genetic mechanisms that may influence susceptibility to psychiatric disorders in people (Rogers et al. 2013; Fox et al. 2021). We are also analyzing primate models of inherited susceptibility to cancer (Ozirmak Lermi et al. 2022), retinal disorders and vision loss (Moshiri et al. 2019), endometriosis (Tapmeier et al. 2021) and other diseases. Our discovery and analyses of these primate models are generating novel information about potential treatments and therapies for use in human clinical practice.



SELECTED PUBLICATIONS

Fox AS, Harris RA, Rosso LD, Raveendran M, Kamboj S, Kinnally EL, Capitanio JP, **Rogers J** (2021). Infant inhibited temperament in primates predicts adult behavior, is heritable, and is associated with anxiety-relevant genetic variation. *Mol Psychiatry*. 26: 6609-6618.

Gao H, Hamp T, Ede J, Schraiber JG, McRae J, (...), **Rogers J**, Marques-Bonet T, Farh KK (2023). The landscape of tolerated genetic variation in humans and primates. *Science*. 380: eabn8153.

Gunter C, Harris RA, Kovacs-Balint Z, Raveendran M, Michopoulos V, Bachevalier J, Raper J, Sanchez MM, **Rogers J** (2022). Heritability of social behavioral phenotypes and preliminary associations with autism spectrum disorder risk genes in rhesus macaques: A whole exome sequencing study. *Autism Res*. 15: 447-463.

Kuderna LFK, Gao H, Janiak MC, Kuhlwillm M, Orkin JD, (...), **Rogers J**, Farh KK, Marques Bonet T (2023). A global catalog of whole-genome diversity from 233 primate species. *Science*. 380: 906-913.

Ozirmak Lermi N, Gray SB, Bowen CM, Reyes-Urbe L, Dray BK, Deng N, Harris RA, Raveendran M, Benavides F, Hodo CL, Taggart MW, Colbert Maresco K, Sinha KM, **Rogers J**, Vilar E (2022). Comparative molecular genomic analyses of a spontaneous rhesus macaque model of mismatch repair-deficient colorectal cancer. *PLoS Genet*. 18: e1010163.

Rogers J, Gibbs RA (2014). Comparative primate genomics: Emerging patterns of genome content and dynamics. *Nat Rev Genet*. 15: 347-359.

Rogers J, Raveendran M, Fawcett GL, Fox AS, Shelton SE, (...), Kalin NH (2013). *CRHR1* genotypes, neural circuits and the diathesis for anxiety and depression. *Mol Psychiatry*. 18: 700-7.

Sorensen EF, Harris RA, Zhang L, Raveendran M, Kuderna LFK, (...), Munch K, Roos C, **Rogers J** (2023). Genome-wide coancestry reveals details of ancient and recent male-driven reticulation in baboons. *Science*. 380: eabn8153.

Tapmeier TT, Rahmioglu N, Lin J, De Leo B, Obendorf M, Raveendran M, (...), **Rogers J**, Zondervan KT (2021). Neuropeptide S receptor 1 is a nonhormonal treatment target in endometriosis. *Sci Transl Med*. 13: eabd6469.

Warren WC, Harris RA, Haukness M, Fiddes IT, Murali SC, (...), **Rogers J**, Eichler EE (2020). Sequence diversity analyses of an improved rhesus macaque genome enhance its biomedical utility. *Science*. 370: eabc6617.

Palesch D, Bosinger SE, Tharp GK, (...), Worley K, **Rogers J**, Silvestri G (2018). Sooty mangabey genome sequence reveals new insights into mechanisms of AIDS resistance in natural SIV hosts. *Nature* 553: 77-81.

SUSAN M. ROSENBERG, PH.D.**Ben F. Love Chair in Cancer Research**

Professor, Departments of Molecular and Human Genetics, Biochemistry & Molecular Biology and Molecular Virology & Microbiology

Leader, Cancer Evolvability Program, Dan L Duncan Comprehensive Cancer Center

Faculty Member, Graduate Program in Genetics & Genomics

Ph.D., University of Oregon

Postdoc, University of Paris VII

Postdoc, University of Utah School of Medicine

Postdoc, National Cancer Institute at Frederick

RESEARCH INTERESTS**Genome Instability in Evolution, Antibiotic Resistance, and Cancer**

Stress-Induced Mutagenesis: For 70 years the world believed that mutations occur at random. The discovery of stress-induced mutagenesis has changed ideas about mutation and evolution and revealed mutagenic mechanisms that are induced by stress responses. The stress responses increase mutagenesis specifically when cells are maladapted to their environments, i.e. are stressed, potentially accelerating evolution. We are elucidating molecular mechanisms of stress-inducible mutation in *E. coli* using genetic, molecular, genomic, functional systems, biological, single-cell, and synthetic approaches. We discovered that the normally high-fidelity mechanism of DNA-break repair is switched to a mutagenic version of that mechanism, using a special error-prone DNA polymerase, specifically when cells are stressed, under the control of at least two cellular stress responses. Stress-induced mutation mechanisms are providing important models for genome instability underlying some cancers and genetic diseases, resistance to chemotherapeutic and antibiotic drugs, pathogenicity of microbes, and many other important evolutionary processes. We are interested in molecular mechanisms that drive evolution.

Antibiotic-Resistance Mutation: Some mutations that confer antibiotic resistance form by mechanisms similar to stress-induced mutagenic DNA break repair, described above, induced by antibiotics themselves. We are examining the mechanisms by which these mutations form, and working to develop drugs to block evolution of antibiotic resistance.

Engineered Proteins Detect Spontaneous DNA-Damage Reaction Intermediates in Living Cells: We created *E. coli* cells that fluoresce red when their DNA is damaged, and use flow cytometry to quantify and recover red cells with spontaneous DNA damage to learn their origins. We also engineer synthetic “freeze-frame” proteins that “trap” DNA-damage reaction intermediates, which we use to discover the origins of spontaneous DNA damage in bacterial and human cells. We quantify fluorescent foci that represent specific DNA structures/intermediates, and map those specific DNA damage structures in genomes with ChIP-seq. Spontaneous DNA damage is the main culprit underlying genome instability in all cells. These tools are allowing us to discover its origins and a new functional class of cancer-driving genes conserved from bacteria to human.

Deep Translational Discovery of Cancer-Gene Functions Using *E. coli*. Genomic instability is a hallmark of cancer, yet the DNA-repair proteins that prevent and sometimes cause instability are highly conserved and similar in all organisms. *E. coli* RecQ DNA helicase has five human orthologs, mutations in which cause genome instability, cancer, and cancer-predisposition syndromes: Bloom, Werner, and Rothmund-Thomson. We found that *E. coli* RecQ works in homology-directed DNA repair opposite to how one human, a yeast and a fly RecQ ortholog do, and thus exemplifies a second paradigm for the function of RecQ-family proteins in living cells. We also modeled p53- (most) cancers in *E. coli* by upregulating the *E. coli* ortholog of human RAD51, which most common cancers upregulate. We discovered that increased RecA causes DNA replication to stall, and that RecQ prevents this, allowing DNA replication. We used bioinformatics and human-cancer RNA data to discover that most common cancers co-upregulate two RecQ orthologs—BLM and RECQL4—with RAD51, and two proteins known to remove replication-fork stalls. Our data imply that, in most common cancers, surprisingly, four DNA-repair proteins that prevent cancer are upregulated and very probably promote cancer when overproduced by allowing DNA replication. We are pursuing other promising bacterial homologs of human cancer proteins to learn their mechanisms of action first in the simpler, more tractable bacterial system to provide mechanisms and models for the molecular bases of cancer, and reveal its Achilles' heels.

**SELECTED PUBLICATIONS**

Liu J, Perren JO, Rogers CM, Nimer S, Wen AX, (...), **Rosenberg SM** (2025). Endogenous DNA damage at sites of terminated transcripts. *Nature*. 640: 240-248.

Russo M, Chen M, Mariella E, Peng H, Rehman SK, (...), **Rosenberg SM**, Shen S, Bardelli A (2024). Cancer drug-tolerant persister cells: from biological questions to clinical opportunities. *Nat Rev Cancer*. 24: b694-717.

Zhai Y, Pribis JP, Dooling SW, (...), Herman C, Hastings PJ, Costa-Mattioli M, **Rosenberg SM** (2023). Drugging evolution of antibiotic resistance at a regulatory network hub. *Sci Adv*. 9: eadg0188.

Zhai Y, Minnick PJ, Pribis JP, Garcia-Villada L, Hastings PJ, Herman C, **Rosenberg SM** (2023). ppGpp and RNA-polymerase backtracking guide antibiotic-induced mutable gambler cells. *Mol Cell*. 83: 1298-1310.

Mei Q, Fitzgerald DM, Liu J, Xia J, Pribis JP, (...), Nussenzweig A, Hastings PJ, **Rosenberg SM** (2021). Two mechanisms of chromosome fragility at replication-termination sites in bacteria. *Sci. Adv*. 7: eabe2846.

Xia J, Chiu LY, (...), Herman C, Miller KM, **Rosenberg SM** (2019). Bacterial-to-human protein networks reveal origins of endogenous DNA damage. *Cell* 176: 127-143.e24.

Pribis JP, Garcia-Villada L, Zhai Y, Lewis-Epstein O, Wang A, (...), Hadany L, Hastings PJ, **Rosenberg SM** (2019). Gamblers: an antibiotic-induced evolvable cell subpopulation differentiated by reactive-oxygen-induced general stress response. *Mol Cell*. 74: 785-800.

Sivaramakrishnan P, Sepulveda LA, Halliday JA, Bravo Núñez MA, Liu J, Golding I, **Rosenberg SM**, Herman C (2017). The transcription fidelity factor GreA impedes DNA break repair in *Escherichia coli*. *Nature*. 550: 214-218.

Al Mamun AA, Lombardo M-J, Shee C, Lisewski AM, Gonzalez C, (...) **Rosenberg SM** (2012). Identity and function of a large gene network underlying mutagenic repair of DNA breaks. *Science*. 338: 1344-8.

Pennington JM, **Rosenberg SM** (2007). Spontaneous DNA breakage in single living *Escherichia coli* cells. *Nat Genet*. 39: 797-802.

Ponder RG, Fonville NC, **Rosenberg SM** (2005). A switch from high-fidelity to error-prone DNA double-strand break repair underlies stress-induced mutation. *Mol Cell*. 19: 791-804.

Hastings PJ, Bull HJ, Klump JR, **Rosenberg SM** (2000). Adaptive amplification: An inducible chromosomal instability mechanism. *Cell*. 103: 723-31.

Rosenberg SM, Longerich S, Gee P, Harris RS (1994). Adaptive mutation by deletions in small mononucleotide repeats. *Science*. 265: 405-7.

FERNANDO SCAGLIA, M.D.

Professor, Department of Molecular and Human Genetics

Co-Director, Pediatric Mitochondrial Medicine Clinic, Texas Children's Hospital

Director, Adult Mitochondrial Medicine Clinic, Baylor St Luke's Medical Center
McNair Campus

Clinical Director, Baylor College of Medicine and Chinese University of Hong
Kong Joint Center for Medical Genetics in Hong Kong

M.D., University of La Plata School of Medicine

Intern, Pediatrics, Emory University School of Medicine

Resident, Pediatrics, Emory University School of Medicine

Fellow, Medical Genetics, Emory University School of Medicine

RESEARCH INTERESTS

My primary research interest is focused on the study of the natural history of mitochondrial disorders supported by the NIH funded North American Mitochondrial Disease Consortia (NAMDC), a registry that focuses on the longitudinal study of patients with mitochondrial disease. Furthermore, I am also involved in clinical trials in children and adults with mitochondrial disorders. One of my current areas of research includes the study of nitric oxide deficiency as the basis for stroke-like episodes in adults and children with a mitochondrial syndrome called MELAS. As a Principal Investigator on several grants that have been funded by national organizations in the U.S., I have laid the groundwork for the study of nitric oxide deficiency in MELAS syndrome and its restoration with the use of arginine and citrulline supplementation. A current NIH grant funds a phase 1 study that aims to determine the maximum tolerated dose and safety profile of citrulline supplementation in adults with MELAS syndrome. Moreover, I am involved in an international clinical trial for pediatric patients evaluating the efficacy of vatiquinone in mitochondrial refractory epilepsy and in a national multi-center trial evaluating the safety and efficacy of dichloroacetate in pyruvate dehydrogenase deficiency. In addition, I have conducted a trial to evaluate the effect of bocidelpar sulfate, a selective modulator of PPAR δ in adults with primary mitochondrial myopathy. Finally, I am also involved in establishing the natural history of congenital disorders of glycosylation with the support of the NIH funded Frontiers in Congenital Disorders of Glycosylation Consortia (FCDGC).

Furthermore, I am interested in determining whether there is a specific metabolomics signature for the different mitochondrial disorders caused by mitochondrial and nuclear gene defects and whether this profile could be used to monitor their natural history and the treatment efficacy when novel therapeutic approaches are trialed. In that capacity, I am the co-chair of a CDE mitochondrial biomarker subgroup that works with NINDS.



SELECTED PUBLICATIONS

Mackay L, Gijavanekar C, Streff H, Price JF, Elsea SH, **Scaglia F** (2023). Novel phenotype of aortic root dilatation and late-onset metabolic decompensation in a patient with TMEM70 deficiency. **Am J Med Genet A**. 191: 1366-1372.

Karaa A, Bertini E, Carelli V, Cohen BH, Enns GM, Falk MJ, Goldstein A, Gorman G, Haas R, Hirano M, Klopstock T, Koenig MK, Kornblum C, Lamperti C, Lehman A, Longo N, Molnar MJ, Parikh S, Phan H, Pitceathly R, Saneto R, **Scaglia F**, Servidei S, Tarnopolsky M, Toscano A, Van Hove J, Vissing J, Vockley G, Finman JS, Brown DA, Shiffer JA, Mancuso M (2023). Efficacy and Safety of Elamipretide in Individuals With Primary Mitochondrial Myopathy: The MMPOWER-3 Randomized Clinical Trial. **Neurology**. 101: e238-e252.

Snyder MT, Manor J, Gijavanekar C, Mizerik E, Kralik SF, Elsea SH, Machol K, Emrick L, **Scaglia F** (2024). Heteroplasmic pathogenic m.12315G>A variant in MT-TL2 presenting with MELAS syndrome and depletion of nitric oxide donors. **Am J Med Genet A**. 194: e63461.

Poon CYL, Leung TY, Wang CC, Daljit S, Nicolaides K, **Scaglia F**, Cheng KYY, Milosavljevic A (2024). Aspirin delays the metabolic clock of gestation in women at risk of preeclampsia: abridged secondary publication. **Hong Kong Med J**. 30 Suppl 1: 45-46.

Walimbe AS, Machol K, Kralik SF, Mizerik EA, Gofin Y, Bekheirnia MR, Gijavanekar C, Elsea SH, Emrick LT, **Scaglia F** (2024). Expanded clinical phenotype and untargeted metabolomics analysis in RARS2-related mitochondrial disorder: a case report. **BMC Neurol**. 24: 87. doi: 10.1186/s12883-024-03571-w.

Gerard A, Mizerik E, Mohila CA, AlAwami S, Hunter JV, Kearney DL, Lalani SR, **Scaglia F** (2024). Intracranial calcifications simulating Aicardi-Goutières syndrome in PARS2-related mitochondrial disease. **Am J Med Genet A**. 194: e63589

Komulainen-Ebrahim J, Kangas SM, López-Martín E, Feyma T, **Scaglia F**, Martínez-Delgado B, Kuismin O, Suo-Palosaari Maria, Olsén P, Hinttala R, Kurian MA, Uusima J (2024). Hyperkinetic Movement Disorder Caused by the Recurrent c.892C>T NACC1 Variant. **Mov Disord Clin Pract**. 11: 708-715.

Zemet R, Hope KD, Edmondson AC, Shah R, Patino M, Yesso AM, Berger JH, Sarafoglou K, Larson A, Lam C, Morava E, **Scaglia F** (2024). Cardiomyopathy, an uncommon phenotype of congenital disorders of glycosylation: Recommendations for baseline screening and follow-up evaluation. **Mol Genet Metab**. 142: 108513.

Lam C, **Scaglia F**, Berry GT, Larson A, Sarafoglou K, (...), Morava E (2024). Frontiers in congenital disorders of glycosylation consortium, a cross-sectional study report at year 5 of 280 individuals in the natural history cohort. **Mol Genet Metab**. 142: 108509.

DARYL A. SCOTT, M.D., PH.D.

Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Programs in Development, Disease Models & Therapeutics and Genetics & Genomics
Director, Medical Research Pathway, School of Medicine, Baylor College of Medicine

M.D./Ph.D., University of Iowa
Resident, Pediatrics, University of Utah
Resident, Clinical Genetics, Baylor College of Medicine

RESEARCH INTERESTS

Our laboratory is dedicated to identifying and characterizing genes and genomic alterations that cause common, life-threatening birth defects and determining the molecular mechanisms by which they impact human health.

Congenital Diaphragmatic Hernia and Cardiovascular Malformations: Children with congenital diaphragmatic hernia (CDH) have an abnormal opening in the diaphragm that allows abdominal organs, like the liver and intestines, to enter the chest. This invasion interferes with normal lung development causing severe respiratory problems at birth. CDH affects about one in every 3,500 newborns. CDH-associated mortality and morbidity are high, particularly in the subset of individuals who have a co-existing cardiovascular malformation (CVM). We use clinical and molecular data from patients and machine learning to identify genes associated with CDH and/or CVM. Genes we have worked on include *GATA4*, *SOX7*, *ZFPM2*, *FREM1*, *FREM2*, *FRAS1*, *NONO*, *NR2F2*, *FZD2*, *HCCS*, *HEY2*, *FBN1*, *SON*, *TRRAP*, *FGFRL1*, and *FOXP1*. We are now using mouse models developed in our laboratory to discover the morphogenetic and molecular mechanisms by which a subset of these genes function during diaphragm and heart development.

1p36 Deletion Syndrome: Deletions of chromosome 1p36 can cause a variety of birth defects including brain anomalies, eye/vision problems, hearing loss, cardiovascular defects, cardiomyopathy and renal anomalies. Approximately one in 5,000 newborns carry either a terminal or interstitial deletion on chromosome 1p36. The *RERE* and *SPEN* genes are located on chromosome 1p36 and encode transcription factors that play important roles during embryonic development. Using a combination of animal models and data from individuals with deleterious variants affecting *RERE*, we have shown that *RERE* plays a critical role in the development of the brain, eye, inner ear, palate, heart and kidneys. We are actively working to determine the molecular mechanisms by which *RERE* deficiency causes defects in each of these organs and to define the spectrum of defects caused by a lack of *SPEN* function. We are also searching for other genes that contribute to the medical problems seen in individuals with 1p36 deletions.

Other Structural Birth Defects and Neurodevelopmental Phenotypes: We work with physicians and scientists from around the world to identify genes and genomic regions that are associated with other structural birth defects and neurodevelopmental phenotypes including developmental delay, intellectual disability and autism spectrum disorder. Recently, we have used machine learning to aid us in these efforts. This has resulted in the discovery of dozens of low-penetrance genes for a variety of phenotypes.



SELECTED PUBLICATIONS

Rivera-Munoz EA, Zhao XE, Rosenfeld JA, Luna PN, Shaw CA, Posey JE, **Scott DA** (2025). Clinical exome sequencing efficacy and phenotypic expansions involving non-isolated congenital anomalies of kidney and urinary tract (CAKUT+). *Eur J Hum Genet*. doi: 10.1038/s41431-025-01929-3. Epub ahead of print. PMID: 40913078.

Volpi J, Zhao X, Owen N, Evans T, Holder-Espinasse M, (...), **Scott DA** (2025). Non-isolated tetralogy of fallot (TOF+): exome sequencing efficacy and phenotypic expansions. *Eur J Hum Genet*. doi: 10.1038/s41431-025-01916-8. Epub ahead of print. PMID: 40796658.

Robinson K, Singh SK, Walkup RB, Fawwal DV, Adeyemo WL, (...), **Scott DA**, Shaw GM, Thomas MA, Weinberg SM, Brand H, Marazita ML, Lipinski RJ, Murray JC, Cornell RA, Leslie-Clarkson EJ (2025). Rare variants in *PRKCI* cause Van der Woude syndrome and other features of peridermopathy. *Am J Hum Genet*. S0002-9297(25)00318-0. doi: 10.1016/j.ajhg.2025.08.008. Online ahead of print.

Kao EC, Mizerik EA, Bacino CA, Dai H, Vossaert L, **Scott DA** (2025). MED12 Loss-of-Function Variants as a Cause of Congenital Diaphragmatic Hernia in Females With Hardikar Syndrome and Nonspecific Intellectual Disability. *Am J Med Genet A*. 197: e63868.

Waskow ER; Undiagnosed Diseases Network; Emrick LT, Rosenfeld JA, Ketkar S, Burrage LC, **Scott DA** (2024). Recessive loss-of-function variants in *DPH1* identified as the molecular cause in a sibling pair previously diagnosed with Fine-Lubinsky syndrome. *Am J Med Genet A*. e63845.

Früh S, Boudkazi S, Koppensteiner P, Sereikaite V, Chen LY, (...), **Scott DA**, Scheiffele P, Strömgaard K, Tafti M, Gassmann M, Fakler B, Shigemoto R, Bettler B (2024). Monoallelic *de novo* *AJAP1* loss-of-function variants disrupt trans-synaptic control of neurotransmitter release. *Sci Adv*. 10: eadk5462.

Kunissetty B, Martin-Giacalone BA, Zhao X, Luna PN, Brooks BP, Hufnagel RB, Shaw CA, Rosenfeld JA, Agopian AJ, Lupo PJ, **Scott DA** (2024). High Clinical Exome Sequencing Diagnostic Rates and Novel Phenotypic Expansions for Nonisolated Microphthalmia, Anophthalmia, and Coloboma. *Invest Ophthalmol Vis Sci*. 65: 25.

Yankee TN, Oh S, Winchester EW, Wilderman A, Robinson K, Gordon T, Rosenfeld JA, VanOudenhove J, **Scott DA**, Leslie EJ, Cotney J (2023). Integrative analysis of transcriptome dynamics during human craniofacial development identifies candidate disease genes. *Nat Commun*. 14: 4623.

Hernández-García A, Pendleton KE, Kim S, Li Y, Kim BJ, Zaveri HP, Jordan VK, Berry AM, Ljungberg MC, Chen R, Lanz RB, **Scott DA** (2023). *SOX7* deficiency causes ventricular septal defects through its effects on endocardial-to-mesenchymal transition and the expression of *Wnt4* and *Bmp2*. *Hum Mol Genet*. 32: 2152-2161.

FRITZ SEDLAZECK, PH.D.

Associate Professor, Department of Molecular and Human Genetics
Faculty Member, Human Genome Sequencing Center

Dr. rer. nat., Bioinformatics, University of Vienna

Dipl. Ing. (FH), Bioinformatics, Upper Austria University of Applied Sciences, Hagenberg

RESEARCH INTERESTS

My research focuses on the identification of coding and non-coding complex variations and their impact on evolution and diseases across a multitude of organisms, with a focus on human diseases. My training in genomics started in 2008, when I started my Ph.D. in computational biology where I designed algorithms to investigate genomic variability of model and non-model organisms through the alignment of short reads. Throughout my entire career, I have been intrigued to investigate genomic variability across tissues, as well as within populations and across populations. This drove my training and investigation into the impact of such variability. To assess these, I collaborated and initiated efforts to determine which technologies or methodologies were most appropriate to discover variations of different forms, as well as the biases that they contain. This work recently led to novel insights in structural variations and their genotypic and phenotypic impact on cardiovascular, Mendelian and neurological diseases and other organisms. My group and I continue to drive the understanding around SVs and their impact on phenotypes in human diseases and across other organisms.

Over my young career as a scientist, I followed a clear path to investigate genomic variability starting with SNPs and focusing over the last 5 years on structural variations.



SELECTED PUBLICATIONS

Rozowsky J, Gao J, Borsari B, Yang YT, Galeev T, (...), **Sedlazeck FJ**, (...), Guigó R, Gingeras TR, Gerstein M (2023). The EN-TE_x resource of multi-tissue personal epigenomes & variant-impact models. **Cell**. 186: 1493-1511. e40.

Olson ND, Wagner J, Dwarshuis N, Miga KH, **Sedlazeck FJ**, Salit M, Zook JM (2023). Variant calling and benchmarking in an era of complete human genome sequences. **Nat Rev Genet**. 24: 464-483.

Wojcik MH, Reuter CM, Marwaha S, Mahmoud M, Duyzend MH, (...), Genomics Research to Elucidate the Genetics of Rare Diseases (GREGoR) Consortium; (...), **Sedlazeck FJ**, Miller DE (2023). Beyond the exome: what's next in diagnostic testing for Mendelian conditions. **Am J Hum Genet**. 110: 1229-1248.

Nurk S, Koren S, Rhie A, Rautiainen M, Bzikadze AV, (...), **Sedlazeck FJ**, (...), Eichler EE, Miga KH, Phillippy AM (2022). The complete sequence of a human genome. **Science**. 376: 44-53.

Gorzynski JE, Goenka SD, Shafin K, Jensen TD, Fisk DG, (...), **Sedlazeck FJ**, Carroll A, Paten B, Ashley EA (2022). Ultrarapid Nanopore Genome Sequencing in a Critical Care Setting. **N Engl J Med**. 386: 700-702.

Mahmoud M, Doddapaneni H, Timp W, **Sedlazeck FJ** (2021). PRINCESS: comprehensive detection of haplotype resolved SNVs, SVs, and methylation. **Genome Biol**. 22: 268.

Lee I, Razaghi R, Gilpatrick T, Molnar M, Gershman A, Sadowski N, **Sedlazeck FJ**, Hansen KD, Simpson JT, Timp W (2020). Simultaneous profiling of chromatin accessibility and methylation on human cell lines with nanopore sequencing. **Nat Methods**. 17: 1191-1199.

Zarate S, Carroll A, Mahmoud M, Krasheninina O, Jun G, Salerno WJ, Schatz MC, Boerwinkle E, Gibbs RA, **Sedlazeck FJ** (2020). Parliament2: Accurate structural variant calling at scale. **Gigascience**. 9: gaaa145.

Luo R, **Sedlazeck FJ**, Lam TW, Schatz MC (2019). A multi-task convolutional deep neural network for variant calling in single molecule sequencing. **Nat Commun**. 10: 998.

Sedlazeck FJ, Rescheneder P, Smolka M, Fang H, Nattestad M, von Haeseler A, Schatz MC (2018). Accurate detection of complex structural variations using single-molecule sequencing. **Nat Methods**. 15: 461-468.

Sedlazeck FJ, Lee H, Darby CA, Schatz MC (2018). Piercing the dark matter: bioinformatics of long-range sequencing and mapping. **Nat Rev Genet**. 19: 329-346.

GAD SHAULSKY, PH.D.

Professor and Vice Chair for Graduate Education, Department of Molecular and Human Genetics

Director, Graduate Program in Genetics & Genomics

Faculty Member, Graduate Programs in Genetics & Genomics and Immunology & Microbiology

Professor, Department of Education, Innovation and Technology

Assistant Dean, Graduate School of Biomedical Sciences

Ph.D., Weizmann Institute of Science

Postdoc, University of California, San Diego

RESEARCH INTERESTS

Allorecognition: Investigating the mechanisms that underlie *Dictyostelium* kin discrimination revealed two polymorphic cell-surface proteins, TgrB1 and TgrC1, which are required for allorecognition (Benabentos, 2009). The sequence polymorphism is sufficient to explain allorecognition in *Dictyostelium* (Hirose, 2011) and this kin-recognition system protects cooperators against cheaters (Ho, 2013). We are investigating the mechanisms that regulate allorecognition under the hypothesis that TgrB1 and TgrC1 function as a ligand-receptor pair (Hirose, 2017), which is at the top of a signal transduction cascade that regulates development and allorecognition. We used genetic suppressor analysis to identify elements that mediate the TgrB1-C1 signal transduction, including the *rapgapB* signal transduction gene (Li, 2016). We recently found that TgrB1 and TgrC1 are components of a greenbeard mechanism: activation of TgrB1 induces altruistic behavior, inactivation of TgrB1 causes cheating (Katoh-Kurasawa, 2024), and inactivation of RapGAPB causes falsebeard cheating (Lehmann, 2024).

The evolution of social behavior in *Dictyostelium*: Social organisms must deal with cheaters - individuals that reap the benefits of sociality without paying the full cost. In *Dictyostelium*, some cells sacrifice themselves and benefit others that may be genetically different, providing a fertile ground for cheating. We found over 100 genes that participate in social interactions (Santorelli, 2008), characterized some of the underlying mechanisms, and tested how cooperators resist cheating (Khare and Shaulsky, 2006; Khare, 2009; Khare and Shaulsky, 2010). We are investigating the role of the TgrB1-C1 pathway in cheating (Katoh-Kurasawa, 2024; Lehmann, 2024).

Functional Genomics: We use transcriptomes to discover gene function in *Dictyostelium* (Booth, 2005; Van Driessche, 2007). We have shown that the transcriptome is a good phenotyping tool for discovering epistatic relationships (Van Driessche, 2005). Using RNA-seq, we compared the developmental transcriptomes of *D. discoideum* and *D. purpureum*, two species that diverged ~350MYA, but whose developmental morphologies are similar. We found vast similarities between the two transcriptomes (Parikh, 2010). We analyzed many mutants, and we developed a system for analysis of transcription factors with RNA-seq and ChIP-seq (Santhanam, 2015). We found complex regulation of transcriptional activity during development (Rosengarten, 2015) and described the long-non-coding transcriptome (Rosengarten, 2017). We analyzed the major transcriptional transitions that characterize *Dictyostelium* development using RNA-seq profiles of 20 mutants (Katoh-Kurasawa, 2021). We are also developing tools for *Dictyostelium* genome exploration, including a deep coverage genomic DNA library (Rosengarten, 2015), gene discovery by chemical mutagenesis at low level and whole-genome sequencing to identify mutations (Li, 2016), and an adaptation of GoldenBraid as a synthetic biology tool for *Dictyostelium* (Kundert, 2020).

Data Mining: We are collaborating with Dr. Zupan's group at the University of Ljubljana, Slovenia, to develop new concepts in genetic analysis. We have developed a tool that performs automated epistasis analysis, GenePath (Demsar, 2001). We developed a gene-function prediction system that relies on compressive data fusion and chaining and demonstrated its utility in predicting the function of bacterial-recognition genes in *D. discoideum* (Zitnik, 2015). We developed dictyExpress, a web tool that can access and analyze transcriptome data (Stajdohar, 2017). We also developed scOrange, a tool for analyzing single cell RNA-seq data (Stražar, 2019) and an image analysis platform that utilizes deep models in a visual programming environment (Godec, 2019).



SELECTED PUBLICATIONS

Lehmann P, Katoh-Kurasawa M, Kundert P, **Shaulsky G** (2024). Going against the family: Perturbation of a greenbeard pathway leads to falsebeard cheating. *iScience* 27: 111125.

Katoh-Kurasawa M, Lehmann P, **Shaulsky G** (2024). The greenbeard gene *tgrB1* regulates altruism and cheating in *Dictyostelium discoideum*. *Nat Commun*. 15: 3984.

Katoh-Kurasawa M, Hrovatin K, Hirose S, Webb A, Ho HI, Zupan B, **Shaulsky G** (2021). Transcriptional milestones in *Dictyostelium* development. *Genome Res* 31: 1498-1511.

Kundert P, Sarrion-Perdigones A, Gonzalez Y, Katoh-Kurasawa M, Hirose S, Lehmann P, Venken KJT, **Shaulsky G** (2020). A GoldenBraid cloning system for synthetic biology in social amoebae. *Nucleic Acids Res*. 48: 4139-4146.

Hirose S, Chen G, Kuspa A, **Shaulsky G** (2017). The polymorphic proteins TgrB1 and TgrC1 function as a ligand-receptor pair in *Dictyostelium* allorecognition. *J Cell Sci*. 130: 4002-4012.

Cai H, Katoh-Kurasawa M, Muramoto T, Santhanam B, Long Y, Li L, Ueda M, Iglesias PA, **Shaulsky G**, Devreotes PN (2014). Nucleocytoplasmic shuttling of a GATA transcription factor functions as a development timer. *Science*. 343: 1249531.

Hirose S, Benabentos R, Ho HI, Kuspa A, **Shaulsky G** (2011). Self-recognition in social amoebae is mediated by allelic pairs of tiger genes. *Science*. 333: 467-70.

Parikh A, Miranda ER, Katoh-Kurasawa M, Fuller D, Rot G, Zagar L, Turk T, Sugang R, Chen R, Zupan B, Loomis WF, Kuspa A, **Shaulsky G** (2010). Conserved developmental transcriptomes in evolutionarily divergent species. *Genome Biol*. 11: R35.

Khare A, Santorelli LA, Strassmann JE, Queller DC, Kuspa A, **Shaulsky G** (2009). Cheater-resistance is not futile. *Nature*. 461: 980-2.

Santorelli LA, Thompson CRL, Villegas E, Svetz J, Dinh C, Parikh A, Sugang R, Kuspa A, Strassmann JE, Queller DC, **Shaulsky G** (2008). Facultative cheater mutants reveal the genetic complexity of cooperation in social amoebae. *Nature*. 451: 1107-10.

CHAD SHAW, PH.D.

Professor, Department of Molecular and Human Genetics

Joint Professor of Statistics and Director of D2K Laboratory, Rice University

Investigator, Jan and Dan Duncan Neurological Research Institute

Faculty Member, Stem Cells and Regenerative Medicine (STaR) Center and

Graduate Program in Quantitative & Computational Biosciences

Ph.D., Mathematical Statistics, Rice University

RESEARCH INTERESTS

Chad Shaw is trained as a mathematical statistician, and he has worked in statistical genomics and bioinformatics for approximately 20 years. He is currently a professor of molecular and human genetics at Baylor and a joint professor of statistics at Rice University. He is also the Director of the D2K Laboratory at Rice University. He has experience in next-generation sequencing, variant analysis, multi-omic data integration, gene expression profiling and variant functionalization. He also has expertise in copy-number analysis and has worked in the area of mechanistic studies of structural variation, with a focus on the role of repetitive elements in new mutations.

He led the development and analysis of an applied probabilistic model for the transmission of new mutations in the context of human genetic disease, which led to the elucidation of the dependency of recurrence risk on parent of origin, parental somatic mosaicism and paternal age. This fundamental contribution to human genetics was featured in many reviews and in the New York Times as a lay press article.

He has been an author on approximately 200 peer-reviewed publications, and his work has been cited approximately 17,000 times. He has trained 5 Ph.D. students in his own laboratory and over 10 students as a thesis committee member. He serves as chairman of the qualifying exam committee for the Quantitative and Computational Biosciences program. His students have performed methodologic research in high dimensional sparse regression, statistical methods for high throughput NGS screens approaches to modifiers of Mendelian disease, eQTL analyses and software tools for variant prioritization in rare disease diagnostics.



SELECTED PUBLICATIONS

Ghazi AR, Kong X, Chen ES, Edelstein LC, **Shaw CA** (2020). Bayesian modelling of high-throughput sequencing assays with malacoda. **PLoS Comput Biol.** 16: e1007504. doi: 10.1371/journal.pcbi.1007504.

Yuan, B., Wang, L., Liu, P. et al (2020). CNVs cause autosomal recessive genetic diseases with or without involvement of SNV/indels. **Genet Med.** 22: 1633–1641.

Liu P, Meng L, Normand EA, Xia F, Song X, Ghazi A, Rosenfeld J, Magoulas PL, Braxton A, Ward P, Dai H, Yuan B, Bi W, Xiao R, Wang X, Chiang T, Vetrini F, He W, Cheng H, Dong J, Gijavanekar C, Benke PJ, Bernstein JA, Eble T, Eroglu Y, Erwin D, Escobar L, Gibson JB, Gripp K, Kleppe S, Koenig MK, Lewis AM, Natowicz M, Mancias P, Minor L, Scaglia F, Schaaf CP, Streff H, Vernon H, Uhles CL, Zackai EH, Wu N, Sutton VR, Beaudet AL, Muzny D, Gibbs RA, Posey JE, Lalani S, **Shaw C**, Eng CM, Lupski JR, Yang Y (2019). Reanalysis of Clinical Exome Sequencing Data. **N Engl J Med.** 380: 2478-2480.

Beck CR, Carvalho CMB, Akdemir ZC, Sedlazeck FJ, Song X, Meng Q, Hu J, Doddapaneni H, Chong Z, Chen ES, Thornton PC, Liu P, Yuan B, Withers M, Jhangiani SN, Kalra D, Walker K, English AC, Han Y, Chen K, Muzny DM, Ira G, **Shaw CA**, Gibbs RA, Hastings PJ, Lupski JR (2019). Megabase Length Hypermutation Accompanies Human Structural Variation at 17p11.2. **Cell.** 176: 1310-1324.e10.

JOSHUA M. SHULMAN, M.D., PH.D.

Effie Marie Cain Chair in Alzheimer's Disease Research

Professor, Departments of Molecular and Human Genetics, Neurology, and Neuroscience

Faculty Member, Graduate Programs in Genetics & Genomics and Neuroscience

Director, Center for Alzheimer's and Neurodegenerative Diseases

Co-Director, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital

Ph.D., University of Cambridge

M.D., Harvard Medical School

Resident in Neurology, Brigham & Women's Hospital, Massachusetts General Hospital

Movement/Memory Disorders Fellow, Brigham & Women's Hospital, Massachusetts General Hospital

RESEARCH INTERESTS

Our research integrates genetic and genomic investigation in human subjects and model organisms, with the goal of understanding brain function and aging and improving the treatment of neurologic disease. We focus on Alzheimer's disease and Parkinson's disease, two incurable neurodegenerative disorders and experimental paradigms for the age-dependent failure of brain cognitive and motor control in humans.

Human Genetics: The clinical manifestation of neurodegenerative disease is the culmination of a multi-tiered pathogenic cascade that evolves over decades—understanding how genetic variants impact this causal chain is essential. We are therefore investigating the impact of genomic variation on directly measured Alzheimer's and Parkinson's disease pathology and related biomarkers, including quantitative measures of motor impairment based on assessments with biosensor devices. We are also deploying whole genome sequencing in the Alzheimer's and Parkinson's disease clinics and returning results to patients and families for precision medicine applications. Lastly, we are actively exploring links between inherited pediatric lysosomal disorders and oligogenic risk for late-onset, adult neurodegenerative diseases.

Drosophila Genetics: Despite the promise of current human genomic strategies, such as genome-wide association studies, next-generation sequencing, and gene expression profiling, they often fail to definitively identify disease causal genes and variants. Therefore, we are taking advantage of the rapid and powerful genetics available in the fruit fly, *Drosophila melanogaster*, in order to accelerate the validation of responsible genes and understanding of relevant mechanisms. The expression of human amyloid-beta, Tau, or alpha-synuclein proteins in the fly nervous system recapitulates many core features of Alzheimer's disease and Parkinson's disease pathogenesis. We are testing candidate human susceptibility genes for functional genetic interactions in these fly models of neurodegeneration. Implicated molecular pathways are probed in greater depth, using both *Drosophila* as well as mouse and human cellular models for translation. Current areas of interest include endolysosomal sorting, RNA metabolism/splicing, neuronal cell adhesion and synaptic mechanisms of neurodegeneration. In order to dissect the dynamic, aging-dependent gene expression changes in brains affected by Alzheimer's and Parkinson's disease, we are also generating and analyzing longitudinal, multi-scale omic datasets from fly and mouse models.



SELECTED PUBLICATIONS

Ye H, Robak LA, Yu M, Cykowski M, **Shulman JM** (2024). Genetics and Pathogenesis of Parkinson's Syndrome. **Annu Rev Pathol.** 18: 95-121.

Yu M, Ye H, De-Paula RB, Mangleburg CG, Wu T, Lee TV, Li Y, Duong D, Phillips B, Cruchaga C, Allen GI, Seyfried NT, Al-Ramahi I, Botas J, **Shulman JM** (2023). Functional screening of lysosomal storage disorder genes identifies modifiers of alpha-synuclein neurotoxicity. **PLoS Genet.** 19: e1010760.

Wu T, Deger JM, Ye H, Guo C, Dhindsa J, Pekarek BT, Al-Ouran R, Liu Z, Al-Ramahi I, Botas J, **Shulman JM** (2023). Tau polarizes an aging transcriptional signature to excitatory neurons and glia. **ELife.** 12: e85251.

Pavešковиć M, De-Paula RB, Ojelade SA, Tantry EK, Kochukov MY, Bao S, Veeraragavan S, Garza AR, Srivastava S, Song SY, Fujita M, Duong DM, Bennett DA, De Jager PL, Seyfried NT, Dickinson ME, Heaney JD, Arenkiel BR, **Shulman JM** (2024). Alzheimer's disease risk gene CD2AP is a dose-sensitive determinant of synaptic structure and plasticity. **Hum Mol Genet.** ddae115.

Mangleburg CG, Wu T, Yalamanchili HK, Guo C, Hsieh YC, Duong DM, Dammer EB, De Jager PL, Seyfried NT, Liu Z, **Shulman JM** (2020). Integrated analysis of the aging brain transcriptome and proteome in tauopathy. **Mol Neurodegener.** 15: 56.

Wan Y-W, Al-Ouran R, Mangleburg CG, (...), Accelerating Medicines Partnership-Alzheimer's Disease Consortium, Liu Z, **Shulman JM**, Mangravite L, Logsdon B (2020). Meta-analysis of the Alzheimer's disease brain transcriptome and functional dissection in mouse models. **Cell Rep.** 32: 107908.

Ye H, Ojelade S, Li-Kroeger D, Zuo Z, Duraine L, He Y, Li Y, Tepass U, Rodal A, Wang L, Bellen HJ, **Shulman JM** (2020). The retromer subunit, VPS29, regulates synaptic transmission and is required for endolysosomal function in the aging brain. **ELife.** 9: e51977

Hsieh Y-C, Guo C, Yalamanchili HK, Abreha M, Al-Ouran R, (...), **Shulman JM** (2019). Tau-mediated disruption of the spliceosome triggers cryptic RNA-splicing and neurodegeneration in Alzheimer's disease. **Cell Rep.** 29: 301-316. e10

Ojelade S, Lee T, Giagtzoglou N, Yu L, Ugur B, (...), **Shulman JM** (2019). Cindr, the *Drosophila* homolog of the Alzheimer's disease risk gene, is required for synaptic transmission and proteostasis. **Cell Rep.** 28: 1799-1813.

Robak LA, Jansen IE, van Rooij J, Uitterlinden AG, Kraaij R, Jankovic J, International Parkinson's Disease Genomics Consortium (IPDGC), Heutink P, **Shulman JM** (2017). Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. **Brain.** 140: 3191-3203.

PAWEL STANKIEWICZ, M.D., PH.D.

Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Program in Genetics & Genomics

M.D., Medical University of Warsaw, Poland

Ph.D., Institute of Mother and Child, Warsaw, Poland

Postdoc, Baylor College of Medicine

Dr. Habil (D.Sc), Institute of Mother and Child, Warsaw, Poland

RESEARCH INTERESTS

Genomic Disorders: The focus of our research is pathogenetics of lung development, and particularly the role of non-coding regulatory elements. We demonstrated that haploinsufficiency of the transcriptional factor *FOXF1* gene on 16q24.1 results in alveolar capillary dysplasia with misalignment of pulmonary veins, a lethal diffuse developmental lung disorder in neonates. We also described the role of the *TBX4* and *FGF10* genes in other lethal developmental lung disorders, including acinar dysplasia and congenital alveolar dysplasia.

We found that somatic mosaicism that also contribute to germline mosaicism is significantly more common than previously thought. We showed that a considerable number of apparently *de novo* mutations causing genomic disorders occur in the previous generation as low-level somatic mosaicism and can thus be recurrently transmitted to future offspring. We also described a “hypermutator phenotype” phenomenon in Fanconi anemia.

We unraveled the complexity of ancestral chromosome 2 fusion in humans, going from 48 to 46 chromosomes in hominin evolution.

We identified the causative role of the *PSMD12*, *BPTF*, *MEF2C*, and *TRIP12* genes and defined the Stankiewicz-Isidor syndrome (OMIM #617516), Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies syndrome (OMIM #617755), Chromosome 5q14.3 deletion syndrome (OMIM #613443), and Clark-Baraitser syndrome (OMIM #617752), respectively.



SELECTED PUBLICATIONS

Szafranski P, Gambin T, Deutsch G, Nassef SA, Bailey MC, Kearney DL, **Stankiewicz P** (2025). The Glu86 Residue in *TBX4* Proves Critical for Human Lung Development. **Am J Med Genet A**. 197(3): e63936.

Zemet R, Du H, Gambin T, Lupski JR, Liu P, **Stankiewicz P** (2023). SNV/indel hypermutator phenotype in biallelic *RAD51C* variant: Fanconi anemia. **Hum Genet**. 142: 721-733.

Poszewiecka B, Gogolewski K, Karolak JA, **Stankiewicz P***, Gambin A* (2023). PhaseDancer: a novel targeted assembler of segmental duplications unravels the complexity of the human chromosome 2 fusion going from 48 to 46 chromosomes in hominin evolution. **Genome Biol**. 24: 205.

Isidor B, (...), Küry S, **Stankiewicz P** (2022). Stankiewicz-Isidor syndrome: expanding the clinical and molecular phenotype. **Genet Med**. 24: 179-91.

Gambin T, Liu Q, Karolak JA, (...), Lupski JR, **Stankiewicz P** (2020). Low-level parental somatic mosaic SNVs in exomes from a large cohort of trios with diverse suspected Mendelian conditions. **Genet Med**. 22: 1768-1776.

Vincent M, Karolak JA, Deutsch G, (...), Le Caignec C, **Stankiewicz P** (2019). Clinical, Histopathological, and Molecular Diagnostics in Lethal Lung Developmental Disorders. **Am J Respir Crit Care Med**. 200: 1093-101.

Cao Y, Tokita MJ, (...), Liu P, **Stankiewicz P** (2019). A clinical survey of mosaic single nucleotide variants in disease-causing genes detected by exome sequencing. **Genome Med**. 11: 48.

Karolak JA, Vincent M, Deutsch G, Gambin T, (...), Le Caignec C, **Stankiewicz P** (2019). Complex Compound Inheritance of Lethal Lung Developmental Disorders Due to Disruption of the TBX-FGF Pathway. **Am J Hum Genet**. 104: 213-28.

Stankiewicz P, Khan TN, Szafranski P, (...), Davis EE, Yang Y (2017). Haploinsufficiency of the Chromatin Remodeler *BPTF* Causes Syndromic Developmental and Speech Delay, Postnatal Microcephaly, and Dysmorphic Features. **Am J Hum Genet**. 101: 503-15.

Küry S, (...), **Stankiewicz P***, Isidor B* (2017). De Novo Disruption of the Proteasome Regulatory Subunit *PSMD12* Causes a Syndromic Neurodevelopmental Disorder. **Am J Hum Genet**. 100: 352-63.



V. REID SUTTON, M.D.

Professor and Vice Chair for Graduate Medical Education, Department of Molecular and Human Genetics

Director, Medical Genetics Residency & Fellowship Programs

Director, Inborn Errors of Metabolism Service, Texas Children's Hospital

Medical Director, Biochemical Genetics Laboratory, Baylor Genetics

M.D., University of Kentucky

Resident, Pediatrics, Washington University in Saint Louis

Fellow, Medical Genetics & Clinical Biochemical Genetics, Baylor College of Medicine

RESEARCH INTERESTS

I have committed myself to advance scientific knowledge and patient care by applying my clinical skills to research questions. I have employed my knowledge and expertise in the diagnosis of genetic syndromes, dysmorphology, genetic mechanisms of disease, inborn errors of metabolism and skeletal dysplasias to answer clinical research questions. I have done this in independent studies of my own design as well as many instances of collaborative research with colleagues engaged in the laboratory investigation of Mendelian diseases.

I have made contributions through gene discovery and defining the phenotypic spectrum of a number of syndromes including Uniparental Disomy for Chromosome 14, Aicardi, Goltz, Ankyloblepharon-Ectodermal Dysplasia Clefting (AEC), Robinow and White-Sutton syndromes. I am the clinical geneticist for the Baylor Center for Genomic Research to Elucidate the Genetics of Rare Disorders (GREGoR) which is an NIH/NHGRI-funded study to discover the genetic basis of Mendelian disorders.

In my role as the Medical Director of the Biochemical Genetics Laboratory at Baylor Genetics, I have overseen the development of large-scale metabolomic profiling for the screening and diagnosis of inborn errors of metabolism, and our laboratory is the first in the world to offer metabolomic profiling on a clinical basis, which has led to both advances in care and new discoveries.

I am co-principal investigator for a multi-site longitudinal study of OI that is funded by the NIH (NCATS, NICHD, NIDCR, NIAMS & NIMH) as part of the Brittle Bone Disorders Consortium of the Rare Disease Clinical Research Network. I am also the clinical team liaison for this project.



SELECTED PUBLICATIONS

Snyder MT, Divin K, Liu N, Sun Q, Wang Y, Luo X, Ben-Moshe Y, Burrage LC, **Sutton VR** (2025). Effective algorithm to differentiate NBS MCADD cases from carriers and non-carriers and an assessment of the utility of the second newborn screen for MCADD. **Mol. Genet. Metab.** 145: 109183.

Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Sillence D, Simon M, **Sutton VR**, Warman ML, Superti-Furga A (2023). Nosology of genetic skeletal disorders: 2023 revision. **Am J Med Genet A**. 191: 1164-1209.

Odom JD, **Sutton VR** (2021). Metabolomics in clinical practice: Improving diagnosis and informing management. **Clinical Chemistry**. 67: 1606-1617.

Liu N, Xiao J, Gijavanekar C, Pappan KL, Ginton KE, Shayota BJ, Kennedy AD, Sun Q, **Sutton VR**, Elsea SH (2021). Comparison of untargeted metabolomic profiling vs traditional metabolic screening to identify inborn errors of metabolism. **JAMA Network Open**. 4: e2114155.

Li Y, Tan Z, Zhang Y, (...) **Sutton VR**, Schiff M, Feillet F, Zhang S, Lin C, Yang L (2021). A noncoding RNA modulator potentiates phenylalanine metabolism in mice. **Science**. 373: 662-673.

Shayota BJ, Zhang C, Shypailo RJ, Mazzeu JF, Carvalho CMB, **Sutton VR** (2020). Characterization of the Robinow syndrome skeletal phenotype, bone micro-architecture and genotype-phenotype correlations with the osteosclerotic form. **Am J Med Genet**. 182: 2632-2640.

Murali CN, Slater B, Mussad S, Cuthbertson D, Nguyen D, Turner A, Azamian M, Tosi L, Rauch F, **Sutton VR**, Lee B, Members of the BBD Consortium, Nagamani SCS (2021). Health-related quality of life in adults with osteogenesis imperfecta. **Clin Genet**. 99: 772-779.

White JJ, Mazzeu JF, Coban-Akdemir Z, Bayram Y, Bahrambeigi V, (...), **Sutton VR**, Lupski JR, Carvalho CMB (2018). WNT Signaling Perturbations Underlie the Genetic Heterogeneity of Robinow Syndrome. **Am J Hum Genet**. 102: 27-43.

Eldomery MKI, Akdemir ZC, Vögtle FN, Charng WL, Mulica P, (...) **Sutton VR** (2017). MIPEP recessive variants cause a syndrome of left ventricular non-compaction, hypotonia and infantile death. **Genome Med**. 8: 106.

Posey JE, Harel T, Liu P, Rosenfeld JA, James RA, (...), **Sutton VR**, Shaw CA, Plon SE, Yang Y, Lupski JR (2017). Resolution of disease phenotypes resulting from multilocus genomic variation. **N Engl J Med**. 376: 21-31.

White J, Beck CR, Harel T, Posey JE, Jhangiani SN, (...), **Sutton VR** (2016). POGZ truncating alleles cause syndromic intellectual disability. **Genome Med**. 8: 3.

NICHOLAS TRAN, PH.D.

Assistant Professor, Department of Molecular and Human Genetics

Ph.D., Washington University in St Louis

Postdoc, Harvard University

RESEARCH INTERESTS

The brain is composed of a remarkably diverse set of neuronal cell types that each play a specific role in supporting brain function. When CNS tissues are damaged by injury or disease, this complex machine becomes dysfunctional, often with limited potential for recovery. A curious phenomenon is that in essentially all neurodegenerative conditions, certain cell types are more affected than others. My lab focuses on understanding what happens to different neuronal populations in neurodegenerative conditions using cutting-edge, single-cell genomic approaches. Our model of choice is the retina, the most accessible part of the brain, which we use both to study blinding disorders like glaucoma and to study basic mechanisms of degeneration. Our ultimate mission is to identify better targets for therapies that protect neurons from degeneration and stimulate axon regeneration.



SELECTED PUBLICATIONS

Jacobi A*, **Tran NM***, Yan W, Benhar I, Tian F, Schaffer R, He Z, & Sanes, JR. (2022). Overlapping transcriptional programs promote survival and axonal regeneration of injured retinal ganglion cells. **Neuron**. 110: 2625-2645.e7.

Tran NM, Shekhar K, Whitney IE, Jacobi A, Benhar I, Hong G, Yan W, Adiconis X, Arnold ME, Lee JM, Levin JZ, Lin D, Wang C, Lieber CM, Regev A, He Z, Sanes JR (2019). Single-Cell Profiles of Retinal Ganglion Cells Differing in Resilience to Injury Reveal Neuroprotective Genes. **Neuron**. 18: 1039-1055.

Ma J, Chu TK, Polo Prieto M, Park Y, Li Y, Chen R, Mardon G, Frankfort BJ, **Tran NM**. Sample multiplexing for retinal single-cell RNA-sequencing **bioRxiv** [Pre-print] 2024.04.23.589797; doi: 10.1101/2024.04.23.589797

Zapadka TE, **Tran NM**, Demb JB. Optic nerve injury impairs intrinsic mechanisms underlying electrical activity in a resilient retinal ganglion cell. **bioRxiv** [Pre-print] 2024.02.20.581201; doi: 10.1101/2024.02.20.581201

Li J, Choi J, Cheng X, Ma J, Pema S, Sanes JR, Mardon G, Frankfort BJ, **Tran NM**, Li Y, Chen R (2024). Comprehensive single-cell atlas of the mouse retina. **iScience** 27: 109916.

Wood CA, **Tran NM** (2024). Cell-type resolved transcriptomic approaches for dissecting selective vulnerability in neurodegeneration. **Neural Regen Res**. 19: 1411-1413.

Yan W, Laboulaye MA, **Tran NM**, Whitney IE, Benhar I, Sanes JR (2020). Mouse Retinal Cell Atlas: Molecular Identification of over Sixty Amacrine Cell Types. **J. Neurosci**. 40: 5177-5195.

Shekhar K, Lapan SW, Whitney IE, **Tran NM**, Macosko EZ, Kowalczyk M, Adiconis X, Levin JZ, Nemesh J, Goldman M, McCarroll SA, Cepko CL, Regev A, Sanes JR (2016). Comprehensive Classification of Retinal Bipolar Neurons by Single-Cell Transcriptomics. **Cell**. 166: 1308-1323.

Lindborg JA, **Tran NM**, Chenette DM, DeLuca K, Foli Y, Kannan R, Sekine Y, Wang X, Wollan M, Kim IJ, Sanes JR, Strittmatter SM (2021). Optic nerve regeneration screen identifies multiple genes restricting adult neural repair. **Cell Rep**. 34: 108777.

Peng YR, **Tran NM**, Krishnaswamy A, Kostadinov D, Martersteck EM, Sanes JR (2017). Satb1 Regulates Contactin 5 to Pattern Dendrites of a Mammalian Retinal Ganglion Cell. **Neuron**. 95: 869-883.



MICHAEL WANGLER, M.D.

Associate Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Programs in Development, Disease Models & Therapeutics and Genetics & Genomics

M.D., Baylor College of Medicine
Residency, Pediatrics, Baylor College of Medicine Affiliate Hospitals
Residency, Medical Genetics, Baylor College of Medicine

RESEARCH INTERESTS

Molecular and Developmental Mechanisms of Mendelian Disorders

Our lab studies rare human disease phenotypes to gain insight into general principles of human health. Methods include clinical studies in rare disease, genomics and model organism genetics particularly *Drosophila melanogaster*. We are currently using *Drosophila* to study Mendelian disorders and their underlying genetic and developmental mechanisms in two major efforts:

1) Model Organisms and the Molecular Pathogenesis of Mendelian Disorders: We use *Drosophila* models for diagnostic paradigms. We are part of the Model Organisms Screening Center (MOSC) for the Undiagnosed Diseases Network (UDN). We also use these methods in underserved populations in Texas called Community TEXOME.

2) Mendelian Disorders of the Peroxisome and Organelle Dynamics: Peroxisomes are fundamental sub-cellular organelles present in all eukaryotic cells. We use clinical and *Drosophila* studies in the elucidation of mechanisms of Peroxisomal Biogenesis Disorders- Zellweger Spectrum disorders (PBD-ZSD). These diseases are expanding from autosomal recessive disorders to a broad range of human diseases related to peroxisomes.



SELECTED PUBLICATIONS

Vuocolo B, German RJ, Lalani SR, Murali CN, Bacino CA, (...), Liu P, Bellen H, **Wangler MF*** (2024). Improving access to exome sequencing in a medically underserved population through the Texome Project. **Genet Med.** 26: 101102. *Corresponding Author.

Huang Y, Jay KL, Huang AY, Wan J, Jangam SV, (...), **Wangler MF***, Martinez-Agosto JA* (2024). Loss-of-function in RBBP5 results in a syndromic neurodevelopmental disorder associated with microcephaly. **Genet Med.** 26: 101218. *Corresponding Author.

Jangam SV, Briere LC, Jay KL, Andrews JC, Walker MA, Rodan LH, High FA, Yamamoto S, Sweetser DA, **Wangler MF***. A *de novo* missense variant in EZH1 associated with developmental delay exhibits functional deficits in *Drosophila melanogaster*. **Genetics.** 2023 Aug 9;224(4). *Corresponding Author.

Wangler MF, Lesko B, Dahal R, Jangam S, Bhadane P, Wilson TE, McPheron M, Miller MJ (2023). Dicarboxylic acylcarnitine biomarkers in peroxisome biogenesis disorders. **Mol Genet Metab.** 140: 107680.

Marcogliese PC, Deal SL, Andrews J, Harnish JM, (...) **Wangler MF***, Yamamoto S* (2022). *Drosophila* functional screening of *de novo* variants in autism uncovers damaging variants and facilitates discovery of rare neurodevelopmental diseases. **Cell Rep.** 38: 110517. *Corresponding Author.

Graves HK, Jangam S, Tan KL, Pignata A, Seto ES, Yamamoto S, **Wangler MF*** (2020). A Genetic Screen for Genes That Impact Peroxisomes in *Drosophila* Identifies Candidate Genes for Human Disease. **G3 (Bethesda).** 10: 69-77. *Corresponding Author

Assia Batzir N, Bhagwat PK, Eble TN, Liu P, Eng CM, (...) **Wangler MF*** (2019). *De novo* missense variant in the GTPase effector domain (GED) of *DNM1L* leads to static encephalopathy and seizures. **Cold Spring Harb Mol Case Stud.** 5: a003673. *Corresponding Author

Splinter K, Adams DR, Bacino CA, Bellen HJ, Bernstein JA, (...) **Wangler MF**, Westerfield M, Wheeler MT, Wise AL, Worthey EA, Yamamoto S, Ashley EA (2018). Undiagnosed Diseases Network. Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease. **N Engl J Med.** 379: 2131-2139.

Wangler MF*, Hubert L, Donti TR, Ventura MJ, Miller MJ, (...) Elsea SH (2018). A metabolomic map of Zellweger spectrum disorders reveals novel disease biomarkers. **Genet Med.** 20: 1274-1283. *Corresponding Author

Yamamoto S, Jaiswal M, Chang WL, Gambin T, (...), Lupski JR, **Wangler MF***, Bellen HJ* (2014). A *Drosophila* genetic resource of mutants to study mechanisms underlying human genetic diseases. **Cell.** 159: 200-214. *Corresponding Author

THOMAS F. WESTBROOK, PH.D.

Robert A. Welch Chair in Chemistry
Emeritus McNair Scholar

Professor, Departments of Molecular and Human Genetics and Biochemistry & Molecular Biology

Faculty Member, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

Ph.D., University of Rochester School of Medicine
Postdoc, Harvard Medical School

RESEARCH INTERESTS

Cancers are driven by genomic and epigenetic alterations that result in the activation of cellular proto-oncogenes and the inactivation of tumor suppressor genes. Although high-throughput genomic approaches have begun to establish extensive catalogs of gene alterations in human tumors, the genes that control tumor genesis, progression, and response to therapies are often concealed by the complex chromosomal instability in cancer cell genomes. This challenge is exacerbated by the lack of functional annotation for the vast majority of genes in the human genome. Thus, functional approaches are critical for identifying the genetic programs underlying cancer pathogenesis. Our laboratory applies genome-wide RNA interference (RNAi) and other technologies to the unbiased discovery of cancer genes and networks. Specifically, we focus on two areas of cancer gene discovery:

Discovering new oncogene-induced “stress pathways” and translating these pathways into cancer therapies: The cancer community has largely studied the effects of oncogenes and tumor suppressors and how they contribute to the “pro-tumorigenic” hallmarks of cancer cells. However, it has also become clear that oncogenes themselves induce a variety of stresses in cancer cells such as metabolic reprogramming, oxidative pressures, mitotic instability, and proteomic imbalance. These stress phenotypes, sometimes collectively referred to as **oncogenic stress**, can serve to antagonize tumor growth and survival. The idea that oncogenes confer a highly stressed state onto cancer cells predicts that strategies to exacerbate one or more of these oncogene-induced stresses may tilt this balance in favor of killing cancer cells. We have been interested in exploiting the idea of oncogene-induced stresses for therapeutic discovery by tackling 3 poorly understood questions: (1) what are the molecular mechanisms by which prominent oncogenes (ex. Myc, Ras, etc.) induce these stresses? (2) how do cancer cells tolerate these stresses? and (3) are these stress support pathways different in normal and tumor cells? By using forward genetic approaches, we have made surprising discoveries about the endogenous cell pathways that are required to tolerate predominant oncogenic drivers like c-Myc (ex. Kessler *et al.*, *Science* 2012). We are now extending these studies by elucidating the stress support pathways that enable cancer cells to tolerate other prominent drivers.

Identifying new oncogene / tumor suppressor networks via functional genetic screens: With the explosion of genomic data emerging from TCGA, COSMIC, and other annotations of cancer genomes, there are fundamental challenges in (1) discerning which mutant genes are critical cancer drivers, (2) how these drivers are connected in genetic / signaling networks, and (3) how these cancer gene networks can be exploited for new therapies. We are addressing these important questions by developing genetic screens in human and mouse systems for new cancer gene networks. By combining new genetic technologies and engineered cell systems, we are uncovering new tumor suppressors (PTPN12, REST, INPP4B, etc.) and oncogenes (PLK1, TEX14, etc.) that control tumor initiation and progression (ex. Westbrook *et al.*, *Nature* 2008; Sun *et al.*, *Cell* 2011; Pavlova *et al.*, *eLife* 2013). Through orthogonal studies, we have assembled these cancer genes into interconnected networks and uncovered new entrypoints for cancer therapies. For example, our group discovered a new tumor suppressor network that is disrupted in more than 70% of aggressive triple-negative breast cancers (TNBCs), with the tyrosine phosphatase PTPN12 acting as a core component of this network. Importantly, disruption of this tumor suppressor network leads to the concerted hyper-activation of a class of receptor tyrosine kinases. These kinases work together to drive TNBC and probably other cancers. Importantly, we have shown that pharmacologic inhibition of these collaborating kinases leads to tumor regression of primary TNBCs *in vivo*. We are currently dissecting the mechanism(s) by which these signaling pathways cooperate, and translating these discoveries into new clinical trials for TNBC patients at Baylor.

**SELECTED PUBLICATIONS**

Hsu TYT, et al. (2015). The spliceosome is a therapeutic vulnerability in Myc-driven cancer. **Nature**. 525: 384-388.

Mahamdallie SS, et al. (2015). Mutations in the transcriptional repressor REST predispose to Wilms tumor. **Nat Genet**. 47: 1471-1474.

Welte T, et al. (2016). Oncogenic mTOR signaling promotes myeloid-derived suppressor cell accumulation and links tumor-initiating capacity to immunosuppression. **Nat Cell Biol**. 18: 632-44.

Wang H, et al. (2015). The Osteogenic Niche Promotes Early-Stage Bone Colonization of Disseminated Breast Cancer Cells. **Cancer Cell**. 27: 193-210.

Izhar L, et al. (2015). A systematic analysis of factors localized to damaged chromatin reveals PARP-dependent recruitment of transcription factors. **Cell Rep**. 11: 1486-1500.

Karlin KL, et al. (2014). The oncogenic STP axis promotes human breast cancer via degradation of the REST tumor suppressor. **Cell Rep**. 9: 1318-1332.

Terunuma A, et al. (2014). MYC-driven 2-hydroxyglutarate is associated with breast cancer prognosis. **JCI**. 124: 398-412.

Park J, et al. (2013). RAS-MAPK-MSK1 pathway modulates ataxin 1 protein levels and toxicity in SCA1. **Nature**. 498: 325-331.

Cheung WKC, et al. (2013). Control of Alveolar Differentiation by the Lineage Transcription Factors GATA6 and HOPX Inhibits Lung Adenocarcinoma Metastasis. **Cancer Cell**. 23: 725-738.

Pei Y, et al. (2012). An animal model of Myc-driven medulloblastoma. **Cancer Cell**. 21: 155-67.

Kessler JD, et al. (2012). A sumoylation-dependent transcriptional subprogram is required for Myc-driven tumorigenesis. **Science**. 335: 348-53.

Sun T, et al. (2011). Activation of multiple proto-oncogenic tyrosine kinases in breast cancer via loss of the PTPN12 phosphatase. **Cell**. 144: 703-18.

KIM C. WORLEY, PH.D.

Professor and Vice Chair for Research Affairs - Basic and Translational,
Department of Molecular and Human Genetics
Faculty Member, Human Genome Sequencing Center
Chair, BCM Faculty Senate

B.S., Massachusetts Institute of Technology

Ph.D., Baylor College of Medicine

Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

My research interests center on building, annotating, understanding and making use of genomes. I have coordinated research in large multi-institutional international research consortia, including analysis and publication of research results for the Human Genome Project, Human Microbiome Project, and comparative genomics projects for over 40 animal species. For these projects, I had a role in creating genome representations through *de novo* genome assembly, improving genome representation through targeted sequencing and structural variation analysis, and contributing to the understanding of genome function through analysis, annotation and computational methods. The number of sequenced human genomes has increased, and genomes representative of diverse humans have become available, but the challenge of interpreting the impact of personal variation and applying this knowledge in a way that serves individual patients and improves the practice of medicine remains an analytical frontier.

Ongoing research interests include:

All of Us: As a part of the *All of Us Evenings with Genetics* Research Education Program, led by Dr. Debra Murray, I led data science training for researchers to study the *All of Us* data. See <https://www.bcm.edu/departments/molecular-and-human-genetics/engagement-and-equity/all-of-us-evenings-with-genetics-research-program> for program information.

Alzheimer's Disease Sequencing Project Consortium (ADSP): I work with Drs. Olivier Lichtarge, Ismael Al-Ramahi, Juan Botas and Joanna Jankowsky on projects to assess the functional impact of variants in the ADSP data. Read more about the consortium here: <https://www.nia.nih.gov/research/dn/alzheimers-disease-sequencing-project-consortia>.

ClinGen (<https://www.clinicalgenome.org>): I coordinate the variant curation expert panel for X-linked inherited retinal diseases. This project with Drs. Rui Chen and Dick Lewis and other experts is curating variants in genes that cause blinding eye diseases, several of which are targets for gene therapies. There are opportunities to learn and practice variant curation here.

RE-JOIN (Restoring Joint Health and Function to Reduce Pain): This consortium is mapping the network of sensory nerves that connect to the temporomandibular (TMJ) and the knee joints to understand how the types and patterns of sensory neuron networks in joints change with disease and aging. Drs. Brendan Lee, Ben Arenkiel, and Russell Ray lead the Baylor mouse knee joint project. I work with the administrative team and the 'omics working group enabling cross-project communication.

Undiagnosed Diseases Network / Undiagnosed Diseases Center: For this project, I lead the sequence analysis and variant interpretation group. We utilize genome sequencing as well as newer assays (RNAseq, long read sequence data, Hi-C data) to identify causal genomic variants and diagnose undiagnosed patients. Find out more about the Baylor UDC at <https://www.bcm.edu/research/research-centers/undiagnosed-diseases-center>.

Other strategic initiatives: I also work on strategic projects related to genomic data science at Baylor including the Consultagene platform (<https://consultagene.org>), researcher access to genomic data and new sequencing technology implementation.



SELECTED PUBLICATIONS

International Human Genome Sequencing Consortium (2001). Initial sequencing and analysis of the human genome. **Nature**. 409: 860-921.

Gibbs RA, (...), **Worley KC**, (...); Rat Genome Sequencing Project Consortium (2004). Genome sequence of the Brown Norway rat yields insights into mammalian evolution. **Nature**. 428: 493-521.

Honeybee Genome Sequencing Consortium (2006). Insights into social insects from the genome of the honeybee *Apis mellifera*. **Nature**. 443: 931-49.

Margulies EH, (...), **Worley KC**, (...), Sidow A (2007). Analyses of deep mammalian sequence alignments and constraint predictions for 1% of the human genome. **Genome Res**. 7: 760-74.

Bovine Genome Sequencing and Analysis Consortium, Elsik CG*, Tellam RL*, **Worley KC*** (2009). The genome sequence of taurine cattle: a window to ruminant biology and evolution. **Science**. 324: 522-8. *corresponding authors.

Human Microbiome Project Consortium (2012). Structure, function and diversity of the healthy human microbiome. **Nature**. 486: 207-14.

English AC, (...), **Worley KC**, Gibbs RA (2012). Mind the gap: upgrading genomes with Pacific Biosciences RS long-read sequencing technology. **PLoS One**. 7: e47768.

Rogers J, Raveendran M, Harris RA, (...), **Worley KC**; Baboon Genome Analysis Consortium (2019). The comparative genomics and complex population history of *Papio* baboons. **Sci Adv**. 5: eaau6947.

Vanderpool D, et. al. (2020). Primate phylogenomics uncovers multiple rapid radiations and ancient interspecific introgression. **PLoS Biol**. 18: e3000954.

Davenport KM, Bickhart DM, **Worley K**, et. al. (2022). An improved ovine reference genome assembly to facilitate in-depth functional annotation of the sheep genome. **Gigascience**. 11.

Lay E, et. al. (2022). LMOD2-related dilated cardiomyopathy presenting in late infancy. **Am J Med Genet A**. 188: 1858-62.

Coleman JR, Baker JN, Ketkar S, (...), Atkinson EG, Murray DD, Lee B, **Worley KC** (2024). Development and evaluation of a training curriculum to engage researchers on accessing and analyzing the All of Us data. **J Am Med Inform Assoc**. 31: 2857-2868. 2024.

TAO WU, PH.D.

Assistant Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Programs in Genetics & Genomics and Cancer & Cell Biology
CPRIT Scholar in Cancer Research

Ph.D., University of Chinese Academy of Sciences, (Institute of Biophysics, Beijing), China
Postdoc, Yale Stem Cell Center & Department of Genetics, Yale School of Medicine, New Haven, CT

RESEARCH INTERESTS

The Wu Lab is dedicated to understanding how mammalian cells make dynamic decisions in response to internal and external signals in both developmental and disease models. Our long-term goal is to transfer the knowledge from the bench to the bedside. Our current central question is to unearth the molecular mechanisms underpinning cellular plasticity unlocking (CPU) and cell reprogramming. Cellular plasticity (CP) refers to the capacity of cells to transfer their state/identity (ID) and function in response to various signals and environmental stimuli. Therefore, such as the cell ID, CP is an intrinsic property and crucial in embryonic development, tissue repair, aging, and human diseases, such as cancer.

Cancer is a systems biological disease. Despite the development of powerful weapons such as chemotherapies, targeted therapies, and immunotherapies in the past decades, treatment resistance remains a pressing challenge and the leading cause of patient mortality. While acquired resistance can be partially attributed to genetic mutations induced by treatment, it could also be driven by CPU and non-mutational epigenetic reprogramming at specific stages. Epigenetic processes in mammals, such as DNA/RNA methylations and histone modifications, are pivotal for controlling cell ID and CP. The profound alterations of epigenetic markers are common signatures in most types of cancer. In 2022, “Unlocking Phenotypic Plasticity,” underpinned by cancer cell aberrant CPU, has been assigned as one of the new hallmarks of cancer, along with another rising hallmark, “Nonmutational Epigenetic Reprogramming.” However, the underlying molecular mechanisms by which the epigenetic mechanisms govern the CPU and drive the cancer cell adaptation/evolution remain elusive.

In my previous research, we discovered a novel non-canonical mammalian DNA modification, “N6-methyladenine” (6mA), with SMRT-ChIP (3rd-generation single-molecule real-time sequencing with native ChIP) in mouse embryonic stem cells. We also identified ALKBH1 as the major demethylase/eraser of DNA 6mA. Then, we pinpointed that the 6mA and ALKBH1 appear to regulate hypoxia response genes, which are well-known for driving drug resistance development in GBM. After I joined BCM, we developed new chemical-based sequencing methods to quantify 6mA methylation at single-base resolution. DNA 6mA’s readers, writers, and erasers could be novel targets that help to bypass the resistance and boost the first-line therapies.

In addition to epigenetic factors, we also focus on the “dark matter” of the human genome, endogenous retrotransposable elements (ERE). We have found that the human endogenous retrovirus-like elements (HERVs) become aberrantly active in the chemo-treatment adaptation of triple-negative breast cancer (TNBC). Furthermore, our recent findings indicated that a subset of cells with high HERVs activity might transiently mediate the persistence of cancer cells at the early stage of the treatment, and HERVs activity coupled with whole transcriptomic and chromatin landscape reprogramming. Currently, we employ embryonic stem cell and cancer patient-derived organoid (PDO) models to investigate the functional roles of non-canonical targets like EREs in the drug-tolerant persistent (DTP) cancerous cells with holistic approaches (genomics, systems genetics, biochemistry, single-cell multi-omics, and machine learning). In the past five years, we and our multidisciplinary collaborators have been developing new technologies and defining novel yardstick to couple epigenetic mechanisms and CPU.

In other words, we are uniquely positioned to potentially uncover critical pieces of the CP puzzle and design new strategies to overcome treatment resistance. The discovery of novel factors for CP control might lead to the next paradigm-shifting in regenerative medicine and cancer biology.



SELECTED PUBLICATIONS

Li X, Guo S, Cui Y, Zhang Z, Luo X, Angelova MT, Landweber LF, Wang Y, **Wu TP** (2022). NT-seq: a chemical-based sequencing method for genomic methylome profiling. **Genome Biol.** 23: 122.

Li Z*, Zhao S*, Nelakanti RV*, Lin K*, **Wu TP***, et al. (2020). N6-methyladenine in DNA antagonizes SATB1 in early development. **Nature.** 583: 625-630. *Equal contribution

Xie Q*, **Wu TP***, Gimple RC*, et al. (2018). N(6)-methyladenine DNA Modification in Glioblastoma. **Cell.** 175: 1228-1243.e20. *Equal contribution

Wu TP, Wang T, et al. (2016). DNA methylation on N(6)-adenine in mammalian embryonic stem cells. **Nature.** 532: 329-33.

Zhu S, Beaulaurier J, Deikus G, **Wu TP**, et al. (2018). Mapping and characterizing N6-methyladenine in eukaryotic genomes using single-molecule real-time sequencing. **Genome Res.** 28: 1067-1078.

Zhou J, Horton JR, Kaur G, Chen Q, Li X, Mendoza F, **Wu T**, et al. (2023). Biochemical and structural characterization of the first-discovered metazoan DNA cytosine-N4 methyltransferase from the bdelloid rotifer Adineta vaga. **J Biol Chem.** 299: 105017.

Wu T, Liu Y, et al. (2014). Histone variant H2A.X deposition pattern serves as a functional epigenetic mark for distinguishing the developmental potentials of iPSCs. **Cell Stem Cell.** 15: 281-294.

Woodcock CB, Yu D, Hajian T, Li J, Huang Y, Dai N, Corrêa IR Jr, **Wu T**, et al. (2019). Human MettL3-MettL14 complex is a sequence-specific DNA adenine methyltransferase active on single-strand and unpaired DNA in vitro. **Cell Discov.** 5: 63.

Wang R, Zheng Y, Zhang Z, Zhu X, **Wu TP***, Jun Ding*. MATES: A Deep Learning-Based Model for Locus-Specific Quantification of Transposable Elements in Single Cell. **BioRxiv** [Pre-Print] 2024.01.09.574909; doi: <https://doi.org/10.1101/2024.01.09.574909>. *Co-corresponding

Li X, Zhang Z, Luo X, Schrier J, Yang AD, **Wu TP** (2021). The exploration of N6-deoxyadenosine methylation in mammalian genomes. **Protein Cell.** 12: 756-768. [invited review]

SHINYA YAMAMOTO, D.V.M., PH.D.

Associate Professor, Department of Molecular and Human Genetics
Associate Director, Graduate Program in Genetics & Genomics
Faculty Member, Graduate Programs in Development, Disease Models & Therapeutics and Neuroscience

D.V.M., The University of Tokyo/Ministry of Agriculture, Forestry and Fisheries of Japan
Ph.D., Baylor College of Medicine
Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

Many projects in the Yamamoto lab are related to rare and undiagnosed diseases. Over 25 million individuals (about the population of Texas) are affected by rare or ultra-rare diseases in the U.S. alone (>300 million worldwide), and many affected individuals experience a long and winding 'diagnostic odyssey' to try to find out the cause of their disorders. While state-of-the-art genomic technologies such as whole-exome sequencing (WES) and whole-genome sequencing (WGS) may provide answers to a subset of these individuals, many are often left with a handful of candidate genetic variants that require experimental studies to understand their functional consequences. As a co-director/leader and member of the Model Organisms Screening Center (MOSC) of the Undiagnosed Diseases Network (UDN) and Baylor College of Medicine (BCM) Center for Precision Medicine Models (CPMM), my lab utilizes the fruit fly *Drosophila melanogaster* to test whether a genetic variant identified in a patient is the cause of their disease, which is pursued in close collaboration with clinicians and human geneticists across the country and around the world. We also study functional consequences of rare variants linked to common neurological disorders such as Alzheimer's disease and autism spectrum disorders and further leverage *Drosophila* genetics to study disease mechanisms. I also lead or co-lead the development of novel computational tools such as ModelMatcher (<https://www.modelmatcher.net>) and MARRVEL (<http://marvel.org>) through close collaboration with bioinformaticians and programmers at BCM to facilitate rare disease diagnosis, research and collaborations.



SELECTED PUBLICATIONS

Yamamoto S, Kanca O, Wangler MF, Bellen HJ (2024). Integrating non-mammalian model organisms in the diagnosis of rare genetic diseases in humans. **Nat Rev Genet.** 25: 46-60.

Harnish JM, Li L, Rogic S, Poirier-Morency G, Kim SY; Undiagnosed Diseases Network, Boycott KM, Wangler MF, Bellen HJ, Hieter P, Pavlidis P, Liu Z, **Yamamoto S** (2022). ModelMatcher: A scientist-centric online platform to facilitate collaborations between stakeholders of rare and undiagnosed disease research. **Hum Mutat.** 43: 743-759.

Marcogliese PC, Deal SL, Andrews J, Harnish JM, ... , Rosenfeld JA, Marom R, Wangler MF, **Yamamoto S** (2022). *Drosophila* functional screening of *de novo* variants in autism uncovers damaging variants and facilitates discovery of rare neurodevelopmental diseases. **Cell Rep.** 38: 110517.

Salazar JL, Yang SA, Lin YQ, Li-Kroeger D, Marcogliese PC, Deal SL, Neely GG, **Yamamoto S** (2021). *TM2D* genes regulate Notch signaling and neuronal function in *Drosophila*. **PLoS Genet.** 17: e1009962.

Luo X, Schoch K, Jangam SV, Bhavana VH, Graves HK, Kansagra S, Jasien JM, Stong N, Keren B, Mignot C, Ravelli C; Undiagnosed Diseases Network, Bellen HJ, Wangler MF, Shashi V, **Yamamoto S** (2021). Rare deleterious *de novo* missense variants in *RNF2/RING2* are associated with a neurodevelopmental disorder with unique clinical features. **Hum Mol Genet.** 30: 1283-1292.

Liu N, Schoch K, Luo X, Pena LDM, Bhavana VH, Kukolich MK, Stringer S, Powis Z, Radtke K, Mroske C, Deak KL, McDonald MT, McConkie-Rosell A, Markert ML, Kranz PG, Stong N, Need AC, Bick D, Amaral MD, Worthey EA, Levy S; Undiagnosed Diseases Network (UDN), Wangler MF, Bellen HJ, Shashi V, **Yamamoto S** (2018). Functional variants in *TBX2* are associated with a syndromic cardiovascular and skeletal developmental disorder. **Hum Mol Genet.** 27: 2454-2465.

Bellen HJ, **Yamamoto S** (2015). Morgan's legacy: fruit flies and the functional annotation of conserved genes. **Cell.** 163: 12-14.

Yamamoto S, Jaiswal M, Charnig WL, Gambin T, Karaca E, Mirzaa G, Wiszniewski W, Sandoval H, Haelterman NA, Xiong B, Zhang K, Bayat V, David G, Li T, Chen K, Gala U, Harel T, Pehlivan D, Penney S, Vissers LE, de Ligt J, Jhangiani S, Xie Y, et. al. (2014). A *Drosophila* genetic resource of mutants to study mechanisms underlying human genetic diseases. **Cell.** 159: 200-214.

Yamamoto S, Charnig WL, Rana NA, Kakuda S, Jaiswal M, Bayat V, Xiong B, Zhang K, Sandoval H, David G, Wang H, Haltiwanger RS, Bellen HJ (2012). A mutation in EGF repeat-8 of Notch discriminates between Serrate/Jagged and Delta family ligands. **Science.** 338: 1229-32.

BING ZHANG, PH.D.**McNair Scholar**

Professor, Department of Molecular and Human Genetics and Lester and Sue Smith Breast Center

Faculty Member, Graduate Programs in Quantitative and Computational Biosciences and Cancer and Cell Biology

Ph.D., Chinese Academy of Sciences, Shanghai, China

Postdoctoral fellow, University of Tennessee, Knoxville

Postdoctoral fellow, Oak Ridge National Laboratory, Oak Ridge, Tennessee

RESEARCH INTERESTS

Advances in high-throughput sequencing, mass spectrometry, and informatics have transformed cancer research. To harness these innovations, I lead an interdisciplinary research team dedicated to developing advanced data analytical methods that translate the vast amount of cancer omics data into actionable biological and clinical insights. Our work spans three strategic domains: computational proteomics, proteogenomics for precision oncology, and data democratization. Through computational proteomics, we decode the intricate dynamics of proteins and their modifications, which are essential for cellular function and the success of therapeutic interventions. In the realm of precision oncology, we use an integrated proteogenomic approach to elucidate the functional consequences of genetic variations, enhancing the personalization of available therapies and informing new treatment development. Furthermore, we simplify the complexity of cancer data through user-friendly interfaces, providing the scientific community with accessible tools to navigate the ever-expanding cancer data landscape. Our commitment in these areas has spawned data-driven hypotheses that illuminate new biological mechanisms, biomarkers, and therapeutic targets, particularly in the fields of targeted and immunotherapies. In close collaboration with cancer biologists and clinicians, we aim to turn these discoveries into tangible benefits for cancer patients.

**SELECTED PUBLICATIONS**

Savage SR, Yi X, Lei JT, Wen B, Zhao H, Liao Y, Jaehnig EJ, Somes LK, Shafer PW, Lee TD, Fu Z, Dou Y, Shi Z, Gao Q, Hoyos V, Gao Q, **Zhang B** (2024). Pan-cancer proteogenomics expands the landscape of therapeutic targets. **Cell**. 187: 4389-4407.

Yi X, Wen B, Ji S, Saltzman AB, Jaehnig EJ, Lei JT, Gao Q, **Zhang B** (2024). Deep Learning Prediction Boosts Phosphoproteomics-Based Discoveries Through Improved Phosphopeptide Identification. **Mol Cell Proteomics**. 23: 100707.

Savage SR, Zhang Y, Jaehnig EJ, Liao Y, Shi Z, Pham HA, Xu H, **Zhang B** (2024). IDPpub: Illuminating the Dark Phosphoproteome Through PubMed Mining. **Mol Cell Proteomics**. 23: 100682.

Zhang B, Bassani-Sternberg M (2023). Current perspectives on mass spectrometry-based immunopeptidomics: the computational angle to tumor antigen discovery. **J Immunother Cancer**. 11: e007073.

Dou Y, Liu Y, Yi X, Olsen LK, Zhu H, Gao Q, Zhou H, **Zhang B** (2023). SEpPQuant enhances the detection of possible isoform regulations in shotgun proteomics. **Nat Commun**. 14: 5809.

Wen B, **Zhang B** (2023). PepQuery2 democratizes public MS proteomics data for rapid peptide searching. **Nat Commun**. 14: 2213.

Huang C, Chen L, Savage SR, Egeuz RV, Dou Y, (...), Zhang H, **Zhang B**; Clinical Proteomic Tumor Analysis Consortium (2021). Proteogenomic insights into the biology and treatment of HPV-negative head and neck squamous cell carcinoma. **Cancer Cell**. 39: 361-379.

Wen B, Li K, Zhang Y, **Zhang B** (2020). Cancer neoantigen prioritization through sensitive and reliable proteogenomics analysis. **Nat Commun**. 11: 1759.

Vasaikar S, Huang C, Wang X, Petyuk VA, Savage SR, (...), **Zhang B**; Clinical Proteomic Tumor Analysis Consortium (2019). Proteogenomic Analysis of Human Colon Cancer Reveals New Therapeutic Opportunities. **Cell**. 177: 1035-1049.

Zhang B, Wang J, Wang X, Zhu J, Liu Q, Shi Z, Chambers MC, Zimmerman LJ, Shaddox KF, Kim S, Davies SR, Wang S, Wang P, Kinsinger CR, Rivers RC, Rodriguez H, Townsend RR, Ellis MJ, Carr SA, Tabb DL, Coffey RJ, Slebos RJ, Liebler DC; the National Cancer Institute Clinical Proteomics Tumor Analysis Consortium (NCI CPTAC) (2014). Proteogenomic characterization of human colon and rectal cancer. **Nature**. 513: 382-387.

LILEI ZHANG, M.D., PH.D.

Associate Professor, Departments of Molecular and Human Genetics, Internal Medicine and Molecular Physiology and Biophysics
Faculty Member, Graduate Programs in Genetics & Genomics and Development, Disease Models & Therapeutics

M.D., Peking University Health Science Center, Beijing, China

Ph.D., Johns Hopkins University, Baltimore, Maryland

Postdoctoral Fellow, Johns Hopkins University, Baltimore, Maryland

Intern, University Hospitals Case Medical Center, Cleveland, Ohio

Resident, Internal Medicine, University Hospitals Case Medical Center, Cleveland, Ohio

Fellow, Medical Genetics, University Hospitals Case Medical Center, Cleveland, Ohio

Postdoctoral Fellow, Case Western Reserve University, Cleveland, Ohio

RESEARCH INTERESTS

Our overarching mission is to translate the study of genetic and epigenetic regulation of cardiovascular disease into novel therapeutic approaches. One of our research focuses is circadian gene regulation in cardiac remodeling. Our work covers the entire circadian regulatory landscape, from the core clock to the slave clock, to the effectors. We discovered that core clock factor REV-ERB is protective for cardiac pathological remodeling and pharmacological activation of REV-ERB prevents heart failure progression even in late-stages. We recently expanded this finding to both HFrEF and HFpEF models and mechanistically demonstrated that REV-ERB suppressed aberrant gene expression, which is required for heart failure development and progression. This was the first example of treating heart failure by manipulating circadian machineries and shows great promise to complement current standard of care. Our finding is now being accelerated towards IND. We also established the very first cardiac slave clock, KLF15, which controls the circadian ischemia reperfusion injury in the heart via regulating NAD⁺.

Another focus of our laboratory is to study inherited cardiac diseases using induced pluripotent stem cell differentiated cardiomyocyte (iPSC-CM) model. We have recently demonstrated that folate can terminate otherwise lethal and recalcitrant arrhythmia in patients with TANGO2 deficiency disorder. This result corroborates what we have observed in large patient cohort and isolated case reports. Additionally, we use iPSC-CMs combined with genome editing, a battery of high throughput phenotyping and machine learning tools to answer human genetics questions in inherited cardiac diseases, including identifying novel disease genes, interpreting variants, understanding disease mechanisms, and testing novel therapeutic strategies.



SELECTED PUBLICATIONS

Xu W, Cao Y, Stephens SB, Arredondo MJ, Chen Y, Perez W, Sun L, Yu AC, Kim JJ, Lalani SR, Li N, Horrigan FT, Altamirano F, Wehrens XH, Miyake CY, **Zhang L** (2024). Folate as a potential treatment for lethal ventricular arrhythmias in TANGO2-deficiency disorder. **JCI Insight**. 9: e171005.

Miyake CY, Mackenzie SJ, **Zhang L** (2024). Top Stories on arrhythmias in TANGO2 deficiency disorder. **Heart Rhythm**. 21: 707-709.

Xu W, Billon C, Li H, Wilderman A, Qi L, Graves A, Rideb JRDC, Zhao Y, Hayes M, Yu K, Losby M, Hampton CS, Adeyemi CM, Hong SJ, Nasiotis E, Fu C, Oh TG, Fan W, Downes M, Welch RD, Evans RM, Milosavljevic A, Walker JK, Jensen BC, Pei L, Burris T, **Zhang L** (2024). Novel Pan-ERR Agonists Ameliorate Heart Failure Through Enhancing Cardiac Fatty Acid Metabolism and Mitochondrial Function. **Circulation**. 149:227-250.

Xu W, Graves A, Weisz-Hubshman M, Hegazy L, Magyar C, Liu Z, Nasiotis E, Samee MAH, Burris T, Lalani S, **Zhang L** (2023). Assigning pathogenicity for TAB2 variants using a novel scalable functional assay and expanding TAB2 disease spectrum. **Hum Mol Genet**. 32: 959-970.

Miyake CY, Lay EJ, Beach CM, Ceresnak SR, Delauz CM, (...), Xu W, Lalani SR, **Zhang L** (2022). Cardiac crises: Cardiac arrhythmias and cardiomyopathy during TANGO2 deficiency related metabolic crises. **Heart Rhythm**. 19: 1673-1681.

Song S, Tien CL, Cui H, Basil P, Zhu N, Gong Y, Li W, Li H, Fan Q, Min Choi J, Luo W, Xue Y, Cao R, Zhou W, Ortiz AR, Stork B, Mundra V, Putluri N, York B, Chu M, Chang J, Yun Jung S, Xie L, Song J, **Zhang L***, Sun Z* (2022). Myocardial Rev-erb-Mediated Diurnal Metabolic Rhythm and Obesity Paradox. **Circulation**. 145: 448-464. * co-corresponding authors

Zhang L*, Jain MK (2021). Circadian regulation of cardiac metabolism. **J Clin Invest**. 131: e148276. * corresponding author

Xu W, Jain MK, **Zhang L** (2021). Molecular link between circadian clocks and cardiac function: a network of core clock, slave clock, and effectors. **Curr Opin Pharmacol**. 57: 28-40.

Li L, Li H, Tien CL, Jain MK, **Zhang L** (2020). Kruppel-Like Factor 15 Regulates the Circadian Susceptibility to Ischemia Reperfusion Injury in the Heart. **Circulation**. 141: 1427-1429.

Zhang L*, Zhang R, Tien CL, Chan RE, Sugi K, Fu C, Griffin AC, Shen Y, Burris TP, Liao X, Jain MK* (2017). REV-ERB α Ameliorates Heart Failure Through Transcription Repression. **JCI Insight**. 2: e95177. *co-corresponding authors

HUI ZHENG, PH.D.**Huffington Foundation Endowed Chair in Aging**

Professor, Departments of Molecular and Human Genetics and Neuroscience
Faculty Member, Graduate Programs in Development, Disease Models & Therapeutics and Genetics & Genomics
Director, Huffington Center on Aging

Ph.D., Baylor College of Medicine

RESEARCH INTERESTS

Alzheimer's disease (AD) is the most common form of neurodegenerative disorder characterized by the deposition of beta-amyloid plaques and the accumulation of tau tangles. My laboratory has a long-standing interest in basic and translational research on Alzheimer's disease. Our expertise is mouse genetics, and we are known for using sophisticated mouse models and innovative approaches to probe the biology and pathophysiology of AD. Our earlier investigation provided critical insights into the physiological functions of the amyloid precursor protein and presenilins, mutations of which are linked to early-onset AD. Our recent effort has expanded from neurons to glial cells and from amyloid pathology to tau tangles. Our overarching hypotheses are AD is caused by faulty clearance of misfolded proteins and manifested by uncontrolled neuroinflammation. Accordingly, our major projects are focused on the investigation of the autophagy-lysosomal pathway and neuron-immune interaction with the goal to understand the disease mechanisms and to identify new therapeutic targets. Along these lines, we identified a highly selective and potent role of TFEB in the clearance of tau tangles and deciphered cell-autonomous and non-cell-autonomous mechanisms in this process. Additionally, we mapped out a complement C3 and C3aR signaling axis that governs network function and innate immunity in the context of aging, AD and tauopathy. Lastly, we revealed a novel epoxy lipid metabolic pathway that becomes dysregulated in AD and show that targeting this pathway by small molecule inhibitors lead to potent anti-inflammatory and neuroprotective effects, supporting the potential of these inhibitors as AD therapy.

WEBSITE: WWW.BCM.EDU/RESEARCH/LABS/HUI-ZHENG/

**SELECTED PUBLICATIONS**

Wang B, Martini-Stoica H, Qi C, Lu TC, Wang S, Xiong W, Qi Y, Sardiello M, Li H, **Zheng H** (2024). TFEB-vacuolar ATPase signaling regulates lysosomal function and microglia activation in tauopathy. **Nat Neurosci.** 27: 48-62.

Gedam M, Comerota MM, Propson NE, Chen T, Jin F, Wang MC, **Zheng H** (2023). Complement C3aR depletion reverses HIF-1 α -induced metabolic impairment and enhances microglial response to A β pathology. **J Clin Invest.** 133: e167501.

Propson NE, Roy ER, Litvinchuk A, Kohl J, **Zheng H** (2021). Endothelial C3a receptor mediates vascular inflammation and blood-brain barrier permeability during aging. **J Clin Invest.** 131: e140966.

Xu Y, Propson NE, Du S, Xiong W, **Zheng H** (2021). Autophagy deficiency modulates microglial lipid homeostasis and aggravates tau pathology and spreading. **Proc Natl Acad Sci U S A.** 118: e2023418118.

Du S, Jin F, Maneix L, Gedam M, Xu Y, Catic A, Wang MC, **Zheng H** (2021). FoxO3 deficiency in cortical astrocytes leads to impaired lipid metabolism and aggravated amyloid pathology. **Aging Cell.** 20: e13432.

Ghosh A, Comerota MM, Wan D, Chen F, Propson NE, Hwang SH, Hammock BD, **Zheng H** (2020). An epoxide hydrolase inhibitor reduces neuroinflammation in a mouse model of Alzheimer's disease. **Sci Transl Med.** 12: eabb1206.

Xu Y, Du S, Marsh JA, Horie K, Sato C, Ballabio A, Karch CM, Holtzman DM, **Zheng H** (2020). TFEB regulates lysosomal exocytosis of tau and its loss of function exacerbates tau pathology and spreading. **Mol Psychiatry.** 26: 5925-39.

Litvinchuk A, Wan YW, Swartzlander DB, Chen F, Cole A, Propson NE, Wang Q, Zhang B, Liu Z, **Zheng H** (2018). Complement C3aR Inactivation Attenuates Tau Pathology and Reverses an Immune Network Deregulated in Tauopathy Models and Alzheimer's Disease. **Neuron.** 100: 1337-1353.e531.

Martini-Stoica H, Cole AL, Swartzlander DB, Chen F, Wan YW, (...), **Zheng H** (2018). TFEB enhances astroglial uptake of extracellular tau species and reduces tau spreading. **J Exp Med.** 215: 2355-2377.

Lian H, Yang L, Cole A, Sun L, Chiang AC, Fowler SW, Shim DJ, Rodriguez-Rivera J, Taglialetela G, Jankowsky JL, Lu HC, **Zheng H** (2015). NF κ B-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease. **Neuron.** 85: 101-15.

QIAN ZHU, PH.D.

Assistant Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Program in Quantitative and Computational Bioscience

Ph.D., Princeton University

Postdoctoral fellow, Dana-Farber Cancer Institute and Boston Children's Hospital

RESEARCH INTERESTS

Dr. Qian Zhu is interested in studying the role of genetic elements and their chromatin interactions in developmental diseases (sickle cell disease, muscular dystrophy), and in breast cancer.

He integrates large-scale datasets such as chromatin accessibility, transcription factor binding, histone modifications, and 3D chromatin structure data to characterize changes in the chromatin and epigenome during normal cell development, and in diseases when chromatin regulators are mutated or dysfunctional. He is recently interested in the nuclear matrix protein Matrin-3, implicated in skeletal muscle dystrophy and amyotrophic lateral sclerosis. He works with biologists to characterize chromatin rewiring of several developmental loci caused by Matrin3 knockout, which can explain pathological processes seen in muscular dystrophy and ALS patients. It is expected that mutations and knockout studies of Matr3 will provide the context for better understanding the interplay between nuclear matrix organization, chromatin structure, and RNA processing.

His second interest is to characterize the role of genetic elements to breast cancer development. Treatment resistance is still a major problem among breast cancer patients. He is interested in characterizing the genetic elements that underlie treatment resistance and therapy response. Specifically, he would like to characterize the role of chromatin structure rewiring as a mechanism of treatment resistance, and the instances of enhancer hijacking and super enhancer formation seen in rearranged tumors. Variations between individual cancer patients in their chromatin accessibility profiles and epigenomes may govern individuals' response to immunotherapy. These works will require overlaying chromatin structure and epigenome profiles on top of existing database of cancer susceptibility loci to better interpret the role of these loci.

His final interest is in the informatics development for novel spatial multi-omic technologies such as spatial transcriptomics, proteomics, and epigenomics. Further integration of these technologies with images (H&E, IFs) is particularly useful in pathological diagnosis and biomarker development. In his CPRIT-funded project, he will develop methodologies to characterize morphological genes whose expression associate with morphological features extracted from images and conduct morphological-based screening for drugs that can target EMT. Ultimately, the spatial transcriptomic experiments not only can aid in disease diagnosis, but also can guide drug-screening by leveraging image features and morphology-gene associations.



SELECTED PUBLICATIONS

T Liu*, **Q Zhu***, Y Kai, T Bingham, HJ Cha, S Mehta, TM Schlaeger, (...), SH Orkin (2023). Matrin3 mediates differentiation through stabilizing chromatin accessibility and chromatin loop-domain interactions, and YY1 mediated enhancer-promoter interactions. **bioRxiv**. doi: <https://doi.org/10.1101/2023.03.30.534959>. (preprint). *equal contribution.

Cha HJ, Uyan Ö, Kai Y, Liu T, **Zhu Q**, Tothova Z, Botten GA, Xu J, Yuan GC, Dekker J, Orkin SH (2021). Inner nuclear protein Matrin-3 coordinates cell differentiation by stabilizing chromatin architecture. **Nat Commun**. 12: 6241. doi: 10.1038/s41467-021-26574-4.

Eng CL, Lawson M, **Zhu Q**, Dries R, Koulina N, Takei Y, Yun J, Cronin C, Karp C, Yuan GC, Cai L (2019). Transcriptome-scale super-resolved imaging in tissues by RNA seqFISH. **Nature**. 568: 235-239.

Zhu Q, Shah S, Dries R, Cai L, Yuan GC (2018). Identification of spatially associated subpopulations by combining scRNAseq and sequential fluorescence in situ hybridization data. **Nat Biotechnol**. 29: 10.1038/nbt.4260.

Dries R, Zhu Q, Dong R, Eng CL, Li H, Liu K, Fu Y, Zhao T, Sarkar A, Bao F, George RE, Pierson N, Cai L, Yuan GC (2021). Giotto: a toolbox for integrative analysis and visualization of spatial expression data. **Genome Biol**. 22: 78.

Liu N, Hargreaves VV, **Zhu Q**, Kurland JV, Hong J, (...), Xu J, Bulky ML, Orkin SH (2018). Direct Promoter Repression by BCL11A Controls the Fetal to Adult Hemoglobin Switch. **Cell**. 173: 430-442.e17.

Zhu Q, Liu N, Orkin SH, Yuan GC (2019). CUT&RUNTools: a flexible pipeline for CUT&RUN processing and footprint analysis. **Genome Biol**. 20: 192.

Cai W, Huang J, **Zhu Q**, Li BE, Seruggia D, Zhou P, (...), Pu WT, Yuan GC, Orkin SH (2020). Enhancer dependence of cell-type-specific gene expression increases with developmental age. **Proc Natl Acad Sci U S A**. 117: 21450-21458.

Zhu Q, Wong AK, Krishnan A, Aure MR, Tadych A, Zhang R, Corney DC, Greene CS, Bongo LA, Kristensen VN, Charikar M, Li K, Troyanskaya OG (2015). Targeted exploration and analysis of large cross-platform human transcriptomic compendia. **Nat Methods**. 12: 211-4.

Zhu Q, Tekpli X, Troyanskaya OG, Kristensen VN (2020). Subtype-specific transcriptional regulators in breast tumors subjected to genetic and epigenetic alterations. **Bioinformatics**. 36: 994-999.

Aure MR, Leivonen SK, Fleischer T, **Zhu Q**, Overgaard J, (...), Lingjærde OC, Sahlberg KK, Kristensen VN (2013). Individual and combined effects of DNA methylation and copy number alterations on miRNA expression in breast tumors. **Genome Biol**. 14: R126.

ANTHONY WILLIAM ZOGHBI, M.D.

Beth K. and Stuart C. Yudofsky Scholar

Assistant Professor, Departments of Psychiatry and Molecular and Human Genetics

Chief of Psychiatric Genetics, Department of Psychiatry

*B.A., Washington University in St. Louis**M.D., Baylor College of Medicine**Adult Psychiatry Residency, Columbia University Irving Medical Center, New York State Psychiatric Institute**T32 Schizophrenia Research Fellowship, Columbia University Irving Medical Center, New York State Psychiatric Institute***RESEARCH INTERESTS**

The primary goal of our lab is to understand the biological basis of neuropsychiatric disorders and translate those insights into improvements in clinical care, disease risk prediction and novel therapeutic development. To achieve this goal, we combine novel phenotyping strategies (e.g., studying severely affected patients), whole genome sequencing, proteomics, and cutting-edge bioinformatics tools development to identify clinically relevant genetic risk factors and biomarkers across psychiatric disorders.

We are also exploring the role of the immune system in psychiatric disorders. Specifically, we aim to identify autoimmune causes of neuropsychiatric disorders using state-of-the-art autoantibody profiling technologies. By integrating genomic and proteomic technologies with advanced computational and machine learning techniques, we aim to identify actionable diagnostic biomarkers and accelerate therapeutic development to improve the lives of those suffering from these disabling conditions.

**SELECTED PUBLICATIONS**

Zoghbi AW*, McClellan JW*, ..., King MC (2024). An evolutionary perspective on complex neuropsychiatric disease. **Neuron** 112: 7–24.

Zoghbi AW, Lieberman JA, Girgis RR (2022). The neurobiology of duration of untreated psychosis: a comprehensive review. **Mol Psychiatry**. 1–23.

Zoghbi AW, Dhindsa RS, Goldberg TE, Mehrizade A, Wang X, Harms MB, Lieberman JA, Markx S, Goldstein DB (2021). High-impact rare genetic variants in severe schizophrenia. **Proc Natl Acad Sci U S A** 118: e2112560118.

Dhindsa RS, **Zoghbi AW**, Krizay DK, Vasavda C, Goldstein DB (2020). A Transcriptome-Based Drug Discovery Paradigm for Neurodevelopmental Disorders. **Annals of Neurology** 89: 199-211.

Zoghbi AW, Lieberman JA (2018). Alive but Not Well: The Limited Validity but Continued Utility of the Concept of Schizophrenia. **Psychological Medicine** 2: 245-246.

Zoghbi AW, Girgis RR, Javitt DC, Lieberman JA (2018). The Past and Future of Novel Therapeutics for Schizophrenia: A Critical and Comprehensive Review. **Journal of Psychiatric Research** 108: 57-83.

HUDA Y. ZOGHBI, M.D.**Ralph D. Feigin M.D. Endowed Chair****Distinguished Service Professor**, Departments of Molecular and Human Genetics, Pediatrics - Neurology and Developmental Neuroscience**Faculty Member**, Graduate Programs in Genetics & Genomics and Neuroscience**Director**, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital**Investigator**, Howard Hughes Medical Institute*M.D., American University of Beirut/Meharry Medical College
Postdoctoral Fellowship, Baylor College of Medicine***RESEARCH INTERESTS**

My laboratory's research is rooted in my early clinical encounters with patients suffering rare and enigmatic disorders. One memorable patient suffered Rett Syndrome; another was part of a family that suffered a neurodegenerative disease that struck each successive generation at younger ages. Our investigations into the pathogenesis of these two diseases have influenced our understanding of basic neurobiology and more common disorders such as autism and Alzheimer's disease. Conversely, our foray into fundamental neurodevelopmental processes governed by Atonal homolog 1 (Atoh 1) has had unexpected ramifications for our understanding of (and potential therapies for) several diseases, from deafness and medulloblastoma to sudden infant death syndrome.

Polyglutamine Pathogenesis and Neurodegeneration. We co-discovered the gene for spinocerebellar ataxia type 1 (SCA1) in 1993 with Harry Orr, Ph.D., at the University of Minnesota and have been collaborating to understand the disease mechanism. Our genetic studies in mice and (in collaboration with Juan Botas, Ph.D.) in fruit flies, led us to propose that the polyglutamine tract stabilizes Ataxin-1 increasing its levels and interactions and causing toxicity due to its enhanced function. We also discovered that the enhanced function of mutant Ataxin-1, with its native partner Capicua (CIC), drives the cerebellar ataxia. Further, we discovered that reducing Ataxin-1 in the cerebellum is a viable therapeutic strategy, but that for other vulnerable brain regions the pathogenic mechanism is distinct. Interestingly, we learned that loss of Ataxin-1 and the subsequent repressor activity loss of the Ataxin-1-CIC complex leads to upregulation of *Bace1* and increased risk of Alzheimer pathology in the forebrain. Our current studies are focused on understanding the mechanisms driving the regional vulnerability in SCA1.

Inspired by our work on SCA1 and the importance of Ataxin-1 levels for brain health, we have pursued cross-species studies to identify modulators of APP, tau, and alpha-synuclein, proteins that drive degeneration in Alzheimer's and Parkinson's disease. We have identified and validated several modulators of tau levels. Exploring the mechanisms by which such modulators regulate tau levels we have gained insight into tau biology and the key molecules involved in its degradation. We are capitalizing on our genetic and mechanistic data to develop potential therapeutic strategies that can help people with Alzheimer's and related dementias.

Rett Syndrome and Autism Spectrum Disorders. We discovered that Rett syndrome is caused by mutations in the X-linked methyl-CpG-binding protein 2 (*MECP2*). Our mouse model studies led to the definition of clinical phenotypes not previously appreciated in *MECP2* disorders and revealed that neurons are quite sensitive to having just slightly too much or too little MeCP2. In collaboration with Jianrong Tang, Ph.D., at Baylor, we found that fornical deep brain stimulation restored hippocampal learning and plasticity. Using an *MECP2* duplication mouse model, we showed that normalizing MeCP2 levels using antisense oligonucleotides reverses disease symptoms including late onset seizures in adult mature animals. These findings set the stage for a clinical trial to treat patients with *MECP2* duplication syndrome. More recently, we discovered that presymptomatic training of Rett mice improved their performance, delayed disease onset by months, and improved neuronal morphology and physiology. We are now focused on understanding the molecular mechanism mediating the benefits from early training. In addition, we are developing strategies to increase MeCP2 levels as potential therapies for Rett patients with partially functioning MeCP2. Lastly, we are pursuing studies to understand the regulation and functions of MeCP2.

Beyond Rett, we are interested in understanding what drives the male sex bias of autism spectrum disorders (ASD). Based on our preliminary data, we propose that hypomorphic and non-coding mutations in X-linked genes render males more vulnerable to ASD; we are testing this hypothesis in collaboration with Evan Eichler, Ph.D., Aravinda Chakravarti, Ph.D., and Tomasz Nowakowski, Ph.D.

**SELECTED PUBLICATIONS**

Kim J, Tadros B, Liang YH, Kim Y, Lasagna-Reeves C, Sonn J, Chung D, Hyman B, Holtzman DM, **Zoghbi HY** (2024). TYK2: A critical regulator of tau levels, phosphorylation, and aggregation in tauopathy. **Nat Neurosci.**, in press.

Kim J, de Haro M, Al-Ramahi I, Garaicoechea L, Jeong H-H, Sonn J, Liu Z, Botas J, **Zoghbi HY** (2023). Evolutionarily conserved regulators of tau identify targets for new therapies. **Neuron.** 111: 824-838.e7.

Coffin SL, Durham MA, Nitschke L, Xhako E, Brown AM, Revelli J-P, Gonzalez EV, Lin T, Handler HP, Dai Y, Trostle AJ, Wan Y-W, Liu Z, Sillitoe RV, Orr HT, **Zoghbi HY** (2023). Disruption of the ATXN1-CIC complex reveals the role of additional nuclear ATXN1 interactors in spinocerebellar ataxia type 1. **Neuron.** 111: 1-12.

He L, Caudill MS, Jing J, Wang W, Sun Y, Tang J, Jiang X, **Zoghbi HY** (2022). A weakened recurrent circuit in the hippocampus of Rett syndrome mice disrupts long-term memory representations. **Neuron.** 110: 1689-1699.

Achilly N, Wang W, **Zoghbi HY** (2021). Presymptomatic training mitigates functional deficits in Rett syndrome mice. **Nature.** 592: 596-600.

Suh J, Romano DM, Nitschke L, Herrick SP, DiMarzio BA, (...), **Zoghbi HY**, Tanzi RE (2019). Loss of Ataxin-1 Potentiates Alzheimer's Pathogenesis by Elevating Cerebral BACE1 Transcription. **Cell.** 178: 1159-1175.e17.

Gennarino VA, Palmer EE, McDonnell LM, (...), Boycott KM, Holder JL Jr, **Zoghbi HY** (2018). A Mild PUM1 Mutation Is Associated with Adult-Onset Ataxia, whereas Haploinsufficiency Causes Developmental Delay and Seizures. **Cell.** 172: 924-936.

Sztainberg Y, Chen H-M, Swann JW, Hao S, Tang B, Wu Z, Tang J, Wan Y-W, Liu Z, Rigo F, **Zoghbi HY** (2015). Reversal of phenotypes in *MECP2* duplication mice using genetic rescue or antisense oligos. **Nature.** 528: 123-6.

Hao S, Tang B, Wu Z, Ure K, Sun Y, Tao H, Gao Y, Patel A, Curry DJ, Samaco RC, **Zoghbi HY**, Tang J (2015). Fornical deep brain stimulation rescues hippocampal memory in Rett syndrome mice. **Nature.** 526: 430-445. *Corresponding author. This paper was the subject of a Nature News and Views commentary by Cobb SR., Oct 15; 526: 331-332.

Amir R, Van den Veyver IB, Wan M, Tran C, Francke U, **Zoghbi HY** (1999). Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2. **Nat Genet.** 23: 185-8.

CHENGHANG (CHUCK) ZONG, PH.D.**McNair Scholar**

Associate Professor, Department of Molecular and Human Genetics
Faculty Member, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

Ph.D., University of California, San Diego
Postdoc, University of Illinois at Urbana-Champaign
Postdoc, Harvard University

RESEARCH INTERESTS

The research of our laboratory focuses on the development of novel single-cell technologies and their applications in biology studies. With the rapid development of next-generation sequencing technology, high-throughput sequencing has become a powerful tool for biological research. In our lab, we are interested in examining the genome at single-cell resolution, in contrast to the genome averaged from an ensemble of cells. As a demonstration of the principle, we can detect somatic mutations existing in individual cancer cells. We are particularly interested in detecting early mutations that drive tumorigenesis and the early stage of tumor heterogeneity that will influence later tumor development. The lab specifically focuses on pancreatic cancer. Supported by NIH's New Innovator's award, we have successfully developed a linear amplification-based whole-genome amplification method (LCS-WGA), which allows us to profile not only the somatic mutations existing in single cells but also the spontaneous DNA damage in single cells for the first time, which we refer to as damagenome. The successful profiling of DNA damagenome promoted us to identify the high-damage genes existing in the human genome and unveil their association with complex human diseases. Furthermore, the even genome coverage of a single cell allows to construct the single-cell tumor evolution tree at unprecedented resolution.

In addition to profiling the genome at single-cell resolution, we are also interested in developing novel methods for single-cell transcriptional profiling. We have developed the first single-cell total-RNA-seq method (MATQ-seq). MATQ-seq has been applied to characterize the early lesions of pancreatic cancer using the mice model, the heterogeneity in tumor and its microenvironment, and various biological processes through collaborations.

Recently we have developed the droplet-based high throughput platform of MATQ-seq: MATQ-drop. MATQ-Drop can process both frozen and FFPE samples, which allows authentic profiling of tumor heterogeneity. Furthermore, we have successfully applied MATQ-Drop to profile the transcriptome of individual synapses (synaptosome). The high-throughput gene expression profiling of individual synapses opens a new avenue to study various neurological processes and diseases. Our goal is to unveil the transcriptome and epigenome changes in various biological processes such as tumorigenesis, aging and neurodegeneration.

**SELECTED PUBLICATIONS**

Niu Y, Zhu Q, **Zong C** (2022). Single-cell Damagenome Profiling by Linear Copying and Splitting based Whole Genome Amplification (LCS-WGA). **Bio-protocol**. 12: e4357.

Liu S, Cao W, Niu Y, Luo J, Zhao Y, Hu Z, **Zong C** (2021). Single-PanIN-seq unveils that ARID1A deficiency promotes pancreatic tumorigenesis by attenuating KRAS-induced senescence. **eLife** 10: e64264.

Zhu Q, Niu Y, **Zong C** (2021). Single-cell damagenome profiling unveils vulnerable genes and functional pathways in human genome toward DNA damage. **Sci. Adv.** 7: eabf3329.

Bota-Rabasedas N, et al. (2021). Contextual cues from cancer cells govern cancer-associated fibroblast heterogeneity. **Cell Rep.** 35: 109009.

Sheng K, Cao W, Niu Y, Deng Q, **Zong C** (2017). Effective detection of variation in single-cell transcriptomes using MATQ-seq. **Nat Methods**. 14: 267-270.

Zong C*, Lu S*, Chapman AR*, Xie XS (2012). Genome-wide detection of single-nucleotide and copy-number variations of a single human cell. **Science**. 338: 1622-6.

Lu S*, **Zong C***, Fan W, Yang M, Li J, Chapman AR, Zhu P, Hu X, Xu L, Yan L, Bai F, Qiao J, Tang F, Li R, Xie XS (2012). Probing meiotic recombination and aneuploidy of single sperm cells by whole-genome sequencing. **Science**. 338: 1627-30.

CHRISTIE M. BALLANTYNE, M.D.

J. S. Abercrombie Chair - Atherosclerosis and Lipoprotein Research

Professor, Departments of Medicine and Molecular and Human Genetics
Chief, Cardiology and Cardiovascular Research, Department of Medicine
Director, The Maria and Alando J. Ballantyne, M.D., Atherosclerosis Clinical Research Laboratory and Center for Cardiometabolic Disease Prevention

M.D., Baylor College of Medicine

Resident, Internal Medicine, The University of Texas Southwestern Medical School

Clinical Fellow, Cardiology, Baylor College of Medicine

American Heart Association/Bugher Foundation Fellowship, Howard Hughes Medical Institute and Institute for Molecular Genetics, Baylor College of Medicine

RESEARCH INTERESTS

Dr. Ballantyne's research interests include the pathophysiology of atherosclerosis, focusing on monocyte activation and adhesion. Ballantyne and his colleagues use both murine and human studies to understand the mechanisms by which hyperlipidemia and obesity influence inflammation.

Ballantyne's clinical research interests include preventive cardiology, lipids, metabolic syndrome, atherosclerosis, genetics and coronary artery disease. As director of the core laboratory for the ARIC study, Ballantyne examines the role of genetic variation combined with novel biomarkers to identify individuals at high risk for cardiovascular disease, metabolic syndrome and diabetes, using genomics and proteomics. His group also studies how genetic variation modifies the response to therapy with the goal of developing personalized diet, lifestyle and pharmacotherapy based on genetic profile and clinical phenotype.



SELECTED PUBLICATIONS

Uddin MM, Saadatagah S, Niroula A, Yu B, Hornsby WE, Ganesh S, (...), **Ballantyne CM**, Natarajan P (2024). Long-term longitudinal analysis of 4,187 participants reveals insights into determinants of clonal hematopoiesis. **Nat Commun.** 15: 7858.

Ballantyne CM, Vasas S, Azizad M, Clifton P, Rosenson RS, Chang T, (...), Hellawell J, Gaudet D. Plozasiran, an RNA interference agent targeting APOC3, for mixed hyperlipidemia (2024). **N Engl J Med.** doi: 10.1056/NEJMoa2404143. Online ahead of print.

Deshotels MR, Hadley TD, Roth M, Agha AM, Pulipati VP, Nugent AK, (...), Davidson MH, **Ballantyne CM**. Genetic testing for hypertriglyceridemia in academic lipid clinics: implications for precision medicine—brief report (2022). **Arterioscler Thromb Vasc Biol.** 42: 1461-1467.

✉ CMB@BCM.EDU

ALISON A. BERTUCH, M.D., PH.D.

Associate Professor, Departments of Pediatrics-Hematology/Oncology and Molecular and Human Genetics; Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

M.S., M.D., and Ph.D., Biology, University of Rochester

Internship and Residency, Pediatrics, Baylor College of Medicine

Clinical Fellow in Pediatric Hematology/Oncology and Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

Dr. Alison Bertuch's research is aimed at understanding the mechanisms of telomere structure and function and DNA double-strand break repair and their intersection. Her research uses yeast as a model system for the rapid identification and investigation of the genes that govern telomere homeostasis as well as human cell lines. In addition, Dr. Alison Bertuch's laboratory studies the role of telomere and DNA repair dysfunction in the development of bone marrow failure in children. A long-term goal is to exploit the knowledge gained from these studies to aid in the treatment of not only bone marrow failure but also cancer.



SELECTED PUBLICATIONS

Lemon LD, Morris DK, **Bertuch AA** (2019). Loss of Ku's DNA end binding activity affects telomere length via destabilizing telomere-bound Est1 rather than altering TLC1 homeostasis. **Sci Rep.** 9: 10607.

Nelson ND, Dodson LM, Escudero L, Sukumar AT, Williams CL, Mihalek I, Baldan A, Baird DM, **Bertuch AA** (2018). The C-Terminal Extension Unique to the Long Isoform of the Shelterin Component TIN2 Enhances Its Interaction with TRF2 in a Phosphorylation- and Dyskeratosis Congenita Cluster-Dependent Fashion. **Mol Cell Biol.** 38. pii: e00025-18.

Emerson CH, Lopez CR, Ribes-Zamora A, Polleys EJ, Williams CL, Yeo L, Zaneveld JE, Chen R, **Bertuch AA** (2018). Ku DNA End-Binding Activity Promotes Repair Fidelity and Influences End-Processing During Nonhomologous End-Joining in *Saccharomyces cerevisiae*. **Genetics.** 209: 115-128.

✉ ABERTUCH@BCM.EDU

MALCOLM BRENNER, M.D., PH.D.**Fayez Sarofim Chair**

Professor, Departments of Medicine, Pediatrics, and Molecular and Human Genetics; Stem Cells and Regenerative Medicine (STaR) Center

Founding Director, Center for Cell & Gene Therapy

MBChB, University of Cambridge

Ph.D., University of Cambridge

FRCPath, FRCP

RESEARCH INTERESTS

Dr. Brenner's primary research interest is the use of gene transfer to augment the immune response to human tumors, using vaccines and adoptive transfer of genetically modified T cells. In neuroblastoma, Dr. Brenner and co-investigators have shown that T cells expressing a chimeric antigen receptor (CAR) for a surface marker (GD2) on neuroblastoma cells can produce tumor responses in more than half the patients with refractory or relapsed disease. The Center for Cell & Gene Therapy is also studying the benefits of T cells, including those modified with CARs, that target other tumor antigens on hematological malignancies and solid tumors and initial clinical results are promising. Efforts are being made to further increase the effectiveness of these T cells by incorporating genes that enhance T cell growth and survival and that render the T cells resistant to the inhibitory effects of many human tumors. To enhance the safety of genetically modified T cells, Dr. Brenner and colleagues have clinically developed an inducible caspase system that will rapidly cause apoptosis of T cells within minutes of administration of a small molecule dimerizing drug, allowing adverse effects from the T cells to be reversed.

✉ MBRENNER@BCM.EDU

EDWARD C. COOPER, M.D., PH.D.

Associate Professor, Departments of Neurology, Neuroscience, and Molecular and Human Genetics; Postdoctoral Training Program in Brain Disorders and Development; Graduate Programs in Genetics & Genomics and Neuroscience

M.D., Yale School of Medicine, Yale University, New Haven

Ph.D., Yale School of Medicine, Yale University, New Haven

Residency, Neurology, University of California, San Francisco

Postdoc and Adjunct Asst. Professor of Neurology and Physiology, University of California, San Francisco

RESEARCH INTERESTS

The Cooper Lab is focused on understanding and developing new treatments for forms of epilepsy affecting infants, children, and adults, mood disorder that often accompanies epilepsy, and related brain disease. These are complex developmental disorders that impact the whole person and the brain as a system. To gain leverage on such tough problems, we have taken clues from human and experimental genetics implicating a molecular pathway—the machinery of the action potential, the neuron's rapid long-distance signal. Of central importance, both as genes often mutated in disease and therapeutic targets, are the voltage-gated potassium and sodium ion channels that generate and conduct the action potential's electrical currents. However, channels do not function alone. Therefore, we also study the protein networks and signal paths that position, regulate, and respond to these channels.

**SELECTED PUBLICATIONS**

Hegde M, Mukherjee, M, Grada Z, (...), **Brenner MK**, et. al. (2016). Tandem CAR T cells targeting HER2 and IL13Ra2 mitigate tumor antigen escape. **J Clin Invest.** 126: 3036-3052.

Ramos CA, Savoldo B, Torrano V, (...), **Brenner MK**, et. al. (2016). Clinical responses with T lymphocytes targeting malignancy-associated k light chains. **J Clin Invest.** 126: 2588-2604.

Papadopolou A, Gerdemann U, Katari UL, (...), **Brenner MK**, et al. (2014). Activity of Broad-Spectrum T Cells as Treatment for AdV, EBV, CMV, BKV, and HHV6 Infections after HSCT. **Sci Transl Med.** 6: 242-248.

Di Stasi A, Tey SK, Dotti GP, (...), Rooney CM, **Brenner MK** (2011). Inducible Apoptosis as a Safety Switch for Adoptive Cell Therapy. **N Engl J Med.** 365: 1673-83.

**SELECTED PUBLICATIONS**

Millichap JJ, Miceli F, De Maria M, Keator C, Joshi N, Tran B, Soldovieri MV, Ambrosino P, Shashi V, Mikati MA, **Cooper EC**, Tagliatela M (2017). Infantile spasms and encephalopathy without preceding neonatal seizures caused by KCNQ2 R198Q, a gain-of-function variant. **Epilepsia.** 58: e10-e15.

Lopez AY, Wang X, Xu M, Maheshwari A, Curry D, Lam S, Adesina AM, Noebels JL, Sun QQ, **Cooper EC** (2017). Ankyrin-G isoform imbalance and interneuronopathy link epilepsy and bipolar disorder. **Mol Psychiatry.** 22: 1464-1472.

Millichap JJ, Park KL, Tsuchida T, Ben-Zeev B, Carmant L, (...), Venkatesan C, Weckhuysen S, **Cooper EC** (2016). KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. **Neurol Genet.** 2: e96.

RYAN DHINDSA, M.D., PH.D.

Assistant Professor, Departments of Pathology & Immunology and Molecular and Human Genetics; Graduate Programs in Genetics & Genomics and Quantitative and Computational Biology;

Investigator, Jan and Dan Duncan Neurological Research Institute

M.D./Ph.D, Columbia University College of Physicians and Surgeons, New York

RESEARCH INTERESTS

My research program focuses on how genomic variation influences human health, particularly in neurological disorders. In my lab, we combine population genetics, human stem cell models, and functional genomics models to investigate the genetic mechanisms of complex diseases and identify novel therapeutic targets. We have led the analysis of hundreds of thousands of human genomes, which has revealed an outstanding role of rare variants in complex human diseases and uncovered new risk genes for disorders such as epilepsy, Parkinson's disease, and others. In parallel, our group develops new statistical and machine learning methods to improve the interpretation of genetic variation. We combine these computational discoveries with focused molecular biological experiments, including CRISPR-based functional genomics screens in stem cell-derived neurons. These approaches allow us to uncover key molecular and cellular events in the development of neurodevelopmental and neurodegenerative diseases at scale. Through collaborations with academia and industry, we aim to translate these insights into targeted therapies and advancing precision medicine.



SELECTED PUBLICATIONS

Dhindsa RS, Burren OS, Sun BB, Prins BP, Matelska D, (...); AstraZeneca Genomics Initiative; Vitsios D, Ashley EA, Whelan CD, Pangalos MN, Wang Q, Petrovski S (2023). Rare variant associations with plasma protein levels in the UK Biobank. **Nature**. 622: 339-347.

Wang Q, **Dhindsa RS**, Carss K, Harper AR, Nag A, (...); AstraZeneca Genomics Initiative; Wasilewski S, Smith KR, March R, Platt A, Haefliger C, Petrovski S (2021). Rare variant contribution to human disease in 281,104 UK Biobank exomes. **Nature**. 597: 527-532.

Dhindsa RS, Zoghbi AW, Krizay DK, Vasavda C, Goldstein DB (2021). A Transcriptome- Based Drug Discovery Paradigm for Neurodevelopmental Disorders. **Ann Neurol**. 89: 199-211.

✉ RYAN.DHINDSA@BCM.EDU X @RYANDHINDSA

RICHARD H. FINNELL, PH.D.

William T. Butler, M.D., Endowed Chair for Distinguished Faculty

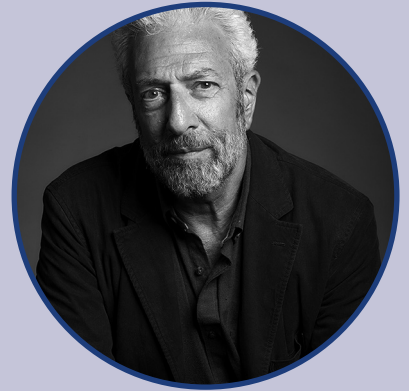
Professor, Departments of Molecular and Cellular Biology, Medicine, and Molecular and Human Genetics; Center for Precision Environmental Health; Graduate Programs in Genetics & Genomics and Development, Disease Models & Therapeutics

Ph.D., University of Oregon Medical School

Postdoctoral fellow, Anatomisches Institut, Universität Zürich, Switzerland

RESEARCH INTERESTS

Dr. Finnell is a pediatric geneticist who has been involved in investigating genetic susceptibility to environmentally induced birth defects, applying stem cell technology to the detection of potential teratogenic compounds in efforts to prevent these birth defects utilizing genome editing technologies to create novel model systems to better understand the pathogenesis of the defects, and applying highly innovative approaches to treating these disabilities. The laboratory focuses on micronutrient transport during embryogenesis and the interaction between gene variants and one carbon metabolism as it relates to the development of birth defects. His research involves global collaborative NGS studies of complex birth defects and using precision medicine approaches to managing high-risk pregnancies.



SELECTED PUBLICATIONS

Kim SE, Chothani PJ, Shaik R, Pollard W, **Finnell RH** (2023). Pax3 lineage-specific deletion of Gpr161 is associated with spinal neural tube and craniofacial malformations during embryonic development. **Dis Model Mech**. 16: dmm050277.

Caiaffa CD, Ambekar YS, Singh M, Lin YL, Wlodarczyk B, Aglyamov SR, Scarcelli G, Larin KV, **Finnell RH** (2024). Disruption of Fuz in mouse embryos generates hypoplastic hindbrain development and reduced cranial nerve ganglia. **Dev Dyn**. doi: 10.1002/dvdy.702. Epub ahead of print.

Iskandar BJ, **Finnell RH** (2022). Spina Bifida. **N Engl J Med**. 387: 444-450.

✉ FINNELL@BCM.EDU

MARGARET A. GOODELL, PH.D.**Vivian L. Smith Chair in Regenerative Medicine**

Chair and Professor, Department of Molecular and Cellular Biology
Professor, Center for Cell and Gene Therapy and Departments of Pediatrics, Molecular and Human Genetics and Pathology & Immunology; Stem Cells and Regenerative Medicine (STaR) Center; Graduate Programs in Cancer & Cell Biology; Development, Disease Models & Therapeutics; and Genetics & Genomics

*Ph.D., Cambridge University**Postdoc, Whitehead Institute, Massachusetts Institute of Technology**Postdoc, Harvard Medical School***RESEARCH INTERESTS**

Murine and human hematopoietic stem cells; genetic and epigenetic regulation and development.

We are interested in the basic biology of hematopoietic stem cells and how their regulation goes awry leading to leukemia development. It has been known for decades that hematopoietic stem cells reside in the bone marrow in a quiescent state and replenish the supply of differentiated cells of the peripheral blood throughout the lifetime of an animal. No other adult cell type retains the capacity for such immense proliferation and differentiation. However, little is known about the cells or factors that regulate their primitive state or control their activation. We study the behavior of these stem cells *in vivo* and *in vitro* using mouse stem cells as a model, as well as pursue the mechanisms which control their behavior on a molecular level using genome-wide profiling strategies and mouse mutants. Many of the genes that control normal stem cell behavior appear to become dysregulated in leukemia and lymphoma.

 **GOODELL@BCM.EDU**
MARTIN M. MATZUK, M.D., PH.D.**Stuart A. Wallace Chair in Pathology**

Professor, Departments of Pathology & Immunology, Molecular & Cellular Biology, Molecular and Human Genetics, and Pharmacology; Graduate Programs in Cancer & Cell Biology; Chemical, Physical & Structural Biology; and Genetics & Genomics
Director, Center for Drug Discovery

*M.D., Ph.D., Washington University School of Medicine**Postdoc, Baylor College of Medicine***RESEARCH INTERESTS**

Our laboratory is focused on 1) using functional genomics to investigate essential fertility pathways, reproductive tract cancers, and TGF-beta family signaling in mammals and 2) applying chemical biology approaches to develop lead compounds for contraception, cancer, and debilitating diseases. We have taken a discovery-based approach to first uncover genes expressed exclusively in the male or female germline and subsequently to define their roles *in vivo* using CRISPR/Cas9 technology and transgenic mouse models. In the process, we have identified novel genes involved in oocyte-somatic cell interactions during ovarian folliculogenesis, germ-cell intercellular bridge formation, acrosome formation, the piRNA pathway, etc. If a knockout results specifically in male infertility, this gene product may be a promising drug target for contraception in men, and our lab has begun to characterize small-molecule contraceptives to target male germ cells. We have successfully created unique mouse models to study ovarian cancer and to decipher the crosstalk of TGF-beta family, hormonal, and small RNA signaling pathways in normal and diseased reproductive tissues and their roles during pregnancy.

 **MMATZUK@BCM.EDU**
**SELECTED PUBLICATIONS**

Hsu JI, Dayaram T, Tovy A, De Braekeleer E, Jeong M, (...), **Goodell MA** (2018). PPM1D Mutations Drive Clonal Hematopoiesis in Response to Cytotoxic Chemotherapy. **Cell Stem Cell**. 23: 700-713.e6.

Brunetti L, Gundry MC, Sorcini D, Guzman AG, Huang YH, (...), **Goodell MA** (2018). Mutant NPM1 Maintains the Leukemic State through HOX Expression. **Cancer Cell**. 34: 499-512.e9.

Gundry MC, Brunetti L, Lin A, Mayle AE, Kitano A, (...), **Goodell MA**, Nakada D (2016). Highly Efficient Genome Editing of Murine and Human Hematopoietic Progenitor Cells by CRISPR/Cas9. **Cell Rep**. 17: 1453-1461.

Yang L, Rodriguez B, Mayle A, Park HJ, Lin X, (...), **Goodell MA** (2016). DNMT3A Loss Drives Enhancer Hypomethylation in FLT3-ITD-Associated Leukemias. **Cancer Cell**. 30: 363-365.

**SELECTED PUBLICATIONS**

Miyata H, Castaneda JM, Fujihara Y, (...), Ikawa M, **Matzuk MM** (2016). Genome engineering uncovers 54 evolutionarily conserved and testis-enriched genes that are not required for male fertility in mice. **Proc Natl Acad Sci U S A**. 113: 7704-10.

Castaneda J, **Matzuk MM** (2015). Toward a rapid and reversible male pill. **Science**. 350: 385-6.

Nagashima T, Li Q, Clementi C, Lydon JP, DeMayo FJ, **Matzuk MM** (2013). BMP2 is required for postimplantation uterine function and pregnancy maintenance. **J Clin Invest**. 123: 2539-50.

Peng J, Li Q, Wigglesworth K, Rangarajan A, Kattamuri C, Peterson RT, Eppig JJ, Thompson TB, **Matzuk MM** (2013). Growth differentiation factor 9: bone morphogenetic protein 15 heterodimers are potent regulators of ovarian functions. **Proc Natl Acad Sci U S A**. 110: E776-85.

ANTHONY MUSTOE, PH.D.

Assistant Professor, Departments of Biochemistry and Molecular Biology and Molecular and Human Genetics; Therapeutic Innovation Center (THINC)
CPRIT Scholar in Cancer Research

B.S., Washington University

Ph.D., University of Michigan

Postdoc, University of North Carolina

RESEARCH INTERESTS

The overarching goal of my laboratory is to define the mechanisms underpinning RNA folding and function. We seek to develop an improved, quantitative understanding of biology and human disease and to translate this knowledge into new therapeutic strategies. Our principal expertise is in developing and applying chemical probing techniques to define RNA structure and dynamics in living cells. We have used our technologies to discover novel functional structures in both non-coding RNAs and messenger RNAs (mRNAs), and to reveal transcriptome-wide roles for mRNA structure in tuning translation efficiency. We are presently applying our techniques to develop a quantitative understanding of how RNA structures modulate recognition and regulation by RNA binding proteins and microRNAs, and how RNA misfolding can lead to disease, particularly cancer. We additionally have multiple collaborations with other groups investigating the structure and function of diverse biomedically important RNAs.



SELECTED PUBLICATIONS

Olson SW, Turner AW, Arney JW, Saleem I, Weidmann CA, Margolis DM, Weeks KM, **Mustoe AM** (2022). Discovery of a large-scale, cell-state-responsive allosteric switch in the 7SK RNA using DANCE-Map. **Mol Cell**. 82: 1708-1723. e10.

Mustoe AM, Busan S, Rice GM, Hajdin CE, Peterson BK, Ruda VM, Kubica N, Nutiu R, Baryza JL, Weeks KM (2018). Pervasive Regulatory Functions of mRNA Structure Revealed by High-Resolution SHAPE Probing. **Cell**. 173: 181-195.e18.

Mustoe AM, Lama NN, Irving PS, Olson SW, Weeks KM (2019). RNA base-pairing complexity in living cells visualized by correlated chemical probing. **Proc Natl Acad Sci U S A**. 116: 24574-24582.

✉ ANTHONY.MUSTOE@BCM.EDU

JEFFREY L. NOEBELS, M.D., PH.D.

The Cullen Trust for Health Care Endowed Chair in Neurogenetics

Professor, Departments of Neurology, Neuroscience, and Molecular and Human Genetics; Graduate Programs in Neuroscience and Development, Disease Models & Therapeutics

Director, Blue Bird Circle Developmental Neurogenetics Laboratory

Ph.D., Stanford University

M.D., Yale University

Postdoc, Harvard Medical School

RESEARCH INTERESTS

The principal research strategy in the Developmental Neurogenetics Laboratory is to apply mutational analysis to learn how genes regulate neuronal excitability and network synchronization within the developing central nervous system. We have linked over 40 genes with various patterns of epilepsy, and discovered hyperexcitability and synchronization defects in Alzheimer's Disease, leading to a paradigm change in understanding the basis for accelerated cognitive decline. Other current projects center on genes for absence seizures, the most common childhood epilepsy; linking epilepsy with lethal cardiac arrhythmias; and network hyperexcitability in the peritumoral cortical microenvironment of glioblastoma. We trace the biology of the mutant circuitry in mice using molecular anatomical, patch clamp, optogenetic and 2 photon imaging. These experimental studies form the basis for development of preclinical strategies to selectively correct the expression of neuronal gene errors early in development. In collaboration with the Baylor Human Genome Sequencing Center, we performed a large-scale translational genomic research study of ion channel genes in epilepsy (The Human Channelopathy Project). We also lead a multisite NIH Center without Walls focusing on risk prediction of variants in ion channel genes linked to neurocardiac phenotypes.



SELECTED PUBLICATIONS

Soeung V, Puchalski RB, **Noebels JL** (2024). The complex molecular epileptogenesis landscape of glioblastoma. **Cell Rep Med**. 5: 101691.

Meyer J, Yu K, Luna-Figueroa E, Deneen B, **Noebels J** (2024). Glioblastoma disrupts cortical network activity at multiple spatial and temporal scales. **Nat Commun**. 15: 4503.

Aiba I, Ning Y, **Noebels JL** (2025). Persistent Na⁺ current couples spreading depolarization to seizures in *Scn8a* gain-of-function mice. **Brain**. 148: 3325-3339.

✉ JNOEBELS@BCM.EDU

DONALD W. (WILL) PARSONS, M.D., PH.D.

Professor, Departments of Pediatrics - Hematology-Oncology and Molecular and Human Genetics; Pathology & Immunology; Human Genome Sequencing Center; Graduate Program in Genetics & Genomics

Ph.D., Department of Pathology, Ohio State University College of Medicine

M.D., Ohio State University College of Medicine

Resident, Pediatrics, Johns Hopkins University

Clinical Fellow, Pediatric Hematology-Oncology, Johns Hopkins University & National Cancer Institute

Clinical Fellow, Neuro-Oncology, Johns Hopkins University

RESEARCH INTERESTS

Dr. Parsons studies the clinical application of genomic technologies in pediatric cancer care. His work has been instrumental in the characterization of the genetic landscapes of a variety of pediatric and adult cancers, including the first identification of IDH1 and IDH2 as cancer genes. Dr. Parsons has helped lead seminal studies evaluating the use of clinical sequencing for childhood cancer patients as part of the NHGRI Clinical Sequencing Evidence-Generating Research (CSER) program: the BASIC3 study (2011-2017) for newly diagnosed patients at Texas Children's Cancer Center and the Texas KidsCanSeq study (2018-) for both newly diagnosed and relapsed patients at multiple study sites across Texas. Dr. Parsons has a particular interest in development and evaluation of molecularly targeted therapies and holds a number of leadership roles in this area including serving as the study chair for the ongoing NCI-COG Pediatric MATCH trial (the first nationwide precision oncology trial for children, adolescents, and young adults with refractory cancers) and as a Steering Committee member and Genomics & Translational Biology lead for the NIH Pediatric Early Phase Clinical Trials Network.

✉ DWPARSON@BCM.EDU

SHARON E. PLON, M.D., PH.D.

Dan L. Duncan Endowed Professorship

Professor, Departments of Pediatrics and Molecular and Human Genetics and Human Genome Sequencing Center; Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

Assistant Dean of Dual Degree Programs and Pathways, School of Medicine

Director, Cancer Genetics Clinical and Research Programs, Texas Children's Hospital

M.D., Ph.D., Harvard University

Resident, Internal Medicine, University of Washington

Postdoc, National Cancer Institute, National Institutes of Health

Fellow, Medical Genetics, Fred Hutchinson Cancer Research Center, Univ. of Washington

RESEARCH INTERESTS

I have had a longstanding focus on the fields of cancer genetics and clinical genomics. My translational research is designed to understand mechanisms of susceptibility to pediatric cancer through large collaborative projects. We have worked closely with Dr. Philip Lupo on a landmark study of the association between birth defects and childhood cancer and are now using whole genome sequencing of these unique patients to identify novel cancer susceptibility genes as well as the hereditary basis of rhabdomyosarcoma, an often-lethal tumor in children. I serve as co-PI with Dr. Donald (Will) Parsons and Dr. Amy McGuire on the NHGRI/NCI- U01 Texas KidsCanSeq trial that studies the incorporation of CLIA clinical genome-scale exome sequencing into the care of childhood cancer patients (solid tumors and brain tumors) in the diverse patient populations across six sites in Texas. I am one of the principal investigators of the Clinical Genome Resource (ClinGen), an international effort to develop databases and websites to improve the clinical interpretation of genetic variation.



SELECTED PUBLICATIONS

Ting MA, Reuther J, Chandramohan R, et al (2021). Genomic analysis and preclinical xenograft model development identify potential therapeutic targets for MYOD1-mutant soft-tissue sarcoma of childhood. **J Pathol.** 255: 52-61.

Parsons DW, Janeway KA, Patton DR, et al (2022). Actionable tumor alterations and treatment protocol enrollment of pediatric and young adult patients with refractory cancers in the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. **J Clin Oncol.** 40: 2224-2234.

Eckstein OS, Allen CE, Williams PM, et al (2022). Phase II study of Selumetinib in children and young adults with tumors harboring activating mitogen-activated protein kinase pathway genetic alterations: Arm E of the NCI-COG Pediatric MATCH Trial. **J Clin Oncol.** 40: 2235-2245.



SELECTED PUBLICATIONS

Parsons DW, Roy A, Yang Y, Wang T, Scollon S, Bergstrom K, (...), Eng CM, Gibbs RA, **Plon SE** (2016). Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. **JAMA Oncol.** 2: 616-624.

Lupo PJ, Schraw JM, Desrosiers TA, Nembhard WN, Langlois PH, (...), **Plon SE** (2019). Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births. **JAMA Oncol.** 5: 1150-1158.

Li H, Sisoudiya SD, Martin-Giacalone BA, Khayat MM, Dugan-Perez S, (...), **Plon SE**, Sabo A, Lupo PJ (2021). Germline Cancer Predisposition Variants in Pediatric Rhabdomyosarcoma: A Report From the Children's Oncology Group. **J Natl Cancer Inst.** 113: 875-883.

NOAH F. SHROYER, PH.D.

Associate Professor, Departments of Medicine-Gastroenterology and Hepatology and Molecular and Human Genetics; Graduate Programs in Cancer & Cell Biology and Development, Disease Models & Therapeutics

Adjunct Associate Professor, Department of Pediatrics-Gastroenterology, Hepatology & Nutrition, Cincinnati Children's Hospital

Ph.D., Cell and Molecular Biology, Baylor College of Medicine

Postdoc, Molecular and Human Genetics, Baylor College of Medicine

RESEARCH INTERESTS

My laboratory is focused on understanding the mechanisms that control intestinal development and homeostasis, and translating this knowledge into novel therapeutic approaches to treat diseases of the intestine such as IBD and colorectal cancer. My laboratory has elucidated roles for epithelial transcription factors such as Atoh1 (Math1), Gfi1, and Spdef in development and differentiation of the intestine. Moreover, my laboratory has translated these findings to human diseases, by showing that Atoh1 and its target Spdef are tumor suppressors that are frequently silenced in colon cancers, and that these genes are essential targets of Notch inhibitory drugs. In addition to these mechanistic studies, we have recently developed novel organ culture methods to direct differentiation of human pluripotent stem cells into intestinal tissue to study intestinal development and disease, and we have used intestinal stem cell-derived organoids in quantitative assays to evaluate intestinal stem cell activity.



SELECTED PUBLICATIONS

Noah TK, **Shroyer NF** (2013). Notch in the intestine: regulation of homeostasis and pathogenesis. **Annu Rev Physiol.** 75: 263-88.

Noah TK, Lo YH, Price A, Chen G, King E, Washington MK, Aronow BJ, **Shroyer NF** (2013). SPDEF functions as a colorectal tumor suppressor by inhibiting β -catenin activity. **Gastroenterology.** 144: 1012-1023.

Spence JR, Mayhew CN, Rankin SA, (...), **Shroyer NF**, Wells JM (2011). Directed differentiation of human pluripotent stem cells into intestinal tissue *in vitro*. **Nature.** 470: 105-9.

Kazanjan A, Noah T, Brown D, Burkart J, **Shroyer NF** (2010). Atonal homolog 1 is required for growth and differentiation effects of notch/gamma-secretase inhibitors on normal and cancerous intestinal epithelial cells. **Gastroenterology.** 139: 918-28.

✉ NOAH.SHROYER@BCM.EDU

IGNATIA B. VAN DEN VEYVER, M.D.

Professor and Vice Chair of Research, Department of Obstetrics & Gynecology
Professor, Department of Molecular and Human Genetics; Graduate Programs in Development, Disease Models & Therapeutics and Genetics & Genomics

Director, Clinical Translational Research Certificate of Added Qualification (CTR-CAQ) program

Director of Prenatal & Reproductive Genetics, Department of Molecular and Human Genetics

M.D., University of Antwerp

Resident, Obstetrics and Gynecology, Univ. of Antwerp Affiliated Hospitals, Belgium

Fellow, Maternal-Fetal Medicine, Baylor College of Medicine

Fellow, Genetics, Baylor College of Medicine

RESEARCH INTERESTS

My lab studies how maternal effect mutations in genes that code for proteins of the oocyte subcortical maternal complex, which is essential for oocytes and embryos, cause infertility due to early embryo arrest, multilocus imprinting defects that lead to recurrent pregnancy failure in particular molar pregnancies, and congenital anomalies in offspring. We also conduct research on the cause of Aicardi syndrome, an elusive likely X-linked, neurodevelopmental disorder, that affects primarily girls who have eye and brain abnormalities, severe seizures and intellectual disability. For my clinical translational research, I investigate the benefits and challenges of introducing new genomic technologies, such as arrays, non-invasive prenatal screening, and genome-wide sequencing into prenatal diagnosis and care. We participate in a multicenter NIH-funded study to evaluate the clinical and diagnostic utility of trio prenatal whole genome sequencing for pregnancies with fetal structural congenital anomalies.



SELECTED PUBLICATIONS

Anvar Z, Jochum MD, Chakchouk I, Sharif M, Demond H, To AK, Kraushaar DC, Wan YW, Mari MC, Andrews S, Kelsey G, **Van den Veyver IB** (2025). Maternal loss of mouse *Nlrp2* alters the transcriptome and DNA methylation in GV oocytes and impairs zygotic genome activation in embryos. **Clin Epigenetics.** 17(1): 92.

Anvar Z, Chakchouk I, Sharif M, Mahadevan S, Nasiotis ET, Su L, Liu Z, Wan YW, **Van den Veyver IB** (2023). Loss of the maternal effect gene *Nlrp2* alters the transcriptome of ovulated mouse oocytes and impacts expression of histone demethylase *KDM1B*. **Reprod Sci.** 30: 2780-93.

Zemet R, Parobek CM, Adams AD, Maktabi MA, Shay L, Meng L, Liu P, Dai H, Xia F, Eng C, **Van den Veyver IB**, Vos-
saert L (2025). Diagnostic yield of exome sequencing for pregnancies with and without fetal anomalies and for stillbirth. **Prenat Diagn.** 45: 1313-24.

✉ IVEYVER@BCM.EDU X @IGNAVDVEYVER

JAMES VERSALOVIC, M.D., PH.D.

Milton J. Finegold Professor of Pathology & Immunology

Professor, Departments of Pathology & Immunology; Pediatrics, Molecular and Human Genetics and Molecular Virology & Microbiology; Graduate Program in Immunology & Microbiology

Co-Director, Medical Scientist Training Program, Baylor College of Medicine

Pathologist-in-Chief and Head of Pathology, Texas Children's Hospital

Director, Texas Children's Microbiome Center, Texas Children's Hospital

M.D., Ph.D., Baylor College of Medicine

Postdoc, Digestive Diseases, Baylor College of Medicine

Resident, Clinical Pathology, Massachusetts General Hospital

Clinical Fellow, Pathology, Harvard Medical School

Postdoc, Comparative Medicine, Massachusetts Institute of Technology

RESEARCH INTERESTS

The Versalovic laboratory seeks to understand the nature of the mammalian gut microbiome and how gut bacteria (and probiotics) impact mucosal immunity and intestinal inflammation. Primary clinical interests are inflammatory bowel disease and colorectal cancer. The body site of primary interest is the mammalian intestine (small and large) using mouse models, mouse and human cell lines, and human specimens. Our group links the study of bacterial genomes and metagenomes to the systems biology of the mammalian intestines.

We are actively exploring microbiome replacement and manipulation of the intestinal microbiome as models of fecal transplantation programs in humans. Our aim is to cure disease by fundamentally changing the function or composition of the intestinal microbiome to prevent or treat disease phenotypes such as IBD and cancer. We believe that this strategy represents the microbial cell and gene therapy of the future.

✉ JAMESV@BCM.EDU

CHERYL WALKER, PH.D.

Margaret and Albert Alkek Presidential Chair in Environmental Health

Director, Center for Precision Environmental Health

Professor, Departments of Molecular & Cellular Biology, Medicine, and Molecular and Human Genetics; Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

Director, NIH T32 Training Program in Precision Environmental Health

B.A. in Molecular, Cellular and Developmental Biology, University of Colorado-Boulder, 1977

Ph.D. in Cell Biology, The University of Texas Southwestern Medical School, 1984

RESEARCH INTERESTS

Our laboratory explores molecular mechanisms of disease pathogenesis, primarily cancer and metabolic diseases, including gene:environment interactions (GxE), and how the epigenome acts as a target, and determinant, of health and disease.

Environmental Determinants of Health and Disease. Our lab studies how early life environmental exposures disrupt the epigenome to increase susceptibility to adult diseases (Treviño et al., 2020). This work offers the potential to develop epigenetic biomarkers of early life exposure and/or future risk of disease, as well as new targets for intervention and disease prevention (Wang et al., 2018)

A New Function for the Epigenetic Machinery. We have also recently discovered that the epigenetic machinery that regulates chromatin also plays a key role remodeling the cytoskeleton (Park et al., 2016; Seervai et al., 2020; Karki, et al., 2021). We are currently studying the role, and potential importance, of this new biology for the neuronal cytoskeleton, and exploring how defects in dual-function chromatin-cytoskeleton remodelers contribute to autism spectrum disorder and other neurological diseases such as Huntington's Disease (Koenning, et al., 2021).

✉ CHERYL.WALKER@BCM.EDU



SELECTED PUBLICATIONS

Hemarajata P, Spinler JK, Balderas MA, **Versalovic J** (2014). Identification of a proton-chloride antiporter (EriC) by Himar1 transposon mutagenesis in *Lactobacillus reuteri* and its role in histamine production. **Antonie Van Leeuwenhoek**. 105: 579-92.

Thomas CM, Hong T, van Pijkeren JP, Hemarajata P, Trinh DV, Hu W, Britton RA, Kalkum M, **Versalovic J** (2012). Histamine derived from probiotic *Lactobacillus reuteri* suppresses TNF via modulation of PKA and ERK signaling. **PLoS One**. 7: e31951.

Preidis GA, Saulnier DM, Blutt SE, Mistretta TA, Riehle KP, Major AM, Venable SF, Barrish JP, Finegold MJ, Petrosino JF, Guerrant RL, Conner ME, **Versalovic J** (2012). Host Response to Probiotics Determined by Nutritional Status of Rotavirus-infected Neonatal Mice. **J Pediatr Gastroenterol Nutr**. 55: 299-307.



SELECTED PUBLICATIONS

Wang T, et al. (2018). The NIEHS TaRGET II Consortium and environmental epigenomics. **Nat Biotechnol**. 36: 225-227.

Treviño LS, et al. (2020). Epigenome environment interactions accelerate epigenomic aging and unlock metabolically restricted epigenetic reprogramming in adulthood. **Nat Commun**. 11: 2316.

Park IY, et al. (2016). Dual Chromatin and Cytoskeletal Remodeling by SETD2. **Cell**. 166: 950-962.

Karki M, et al. (2021). A cytoskeletal function for PBRM1 reading methylated microtubules. **Sci Adv**. 7: eabf2866.

Koenning M, et al. (2021). Neuronal SETD2 activity links microtubule methylation to an anxiety-like phenotype in mice. **Brain**. 144: 2527-2540.

ROBERT A. WATERLAND, PH.D.

Professor, Departments of Pediatrics and Molecular and Human Genetics; USDA/ARS Children's Nutrition Research Center; Graduate Program in Genetics & Genomics

Ph.D., Cornell University
Postdoc, Duke University

RESEARCH INTERESTS

In the Waterland laboratory, we work to understand how nutrition and other environmental influences on developmental epigenetics affect risk of disease later in life. Epigenetic mechanisms are established during development to regulate cell type-specific gene expression. Of these we focus on DNA methylation because it is the most stable, enabling lifelong persistence. Following up on our earlier studies on early nutritional influences at the agouti viable yellow locus (a mouse metastable epiallele) we are identifying human metastable epialleles and characterizing phenotypic consequences of individual epigenetic variation at these loci.

Another focus is the role of epigenetic dysregulation in obesity. We use mouse models to study how fetal and early postnatal exposures affect developmental epigenetics in the hypothalamus to alter lifelong energy balance.

In collaboration with experts in nutrition, computational biology, developmental neuroanatomy, and epidemiology, we apply genome-wide epigenomic profiling (Bisulfite-seq, RNA-seq, etc.) and sophisticated computational analysis. Our mouse work also employs methods to study neuroanatomical and cell type-specific epigenetic alterations.



SELECTED PUBLICATIONS

Gunasekara CJ, Hannon E, MacKay H, Coarfa C, McQuillin A, Clair DS, Mill J, **Waterland RA** (2021). A machine learning case-control classifier for schizophrenia based on DNA methylation in blood. **Transl Psychiatry**. 11: 412.

MacKay H, Scott CA, Duryea JD, Baker MS, Laritsky E, Elson AE, Garland T, Fiorotto ML, Chen R, Li Y, Coarfa C, Simerly RB, **Waterland RA** (2019). DNA methylation in AgRP neurons regulates voluntary exercise behavior. **Nat Commun**. 10: 5364.

Gunasekara CJ, Scott CA, Laritsky E, Baker MS, MacKay H, (...), **Waterland RA** (2019). A genomic atlas of systemic interindividual epigenetic variation in humans. **Genome Biol**. 20: 105.

✉ WATERLAND@BCM.EDU

MINGSHAN XUE, PH.D.

Associate Professor, Departments of Neuroscience and Molecular and Human Genetics; Graduate Programs in Development, Disease Models & Therapeutics; Genetics & Genomics; and Neuroscience

Investigator, Jan and Dan Duncan Neurological Research Institute

Ph.D., Baylor College of Medicine
Postdoctoral fellow, University of California, San Diego

RESEARCH INTERESTS

The long-term research goal of my laboratory is to understand how dysfunction of neural circuits contributes to the pathogenesis of neurodevelopmental disorders and harness this knowledge to develop therapies. Human genetic studies of neurodevelopmental disorders continue to uncover pathogenic mutations in genes encoding synaptic proteins. However, the functional roles of these proteins in neural circuits and behaviors are poorly understood because in-depth neurological and behavioral studies in animal models are often lacking. Consequently, the pathological mechanisms underlying these synaptic disorders remain elusive and the therapeutic interventions are limited. We believe that this knowledge gap can be significantly narrowed by studying a few prioritized genes that are highly penetrant and affect a broad spectrum of neurological and neuropsychiatric features common among neurodevelopmental disorders. Thus, we are currently focusing on the mechanisms underlying circuit dysfunctions in mouse models of autism and epileptic encephalopathies, and ASO or AAV-based genetic therapies for these disorders. We collaborate with scientists from both academia and industry on multiple projects.



SELECTED PUBLICATIONS

Kim JH, Chen W, Chao ES, Rivera A, Kaku HN, Jiang K, Lee D, Chen H, Vega JM, Chin TV, Jin K, Nguyen KT, Zou SS, Moin Z, Nguyen S, **Xue M** (2024). GABAergic/glycinergic and glutamatergic neurons mediate distinct neurodevelopmental phenotypes of STXBP1 encephalopathy. **J Neurosci**. 44: e1806232024

Lee D, Chen W, Kaku HN, Zhuo X, Chao ES, Soriano A, Kuncheria A, Flores S, Kim JH, Rigo F, Jafar-Nejad P, Beaudet AL, Caudill MS, **Xue M** (2023). Antisense oligonucleotide therapy rescues disturbed brain rhythms and sleep in juvenile and adult mouse models of Angelman syndrome. **eLife**. 12: e81892.

Chen W, Cai ZL, Chao ES, (...), Zoghbi HY, Tang J, Swann JW, **Xue M** (2021). Stxbp1/Munc18-1 haploinsufficiency impairs inhibition and mediates key neurological features of STXBP1 encephalopathy. **eLife**. 9: e48705.

✉ MXUE@BCM.EDU X @MINGSHANXUE

BAYLOR COLLEGE OF MEDICINE

Located in Houston, Baylor College of Medicine is internationally recognized as a premiere academic health science center. The College is known for excellence in education, research and patient care.

In 1903, the medical school began an affiliation with Baylor University that lasted until 1969, when Baylor College of Medicine became an independent institution. Originally located in Dallas, the College moved to Houston in 1943 to become the educational cornerstone of the Texas Medical Center.

Baylor College of Medicine is co-owner of Baylor St. Luke's Medical Center and has affiliations with seven additional teaching hospitals, each known for medical excellence. It also ranks consistently among the top U.S. medical schools in funding for research and development. The reputation of the College's distinguished faculty attract graduate, medical and health professions students from across the United States and throughout the world.



Baylor College of Medicine's vision is to improve health through science, scholarship and innovation and its mission is to create knowledge and apply science and discoveries to further education, healthcare and community service locally and globally.



TEXAS MEDICAL CENTER



Aerial View of the Texas Medical Center

The Texas Medical Center is the largest medical complex in the world and comprises more than 1,345 acres dedicated to biomedical research and care. The total acreage combined with \$25 billion in gross domestic product makes the Texas Medical Center the eighth largest business district in the U.S. Among its components are several medical schools, renowned hospitals, academic and research institutions, nursing programs, public health organizations, universities, pharmacy schools, a dental school and 13 support organizations.

Although the member institutions of the TMC operate under independent direction, there is considerable inter-institutional cooperation and scientific collaboration. Frequent seminars permit students and faculty of the many institutions to benefit from the broad base of local scientific expertise.

The Texas Medical Center is home to the world's largest children's hospital, Texas Children's Hospital, and the world's largest cancer hospital, the University of Texas MD Anderson Cancer Center. The TMC has 10 million visits per year and over 106,000 people are employed at its member institutions. It has the highest concentration of life sciences professionals in the country.

Adjacent to the Museum District, the Texas Medical Center is located in one of the most attractive areas in Houston. The TMC adjoins the trees and ponds of Hermann Park, with its zoo, golf course, fountains, hike-and-bike trails and children's areas such as playgrounds, ponds and a miniature railroad. Both the nearby University of Houston and Rice University add to the youthful, academic ambience of this section of the city. There are many cafés, bookstores, music and theater groups, film series and art exhibits.



Texas Children's Pavillion for Women and Texas Children's Hospital

HOUSTON

When you think about Houston, do you envision cowboys and tumbleweeds? Well, forget those ideas. Contrary to these preconceived notions, Houston – the fourth most populous city in the United States – boasts modern industries, a thriving intellectual and cultural environment, lush vegetation, and much more.

Houston is an international city that is a leader in the arts, education and healthcare, and has a top-rated culinary scene that is continuing to gain national attention. The same vision and entrepreneurial spirit that made Houston the energy capital of the world has given rise to global companies in a wide array of industries.

Toss out any images of dusty plains, because Houston is full of trees and boasts 20,000 acres of parks, public green space and open water. The city offers an abundance of recreational activities, restaurants, shopping, cultural performances, entertainment and sporting events.

Take a quick look at what makes Houston such a great place to live, get an education and work:

The people: Houston is the fourth largest U.S. city. Thirty-seven percent are 24 or younger, and 32 percent are between ages 25-44. Houston has a multicultural population of more than 5.5 million and is considered to be the most diverse, large metropolitan area in the United States.

The low cost of living: This means affordable housing. Plus, there are no state or local income taxes. How can it get better?

The job market: Houston has an expanding economy in diverse industries. Have you checked out careers at Baylor?

The weather: In the winter, you may need a light jacket but ice or snow won't keep you from enjoying the outdoors. With an average temperature year-round of 68 degrees and average rainfall of 46 inches, you can enjoy the outdoors as



much as you'd like.

The entertainment: Really, it's impossible to be bored here. There are entertainment options for all ages, including a permanent ballet, opera, symphony and theater companies, dozens of top-notch museums and so much more. Don't forget that Houston is home to NASA's Johnson Space Center, too.

The food: Houston has 11,000 restaurants (and counting!), which serve every type of cuisine you could think of, both brick-and-mortar establishments and food trucks. It's not just BBQ and Tex-Mex (though you're missing out if you haven't tried these cuisines here).

The sports: Sports fans, you'll never wait too long for the next game. You'll find plenty of professional and college sports here.

The shopping: You'll save money with the low cost of living in Houston, but there's no shortage of stores, malls, boutiques and more in the city!

The education: Houston offers more than 40 colleges, universities and institutes.

BAYLOR COLLEGE OF MEDICINE, AFFILIATED HOSPITALS, INSTITUTIONS AND FACILITIES



Baylor College of Medicine

ONE BAYLOR PLAZA
HOUSTON, TEXAS, USA 77030
MS BCM225

BCM.EDU/GENETICS

BLUESKY: @BCMGENETICS.BSKY.SOCIAL

FACEBOOK: [HTTPS://WWW.FACEBOOK.COM/BCM.MHG](https://www.facebook.com/bcm.mhg)

INSTAGRAM: @BCMGENETICS

X: @BCMGENETICS

Support the Department of Molecular and Human
Genetics at Baylor College of Medicine

