Baylor College of Medicine

# MOLECULAR AND HUMAN GENETICS

# 2023

## 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.

## BAYLOR COLLEGE OF MEDICINE DIVERSITY AND INCLUSION POLICY

Baylor College of Medicine fosters diversity among its students, trainees, faculty and staff as a prerequisite to accomplishing our institutional mission, and setting standards for excellence in training healthcare providers and biomedical scientists, promoting scientific innovation, and providing patient-centered care.

- Diversity, respect, and inclusiveness create an environment that is conducive to academic excellence, and strengthens our institution by increasing talent, encouraging creativity, and ensuring a broader perspective.

- Diversity helps position Baylor to reduce disparities in health and healthcare access and to better address the needs of the community we serve.

- Baylor is committed to recruiting and retaining outstanding students, trainees, faculty and staff from diverse backgrounds by providing a welcoming, supportive learning environment for all members of the Baylor community.

## 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 police (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

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 great strides in the evolution of genetic medicine.

The Department remains a top-ranked genetics program, ranking first among other U.S. genetic departments in total awarded NIH funding and number of grants for over a decade.

We continue to lead in the diagnostic testing arena with Baylor Genetics, our joint venture with H.U. Group Holdings, Inc. This jointly governed laboratory supports the academic mission and innovation of the department while promising to extend the impact of genetic diagnostic testing worldwide including, most recently, for infectious diseases.

Our faculty continue to deliver our clinical, training and research missions at home and abroad through our ongoing partnership with the Chinese University of Hong Kong Center for Medical Genetics.

During this past year, Baylor was recognized on Gizmodo's Degrees of the Future 2022 list as one of the top genetics and genomics programs and as a Center of Excellence by the National Organization of Rare Disorders.

In addition, new and continuing consortia with the National Institutes of Health and industry are leading to new gene discoveries and advancements in the implementation of genetics and genomics. These consortia include the *All of Us* program, GREGoR: Genomic Research to Elucidate the Genetics of Rare disease, the Knockout Mouse Phenotyping Program, the Center for Precision Medicine Models, Clinical Genome Resource, Clinical Sequencing Evidence-Generating Research, and the Rare Diseases Clinical Research Networks.

We recently formed a new center to continue the work of Baylor's Undiagnosed Disease Network (UDN) clinical site, DNA sequencing core and model organisms screening center by providing clinical services and genetic testing and analysis to assess patients who have not received a diagnosis for their condition. This new Undiagnosed Diseases Center (UDC) will utilize the new self-service capabilities of the Consultagene platform.

Another exciting development has been the beginning of Baylor's *All of Us Evenings with Genetics* Research Program, a program that aims to engage researchers from diverse backgrounds, including those from underrepresented groups, in utilizing the NIH's *All of Us* Research Program data resources to advance precision medicine.

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,

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

# CONTENTS

# ABOUT THE DEPARTMENT

*Huda Zoghbi, M.D. and Rodney Samaco, Ph.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 five decades of organized genetics activity at Baylor College of Medicine. Starting 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 in Molecular and Human Genetics, 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; prenatal, pediatric and adult medical genetics care; and cutting-edge genetic diagnostic services.

We have more than 530 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. Our faculty include three members of the National Academy of Sciences, seven members of the National Academy of Medicine and nine fellows of the American Association for the Advancement of Science.

The Human Genome Sequencing Center led by Dr. Richard Gibbs, Wofford Cain Chair in Molecular and Human Genetics, is a major strength of the environment. Other academic centers and units led by genetics faculty include the Neurological Research Institute led by Dr. Huda Zoghbi and the Huffington Center on Aging led by Dr. Hui Zheng.

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. Our facilities are equipped with state-of-the-art instrumentation for research in molecular, cellular and biochemical genetics. There are also several specialized research centers that galvanize collaboration among faculty at Baylor within the department. We also have extended our mission globally with a clinical center 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 about 175,000 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

**CHAIRMAN**

Brendan Lee, M.D., Ph.D.

**DEPARTMENT ADMINISTRATOR**

Laura Rosales, Ed.D., M.B.A.

**FACULTY ADVISORY COMMITTEE**

**DIAGNOSTIC LABORATORY AFFAIRS**
**Vice Chair**

Christine Eng, M.D.

**RESEARCH AFFAIRS**
**Vice Chairs**

Kim Worley, Ph.D.
Basic & Translational

Sandesh Nagamani, M.D.
Clinical

**EDUCATIONAL AFFAIRS**
**Vice Chairs**

Gad Shaulsky, Ph.D.
Graduate Education

Lorriane Potocki, M.D.
Undergraduate Medical Education

Daniel Riconda, M.S., C.G.C.
Masters of Genetic Counseling Program

V. Reid Sutton, M.D.
Graduate Medical Education

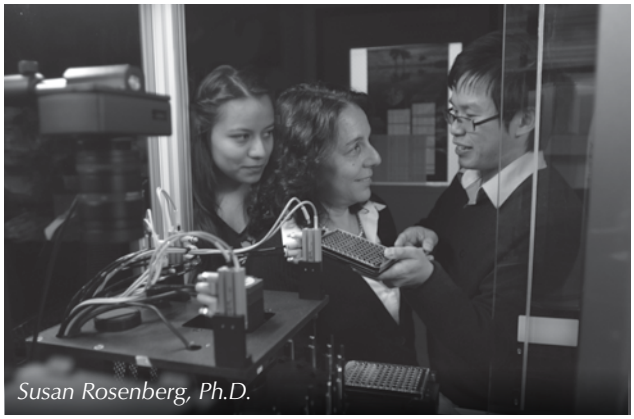
**CLINICAL AFFAIRS**
**Vice Chair**

Carlos Bacino, M.D.

**OFFICE OF COMMUNITY ENGAGEMENT & DIVERSITY**
**Co-Directors**

Debra Murray, Ph.D.

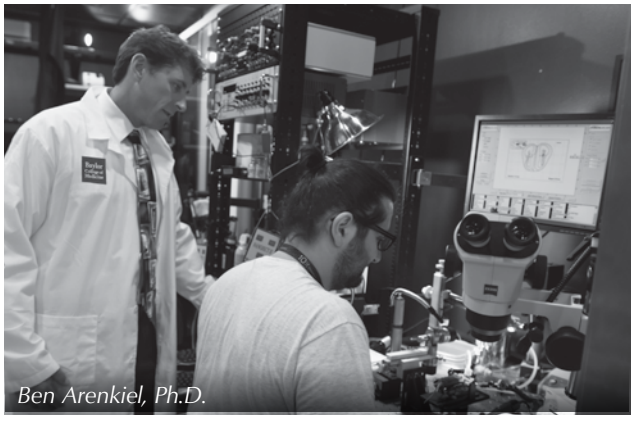
Laura Rosales, Ed.D., M.B.A.



*Susan Rosenberg, Ph.D.*


*Penelope Bonnen, Ph.D. and Alison Bertuch, M.D., Ph.D.*

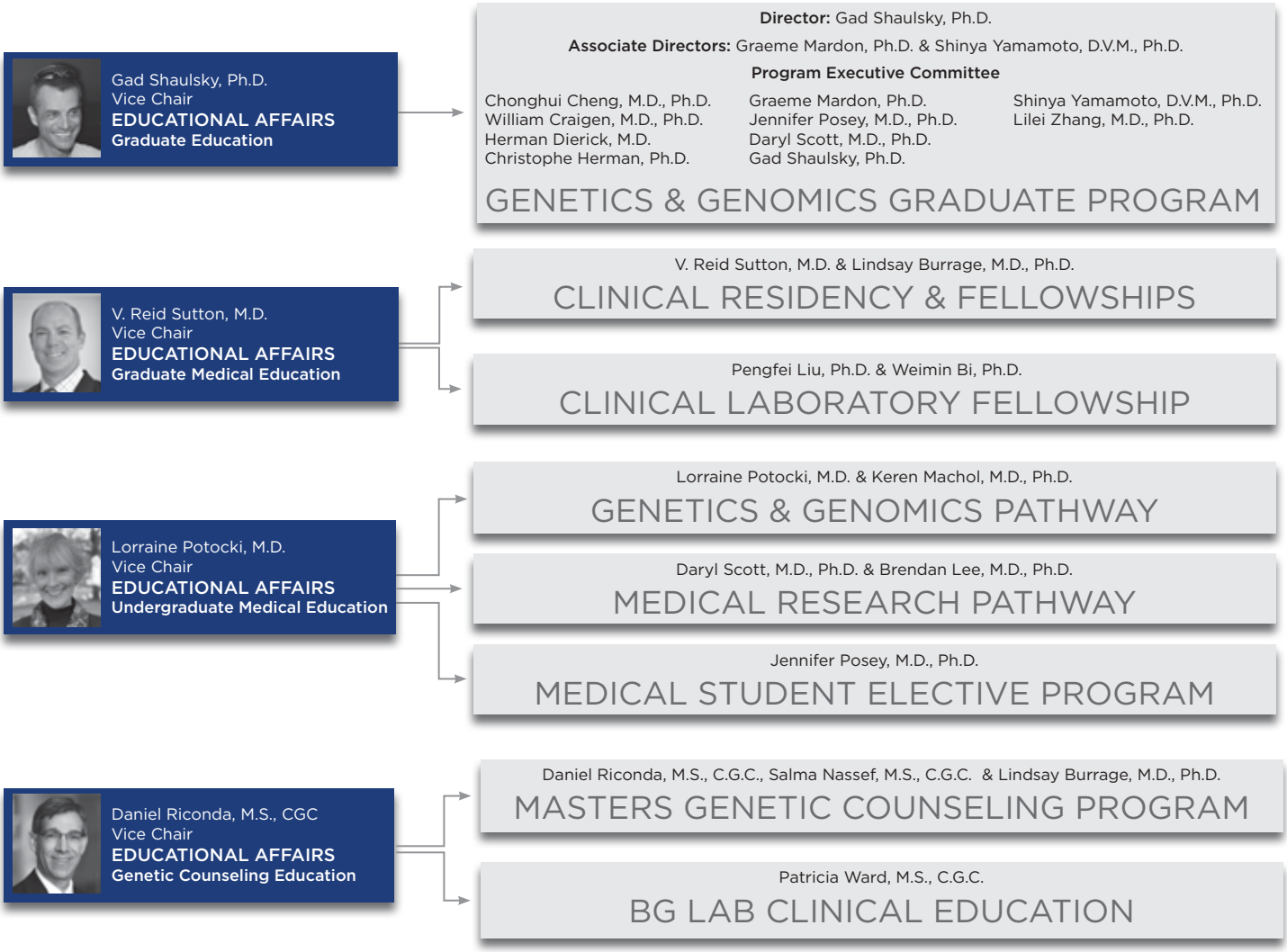
*Andy Groves, Ph.D.*



*Ben Arenkiel, Ph.D.*

# 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 considerably further in Houston where the cost of living is considerably lower than in other large U.S. cities. Students who enroll in 2023-2024 will receive $35,500 per year. Tuition, medical and dental insurance are also 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 very broad range from the study of the basic principles of DNA replication and repair to DNA recombination, cell cycle control, aging, 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 rapidly 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 advisor.

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 term 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 advisor 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 the 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
Graeme Mardon, Ph.D., Associate 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 is 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 (1) building upon the foundation of basic genetic principles provided in the pre-clerkship curriculum with additional educational experiences in medical genetics, (2) enhancing the medical student experience to include a broad range of patients with genetic conditions, (3) developing the student's appreciation for the nuances inherent in performing and interpreting clinical diagnostic analyses in biochemical genetics, molecular genetics and cytogenetics, (4) 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, (5) preparing students to author a scholarly publication and/or presentation, and (6) providing students a means to network and discuss various topics and career paths in medical genetics.

**Track Directors**
Lorraine Potocki, M.D.
Keren Machol, M.D., Ph.D.

## POSTDOCTORAL RESEARCH TRAINING

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

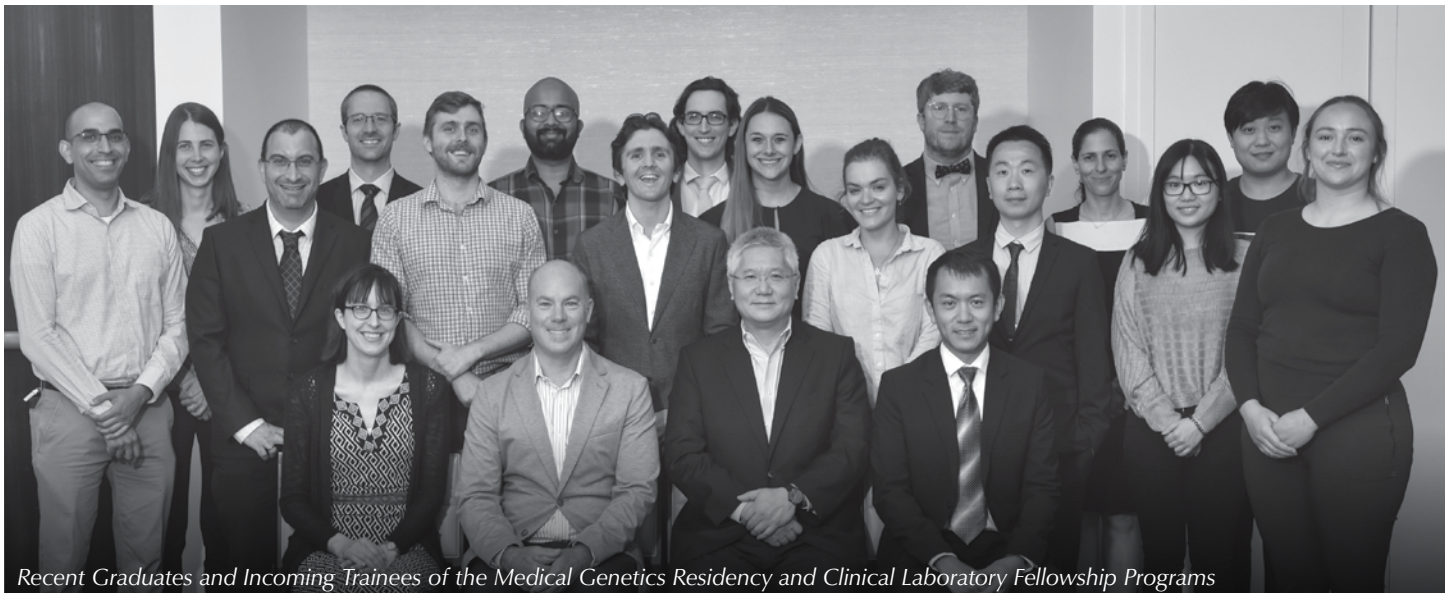
## RESIDENCY AND FELLOWSHIP TRAINING PROGRAMS

**The Medical Genetics and Genomics Residency Programs** are accredited by the Accreditation Council for Graduate Medical Education (ACGME). We 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 & 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 large 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.

Our **Clinical Biochemical Genetics** and **Laboratory Genetics and Genomics (LGG)** fellowships are also



*Recent Graduates and Incoming Trainees of the Medical Genetics Residency and Clinical Laboratory Fellowship Programs*

accredited by the ACGME. We offer two-year fellowship training in both programs. LGG is a specialty of the ABMGG that incorporates training in both 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 over 20 laboratory directors as well as 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

Pengfei Liu, Ph.D., LGG Program Director
Weimin Bi, 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, expert services for genetic disorders and collaborative research with cutting-edge genetic and genomic technology.

The aims of the Center are to (1) design, establish and conduct professional development activities and training in medical genetics and genetic counseling to fit the increasing need in Asia, (2) establish a leading referral center in Asia for prenatal and postnatal diagnosis and treatment for patients and families affected by genetic disorders, (3) conduct cutting-edge, interdisciplinary research that will lead to advances in screening, diagnosis and therapy of genetic disorders as well as new discovery of the underlying genetic mechanism of diseases, and (4) 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 Students and Alumni*

## GENETIC COUNSELING PROGRAM

The Baylor College of Medicine Genetic Counseling Program was accredited in February of 2018 and graduated its first class of eight students in June of 2020. The program now admits 9 students and has plans to increase enrollment further in the future. The 22-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 and the Children's Hospital of San Antonio, 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
Lindsay Burrage, M.D., Ph.D., Medical Director

# DIVISION OF CLINICAL AFFAIRS


## GENETICS CLINICS

Baylor College of Medicine's Clinical Genetics Program holds the position as the largest clinical genetics program in the country, with 14 clinics spanning across multiple genetics-based disciplines. The clinical program takes a collaborative approach that provides patients with the highest quality, individualized care available.

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 outside (TCH West Campus and The Woodlands Texas Children's Hospital). The outpatient pediatric genetics clinics are among the largest genetics clinics in the country and see over 5,000 patients annually. Specialty clinics within the Texas Children's Genetics Clinic include the metabolic clinic, neurofibromatosis clinic, skeletal dysplasia clinic and the cancer genetics clinic. We also have many multidisciplinary team clinics like the Angelman Syndrome Clinic, the Center for Genetic Disorders of Obesity, Mitochondrial Medicine Clinic, and the Gender Medicine Program. The Department of Molecular and Human Genetics clinical and genetic counseling faculty also staff joint clinics with other departments such as otolarynogology (otogenetics) and neurology (neurogenetics/tuberous sclerosis).

The Adult Genetics Clinic is also one of the largest genetics clinics in the country, 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 our virtual Consultagene Clinic). We see patients 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 C.S. Nagamani, M.D. and Shweta Dhar, M.D., M.S.*

As the largest of its kind in the U.S., the Baylor Prenatal and Reproductive Genetics Clinic at Texas Children's Pavilion for Women with its seven associated Texas Children's community maternal-fetal medicine clinics is comprised of physicians and genetic counselors that specialize in prenatal and reproductive genetic risk assessment and the latest genetic testing technologies. Through its partnership with the department and the Texas Children's Fetal Center, the clinic offers world renowned clinical and research expertise in prenatal and reproductive genetic screening, diagnostic testing and counseling. Prenatal and reproductive genetic services and counseling are also offered at Ben Taub Tower Specialty Clinics and virtually through the Consultagene Clinic.

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

## 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 - Clinical Care Center
6701 Fannin St., 16th Floor
Houston, TX 77030

### Prenatal & Reproductive Genetics
Texas Children's Pavillion for Women
6651 Main Street
Houston, TX 77030

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

### Clinical Faculty
April Adams, M.D.
Carlos A. Bacino, M.D.
Mir Reza Bekheirnia, M.D.
Lindsay Burrage, M.D., Ph.D.
William J. Craigen, M.D., Ph.D.
Shweta Dhar, M.D., M.S.
Christine M. Eng, M.D.
Kevin Glinton, M.D., Ph.D.
Monika Weisz Hubshman, M.D., Ph.D.
Seema Lalani, M.D.

### Clinical Faculty (cont.)

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.
Chaya Murali, M.D.
Sandesh C.S. Nagamani, M.D.
Sharon E. Plon, M.D., Ph.D.
Jennifer Ellen Posey, 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.
Claudia Soler-Alfonso, M.D.
V. Reid Sutton, M.D.
Ignatia B. Van den Veyver, M.D.
Michael Francis Wangler, M.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
Susan Fernbach, B.A., R.N.
Alicia Turner, 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 approximately 50 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 genetic counselors provide services to patients throughout Houston and surrounding community areas, including Katy, The Woodlands and Sugar Land, and via telegenetic counseling through the Consultagene service. Prenatal genetic counselors often see couples who have an increased chance of having a child with a genetic condition or birth defect, women who will be over 35 years of age at the time of delivery, couples who have had recurrent miscarriages, couples who are carriers of a genetic condition or couples who have had abnormal genetic or prenatal screening tests, such as ultrasound or amniocentesis.

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 also 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 Clinic, and the Lester and Sue Smith Breast Center. 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, adults with intellectual disability or mitochondrial disorders.

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

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.
Lauren Desrosiers, M.S., C.G.C.
Tanya N. Eble, 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.
Hannah Helber, M.S., C.G.C.
Olivia Juarez, M.M.Sc., C.G.C.
Dana Knutzen, M.S., C.G.C.
Rebecca Littlejohn, 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.
Haley Streff, M.S., C.G.C.
Melissa Stuebben, M.S., C.G.C.
Cathy Sullivan, M.S., C.G.C.
Patricia Ward, M.S., C.G.C.
Lauren Westerfield, M.S., C.G.C.

### Genetic Counseling Staff

Taylor Beecroft, M.S., C.G.C.
Grant W. Bonesteele, M.S., C.G.C.
Shannon Bonner, M.S., C.G.C.
Wanda Dosal, RN
Stacey Edwards, M.S., C.G.C.
Dina El Achi, M.S.
Mikaela K. Francisco, M.S., C.G.C.
Jessica Honkomp, M.S., C.G.C.
Shontiara Johnson, M.S.
Farah Ladha, M.S., C.G.C.
Emily Magness, M.S., C.G.C.
Bailey Mitchell, M.S.
Morgan Nutter, M.S.
Lisa Saba, M.S., C.G.C.
Roa Sadat, M.M.Sc., C.G.C.
Emily Soludczyk, M.S., C.G.C.
Ashley Spector, M.S., C.G.C.
Abigail Yesso, M.S., C.G.C.
Shelly Zelnick, M.S., C.G.C.

# 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 innovation and operational excellence. By building on the Department of Molecular and Human Genetics's strengths in research and discovery, Baylor Genetics' mission is to provide quality genetic testing services relevant to twenty-first-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, COVID-19. In addition, 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 is located in Houston's Texas Medical Center with over 200 employees, over 3,000 tests available and clients in all 50 states and in 16 countries. Baylor Genetics is well-equipped with cutting-edge diagnostic equipment, allowing it to efficiently generate the most accurate clinical genetic data.

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

*Laboratory Technicians at Baylor Genetics*

are committed to the education and training of the next generation of clinical and laboratory diagnosticians through our participation in the ABMGG fellowship programs.

### Diagnostic Laboratory Faculty

Carlos Bacino, M.D.
Weimin Bi, Ph.D.
Sau Wai Cheung, Ph.D., M.B.A.
Hongzheng Dai, Ph.D.
Sarah Elsea, Ph.D.
Christine Eng, M.D.
Ning Liu, Ph.D.
Pengfei Liu, Ph.D.
Linyan Meng, Ph.D.
Brian Yang Merritt, M.D.
Nichole Owen, Ph.D.
Katharina Schultze, Ph.D.
Janice Smith, Ph.D.
Qin Sun, Ph.D.
Vernon Sutton, M.D.
Liesbeth Vossaert, Ph.D.
Yue Wang, Ph.D.
Fan Xia, Ph.D.
Xiaonan Zhao, Ph.D.

# COMMUNITY ENGAGEMENT AND DIVERSITY

**The Office of Community Engagement and Diversity** in the Department of Molecular and Human Genetics works alongside Baylor College of Medicine's Office of Institutional Diversity, Equity and Inclusion. In addition to genetic education programs for the community at large, the office and the department's **Diversity and Inclusion Strategic Planning Committee** have created a dashboard to guide future action steps to promote an environment that fosters inclusion, education and understanding for its faculty, trainees and staff. The office advances multiple approaches to education, recruitment and diversity and inclusion activities.

*Baylor TCH Rare Disease Day*

The **Evenings with Genetics series** has served the community for 16 years. The department partners with Texas Children's Hospital to offer this free seminar series open to the public. A genetics faculty member paired with faculty from another specialty area, plus a parent expert 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 include simultaneous translation to Spanish. During this past year, we celebrated our 16th anniversary with the second annual "Race and Genetics: Perspectives of Precision Medicine" webinar series during Black History Month.

Through a collaboration with the UT Texas Center for Disability Studies, the Texas Department of State Health Services and Texas Children's, 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** (virtual) is provided annually to present the genetics and genomics career path to high school and undergraduate students. The office will offer "Understanding Genetic Variations" sessions at national student research meetings (Annual Biomedical Research Conference for Minority Students, Society for Advancement of Chicanos/Hispanics & Native Americans in Science) to introduce genetics and genomics and encourage participation in the field.

The **Medical Genetics Diversity Visiting Students Program** was developed by the office to provide underrepresented fourth-year medical students a 4-week clinical rotation beginning in 2022. In 2021, we began the **Clinical Research Education Training Program (CRETP)** to introduce underrepresented first and second-year medical students to the field of medical genetics. The 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.

**"Let's Learn about One Another"** is a series of interactive presentations that began in the summer of 2020 to address the social injustice climate. The "Let's Learn" program includes perspectives from the department's widely diverse members. The program has offered the "Let's Learn about One Another: Understanding the African American Experience in America" (2020), "Let's Learn about One Another: Understanding the Asian American and Pacific Islander Experience in America" (2021), and "Let's Learn about One Another: Understanding the Hispanic/Latin/a/o Experience in America (2022) with faculty, graduate students, postdoctoral trainees and staff members sharing their experiences. The office also curates an online library of articles regarding diversity, inclusion and equity for department faculty, trainees and staff.

### Co-Directors

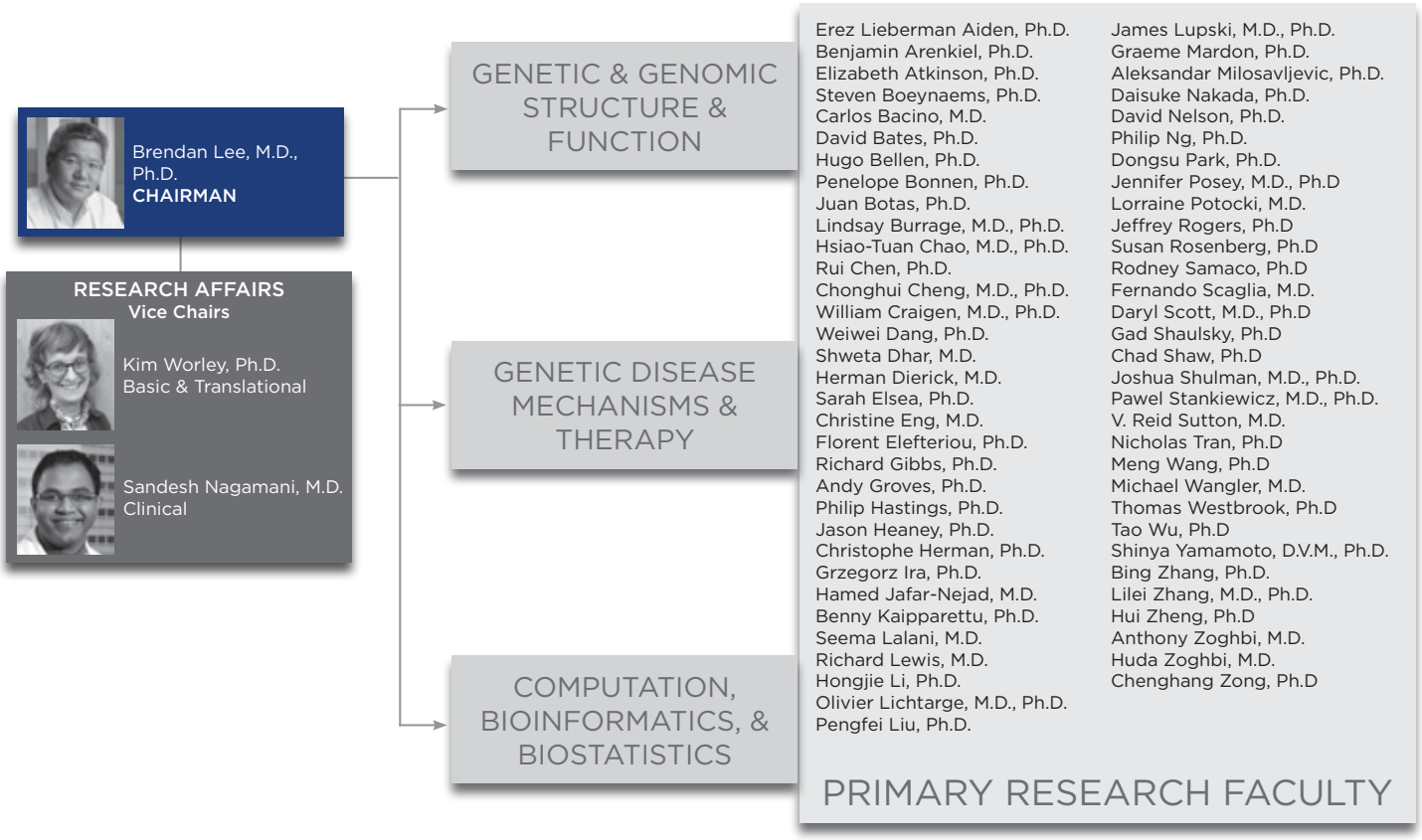
Debra Murray, Ph.D.
Laura Rosales, Ed. D., M.B.A.

### Diversity and Inclusion Strategic Planning Committee

Yangjin Bae, Ph.D.
Susan Fernbach, B.A., R.N.
Kevin Glinton, M.D.
Benny Kaipparettu, Ph.D.
David Li-Kroeger, Ph.D.
Graeme Mardon, Ph.D.
Liz Mizerik, M.S., C.G.C.
Chaya Murali, M.D.
Sandesh Nagamani, M.D.
Cameron Noreiga-Babb, B.S., M.P.H.
Gladys Pryor, B.S.
Brandy Thibodeaux, B.S.
Claudia Soler-Alfonso, M.D.

# 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

# EREZ AIDEN, PH.D.

**Assistant Professor**, Department of Molecular and Human Genetics
**Assistant Professor**, Departments of Computer Science and Computational and Applied Mathematics, Rice University
**Faculty Member**, Graduate Programs in Genetics & Genomics and Quantitative & Computational Biosciences
**CPRIT Scholar in Cancer Research**
**Emeritus McNair Scholar**

*Ph.D., Harvard University and Massachusetts Institute of Technology*
*Fellow, Society of Fellows, Harvard University*

## RESEARCH INTERESTS

A genome is a miraculous physical mechanism for compactly storing and rapidly accessing information. Recall that if you put a pair of headphones into your pocket, and pull them out a bit later, they've invariably become phenomenally extremely entangled. But the giant neurons of the sea hare, Aplysia, can take 200 trillion base pairs – half a petabyte of information, a genomic string the length of Long Island – and fold them up into a nucleus smaller than cubic millimeter, while keeping all those bits accessible at all times.

A central focus of our laboratory is the question of how this is achieved. How are the genomes of humans and other organisms folded, in three dimensions, inside the nucleus of a functioning cell? How is this folding process controlled? And how does this folding process, in turn, regulate other cellular processes? To answer these questions, we combine the development of new molecular technologies, high-throughput DNA sequencing and powerful computational and biophysical methods.

The lab is also extremely interested in the application of massive datasets - including, but not limited to, DNA sequence - as an approach to making previously intractable measurements possible. Three-dimensional genome sequencing is one example, but there are many, many others, ranging across many fields. Recently, our work led to the creation of the Google Ngram Viewer.

## SELECTED PUBLICATIONS

**Lieberman-Aiden E***, van Berkum NL*, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, Sabo PJ, Dorschner MO, Sandstrom R, Bernstein B, Bender MA, Groudine M, Gnirke A, Stamatoyannopoulos J, Mirny LA, Lander ES, Dekker J (2009). Comprehensive mapping of long-range interactions reveals folding principles of the human genome. **Science**. 326: 289-93. *Equal contribution

Mikkelsen TS, Ku M, Jaffe DB, Issac B, **Lieberman E**, Giannoukos G, Alvarez P, Brockman W, Kim TK, Koche RP, Lee W, Mendenhall E, O'Donovan A, Presser A, Russ C, Xie X, Meissner A, Wernig M, Jaenisch R, Nusbaum C, Lander ES, Bernstein BE (2007). Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. **Nature**. 448: 553-60.

Michel JB*, Shen YK, Aiden AP, Veres A, Gray MK; Google Books Team, Pickett JP, Hoiberg D, Clancy D, Norvig P, Orwant J, Pinker S, Nowak MA, **Aiden EL*** (2011). Quantitative analysis of culture using millions of digitized books. **Science**. 331: 176-82. *Co-corresponding, equal contribution

**Lieberman E***, Michel JB*, Jackson J, Tang T, Nowak MA (2007). Quantifying the evolutionary dynamics of language. **Nature**. 449: 713-6. *Equal contribution

Ohtsuki H, Hauert C, **Lieberman E**, Nowak MA (2006). A simple rule for the evolution of cooperation on graphs and social networks. **Nature**. 441: 502-5.

Lieberman E, Hauert C, Nowak MA (2005). Evolutionary dynamics on graphs. **Nature**. 433: 312-6.

**Lieberman Aiden E** (2011). GE Prize essay. Zoom!: exploring how the genome folds by using three dimensional genome sequencing. **Science**. 334: 1222-3.

Shendure J, **Lieberman Aiden E** (2012). The expanding scope of DNA sequencing. **Nat Biotechnol**. 30: 1084-94.

Dekker J, Wysocka J, Mattaj I, **Lieberman Aiden E**, Pikaard C (2013). Nuclear biology: what's been most surprising? **Cell**. 152: 1207-8.

# BENJAMIN R. ARENKIEL, PH.D.

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

*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

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.

Herman AM, Huang L, Murphey DK, Garcia I, **Arenkiel BR** (2014). Cell type-specific and time-dependent light exposure contribute to silencing in neurons expressing Channelrhodopsin-2. **ELife**. 3: e01481.

Garcia I, Huang L, Ung K, **Arenkiel BR** (2012). Tracing Synaptic Connectivity onto Embryonic Stem Cell-Derived Neurons. **Stem Cells**. 30: 2140-51.

# ELIZABETH ATKINSON, PH.D.

**Assistant Professor**, Department of Molecular and Human Genetics

*Ph.D., Washington University in St. Louis*
*Postdoc, 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 key (brain) genes in 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. 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.

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

Nievergelt CM, Maihofer AX, Klengel T, **Atkinson EG**, (...), Koenen KC (2019). International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. **Nat Comm.** 10: 4558.

Martin AR, Lin M, Granka JM, Myrick JW, Liu X, Sockell A, **Atkinson EG**, (...), Henn BM (2017). An Unexpectedly Complex Architecture for Skin Pigmentation in Africans. **Cell**. 171: 1340-1353.e14.

Sugden LA, **Atkinson EG**, Fischer AP, Rong S, Henn BM, Ramachandran S (2018). Localization of adaptive variants in human genomes using averaged one-dependence estimation. **Nat Comm.** 9: 703.

Gopalan S, **Atkinson EG**, Buck LT, Weaver TD, Henn BM (2021). Inferring archaic introgression from hominin genetic data. **Evol Anthropol.** 30: 199-220.

Martin AR, **Atkinson EG**, Chapman SB, Stevenson A, Stroud RE, (...); NeuroGAP-Psychosis Study Team (2021). Low-coverage sequencing cost-effectively detects known and novel variation in underrepresented populations. **Am J Hum Genet.** 108: 656-668.

Trubetskoy, V., Schizophrenia Working Group of the Psychiatric Genomics Consortium (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. **Nature.** 604: 502–508.

ELIZABETH.ATKINSON@BCM.EDU @EGATKINSON

# 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. I am directly involved in the supervision and training of medical students, residents and fellows. As the Medical Director of the Cytogenetics Laboratory at Baylor Genetics, 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. We have followed a large group of Angelman syndrome patients at Texas Children's Hospital for developmental, clinical and EEG evaluations on a yearly basis (Natural History study). This study has allowed us to understand progression, complications and co-morbidities associated with this condition. We have also concluded two different clinical trials using betaine, creatine and folic acid/metafolin to promote methylation and revert silencing of the paternal allele. Our group is participating in a phase II clinical research trial through a pharmaceutical company using a locked nucleic acid RO7248824 (antisense oligonucleotide drug) given intrathecally to establish dosage and safety. Our group is also involved in another antisense Phase II trial sponsored by IONIS (ION582) administered intrathecally. These antisense drugs attempt to activate the paternal UBE3A gene and ameliorate the symptoms of Angelman syndrome by altering patterns of imprinting. We currently run a multidisciplinary clinic 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 3 clinical research trial using a recombinant cartilage natriuretic peptide (CNP) also known as vosoritide (BMN-111), a drug we anticipate will promote linear and more proportionate skeletal growth in these patients. This drug was recently approved by the FDA for 5 years and older. We continue with studies on children under 5 years of age. We are part of two other trials, one using a long-acting recombinant CNP, and the last using an FGFR3 decoy therapy agent.

**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 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.

# 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

**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., University of Ghent, 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 that biochemical pathways that also play a role in Parkinson's disease, Amyotrophic Lateral Sclerosis, and Alzheimer's Disease are affected. 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 and John Postlethwhait and Monte Westerfield at the University of Oregon were selected by the Undiagnosed Diseases Network (UDN) to direct the Model Organism Screening Center (MOSC) for the UDN of the U.S. Through close collaborations with human geneticists and physicians, we have identified variants in human genes that are associated with neurological diseases in children. We have so far participated in the discovery of the genetic causes of 35 human diseases in the past five 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 drugs for four diseases.

My lab also plays an important role in developing new tools to manipulate flies as well as generating reagents for the fly community. I have been the PI of the Gene Disruption Project for 17 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.

I have excellent resources via NIH and private foundations and I am truly dedicated to graduate education and postdoctoral training as is obvious from the success of my former trainees.

**WEBSITE: FLYPUSH.RESEARCH.BCM.EDU**

## SELECTED PUBLICATIONS


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.

Marcogliese PC, Dutta D, (...), Yeo NC, **Bellen HJ** (2022). Loss of IRF2BPL impairs neuronal maintenance through excess Wnt signaling. **Sci Adv.** 8: eabl5613.

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.e6.

Link N, Chung H, Jolly A, (...), Lupski JR, **Bellen HJ** (2019). Mutations in ANKLE2, a ZIKA virus target, disrupt an asymmetric cell division pathway in *Drosophila* neuroblasts to cause microcephaly. **Dev Cell.** 51: 713-729.e6.

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.

Yoon WH, Sandoval H, Nagarkar-Jaiswal S, Jaiswal M, Yamamoto S, Haelterman NA, (...), Wangler MF, Karaca E, Lupski JR, **Bellen HJ** (2017). Loss of Nardilysin, a mitochondrial co-chaperone for α-ketoglutarate dehydrogenase, promotes mTORC1 activation and neurodegeneration. **Neuron.** 93: 115-131.

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, Charng 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.

**Professor**, Department of Molecular and Human Genetics
**Investigator**, Jan and Dan Duncan Neurological Research Institute
**Faculty Member,** Center for Alzheimer's and Neurogenerative Disease, Therapeutic Innovation Center, Dan L Duncan Comprehensive Cancer Center

*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 biophysical 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.

## SELECTED PUBLICATIONS

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

Fazal R, **Boeynaems S**, Swijsen A, De Decker M, Fumagalli L, (...), Van Damme P (2021). HDAC6 inhibition restores TDP-43 pathology and axonal transport defects in human motor neurons with TARDBP mutations. **EMBO J.** 40: e106177. *co-first authors

Tazelaar GHP*, **Boeynaems S***, De Decker M*, van Vugt J, Kool L, (...), Project MinE ALS Sequencing Consortium, (...), van Es MA (2020). ATXN1 repeat expansions confer risk for amyotrophic lateral sclerosis and contribute to TDP-43 mislocalization. **Brain Commun.** 2: fcaa064. *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.

**Boeynaems S***, Bogaert E*, Michiels E, Gijselinck I, Sieben A, (...), Van Den Bosch L (2016). *Drosophila* screen connects nuclear transport genes to DPR pathology in c9ALS/FTD. **Sci Rep.** 6: 20877. *co-first authors

# 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.

**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

*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.**, in press.

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 G, 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 CGG 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.

**Assistant 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 model of argininosuccinate lyase deficiency (ASLD). We are using an ASL-deficient mouse model to investigate mechanisms underlying the chronic hepatic complications observed in our patients. 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. We are currently dissecting the role of altered energy metabolism and hepatic glycogen accumulation in ASL-deficient mice. We are also exploring molecular and biochemical mechanisms by which ASL deficiency causes chronic liver disease using in vitro and in vivo models.

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 BCM, I have a leadership role in the sequence analysis team (e.g. whole 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 new BCM 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

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.

Almannai M, Marom R, Divin K, Scaglia F, Sutton VR, Craigen WJ, Lee B, **Burrage LC**, Graham BH (2017). Milder clinical and biochemical phenotypes associated with the c.482G>A (p.Arg161Gln) pathogenic variant in cobalamin C disease: Implications for management and screening. **Mol Genet Metab.** 122: 60-66.

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.

Chong JX*, **Burrage LC***, (...), University of Washington Center for Mendelian Genomics, Bamshad MJ (2015). Autosomal-Dominant Multiple Pterygium Syndrome is Caused by Mutations in MYH3. **Am J Hum Genet**. 96: 841-9. *contributed equally.

**Burrage LC**, Charng WL, Eldomery MK, Willer JR, Davis EE, (...), Lupski JR, Bongers EMHF, Yang Y (2015). *De Novo* GMNN Mutations Cause Autosomal Dominant Primordial Dwarfism Associated with Meier-Gorlin Syndrome. **Am J Hum Genet**. 97: 904-13.

# 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**, 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 neuro-physiologic underpinnings of neurodevelopmental disorders such as intellectual disability, epilepsy, autism, schizophrenia and other neuropsychiatric conditions. In particular, one emerging theme in the field is that disrupted inhibitory neuronal development and function 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 inhibitory neurobiology in health and disease. 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 of neurodevelopmental disorders 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 excitatory and 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.

In addition to the laboratory research activities, our team leads an Epilepsy Genetics Initiative at the Duncan NRI to identify genetic determinants of undiagnosed developmental and epileptic encephalopathies and we established a multidisciplinary *EBF3*-related autism spectrum, ataxia, and other neurodevelopmental disorders clinic at TCH. We now follow the largest group of *EBF3*-related HADDS and 10q26 deletion syndrome patients to date in a single institution and conduct comprehensive phenotypic-genotypic analysis with neurocognitive profiling and neuroimaging. Finally, we are leading a Phase 0 natural history study for *STXBP1*-related epileptic encephalopathy with the goal of continuing to Phase 1 gene therapy studies. The findings from the clinical studies also inform our laboratory research efforts to understand how gene disruptions alter inhibitory and excitatory neuronal development, perturb neural network activity and lead to cognitive and behavioral abnormalities in neurodevelopmental and psychiatric disorders.

## SELECTED PUBLICATIONS

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, Emrick 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.

Handoko M, Emrick LT, Rosenfeld JA, Wang X, Tran AA, Turner A, Belmont JW; Undiagnosed Diseases Network, Lee BH, Bacino CA, **Chao HT** (2019). Recurrent mosaic MTOR c.5930C > T (p.Thr1977Ile) variant causing megalencephaly, asymmetric polymicrogyria, and cutaneous pigmentary mosaicism: Case report and review of the literature. **Am J Med Genet A.** 179: 475-479.

**Chao HT***, Liu L*, Bellen HJ (2017). Building dialogues between clinical and biomedical research through cross-species collaborations. **Semin Cell Dev Biol.** 70: 49-57. *equal contribution

Wang J*, Al-Ouran R*, Hu Y*, Kim SY*, (...), **Chao HT**, Comjean A, Mohr SE; UDN, Perrimon N, Liu Z, Bellen HJ (2017). MARRVEL: Integration of Human and Model Organism Genetic Resources to Facilitate Functional Annotation of the Human Genome. **Am J Hum Genet.** 100: 843-853. *equal contribution

**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 signalling 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.

# RUI CHEN, PH.D.

**Professor**, Department of Molecular and Human Genetics; Human Genome Sequencing Center
**Faculty Member**, Graduate Programs in Genetics & Genomics; Quantitative & Computational Biosciences; and Developmental Biology

*Ph.D., Baylor College of Medicine*
*Postdoc, Baylor College of Medicine*

## RESEARCH INTERESTS

Our lab is broadly interested in identifying genetic factors underlying human diseases, investigating molecular mechanisms of disease using animal models, and developing novel therapeutic approaches. We are currently focusing on:

**Genetics of human inherited retinal degenerative diseases:** Collectively, ocular diseases affect a large population in the world with 40 million people blind and another 100 million with substantial visual impairment. Together with our collaborators, we are currently working on identifying genes involved in various inherited retinal diseases (IRD), such as Leber congenital amaurosis (LCA), Usher syndrome, retinitis pigmentosa (RP), cone and rod dystrophy, and Stargardt's disease. So far, we have recruited over 7,000 patients with IRDs across the world. A combination of next-generation sequencing (NGS) based panel, whole exome, and whole genome sequencing has been conducted. These efforts have led to accurate molecular diagnoses of about 70% of the patients. In addition, we have identified and published 15 new IRD-associated genes. Continued investigation of the underlying genetics of unsolved IRD patients is one of our main focuses, including but not limited to identifying novel IRD-associated genes, improving our ability to identify and interpret complex or non-coding mutations, and exploring digenic and oligogenic complex inheritance.

**Molecular mechanisms and novel therapeutic of retinal degenerative diseases:** We will use mice as the model to investigate the molecular mechanism of IRD diseases. From the list of novel IRD genes identified in our group, we have selected and generated knock-out and/or knock-in mice models for several genes, such as *Spata7*, *Cwc27*, and *Reep6*, that are either currently under-investigated or represent new genetic pathways. A combination of genetic, genomic, and biochemical approaches is used to characterize these mouse models and elucidate the underlying molecular mechanism of the disease. In parallel, using the engineered mice as the model, we have performed rAAV-based gene therapy. Furthermore, we are exploring the idea of developing novel therapy methods that can address a significant portion of IRD patients by targeting converging pathways and/or downstream effector genes. Finally, the cell-based therapy approach is also being explored.

**New non-human primate model for human diseases:** One major limitation to the development of effective therapies is the use of animal models that poorly replicate human conditions. Well-defined NHP models that are more predictive of human conditions are necessary to more efficiently advance new therapies. In collaboration with multiple primate centers across the country, we have conducted molecular screens for over 2,000 individual monkeys carrying a spontaneous occurred mutation in IRD and other human diseases. We have now identified and established the breeding colony carrying *PDE6C* mutations. In addition, carriers with a mutation in many genes associated with IRD and other human diseases have been identified. These models will serve as an invaluable resource for future therapy development and mechanistic studies.

**Single-cell genomics and Human cell atlas:** Single-cell omics is a rapidly growing new field that provides many advantages over traditional 'bulk' tissue profiling methods, such as the ability to resolve intratissue heterogeneity in cell types, profile the disease microenvironments, and study rare subpopulations. Over the last several years, single-cell genomic and transcriptome methods have had major impact on many areas of biomedical research. In addition to single-cell genomic and transcriptome method, additional omics technologies, such as chromatin profiling, DNA methylation, and proteomics, are under rapid development. Together these single-cell omics technologies are becoming essential tools that are revolutionizing many diverse fields of biomedical research. Our lab has applied this emerging technology to our research and is also actively engaged in expanding the application and further developing the technology. We are funded by the Chan Zuckerberg Initiative (CZI) as part of the Human Cell Atlas (HCA) Seed Network project, particularly focusing on generating a reference map for the human retina at the single cell resolution.

## SELECTED PUBLICATIONS

Liang Q, Dharmat R, Owen L, Shakoor A, Li Y, Kim S, Vitale A, Kim I, Morgan D, Liang S, Wu N, Chen K, DeAngelis MM, **Chen R** (2019). Single-nuclei RNA-seq on human retinal tissue provides improved transcriptome profiling. **Nat Commun.** 10: 5743.

Kim S, Lowe A, Dharmat R, Lee S, Owen LA, (...), **Chen R**, Liu W (2019). Generation, transcriptome profiling, and functional validation of cone-rich human retinal organoids. **Proc Natl Acad Sci U S A.** 116: 10824-10833.

Moshiri A, **Chen R**, Kim S, Harris RA, Li Y, (...), Thomasy SM (2019). A nonhuman primate model of inherited retinal disease. **J Clin Invest.** 129: 863-874.

Wang J, Zhao L, Wang X, Chen Y, Xu M, Soens ZT, Ge Z, Wang PR, Wang F, **Chen R** (2018). GRIPT: a novel case-control analysis method for Mendelian disease gene discovery. **Genome Biol.** 19: 203.

Dharmat R, Eblimit A, Robichaux MA, Zhang Z, Nguyen TT, Jung SY, He F, Jain A, Li Y, Qin J, Overbeek P, Roepman R, Mardon G, Wensel TG, **Chen R** (2018). SPATA7 maintains a novel photoreceptor-specific zone in the distal connecting cilium. **J Cell Biol.** 217: 2851-2865.

Xu M, Xie YA, Abouzeid H, Gordon CT, Fiorentino A, (...), **Chen R** (co-corresponding), Allikmets R, Schorderet DF (2017). Mutations in the Spliceosome Component *CWC27* Cause Retinal Degeneration with or without Additional Developmental Anomalies. **Am J Hum Genet.** 100: 592-604.

Arno G, Agrawal SA, Eblimit A, Bellingham J, Xu M, (...), **Chen R** (2016). Mutations in *REEP6* Cause Autosomal-Recessive Retinitis Pigmentosa. **Am J Hum Genet.** 99: 1305-1315.

Zhao L, Chen Y, Bajaj AO, Eblimit A, Xu M, Soens ZT, Wang F, Ge Z, Jung SY, He F, Li Y, Wensel TG, Qin J, **Chen R** (2016). Integrative subcellular proteomic analysis allows accurate prediction of human disease-causing genes. **Genome Res.** 26: 660-9.

Koenekoop RK, Wang H, Majewski J, Wang X, Lopez I, Ren H, (...), **Chen R** (2012). Mutations in *NMNAT1* cause Leber congenital amaurosis and identify a new disease pathway for retinal degeneration. **Nat Genet.** 44: 1035-9.

Wang H, den Hollander AI, Moayedi Y, Abulimiti A, Li Y, Collin RW, Hoyng CB, Lopez I, Bray M, Lewis RA, Lupski JR, Mardon G, Koenekoop RK, **Chen R** (2009). Mutations in SPATA7 cause Leber congenital amaurosis and juvenile retinitis pigmentosa. **Am J Hum Genet.** 84: 380-7.

# 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

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 XG, 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**, Molkentin 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.

**Assistant Professor**, Department of Molecular and Human Genetics and Huffington Center on Aging
**Faculty Member**, Graduate Programs in Cancer & Cell Biology 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

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**. doi: 10.1038/s43587-021-00091-x. Online ahead of print. *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.** doi: 10.1007/s11357-021-00412-3. Online ahead of print. *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, McCauley BS, **Dang W** (2020). Loss of chromatin structural integrity is a source of stress during aging. **Hum Genet.** 139: 371.

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, Robison 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, Shilatifard 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.

**Associate Professor**, Department of Molecular and Human Genetics
**Medical Director**, Adult Genetics Clinic
**Section Chief**, Internal Medicine - Genetics, Michael E. DeBakey VAMC

*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

As the Medical Director for the Adult Genetics Clinics at BCM, I am proud to say that this is one of the largest Adult Genetics Service in the country. My primary clinical focus lies in the diagnosis and management of adults with genetic conditions, known or suspected. These include diagnosis and management of single gene disorders, chromosomal disorders and familial cancer syndromes, risk assessment for cancer and reproductive planning as well as testing for known genetic disorders in the family. I have developed an interest and expertise in the management of connective tissue disorders in adults, particularly Ehlers Danlos Syndrome (EDS) and run a specialized EDS clinic.

I am also involved in the education of medical students at BCM particularly in the field of adult genetics. I direct the Genetics course for MS2 and am always looking for opportunities to enhance the genetic education of our medical students and residents through various electives. The Genetics & Genomics Pathway at BCM was established in 2011 and is one of the first such medical pathways in the nation. As one of the pathway directors, I ensure that students get an unparalleled experience in genetics through their medical school career at BCM. My research activities include the diagnosis of rare genetic disorders through the Undiagnosed Disease Network Project currently ongoing at BCM in collaboration with several other centers in the country. Finally, through my position as chair of the Adult Genetics Special Interest Group (SIG) at ACMG, I was able to launch the Adult & Cancer Diagnostic Dilemmas session at the annual meeting.

## SELECTED PUBLICATIONS

Zhao S, Chen WJ, **Dhar SU**, Eble TN, Kwok OM, Chen LS (2019). Needs assessment in genetic testing education: A survey of parents of children with autism spectrum disorder in the united states. **Autism Res.** 12: 1162-1170.

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 DNM1L 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.

Liu P, Erez A, Nagamani SC, **Dhar SU**, et. al. (2011). Chromosome catastrophes involve replication mechanisms generating complex genomic rearrangements. **Cell**. 146: 889-903.

Posey JE, Rosenfeld JA, James RA, Bainbridge M, Niu Z, Wang X, **Dhar S**, (...), Plon SE (2016). Molecular diagnostic experience of whole-exome sequencing in adult patients. **Genet Med.** 18: 678-85.

Bekheirnia MR, Zhang W, Eble T, Willis A, Shaibani A, Wong LJ, Scaglia F, **Dhar SU** (2012). *POLG* mutation in a patient with cataracts, early-onset distal muscle weakness and atrophy, ovarian dysgenesis and 3-methylglutaconic aciduria. **Gene**. 499: 209-12.

**Dhar SU**, et. al (2011). Outcomes of integrating genetics in management of patients with retinoblastoma. **Arch Ophthalmol.** 129: 1428-34.

# 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

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.

**Dierick HA**, Gabbiani F (2015). *Drosophila* Neurobiology: No Escape from 'Big Data' Science. **Curr Biol.** 25: R606-8.

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** (2008). Fly fighting: octopamine modulates aggression. **Curr Biol.** 18: R161-3.

**Dierick HA** (2007). A method for quantifying aggression in male *Drosophila melanogaster*. **Nat Protoc.** 2: 2712-8.

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

**Dierick HA**, Greenspan RJ (2006). Molecular analysis of flies selected for aggressive behavior. **Nat Genet.** 38: 1023-31.
Greenspan RJ, **Dierick HA** (2004). 'Am not I a fly like thee?' From genes in fruit flies to behavior in humans. **Hum Mol Genet.** 13: R267-273 (Review).

# 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 and pharmacological 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 these 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-a 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 citrate transporter 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, neurogenerative 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, the large-scale projects in the BCM-Human Genome Sequencing Center, such as *All of Us,* provide insight into genomic variation in diverse populations and facilitate personalized medicine approaches to medical care.

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.

Current projects also include: (1) investigating the role of NAD kinase in both Alzheimer's disease and pancreatic cancer toward developing personalized approaches to treatment and prevention of disease. These studies use cell culture and conditional mouse models to improve our understanding of the underlying etiology of the associated neurodegenerative and neoplastic mechanisms; (2) 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; and (3) improving genomic variant curation and interpretation to facilitate earlier diagnosis for rare disease.

## SELECTED PUBLICATIONS

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.

Mullegama SV, Klein SD, Williams SR, Innis JW, Probst FJ, Haldeman-Englert C, Martinez-Agosto JA, Yang Y, Tian Y, **Elsea SH**, Ezashi T (2021). Transcriptome analysis of MBD5-associated neurodevelopmental disorder (MAND) neural progenitor cells reveals dysregulation of autism-associated genes. **Sci Rep**. 11: 11295.

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.

Li X, Milosavljevic A, **Elsea SH**, Wang CC, Scaglia F, Syngelaki A, Nicolaides KH, Poon LC (2021). Effective Aspirin Treatment of Women at Risk for Preeclampsia Delays the Metabolic Clock of Gestation. **Hypertension**. 78: 1398-1410.

Gandhi A, Zhou D, Alaimo J, Chon E, Fountain MD, **Elsea SH** (2021). Composite Sleep Problems Observed Across Smith-Magenis Syndrome, MBD5-Associated Neurodevelopmental Disorder, Pitt-Hopkins Syndrome, and ASD. **J Autism Dev Disord.** 51: 1852-1865.

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.

Le TN, Williams SR, Alaimo JT, **Elsea SH** (2019). Genotype and phenotype correlation in 103 individuals with 2q37 deletion syndrome reveals incomplete penetrance and supports *HDAC4* as the primary genetic contributor. **Am J Med Genet A.** 179: 782-791.

SARAH.ELSEA@BCM.EDU

# 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 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, Tylki-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 velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase. **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, Dobrzeniecka S, Rochefort D, Neugnot-Cerioli 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, Scheffzek 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.

# 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, Baylor College of Medicine

*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 BCM 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 ten percent 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) and to generate the first comprehensive map of human genetic variation (the HapMap project). The HGSC now employs more than 180 staff, including eighteen faculty.

Since 2007, new technologies have allowed unprecedented advances in human genetics. The HGSC pioneered whole exome capture methods and published the first 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. In 2011, we began deploying these methods into routine clinical practice and now provide full gene sequencing to hundreds of individual patients each month. The HGSC is also part of the national program for systematic discovery of the cause of human single genome defects and has an active bioinformatics program, with research projects involving biologists and computer scientists. To advance the use of genomics in adult clinics the HGSC has developed methods for screening for cardiovascular genetic risk and has recently joined the national *All of Us* consortium. Problems under study focus on developing tools for generating, manipulating, and analyzing genome data.

## SELECTED PUBLICATIONS


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.

Reid JG, Carroll A, Veeraraghavan N, Dahdouli M, Sundquist A, English A, Bainbridge M, White S, Salerno W, Buhay C, Yu F, Muzny D, Daly R, Duyk G, **Gibbs RA**, Boerwinkle E (2014). Launching genomics into the cloud: deployment of Mercury, a next generation sequence analysis pipeline. **BMC Bioinformatics.** 15: 30.

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, Wiszniewski 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, Nazareth L, Bainbridge M, Dinh H, Jing C, Wheeler DA, McGuire AL, Zhang F, Stankiewicz P, Halperin JJ, Yang C, Gehman C, Guo D, Irikat RK, Tom W, Fantin NJ, Muzny DM, **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.


AGIBBS@BCM.EDU

# ANDY GROVES, PH.D.

## Vivian L. Smith Endowed Professor in Neuroscience

**Professor**, Departments of Molecular and Human Genetics and Neuroscience
**Director**, Graduate Program in Development, Disease Models & Therapeutics
**Faculty Member,** Graduate Programs in Genetics & Genomics; Neuroscience; and Integrative Molecular and Biomedical Sciences

*Ph.D., Ludwig Institute for Cancer Research, University College London*
*Postdoc, California Institute of Technology*

## RESEARCH INTERESTS

Research in our lab spans the development of the inner ear from its earliest beginnings as a piece of embryonic ectoderm to the development of the highly patterned organ of Corti in the cochlea. We are also interested using our understanding of developmental processes to address why the sensory tissue of the cochlea fails to regenerate after damage and to identify genes involved in hereditary deafness.

We have an ongoing collaboration with Shinya Yamamoto's lab at Baylor in which we are trying to use the fruit fly, *Drosophila,* to identify new mutations in genes that affect hearing. We are also working with Huda Zoghbi's lab to identify targets of transcription factors that promote the differentiation of sensory hair cells. Finally, we also work on some aspects of craniofacial development, prompted by the discovery of the Foxi3 transcription factor, a Forkhead gene that plays crucial roles in the development of the inner ear and the branchial arch region and which causes canine ectodermal dysplasia in three breeds of hairless dogs.

## SELECTED PUBLICATIONS


Tao L, Yu H, Llamas J, Trecek T, Wang X, Stojanova Z, **Groves AK** Segil N. (2021). Enhancer decommissioning imposes an epigenetic barrier to sensory hair cell regeneration. **Dev Cell.** 56: 1–15

Gnedeva K, Wang X, McGovern MM, Barton M, Tao L, (...), **Groves AK**, Warchol M, Segil N (2020). Organ of Corti size is governed by Yap/Tead-mediated progenitor self-renewal. **Proc Natl Acad Sci U S A.** 117: 13552-13561.

Brown RM 2nd, Nelson JC, Zhang H, Kiernan AE, **Groves AK** (2020). Notch-mediated lateral induction is necessary to maintain vestibular prosensory identity during inner ear development. **Dev Biol.** 462: 74-84.

Jen HI, Hill MC, Tao L, Sheng K, Cao W, (...), **Groves AK** (2019). Transcriptomic and epigenetic regulation of hair cell regeneration in the mouse utricle and its potentiation by Atoh1. **ELife.** 8. pii: e44328.

Xie WR, Jen HI, Seymour ML, Yeh SY, Pereira FA, **Groves AK**, Klisch TJ, Zoghbi HY (2017). An Atoh1-S193A Phospho-Mutant Allele Causes Hearing Deficits and Motor Impairment. **J Neurosci.** 37: 8583-8594.

Basch ML, Brown RM, Jen HI, Semerci F, Depreux F, (...), **Groves AK** (2016). Fine-tuning of Notch signaling sets the boundary of the organ of Corti and establishes sensory cell fates. **ELife**. 5. pii: e19921. doi: 10.7554/eLife.19921.

Birol O, Ohyama T, Edlund RK, Drakou K, Georgiades P, **Groves AK** (2016). The mouse Foxi3 transcription factor is necessary for the development of posterior placodes. **Dev Biol.** 409: 139-151.

Cai T, Jen HI, Kang H, Klisch TJ, Zoghbi HY, **Groves AK** (2015). Characterization of the transcriptome of nascent hair cells and identification of direct targets of the Atoh1 transcription factor. **J Neurosci.** 35: 5870-83.

Doetzlhofer A, Basch ML, Ohyama T, Gessler M, **Groves AK**, Segil N (2009). Hey2 regulation by FGF provides a Notch-independent mechanism for maintaining pillar cell fate in the organ of Corti. **Dev Cell.** 16: 58-69.

White PM, Doetzlhofer A, Lee YS, **Groves AK**, Segil N (2006). Mammalian cochlear supporting cells can divide and trans-differentiate into hair cells. **Nature**. 441: 984-7.

# PHILIP JOHN HASTINGS, PH.D.

**Professor**, Department of Molecular and Human Genetics
**Faculty Member,** Graduate Program in Genetics & Genomics

*Ph.D., University of Cambridge*
*Postdoc, Harvard University*

## RESEARCH INTERESTS

Part of my current work is on the genetic responses to stress in *Escherichia coli*. We have shown that gene amplification occurs in response to stress, and is, therefore, an adaptive process comparable to the well-known adaptive mutation response. We are using genetic and molecular techniques to elucidate the mechanism by which adaptive amplification occurs. Because this genetic instability would be part of an adaptive response, we expect to be able to induce it, and thus study the processes by which genetic instability occurs. This might provide a model system in which to study the induction of chromosomal instability in oncogenesis (about 80 percent of cancers show chromosomal instability), and in evolution.

We have discovered that amplification is initiated by a template-switch mechanism during replication. By comparing our data to those derived from yeast and human cancer and genomic disease, we have derived a model for the origin of chromosomal structural changes for all organisms. This then suggests a mechanism for the origin of copy number variation (the major genetic difference between individuals) and for genomic disease. The model involves modification of the mechanism of replication fork repair occurring in cells experiencing a programmed stress-response. We are testing predictions of this model both in *E. coli* and in human.

## SELECTED PUBLICATIONS

Beck CR, Carvalho CMB, Akdemir ZC, Sedlazeck FJ, Song X, (...), **Hastings PJ**, Lupski JR (2019). Megabase Length Hypermutation Accompanies Human Structural Variation at 17p11.2. **Cell**. 176: 1310-1324.e10.

Pribis JP, García-Villada L, Zhai Y, Lewin-Epstein O, Wang AZ, (...), **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.e7.

Nehring RB, Gu F, Lin HY, Gibson JL, Blythe MJ, Wilson R, Bravo Núñez MA, **Hastings PJ**, Louis EJ, Frisch RL, Hu JC, Rosenberg SM (2016). An ultra-dense library resource for rapid deconvolution of mutations that cause phenotypes in *Escherichia coli*. **Nucleic Acids Res.** 44: e41.

Carvalho CM, Pfundt R, King DA, Lindsay SJ, Zuccherato LW, (...), **Hastings PJ**, Brunner HG, Lupski JR (2015). Absence of heterozygosity due to template switching during replicative rearrangements. **Am J Hum Genet.** 96: 555-64.

Moore JM, Magnan D, Mojica AK, Núñez MA, 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.

Carvalho CM, Pehlivan D, Ramocki MB, Fang P, Alleva B, Franco LM, Belmont JW, **Hastings PJ**, Lupski JR (2013). Replicative mechanisms for CNV formation are error prone. **Nat Genet.** 45: 1319-26.

Wimberly H, Shee C, Thornton PC, Sivaramakrishnan P, Rosenberg SM, **Hastings PJ** (2013). R-loops and nicks initiate DNA breakage and genome instability in non-growing *Escherichia coli*. **Nat Commun.** 4: 2115.

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

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

Lin D, Gibson IB, Moore JM, Thornton PC, Leal SM, **Hastings PJ** (2011). Global chromosomal structural instability in a subpopulation of starving *Escherichia coli* cells. **PLoS Genet.** 7: e1002223.

# 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
**Associate Member**, Texas Medical Center Digestive Diseases Center
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 first arise during embryogenesis as pluripotent-like cells. In the developing testis, somatic cells induce differentiation of these primordial germ cells to a unipotent spermatogonial stem cell fate. Using mouse models, we have shown that disruption of this sex-specific differentiation event causes the formation of TGCTs. Ongoing studies are using genome editing in mice, developmental biology approaches, and single-cell RNA sequencing to (1) characterize the mechanisms by which male germ cell sex-specific differentiation is disrupted, (2) test the contribution of a shift in pluripotent states (i.e. naïve to primed pluripotency) to germ cell transformation into tumor stem cells, and (3) functionalize TGCT susceptibility loci identify in human genome-wide association studies.

**Identifying the function of protein-coding genes in the mouse genome.** 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 phenotyping of knockout mouse lines. KOMP2 has also implemented embryo phenotyping pipelines for null alleles that cause lethality in the homozygous (recessive) state. KOMP2 is currently piloting a pipeline that uses (1) bioinformatics to predict genes that are haplo-essential, i.e. cause lethality in the heterozygous (dominant) state, and (2) CRISPR/Cas9 genome editing in mouse embryos, time-lapsed imaging of cultured, pre-implantation stage embryos and imaging of post-implantation stage embryos, and high-throughput embryo genotyping to characterize developmental defects associated with heterozygous loss-of-function.

**Developing and employing reporter mouse strains to evaluate new genome editing delivery systems.** Delivery of genome editing systems such as CRISPR/Cas9 to somatic tissues has the potential to treat or cure some of the most severe human diseases. However, there are significant challenges, including identification of delivery systems for specific tissues and evaluation of overall efficacy and safety, that must be addressed. The Somatic Cell Genome Editing (SCGE) Program is a trans-NIH initiative addressing key barriers to the therapeutic use of somatic genome editing in humans. As part of this effort, The BCM-Rice Small Animal Testing Center is creating mouse models for *in vivo* reporting of somatic genome editing efficiency and using these reporter strains to evaluate novel genome editing delivery systems developed by member of the SCGE.

**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 of uncertain clinical significance and are critical for testing therapeutic paradigms. The Center for Precision Medicine Models leverages the expertise, infrastructures, and established collaborations between the Mendelian disease clinical and gene discovery programs; animal modeling programs; and database infrastructure programs within the Department of Molecular and Human Genetics. The Center supports local, national, and international programs and individual researchers in the development of precision models 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.

## SELECTED PUBLICATIONS

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.

Saha K, Sontheimer EJ, Brooks PJ, Dwinell MR, Gersbach CA, (...), **Heaney JD**, (...); SCGE Consortium (2021). The NIH Somatic Cell Genome Editing Program. **Nature**. 592: 195-204.

Birling MC, Yoshiki A, Adams DJ, Ayabe S, Beaudet AL, (...), **Heaney JD**, (...); International Mouse Phenotyping Consortium (IMPC), Teboul L, Murray SA (2021). A resource of targeted mutant mouse lines for 5,061 genes. **Nat Genet**. 53: 416-419.

Swan A, Schütt C, Rozman J, del Mar Muniz Moreno M, Brandmaier S, (...), **Heaney JD**, (...), Hrabé de Angelis M (2020). Mouse mutant phenotyping at scale reveals novel genes controlling bone mineral density. **PLOS Genet.** 16(12):e1009190.

Hai L, Szwarc MM, Lanza DG, **Heaney JD**, Lydon JP (2019). Using CRISPR/Cas9 engineering to generate a mouse with a conditional allele for the promyeloctic leukemia zinc finger transcription factor. **Genesis** 57(3): e23281. PMC6422732

Cacheiro P, Muñoz-Fuentes V, Murray SA, Dickinson ME, Bucan M, (...), **Heaney JD**, (...); Genomics England Research Consortium; International Mouse Phenotyping Consortium (2020). Human and mouse essentiality screens as a resource for disease gene discovery. **Nat Commun.** 11: 655.

Lanza DG, Gaspero A, Lorenzo I, Liao L, Zheng P, Wang Y, Deng Y, Cheng C, Zhang C, Seavitt JR, DeMayo FJ, Xu J, Dickinson ME, Beaudet AL, **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**, Walkiewucz 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., Universite 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, but our work challenge 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

Glycosylation is the most common post-translational modification of extracellular and secreted proteins and plays major roles in various aspects of cellular and organismal biology. We use *Drosophila* and mouse genetics, cell culture experiments and biochemical assays (in collaboration) to understand the role of glycosylation in animal development and pathophysiology of human disease. A major focus of our work is on glycosyltransferases that add *O*-glucose glycans to epidermal growth factor-like (EGF) repeats and their role in the regulation of the Notch signaling pathway. Another project focuses on a cytoplasmic enzyme called *N*-glycanase 1, mutations that have been identified in a multi-system developmental disorder called NGLY1 deficiency. We hope that our findings will shed light on the pathophysiology of the human diseases caused or modified by alterations in the function of these enzymes and will provide a framework to identify mechanism-based therapies for them.

**Role of *O*-linked glycosylation in the regulation of Notch signaling**. An evolutionarily conserved enzyme called POGLUT1 (Rumi) adds *O*-linked glucose to EGF repeats harboring a CX**S**X(P/A)C consensus motif. Several xylosyltransferases extend the *O*-glucose by adding one or two xylose residues to it. Notably, we have found that in some contexts, the Notch pathway is sensitive to the gene dosage of the enzymes responsible for the addition of the xylose-xylose-glucose-*O* glycans to EGF repeats. Moreover, our recent reports on the identification of **hypomorphic *POGLUT1* alleles in patients with a new form of limb-girdle muscular dystrophy (LGMD-2Z)** indicate that myogenesis is highly sensitive to Notch glycosylation by POGLUT1. Our current studies are aimed at elucidating **the molecular bases for tissue-specific regulation of Notch signaling by xylose-xylose-glucose-*O* glycans**. Another major goal is **to understand how the corresponding glycosyltransferases regulate Notch signaling in a dosage-dependent manner.** These studies might help us establish a framework for therapeutic modulation of the Notch pathway in diseases caused or exacerbated by aberrant Notch signaling.

**A mouse model for Alagille Syndrome.** Alagille syndrome (ALGS) is an autosomal dominant disorder characterized by a congenital cholangiopathy of variable severity accompanied by cardiac, skeletal, renal and other abnormalities. In 94% of cases, ALGS is caused by mutations in *JAG1*, which encodes one of the ligands for the Notch pathway. We have previously reported a mouse model for the ALGS and have identified *Poglut1* as a dominant genetic suppressor of the ALGS biliary phenotypes. We have also identified the transcription factor *Sox9* and another glycosyltransferase as novel dosage-sensitive modifiers of the *Jag1[+/–]* phenotypes in mice. Ongoing experiments are aimed at **using this model and its genetic modifiers to better understand the pathophysiology of ALGS and to develop a therapy for this disease.** This project has the potential to provide novel insight into the formation of the biliary tree, both during normal development and upon liver injury.

**Using fly and mouse models to understand the pathophysiology of NGLY1 deficiency.** Human patients with mutations in *N*-glycanase 1 exhibit a host of developmental abnormalities including a delay in physical and intellectual development, movement disorders, osteopenia and lack of tears. NGLY1 is a "deglycosylation" enzyme and is thought to remove *N*-linked glycans from misfolded proteins during ER-associated degradation (ERAD). Using flies, mice and mammalian cells, we have identified two major signaling pathways affected by the loss of NGLY1: BMP signaling and AMPK signaling. The goal of this project is **to elucidate the mechanisms underlying the NGLY1 deficiency phenotypes and to identify potential therapeutic targets for this disease.** This project is helping us redefine the roles of deglycosylation in ERAD.

## SELECTED PUBLICATIONS

Pandey A, Adams JM, Han SY, **Jafar-Nejad H** (2022). NGLY1 Deficiency, a Congenital Disorder of Deglycosylation: From Disease Gene Function to Pathophysiology. **Cells.** 11: 1155.

Pandey A, Niknejad N, **Jafar-Nejad H** (2021). Multifaceted regulation of Notch signaling by glycosylation. **Glycobiology.** 31: 8-28.

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.

Pandey A, Harvey BM, Lopez MF, Ito A, Haltiwanger RS, **Jafar-Nejad H** (2019). Glycosylation of Specific Notch EGF Repeats by O-Fut1 and Fringe Regulates Notch Signaling in *Drosophila*. **Cell Rep**. 29: 2054-2066.e6.

Pandey A, Li-Kroeger D, Sethi MK, Lee TV, Buettner FFR, Bakker H, **Jafar-Nejad H** (2018). Sensitized genetic backgrounds reveal differential roles for EGF repeat xylosyltransferases in *Drosophila* Notch signaling. **Glycobiology**. 28: 849-859.

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 KAIPPARETTU, 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-organelle 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*, **Kaipparettu 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, **Kaipparettu 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, **Kaipparettu 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, **Kaipparettu 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*, **Kaipparettu 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, (...), **Kaipparettu 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, (...), **Kaipparettu 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, **Kaipparettu 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, **Kaipparettu 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 and cardiovascular disorders in the pediatric population. We have used molecular cytogenetic diagnostic tools such as chromosomal microarray analysis (CMA) and exome sequencing (ES) in understanding the genetic basis of birth defects. We have also studied the clinical utility of rapid ES in neonatal intensive care units. 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. Using ES, we have identified several novel Mendelian disorders responsible for neurodevelopmental disorders in the pediatric population. In 2016, we first described a cohort of patients with TANGO2 disease and are currently recruiting families for the natural history study. We are also using an academic web-based virtual platform called Consultagene to combine virtual health delivery with genome sequencing in a medically underserved pediatric population with rare diseases, living along the Texas-Mexico border.

## SELECTED PUBLICATIONS

**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.

Probst FJ, James RA, Burrage LC, Rosenfeld JA, Bohan TP, Ward Melver CH, (...), **Lalani SR** (2015). *De novo* deletions and duplications of 17q25.3 cause susceptibility to cardiovascular malformations. **Orphanet J Rare Dis.** 10: 75.

**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.

**Lalani SR**, et. al. (2013). *MCTP2* is a dosage-sensitive gene required for cardiac outflow tract development. **Hum Mol Genet.** 22: 4339-48.

SEEMAL@BCM.EDU

# 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
**Co-Director**, The Rolanette and Berdon Lawrence 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 (TGFβ, Wnt and Notch), and extracellular matrix proteins and their modifications (e.g., collagen prolyl-hydroxylation) that contribute to the 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.

The mechanistic discoveries of my laboratory research program are translated into the clinical arena 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 two NIH rare diseases clinical research consortia (the Brittle Bone Disorders Consortium and the Urea Cycle Disorders Consortium). My clinical research program began with stable isotopic measurements in humans and urea cycle disorder patients to better diagnose and assess new treatments. These human studies evolved into the assessment of nitric oxide flux in patients with UCDs and specifically in those with argininosuccinic aciduria. I have participated in and led both investigator-initiated and industry-sponsored interventional studies including the design and implementation of Phase II and III studies of a novel ammonia scavenger glyceryl-triphenylbutyrate in urea cycle patients; combinatorial phenylbutyrate/arginine treatment and nitric oxide supplementation in patients with argininosuccinic aciduria; and phenylbutyrate in maple syrup urine disease. In the area of skeletal dysplasias, I have studied the utility of zoledronic acid, teriparatide and anti-TGFβ treatments in pediatric and adult osteogenesis imperfecta. Our preclinical gene therapy studies have led to a clinical trial of helper-dependent adenoviral gene therapy in osteoarthritis. Finally, 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.

## 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.

Marom R, Burrage LC, Venditti R, Clément A, Blanco-Sánchez B, (...), Undiagnosed Diseases Network, 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.

Lim J, Lietman C, Grol MW, Castellon A, Dawson B, (...), **Lee BH** (2021). Localized chondro-ossification underlies joint dysfunction and motor deficits in the *Fkbp10* mouse model of osteogenesis imperfecta. **Proc Natl Acad Sci U S A.** 118: e2100690118.

Jin Z, Kho J, Dawson B, Jiang MM, Chen Y, Ali S, Burrage LC, Grover M, Palmer DJ, Turner DL, Ng P, Nagamani SC, **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 Program 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 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, Choroideremia, 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. Igna 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. James 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 (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 included 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 Syndrome, and investigations of yet-unsolved forms of ectodermal dysplasia.

Dr. Lewis also serves on the Steering Committee of Baylor's Undiagnosed Disease Network program. 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 the 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

Zaenglein AL, Levy ML. Stefanko NS, (...), **Lewis RA**, (...) PeDRA Use of Retinoids in Ichthyosis Work Group. Consensus Recommendations for the Use of Retinoids in Ichthyosis and other Disorders of Cornification in Children and Adolescents (2021). **Pediat Dermatol.** 38: 164-180**.**

Keehan LA, Jiang M-M, Marom R, (...), **Lewis RA**, (...), Craigen 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.

Luo X, Rosenfeld JA, Yamamoto S, Harel T, (...), **Lewis RA**, (...) Lupski JR, Lee B, Bellen HJ, Wangler MF (2017). Clinically Severe CACNA1A Alleles Affect Synaptic Function and Neurodegeneration Differentially. **PLoS Genet.** 13: e1006905.

Wong BK, Sutton VR, **Lewis RA**, Van den Veyver IB (2017). Independent Variant Analysis of TEAD1 and OCRL1 in 38 Aicardi Syndrome Patients. **Mol Genet Genomic Med.** 5: 117-121.

Harel T, Yoon WH, Garone C, (...), **Lewis RA**, (...), Potocki L, Graziano C, Bellen HJ, Lupski JR (2016). Recurrent de novo and Biallelic Variation of ATAD3A, Encoding a Mitochondrial Membrane Protein, Results in Distinct Neurological Syndromes. **Am J Hum Genet.** 99: 831-845.

Lindstrand A, Frangakis S, Carvalho CM, Richardson EB, (...), **Lewis RA**, Banin E, Lupski JR, Davis EE, Katsanis N (2016). Copy-Number Variation Contributes to the Mutational Load of Bardet-Biedl Syndrome. **Am J Hum Genet.** 99: 318-36.

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

*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 (Li et al., 2017 Cell; Li et al 2020 Current Biology). Recently, we developed a single-nucleus RNA-seq method in flies (McLaughlin, ..., Li, 2021 eLife) and applied it to the Fly Cell Atlas (FCA) project, 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 (J. Li, Han, H. Li, 2020 Cell) 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 (H. Li and Jasper, 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

McLaughlin CN, Brbić M, Xie Q, Li T, Horns F, Kolluru SS, Kebschull 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

**H Li***, J Janssens*, M Waegeneer, S Kolluru, K Davie, (...), FCA Consortium, H Jasper, B Oliver, N Perrimon, B Deplancke, S Quake, L Luo, S Aerts (2021). Fly Cell Atlas: a single-nucleus transcriptomic atlas of the adult fruit fly. **Science** 375: eabk2432.

**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, Kebschull 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.

**Li H**, Qi Y, Jasper H (2016). Preventing Age-Related Decline of Gut Compartmentalization Limits Microbiota Dysbiosis and Extends Lifespan. **Cell Host Microbe**. 19: 240-53.

**Li H**, Qi Y, Jasper H (2016). Ubx dynamically regulates Dpp signaling by repressing Dad expression during copper cell regeneration in the adult *Drosophila* midgut. **Dev Biol.** 419: 373-381.

**Li H**, Jasper H (2016). Gastrointestinal stem cells in health and disease: from flies to humans. **Dis Model Mech.** 9: 487-99.

**Li H**, Qi Y, Jasper H (2013). Dpp signaling determines regional stem cell identity in the regenerating adult *Drosophila* gastrointestinal tract. **Cell Rep.** 4: 10-8.

# 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


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, Novikov I, Bachman B, Jung SY, Haas PJ, Labrie JL, Pickering CR, Adikesavan AK, Regenbogen S, Kato L, Lelescu A, Buchovecky CM, Zhang H, Bao SH, Boyer S, Weber G, Scott KL, Chen Y, Spangler S, Donehower LA, **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.

Marciano DC, Lua RC, Herman C, **Lichtarge O** (2016). Cooperativity of Negative Autoregulation Confers Increased Mutational Robustness. **Phys Rev Lett.** 116: 258104.

Neskey DM, Osman AA, Ow TJ, Katsonis P, McDonald T, Hicks SC, (...), **Lichtarge O** (2015). Evolutionary Action Score of TP53 Identifies High-Risk Mutations Associated with Decreased Survival and Increased Distant Metastases in Head and Neck Cancer. **Cancer Res.** 75: 1527-36.

Peterson SM, Pack TF, Wilkins AD, Urs NM, Urban DJ, Bass CE, **Lichtarge O**, Caron MG (2015). Elucidation of G-protein and β-arrestin functional selectivity at the dopamine D2 receptor. **Proc Natl Acad Sci U S A**. 112: 7097-102.

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.


LICHTARGE@BCM.EDU

# PENGFEI LIU, PH.D., FACMGG

**Assistant Professor**, Department of Molecular and Human Genetics
**Director**, ACGME/ABMGG Laboratory Genetics and Genomics Fellowship Program
**Associate Director of Clinical Research**, Baylor Genetics

*Ph.D., Baylor College of Medicine*

## RESEARCH INTERESTS

The ultimate research goals of the Liu lab are to (1) develop novel approaches to improve the implementation of genomic medicine, and to (2) utilize clinical diagnostic big data to generate knowledge that advances genomic science.

In the Undiagnosed Diseases Network (UDN) sequencing core, I have been leading the development and implementation of clinical whole genome sequencing (cWGS) for the diagnostics of Mendelian disorders. We have been working to establish a robust analytical pipeline with automation to perform reanalysis of cWGS data. To streamline interpretation of intronic variants revealed by cWGS, we have focused on neurological diseases, aiming to develop a fast, low-cost protocol that enables RNAseq profiling of patient-specific induced neurons trans-differentiated from clinically accessible tissues. Our group has also been investigating on various sequencing modalities beyond the currently widely used short-read based WGS technology for their potential in clinical diagnostics.

In another project, we seek to use the unique selection of patients with recurrent genomic deletions to elucidate the impact and mechanisms of genetic modifiers. We propose to integrate patient-based genomic analysis with cell-based genetic engineering and functional characterization to enhance the detection power of disease-risk alleles. Findings from this project are expected to bridge the gap between our understanding of highly penetrant, rare Mendelian variants and variants with higher population frequencies and association with complex diseases.

## SELECTED PUBLICATIONS

Yuan, B, Schulze, K, (...), **Liu P** (2021). Sequencing individual genomes with recurrent deletions reveals allelic architecture and disease loci for autosomal recessive traits. **medRxiv**. doi: 10.1101/2021.02.16.21251842 (preprint).

**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.

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

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

**Liu P**, Lacaria M, Zhang F, Withers M, Hastings PJ, Lupski JR (2011). Frequency of nonallelic homologous recombination is correlated with length of homology: evidence that ectopic synapsis precedes ectopic crossing-over. **Am J Hum Genet**. 89: 580.

# JAMES R. LUPSKI, M.D., PH.D., D.SC. (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
**Associate Director**, Graduate Program in Genetics & Genomics

*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 melanogaste*r 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 begins with the observation that the Epidermal Growth Factor Receptor (Egfr, a receptor tyrosine kinase) signaling pathway is both necessary and sufficient to trigger the differentiation of nearly all cell types in the *Drosophila* retina. This finding posed the question of how activation of a single pathway could trigger the differentiation of more than ten different cell types in the same tissue at the same time during development. Given the fundamental importance of Egfr signaling throughout higher eukaryotes in cancer, cell differentiation, proliferation, and survival, it is of broad significance to unravel this conundrum. To this end, we have generated extensive single cell RNA-sequencing data on multiple stages of the developing and adult *Drosophila* eye, as well single cell chromatin accessibility data (ATAC-seq), and whole eye disc ChIP-seq for Pointed, the nuclear effector of Egfr signaling. Integration and mining of these data has led to multiple hypotheses of how the Egfr pathway is reiteratively used to regulate retinal cell fate determination which we are currently testing. In addition, these data have revealed many other new insights into *Drosophila* eye development with unprecedented resolution and provide a fertile starting point for myriad studies.

## SELECTED PUBLICATIONS


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.

Jusiak B, Wang F, Karandikar UC, Kwak SJ, Wang H, Chen R, **Mardon G** (2014). Genome-wide DNA binding pattern of the homeodomain transcription factor Sine oculis (So) in the developing eye of *Drosophila melanogaster*. **Genomics Data**. 2: 153-155.

Karandikar UC, Jin M, Jusiak B, Kwak SJ, Chen R, **Mardon G** (2014). *Drosophila eyes absent* is required for normal cone and pigment cell development. **PLoS One.** 9: e102143.

Atkins M, Jiang Sansores-Garcia L, Jusiak B, Halder G, **Mardon G** (2013). Dynamic rewiring of the *Drosophila* retinal determination network switches its function from selector to differentiation. **PLoS Genet.** 9: e1003731.

Pepple KL, Atkins M, Venken K, Wellnitz K, Harding M, Frankfort BJ, **Mardon G** (2008). Two-step selection of a single R8 photoreceptor: a bistable loop between *senseless* and *rough* locks in R8 fate. **Development** 135: 4071-4079.

Frankfort B, Nolo R, Zhang Z, Bellen H, **Mardon G** (2001). *senseless* repression of *rough* is required for R8 photoreceptor differentiation in the developing *Drosophila* eye. **Neuron** 32: 403-414.

Chen R, Amoui M, Zhang Z, **Mardon G** (1997). Dachshund and Eyes Absent Proteins form a complex and function synergistically to induce ectopic eye development in *Drosophila*. **Cell** 91: 893-903



GMARDON@BCM.EDU

# 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 form 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, Stamatoyannopoulos 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.

AMILOSAV@BCM.EDU

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

**Professor and Vice Chair for Research Affairs - Clinical,** Department of Molecular and Human Genetics
**Director**, Clinical Translational Core for the BCM 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

My research is focused on translational medicine, specifically, evaluating new and potential therapies for various genetic disorders. The main focus of my research program is clinical investigation including the conduct of natural history studies, proof-of-concept pilot studies, and interventional clinical trials in patients with inborn errors of metabolism and skeletal dysplasias.

**Inborn Errors of Metabolism:** As the Co-Principal Investigator for the NIH Rare Diseases Clinical Research Network's Urea Cycle Disorders Consortium, I am actively involved in conducting natural history studies, data-mining projects and exploratory studies aimed at improving therapies for UCDs. As the PI for the Pilot/Feasibility core of the consortium, I am involved in facilitating projects that will develop and validate new biomarkers for disease activity and endpoints that can be used in clinical investigation. As the PI for the Career Enhancement Core for the consortium, I am glad to be championing the career advancement of young investigators in the field of inborn errors of metabolism.

**Skeletal dysplasia:** I also serve as a lead investigator of the NIH Rare Diseases Clinical Research Network's Brittle Bone Disorders Consortium. I have contributed significantly to the natural history studies of osteogenesis imperfecta. I have developed clinical endpoints and biomarkers to assess disease burden from the perspective of clinical trial readiness and have had lead roles in clinical trials evaluating novel therapies for OI including the first disease-specific therapy with anti-transforming growth factor beta antibody. I also am a site PI at BCM for clinical trials that are sponsored by the pharmaceutical industry.

**Clinical Interests:** As an internist and adult clinical geneticist, I provide care to adults with a wide variety of heritable conditions. As the Director of the Clinic for Metabolic and Genetic disorders of bone, I evaluate and treat patients with osteogenesis imperfecta, heritable disorders of bone, IDD, Mendelian forms of cancer and heritable connective tissue disorders.

## 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.

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, Carracedo 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**, Shchelochkov OA, Mullins MA, Carter S, Lanpher BC, Sun Q, et al. (2012). A randomized controlled trial to evaluate the effects of high-dose versus low-dose of arginine therapy on hepatic function tests in argininosuccinic aciduria. **Mol Genet Metab.** 107: 315-21.

**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.

**Associate 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

Shi X, Jiang Y, Kitano A, Hu T, Murdaugh RL, Li Y, Hoegenauer KA, Chen R, Takahashi K, **Nakada D** (2021). Nuclear NAD<sup>+</sup> 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, Iwawaki 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.

Gundry MC, Brunetti L, Lin A, Mayle AE, Kitano A, Wagner D, Hsu JI, Hoegenauer KA, Rooney CM, Goodell MA, **Nakada D** (2016). Highly Efficient Genome Editing of Murine and Human Hematopoietic Progenitor Cells by CRISPR/Cas9. **Cell Rep.** 17: 1453-1461.

Saito Y, Chapple RH, Lin A, Kitano A, **Nakada D** (2015). AMPK Protects Leukemia-Initiating Cells in Myeloid Leukemias from Metabolic Stress in the Bone Marrow. **Cell Stem Cell.** 17: 585-96.

# 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 Cancer & Cell Biology, 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 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, Donkervoort 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 multiminicore 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 (HDAd). HDAd (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 HDAd 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 HDAd 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 HDAd preferentially into the liver of mice, dogs and nonhuman primates. We have developed a minimally invasive, balloon occlusion catheter-based method to deliver HDAd 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 HDAd with the primary goal of treating cystic fibrosis. We have developed a novel method of aerosolizing HDAd 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 HDAd. These important studies will provide information regarding the host-vector interactions which will be very useful for further improving the safety and efficacy of HDAd-mediated gene therapy.

Another active area of research in my lab is gene editing of human induced pluripotent stem cells (iPSCs) by HDAds. Gene editing of iPSCs has emerged as a powerful tool in research and has great potential in medicine. The major appeal of HDAd-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 HDAd 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**, Departments of Molecular and Human Genetics and Pathology & Immunology
**Faculty Member**, Graduate Program in Genetics & Genomics; Center for Skeletal Medicine and Biology; and The Rolanette and Berdon Lawrence Bone Disease Program of Texas

*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. Adult skeletal stem cells (SSCs) are critical for the life-long maintenance and regeneration of bone and bone marrow. These cells are also critical in the bone marrow (BM) microenvironment to regulate hematopoiesis with likely participation in leukemia and cancer metastasis. However, the *in vivo* characteristics and function of SSCs remain fundamental and still unanswered questions. To address these questions, we have developed a new strategy utilizing genetic pulse-chase models and advanced intravital imaging technology. Using this approach, we 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 the 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 (Ortinau 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.

Proper maintenance of the bone and marrow cavity is essential for skeletal and immune cell integrity. However, which BM populations regulate medullary cavity maintenance is largely unknown. We recently identified that a subset of Cxcl12+ cells appear in the 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 the 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 stromal progenitor cells with anti-osteogenic function and their regulation mechanism for BM medullary cavity maintenance and normal bone repair. We are also studying the mechanisms by which niche cells regulate HSCs and understanding how perturbations to these interactions can promote disease states such as hematopoietic aging and malignancies.

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 severe stress and injury. However, their cellular origin and mechanisms that govern tendon and connective tissue regeneration and repair remain unknown. We work on these important questions using a variety of genetic, immunologic, and microscopic technologies with the goal of identifying molecules and mechanisms that regulate stem cells of different tissue origins. These studies will elucidate fundamental aspects of skeletal tissue regeneration and may lead to the development of new regenerative medicine strategies.

## SELECTED PUBLICATIONS

Yang D, Ortinau L, Jeong Y, **Park D** (2022). Advances and challenges in intravital imaging of craniofacial and dental progenitor cells. **Genesis.** e23498.

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. * Corresponding authors

Jeong Y, **Park D*** (2020). Targeting periosteal SSCs for aged bone defects. **Aging (Albany NY).** 12: 3124-3125.

Ortinau 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**, Park I, Lee D, Choi YB, Lee H, Yun Y (2007). The adaptor protein Lad associates with the G protein beta subunit and mediates chemokine-dependent T-cell migration. **Blood**. 109: 5122-8.

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

# JENNIFER POSEY M.D., PH.D.

**Assistant Professor**, Department of Molecular and Human Genetics

*M.D., Baylor College of Medicine*
*Ph.D., Baylor College of Medicine*
*Intern and Resident, Internal Medicine, Columbia University Medical Center*
*Fellow, Medical Genetics, Baylor College of Medicine*

## RESEARCH INTERESTS

As a physician-scientist and a medical and human geneticist, my ultimate goal is to be able to translate our understanding of the relationship between an individual's genotype and phenotype into actionable and treatable information in the clinic. The first step toward this goal is the elucidation of the complex relationships between genotypes and human disease phenotypes. My research program is focused on the following three scientific inquiries, each of which will lead to a more precise understanding of these relationships:

### 1. What is the genetic etiology of Postural Orthostatic Tachycardia Syndrome (POTS), and to what extent do genetic heterogeneity and more complex modes of inheritance play a role in the clinical expression of POTS?

POTS represents one of many adolescent- or adult-onset conditions for which the molecular contribution – and genetic architecture – of disease is not well understood (Posey et al., 2016). Despite numerous examples of families with POTS following an autosomal dominant mode of inheritance, candidate disease genes have not been forthcoming, supporting the possibility that genetic heterogeneity, or perhaps more complex modes of inheritance, may play a role in the clinical expression of this condition. To address this possibility, we have built a cohort of individuals and families with POTS and other forms of autonomic dysfunction and are applying and analyzing genomic methods to identify the molecular etiologies of disease in these individuals.

### 2. How common are dual molecular diagnoses, and can we take advantage of structured phenotype data to predict which individuals with rare conditions are more likely to have two (or more) molecular diagnoses contributing to disease expression?

Dual or multiple, molecular diagnoses break from the 'one-gene-one-disease' paradigm, resulting in two or more independently segregating Mendelian conditions within an individual. Despite being long-recognized to occur in 'rare' cases, the true frequency of multiple molecular diagnoses has only more recently been described with the emergence of genome-wide techniques, such as array comparative genomic hybridization (aCGH) and ES, enabling a comprehensive identification of rare variation. In collaboration with the BG diagnostic laboratory and the BHCMG, we demonstrated that multiple molecular diagnoses are identified in at least 4.9% of individuals for whom ES is diagnostic (Posey, Harel, et al., 2017). We are now expanding this cohort and utilizing structured phenotype data to develop methods to predict which individuals may have multiple molecular diagnoses.

### 3. What are the roles of nuclear and mitochondrial genome variation in the expression of atypical forms of diabetes?

Diabetes has been broadly classified into type 1 diabetes (T1D) associated with auto-immune destruction of the pancreas, and type 2 diabetes (T2D) with adult-onset insulin resistance and/or impaired glucose tolerance. Despite these classifications, approximately 1-4% of individuals < 18 years with diabetes have a monogenic form that is clinically (phenotypically) distinct from T1D and T2D. As a member of the Rare and Atypical DIAbetes NeTwork (RADIANT) consortium, we are applying genomic methods to identify the molecular etiology of rare, monogenic forms of diabetes.

## SELECTED PUBLICATIONS

Assia Batzir N, **Posey JE**, Song X, Akdemir ZC, Rosenfeld JA, (...); Baylor-Hopkins Center for Mendelian Genomics, Lupski JR, Sutton VR (2020). Phenotypic expansion of *POGZ*-related intellectual disability syndrome (White-Sutton syndrome). **Am J Med Genet A.** 182: 38-52.

Assia Batzir N, Kishor Bhagwat P, Larson A, Coban Akdemir Z, (...); Baylor-Hopkins Center for Mendelian Genomics, **Posey JE**, Lupski JR, Beaudet AL, Wangler MF (2020). Recurrent arginine substitutions in the *ACTG2* gene are the primary driver of disease burden and severity in visceral myopathy. **Hum Mutat.** 41: 641-654.

Hansen AW, Murugan M, Li H, Khayat MM, Wang L, (...), **Posey JE**, Yang Y, Wangler MF, Eng CM, Sutton VR, Lupski JR, Boerwinkle E, Gibbs RA (2019). A Genocentric Approach to Discovery of Mendelian Disorders. **Am J Hum Genet.** 105: 974-986.

Herman I, Jolly A, Du H, Dawood M, Abdel-Salam GMH, (...), **Posey JE**, Lupski JR (2022). Quantitative dissection of multilocus pathogenic variation in an Egyptian infant with severe neurodevelopmental disorder resulting from multiple molecular diagnoses. **Am J Med Genet A.** 188: 735-750.

Jolly A, Bayram Y, Turan S, Aycan Z, Tos T, (...), **Posey JE**, Lupski JR (2019). Exome Sequencing of a Primary Ovarian Insufficiency Cohort Reveals Common Molecular Etiologies for a Spectrum of Disease. **J Clin Endocrinol Metab.** 104: 3049-3067.

Punetha J, Mackay-Loder L, Harel T, Coban-Akdemir Z, Jhangiani SN, Gibbs RA, Lee I, Terespolsky D, Lupski JR, **Posey JE** (2018). Identification of a pathogenic PMP2 variant in a multi-generational family with CMT type 1: Clinical gene panels versus genome-wide approaches to molecular diagnosis. **Mol Genet Metab.** 125: 302-304.

Karaca E, **Posey JE**, Coban Akdemir Z, Pehlivan D, Harel T, (...), Lupski JR (2018). Phenotypic expansion illuminates multilocus pathogenic variation. **Genet Med.** 20: 1528-1537.

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

**Posey JE**, Martinez R, Lankford JE, Lupski JR, Numan MT, Butler IJ (2017). Dominant Transmission Observed in Adolescents and Families With Orthostatic Intolerance. **Pediatr Neurol.** 66: 53-58.e5.

**Posey JE**, Mohrbacher N, Smith JL, Patel A, Potocki L, Breman AM (2016). Triploidy mosaicism (45,X/68,XX) in an infant presenting with failure to thrive. **Am J Med Genet A**. 170: 694-8.

JENNIFER.POSEY@BCM.EDU @POSEYPOD

# 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 track 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.

Varon A, Whitt Z, Kalika PM, **Potocki L**, Barbouth DS, Walz K (2019). Arnold-Chiari type 1 malformation in Potocki-Lupski syndrome. **Am J Med Genet A.** 179: 1366-1370.

McCool C, Spinks-Franklin A, Noroski LM, **Potocki L** (2017). Potocki-Shaffer syndrome in a child without intellectual disability-The role of PHF21A in cognitive function. **Am J Med Genet A**. 173: 716-720.

Jefferies JL, Pignatelli RH, Martinez HR, Robbins-Furman PJ, Liu P, Gu W, Lupski JR, **Potocki L** (2012). Cardiovascular findings in duplication 17p11.2 syndrome. **Genet Med**. 14: 90-4.

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.

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 biomedical and basic biological research, the need for detailed information about the genomics of nonhuman primates becomes more important and 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. As a member of the Human Genome Sequencing Center, I plan and execute various studies of nonhuman primate genomes. Working with other HGSC faculty and staff, as well as people outside BCM, we have produced *de novo* whole genome assemblies for several primates, including baboons (*Papio anubis*), sooty mangabeys (*Cercocebus atys*), marmosets (*Callithrix jacchus*), gibbons (*Nomascus leucogenys*), mouse lemurs (*Microcebus murinus*), owl monkeys (*Aotus nancymaae*) and other species. These projects involve deep whole genome sequencing of one individual per species, and computational assembly of the sequence data to produce a reference genome sequence that will be a resource for all future genetic analyses of that species. These projects also include the sequencing of additional individuals to identify intra-species genetic variation and RNA sequencing to characterize gene expression. The result is high-quality genomic information that facilitates both disease-related research and analyses of genome evolution (Rogers and Gibbs, 2014; Warren et al. 2020; Thomas et al. 2018). We have also conducted an extensive survey of genomic variation in the most widely studied nonhuman primate, the rhesus macaque (*Macaca mulatta*). By sequencing the genomes or exomes of more than 2,000 rhesus macaques from various research colonies we have discovered hundreds of thousands of functionally significant genetic variants that can be used to examine the effects of specific genes on various disease-related phenotypes. 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 second major line of research in my laboratory is the targeted analysis of particular nonhuman primate models of human genetic diseases. In collaboration with psychiatrists and neurobiologists, we have studied individual variation in behavior among macaques and baboons (Rogers, 2018; Fox et al. 2021) and explored the underlying neurobiological mechanisms. The multifaceted behavior of primates, including their capacity for complex social interactions, makes them outstanding subjects for behavioral and neurogenetic investigation (Oler et al., 2010; Rogers et al., 2013; Fawcett et al., 2014; Gunter et al., 2022). The primate models point us 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 (Dray et al., 2018), retinal disorders and early onset progressive vision loss (Moshiri et al., 2019), endometriosis (Tapmeier et al. 2021) and others.

While most of our effort is focused on the projects above, I also maintain an active interest in genetic analyses of wild primate populations. I am leading a large international consortium of researchers who are investigating genetic differentiation among wild populations of six species of baboons (genus *Papio*). We found that these species, although genetically and phenotypically quite distinct, have an evolutionary history that includes multiple episodes of inter-species admixture and gene flow (Rogers et al., 2019). This makes the living baboons an excellent model for human genome evolution and our ancient admixture with Neanderthals and Denisovans. In other projects, we and our colleagues are studying wild kinda baboons (*Papio kindae*) in Zambia (Jolly et al., 2011) and are developing whole genome sequence data for hundreds of primate species from all across the globe.

## SELECTED PUBLICATIONS

Dray BK, Raveendran M, Harris RA, Benavides F, Gray SB, (...), **Rogers J** (2018) Mismatch repair gene mutations lead to Lynch Syndrome colorectal cancer in rhesus macaques. **Genes and Cancer**. 9: 142-152.

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.

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

Worley K, Warren W, **Rogers J,** The Marmoset Genome Sequencing and Analysis Consortium (2014). The common marmoset genome provides insight into primate biology and evolution. **Nat Genet**. 46: 850-857.

**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.

Jolly CJ, Burrell AS, Phillips-Conroy JE, **Rogers J** (2011). Kinda baboons (*Papio kindae*) and grayfoot chacma baboons (*P. ursinus griseipes*) hybridize in the Kafue River valley, Zambia. **Am J Primatol**. 73: 291-303.

**Rogers J**, Raveendran M, Harris RA, Mailund T, Leppälä K, (...), Jolly CJ, Gibbs RA, Worley KC; Baboon Genome Analysis Consortium (2019). The comparative genomics and complex population history of *Papio* baboons. **Sci Adv**. 5: eaau6947.

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.

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.

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.

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.

JR13@BCM.EDU

# 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 then. 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

Mei Q*, Fitzgerald DM*, Liu J, Xia J, Pribis JP, Zhai Y, Nehring RB, Paiano J, Li H, 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.

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.

Fitzgerald D, Hastings PJ, **Rosenberg SM** (2017). Stress-induced mutagenesis: implications in cancer and drug resistance. **Annu Rev Cancer Biol**. 1: 119-40.

Shee C, (...), Harris RS, Miller KM, **Rosenberg SM** (2013). Engineered proteins detect spontaneous DNA breakage in human and bacterial cells. **ELife**. 2: e01222.

Wimberly H, Shee C, Thornton PC, Sivaramakrishnan P, **Rosenberg SM**, Hastings PJ (2013). R-loops and nicks initiate DNA breakage and genome instability in non-growing *Escherichia coli*. **Nat Commun**. 4: 2115.

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.

Shee C, Gibson JL, Darrow MC, Gonzalez C, **Rosenberg SM** (2011). Impact of a stress-inducible switch to mutagenic repair of DNA breaks on mutation in *Escherichia coli*. **Proc Natl Acad Sci U S A**. 108: 13659-64.

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.

# RODNEY C. SAMACO, PH.D.

**Assistant Professor**, Department of Molecular and Human Genetics
**Faculty Member**, Graduate Programs in Genetics & Genomics and Neuroscience

*Ph.D., Baylor College of Medicine*

## RESEARCH INTERESTS

Our primary research interest is to identify and understand the key molecular and neuroanatomical determinants of behavior using mouse and rat models of neurobehavioral and neuropsychiatric endophenotypes.

Behavior is governed by both genetic and environmental factors, yet the genetic basis for normal behavior remains poorly explored in spite of a need to better understand it for human health. Through the use of genetically engineered mouse and rat models combined with neurobehavioral measurements, *in vivo* neurophysiological recordings and high-throughput molecular and biochemical approaches, our lab studies the spatial and temporal requirement of genes either causative or implicated in the features associated with disorders of the brain. We aim to forge definitive links between genetic perturbations and alterations at the cellular, molecular and neural network levels that are responsible for behavioral impairments. Such work will provide the foundation for studies designed to improve behavioral phenotypes in mouse models of brain disorders by either genetic or pharmacological means, and will have clinical implications for human conditions characterized by impairments in these domains.

## SELECTED PUBLICATIONS

McGraw CM, Ward CS, **Samaco RC** (2017). Genetic Rodent Models of Brain Disorders: Perspectives on Experimental Approaches and Therapeutic Strategies. **Am J Med Genet C Semin Med Genet**. 175: 368-379.

Meehan TF, Mason J, (...), International Mouse Phenotyping Consortium, (...), Smedley D (2017). Disease model discovery from 3,328 gene knockouts by The International Mouse Phenotyping Consortium. **Nat Genet**. 49: 1231-1238.

Chahrour M, O'Roak BJ, Santini E, **Samaco RC**, Kleiman R, Manzini MC (2016). Current Perspectives in Autism Spectrum Disorder: From Genes to Therapy. **J Neurosci**. 36: 11402-11410.

Ward CS, Huang TW, Herrera JA, **Samaco RC**, Pitcher MR, Herron A, Skinner SA, Kaufmann WE, Glaze DG, Percy AK, Neul JL (2016). Loss of MeCP2 Causes Urological Dysfunction and Contributes to Death by Kidney Failure in Mouse Models of Rett Syndrome. **PLoS ONE**. 11: e0165550.

Veeraragavan S, Wan YW, Connolly DR, Hamilton SM, Ward CS, Soriano S, Pitcher MR, McGraw CM, Huang SG, Green JR, Yuva LA, Liang AJ, Neul JL, Yasui DH, LaSalle JM, Liu Z, Paylor R, **Samaco RC** (2016). Loss of MeCP2 in the rat models regression, impaired sociability and transcriptional deficits of Rett syndrome. **Hum Mol Genet**. 25: 3284-3302.

Hao S, Tang B, Wu Z, Ure K, Sun Y, Tao H, Gao Y, Patel AJ, Curry DJ, **Samaco RC**, Zoghbi HY, Tang J (2015). Forniceal deep brain stimulation rescues hippocampal memory in Rett syndrome mice. **Nature**. 526: 430-4.

**Samaco RC**, McGraw CM, Ward CS, Sun Y, Neul JL, Zoghbi HY (2013). Female Mecp2+/- mice display robust behavioral deficits on two different genetic backgrounds providing a framework for pre-clinical studies. **Hum Mol Genet**. 22: 96-109.

Katz DM, Berger-Sweeney JE, Eubanks JH3, Justice MJ, Neul JL, (...), **Samaco RC**, Schaevitz LR, St. Hillaire-Clarke C, Young JL, Zoghbi HY, Mamounas LA (2012). Preclinical research in Rett syndrome: setting the foundation for translational success. **Disease Models and Mechanisms**. 5: 733-745.

**Samaco RC**, Mandel-Brehm C, McGraw CM, Shaw CA, McGill BE, Zoghbi HY (2012). Crh and Oprm1 mediate anxiety-related behavior and social approach in a mouse model of MECP2 duplication syndrome. **Nat Genet**. 44: 206-11.

McGraw CM, **Samaco RC**, Zoghbi HY (2011). Adult neural function requires MeCP2. **Science**. 333: 186.

# FERNANDO SCAGLIA, M.D.

**Professor**, Department of Molecular and Human Genetics
**Co-Director**, Pediatric Mitochondrial Medicine Clinic, Texas Children's Hospital
**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 NAMDC (North American Mitochondrial Disease Consortia), an NIH-funded 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 PI on several grants that have been funded by national organizations in the United States, 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. In addition, I also conduct a trial to evaluate the effect of ASP0367, a selective modulator of PPARδ in adults with primary mitochondrial myopathy.

Furthermore, I am interested in determining whether there is a specific metabolomics profile 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.

## SELECTED PUBLICATIONS

Almannai M, El-Hattab AW, Azamian MS, Ali M, **Scaglia F** (2022). Mitochondrial DNA maintenance defects: potential therapeutic strategies. **Mol Genet Metab.** 137:40-48.

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.

Emmanuele V, Ganesh J, Vladutiu G, Haas R, Kerr D, (...), **Scaglia F**, Hoppel C, Rosales XQ, Barca E, Buchsbaum R, Thompson JL, DiMauro S, Hirano M; North American Mitochondrial Disease Consortium (NAMDC) (2022). Time to harmonize mitochondrial syndrome nomenclature and classification: A consensus from the North American Mitochondrial Disease Consortium (NAMDC). **Mol Genet Metab.** 136: 125-131.

Karaa A, MacMullen LE, Campbell JC, Christodoulou J, Cohen BH, (...), **Scaglia F**, Sherman AV, Yeske P, Falk MJ (2022). Community Consensus Guidelines to Support FAIR Data Standards in Clinical Research Studies in Primary Mitochondrial Disease. **Adv Genet (Hoboken)**. 3: 2100047.

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.

Odom J, Amin H, Gijavanekar C, Elsea SH, Kralik S, Chinen J, Lin Y, Yates AMM, Mizerik E, Potocki L, **Scaglia F** (2022). A phenotypic expansion of TRNT1 associated sideroblastic anemia with immunodeficiency, fevers, and developmental delay. **Am J Med Genet A.** 188: 259-268.

Li X, Milosavljevic A, Elsea SH, Wang CC, **Scaglia F**, Syngelaki A, Nicolaides KH, Poon LC (2021). Effective Aspirin Treatment of Women at Risk for Preeclampsia Delays the Metabolic Clock of Gestation. **Hypertension**. 78: 1398-1410.

Lim J, Shayota BJ, Lay E, Elsea SH, Bekheirnia MR, Tessier MEM, Kralik SF, Rice GM, Soler-Alfonso C, **Scaglia F** (2021). Acute Strokelike Presentation and Long-term Evolution of Diffusion Restriction Pattern in Ethylmalonic Encephalopathy. **J Child Neurol.** 36: 841-852.

Murali CN, Soler-Alfonso C, Loomes KM, Shah AA, Monteil D, Padilla CD, **Scaglia F**, Ganetzky R (2021). TRMU deficiency: A broad clinical spectrum responsive to cysteine supplementation. **Mol Genet Metab**. 132: 146-153.

Almannai M, El-Hattab AW, Ali M, Soler-Alfonso C, **Scaglia F** (2020). Clinical trials in mitochondrial disorders, an update. **Mol Genet Metab**. 131: 1-13.

# 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* gene is located on chromosome 1p36 and encodes a nuclear receptor coregulator that plays an important role during embryonic development. Using a combination of animal models and data from individuals with mutations of *RERE*, we have shown that RERE plays a critical role in the development of the brain, eye, inner ear, heart and kidneys. We are actively working to determine the molecular mechanisms by which RERE deficiency causes defects in each of these organs. We are also searching for other genes that contribute to the medical problems seen in individuals with 1p36 deletions.

**Esophageal Atresia/Tracheoesophageal Fistula (EA/TEF):** Another life-threatening birth defect of interest is esophageal atresia/tracheoesophageal fistula (EA/TEF). During development, the esophagus (stomach tube) and the trachea (windpipe) develop from a common progenitor called the anterior foregut tube. In about one in 3,500 newborns, the development of these tubes is abnormal resulting in failure of the esophagus to reach the stomach (esophageal atresia) or an abnormal connection between the trachea and esophagus (tracheoesophageal fistula). Approximately 50% of EA/TEF cases occur in association with additional anomalies and 10% of cases have a constellation of findings known as VACTERL (Vertebral, Anal, Cardiac, TracheoEsophageal Fistula, Renal and Limb) association. We are using clinical and molecular data from research, clinical and public databases, in conjunction with machine learning, to identify new genes for EA/TEF and the other structural anomalies associated with VACTERL association.

**Neurodevelopmental Phenotypes:** We work with physicians and scientists from around the world to identify genes and genomic regions that are associated with neurodevelopmental phenotypes including developmental delay, intellectual disability and autism.

## SELECTED PUBLICATIONS

Hardcastle A, Berry AM, Campbell IM, Zhao X, Liu P, (...), **Scott DA** (2022). Identifying phenotypic expansions for congenital diaphragmatic hernia plus (CDH+) using DECIPHER data. **Am J Med Genet A.** 188: 2958-2968.

Gofin Y, Zhao X, Gerard A, Scaglia F, Wangler MF, Schrier Vergano SA, **Scott DA** (2022). Evidence for an association between Coffin-Siris syndrome and congenital diaphragmatic hernia. **Am J Med Genet A.** 188: 2718-2723.

Gofin Y, Wang T, Gillentine MA, Scott TM, Berry AM, Azamian MS, Genetti C, Agrawal PB, Picker J, Wojcik MH, Delgado MR, Lynch SA, Scherer SW, Howe JL, Bacino CA, DiTroia S, VanNoy GE, O'Donnell-Luria A, Lalani SR, Graf WD, Rosenfeld JA, Eichler EE, Earl RK, **Scott DA** (2022). Delineation of a novel neurodevelopmental syndrome associated with PAX5 haploinsufficiency. **Hum Mutat.** 43: 461-470.

Kim BJ, Zaveri HP, Kundert PN, Jordan VK, Scott TM, Carmichael J, **Scott DA** (2021). RERE deficiency contributes to the development of orofacial clefts in humans and mice. **Hum Mol Genet**. 30: 595-602.

Kim BJ, **Scott DA** (2021). RERE deficiency causes retinal and optic nerve atrophy through degeneration of retinal cells. **Dev Dyn.** 250:1398-1409

Radio FC, Pang K, Ciolfi A, Levy MA, Hernández-García A, Pedace L, (...), **Scott DA**, Holder JL Jr, Tartaglia M (2021). SPEN haploinsufficiency causes a neurodevelopmental disorder overlapping proximal 1p36 deletion syndrome with an episignature of X chromosomes in females. **Am J Hum Genet.** 108: 502-516.

Scott TM, Campbell IM, Hernandez-Garcia A, Lalani SR, Liu P, Shaw CA, Rosenfeld JA, **Scott DA** (2021). Clinical exome sequencing data reveal high diagnostic yields for congenital diaphragmatic hernia plus (CDH+) and new phenotypic expansions involving CDH. **J Med Genet.** 59: 270-278.

Gofin Y, Mackay LP, Machol K, Keswani S, Potocki L, Di Gregorio E, Naretto VG, Brusco A, Hernandez-Garcia A, **Scott DA** (2021). Evidence that FGFRL1 contributes to congenital diaphragmatic hernia development in humans. **Am J Med Genet A**. 185: 836-840.

Barish S, Barakat TS, Michel BC, Mashtalir N, Phillips JB, (...), **Scott DA**, Bellen HJ (2020). BICRA, a SWI/SNF Complex Member, Is Associated with BAF-Disorder Related Phenotypes in Humans and Model Organisms. **Am J Hum Genet**. 107: 1096-1112.

Scott TM, Guo H, Eichler EE, Rosenfeld JA, Pang K, (...), **Scott DA** (2020). BAZ2B haploinsufficiency as a cause of developmental delay, intellectual disability, and autism spectrum disorder. **Hum Mutat.** 41: 921-925.

# 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

*Ph.D., Weizmann Institute of Science*
*Postdoc, University of California, San Diego*

## RESEARCH INTERESTS

**Allorecognition:** *Dictyostelium* cells preferentially cooperate with relatives (Ostrowski, 2008), and we are investigating the mechanisms that underlie this kin discrimination. We found two cell-cell adhesion genes, *tgrB1* and *tgrC1*, that are highly polymorphic in natural populations and required for allorecognition (Benabentos, 2009), and showed that the sequence polymorphism in these genes is sufficient to explain allorecognition in *Dictyostelium* (Hirose, 2011). This kin-recognition system protects cooperators against cheaters (Ho, 2013) and is temporally regulated, which allows it to evolve despite its essential role in development (Ho, 2015). 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. The TgrB1-C1 system replaces cAMP as the central signaling system during tissue integration (Hirose, 2021), and we are investigating the downstream signal transduction mechanisms that were initially found using a genetic suppressor screen (Li, 2016).

**The evolution of social behavior in *Dictyostelium:*** Social organisms must deal with cheaters - individuals that reap the benefits of sociality without paying the costs. In *Dictyostelium*, some cells sacrifice themselves and benefit other cells that may be genetically different, providing a fertile ground for cheating. We have found over 100 genes that participate in social interactions (Santorelli, 2008) and used genetic tools to characterize mechanisms that determine social interactions and test how cooperators resist cheating (Khare and Shaulsky, 2006; Khare, 2009; Khare and Shaulsky, 2010). We are investigating the role of the TgrB1-C1 signaling system in cheating.

**Functional Genomics:** We have used transcriptomes to discover gene function in *Dictyostelium* (Booth, 2005; Van Driessche, 2007). We also showed 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 are analyzing the major transcriptional transitions that characterize *Dictyostelium* development using RNA-seq profiles of 20 mutants (Katoh-Kurasawa, 2021). We are also developing new tools for exploration of the *Dictyostelium* genome, 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 and his group at the University of Ljubljana, Slovenia to develop new concepts in genetic analysis. Previously 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 also developed dictyExpress, a web tool that can access and analyze our transcriptional profiling data (Stajdohar, 2017). Two of our recent collaborative projects include 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

Hirose S, Katoh-Kurasawa M, **Shaulsky G** (2021). Cyclic AMP is dispensable for allorecognition in *Dictyostelium* cells overexpressing PKA-C. **J Cell Sci.** 134: jcs258777.

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.

Ho HI, **Shaulsky G** (2015). Temporal regulation of kin recognition maintains recognition-cue diversity and suppresses cheating. **Nat Commun**. 6: 7144.

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, Curk T, Sucgang 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, Sucgang 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
**Adjunct Professor of Statistics**, 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 at BCM and Adjunct Professor of Statistics at Rice University. He is also the Senior Director of Innovation at Baylor Genetics Laboratory.

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.

**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

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, in particular, the role of non-coding regulatory elements. We demonstrated that haploinsufficiency of the transcriptional factor *FOXF1* gene on 16q24.1 results in a lethal neonatal diffuse developmental lung disorder, alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV). Moreover, we unraveled the role of the *TBX4* and *FGF10* genes in other developmental lung diseases, including acinar dysplasia and congenital alveolar dysplasia.

We found that somatic mosaicism for CNVs 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 continue to study the scale and clinical importance of this phenomenon.

Moreover, we investigate the molecular mechanisms and phenotypic consequences of genomic rearrangements. We reported the role of *BPTF*, *PSMD12*, and *TRIP12* in neurodevelopmental disorders.

## SELECTED PUBLICATIONS

Isidor B, (...), Küry S, **Stankiewicz P** (2022). Stankiewicz-Isidor syndrome: expanding the clinical and molecular phenotype. **Genet Med.** 24: 179-91.

Karolak JA, Deutsch G, (...) **Stankiewicz P** (2022). Transcriptome and Immunohistochemical Analyses in *TBX4*- and *FGF10*-Deficient Lungs Imply TMEM100 as a Mediator of Human Lung Development. **Am J Respir Cell Mol Biol.** 66: 694-97.

Domogala DD, Gambin T, Zemet R, (...), Liu P, **Stankiewicz P** (2021) Detection of low-level parental somatic mosaicism for clinically relevant SNVs and indels identified in a large exome sequencing dataset. **Hum Genomics.** 15: 72.

Glinton KE, (...), Yang Y, **Stankiewicz P** (2021). Phenotypic expansion of the *BPTF*-related neurodevelopmental disorder with dysmorphic facies and distal limb anomalies. **Am J Med Genet A.** 185: 1366-78.

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. *Corresponding Authors.

PAWELS@BCM.EDU

# 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, we have developed 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 the 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

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, 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 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.

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.

# MENG WANG, PH.D.

## Robert C. Fyfe Chair in the Huffington Center on Aging

**Professor**, Department of Molecular and Human Genetics and Huffington Center on Aging
**Associate Director**, Graduate Program in Genetics and Genomics
**Faculty Member**, Graduate Program in Development, Disease Models & Therapeutics

*Ph.D., University of Rochester*
*Postdoc, Massachusetts General Hospital, Harvard Medical School*

## RESEARCH INTERESTS

Our research goals are to advance our knowledge on the fundamental mechanisms of somatic aging, lipid metabolism and reproductive senescence. These intertwined biological processes exert profound influence on human health, and are the major risk factors for various chronic and degenerative diseases. Our laboratory has been studying the molecular mechanisms governing these key biological processes and their complex interrelationship, by harnessing the power of functional genomics in *Caenorhabditis elegans* with metabolomics/lipodomics, chemical engineering and optical biophysics.

Our research has uncovered a lysosome-to-nucleus retrograde lipid messenger pathway, provided in-depth biochemical mechanisms for its action, and demonstrated its novel roles in regulating longevity. We have also discovered a previously unknown communication mode between bacteria and host mitochondria, deciphered bacteria-derived metabolites mediating this ancient dialogue and their signaling mechanisms, and determined their vital effects on host's lipid metabolism and longevity. In addition, our work provides evidences that volatile metabolites signal through specific olfactory neuroendocrine nexus to shape reproductive and metabolic strategies. Technically, we have developed and applied hyperspectral and isotope-labeling-coupled stimulated Raman scattering (SRS) microscopy systems for investigating *in vivo* spatiotemporal dynamics of metabolite molecules and its previously unknown association with metabolic pathologies. Based on SRS microscopy, we have assembled high-throughput platforms for both forward and reverse genetic screens, leading to the discovery of new regulatory mechanisms of lipid metabolism.

Ongoing projects in my laboratory include: (1) investigating the systemic role of lipid signaling in the regulation of longevity; (2) studying the mechanistic link governing the signaling crosstalk between bacteria and host mitochondria; (3) characterizing the cellular and molecular mechanism regulating reproductive homeostasis during aging; (4) analyzing lipid dynamics using quantitative SRS label-free imaging.

## SELECTED PUBLICATIONS


Ramachandran PV, Savini M, Folick AK, Hu K, Masand R, Graham BH, **Wang MC** (2019). Lysosomal Signaling Promotes Longevity by Adjusting Mitochondrial Activity. **Dev Cell**. 48: 685-696.e5.

Han B, Sivaramakrishnan P, Lin CJ, Neve IAA, He J, Tay LWR, Sowa JN, Sizovs A, Du G, Wang J, Herman C, **Wang MC** (2018). Microbial Genetic Composition Tunes Host Longevity. **Cell**. 173: 1058.

Yu Y, Mutlu AS, Liu H, **Wang MC** (2017). High-throughput screens using photo-highlighting discover BMP signaling in mitochondrial lipid oxidation. **Nat Commun**. 8: 865.

Sowa JN, Mutlu AS, Xia F, **Wang MC** (2015). Olfaction Modulates Reproductive Plasticity through Neuroendocrine Signaling in *Caenorhabditis elegans*. **Curr Biol**. 25: 2284-9.

Folick A, Oakley HD, Yu Y, Armstrong EH, Kumari M, Sanor L, Moore DD, Ortlund EA, Zechner R, **Wang MC** (2015). Aging. Lysosomal signaling molecules regulate longevity in *Caenorhabditis elegans*. **Science**. 347: 83-6.

Fu D, Yu Y, Folick A, Currie E, Farese RV Jr, Tsai TH, Xie XS, **Wang MC** (2014). *In vivo* metabolic fingerprinting of neutral lipids with hyperspectral stimulated Raman scattering microscopy. **J Am Chem Soc**. 136: 8820-8.

# MICHAEL WANGLER, M.D.

**Assistant 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*
*Internship, Baylor College of Medicine Affiliate Hospitals*
*Residency, Pediatrics, Baylor College of Medicine Affiliate Hospitals*
*Residency, Clinical Genetics, Medical Genetics, Baylor College of Medicine*

## RESEARCH INTERESTS

### Molecular and Developmental Mechanisms of Mendelian Disorders

Our lab studies rare human disease phenotypes in order 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 have also started a similar effort in underserved populations 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

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

Schulze KV, Hanchard NA, **Wangler MF*** (2020). Biases in arginine codon usage correlate with genetic disease risk. **Genet Med.** 22: 1407-1412. *Corresponding Author

Assia Batzir N, Kishor Bhagwat P, Larson A, Coban Akdemir Z, Bagłaj M, (...) Baylor-Hopkins Center for Mendelian Genomics, Posey JE, Lupski JR, Beaudet AL, **Wangler MF*** (2020). Recurrent arginine substitutions in the ACTG2 gene are the primary driver of disease burden and severity in visceral myopathy. **Hum Mutat.** 41: 641-654. *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

**Wangler MF**, Yamamoto S, Chao HT, Posey JE, Westerfield M, (...) Bellen HJ (2017). Model Organisms Facilitate Rare Disease Diagnosis and Therapeutic Research. **Genetics**. 207: 9-27.

Luo X, Rosenfeld JA, Yamamoto S, Harel T, Pastore M, (...), Members of the UDN, Lotze T, Lupski JR, Lalani S, Yang Y, Lee B, Bellen HJ, **Wangler MF*** (2017). Missense *de novo* variants in the CACNA1A associated with severe early onset ataxias can be gain or loss of function in *Drosophila*. **PLoS Genet**. 13: e1006905. *Corresponding Author

# THOMAS F. WESTBROOK, PH.D.

## Robert A. Welch Chair in Chemistry

**Professor**, Departments of Molecular and Human Genetics and Biochemistry & Molecular Biology
**Faculty Member**, Graduate Programs in Cancer & Cell Biology and Genetics & Genomic
**McNair Scholar**

*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's 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 are these drivers connected in genetic / signaling networks, and **(3)** how can these cancer gene networks 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 BCM.

## 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 Elect,** 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:** I lead data science training for researchers to leverage the data available in the *All of Us* Research Hub. This project is a part of the *All of Us Evenings with Genetics* Research Program, led by Drs. Debra Murray and Brendan Lee. The data provides opportunities for gene-disease association study replication using the extensive whole genome sequence data, with clinical records, environmental data and survey data. Trainees and faculty with computational experience can engage with the program as trainers and consultants. Early-stage investigators can apply to the mentoring program at https://www.bcm.edu/departments/molecular-and-human-genetics/engagement-and-diversity/all-of-us-evenings-with-genetics-research-program.

**ClinGen (https://www.clinicalgenome.org):** I coordinate the variant curation expert panel for X-linked inherited retinal diseases (https://www.clinicalgenome.org/affiliation/50086/). This project with Rui Chen, Dick Lewis and many other experts seeks to curate variants in seven X-linked genes that cause blinding eye diseases, several of which are targets for gene therapies. There are opportunities to learn and practice variant curation in support of this.

**Alzheimer's Disease Sequencing Project Consortium (ADSP):** I lead the structural variant working group seeking to assess and interpret the impact of structural variants with Fritz Sedlazeck, Richard Gibbs and Anita DeStefano. I also work with 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.

**Undiagnosed Diseases Network / Undiagnosed Diseases Center:** For this project, I lead the sequence analysis and variant interpretation group. We utilize both traditional exome and 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 BCM 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, Weinstock GM, Metzker ML, Muzny DM, Sodergren EJ, (...), **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, Cooper GM, Asimenos G, (...), **Worley KC**, (...), Green ED, 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, Richards S, Han Y, Wang M, Vee V, Qu J, Qin X, Muzny DM, Reid JG, **Worley KC**, Gibbs RA (2012). Mind the gap: upgrading genomes with Pacific Biosciences RS long-read sequencing technology. **PLoS One**. 7: e47768.

Bradnam KR, Fass JN, (...), **Worley KC**, Yin S, Yiu SM, Yuan J, Zhang G, Zhang H, Zhou S, Korf IF (2013). Assemblathon 2: evaluating *de novo* methods of genome assembly in three vertebrate species. **Gigascience**. 2: 10.

Rogers J, Raveendran M, Harris RA, Mailund T, Leppälä K, (...), Zinner D, Roos C, Jolly CJ, Gibbs RA, **Worley KC**; Baboon Genome Analysis Consortium (2019). The comparative genomics and complex population history of *Papio* baboons. **Sci Adv.** 5: eaau6947.

Vanderpool D, Minh BQ, (...), Gibbs RA, **Worley KC**, Rogers J, Hahn MW (2020). Primate phylogenomics uncovers multiple rapid radiations and ancient interspecific introgression. **PLoS Biol.** 18: e3000954.

Davenport KM, Bickhart DM, **Worley K**, Murali SC, Salavati M, Clark EL, Cockett NE, Heaton MP, Smith TPL, Murdoch BM, Rosen BD (2022). An improved ovine reference genome assembly to facilitate in-depth functional annotation of the sheep genome. **Gigascience**. 11.

Lay E, Azamian MS, Denfield SW, Dreyer W, Spinner JA, Kearney D, Zhang L, **Worley KC**, Bi W, Lalani SR (2022). LMOD2-related dilated cardiomyopathy presenting in late infancy. **Am J Med Genet A.** 188: 1858-62.

# TAO WU, PH.D.

**Assistant Professor**, Department of Molecular and Human Genetics
**CPRIT Scholar in Cancer Research**

*Ph.D., University of Chinese Academy of Sciences, (Institute of Biophysics)*
*Postdoctoral Associate, Yale Stem Cell Center, Yale School of Medicine*

## RESEARCH INTERESTS

The core question we want to answer is how the epigenetic factors dynamically regulate the cell fate decision and the response to external stimulation, specifically underlying cancer therapeutic resistance. Our final goal is to apply the fundamental knowledge for curing human diseases. Cancer is a systems biological disease. The tumor is a complex and robust biological system. Although we have developed powerful weapons such as chemotherapies, molecularly targeted therapies and immunotherapies to kill cancer cells, cancer treatment resistance is still a pressing challenge in current cancer research and treatment. Although acquired resistance can be developed by genetic mutations of tumor cells during treatment, it could also be due to many non-genetic factors such as activation of compensatory signaling pathways or stimuli-response epigenetic regulatory processes. Epigenetic regulatory processes in mammals, such as DNA methylations and histone modifications, are pivotal for controlling cellular functions. The profound alterations of DNA methylation (5mC) and histone modifications are common signatures in most types of cancer. Meanwhile, vast efforts were devoted to developing the drugs or small molecules by targeting epigenetic regulators, which can manipulate epigenomic modifications (such as HDACs for H3K27ac or DNMTs for DNA 5mC) in cancer cells to alter the activity of the responsive genes. However, the underlying molecular mechanisms of cancer epigenetics are still elusive.

In previous work, I discovered a novel DNA modification "N6-methyladenine" (6mA, DNA methylation that had never been identified in mammals before) with SMRT-ChIP (3$^{rd}$-generation single-molecule real-time sequencing with native ChIP samples) in mouse embryonic stem cells. We also identified ALKBH1 as the major demethylase of DNA 6mA. In 2018, we pinpointed that the 6mA is elevated in glioblastoma stem cells and high-grade glioblastoma (GBM) patient samples. In contrast, the 6mA's abundance is much lower in the non-stem-like GBM cells or low-grade GBM patient's samples. Furthermore, the demethylase ALKBH1 appears to regulate hypoxia response genes which were well-known for driving the drug resistance in GBM. Based on these discoveries, we hypothesize that DNA 6mA might be a driver epigenetic mutation and its regulators could constitute an essential pathway that manipulates cancer therapeutic resistance. The DNA 6mA's readers, writers or erasers, could be novel targets that could be targeted to bypass the resistance and boost the current therapies.

In our lab, we focus on the research projects to explore novel epigenetic regulatory processes and identify new epigenomic targets of the treatment-resistant cancerous cells with holistic approaches (genomics, genetics, biochemistry, systems biology and high-throughput screening). With the adapted single-molecule SMRT sequencing, single-cell sequencing and customized *CRISPR/Cas9* screening approaches, we will explore new epigenetic players in cancer model systems.

## 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(7817):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.

Benchetrit H, Herman S, van Wietmarschen N, **Wu T**, et al. (2015). Extensive Nuclear Reprogramming Underlies Lineage Conversion into Functional Trophoblast Stem-like Cells. **Cell Stem Cell.** 17: 543-56.

**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.

Zhang M, Yang S, Nelakanti R, Zhao W, Liu G, Li Z, Liu X, **Wu T**, et al. (2020). Mammalian ALKBH1 serves as an N6-mA demethylase of unpairing DNA. **Cell Res.** 30: 197-210.

Li X, Zhang Z, Luo X, Schrier J, Yang AD, **Wu TP** (2021). The exploration of N6-deoxyadenosine methylation in mammalian genomes. **Protein & Cell.** doi: 10.1007/s13238-021-00866-3. Online ahead of print.

# SHINYA YAMAMOTO, D.V.M., PH.D.

**Assistant Professor**, Department of Molecular and Human Genetics
**Faculty Member**, Graduate Programs in Development, Disease Models & Therapeutics; Genetics & Genomics; 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. In fact, 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 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 *Drosophila* 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 abroad. I am also involved in the development of novel computational tools such as MARRVEL (http://marrvel.org) and ModelMatcher (https://www.modelmatcher.net) with bioinformaticians and programmers at BCM to facilitate rare disease diagnosis, research and collaborations.

Over the years, my interest has expanded to include more common neurological disorders such as autism spectrum disorders (ASD), Alzheimer's disease, psychiatric diseases and drug addiction. More recently, we are also developing creative strategies to study infectious diseases such as Zika virus-mediated microcephaly and COVID-19, given their socioeconomic importance. In summary, while members of my lab and I work on diverse research topics, all projects are built on a common foundation that harnesses the 'awesome power of fly genetics.'

## SELECTED PUBLICATIONS

**Yamamoto S**, Charng 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.

**Yamamoto S**, Jaiswal M, Charng 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.

Bellen HJ, **Yamamoto S** (2015). Morgan's legacy: fruit flies and the functional annotation of conserved genes. **Cell**. 163: 12-14.

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.

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.

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.

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.

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.

# BING ZHANG, PH.D.

## McNair Scholar

**Professor**, Department of Molecular and Human Genetics and Lester and Sue Smith Breast Center
**Faculty Member**, Graduate Program in Quantitative and Computational Biosciences and Graduate Program in 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

My research interests encompass the broad areas of bioinformatics, computational proteomics, proteogenomics and cancer systems biology. During the past decade, through support from the National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC), I have established an internationally recognized research program in computational cancer proteogenomics, focusing on integrating genomic and proteomic data to better understand cancer biology and to improve cancer diagnosis and treatment. My group led the first integrative proteogenomic characterization of human cancer in a colorectal cancer cohort, which was published in *Nature* in 2014. The proteogenomics approach has now been applied to more than 10 cancer types within and outside CPTAC. My group participated in fourteen proteogenomics studies published in *Nature*, *Cell* and *Cancer Cell*. Together, these studies have demonstrated that integrated proteogenomic analysis provides functional context to interpret genomic abnormalities and that proteogenomics holds great potential to enable new advances in cancer biology, diagnosis, prognosis and targeted and immunotherapies.

To facilitate omics and multi-omics data analysis, my group has developed multiple widely used bioinformatics tools. CustomProDB is one of the first computational proteogenomics tools, and its expansion into NeoFlow enables proteogenomics-based neoantigen prioritization. The pathway and network analysis tool WebGestalt has been serving the biology research community for 17 years. In 2021 alone, WebGestalt was used >160,000 times by >56,000 users and was cited in >900 papers. The LinkedOmics web application makes multi-omics data from CPTAC and TCGA directly available and useful to the cancer research community. Published in 2018, the tool has already been used >150,000 times by >57,000 users, with >1000 citations.

Cancer proteogenomics is becoming a "data-rich" field. My team will continue developing bioinformatics methods and tools to expedite the extraction of novel biological and clinical insights from the continually growing volume of data. We are also working actively with clinical collaborators to translate data-driven computational discoveries into treatment advances for patients.

## SELECTED PUBLICATIONS

Huang C, Chen L, Savage SR, Eguez 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.

Li K, Jain A, Malovannaya A, Wen B, **Zhang B** (2020). DeepRescore: Leveraging deep learning to improve peptide identification in immunopeptidomics. **Proteomics**. 20: e1900334.

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.

Wen B, Wang X, **Zhang B** (2019). PepQuery enables fast, accurate, and convenient proteomic validation of novel genomic alterations. **Genome Res**. 29: 485-493.

Vasaikar SV, Straub P, Wang J, **Zhang B** (2018). LinkedOmics: analyzing multi-omics data within and across 32 cancer types. **Nucleic Acids Res**. 46: D956-D963.

**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.

**Assistant 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

The overarching theme of our laboratory is to understand the genomic and epigenomic regulation of the cardiovascular system in health and in disease with an emphasis on heart failure and cardiomyopathies.

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. This was *the first example of treating heart failure by manipulating circadian machineries*. We also established the very first cardiac slave clock, KLF15, which controls the circadian ischemia reperfusion injury in the heart. Recently, we *discovered the first circadian lncRNA, Circa*. Circa is uniquely expressed in the adult cardiomyocytes and protects the heart during pressure overload and myocardial infarction through global regulation of alternative splicing via interaction with hnRNP A1. Our goal is to gain knowledge on circadian gene regulation in the heart and ultimately hope to use this information to design novel therapeutics for heart failure.

Another focus of our laboratory is to study patient-derived induced pluripotent stem cell differentiated cardiomyocytes from patients with inherited cardiomyopathies. Using a comprehensive panel of phenotyping tools (biophysics, electrophysiology, energetics, and imaging) combined with genome editing tools, we aim to establish a platform to diagnose the molecular defects, characterize the pathogenic pathways and develop targeted therapy for inherited cardiomyopathies.

## SELECTED PUBLICATIONS

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.

Xu W, Li L, **Zhang L** (2020). NAD+ Metabolism as an Emerging Therapeutic Target for Cardiovascular Diseases Associated With Sudden Cardiac Death. **Front Physiol**. 11: 901.

**Zhang L***, Zhang R, Tien CL, Chan RE, Sugi K, Fu C, Griffin AC, Shen Y, Burris TP, Liao X, Jain MK* (2017). REV-ERBα Ameliorates Heart Failure Through Transcription Repression. **JCI Insight**. 2: e95177. doi: 10.1172/jci.insight.95177. (*co-corresponding authors)

Hsieh PN, **Zhang L**, Jain MK (2017). Coordination of cardiac rhythmic output and circadian metabolic regulation in the heart. **Cell Mol Life Sci.** 75: 403-416. doi: 10.1007/s00018-017-2606-x.

**Zhang L**, Jain MK (2016). Beating against the clock. **PNAS.** 113: 2558-9.

**Zhang L**, Prosdocimo DA, Bai X, Campbell F, Liao X, Coller J, Jain MK (2015). KLF15 Establishes the Landscape of Circadian Expression in the Heart. **Cell Rep.** 13: 2368-75.

**Zhang L**, Wang T, Valle D (2015). Reduced PLP2 expression increases ER stress-induced neuronal apoptosis and risk for adverse neurological outcomes after hypoxia ischemia injury. **Hum Mol Genet.** 24: 7221-6.

Han S, Zhang R, Jain R, Shi H, **Zhang L**, Zhou G, Sangwung P, Tugal D, Atkins GB, Prosdocimo DA, Lu Y, Han X, Tso P, Liao X, Epstein JA, Jain MK (2015). Circadian control of bile acid synthesis by a KLF15-Fgf15 axis. **Nat Commun.** 6: 7231.

Liao X, Zhang R, Lu Y, Prosdocimo DA, Sangwung P, **Zhang L**, Zhou G, Anand P, Lai L, Leone TC, Fujioka H, Ye F, Rosca MG, Hoppel CL, Schulze PC, Abel ED, Stamler JS, Kelly DP, Jain MK (2015). Kruppel-like factor 4 is critical for transcriptional control of cardiac mitochondrial homeostasis. **J Clin Invest.** 125: 3461-76.

Prosdocimo DA, John JE, **Zhang L**, Efraim ES, Zhang R, Liao X, Jain MK (2015). KLF15 and PPARα Cooperate to Regulate Cardiomyocyte Lipid Gene Expression and Oxidation. **PPAR Res.** 2015: 201625.

# 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

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.

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.

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.

Propson NE, Roy ER, Litvinchuk A, Köhl J, **Zheng H** (2021). Endothelial C3a receptor mediates vascular inflammation and blood-brain barrier permeability during aging. **J Clin Invest.** 131: e140966.

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**. doi: 10.1038/s41380-020-0738-0. Online ahead of print.

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.e5.31.

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.

Martini-Stoica H, Xu Y, Ballabio A, **Zheng H** (2016). The autophagy-lysosomal pathway in neurodegeneration: A TFEB perspective. **Trends Neurosci**. 39: 221-34.

Lian H, Yang L, Cole A, Sun L, Chiang AC, Fowler SW, Shim DJ, Rodriguez-Rivera J, Taglialatela G, Jankowsky JL, Lu HC, **Zheng H** (2015). NFκB-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease. **Neuron**. 85: 101-15.

Polito VA, Li H, Martini-Stoica H, Wang B, Yang L, (...), **Zheng H** (2014). Selective clearance of aberrant tau proteins and rescue of neurotoxicity by transcription factor EB. **EMBO Mol Med**. 6: 1142-60.

# ANTHONY WILLIAM ZOGHBI, M.D.

**Assistant Professor**, Departments of Psychiatry and Molecular and Human Genetics
Chief of Psychiatric Genetics in the Department of Psychiatry
**Beth K. and Stuart C. Yudofsky Scholar**

*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 my lab is to understand the genomic basis of neuropsychiatric disease and translate those insights into improvements in clinical care, disease risk prediction and novel therapeutic development. Specifically, we use novel phenotyping strategies such as extreme phenotype sampling combined with whole genome sequencing and cutting-edge bioinformatics tools to improve the ability to identify genetic causes of disease. Our work is currently focused on studying rare genetic variation in severe forms of schizophrenia and obsessive-compulsive disorder, though we intend to apply similar strategies across neuropsychiatric disorders.

In addition to our interest in rare variation, we are also exploring the interplay between common polygenic risk and rare variants, structural variation, and pharmacogenetics in extreme phenotypes. Through this second area of interest, we aim to better understand the genomic architecture of psychiatric disorders and use genomic data in combination with environmental risk factors to predict those who will be at highest risk for developing a given disease.

The long-term goal of our research is to usher in the clinical implementation of genomics in psychiatry. We envision that this will involve a combination of genomic disease risk stratification for improved biomarker identification and targeted clinical trials, elucidating genetic predictors of treatment resistance and identifying novel genetic targets for therapeutic development.

## SELECTED PUBLICATIONS

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.

Halvorsen, M, Samuels J, Wang Y, Greenberg BD, Fyer AJ, McCracken JT, Geller DA, Knowles JA, **Zoghbi AW**, Grados M, Riddle MA, Bienvenu OJ, Nestadt PJ, Krasnow J, Goes FS, Maher B, Nestadt G, Goldstein DB (2021). A burden of rare damaging coding variants in Obsessive-Compulsive Disorder. **Nature Neuroscience** 8: 1071-1076.

**Zoghbi AW**, Bernanke JA, Gleichman J, et. al. (2019). Schizotypal personality disorder in individuals with the Attenuated Psychosis Syndrome: Frequent co-occurrence without an increased risk for conversion to threshold psychosis. **Journal of Psychiatric Research** 114: 88-92.

**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.

Girgis, RR, **Zoghbi AW**, 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.

**Zoghbi AW**, Al Jurdi RK, Deshmukh PR, Chen DC, Xiu MH, Tan YL, Yang FD, Zhang XY (2014). Cognitive function and suicide risk in Han Chinese inpatients with schizophrenia. **Psychiatry Research** 11: 625-628.

ANTHONY.ZOGHBI@BCM.EDU

# HUDA Y. ZOGHBI, M.D.

## Ralph D. Feigin M.D. Endowed Chair

**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*
*Postdoc, 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. Conversely, our foray into fundamental neurodevelopmental processes governed by Atonal homolog 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 Dr. Harry Orr 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, 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. Consistent with this we discovered that a 30-50% increase in wild-type Ataxin-1 causes cerebellar degeneration and ataxia in mice. We also discovered that the enhanced function of mutant Ataxin-1 with its native partner Capicua 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 subsequently the repressor activity 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 and Parkinson disease.

***Atoh1* (aka *Math1*) and Neurodevelopment.** We identified the mouse homolog of the *Drosophila* gene *atonal*, which controls the development of the fly's chordotonal organs. We showed *Atoh1* null mice lack cerebellar granule neurons, pontine neurons, hair cells in the vestibular and auditory systems, D1 interneurons of the spinocerebellar tracts, Merkel cells, and intestinal secretory cells. *Atoh1* controls the genesis and/or differentiation of multiple components of the conscious and unconscious proprioceptive pathway and the neurons critical for interoception, chemosensitivity, and neonatal breathing. We are interested in understanding how this one gene guides the differentiation of diverse neurons from one progenitor population. To this end, we are pursuing single cell sequencing and detailed molecular studies during development.

**Rett Syndrome.** 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 (BCM), we found that forniceal deep brain stimulation restored hippocampal learning and plasticity. Using a *MECP2* duplication mouse model, we found that normalizing MeCP2 levels using antisense oligonucleotides reverse the symptoms including late onset seizures in adult mature animals. More recently, we discovered that presymptomatic training of Rett mice improved their performance, delayed disease onset by months, and improved neuronal morphology and physiology. Our work is now focused on three main areas: the identification of a biomarker that serves as a proxy for MeCP2 levels, understanding of MeCP2 regulation, and the network dysfunction in Rett syndrome, with the ultimate goal of targeting regulators of MeCP2 levels as well as network modulation as potential therapies.

## SELECTED PUBLICATIONS

Achilly N, Wang W, **Zoghbi HY** (2021). Presymptomatic training mitigates functional deficits in Rett syndrome mice. **Nature**. 592: 596-600.

Nitschke L, Tewari A, Coffin SL, Xhako E, Pang K, Gennarino VA, Johnson JL, Blanco FA, Liu Z, **Zoghbi HY** (2020). miR760 regulates ATXN1 levels via interaction with its 5′ untranslated region. **Genes Dev.** 34: 1147-1160.

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.

Rousseaux MWC*, Tschumperlin T*, Lu HC*, (...), **Zoghbi HY**♯, Orr HT♯ (2018). ATXN1-CIC Complex Is the Primary Driver of Cerebellar Pathology in Spinocerebellar Ataxia Type 1 through a Gain-of-Function Mechanism. **Neuron**. 97: 1235-1243.e5. (*co-first authors; ♯co-corresponding authors)

Gennarino VA, Palmer EE, McDonell 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). Forniceal 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.

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

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

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.

**Assistant Professor**, Department of Molecular and Human Genetics
**Faculty Member**, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics
**McNair Scholar**

*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-Rabassedas 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.

# KJERSTI AAGAARD, M.D., PH.D.

## Henry and Emma Meyer Chair in Obstetrics and Gynecology

**Vice Chair of Research**, Department of Obstetrics and Gynecology
**Professor**, Departments of Obstetrics and Gynecology and Molecular and Human Genetics; Graduate Programs in Development, Disease Models & Therapeutics and Genetics & Genomics

*Ph.D., Mayo Graduate School of Medicine*
*M.D., University of Minnesota Medical School*
*M.Sc., University of Utah*
*Resident, Obstetrics and Gynecology, University of Minnesota*
*Fellow, Maternal-Fetal Medicine, University of Utah School of Medicine*

### RESEARCH INTERESTS

Dr. Aagaard's highly collaborative laboratory and clinical research teams are dedicated to discovering the genomic, epigenomic, and metagenomic mechanisms underlying perinatal health and disease. Our interest and publications in this arena date back to 2004 and have evolved into clinical and translational research in murine, nonhuman primate, and human studies. There are currently three major focuses in our laboratory: (1) the effect of in utero exposures on the fetal epigenome, (2) understanding the genomic and epigenomic mechanisms involved in perinatal disorders and notably the developmental origins of adult metabolic disease, and (3) understanding the role of the microbiome in perinatal health with metagenomic interrogations. Since receipt of her first K12 in 2005 as a fellow, Dr. Aagaard has been continuously funded by NIH (NICHD, NIDDK, NIGMS and the Office of the Director), Burroughs Welcome Fund Preterm Birth Initiative, and most recently the Gates Foundation/USAIDS. Each of these employs integrative translational research with an emphasis on bioinformatics for imputation of complex metadata fields. Her research group aims to focus on mentoring translational research, notably with "big team science" and highly collaborative multi-site and center research.

AAGAARDT@BCM.EDU

### SELECTED PUBLICATIONS

**Aagaard K**, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J (2014). The placenta harbors a unique microbiome. **Sci Transl Med**. 6: 237ra65.

Ma J, Purcell H, Showalter L, **Aagaard KM** (2015). Mitochondrial DNA sequence variation is largely conserved at birth with rare de novo mutations in neonates. **Am J Obstet Gynecol**. 212: 530.e1-8.

**Marmoset Genome Sequencing and Analysis Consortium** (2014). The common marmoset genome provides insight into primate biology and evolution. **Nat Genet**. 46: 850-7.

**Twin GWAS Consortium** (2016). Identification of common genetic variants influencing spontaneous dizygotic twinning and female fertility. **Am J Hum Genet**. 98: 898-908.

# CHRISTOPHER I. AMOS, PH.D.

## Martha Ann and Harold M. Selzman, M.D. Endowed Chair in the Institute for Clinical and Translational Research

**Professor,** Departments of Medicine and Molecular and Human Genetics
**Adjunct Professor**, Dartmouth College & Nanjing University

*Ph.D., Louisiana State University Medical Center, New Orleans*
*FACMG, Interinstitutional Medical Genetics Training Program, NIH*

### RESEARCH INTERESTS

This lab focuses on developing and applying methods for identifying genetic influences on complex diseases, particularly targeting cancer etiology and autoimmune diseases. A major project is an international study of lung cancer susceptibility and early detection. Major outputs from this study include the identification of variants in a *CHRNA5* that influence smoking behavior and lung cancer risk and an uncommon nonsense variant of *BRCA2* that greatly increases the risk for lung cancer and other smoking-related cancers but not breast cancer. We are using CRISPR/Cas9 techniques to study the impact of this variant in cellular models of lung cancer.

A second major project is collecting samples from patients with early-stage lung cancer and performing comprehensive profiling (RNA and DNA sequencing, copy number analysis and integrative pathway-based approaches) to identify predictors of relapse. We also study selected rare autoimmune diseases for which genetic and environmental factors interact to increase disease risk greatly. We also develop and apply novel strategies of machine learning that can identify interactions among multiple genetic and environmental causes of disease.

### SELECTED PUBLICATIONS

Ji X, Bossé Y, (...), **Amos CI** (2018). Identification of susceptibility pathways for the role of chromosome 15q25.1 in modifying lung cancer risk. **Nat Commun**. 9: 3221.

Byun J, Schwartz AG, Lusk C, (...), **Amos CI** (2018). Genome-wide association study of familial lung cancer. **Carcinogenesis**. 39: 1135-1140.

Li Y, Xiao X, Han Y, Gorlova O, Qian D, (...), **Amos CI** (2018). Genome-wide interaction study of smoking behavior and non-small cell lung cancer risk in Caucasian population. **Carcinogenesis**. 39: 336-346.

McKay JD, Hung RJ, (...), **Amos CI** (2017). Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. **Nat Genet**. 49: 1126-1132.

 CHRISA@BCM.EDU

## CHRISTIE M. BALLANTYNE, M.D.

### J. S. Abercrombie Chair - Atherosclerosis and Lipoprotein Research

**Professor**, Departments of Medicine, Molecular and Human Genetics and Molecular Physiology and Biophysics
**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

Murdock DR, Venner E, Muzny DM, Metcalf GA, Murugan M, Hadley TD, (...), **Ballantyne CM**, Gibbs RA (2021). Genetic testing in ambulatory cardiology clinics reveals high rate of findings with clinical management implications. **Genet Med.** doi: 10.1038/s41436-021-01294-8. Online ahead of print.

Hadley TD, Agha AM, **Ballantyne CM** (2021). How do we incorporate polygenic risk scores in cardiovascular disease risk assessment and management? **Curr Atheroscler Rep**. 23: 28.

Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, **Ballantyne CM**, (...), Rader DJ (2018). Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. **J Am Coll Cardiol**. 72: 662-680.

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.

### 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.

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

Millichap JJ, Miceli F, De Maria M, Keator C, Joshi N, Tran B, Soldovieri MV, Ambrosino P, Shashi V, Mikati MA, **Cooper EC**, Taglialatela 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.

 ECC1@BCM.EDU

# MARY E. DICKINSON, PH.D.

## Kyle and Josephine Morrow Endowed Chair in Molecular Physiology and Biophysics

**Dean of Research**, Baylor College of Medicine
**Professor**, Departments of Molecular and Human Genetics and Molecular Physiology and Biophysics; Graduate Program in Genetics & Genomics

*B.S., Vanderbilt University*
*Ph.D., Columbia University*
*Postdoc, California Institute of Technology*

### RESEARCH INTERESTS

My laboratory uses a multidisciplinary approach combining mouse genetics, developmental biology, imaging and bioengineering to understand mechanisms underlying angiogenesis and cardiovascular birth defects. Our work focuses on determining how mechanical forces influence the genetic programs that guide mammalian development.

### SELECTED PUBLICATIONS

**Dickinson ME***, Flenniken AM*, Ji X, Teboul L*, Wong MD*, (...), Beaudet AL, Bucan M, Murray SD (2016). High-throughput discovery of novel developmental phenotypes. **Nature**. 537: 508-514.

Poché RA, Hsu CW, McElwee ML, Burns AR, **Dickinson ME** (2015). Macrophages engulf endothelial cell membrane particles preceding pupillary membrane capillary regression. **Dev Biol**. 403: 30-42.

Udan RS, Piazza VG, Hsu CW, Hadjantonakis AK, **Dickinson ME** (2014). Quantitative imaging of cell dynamics in mouse embryos using light-sheet microscopy. **Development**. 141: 4406-14.

Udan RS, Vadakkan TJ, **Dickinson ME** (2013). Dynamic responses of endothelial cells to changes in blood flow during vascular remodeling of the mouse yolk sac. **Development**. 140: 4041-50.

MDICKINS@BCM.EDU

# 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

**Finnell RH**, Caiaffa CD, Kim SE, Lei Y, Steele J, Cao X, Tukeman G, Lin YL, Cabrera RM, Wlodarczyk BJ (2021). Gene Environment Interactions in the Etiology of Neural Tube Defects. **Front Genet.** 12: 659612.

Chen Z, Lei Y, Zheng Y, Aguiar-Pulido V, Ross ME, Peng R, Jin L, Zhang T, **Finnell RH**, Wang H (2018). Threshold for neural tube defect risk by accumulated singleton loss-of-function variants. **Cell Res.** 28: 1039-1041.

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

### 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.

# KENDAL D. HIRSCHI, PH.D.

**Professor**, Departments of Pediatrics and Molecular and Human Genetics; USDA/ARS Children's Nutrition Research Center; Graduate Programs in Cancer & Cell Biology and Genetics & Genomics
**Associate Director of Research**, Vegetables and Fruit Improvement Center, Texas A&M University

*Ph.D., University of Arizona*
*Postdoc, Whitehead Institute*

### RESEARCH INTERESTS

We study both model systems biology in plants as well as translational research related to agricultural improvement. At the molecular level, our goals are to understand the structure, biological function and regulation of plant genes that control stress responses. Many of our molecular approaches use the standard genetic "tool kit."

Another major goal in our group is to learn how to manipulate the expression and function of genetic information to increase the nutritional content of crop plants, improve plant productivity and cleanse polluted soils. For this second objective, we collaborate with clinical researchers at the Children's Nutrition Research here at Baylor and faculty at the Vegetable and Fruit Improvement Center at Texas A&M. Obtaining help from nutritional scientists, we perform clinical trials addressing how changes in plant architecture alter nutrient bioavailability.

### SELECTED PUBLICATIONS

**Hirschi KD** (2020). Genetically Modified Plants: Nutritious, Sustainable, yet Underrated. **J Nutr.** 150: 2628-2634.

McNeill EM, **Hirschi KD** (2020). Roles of Regulatory RNAs in Nutritional Control. **Annu Rev Nutr.** 40: 77-104.

Scholz-Starke J, Primo C, Yang J, Kandel R, Gaxiola RA, **Hirschi KD** (2019). The flip side of the *Arabidopsis* type I proton-pumping pyrophosphatase (AVP1): Using a transmembrane $H^+$ gradient to synthesize pyrophosphate. **J Biol Chem.** 294: 1290-1299.

**Hirschi KD** (2022). Milking miRNAs for All Their Worth. **J Nutr.** 152: 1-2

Spinler JK, Oezguen N, Runge JK, Luna RA, Karri V, Yang J, **Hirschi KD** (2020). Dietary impact of a plant-derived microRNA on the gut microbiome. **ExRNA.** 2: 1-11.


KENDALH@BCM.EDU

## PHILIP J. LUPO, PH.D.

**Professor**, Departments of Pediatrics and Molecular and Human Genetics; Graduate Programs in Cancer & Cell Biology and Genetics & Genomics
**Endowed Chair in Molecular Epidemiology**, Texas Children's Cancer and Hematology Center
**Director,** Epidemiology and Population Sciences Program, Texas Children's Cancer and Hematology Center
**Chair**, Children's Oncology Group Epidemiology Committee

*Ph.D., University of Arizona*
*Postdoc, Whitehead Institute*

### RESEARCH INTERESTS

I am a genetic epidemiologist and Director of the Epidemiology and Population Sciences Program in the Texas Children's Cancer and Hematology Center. I have a particular interest in the use of novel epidemiologic study designs and methods to determine susceptibility factors for pediatric conditions – including childhood cancer and birth defects. This work is facilitated through my involvement in the Children's Oncology Group (COG), where I am Chair of the Epidemiology Committee. Examples of my current research projects include: 1) the Reducing Ethnic Disparities in Acute Leukemia (REDIAL) Consortium, whose goal is to improve outcomes among Latino children diagnosed with acute leukemia; and 2) the Genetic Overlap Between Anomalies and Cancer in Kids (GOBACK) Study, a multistate collaboration evaluating the risk of cancer in children with birth defects. The ultimate goal of my research is to discover factors that can be used in new prevention efforts and targeted interventions to limit the adverse consequences of pediatric diseases.

### SELECTED PUBLICATIONS

**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.

Luke B, Brown MB, Nichols HB, Schymura MJ, Browne ML, (...), **Lupo PJ** (2020). Assessment of Birth Defects and Cancer Risk in Children Conceived via In Vitro Fertilization in the US. **JAMA Netw Open.** 3: e2022927.

Li H, Sisoudiya SD, *Martin-Giacalone BA, Khayat MM, Dugan-Perez S, (...), **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.

PHILIP.LUPO@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.

### 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). BMPR2 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.

MMATZUK@BCM.EDU

## 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

**Noebels J** (2017). Precision physiology and rescue of brain ion channel disorders. **J Gen Physiol.** 149: 533-546.

Miao Q-L, Herlitze S, Mark MD, **Noebels JL** (2020) Adult loss of Cacna1a in mice recapitulates childhood absence epilepsy by distinct thalamic bursting mechanisms. **Brain.** 143: 161-174.

Hatcher A, Yu K, Meyer J, Aiba I, Deneen B, **Noebels JL**. (2020). Pathogenesis of peritumoral hyperexcitability in an immunocompetent CRISPR-based glioblastoma model. **J Clin Invest.** 130: 2286-2300.

 JNOEBELS@BCM.EDU

## DONALD W. (WILL) PARSONS, M.D., PH.D.

**Associate 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' research program focuses on 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. His group is currently engaged in a number of projects seeking to genomically characterize pediatric cancers in order to identify potential molecular targets for therapy and facilitate the pre-clinical testing of novel therapeutics. Dr. Parsons was one of the principal investigators of the BASIC3 study, an NHGRI and NCI-funded U01 Clinical Sequencing Exploratory Research (CSER) program project involving clinical exome sequencing of tumor and blood specimens from children with newly diagnosed solid tumors, and is now helping to lead the KidsCanSeq study (which includes multimodal clinical genomic analysis of patients from multiple Texas institutions) as part of that same consortium. He is also the Children's Oncology Group (COG) study chair for the NCI-COG Pediatric MATCH trial, the first nationwide precision oncology clinical trial for children with relapsed and refractory cancers.

### SELECTED PUBLICATIONS

Allen CE, Laetsch TW, Mody R, et al. (2017). Target and agent prioritization for the Children's Oncology Group-National Cancer Institute Pediatric MATCH Trial. **J Natl Cancer Inst**. 109(5).

Sumazin P, Chen Y, Treviño LR, et al. (2016). Genomic analysis of hepatoblastoma identifies distinct molecular and prognostic subgroups. **Hepatology**. 65: 104-121.

**Parsons DW**, Roy A, Yang Y et al. (2016). Diagnostic yield of clinical tumor and germline whole exome sequencing for children with solid tumors. **JAMA Oncol**. 2: 616-624.

Roy A, Kumar V, Zorman B, et al. (2015). Recurrent internal tandem duplications of *BCOR* in clear cell sarcoma of the kidney. **Nat Commun**. 6: 8891.

DWPARSON@BCM.EDU

## SHARON E. PLON, M.D., PH.D.

**Dan L Duncan 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

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.

SPLON@BCM.EDU @SPLON

## 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.

Kazanjian 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**, Departments of Obstetrics & Gynecology and 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 Clinical 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 in mice and embryonic stem cell models how maternal effect mutations in genes that code for proteins of a complex that is essential for oocytes and embryos, cause multilocus imprinting defects that lead to recurrent pregnancy failure, early embryo arrest and birth defects in offspring. We also conduct research on the cause of Aicardi syndrome, an elusive X-linked 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, and non-invasive screening into prenatal diagnosis and care. We are conducting a multicenter NIH-funded study to evaluate the clinical and diagnostic utility of trio prenatal whole genome sequencing for pregnancies with complicated fetal structural congenital anomalies.

### SELECTED PUBLICATIONS

Mahadevan S, Sathappan V, Utama B, Lorenzo I, Kaskar K, **Van den Veyver IB** (2017). Maternally expressed NLRP2 links the subcortical maternal complex (SCMC) to fertility, embryogenesis and epigenetic reprogramming. **Sci Rep.** 7: 44667.

Anvar Z, Chakchouk I, Demond H, Sharif M, Kelsey G, **Van den Veyver IB** (2021). DNA Methylation Dynamics in the Female Germline and Maternal-Effect Mutations That Disrupt Genomic Imprinting. **Genes (Basel).** 12: 1214

Crovetti B, Maktabi MA, Erfani H, Panchalee T, Wang Q, Vossaert L, **Van den Veyver I** (2021). Circulating trophoblast numbers as a potential marker for pregnancy complications. **Prenat Diagn.** 42: 1182-9.

 IVEYVER@BCM.EDU @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

### 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.

## 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

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.

Seervai RNH, et al. (2020). The Huntingtin-interacting protein SETD2/HYPB is an actin lysine methyltransferase. **Sci Adv.** 6: eabb7854.

Karki M, et al. (2021). A cytoskeletal function for PBRM1 reading methylated microtubules. **Sci Adv.** 7:veabf2866.

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.

**Assistant 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 pathogeneses 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

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**. Antisense oligonucleotide therapy rescues disturbed brain rhythms and sleep in juvenile and adult mouse models of Angelman syndrome. **bioRxiv**. 2022; doi: 10.1101/2022.06.18.496687. (preprint)

Kim JH, Chen W, Chao ES, Chen H, **Xue M**. Glutamatergic and GABAergic neurons mediate distinct neurodevelopmental phenotypes of STXBP1 encephalopathy. **bioRxiv**. 2021; doi: 10.1101/2021.07.13.452234. (preprint).

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 @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.


Baylor College of Medicine Medical Center McNair Campus

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.

*The Roy and Lillie Cullen Building, which opened in 1947, was the first building constructed in the Texas Medical Center.*

# 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 three medical schools, 21 renowned hospitals, eight academic and research institutions, six nursing programs, three public health organizations, two universities, two pharmacy schools, a dental school and 13 support organizations. In addition, Rice University is within walking distance.

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.

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.


*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.

*Spectacular buildings overlook parks, bayous, and picnic areas in the heart of Houston's downtown.*

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 BCM?

**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.

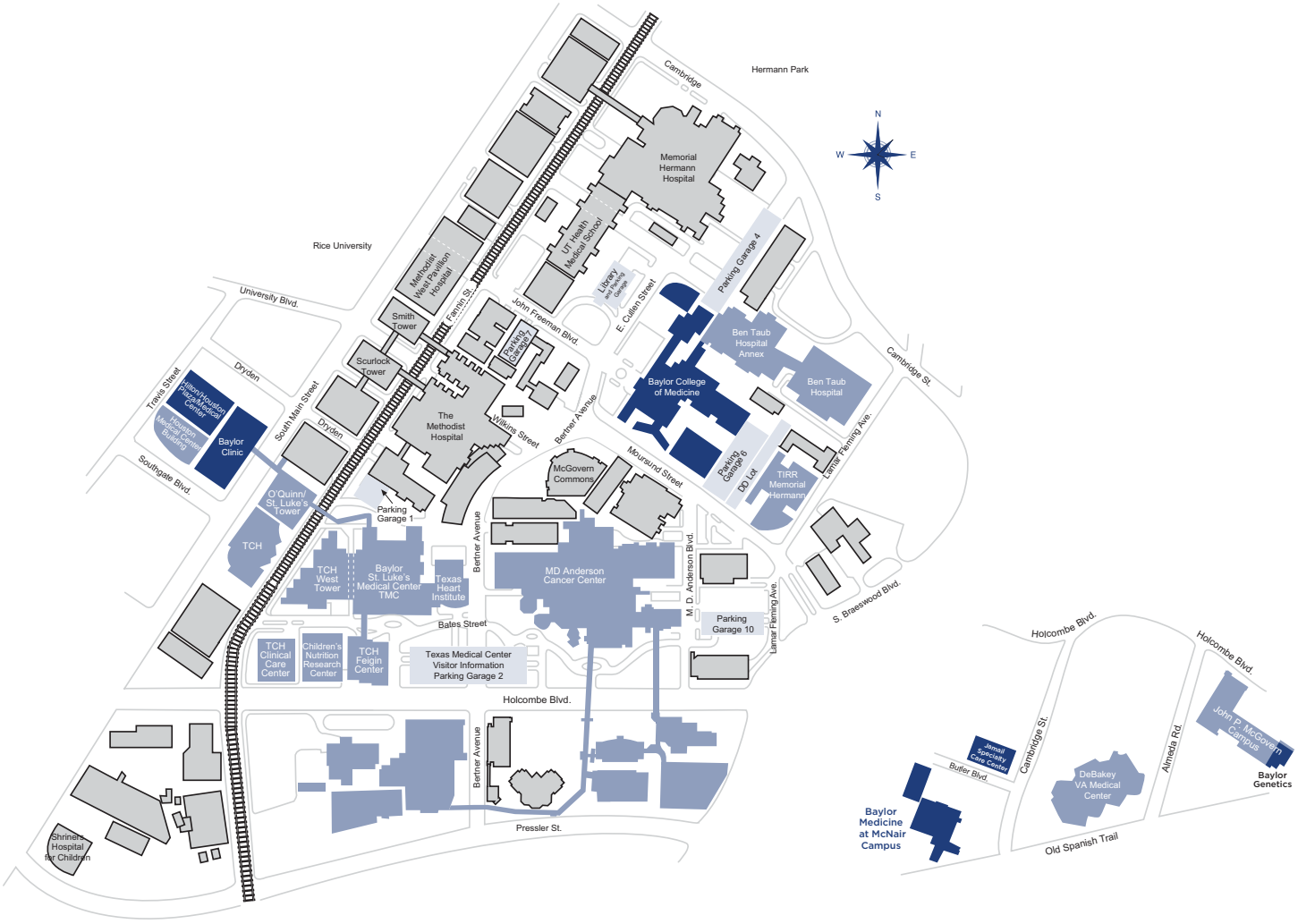
**The food**: Houston has 11,000 restaurants (and counting!), which serve every type of cuisine you could think of, both brick-and-mortar establishments and food trucks. It's not just BBQ and Tex-Mex (though you're missing out if you haven't tried these cuisines here).

**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
TWITTER: @BCMGENETICS
INSTAGRAM: @BCM_GENETICS

Keep up to date on all the latest news and advances from the Department of Molecular and Human Genetics at Baylor College of Medicine. Scan this QR code on your smart phone to visit our website at bcm.edu/genetics