



**MOLECULAR  
AND HUMAN  
GENETICS**

**2021**

## **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 policy (O2.2.25, O2.2.26) 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](http://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 practice and science of genetics and genomics. The integrated research, clinical, and diagnostic activities housed within our department have led in the transformation of genetic medicine. In spite of the challenges of the COVID19 pandemic, our team continues to excel in all aspects of our mission.

We continue to be a top-ranked genetics department. Among other U.S. genetics departments, our department has consistently ranked first in total awarded NIH funding and total number of NIH grants.

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

On the clinical front, in 2016, we established the Baylor College of Medicine & Chinese University of Hong Kong Center for Medical Genetics where our faculty is delivering the department's clinical, training, and research missions to a global venue.

Since then, we led the development of a new masters in genetic counseling program and in 2018, it's inaugural class began their studies. Also in 2018, we launched a new web-based platform called Consultagene, with the aim of expanding the department's comprehensive genetic services and providing patient education, genetic counseling, peer-to-peer medical consultations in a virtual setting.

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, the Undiagnosed Diseases Network, the Centers for Mendelian Genomics, the Knock-out Mouse Phenotyping Program, the Center for Precision Medicine Models, Clinical Genome Resource, Clinical Sequencing Evidence-Generating Research, and the Rare Diseases Clinical Research Network.

Ultimately, the innovation that has characterized our department continues to reside in our two greatest assets: our renowned faculty and trainees.

Best regards,

A handwritten signature in black ink, appearing to read 'B Lee'.

Brendan Lee, MD, PhD  
Robert and Janice McNair Endowed Chair  
in Molecular and Human Genetics

# CONTENTS

About the Department **4**

Graduate and Medical Education **6**

Clinical Affairs **11**

Diagnostic Laboratory Affairs **15**

Community Outreach **17**

Research Faculty **18**

Primary Appointments **19**

Secondary Appointments **86**

Baylor College of Medicine **98**

Texas Medical Center **99**

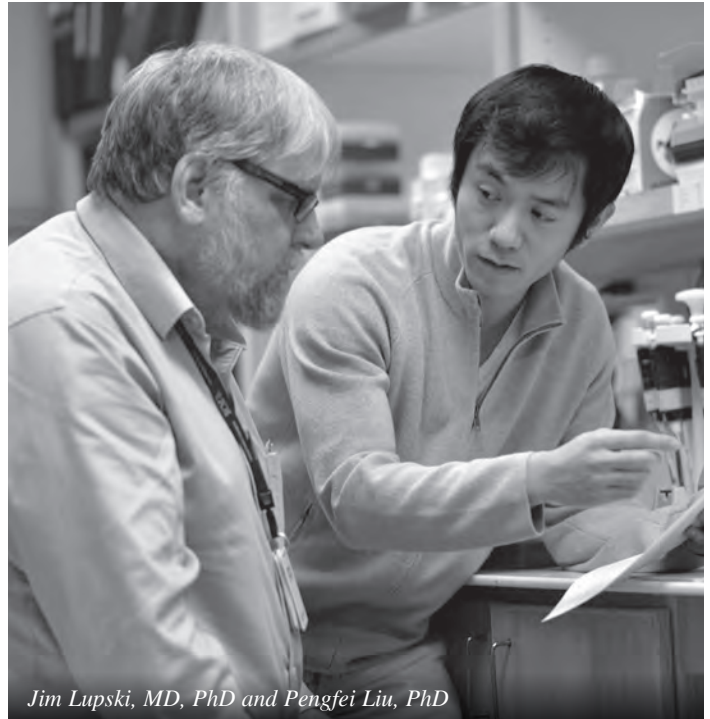
Houston **100**

Baylor College of Medicine Affiliated  
Hospitals, Institutions, and Facilities Map **101**

# ABOUT THE DEPARTMENT



*Huda Zoghbi, MD and Rodney Samaco, PhD*



*Jim Lupski, MD, PhD and Pengfei Liu, PhD*

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 the Henry and Emma Meyer Chair of Molecular and Human Genetics, Dr. 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.

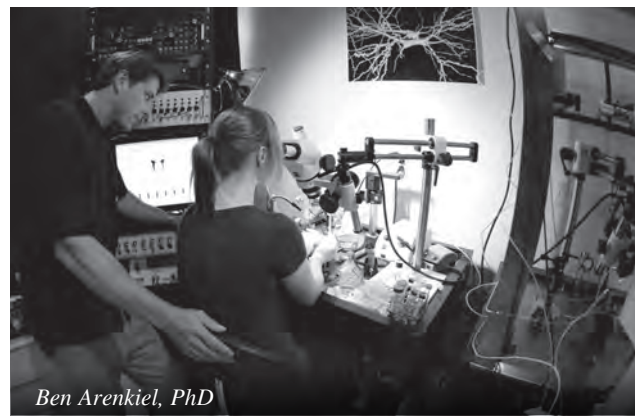
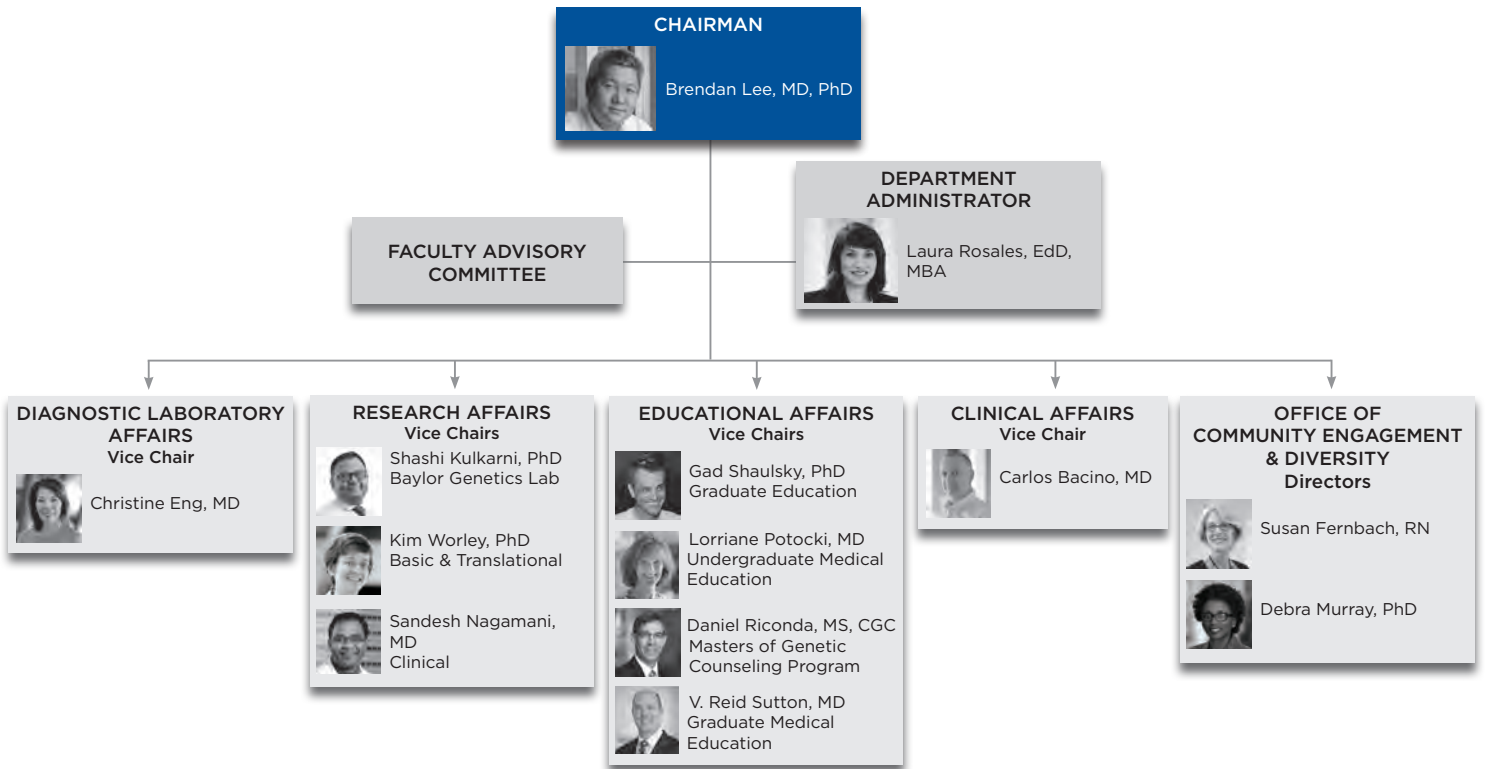
There are over 140 primary faculty spanning all of the missions of the Department. The research faculty are joined by clinical faculty, genetic counseling faculty, and diagnostic laboratory faculty in our mission to transform the practice of medicine with the science of genetics. Our primary faculty include three members of the National Academy of Sciences, six members of the National Academy of Medicine, and six fellows of the American Associa-

tion for the Advancement of Science.

The Human Genome Sequencing Center led by Richard Gibbs, PhD, Wofford Cain Chair in Molecular and Human Genetics, is a major strength of the environment, and the Genome Center faculty members all have primary academic appointments in the Department. 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.

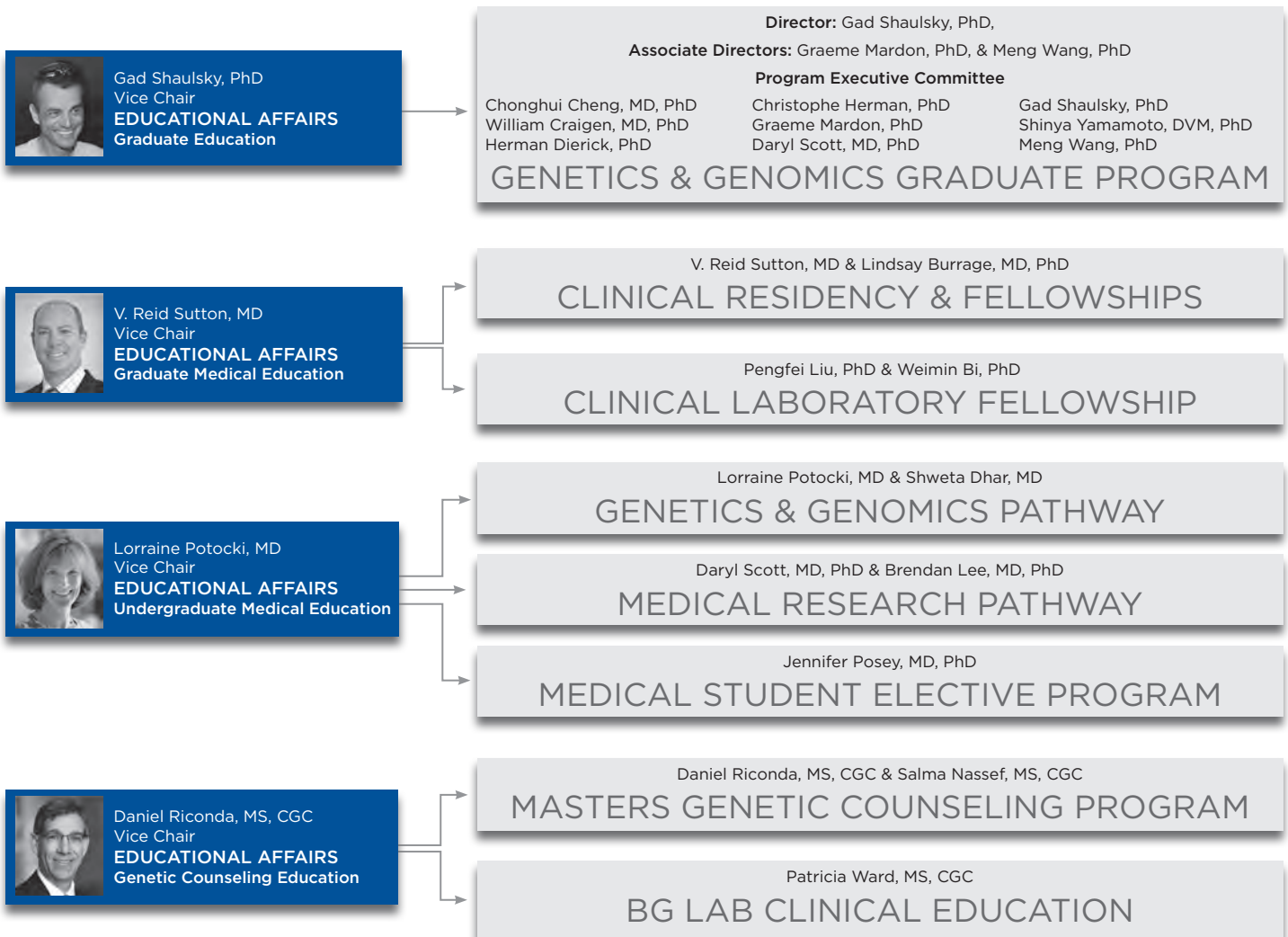
Among genetics departments at U.S. medical schools, we continue to rank highest in both the number of grants and total funding from the National Institutes of Health. Our facilities are equipped with state-of-the-art instrumentation for research in molecular, cellular, and biochemical genetics. Within the Department are also several specialized research centers that galvanize collaboration among faculty at Baylor. 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



# GRADUATE AND MEDICAL EDUCATION

## Division of Educational Affairs



## Graduate Program in Genetics & Genomics

The Graduate Program in Genetics and 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. In order to encourage our students to fulfill their potential and to excel in their work, we provide a competitive stipend, which stretches considerably further in Houston where cost of living is considerably lower than other large U.S. cities. Students who enroll in 2021-2022 will receive \$34,500 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, through 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, PhD*

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 training in mathematics, statistics and computational biology.

The concentration of the course work 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, 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. Following admission to candidacy, students will receive a \$1,000 travel grant from the department to initiate their participation in national meetings.

The final step to completion of the PhD 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, PhD, Associate Director  
Meng Wang, PhD, Associate Director

#### **Graduate Program Administrator**

Judi Coleman

## Medical Student Education

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. Formerly known as the Medical School Genetics Track, the Genetics & Genomics Pathway at BCM was established in 2011 and is the first of its type in the nation that provides an unique and valuable opportunity to the medical students to integrate genetics early on in their medical careers.

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) enhanc-

ing 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, MD  
Shweta Dhar, MD, MS

## 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 of these 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 clini-

cal services and clinical faculty; the comprehensive diagnostic laboratory which includes areas of cytogenetics, biochemical genetics, and molecular genetics; the active prenatal diagnosis program; and a number of 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.



*Medical Genetics Residency & Laboratory Fellowship Programs Trainees and Graduates*

Laboratory fellowships are also accredited by the AC-GME. We offer two-year fellowship training in Clinical Biochemical Genetics and Laboratory Genetics and Genomics (LGG). LGG is a new specialty of the ABMGG that incorporates training in both molecular and cytogenetic techniques, interpretation, and laboratory management in a single 24-month program.

Training takes place at our diagnostic laboratory, Baylor Genetics, where there are over two dozen laboratory directors as well as 30+ physicians and genetic counselors who support the program through direct supervision of fellows as well as through the didactic curriculum.

#### **Program Leadership**

V. Reid Sutton, MD, Director of Clinical Residency and Fellowship Programs  
Lindsay Burrage, MD, PhD, Assistant Program Director

Pengfei Liu, PhD, LGG Program Director  
Weimin Bi - LGG Associate Program Director

#### **ABMGG Residency & Fellowship Program Coordinator**

Kara Bartel

## **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 training in clinical 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, MD



2020 Graduating Class of the Genetic Counseling Program

## Genetic Counseling Program

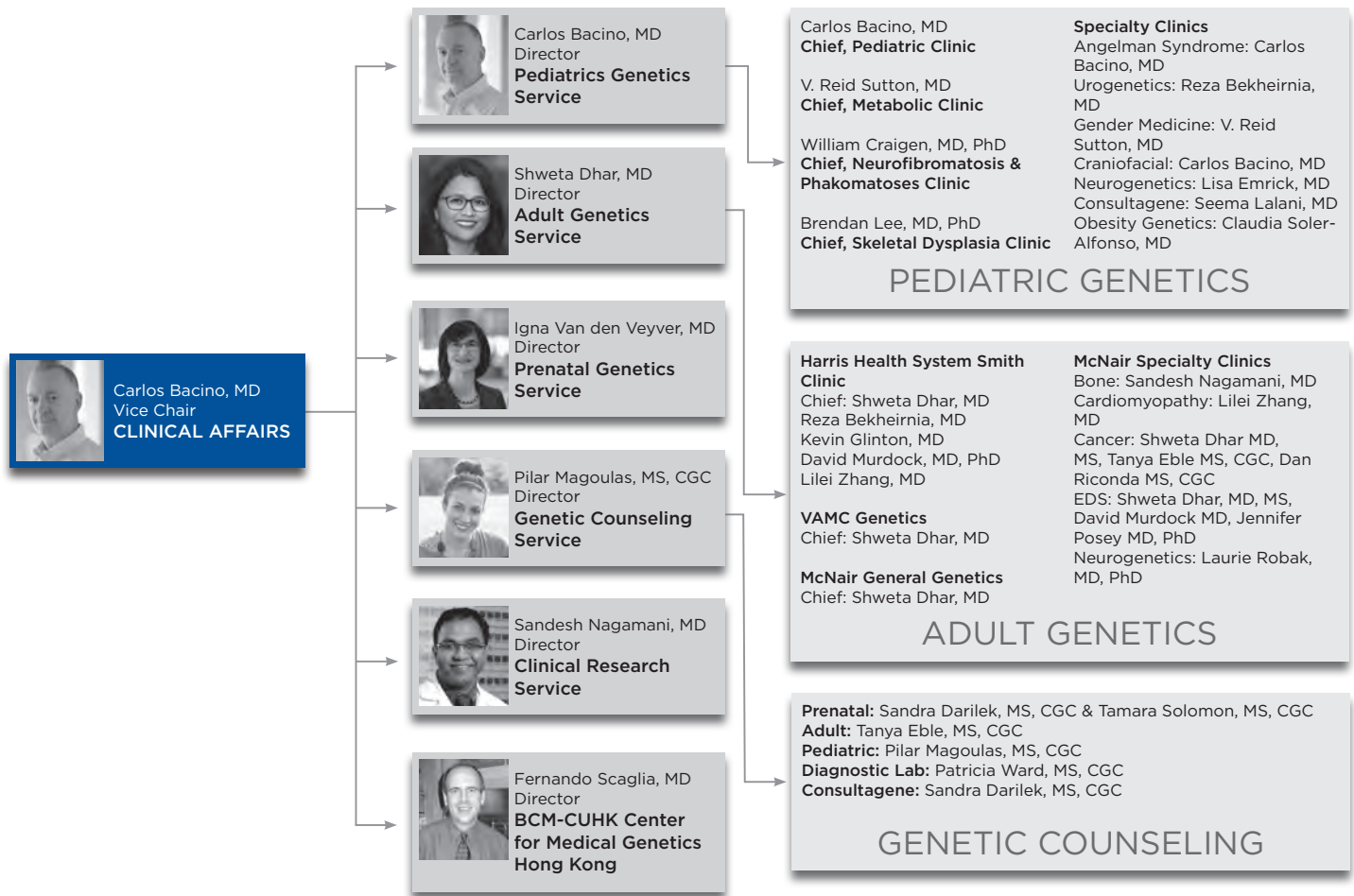
The Baylor College of Medicine Genetic Counseling Program was accredited in February of 2018 and graduated its first class of eight students in June of 2020. Beginning in 2020, the program will now admit 9 students and has plans to increase enrollment further in the future. The 22-month master of science degree program is 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 will empower graduates to be empathic professionals with effective critical thinking skills. Clinical rotations include a

variety of genetics clinics at Texas Children's Hospital, the VA Medical Center, the McNair campus clinics, the Baylor Clinic, The Pavilion for Women, and the Children's Hospital of San Antonio, 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, MS, CGC, Director  
 Salma Nassef, MS, CGC, Associate Director  
 Lindsay Burrage, MD, Medical Director

## Division of Clinical Affairs



## Genetics Clinics

**B**aylor 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 5000 patients annually. Specialty clinics within the Texas Children's Genetics Clinic include the metabolic clinic, neurofibromatosis clinic, skel-

etal 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, 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 otolaryngology (otogenetics), neurology (neurogenetics/tuberous sclerosis), plastic surgery (Craniofacial/Craniosynostosis clinics).

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 3 different healthcare settings (Baylor Medicine, Harris Health system, the Michael E. DeBakey VAMC, 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 clinics, we also have a specialized Ehlers-Danlos Syndrome clinic, a Metabolic and Genetic Disorders of the Bone Clinic, and a Cardiomyopathy clinic.

As the largest of its kind in the U.S., the Baylor Prenatal and Reproductive Genetics Clinic at Texas Children's Pavilion for Women, and its five 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



*Sandesh C.S. Nagamani, MD and Shweta Dhar, MD, MS*

expertise in prenatal and reproductive genetic screening and diagnostic testing, and counseling. Prenatal and reproductive genetic counseling is also available virtually at our Consultagene Clinic.

By having a strong foundation of physicians and other team members, which include genetic counselors, metabolic nurses, and dietitians, we are able to achieve the optimal 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 College of Medicine Medical Center - McNair Campus  
7200 Cambridge St., 9th Floor  
Suite 9A, Houston, TX 77030

**Telegenetic Counseling**

Consultagene Clinic  
[www.consultagene.org](http://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

**Clinical Faculty**

- April Adams, MD
- Carlos A. Bacino, MD
- Mir Reza Bekheirnia, MD
- Lindsay Burrage, MD, PhD
- William J. Craigen, MD, PhD
- Shweta Dhar, MD, MS
- Christine M. Eng, MD
- Kevin Ginton, MD, PhD
- Seema Lalani, MD
- Brendan Lee, MD, PhD
- James R Lupski, MD, PhD
- Keren Machol, MD
- Ronit Marom, MD, PhD
- Chaya Murali, MD
- David R. Murdock, M.D.
- Sandesh C.S. Nagamani, MD
- Sharon E Plon, MD, PhD
- Jennifer Ellen Posey, MD, PhD
- Lorraine Potocki, MD
- Laurie Robak, MD, PhD

**Clinical Faculty (cont.)**

Fernando Scaglia, MD  
 Daryl A. Scott, MD, PhD  
 Claudia Soler-Alfonso, MD  
 V. Reid Sutton, MD  
 Ignatia B. Van den Veyver, MD  
 Michael Francis Wangler, MD  
 Lilei Zhang, MD, PhD

**Nursing Faculty**

Alicia Turner, MSN, RN, FNP-C  
 Susan Fernbach BA, RN

**Nursing Staff**

Saima Ali, MSN, RN, FNP-C  
 Dianne Bauri, MS, RN, FNP-C

**Genetic Counseling**

**T**he Department of Molecular and Human Genetics is home to approximately 45 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, Sugar Land, Texas, and via tele-genetic 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 Texas Children's Hospital main campus and The Woodlands. 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 gender medicine, craniofacial and craniosynostosis, hematology, cardiology, neurology 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, connective tissue disorders, such as Ehlers-Danlos syndrome, or mitochondrial disorders.

In addition to the clinical genetic counselors, the Department has many 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 also 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**

Sandra Darilek, MS, CGC  
Tanya N. Eble, MS, CGC  
Laura I. Ellis, MS, CGC  
Jamie Fong, MS, CGC  
Rachel Franciskovich, MS, CGC  
Georgiann Garza, MS  
Sarah Huguenard, MS, CGC  
Melissa Hsu, MS, CGC  
Dana Knutzen, MS, CGC  
Andrea M. Lewis, MS, CGC  
Rebecca Littlejohn, MS, CGC  
Pilar Magoulas, MS, CGC  
Veena S. Mathur, MS, CGC  
Jill Anne Mokry, MS, CGC  
Andrea Moon, MS, CGC  
Salma A. Nassef, MS, CGC  
Kimberly M. Nugent, MS, CGC  
Sandra K. G. Peacock, MS, CGC  
Daniel Riconda, MS, CGC  
Patricia Robbins-Furman, MPH, BS, CGC  
Eric S. Schmitt, PhD, MS, CGC  
Sarah R. Scollon, MS, CGC  
Tamara Solomon, MS, CGC  
Samantha Stover, MS, CGC  
Haley Streff, MS, CGC  
Cathy Sullivan, MS, CGC  
Patricia Ward, MS, CGC  
Lauren Westerfield, MS, CGC

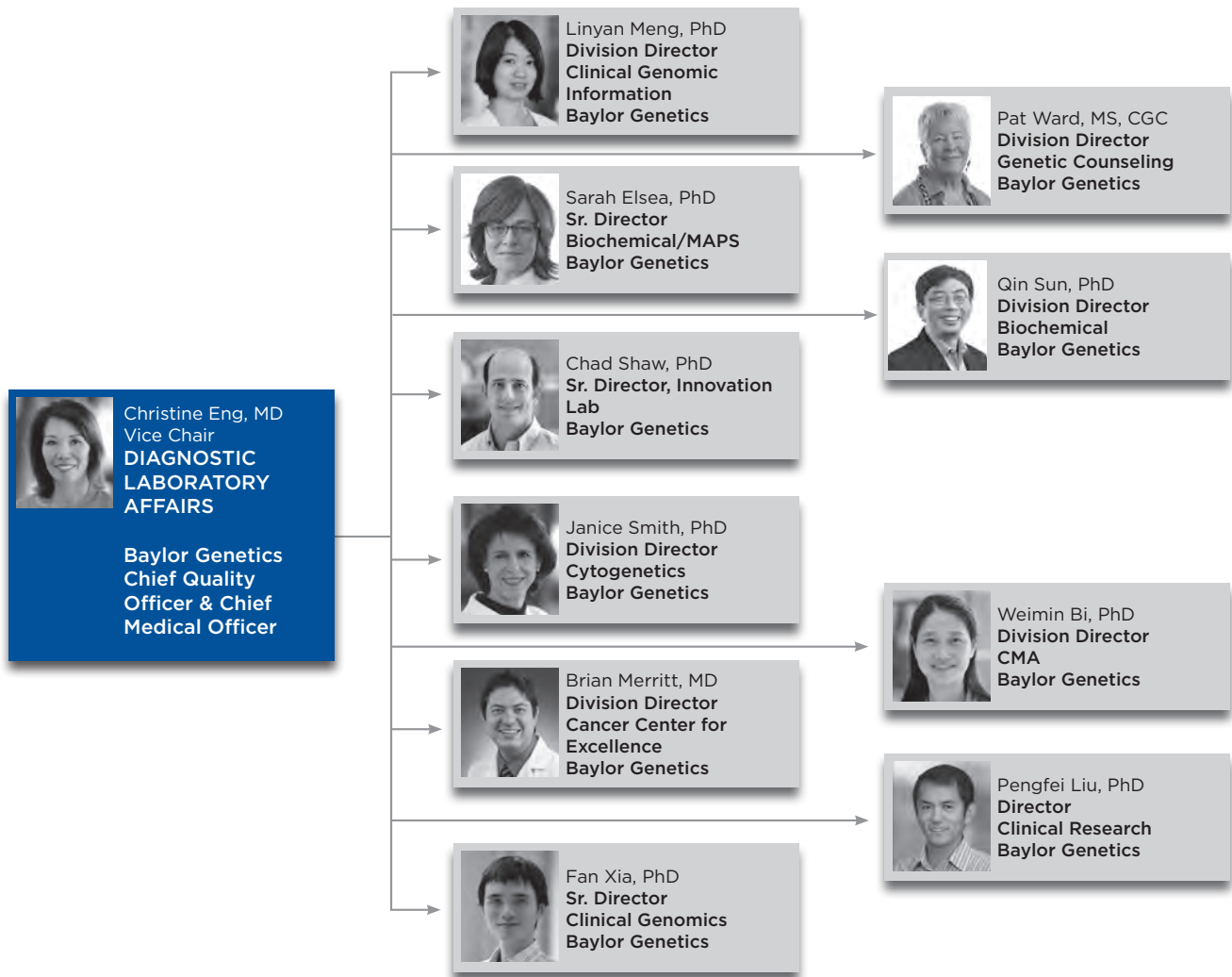
**Genetic Counseling Staff**

Rachel Ault, MS, CGC  
Taylor Beecroft, MS, CGC  
Matthew Burgess, MAPP, CGC  
Ashlee Byrnes, MS, CGC  
Katie Chan, MS, CGC  
Lauren Desrosiers, MS, CGC  
Wanda Dosal, RN  
Stacey Edwards, MS, CGC  
Amanda Gerard, MS, CGC  
Hannah Helber, MS, CGC  
Megan Hoenig, MS, CGC  
Jessica Honkomp, MS, CGC  
Olivia Juarez, MMSC  
Emily Magness, MS, CGC  
Liz Mizerik, MS, CGC  
Tiffany Nguyen Dolphyn, MS, CGC  
Roa Sadat, MS, CGC  
Rachel Thomas, MS, CGC



# DIAGNOSTIC LABORATORY AFFAIRS

## Division of Diagnostic Laboratory Affairs



## Baylor Genetics

Established in February 2015, Baylor Genetics, a joint venture between Baylor College of Medicine and H.U. Group Holdings, Inc., strives to continue the tradition of genetic 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 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, MD  
Weimin Bi, PhD  
Sau Wai Cheung, PhD, MBA  
Hongzheng Dai, PhD  
Sarah Elsea, PhD  
Christine Eng, MD  
Shashikhant Kulkarni, MS, Ph.D, FACMG  
Ning Liu, PhD  
Pengfei Liu, PhD  
Linyan Meng, PhD  
Brian Yang Merritt, MD  
Jennifer Scull, PhD  
Chad A. Shaw, PhD  
Janice Smith, PhD  
Qin Sun, PhD  
Vernon Sutton, MD  
Yue Wang, PhD  
Shu Wen, MD, PhD  
Lee-Jun Wong, PhD  
Fan Xia, PhD

# COMMUNITY ENGAGEMENT AND DIVERSITY

**T**he Office of Community Engagement and Diversity within the Department of Molecular and Human Genetics has expanded significantly over the past year. The co-directors of the office, Susan Fernbach, RN, BSN and Debra Murray, PhD, are Faculty Ambassadors for the BCM Office of Institutional Diversity, Inclusion, and Equity. The department's Diversity and Inclusion Strategic Planning Committee has grown to include Laura Rosales, MBA, D Ed. and Graeme Mardon, PhD. The committee created a department dashboard to guide future action steps to promote an environment that fosters inclusion for faculty, trainees, and staff.



*Baylor TCH Rare Disease Day*

The office offers multiple approaches to education, recruitment, and diversity and inclusion activities.

The **Evenings with Genetics** series has served the community for 14 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. This series has expanded to include statewide genetic outreach, in collaboration with the UT Texas Center for Disability Studies and the Texas Department of State Health Services.

A **Lunch and Learn** series (in-person) and the **Careers in Genetics and Genomics** series (virtual) are provided annually to present the genetics and genomics career path to high school and undergraduate students. The office will offer sessions at national meetings (Annual Biomedical Research Conference for Minority Students, Latin Medical Student Association) to introduce genetics and genomics and encourage participation in the field.

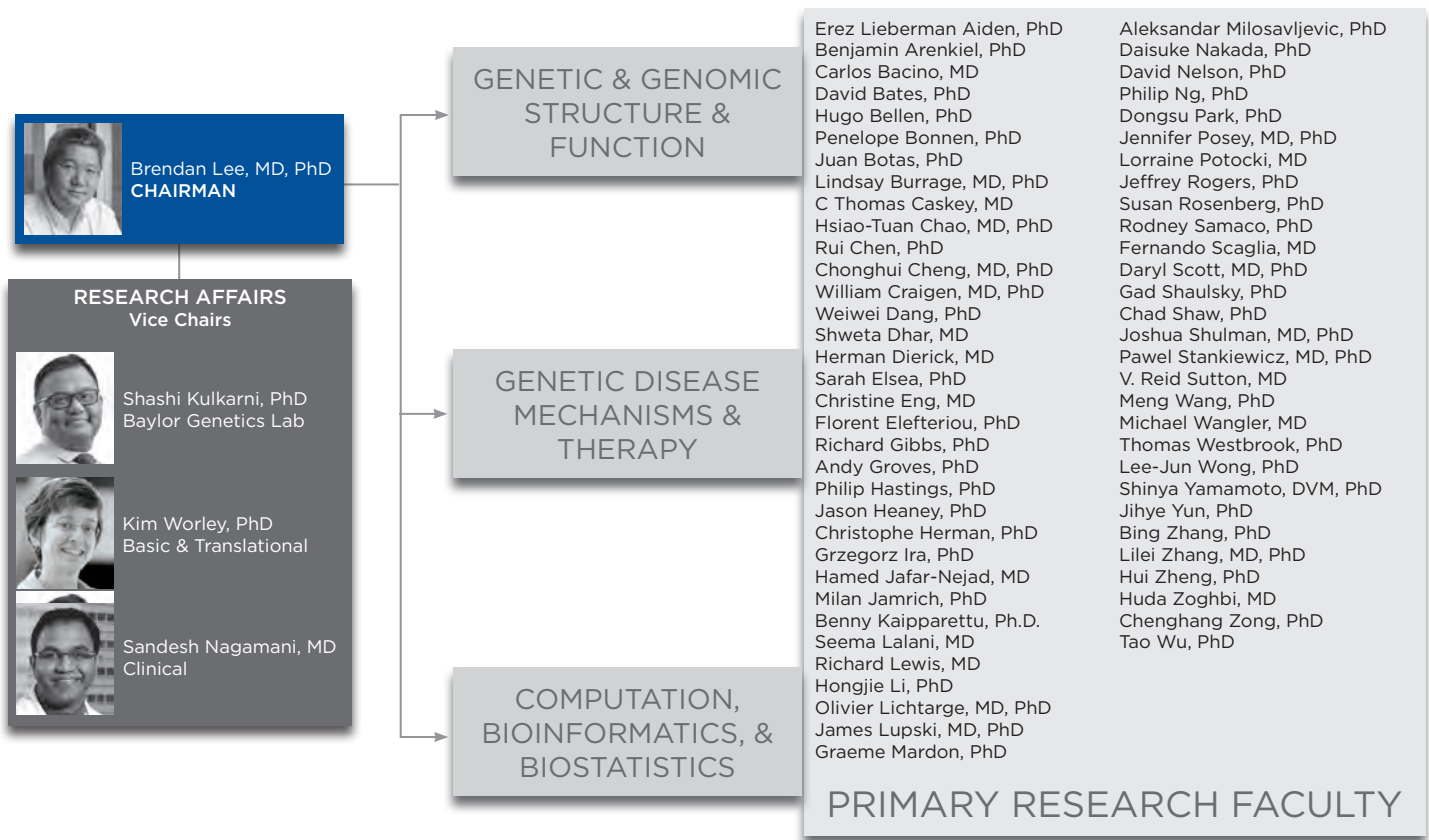
The **Medical Genetics Diversity Visiting Students Program** was developed by the office to provide under-represented 4th year medical students a 4-week clinical rotation beginning in 2021. Another virtual program, the **Town Hall Medical Genetics Career Options**, will offer 3rd and 4th year medical students the opportunity to learn about these careers from department faculty. This program is set to begin in Spring 2021.

Diversity and inclusion activities include the **"Let's Learn about One Another: the African American Experience"** program that began in the summer of 2020 to address the social injustice climate. The Let's Learn program will continue to expand to include perspectives from the department's widely diverse members. The office also curates an online library of articles regarding diversity, inclusion, and equity for department faculty, trainees, and staff.

## **Co-Directors**

Susan Fernbach, RN, BSN  
Debra Murray, PhD

## 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, PHD

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  
 McNair Scholar

PhD, 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.

E-mail: [Erez.Aiden@bcm.edu](mailto:Erez.Aiden@bcm.edu)



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

## BENJAMIN R. ARENKIEL, PhD

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

*PhD, 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.

E-mail: [arenkiel@bcm.edu](mailto:arenkiel@bcm.edu)



### 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, Moayed 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.

## CARLOS A. BACINO, MD, 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

MD, 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 actively involved in the diagnosis and management of pediatric patients with birth defects and rare genetic disorders. I am also involved in bone disorders and participate at 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 many 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. 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/metformin to promote methylation and revert silencing of the paternal allele. These trials attempted to ameliorate the symptoms of Angelman syndrome by altering patterns of imprinting. We also did look at the effects of levo-dopa in children with AS in a separate trial. 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 a private pharmaceutical company, I am involved in several studies, 1) looking at anthropometric measurements in a cohort of patients with achondroplasia, 2) enrolling patients with achondroplasia for 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 is a double-blind drug-placebo trial divided in two groups for patients over and under 5 years of age.

**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 on novel genes and disease mechanisms. I am currently the co-PI of this effort.

E-mail: [cbacino@bcm.edu](mailto:cbacino@bcm.edu)



### SELECTED PUBLICATIONS

Tokita MJ, Braxton AA, Shao Y, Lewis AM, Vincent M, Küry S, Besnard T, Isidor B, Latypova X, Bézieau S, Liu P, Motter CS, Melver CW, Robin NH, Infante EM, McGuire M, El-Gharbawy A, Littlejohn RO, McLean SD, Bi W, **Bacino CA**, Lalani SR, Scott DA, Eng CM, Yang Y, Schaaf CP, 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-Pierrri 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-Pierrri 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.

Burrage LC, Person RE, Flores A, Villanos MT, Bi W, Wiszniewska J, **Bacino CA** (2012). *De novo* interstitial duplication of 15q11.2-q13.1 with complex maternal uniparental trisomy for the 15q11-q13 region in a patient with Prader-Willi syndrome. **Am J Med Genet A.** 158A: 2557-63.

**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.

Tompson SW, **Bacino CA**, Safina NP, Bober MB, Proud VK, Funari T, Wangler MF, Nevarez L, Ala-Kokko L, Wilcox WR, Eyre DR, Krakow D, Cohn DH (2010). Fibrochondrogenesis results from mutations in the *COL11A1* type XI collagen gene. **Am J Hum Genet.** 87: 708-12.

## DAVID BATES, PHD

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

PhD, 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.

E-mail: [bates@bcm.edu](mailto:bates@bcm.edu)



### 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, DVM, PhD

### MARCH OF DIMES CHAIR IN DEVELOPMENTAL BIOLOGY

Investigator, Howard Hughes Medical Institute

Professor, Departments of Molecular and Human Genetics and Neuroscience

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

Business Engineer, University of Brussels, Belgium

DVM, University of Ghent, Belgium

PhD, 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 are affected that also play a role in Parkinson's disease, Amyotrophic Lateral Sclerosis, and Alzheimer's Disease. These pathways are now being studied intensely in the lab.

My lab as well as the laboratories of Michael Wangler and Shinya Yamamoto here at BCM and John Postlethwait 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 US. 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 30 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 for four genes.

My lab also plays an important role in developing new tools to manipulate flies as well as to generate reagents for the fly community. I have been the PI of the Genome Disruption Project (GM067858) 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 allow 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 the HHMI and the NIH, and I am truly dedicated to graduate education and postdoctoral training as is obvious from the success of my former trainees.

E-mail: [hbellen@bcm.edu](mailto:hbellen@bcm.edu)

website: <http://flypush.imgen.bcm.tmc.edu/>



### SELECTED PUBLICATIONS

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.

Şentürk M, Lin G, Zuo Z, Mao D, Watson E, Mikos AG, **Bellen HJ** (2019). Ubiquitins regulate autophagic flux through mTOR signalling and lysosomal acidification. **Nat Cell Biol**. 21: 384-396.

Splinter K, Adams DR, Bacino CA, **Bellen HJ**, (...), Wangler MF, Westerfield M, Wheeler MT, Wise AL, Worthey EA, Yamamoto S, Ashley EA; Undiagnosed Diseases Network (2018). Effect of genetics diagnosis on patients with previously undiagnosed disease. **N Engl J Med**. 379: 2131-2139.

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  $\alpha$ -synuclein gain. **Cell Metab**. 28: 605-618.

Lee PT, Zirin J, Kanca O, (...), Levis RW, Spradling AC, Perrimon N, **Bellen HJ** (2018). A gene-specific T2A-GAL4 library for *Drosophila*. **ELife**. 7: e35574.

Tan KL, Haelterman NA, (...), Milewicz DM, **Bellen HJ** (2018). *Ari-1* regulates myonuclear organization together with *Parkin* and is associated with aortic aneurysms. **Dev Cell**. 45: 226-244.

Liu L, MacKenzie KR, Putluri N, Maletic-Savatic 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.

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  $\alpha$ -ketoglutarate dehydrogenase, promotes mTORC1 activation and neurodegeneration. **Neuron**. 93: 115-131.

Chen K, Ho TS, Lin G, Tan KL, Rasband MN, **Bellen HJ** (2016). Loss of Frataxin activates the iron/sphingolipid/PDK1/Mef2 pathway in mammals. **ELife**. 5: e20732.

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, Charnig 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.

## PENELOPE E. BONNEN, PhD

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

PhD, 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.

E-mail: [pbonnen@bcm.edu](mailto:pbonnen@bcm.edu)



### 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, PhD

**Professor**, Departments of Molecular and Human Genetics and Molecular & Cellular Biology

**Faculty Member**, Graduate Programs in Genetics & Genomics and Quantitative & Computational Biosciences

PhD, 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 disease, HD), alpha-synuclein (Parkinson 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 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 allows 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.

**E-mail:** [jbotas@bcm.edu](mailto:jbotas@bcm.edu)



### SELECTED PUBLICATIONS

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  $\alpha$ -Synuclein Levels via a Tiered Cross-Species Validation Approach. **J Neurosci.** 38: 9286-9301.

Al-Ramahi I, Giridharan SSP, Chen YC, Patnaik S, (...), Weisman LS, **Botas J**, Marugan JJ (2017). Inhibition of PIP4Ky ameliorates the pathological effects of mutant huntingtin protein. **ELife.** 6. pii: e29123.

Rousseaux MW, de Haro M, Lasagna-Reeves CA, De Maio A, (...), Westbrook TF, Troncoso JC, **Botas J**, Zoghbi HY (2016). TRIM28 regulates the nuclear accumulation and toxicity of both alpha-synuclein and tau. **ELife.** 5. pii: e19809.

Lasagna-Reeves CA, de Haro M, Hao S, Park J, Rousseaux MW, Al-Ramahi I, (...), Tang J, **Botas J**, Zoghbi HY (2016). Reduction of Nuak1 Decreases Tau and Reverses Phenotypes in a Tauopathy Mouse Model. **Neuron.** 92: 407-418.

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.

Lu B, Al-Ramahi I, Valencia A, (...), Difiglia M, **Botas J**, Palacino J (2013). Identification of *NUB1* as a suppressor of mutant Huntingtin toxicity via enhanced protein clearance. **Nat Neurosci.** 16: 562-70.

de Haro M, Al-Ramahi I, Jones KR, Holth JK, Timchenko LT, **Botas J** (2013). Smaug/SAMD4A restores translational activity of CUGBP1 and suppresses CUG-induced myopathy. **PLoS Genet.** 9: e1003445.

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

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

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

## LINDSAY C. BURRAGE, MD, PhD

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

MD, PhD, 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 lead the clinical section of 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.

E-mail: [burrage@bcm.edu](mailto:burrage@bcm.edu)



### SELECTED PUBLICATIONS

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, Frankel AE, Stone E, Alters S, Johnson DE, Rowlinson SW, Georgiou G, 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.

Miller M, Kennedy AD, Eckhart AD, **Burrage LC**, Wulff JE, Miller LAD, Milburn MV, Ryals JA, Beaudet AL, Sun Q, Sutton VR, Elsea SH (2015). Untargeted Metabolomic Analysis for the Clinical Screening of Inborn Errors of Metabolism. *J Inherit Metab Dis.* 38: 1029-39.

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.

## C. THOMAS CASKEY, MD, FACP, FACMG, FRSC

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

*MD, Duke University Medical School  
Honorary, Chemistry, University of South Carolina*

### RESEARCH INTERESTS

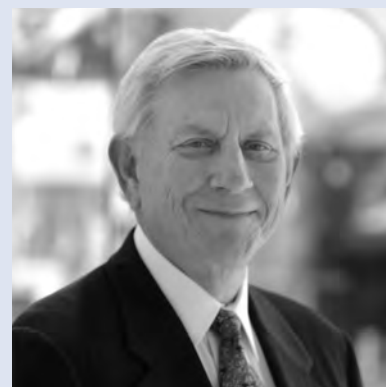
Dr. Caskey was the CEO of The Brown Foundation Institute of Molecular Medicine at UTHSC-Houston. Dr. Caskey served as Senior VP, Human Genetics and Vaccines Discovery at Merck Research Laboratories, West Point, and as President of the Merck Genome Research Institute.

Dr. Caskey is Board Certified in Internal Medicine, Medical Genetics, and Molecular Genetics with 25 years of patient care experience. Member of: National Academy of Sciences, Institute of Medicine (Chair, Board on Health Sciences Policy), Royal Society of Canada, past President: American Society of Human Genetics & Human Genome Organization, and Texas Academy of Medicine, Engineering and Science. He is an editor of the Annual Reviews of Medicine.

Dr. Caskey received numerous academic and industry honors. His genetic research identified genetic basis of 25 major inheritable diseases and clarified the understanding of "anticipation" in triplet repeat diseases (Fragile X, myotonic dystrophy and over 25 others). His personal identification patent is the basis of worldwide application for forensic science and he is also a consultant to the FBI in forensic science.

Dr. Caskey is currently directing a program of Precision Medicine with Young Presidents Organization (YPO) co-sponsored by The Cullen Foundation for Higher Education. The program won the YPO International Award for most innovative education program. He is a Consultant to Human Longevity, Inc. and a member of the Board of Metabolon, Inc., both, leaders in precision medicine technology. Recent publications address the utility of genome wide sequencing to preventive adult onset diseases. His current research focuses on the application of whole genome sequence and metabolomics of individuals toward the objective of disease risk and its prevention.

**E-mail:** [tcaskey@bcm.edu](mailto:tcaskey@bcm.edu)



### SELECTED PUBLICATIONS

Long T, Hicks M, Yu HC, Biggs WH, Kirkness EF, (...), **Caskey CT**, Schork NJ, Garner C, Spector TD, Venter JC, Telenti A (2017). Whole-genome sequencing identifies common-to-rare variants associated with human blood metabolites. **Nat Genet.** 49: 568-578.

Guo L, Milburn MV, Ryals JA, Lonergan SC, Mitchell MW, Wulff JE, Alexander DC, Evans AM, Bridgewater B, Miller L, Gonzalez-Garay ML, **Caskey CT** (2015). Plasma metabolomic profiles enhance precision medicine for volunteers of normal health. **Proc Natl Acad Sci U S A.** 112: E4901-10.

Gonzalez-Garay ML, McGuire AL, Pereira S, **Caskey CT** (2013). Personalized genomic disease risk of volunteers. **Proc Natl Acad Sci U S A.** 110: 16957-62.

**Caskey CT**, Gonzalez-Garay ML, Pereira S, McGuire AL (2014). Adult genetic risk screening. **Annu Rev Med.** 65: 1-17.

Schaaf CP, Gonzalez-Garay ML, Xia F, Potocki L, Gripp KW, Zhang B, Peters BA, McElwain MA, Drmanac R, Beaudet AL, **Caskey CT**, Yang Y (2013). Truncating mutations of *MAGEL2* cause Prader-Willi phenotypes and autism. **Nat Genet.** 45: 1405-8.

**Caskey CT** (2010). Using genetic diagnosis to determine individual therapeutic utility. **Annu Rev Med.** 61: 1-15.

**Caskey CT** (2007). The drug development crisis: efficiency and safety. **Annu Rev Med.** 58: 1-16.

Bai C, Connolly B, Metzker ML, Hilliard CA, Liu X, Sandig V, Soderman A, Galloway SM, Liu Q, Austin CP, **Caskey CT** (2000). Overexpression of M68/DcR3 in human gastrointestinal tract tumors independent of gene amplification and its location in a four-gene cluster. **Proc Natl Acad Sci U S A.** 97: 1230-5.

Brown SD, Twells RC, Hey PJ, Cox RD, Levy ER, Soderman AR, Metzker ML, **Caskey CT**, Todd JA, Hess JF (1998). Isolation and characterization of *LRP6*, a novel member of the low density lipoprotein receptor gene family. **Biochem Biophys Res Commun.** 248: 879-88.

Timchenko L, Nastainczyk W, Schneider T, Patel B, Hofmann F, **Caskey CT** (1995). Full-length myotonin protein kinase (72 kDa) displays serine kinase activity. **Proc Natl Acad Sci U S A.** 92: 5366-70.

Ashizawa T, Wong LJ, Richards CS, **Caskey CT**, Jankovic J (1994). CAG repeat size and clinical presentation in Huntington's disease. **Neurology.** 44: 1137-43.

Redman JB, Fenwick RG Jr, Fu YH, Pizzuti A, **Caskey CT** (1993). Relationship between parental trinucleotide GCT repeat length and severity of myotonic dystrophy in offspring. **JAMA.** 269: 1960-5.

Pieretti M, Zhang FP, Fu YH, Warren ST, Oostra BA, **Caskey CT**, Nelson DL (1991). Absence of expression of the *FMR-1* gene in fragile X syndrome. **Cell.** 66: 817-22.

## HSIAO-TUAN CHAO, MD, PhD

**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  
**McNair Scholar**

MD, Baylor College of Medicine

PhD, 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 advances 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.

In my laboratory at the NRI, 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. A wide variety of approaches and techniques are employed in our laboratory including genetically engineered mouse and fruit fly models, structural and functional analyses with electrophysiology, imaging, transcriptomics, molecular and cellular assays, and comprehensive behavioral profiling. Our goal is to determine the role of inhibitory dysfunction in the pathogenesis of neurodevelopmental disorders by deciphering how genetic alterations perturb inhibition in the brain, impact neural development, and lead to abnormal neurologic output.

In addition to the laboratory research activities, I am a member of the Undiagnosed Diseases Network (UDN) and focus clinically on *EBF3*-related Hypotonia, Ataxia, and Delayed Development syndrome (HADDs). In 2017, I established a multidisciplinary HADDs clinic at TCH in partnership with Dr. Michael Wangler. We now follow the largest group of HADDs patients to date in a single institution. Through the clinic, we conduct developmental, clinical, and genetic evaluations on a yearly basis. This natural history study allows us to expand our understanding of the genotype-phenotype correlations, progression, complications, and comorbidities associated with this condition. The findings from the clinical study also informs our laboratory research efforts to understand how *EBF3* gene disruptions alter inhibitory and excitatory neuronal development, perturb neural network activity, and lead to cognitive and behavioral abnormalities.

E-mail: [hc140077@bcm.edu](mailto:hc140077@bcm.edu)



### SELECTED PUBLICATIONS

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.

Wangler MF\*, Yamamoto S\*, **Chao HT**, Posey JE, Westfield M, Postlethwait J; Members of the Undiagnosed Diseases Network (UDN), Hieter P, Boycott KM, Campeau PM, Bellen HJ (2017). Model Organisms Facilitate Rare Disease Diagnosis and Therapeutic Research. **Genetics**. 207: 9-27. \*equal contribution

Leduc MS, **Chao HT**, Qu C, Walkiewicz M, Xiao R, Magoulas P, Pan S, Beuten J, He W, Bernstein JA, Schaaf CP, Scaglia F, Eng CM, Yang Y (2017). Clinical and molecular characterization of *de novo* loss of function variants in HNRNPU. **Am J Med Genet A**. 173: 2680-2689.

**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\*, Wan YW, Wangler MF, Yamamoto S, **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

Chang CL, Trimbuch T, **Chao HT**, Jordan JC, Herman MA, Rosenmund C (2014). Investigation of synapse formation and function in a glutamatergic-GABAergic two-neuron microcircuit. **J Neurosci**. 34: 855-68.

**Chao HT**, Chen H, Samaco RC, Xue M, Chahrour M, Yoo J, Neul JL, Gong S, Lu HC, Heintz N, Ekker M, Rubenstein JL, Noebels JL, Rosenmund C, Zoghbi HY (2010). Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. **Nature**. 468: 263-9.

Xue M\*, Craig TK\*, Xu J, **Chao HT**, Rizo J, Rosenmund C (2010). Binding of the complexin N terminus to the SNARE complex potentiates synaptic-vesicle fusogenicity. **Nat Struct Mol Biol**. 17: 568-75. \*equal contribution

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

## RUI CHEN, PHD

**Professor**, Department of Molecular and Human Genetics; Human Genome Sequencing Center

**Faculty Member**, Graduate Programs in Genetics & Genomics; Quantitative & Computational Biosciences; and Developmental Biology

*PhD*, Baylor College of Medicine

*Postdoc*, Baylor College of Medicine

### RESEARCH INTERESTS

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

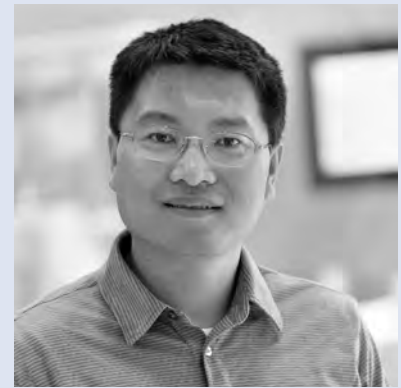
**Genetics of human inherited retinal degenerative diseases:** Collectively, ocular diseases affect large population in the world with 40 million people are blind and another 100 million with substantial visual impairment. Together with our collaborators, we are currently working on identifying genes 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 diagnosis of about 70% of the patients. In addition, we have identified and published 15 new IRD associated genes. Continued investigation of underlying genetics of unsolved IRD patients is one of our main focuses, including but not limited in 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 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 model for several genes, such as *Spata7*, *Cwc27*, and *Reep6*, that are either currently under investigated or represent new genetics pathways. A combination of genetic, genomic, and biochemical approaches is used to characterize these mouse models and elucidate 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 method that can address a significant portion of IRD patients by targeting converging pathways and/or downstream effector genes. Finally, 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 screen for over 2,000 individual monkey carrying 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 mutation in many genes associated with IRD and other human diseases have been identified. These models will serve as 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 reference map for the human retina at the single cell resolution.

**E-mail:** ruichen@bcm.edu



### 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, Wang J, Shakoor A, Li Y, Morgan DJ, Hejazi AA, Cvekl A, DeAngelis MM, Zhou ZJ, **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, Raveendran M, Davis S, Liang Q, Pomerantz O, Wang J, Garzel L, Cameron A, Yiu G, Stout JT, Huang Y, Murphy CJ, Roberts J, Gopalakrishna KN, Boyd K, Artemyev NO, Rogers J, Thomas 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, Moayed 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, PHD

Associate 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

MD, Peking University Health Science Center  
PhD, 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 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 reactivated 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 governs 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 on 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.

E-mail: [chonghui.cheng@bcm.edu](mailto:chonghui.cheng@bcm.edu)



### SELECTED PUBLICATIONS

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.

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.

Wang W, Zhang H, Liu S, Kim CK, Xu Y, Hurley LA, Nishikawa R, Nagane M, Hu B, Stegh AH, Cheng SY, **Cheng C** (2017). Internalized CD44s splice isoform attenuates EGFR degradation by targeting Rab7A. *Proc Natl Acad Sci U S A.* 114: 8366-8371.

Liu S, **Cheng C** (2017). Akt Signaling Is Sustained by a CD44 Splice Isoform-Mediated Positive Feedback Loop. *Cancer Res.* 77: 3791-3801.

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, Strelakova 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.

Liu S, **Cheng C** (2013). Alternative RNA Splicing and Cancer. *Wiley Interdiscip Rev RNA.* 4: 547-66.



## WILLIAM J. CRAIGEN, MD, PHD

**Professor**, Departments of Molecular and Human Genetics and Pediatrics  
**Faculty Member**, Graduate Programs in Development, Disease Models & Therapeutics; Genetics & Genomics; and Translational Biology & Molecular Medicine

**Director**, Neurofibromatosis Clinic, Texas Children's Hospital  
**Medical Director**, Mitochondrial Laboratory, Baylor Genetics

*MD, PhD, 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. One area of interest in the lab is in understanding the role of the mitochondrial outer membrane permeability in the regulation of cellular energy economy, apoptosis and mammalian organ function. Voltage-dependent Anion Channels (VDAC1-3: also known as mitochondrial porins) are a family of mitochondrial outer membrane proteins that conduct small molecules across the outer membrane. VDACS also bind cytosolic kinases such as hexokinase isoforms, and may act to tether other multi-protein complexes to mitochondria. One isoform (VDAC2) functions in suppressing apoptosis by binding the multi-domain pro-apoptotic protein BAK, while other isoforms play roles in glucose metabolism, learning and memory, and fertility. Using model organisms we are interested in determining the specific functions of each isoform in biology and relating VDAC function to disease states. These studies involve biochemical, physiologic, and genetic experimentation.

**Human Metabolic Disorders:** Despite advances in identifying human metabolic diseases, pathophysiologic mechanisms are poorly understood and specific treatment strategies lacking. Others projects in the laboratory involve studies of metabolic pathways leading to human inherited disorders. Using mutant mice, our current studies are designed to understand the metabolic disturbances that are associated defects in phospholipid and fatty acid metabolism, purine and creatine synthesis, and mitochondrial respiratory chain activities. We are interested in defining cell type-specific functions for the enzymes of intermediary metabolism using knockout mice in conjunction with tissue-specific transgene expression.

**E-mail:** [wcrainen@bcm.edu](mailto:wcrainen@bcm.edu)



### SELECTED PUBLICATIONS

**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.

**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, PhD**

**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**

*PhD, Southern Illinois University*  
*Postdoc, University of Pennsylvania*

**RESEARCH INTERESTS**

Our laboratory is studying epigenetic regulation mechanisms during 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 a moderate retardation of aging and a delay in the onset of age-associated diseases, such as cancer, would have tremendous impact on the quality of life for the general public. However, aging and how it contributes to the development of age-associated diseases remain poorly understood. Epigenetic changes, including histone modifications and proteome, 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. This mechanistic study will form the basis in future development of therapeutic target for treating age-associated diseases and improving human health span.

Epigenetics generally includes all cellular alterations beyond genetic changes that result in observable phenotypes. In practice, epigenetics usually means persistent covalent alterations to chromatin, such as histone acetylation and DNA methylation. Recent proteomics and acetylomics studies have broadened our views of epigenetics and many more enzymes and factors can carry modifications that confer epigenetic phenomena. It is very clear now epigenetics represents a complex regulation network on top of the genetic code. In medicine, epigenetics holds a very promising future because interventions in epigenetics can alter genetic outcomes and the strength of such intervention can be fine-tuned.

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 also because many molecular mechanisms of chromatin are highly conserved from yeast to complex eukaryotes. We use the budding yeast replicative aging as a model to study how epigenetic regulations can modulate longevity. In the past, we have shown that elevated levels of histone H4K16 acetylation near telomeres is a hallmark of old cells. It is regulated by a pair of enzymes Sir2 and Sas2 in yeast and is a causal factor in determining lifespan. 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. Changes in aging and senescence phenotype are investigated by knocking down conserved enzymes. Epigenetic features are tracked during senescence and compared between young and old stem cells. Studying mechanistic conservation using mammalian cell models will provide valuable insights into mammalian aging and conditions predisposed to cancer development.

**E-mail:** [weiwei.dang@bcm.edu](mailto:weiwei.dang@bcm.edu)

**SELECTED PUBLICATIONS**

Sen P, **Dang W**, Donahue G, Dai J, Dorsey J, Cao X, Liu W, Cao K, Perry R, Lee JY, Wasko BM, Carr DT, He C, Robison B, Wagner J, Gregory BD, Kaerberlein M, Kennedy BK, Boeke JD, Berger SL (2015). H3K36 methylation promotes longevity by enhancing transcriptional fidelity. **Genes Dev.** 29: 1362-76.

Jo MC, Liu W, Gu L, **Dang W**, Qin L (2015). High-throughput analysis of yeast replicative aging using a microfluidic system. **Proc Natl Acad Sci USA.** 112: 9364-9.

**Dang W**, Sutphin GL, Dorsey JA, Otte GL, Cao K, Perry RM, Wanat JJ, Saviolaki D, Murakami CJ, Tsuchiyama S, Robison B, Gregory BD, Vermeulen M, Shiekhhattar R, Johnson FB, Kennedy BK, Kaerberlein 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.** 6: 952-66.

McCauley BS, **Dang W** (2014). Histone methylation and aging: Lessons learned from model systems. **Biochim Biophys Acta.** 1839: 1454-62.

McCormick MA, Mason AG, Guyenet SJ, **Dang W**, Garza RM, Ting MK, Moller RM, Berger SL, Kaerberlein M, Pillus L, La Spada AR, Kennedy BK (2014). The SAGA Histone Deubiquitinase Module Controls Yeast Replicative Lifespan via Sir2 Interaction. **Cell Rep.** 2: 477-86.

**Dang W** (2014). The controversial world of sirtuins. **Drug Discovery Today: Technologies.** 12: e9-12.

Tsuchiyama S, Kwan E, **Dang W**, Bedalov A, Kennedy BK (2013). Sirtuins in yeast: phenotypes and tools. **Methods Mol Biol.** 1077: 11-37.

Yuan H, Rossetto D, Mellert H, **Dang W**, Srinivasan M, Johnson J, (...) Marmorstein R (2012). MYST protein acetyltransferase activity requires active site lysine autoacetylation. **EMBO J.** 31: 58-70.

Edwards CR, **Dang W**, Berger SL (2011). Histone H4 lysine 20 of *Saccharomyces cerevisiae* is monomethylated and functions in subtelomeric silencing. **Biochemistry.** 50: 10473-83.

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

Lin YY, Lu JY, Zhang J, Walter W, **Dang W**, et al. (2009). Protein acetylation microarray reveals that NuA4 controls key metabolic target regulating gluconeogenesis. **Cell.** 136: 1073-84.

## SHWETA DHAR, MD, MS

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  
 MS, 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 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 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 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.

E-mail: [ddhar@bcm.edu](mailto:ddhar@bcm.edu)



### 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, Elsea SH, Robak LA, Scaglia F, Goldman AM, **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**, (...), Cheung SW, Hastings PJ, Stankiewicz P, Lupski JR, Bi W (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.

**Dhar SU**, et. al(2011). Significant differences among physician specialties in management recommendations of BRCA1 mutation carriers. **Breast Cancer Res Treat.** 129: 221-7.

## HERMAN A. DIERICK, MD

Associate Professor, Departments of Molecular and Human Genetics and Neuroscience

Faculty Member, Graduate Programs in Genetics & Genomics and Neuroscience

MD, 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 contributes 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 micro array 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.

E-mail: [dierick@bcm.edu](mailto:dierick@bcm.edu)



### 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 Atrophia 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, PhD

**Professor**, Departments of Molecular and Human Genetics and Orthopedic Surgery  
**Associate Director**, Center for Skeletal Medicine and Biology

*PhD, Claude Bernard University*  
*Postdoc, Baylor College of Medicine*

### RESEARCH INTERESTS

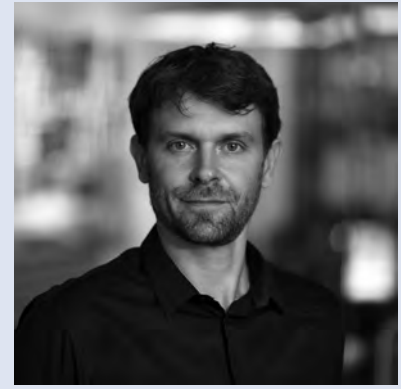
Our research is about deciphering biological mechanisms that control bone development, remodeling, repair and cancer metastasis to identify novel therapeutic strategies that can prevent or treat skeletal diseases.

One main focus of the laboratory is on the etiology of the skeletal maladies observed in individuals with neurofibromatosis type I (NF1). Some of these patients exhibit skeletal abnormalities associated with high morbidity, including unilateral tibia bowing, fracture non-union and dystrophic scoliosis. We use genetic and pharmacological strategies to identify both cell 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 about the role of neurofibromin, the RAS-GAP protein encoded by the *NF1* gene, in endochondral bone formation, remodeling and mineralization.

A second major focus area of the laboratory is related to the interaction between the autonomic nervous system and bone cells. Autonomic nerves regulate body involuntary functions such as heart rate or breathing, but also the process of bone remodeling. 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 conditions including bone aging, chronic stress, depression and their impact on bone remodeling and skeletal breast cancer metastasis.

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 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 hyper osmotic, avascular and mechanically loaded environment.

**E-mail:** florent.elefteriou@bcm.edu



### SELECTED PUBLICATIONS

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**. doi: 10.1038/s41436-020-0885-3. Epub ahead of print. PMID: 32601387.

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, Merkel AR, Brekken RA, Sterling JA, **Elefteriou F** (2017). Skeletal Colonization by Breast Cancer Cells Is Stimulated by an Osteoblast and  $\beta$ 2AR-Dependent Neo-Angiogenic Switch. **J Bone Miner Res**. 32: 1442-1454

Vignaux G, Ndong JD, Perrien DS, **Elefteriou F** (2015). Inner Ear Vestibular Signals Regulate Bone Remodeling via the Sympathetic Nervous System. **J Bone Miner Res**. 30: 1103-11.

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, Perrien DS, Joubert S, Baglio SR, Granchi D, Stevenson DA, Rios JJ, Nyman JS, **Elefteriou F** (2014). Asfotase- $\alpha$  improves bone growth, mineralization and strength in mouse models of neurofibromatosis type-1. **Nat Med**. 20: 904-10.

Ma Y, Krueger JJ, Redmon SN, Uppuganti S, Nyman JS, Hahn MK, **Elefteriou F** (2013). Extracellular norepinephrine clearance by the norepinephrine transporter is required for skeletal homeostasis. **J Biol Chem**. 288: 30105-13.

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.

**Elefteriou F**, et al. (2005). Leptin regulation of bone resorption by the sympathetic nervous system and CART. **Nature**. 434: 514-20.

## SARAH H. ELSEA, PHD

Professor, Department of Molecular and Human Genetics  
Senior Director of Biochemical Genetics, Baylor Genetics

PhD, Vanderbilt University  
Postdoc, Vanderbilt University  
Postdoc, Baylor College of Medicine

### RESEARCH INTERESTS

Despite many advances in the diagnosis of rare disease, the pathophysiological mechanisms underlying these disorders are poorly understood. Our research goals are targeted toward defining the biochemical mechanisms and molecular pathways impacted in human genetic disease. The genetic analysis of neurodevelopmental disorders complicated by obesity and circadian rhythm defects, including autism, intellectual disability, seizures, and behavioral phenotypes, is a primary focus. This includes the clinical and molecular analysis of genomic conditions, wherein deletion or duplication of a portion of the genome is the primary underlying etiology, leading to altered gene dosage. Disorders include Smith-Magenis syndrome, Potocki-Lupski syndrome, 2q23.1 deletion syndrome, 2q23.1 duplication syndrome, 2q37.3 deletion syndrome, Pitt-Hopkins syndrome, and others. Our goals are to improve diagnosis, enhance understanding of phenotypes, and develop a working knowledge of the molecular relationships among neurodevelopmental disorders toward targeted therapeutics. To further support these studies, we have created and maintain a Smith-Magenis syndrome patient registry.

In order to investigate the molecular and cellular basis of these rare, pleiotropic disorders, we have utilized a multidisciplinary approach including mouse, frog, zebrafish, and human cellular models, such as induced pluripotent stem cells and neural progenitor cells. Current studies are focused toward understanding the molecular and cellular relationships between and among a subgroup of neurodevelopmental disorders with overlapping phenotypes using expression profiling, metabolomics, and other functional approaches. Genes and pathways include *RAI1*, *MBD5*, *HDAC4*, *TCF4*, *FMRI*, and *DEAF1*, among others, with associated syndromes exhibiting commonly altered pathways, including circadian rhythm, metabolic, and developmental gene networks that may be targets for therapeutic intervention. For example, one of the hallmark features of Smith-Magenis syndrome is a circadian rhythm defect. Our work has shown that *RAI1* directly regulates *CLOCK*, a master regulator of circadian rhythm, providing strong evidence for molecular and cellular etiology behind the sleep phenotype and identifying a pathway that can be therapeutically targeted.

New projects include investigation of the role of NAD kinase in both Alzheimer's disease and pancreatic cancer and the role of this genetic and biochemical pathway in tumor growth toward developing personalized approaches to treatment. Utilizing cell culture model systems and conditional mouse models to improve understanding of the underlying etiology of these neurodegenerative and neoplastic mechanisms is a primary goal.

We have developed at Baylor Genetics a clinical metabolomics pipeline for diagnosis and management of inborn errors of metabolism. Clinical and research studies have focused toward the development and utilization of metabolomic profiling and analysis of metabolic pathways toward biomarker discovery in a variety of inherited and acquired disorders. Our work is focused toward development of personalized medicine approaches for treatment of neurodevelopmental and metabolically-driven conditions utilizing genomic, metabolomic, and transcriptomic approaches toward improving quality of life for individuals impacted by these conditions. We have performed metabolomic profiling of more than 3500 clinical and research samples, providing a functional analysis of genomic variants that has improved diagnosis and management of individuals with a variety of metabolic conditions and contributed to biomarker discovery in metabolic disorders.

While most of our studies have a molecular basis, we also work to educate others about rare disease and to provide parents, caregivers, and siblings of individuals with neurodevelopmental syndromes with the tools they need to maintain healthy families. Our data show that families are doing very well despite the high prevalence of anxiety and depression among both mothers and fathers and that while younger typically developing siblings may have some difficulties, adult siblings are doing very well, with many choosing careers in education or healthcare for individuals with developmental disabilities.

E-mail: [elsea@bcm.edu](mailto:elsea@bcm.edu)



### SELECTED PUBLICATIONS

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.

Cappuccio G, Donti TR, Hubert L, Sun Q, **Elsea SH** (2019). Opening a window on lysosomal acid lipase deficiency: Biochemical, molecular, and epidemiological insights. **J Inherit Metab Dis.** 42: 509-518.

Shayota BJ, **Elsea SH** (2019). Behavior and sleep disturbance in Smith-Magenis syndrome. **Curr Opin Psychiatry.** 32: 73-78.

Kennedy AD, Wittmann BM, Evans AM, Miller LAD, Toal DR, Lonergan S, **Elsea SH**, Pappan KL (2018). Metabolomics in the clinic: A review of the shared and unique features of untargeted metabolomics for clinical research and clinical testing. **J Mass Spectrom.** 53: 1143-1154.

Wangler MF, Hubert L, Donti TR, Ventura MJ, Miller MJ, Braverman N, Gawron K, Bose M, Moser AB, Jones RO, Rizzo WB, Sutton VR, Sun Q, Kennedy AD, **Elsea SH** (2018). A metabolomic map of Zellweger spectrum disorders reveals novel disease biomarkers. **Genet Med.** 20: 1274-1283.

Sobering AK, Stevens JB, Smith JL, Nelson B, Donald T, **Elsea SH** (2018). Genetic diagnosis of Down syndrome in an underserved community. **Am J Med Genet A.** 176: 483-486.

Mullegama SV, Alaimo JT, Fountain MD, Burns B, Balog AH, Chen L, **Elsea SH** (2017). *RAI1* Overexpression Promotes Altered Circadian Gene Expression and Dysomnia in Potocki-Lupski Syndrome. **J Pediatr Genet.** 6: 155-164.

Chen L, Jensik PJ, Alaimo JT, Walkiewicz M, Berger S, Roder E, Faqeh EA, Bernstein JA, Smith ACM, Mullegama SV, Saffen DW, **Elsea SH** (2017). Functional analysis of novel DEAF1 variants identified through clinical exome sequencing expands DEAF1-associated neurodevelopmental disorder (DAND) phenotype. **Hum Mutat.** 38: 1774-1785.

Pankowicz FP, Barzi M, Legras X, Hubert L, (...), Borowiak M, Sumazin P, **Elsea SH**, Bissig-Choisat B, Bissig KD (2016). Reprogramming metabolic pathways *in vivo* with CRISPR/Cas9 genome editing to treat hereditary tyrosinaemia. **Nat Commun.** 7: 12642.

Mullegama SV, **Elsea SH** (2016). Clinical and Molecular Aspects of MBD5-Associated Neurodevelopmental Disorder (MAND). **Eur J Hum Genet.** 24: 1376.

## CHRISTINE M. ENG, MD

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

MD, Tulane University School of Medicine

### RESEARCH INTERESTS

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

My major clinical research interest is in lysosomal storage diseases, particularly Fabry disease, Gaucher disease, and Mucopolysaccharidosis type 2, with emphasis on both clinical and laboratory approaches to the elucidation of the natural history, molecular genetics, and evaluation of treatments in clinical trials. Previous accomplishments in my laboratory include the further characterization of the natural history of the classical and cardiac variant forms of the disease, study of genotype-phenotype correlations, and 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.

E-mail: [ceng@bcm.edu](mailto:ceng@bcm.edu)



### SELECTED PUBLICATIONS

Zimran A, Pastores GM, Tytki-Szymanska A, Hughes DA, Elstein D, Mardach R, Eng C, Smith L, Heisel-Kurth M, Charrow J, Harmatz P, Fernhoff P, Rhead W, Longo N, Giraldo P, Ruiz JA, Zahrieh D, Crombez E, Grabowski GA (2013). Safety and efficacy of velaglycerase alfa in Gaucher disease type 1 patients previously treated with 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, Schwartzenruber J, Patry L, Dobrzaniecka S, Rochefort D, Neugnot-Cerioli M, Lacaillie 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, del Gaudio D, Kang SH, Lalani SR, Li J, McAdoo S, Burke A, Shaw CA, Stankiewicz P, Chinault AC, Van den Veyver IB, Roa BB, Beaudet AL, Eng CM (2006). Prenatal diagnosis of chromosomal abnormalities using array-based comparative genomic hybridization. *Genet Med*. 8: 719-27.

Eng CM, Germain DP, Banikazemi M, Warnock DG, Warner C, Hopkin RJ, Bultas J, Lee P, Sims K, Brodie SE, Pastores GM, Strotmann JM, Wilcox WR (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, PhD

### 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

PhD, University of Melbourne

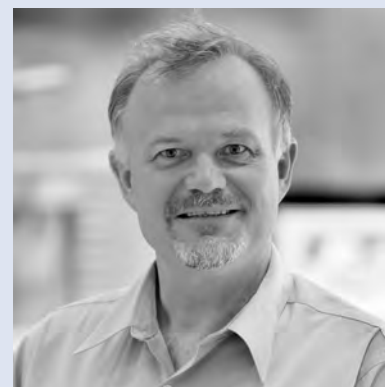
Postdoc, Baylor College of Medicine

### 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 contribution of approximately ten percent of the sequence in 2003. The group subsequently collaborated to sequence many key species (*Drosophila melanogaster*, the 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.

E-mail: [agibbs@bcm.edu](mailto:agibbs@bcm.edu)



### 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, Zackai EH, Harr MH, Sutton VR, Nalam RL, Zhu W, Nash M, Ryan MM, Yapli-to-Lee J, Hunter JV, Deardorff MA, Penney SJ, Beaudet AL, Plon SE, Boerwinkle EA, Lupski JR, Eng CM, Muzny DM, Yang Y, **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.



## ANDY GROVES, PHD

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

*PhD, 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 in 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.

**E-mail:** [akgroves@bcm.edu](mailto:akgroves@bcm.edu)



### SELECTED PUBLICATIONS

Gnedeva K, Wang X, McGovern MM, Barton M, Tao L, Trecek T, Monroe TO, Llamas J, Makmura W, Martin JF, **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, Zhang H, Yu HV, Llamas J, Zong C, Martin JF, Segil N, **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, Edlund RK, Zhang H, Norton CR, Gridley T, Cole SE, Doetzlhofer A, Maletic-Savatic M, Segil N, **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.

Li T, Giagtzoglou N, Eberl DF, Jaiswal SN, Cai T, Godt D, **Groves AK**, Bellen HJ (2016). The E3 ligase *Ubr3* regulates Usher syndrome and MYH9-related disorder proteins in the auditory organs of *Drosophila* and mammals. **ELife**. 5. pii: e15258. doi: 10.7554/eLife.15258.

Birol O, Ohshima 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.

Shirokova V, Biggs LC, Jussila M, Ohshima T, **Groves AK**, Mikkola ML (2016). *Foxi3* deficiency compromises hair follicle stem cell specification and activation. **Stem Cells**. 34: 1896-1908.

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.

Cai T, Seymour ML, Zhang H, Pereira FA, **Groves AK** (2013). Conditional deletion of *atoh1* reveals distinct critical periods for survival and function of hair cells in the organ of corti. **J Neurosci**. 33: 10110-22.

Doetzlhofer A, Basch ML, Ohshima 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, PhD

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

PhD, 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 to 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.

E-mail: [hastings@bcm.edu](mailto:hastings@bcm.edu)



### 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.

Xia J, Chiu LY, Nehring RB, Bravo Núñez MA, Mei Q, (...), **Hastings PJ**, Bates D, Queitsch C, Hilsenbeck SC, Coarfa C, Hu JC, Siegele DA, Scott KL, Liang H, Mancini MA, Herman C, Miller KM, Rosenberg SM (2019). Bacteria-to-Human Protein Networks Reveal Origins of Endogenous DNA Damage. *Cell*. 176: 127-143.e24.

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.

Liu P, Lacia 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: 580-8.

## JASON HEANEY, PhD

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

PhD, Pennsylvania State University  
 Postdoc, Case Western Reserve University

### RESEARCH INTERESTS

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

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

**Characterizing haploessential genes.** The Knockout Mouse Production and Phenotyping (KOMP2) Project has established an infrastructure for high-throughput generation of null (loss-of-function) allele mouse lines with CRISPR/Cas9 genome editing and broad-based adult and embryo phenotyping of the null lines. KOMP2 has implemented embryo phenotyping pipelines for null alleles that cause lethality in the homozygous (recessive) as well as heterozygous (dominant) state. *De novo* dominant loss-of-function (haploessential) genes likely contribute to the 50% of miscarriages and 80% of still births where chromosomal abnormalities are not identified. We are (1) utilizing bioinformatics strategies to predict and prioritize haploinsufficient genes, (2) using 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, (3) functionalizing genes predicted to contribute to human miscarriages and stillbirths, and (4) identifying gene families and cellular pathways enriched for haploessentiality.

**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 BCM Center for Precision Medicine Models leverages the expertise, infrastructures, and established collaborations between the Mendelian disease clinical and gene discovery programs; fly, mouse, and nonhuman primate 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.

E-mail: [heaney@bcm.edu](mailto:heaney@bcm.edu)



### SELECTED PUBLICATIONS

Cacheiro P, Muñoz-Fuentes V, Murray SA, Dickinson ME, Bucan M, Nutter LMJ, Peterson KA, Haselimashhadi H, Flenniken AM, Morgan H, Westerberg H, Konopka T, Hsu CW, Christiansen A, Lanza DG, Beaudet AL, **Heaney JD**, Fuchs H, Gailus-Durner V, Sorg T, Prochazka J, Novosadova V, Lelliott CJ, Wardle-Jones H, Wells S, Teboul L, Cater H, Stewart M, Hough T, Wurst W, Sedlacek R, Adams DJ, Seavitt JR, Tocchini-Valentini G, Mammano F, Braun RE, McKerie C, Heralut Y, de Angelis MH, Mallon AM, Lloyd KCK, Brown SDM, Parkinson H, Meehan TF, Smedley D; 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.

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

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.

Szafrański P, Karolak JA, Lanza D, Gajęcka M, **Heaney J**, Stankiewicz P. CRISPR/Cas9-mediated deletion of lncRNA Gm26878 in the distant Foxf1 enhancer region. **Mamm Genome.** 28: 275-282.

Santiago-Sim T, Burrage LC, (...), **Heaney JD**, Walkiewicz MA (2017). Biallelic Variants in OTUD6B Cause an Intellectual Disability Syndrome Associated with Seizures and Dysmorphic Features. **Am J Hum Genet.** 100: 676-688.

Lanza DG, Dawson EP, Rao P, **Heaney JD** (2016). Misexpression of cyclin D1 in embryonic germ cells promotes testicular teratoma initiation. **Cell Cycle.** 15: 919-30.

Maywald RL, Doerner SK, Pastorelli L, De Salvo C, Benton SM, Dawson EP, Lanza DG, Berger NA, Markowitz SD, Lenz HJ, Nadeau JH, Pizarro TT, **Heaney JD** (2015). IL-33 activates tumor stroma to promote intestinal polyposis. **Proc Natl Acad Sci U S A.** 112: E2487-96.

## CHRISTOPHE HERMAN, PHD

**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

*PhD, Université libre de Bruxelles*

*Postdoc, Massachusetts Institute of Technology*

*Postdoc, University of California, San Francisco*

### RESEARCH INTERESTS

#### Transcription errors and Epigenetic Inheritance

Phenotypic inheritance relies on the correct transfer of the 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 on 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.

**E-mail:** [herman@bcm.edu](mailto:herman@bcm.edu)



### 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, PHD

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

PhD, 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 a 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 in 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 molecular basis of genetic instability observed in cancer.

E-mail: [gira@bcm.edu](mailto:gira@bcm.edu)



### 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 Pol $\delta$  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, MD

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

MD, Tehran University of Medical Sciences, Iran  
Postdoc, University of Ottawa, Canada  
Postdoc, Baylor College of Medicine

### RESEARCH INTERESTS

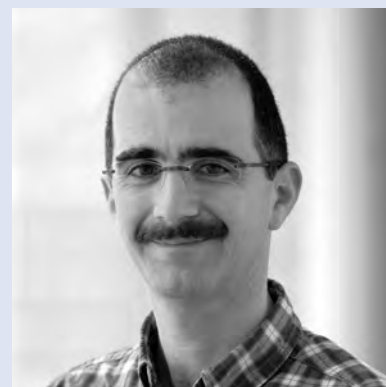
Glycosylation is the most common post-translational modification of extracellular and secreted proteins and plays major roles in various aspects of cellular and organismal biology. We use *Drosophila* and mouse genetics, cell culture experiments and biochemical assays (in collaboration) to understand 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 in which 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 an O-linked glucose to EGF repeats harboring a CXSX(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 report on the identification of a hypomorphic *POGLUT1* allele in patients with a new form of limb-girdle muscular dystrophy (LGMD-2Z) indicates 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 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 genetics 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 another pathway involved in cellular metabolism. 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.

E-mail: [hamedj@bcm.edu](mailto:hamedj@bcm.edu)



### SELECTED PUBLICATIONS

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,  $\alpha$ -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.

Adams JM, **Jafar-Nejad H** (2019). Determining Bile Duct Density in the Mouse Liver. *J Vis Exp*. 146: e59587. doi: 10.3791/59587.

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.

Lee TV\*, Pandey A\*, **Jafar-Nejad H** (2017). Xylosylation of the Notch receptor preserves the balance between its activation by *trans*-Delta and inhibition by *cis*-ligands in *Drosophila*. *PLoS Genet*. 13: e1006723.

Servián-Morilla E\*, Takeuchi H\*, Lee TV\*, (...), **Jafar-Nejad H**, Paradas C (2016). A *POGLUT1* mutation causes a muscular dystrophy with reduced Notch signaling and satellite cell loss. *EMBO Mol Med*. 8: 1289-1309. \*Equal contribution.

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.

## MILAN JAMRICH, PhD

**Professor**, Departments of Molecular and Human Genetics and Molecular & Cellular Biology

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

PhD, Ruprecht Karl University, Heidelberg

Postdoc, Yale University

### RESEARCH INTERESTS

The overall aim of our research is to define the molecular basis of embryonic pattern formation. Pattern formation is a process that leads to ordered spatial arrangements of differentiated tissues. It is not only interesting from a theoretical standpoint, but from a medical perspective as well. Each year in USA alone, more than 250,000 infants are born with congenital malformation due to incorrect embryonic patterning. It is our goal to identify genes that are involved in pattern formation and characterize developmental processes that lead to correct and incorrect pattern formation. The major research effort in our laboratory is focused on study of homeobox and fork head genes that are involved in the patterning of the embryo. In the last few years, we have identified several genes that are important in early stages of head development.

We have found that a novel homeobox gene *Rx*, is essential for normal eye development. *Rx* is initially expressed in retinal progenitor cells and later in retinal stem cells. *Xenopus* embryos injected with *Rx* RNA develop ectopic retinal tissue and display hyperproliferation in the neuroretina. Mouse embryos carrying a null allele of this gene do not form optic cups and consequently do not develop eyes. These observations suggest that *Rx* regulates the fate or the proliferative abilities of retinal cells and controls the survival of retinal stem cells (Mathers *et al.*, 1997).

We have isolated a *Xenopus* forkhead gene *Xlens1* that is the earliest marker of lens formation and is involved in the control of lens proliferation and differentiation (Kenyon *et al.*, 1999). We have cloned and characterized its murine functional homologue, the forkhead gene *Foxe3*, which is expressed in the early stages of mouse lens formation. *Foxe3*, like *Xlens1*, is expressed in the initial stages of lens induction. It turns off its expression in differentiating fiber cells and remains active only in the relatively undifferentiated, proliferative cells of the anterior lens epithelium. *Foxe3* maps to a region on chromosome 4 that contains the *dysgenetic* lens locus. We have found that two mutations in the forkhead box of the *Foxe3* allele from *dyl* mice cause amino acid changes in positions thought to be essential for the structure and function of winged helix domains (Brownell *et al.*, 2000).

Furthermore, we have found that a mutation affecting C-terminal region of the human FOXE3 protein is responsible for anterior segment dysgenesis and cataracts (Semina *et al.*, 2000). We are currently testing gene therapy strategies that would correct this genetic defect.

E-mail: [jamrich@bcm.edu](mailto:jamrich@bcm.edu)



### SELECTED PUBLICATIONS

Lu F, Kar D, Gruenig N, Zhang ZW, Cousins N, Rodgers HM, Swindell EC, **Jamrich M**, Schuurmans C, Mathers PH, Kurrasch DM (2013). *Rax* is a selector gene for mediobasal hypothalamic cell types. **J Neurosci**. 33: 259-72.

Liu W, Lagutin O, Swindell E, **Jamrich M**, Oliver G (2010). Neuroretina specification in mouse embryos requires Six3-mediated suppression of Wnt8b in the anterior neural plate. **J Clin Invest**. 120: 3568-77.

Medina-Martinez O, Amaya-Manzanares F, Liu C, Mendoza M, Shah R, Zhang L, Behringer RR, Mahon KA, **Jamrich M** (2009). Cell-autonomous requirement for *Rx* function in the mammalian retina and posterior pituitary. **PLoS ONE**. 4: e4513.

Swindell EC, Liu C, Shah R, Smith AN, Lang RA, **Jamrich M** (2008). Eye formation in the absence of retina. **Dev Biol**. 322: 56-64.

Medina-Martinez O, **Jamrich M** (2007). Foxe view of lens development and disease. **Development**. 134: 1455-63.

Wang J, Cortina G, Wu SV, Tran R, Cho JH, Tsai MJ, Bailey TJ, **Jamrich M**, Ament ME, Treem WR, Hill ID, Vargas JH, Gershman G, Farmer DG, Reyen L, Martin MG (2006). Mutant neurogenin-3 in congenital malabsorptive diarrhea. **N Engl J Med**. 355: 270-80.

Medina-Martinez O, Brownell I, Amaya-Manzanares F, Hu Q, Behringer RR, **Jamrich M** (2005). Severe defects in proliferation and differentiation of lens cells in *Foxe3* null mice. **Mol Cell Biol**. 25: 8854-63.

Van Raay TJ, Moore, KB, Iordanova I, Steele M, **Jamrich M**, Harris WA, Vetter, ML (2005). Frizzled 5 Signaling Governs the Neural Potential of Progenitors in the Developing *Xenopus* Retina. **Neuron**. 46: 23-36.

Tseng HT, Shah R, **Jamrich M** (2004). Function and regulation of *FoxF1* during *Xenopus* gut development. **Development**. 131: 3637-47.

Zhang L, El-Hodiri H, Ma HF, Zhang X, Servetnick M, Wensel TG, **Jamrich M** (2003). Targeted expression of the dominant negative FGFR-4a in the eye using *Xrx1A* regulatory sequences interferes with normal retinal cell development. **Development**. 130: 4177-86.

Semina EV, Brownell I, Murray JC, **Jamrich M** (2001). Mutations in the human forkhead transcription factor *FOXE3* are associated with anterior segment ocular dysgenesis and cataracts. **Hum Mol Genet**. 10: 231-6.

Mathers PH, Grinberg A, Mahon KA, **Jamrich M** (1997). The *Rx* homeobox gene is essential for vertebrate eye formation. **Nature**. 387: 603-7.

## BENNY ABRAHAM KAIPPARETTU, PhD

Associate Professor, Department of Molecular and Human Genetics

PhD, 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 trans-mitochondrial cybrid (cybrid) models as a discovery tool. In cybrid models, we compare mitochondria from different cells under a commonly defined nuclear background. Thus, cybrids are an excellent tool to decipher the inter-organellar communication between mitochondria and the nucleus systematically. We utilize cybrid models coupled with multiple-OMICs approaches to identify genes and pathways regulated by mitochondria-nuclear communication. Discoveries from cybrids are then validated using cell lines, mouse models, patient-derived xenografts (PDXs) and clinical data.

**Metabolic reprogramming and drug resistance:** Compared to other breast cancer subtypes, triple-negative breast cancer (TNBC) is associated with a worse overall outcome owing to the lack of targeted therapies. We have published the pioneering report on the clinical significance of mitochondrial energy reprogramming to fatty acid  $\beta$ -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 focus on materials that can be altered by cellular metabolic or biochemical modulations

E-mail: [kaippare@bcm.edu](mailto:kaippare@bcm.edu)



### 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 Provs 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, Shen H, Buhay C, Kang H, Kim SC, Fahey CC, Hacker KE, Bhanot G, Gordenin DA, Chu A, Gunaratne PH, Biehl M, Seth S, **Kaipparettu BA**, Bristow CA, (...), 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, Narayanan TN, Vithayathil SA, Ge L, Zhan X, Gupta S, Martí AA, Vajtai R, Ajayan PM, **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). Trans-mitochondrial cybrids: tools for functional studies of mutant mitochondria. *Methods Mol Biol*. 837: 219-30. \*corresponding author

**Abraham BK**, Fritz P, McClellan M, Hauptvogel P, Athelogou M, Brauch H (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.



## SHASHIKANT KULKARNI, MS, PhD, FACMG

Professor and Vice Chair for Research Affairs - Baylor Genetics Lab, Department of Molecular and Human Genetics  
Chief Scientific Officer and Senior Vice President of Operations, Baylor Genetics

*PhD, Medical Genetics, All India Institute of Medical Sciences, India*  
*Visiting Fellow, Hammersmith Hospital, Imperial College, London, United Kingdom*  
*Postdoctoral fellow, Brigham and Women's Hospital, Harvard Medical School*

### RESEARCH INTERESTS

**Using multi-omic approaches to understand cancer biology by elucidating alterations and mechanisms relevant for pathogenesis:** We use whole genome, exome, and transcriptome sequencing to discover recurring mutations that are potentially relevant for Acute Myeloid Leukemia (AML) pathogenesis and to understand clonal diversity and relapse (Cell and Nature 2012; NEJM 2013). Although this information has changed our understanding of the disease, it is not yet clear how to perform optimal genomic testing for each AML patient to improve clinical outcomes. As a proof of concept, we have successfully performed clinical whole genome sequencing on AML patients with diagnostic uncertainty in clinically relevant timeframe to find clinically actionable findings (JAMA 2012). These efforts are being extended to evaluate the clinical utility of genomic sequencing in several tumor types both in germline and somatic setting (Cell, 2018; Hum Mut 2018). We are exploring the following projects: A) multi-omic before and after induction therapy to define the mutational spectrum and clonal architecture of each sample and to precisely define the response to initial therapy; B) RNA-seq to assess the expression of all somatic mutations identified will be performed, to identify expressed fusion genes and to identify dysregulated genes that are not mutated.

**Developing Standards and Guidelines for the Interpretation of Sequence Variants:** One of the major bottlenecks for implementation of individualized genomic medicine is lack of clinical grade genomic knowledgebase to facilitate consistent clinical interpretation of sequence variants. Our group is one of several participating laboratory of a major NHGRI/NIH funded multi-institutional effort called ClinGen (Clinical Genome Resource Program). The purpose of ClinGen (<http://clinicalgenome.org>) is to create a centralized repository and interconnected resources of clinically relevant variants, which are critically needed by the clinical and research communities. We are expanding the scope of this effort by creating somatic variant expert curation of clinically actionable knowledge (Gen Med 2017, Hum Mut 2018). This expert curated variant interpretation somatic variation database which will be housed at publicly available NCBI's ClinVar database.

**Design and Optimization of Next-Generation Sequencing Technical and Informatics Pipelines for Clinical Laboratory Practice:** We are actively involved in defining standards for next generation sequencing in clinical diagnostics in collaboration with the Centers for Disease Control and Prevention through the Clinical Next-Generation Sequencing Quality Standards National Working Group comprised of key opinion leaders in the field (J Mol Diag 2018, Nat Biotech 2012, Nat Biotech 2015). Additionally, we are working with Clinical Laboratory Standards Institute's ([www.CLSI.org](http://www.CLSI.org)) professional guidelines committee for whole genome copy number assays for clinical diagnostics. CLSI standards and guidelines are considered as gold standard and are followed by clinical labs nationally and internationally for raising levels of quality, safety, and efficiency in laboratory testing and reporting.

E-mail: [shashikk@bcm.edu](mailto:shashikk@bcm.edu)



### SELECTED PUBLICATIONS

Huang KL, Mashl RJ, Wu Y, Ritter DI, (...), **Kulkarni S**, DiPersio JF, Reimand J, Meric-Bernstam F, Chen K, Shmulevich I, Plon SE, Chen F, Ding L (2018). Pathogenic Germline Variants in 10,389 Adult Cancers. **Cell**. 173: 355-370.e14.

Li MM, Datto M, Duncavage EJ, **Kulkarni S**, Lindeman NI, Roy S, Tsimberidou AM, Vnencak-Jones CL, Wolff DJ, Younes A, Nikiforova MN (2017). Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. **J Mol Diagn**. 19: 4-23.

Griffith M, Griffith OL, Krysiak K, (...), **Kulkarni S**, DiPersio JF, Mardis E, Wilson RK, Ley TJ (2016). Comprehensive genomic analysis reveals FLT3 activation and a therapeutic strategy for a patient with relapsed adult B-lymphoblastic leukemia. **Exp Hematol**. 44: 603-613.

Griffith M, Miller C, Griffith O, (...), **Kulkarni S**, Cordes M, Fronick C, Fulton R, Maher C, Ding L, Klco J, Mardis E, Ley T, Wilson R (2015). Optimizing Cancer Genome Sequencing and Analysis. **Cell Systems**. 1: 210-323.

Klco J, Miller C, Griffith M, (...), **Kulkarni S**, Ozenberger B, Welch J, Walter M, Graubert T, Westervelt, P, Radich J, Link D, Mardis E, DiPersio, J, Wilson R, Ley T (2015). Association Between Mutation Clearance After Induction Therapy and Outcomes in Acute Myeloid Leukemia. **JAMA**. 314: 811-22.

Gargis AS, Kalman L, Bick DP, Da Silva C, Dimmock DP, Funke BH, Gowrisankar S, Hedge MR, **Kulkarni S**, et. al. (2015). Good laboratory practice for clinical next-generation sequencing informatics pipelines. **Nat Biotechnol**. 33: 689-93.

Ungewickell A, Bhanduri A, Rios E, Reuter J, Lee C, Mah A, Zehnder A, Ohgami R, **Kulkarni S**, Armstorng R, Weng W, Gratzinger D, Tavallae M, Rook A, Snyder M, Kim Y, Khavari P (2015). Genomic analysis of mycosis fungoides and Sézary syndrome identifies recurrent alterations in TNFR2. **Nat Genet**. 47: 1056-60.

Lyon E, Cockerill FR 3rd, Bale SJ, Beadling C, Bry L, Hagenkord J, **Kulkarni S**, Press R, Palomaki GE (2015). Next generation sequencing in clinical diagnostics: experiences of early adopters. **Clin Chem**. 61: 41-9.

Perrino CM, Huchtagowder V, Evenson M, **Kulkarni S**, Humphrey PA (2015). Genetic alterations in renal cell carcinoma with rhabdoid differentiation. **Hum Pathol**. 46: 9-16.

Hagemann IS, Devarakonda S, Lockwood CM, Spencer DH, Guebert K, Bredemeyer AJ, Al-Kateb H, Nguyen TT, Duncavage EJ, Cottrell CE, **Kulkarni S**, et. al. (2015). Clinical next-generation sequencing in patients with non-small cell lung cancer. **Cancer**. 121: 631-9.

## SEEMA R. LALANI, MD

Professor, Department of Molecular and Human Genetics

MD, 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 in understanding the genetic basis of birth defects. Using clinical exome sequencing, we have identified novel Mendelian disorders utilizing the large datasets available at Baylor Genetics.

In addition, we have recruited over 150 families with Wolff-Parkinson-White (WPW) syndrome and are interested in understanding the genetic basis of this pre-excitation syndrome that affects 1-3/1000 individuals. We are also recruiting families with TANGO2 mutation to understand the mechanisms underlying metabolic crises and rhabdomyolysis in the affected individuals.

E-mail: [seemal@bcm.edu](mailto:seemal@bcm.edu)



### SELECTED PUBLICATIONS

Coban-Akdemir ZH, Charng WL, Azamian M, Paine IS, Punetha J, Grochowski CM, Gambin T, Valdes SO, Cannon B, Zapata G, Hernandez PP, Jhangiani S, Doddapaneni H, Hu J, Boricha F, Muzny DM, Boerwinkle E, Yang Y, Gibbs RA, Posey JE, Wehrens XHT, Belmont JW, Kim JJ, Miyake CY, Lupski JR, **Lalani SR** (2020). Wolff-Parkinson-White syndrome: De novo variants and evidence for mutational burden in genes associated with atrial fibrillation. *Am J Med Genet A*. 182: 1387-1399.

**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.

Szafrański P, Von Allmen GK, Graham BH, Wilfong AA, Kang SH, Ferreira JA, Upton SJ, Moeschler JB, Bi W, Rosenfeld JA, Shaffer LG, Wai Cheung S, Stankiewicz P, **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**, Ware SM, Wang X, Zapata G, Tian Q, Franco LM, (...), Belmont JW (2013). MCTP2 is a dosage-sensitive gene required for cardiac outflow tract development. *Hum Mol Genet*. 22: 4339-48.

## BRENDAN LEE, MD, PhD

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

Co-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

*PhD, State University of New York Downstate Medical Center*

*MD, 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 disease (those involving nitric oxide dysregulation). This has led us to study the consequences of metabolic derangements broadly in the endocrine, cardiovascular, skeletal, renal, and neurological systems. In the area of structural birth defects, we have studied paracrine and endocrine signaling pathways that regulate skeletal development including morphogens (TGF $\beta$ , 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. These developmental pathways have led us to ask how their dysregulation lead 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-TGF $\beta$  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 diagnosis of genetic diseases via gene discovery and mechanistic studies in the NIH Undiagnosed Diseases Network.

E-mail: [blee@bcm.edu](mailto:blee@bcm.edu)



### SELECTED PUBLICATIONS

Murdock DR, Dai H, Burrage LC, Rosenfeld JA, Ketkar S, Müller MF, Yépez VA, Gagneur J, Liu P, Chen S, Jain M, Zapata G, Bacino CA, Chao HT, Moretti P, Craigen WJ, Hanchard NA, Lee B (2020). Transcriptome-directed analysis for Mendelian disease diagnosis overcomes limitations of conventional genomic testing. *J Clin Invest.*, in press.

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

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

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.

Tao J, Jiang MM, Jiang L, Salvo JS, Zeng HC, Dawson B, Bertin TK, Rao PH, R. Chen R, Donehower LA, Gannon F, Lee B (2014). Notch activation as a driver of osteogenic sarcoma. *Cancer Cell.* 26: 390-401

Grafe I, Yang T, Alexander S, Homan EP, Lietman C, Jiang MM, Bertin T, Munivez E, Chen Y, Dawson B, Ishikawa Y, Weis MA, Sampath TK, Ambrose C, Eyre D, Bächinger HP, Lee B (2014). Excessive transforming growth factor- $\beta$  signaling is a common mechanism in osteogenesis imperfecta. *Nat Med.* 20: 670-5.

Orwoll ES, Shapiro J, Veith S, Wang Y, Lapidus J, Vanek C, Reeder JL, Keaveny TM, Lee DC, Mullins MA, Nagamani SC, Lee B (2014). Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. *J Clin Invest.* 124: 491-8.

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.

Ruan MZ, Erez A, Guse K, Dawson B, Bertin T, Chen Y, Jiang MM, Yustein J, Gannon F, Lee B (2013). Proteoglycan 4 expression protects against the development of osteoarthritis. *Sci Transl Med.* 5: 176ra34.

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, MD, MS

**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

*MD, University of Michigan Medical School*

*MS, 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 at 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 cause for juvenile macular degeneration), the Laurence-Moon-Bardet-Biedl Syndromes (progressive retinal dystrophy with obesity, polydactyly, 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 (in BBS) were defined from their extensive studies of his BBS 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 the Center for Mendelian Genomics include the discovery of the gene for the "Hutterite-type" juvenile-onset cataract and the recognition that this gene may also cause subsequent sudden death of these individuals as they grow into 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.

E-mail: [rlewis@bcm.edu](mailto:rlewis@bcm.edu)



### SELECTED PUBLICATIONS

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, Chinn IK, Mace EM, Vogel TP, Carisey AF, Benavides F, Coban-Akdemir ZH, Gibbs RA, Jhangiani SN, Muzny DM, Carvalho CMB, Schady DA, Jain M, Rosenfeld JA, Emrick L, Lewis RA, Lee B; Undiagnosed Diseases Network members, Zieba BA, Küry S, Krüger E, Lupski JR, Bostwick BL, 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.

Chen CA, Yin J, Lewis RA, Schaaf CP (2017). Genetic Causes of Optic Nerve Hypoplasia. *J Med Genet.* 54: 441-449.

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.

Wang X, Feng Y, Li J, Zhang VW, Wang J, Lewis RA, Wong L-J (2016). Retinal Diseases Caused by Mutations in Genes not specifically Associated with the Clinical Diagnosis. *PLoS One* 11: e0165405.

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.

Linkstrand 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, PHD

Assistant Professor, Department of Molecular and Human Genetics and Huffington Center for Aging

PhD, University of Rochester, Rochester, New York  
Postdoctoral fellow, Stanford University

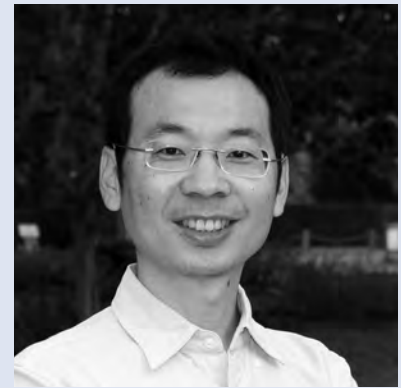
### RESEARCH INTERESTS

**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, ..., Luo, Li, 2020 *bioRxiv*) 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 the single-bacterium genomics to explore gut microbiota changes during aging and study how they contributes 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.

E-mail: [Hongjie.Li@bcm.edu](mailto:Hongjie.Li@bcm.edu)



### SELECTED PUBLICATIONS

McLaughlin CN, Brbić M, Xie Q, Li T, Horns F, Kolluru SS, Keschull JM, Vacek D, Xie A, Li J, Jones RC, Leskovec J, Quake SR, Luo L, **Li H** (2020). Single-cell transcriptomes of developing and adult olfactory receptor neurons in *Drosophila*. **bioRxiv** doi: 10.1101/2020.10.08.332130

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** (2020). Temporal evolution of single-cell transcriptomes of *Drosophila* olfactory projection neurons. **bioRxiv** doi: 10.1101/2020.09.24.312397

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

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

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

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

**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, MD, PhD****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)

*PhD, Stanford University*

*MD, 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 to harness the synthetic potential of organisms. In the short-term we seek to interpret the mutational action of human genome variations on health and to 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 and cancer. 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 current 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 population. In head and neck cancer patients, EA stratifies outcomes and suggests alternate therapy for some patients. In the future, we hope to unite these different approaches into a coherent path to compute precision therapy that is personalized to each patient based on their unique profile of genome variations.

**E-mail:** [lichtarge@bcm.edu](mailto:lichtarge@bcm.edu)

**SELECTED PUBLICATIONS**

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.

Osman AA, Neskey DM, Katsonis P, Patel AA, Ward AM, Hsu TK, (...), **Lichtarge O**, Myers JN (2015). Evolutionary Action Score of TP53 Coding Variants Is Predictive of Platinum Response in Head and Neck Cancer Patients. **Cancer Res**. 75: 1205-15.

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  $\beta$ -arrestin functional selectivity at the dopamine D2 receptor. **Proc Natl Acad Sci U S A**. 112: 7097-102.

Nagarajan M\*, Wilkins AD\*, Bachman BJ\*, (...), Spangler S\*, **Lichtarge O\*** (2015). Predicting Future Scientific Discoveries Based on a Networked Analysis of the Past Literature. **Proceedings of the 21th ACM SIGKDD international conference on Knowledge discovery and data mining (Sydney, Aus)**.

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 inhibitor by artesunate. **Cell**. 158: 916-28.

Shoji-Kawata S, Sumpter R, Leveno M, Campbell GR, Zou Z, Kinch L, (...), **Lichtarge O**, Grishin NV, Spector SA, Kaloyanova DV, Levine B (2013). Identification of a candidate therapeutic autophagy-inducing peptide. **Nature**. 494: 201-6.

## JAMES R. LUPSKI, MD, PHD, DSc (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

PhD, New York University

MD, 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

DSc, 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 traits including birth defects? How many human Mendelian and complex traits are due to structural changes and/or gene copy number variation (CNV)? What are the molecular mechanisms for human genomic rearrangements? The answers to these questions will impact both prenatal and postnatal genetic diagnostics, as well as patient management and therapeutics. Moreover, the answers have profound implications for human evolution.

For six decades, the molecular basis of disease has been addressed in the context of how mutations effect the structure, function, or regulation of a gene or its protein product. However, we have been living in a genocentric world. During the last decade, it has become apparent that many disease traits are best explained on the basis of genomic alterations. Furthermore, it has become abundantly clear that architectural features of the human genome can result in genomic instability and susceptibility to DNA rearrangements that cause disease traits – I have referred to such conditions as genomic disorders.

Twenty-five years ago, it became evident that genomic rearrangements and gene dosage effects, rather than the classical model of coding region DNA sequence alterations, could be responsible for a common, autosomal dominant, adult-onset neurodegenerative trait—Charcot-Marie-Tooth neuropathy type 1A (CMT1A). With the identification of the CMT1A duplication and its reciprocal deletion causing hereditary neuropathy with liability to pressure palsies (HNPP), the demonstration that *PMP22* copy-number variation (CNV) could cause inherited disease in the absence of coding-sequence alterations, was initially hard to fathom. How could such subtle changes—three copies of the normal “wild-type” *PMP22* gene rather than the usual two—underlie neurologic disease?

Nevertheless, it has become apparent during this last decade and a half that neurodegeneration can represent the outcome of subtle mutations acting over prolonged time periods in tissues that do not generally regenerate, regardless of the exact molecular mechanism. This concept has revealed itself through 1) conformational changes causing prion disease, 2) the inability to degrade accumulated toxic proteins in amyloidopathies,  $\alpha$ -synucleinopathies, and polyglutamine expansion disorders, and 3) alteration in gene copy number and/or expression levels through mechanisms such as uniparental disomy (UPD), chromosomal aberrations (e.g., translocations), and submicroscopic genomic rearrangements including duplications, deletions, and inversions. Specific deletions and duplications have recently been shown to be associated with both autism and schizophrenia, as well as with obesity.

Currently, structural variation of the human genome is commanding a great deal of attention. In the postgenomic era, the availability of human genome sequence for genome-wide analysis has revealed higher-order architectural features (i.e., beyond primary sequence information) that may cause genomic instability and susceptibility to genomic rearrangements. Nevertheless, it is perhaps less generally appreciated that any two humans contain more base-pair differences due to structural variation of the genome than resulting from single-nucleotide polymorphisms (SNPs). *De novo* genomic rearrangements have been shown to cause both chromosomal and Mendelian disease, as well as sporadic traits, but our understanding of the extent to which genomic rearrangements, gene CNV, and/or gene dosage alterations are responsible for common and complex traits remains rudimentary.

Central to our understanding of human biology, evolution, and disease is an answer to the following questions: What is the frequency of *de novo* structural genomic changes in the human genome? What are the molecular mechanisms for genomic rearrangements? and What is the genomic code?

E-mail: [jlupski@bcm.edu](mailto:jlupski@bcm.edu)



### SELECTED PUBLICATIONS

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.

Mayle R, Campbell IM, Beck CR, Yu Y, Wilson M, Shaw CA, Bjergbaek L, **Lupski JR**, Ira, G. (2015). Mus81 and converging forks limit the mutagenicity of replication fork breakage. **Science.** 349: 742-747.

Wu N, Ming X, Xiao J (...) **Lupski JR**, Qiu G, Zhang F (2015). *TBX6* null variants and a common hypomorphic allele in congenital scoliosis. **N Engl J Med.** 372: 341-350.

Yamamoto S, Jaiswal M, Charnig WL, (...) **Lupski JR**, Wangler MF, Bellen HJ (2014). A *Drosophila* Genetic Resource of Mutants to Study Mechanisms Underlying Human Genetic Diseases. **Cell.** 159: 200-214.

Karaca E, Weitzer S, Pehlivan D, (...) **Lupski JR** (2014). Human *CLP1* mutations alter tRNA biogenesis, affecting both peripheral and central nervous system function. **Cell.** 157: 636-50.

Yang Y, Muzny DM, Xia F, (...) **Lupski JR**, Plon SE, Gibbs RA, Eng CM (2014). Molecular findings among patients referred for clinical whole-exome sequencing. **JAMA.** 312: 1870-9.

Carvalho, CMB, Pehlivan D, Ramocki MB, Fang P, Franco LM, Belmont JW, Hastings PJ, **Lupski JR** (2013). Replicative mechanisms of chromosomal change are error prone: high frequency of mutation near breakpoint junctions. **Nat Genet.** 45: 1319-26.

Carvalho CM, Ramocki MB, Pehlivan D, (...) **Lupski JR** (2011). Inverted genomic segments and complex rearrangements are mediated by inverted repeats in the human genome. **Nat Genet.** 43: 1074-81.

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.

Zhang F, Khajavi M, Connolly A, Towne CF, Batish SV, **Lupski JR** (2009). The DNA replication FoSTeS/MMBIR mechanism can generate human genomic, gene, and exon complex rearrangements. **Nat Genet.** 41: 849-53.

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, PHD**

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; Integrative Molecular and Biomedical Sciences; and Developmental Biology  
**Associate Director**, Graduate Program in Genetics & Genomics  
**Program Director**, NIH Training Grant T32 EY07102  
**Course Director**, Method and Logic in Molecular Biology and Molecular and Genetics and Genomics in Vision Research

*PhD, 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 two animals, the mouse *Mus musculus* and the fruit fly *Drosophila melanogaster*, as model systems 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. In addition, the mouse provides a powerful model system to decipher the function of newly identified human retinal disease genes and to conduct gene therapy studies.

Our main *Drosophila* project uses a combinatorial approach of genetics, genomics, and computational biology to dissect the roles of four retinal determination genes: *eyeless*, *toy*, *eyes absent*, and *sine oculis*, all of which encode highly conserved transcription factors that are both necessary and sufficient for eye development. We are using molecular genetics and genomics to identify direct targets of these transcription factors and the pathways they regulate to control normal retinal development. In addition, we are using novel genomic rescue strategies to definitively dissect the *in vivo* function of these genes. Finally, we are using the CRISPR/Cas9 system to create new alleles to conduct functional studies of *eyeless* and *toy*.

In the mouse, we have created knockout models for two genes that cause congenital blindness in humans, *Spata7* and *Kcnj13*. Loss-of-function of these genes results in early visual system defects in both humans and in our mouse models, which fully recapitulate the human disease condition. We are using these models to fully dissect molecular mechanisms by which the genes act *in vivo* and as tools for conducting gene therapy studies. Our most recent models for *Kcnj13* have been created using CRISPR/Cas9 and have greatly increased the speed with which we can dissect gene function *in vivo*.

**E-mail:** gmardon@bcm.edu

**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.

Roman D, Zhong H, Yaklichkin S, Chen R, **Mardon G** (2018). Conditional loss of *Kcnj13* in the retinal pigment epithelium causes photoreceptor degeneration. **Exp Eye Res.** 176: 219-226.

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.

Retshabile G, Mlotshwa BC, Williams L, Mwesigwa S, Mboowa G, Huang Z, Rustagi N, Swaminathan S, Katagiry E, Kyobe S, Wayengera M, Kisitu GP, Kateete DP, Wampande EM, Maplanka K, Kasvosve I, Pettitt ED, Matshaba M, Nsangi B, Marape M, Tsimako-Johnstone M, Brown CW, Yu F, Kekitiinwa A, Joloba M, Mpoloka SW, **Mardon G**, Anabwani G, Hanchard NA; Collaborative African Genomics Network (CAfGEN) of the H3Africa Consortium (2018). Whole-Exome Sequencing Reveals Uncaptured Variation and Distinct Ancestry in the Southern African Population of Botswana. **Am J Hum Genet.** 102: 731-743.

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.

Zhong H, Chen Y, Li Y, Chen R, **Mardon G** (2015). CRISPR-engineered mosaicism rapidly reveals that loss of *Kcnj13* function in mice mimics human disease phenotypes. **Sci Rep.** 5: 8366.

Zhong H, Eblimit A, Moayed Y, Boye SL, Chiodo VA, Chen Y, Li Y, Nichols RM, Hauswirth WW, Chen R, **Mardon G** (2015). AAV8(Y733F)-mediated gene therapy in a *Spata7* knockout mouse model of Leber congenital amaurosis and retinitis pigmentosa. **Gene Ther.** 22: 619-27.



## ALEKSANDAR MILOSAVLJEVIC, PhD

**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)

*PhD, University of California, Santa Cruz*

### RESEARCH INTERESTS

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

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

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

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

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

**E-mail:** [amilosav@bcm.edu](mailto:amilosav@bcm.edu)



### 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, Lakshmi Subramanian S, 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, Bilienky 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.

## SANDESH C. SREENATH NAGAMANI, MBBS, MD

Associate 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 (IDRC)

MBBS, University of Mysore  
 MD, 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 concerns 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 Disease 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. We have discovered that some distinct features of UCDs could be a result of perturbations of non-ureagenic functions of urea cycle enzymes. In particular, we have shown that nitric oxide (NO) deficiency in the UCD argininosuccinate lyase deficiency (ASLD) contributes to the phenotype of the disorder. We are now translating these molecular findings into the clinical realm by performing clinical trials to evaluate the effects of NO supplementation on vascular and neurocognitive parameters in ASLD.

**Skeletal dysplasia:** As a lead investigator of the NIH RDCRN's Brittle Bone Disorders Consortium, I am involved in the conduct of many studies in individuals with osteogenesis imperfecta, the most common Mendelian form of osteoporosis. One of the key trials involves evaluating the safety and efficacy of TGF-beta inhibition in individuals with severe forms of OI.

**Clinical Interests:** As an 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, early-onset osteoporosis, and other common forms of metabolic bone diseases.

E-mail: [nagamani@bcm.edu](mailto:nagamani@bcm.edu)



### SELECTED PUBLICATIONS

Lee JS, Adler L, Karathia H, Carmel N, Rabinovich S, (...), **Nagamani SCS**, Unda M, Wilson DM 3rd, Elhasid R, Caracedo A, Samuels Y, Hannehalli 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, Jin Z, Shchelochkov OA, Burrage LC, Reddy AK, Jiang H, Abo-Zahrah R, Ma S, Zhang P, Bissig KD, Kim JJ, Devaraj S, Rodney GG, Erez A, Bryan NS, **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.

Rabinovich S, Adler L, Yizhak K, Sarver A, Silberman A, Agron S, Stettner N, Sun Q, Brandis A, Helbling D, Korman S, Itzkovitz S, Dimmock D, Ulitsky I, **Nagamani SC**, Ruppin E, Erez A (2015). Diversion of aspartate in ASS1-deficient tumours fosters *de novo* pyrimidine synthesis. *Nature*. 527: 379-83.

Orwoll ES, Shapiro J, Veith S, Wang Y, Lapidus J, Vanek C, Reeder JL, Keaveny TM, Lee DC, Mullins MA, **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.

Erez A, **Nagamani SC**, Shchelochkov OA, Premkumar MH, Campeau PM, Chen Y, et al. (2011). Requirement of argininosuccinate lyase for systemic nitric oxide production. *Nat Med*. 17: 1619-26.

## DAISUKE NAKADA, PHD

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

PhD, 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.

E-mail: [nakada@bcm.edu](mailto:nakada@bcm.edu)



### SELECTED PUBLICATIONS

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). ER $\alpha$  promotes murine hematopoietic regeneration through the Ire1 $\alpha$ -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 JJ, 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.

**Nakada D\***, Oguro H, Levi BP, Ryan N, Kitano A, Saitoh Y, Takeichi M, Wendt GR, Morrison SJ\* (2014). Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. **Nature**. 505: 555-8. \*Corresponding authors

**Nakada D**, Saunders TL, Morrison SJ (2010). Lkb1 regulates cell cycle and energy metabolism in haematopoietic stem cells. **Nature**. 468: 653-8.

**DAVID L. NELSON, PhD****THE CULLEN FOUNDATION PROFESSORSHIP IN MOLECULAR GENETICS**

Professor, Department of Molecular and Human Genetics

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

Program Director, Graduate Program in Cancer and Cell Biology

*PhD, 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 recent developments in human genetics has been the identification of unstable trinucleotide repeats involved in high frequency mutations leading to more than one dozen genetic disorders, including myotonic dystrophy and Huntington's disease. With collaborators, Dr. Nelson described the first of these unstable DNA sequences, a CCG trinucleotide repeat in the *FMR1* gene and responsible for the fragile X site and mental retardation found in people with Fragile X syndrome. This is the most common form of inherited mental retardation, with a frequency of  $\sim 1/2000$  males in the general population. The mechanism by which this mutation leads to disease is through loss of function of the *FMR1* gene product due to diminished expression resulting from aberrant methylation of the gene. Recent evidence suggests that the gene product of *FMR1* interacts with complexes of RNA and ribosomes, implying a role in regulation of translation. Efforts in the Nelson group are focused on dissecting this pathway and understanding the development of DNA instability at this locus.

The Nelson group also studies disorders found in *FMR1* premutation carriers (55-200 repeats). Males with CCG 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 and show neuronal degeneration and 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 CCG repeat was both necessary and sufficient to affect mammalian neurons. The group is also studying Fragile X associated primary ovarian insufficiency, a disorder of early menopause found in some female carriers of the premutation using mouse models. These models have led to improved understanding of mechanism, including a role for several RNA-binding functions such as TDP-43 and alterations in 5-hydroxymethylcytosine, suggesting widespread dysregulation of gene expression.

**E-mail:** [nelson@bcm.edu](mailto:nelson@bcm.edu)**SELECTED PUBLICATIONS**

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.

Cook D, Nuro E, Jones EV, Altimimi HF, Farmer WT, Gandin V, Hanna E, Zong R, Barbon A, **Nelson DL**, Topisirovic I, Rochford J, Stellwagen D, Béique JC, Murai KK (2014). FXR1P limits long-term memory, long-lasting synaptic potentiation, and *de novo* GluA2 translation. **Cell Rep.** 9: 1402-16.

Galloway JN, Shaw C, Yu P, Parghi D, Poidevin M, Jin P, **Nelson DL** (2014). CCG 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.

**Nelson DL**, Orr HT, Warren ST (2013). The unstable repeats - Three evolving faces of neurological disease. **Neuron.** 77: 825-843.

Xu Z, Poidevin M, Li X, Li Y, Shu L, **Nelson DL**, Li H, Hales CM, Gearing M, Wingo TS, Jin P (2013). Expanded GGGGCC repeat RNA associated with amyotrophic lateral sclerosis and frontotemporal dementia causes neurodegeneration. **Proc Natl Acad Sci U S A.** 110: 7778-83.

Yrigollen CM, Durbin-Johnson B, Gane L, **Nelson DL**, Hagerman R, Hagerman PJ, Tassone F (2012). AGG interruptions within the maternal *FMR1* gene reduce the risk of offspring with fragile X syndrome. **Genet Med.** 14: 729-36.

Guo W, Allan AM, Zong R, Zhang L, Johnson EB, Schaller EG, Murthy AC, Goggin SL, Eisch AJ, Oostra BA, **Nelson DL**, Jin P, Zhao X (2011). Ablation of Fmrp in adult neural stem cells disrupts hippocampus-dependent learning. **Nat Med.** 17: 559-565

Hashem V, Galloway JN, Mori M, Willemsen R, Oostra BA, Paylor R, **Nelson DL** (2009). Ectopic expression of CCG containing mRNA is neurotoxic in mammals. **Hum Mol Genet.** 18: 2443-51.

Zhang J, Fang Z, Lee CC, Albrecht U, Oostra B, **Nelson DL** (2008). Members of the Fragile X protein family regulate mammalian circadian behavior. **Am J Hum Genet.** 83: 43-52.

## PHILIP NG, PHD

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

PhD, 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.

E-mail: [png@bcm.edu](mailto:png@bcm.edu)



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

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

Brunetti-Pierrri 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.

Brunetti-Pierrri N, Grove NC, Zuo Y, Edwards R, Palmer D, Cerullo V, Teruya J, **Ng P** (2009). Bioengineered Factor IX Molecules with Increased Catalytic Activity Improve the Therapeutic Index of Gene Therapy Vectors for Hemophilia B. **Hum Gene Ther**. 20: 479-85.

## DONGSU PARK, PHD

**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

*PhD, Baylor College of Medicine*

*Postdoc, Massachusetts General Hospital & Harvard Stem Cell Institute*

### RESEARCH INTERESTS

**Identification of skeletal stem cell heterogeneity and regulatory mechanism *in vivo*:** The main interest of my lab is to understand the biology of mesenchymal/skeletal stem cells in tissue regeneration and cancer. Mesenchymal cells are critical for maintenance and regeneration of most tissues with particular importance in the life-long regeneration of bone. These cells are also critical in the bone marrow microenvironment to regulate hematopoiesis with likely participation in leukemia and cancer metastasis. However, the *in vivo* characteristics and function of mesenchymal/skeletal stem cells represent fundamental and still unanswered questions. Modulation of mesenchymal regeneration in skeletal and non-skeletal tissues remains a major therapeutic challenge. 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 long-term repopulating, functionally distinct adult periosteal skeletal stem cells (P-SSCs) *in vivo*. These P-SSCs are critical for periosteal (outer) bone maintenance, specifically express CCL5 receptors, CCR5, and have a unique CCL5-dependent migratory mechanism required for bone injury repair (Ortinou et al, *Cell Stem Cell*, 2019). We now aim to address functional heterogeneity and epigenetic regulation of skeletal stem cells in the context of skeletal aging and to explore the clinical relevance of these cells in bone disorders and cancer bone metastasis.

***In vivo* mechanism of HSC niche cells:** The maintenance and function of HSCs are finely controlled by a specialized microenvironment, HSC niche. SSCs are a key component for the HSC niche and are essential to protect HSCs from external stress. However, due to the lack of *in vivo* HSC tracking model, how stress signals control endogenous HSCs and their niche interaction is largely unknown. We previously found that bone marrow stresses regulate the HSC lineage commitment and identified important factors in myeloid/erythroid-lineage differentiation under marrow stress conditions. Recently, we generated a novel animal model to selectively label endogenous HSCs and found a clear displacement of HSCs away from CXCL12-expressing niche cells upon interferon treatment. We are now elucidating 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.

**Identification of muscle and tendon stem cells:** My laboratory is also interested in the identity and function of mesenchymal populations in non-skeletal tissues such as muscle and tendon. However, their cellular origin and mechanisms that govern tissue regeneration and repair remain unanswered. A key question is whether mesenchymal stem/progenitor cells from different tissues behave differently *in vitro* and *in vivo*. My laboratory has the tools to answer these important questions using a variety of genetic, immunologic, and microscopic technologies with the goal of identifying molecules and mechanisms that regulate mesenchymal cells of different tissue origin. These studies will elucidate fundamental aspects of tissue regeneration and may lead to the development of new regenerative medicine strategies.

**E-mail:** [Dongsu.Park@bcm.edu](mailto:Dongsu.Park@bcm.edu)



### SELECTED PUBLICATIONS

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

Ortinou LC, Wang H, Lei K, Deveza L, Jeong Y, Hara Y, Grafe I, Rosenfeld SB, Lee D, Lee B, Scadden DT, **Park D** (2019). Identification of Functionally Distinct Mx1+ $\alpha$ SMA+ 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.

Li X, Romain RD, **Park D**, Scadden DT, Merchant JL, Arnaout MA (2014). Stress Hematopoiesis Is Regulated by the Krüppel-Like Transcription Factor ZBP-89. *Stem Cells*. 32: 791-801.

**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 Biotechnol*. 24: 1581-90.

## JENNIFER POSEY MD, PhD

Assistant Professor, Department of Molecular and Human Genetics

MD, Baylor College of Medicine

PhD, 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 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.

E-mail: [jennifer.posey@bcm.edu](mailto:jennifer.posey@bcm.edu)



### 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.

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, Jhangiani SN, Bayram Y, Song X, Bahrambeigi V, Yuregir OO, Bozdogan S, Yesil G, Isikay S, Muzny D, Gibbs RA, Lupski JR (2018). Phenotypic expansion illuminates multi-locus pathogenic variation. *Genet Med*. 20: 1528-1537.

**Posey JE**, Harel T, Liu P, Rosenfeld JA, James RA, Coban Akdemir ZH, Walkiewicz M, Bi W, Xiao R, Ding Y, Xia F, Beaudet AL, Muzny DM, Gibbs RA, Boerwinkle E, Eng CM, 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.

**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.

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

## LORRAINE POTOCKI, MD, 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

MD, 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 has only recently been 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.

E-mail: [lpotocki@bcm.edu](mailto:lpotocki@bcm.edu)



### SELECTED PUBLICATIONS

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.

Neira-Fresneda J, **Potocki L** (2015). Neurodevelopmental Disorders Associated with Abnormal Gene Dosage: Smith-Magenis and Potocki-Lupski Syndromes. **J Pediatr Genet**. 4: 159-67.

Magoulas PL, Liu P, Gelowani V, Soler-Alfonso C, Kivuva EC, Lupski JR, **Potocki L** (2014). Inherited dup(17)(p11.2p11.2): expanding the phenotype of the Potocki-Lupski syndrome. **Am J Med Genet A**. 164A: 500-4.

Murali C, Fernbach SD, **Potocki L** (2014). Handing the pen to the patient: reflective writing for children and families affected by genetic conditions. **Am J Med Genet A**. 164A: 3021-6.

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, Eiffert 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.

Swarr DT, Bloom D, Lewis RA, Elenberg E, Friedman EM, Glotzbach C, Wissman SD, Shaffer LG, **Potocki L** (2010). Potocki-Shaffer syndrome: comprehensive clinical assessment, review of the literature, and proposals for medical management. **Am J Med Genet A**. 152A: 565-72.

Treadwell-Deering DE, Powell MP, **Potocki L** (2010). Cognitive and behavioral characterization of the Potocki-Lupski syndrome (duplication 17p11.2). **J Dev Behav Pediatr**. 31: 137-43.

**Potocki L**, Bi W, Treadwell-Deering D, Carvalho CM, Eiffert A, Friedman EM, Glaze D, Krull K, Lee JA, Lewis RA, Mendoza-Londono R, Robbins-Furman P, Shaw C, Shi X, Weissenberger G, Withers M, Yatsenko SA, Zackai EH, Stankiewicz P, 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, Kimonis V, Summers AM, Meschino WS, Anyane-Yeboa K, Kashork CD, Shaffer LG, 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, PHD

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

PhD, 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 in biomedical and basic biological research increases, the need for detailed information about the genomics of nonhuman primates also grows.

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 nancymae*) 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). We have also conducted an extensive survey of genomic variation in the most widely used nonhuman primate, the rhesus macaque (*Macaca mulatta*). By sequencing the genomes of more than 600 rhesus monkeys from various research colonies we have discovered many 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 (Johnson et al., 2015; Rogers, 2018), 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). The primate models point us to genetic mechanisms that may influence susceptibility to psychiatric disorders in people (Rogers et al., 2013). 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., in press) and genetic factors that increase risk for a specific form of severe cardiomyopathy.

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 led a large international consortium of researchers who investigated genetic differentiation among 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., in press). This makes the living baboon species an excellent model for human genome evolution and our ancient admixture with Neanderthals and Denisovans. In another project, we and our colleagues are studying wild kinda baboons (*Papio kindae*) in Zambia (Jolly et al., 2011), a species only recently recognized as distinct from other baboons and which has received little formal scientific attention.

E-mail: jr13@bcm.edu



### SELECTED PUBLICATIONS

Dray BK, Raveendran M, Harris RA, Benavides F, Gray SB, Perez CJ, McArthur M, Williams LE, Baze WB, Doddapaneni H, Muzny DM, Abee CR, **Rogers J** (2018) Mismatch repair gene mutations lead to Lynch Syndrome colorectal cancer in rhesus macaques. **Genes and Cancer**. 9: 142-152.

**Rogers J** (2018). The behavioral genetics of nonhuman primates: Status and Prospects. **Amer J Phys Anthropol**. 165: 23-36.

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.

Xue C, Raveendran M, Harris RA....Gibbs RA, Muzny DM, Yu F, **Rogers J** (2016). The population genomics of rhesus macaques based on whole genome sequences. **Genome Res**. 26: 1651-1662.

Johnson ZP, Brent L, Alvarenga JC, Comuzzie AG, Shelledy W, Ramirez S, Cox LA, Mahaney MC, Huang YY, Mann JJ, Kaplan JR, **Rogers J** (2015). Genetic influences on response to novel objects and dimensions of personality in baboons. **Behav Genet**. 45: 215-227.

Carbone L, Harris RA, The Gibbon Genome Analysis Consortium, Worley KC, **Rogers J**, Wilson RK, Gibbs RA (2014). The gibbon genome provides a novel perspective on the accelerated karyotype evolution of small apes. **Nature**. 53: 195-201.

**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.

Fawcett GL, Dettmer AM, Kay D, Raveendran M, Higley JD, Ryan ND, Cameron JL, **Rogers J** (2014). Quantitative genetics of response to novelty and other stimuli by infant rhesus macaques (*Macaca mulatta*) across three behavioral assessments. **Int J Primatol**. 35: 325-339.

**Rogers J**, Raveendran M, Fawcett GL, Fox AS, Shelton SE, Oler JA, Cheverud J, Muzny DM, Gibbs RA, Davidson RJ, 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.

Oler JA, Fox AS, Shelton SE, **Rogers J**, Dyer TD, Davidson RJ, Shelledy W, Oakes TR, Blangero J, Kalin NH (2010). Amygdalar and hippocampal substrates of anxious temperament differ in their heritability. **Nature**. 466: 864-8.

**SUSAN M. ROSENBERG, PhD****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

PhD, 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**

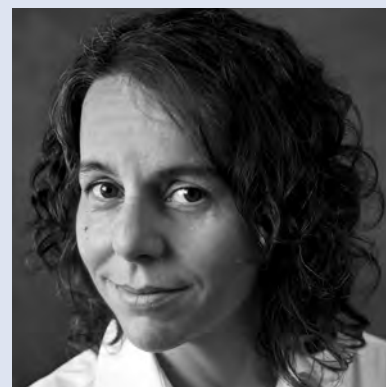
**Stress-Induced Mutagenesis:** For 70 years the world believed that mutations occur at random. The discovery of stress-induced mutagenesis has changed ideas about mutation and evolution and revealed mutagenic mechanisms that are induced by stress responses. The stress responses increase mutagenesis 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-Genes 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<sup>-</sup> (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.

E-mail: [smr@bcm.edu](mailto:smr@bcm.edu)

**SELECTED PUBLICATIONS**

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.

Xia J\*, Chen L-T\*, Mei Q\*, (...), **Rosenberg SM** (2016). Holliday-junction trap shows how cells use recombination and a junction-guardian role of RecQ helicase. *Sci Adv*. 2: e1601605.

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, Lin D, Nehring RB, Saint-Ruf C, Gibson JL, Frisch RL, Lichtarge O, Hastings PJ, **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, **Rosenberg SM** (2012). Two mechanisms produce mutation hotspots at DNA breaks in *Escherichia coli*. *Cell Rep*. 2: 714-21.

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.

Harris RS, Longerich S, **Rosenberg SM** (1994). Recombination in adaptive mutation. *Science*. 264: 258-60.

## RODNEY C. SAMACO, PHD

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

PhD, Baylor College Of Medicine

### RESEARCH INTERESTS

Our primary research interest is to identify and understand the key molecular and neuro-anatomical 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.

E-mail: [rodney.samaco@bcm.edu](mailto:rodney.samaco@bcm.edu)



### 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*<sup>+/-</sup> 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, Pozzo-Miller L, Blue ME, Christian D, Crawley JN, Giustetto M, Guy J, Howell CJ, Kron M, Nelson SB, **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, MD

**Professor**, Department of Molecular and Human Genetics  
**Director**, Baylor College of Medicine and Chinese University of Hong Kong  
 Joint Center for Medical Genetics in Hong Kong

*MD, 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 involves the study of the natural history and the molecular characterization of mitochondrial cytopathies. There is cumulative evidence based on isolated cases reports and limited neuroradiological, biochemical, and molecular studies that mitochondrial dysfunction may be linked to autism spectrum disorders (ASDs). It has been hypothesized that ASDs are prevalent in subjects with mitochondrial cytopathies.

One of the current projects is to characterize from a clinical, biochemical and molecular standpoint the autistic endophenotype in subjects with mitochondrial disease. A detailed clinical and molecular understanding of a potential mitochondrial dysfunction linked to this group of neurobehavioral disorders, if present, offers the possibility of evaluating more specific therapies and improved clinical outcomes for ASD phenotypes. In addition, I am interested in ascertaining the prevalence of mitochondrial DNA depletion in the setting of acute liver failure in infants. A search of candidate nuclear genes involved in the maintenance of mitochondrial DNA integrity and responsible for the phenotype of recessive mitochondrial encephalomyopathies is currently underway by using exome sequencing.

Moreover, I have been involved in two clinical research studies that are evaluating nitric oxide flux and production and glucose kinetics in subjects with MELAS syndrome. This syndrome is associated with metabolic stroke episodes. These episodes could reflect the effect of nitric oxide depletion in the small vasculature. By assessing nitric oxide production and the effect of arginine and citrulline supplementation in these subjects, potential therapeutic strategies could be offered to them. The glucose kinetics study would shed light on the different types of pathological mechanisms of diabetes in MELAS syndrome helping to identify potential biomarkers and therapies.

**E-mail:** [fscaglia@bcm.edu](mailto:fscaglia@bcm.edu)



### SELECTED PUBLICATIONS

El-Hattab AW, Emrick LT, Craigen WJ, **Scaglia F** (2012). Citrulline and arginine utility in treating nitric oxide deficiency in mitochondrial disorders. *Mol Genet Metab.* 107: 247-52.

Campbell IM, Yatsenko SA, Hixson P, Reimschisel T, Thomas M, Wilson W, Dayal U, Wheless JW, Crunk A, Curry C, Parkinson N, Fishman L, Riviello JJ, Nowaczyk MJ, Zeesman S, Rosenfeld JA, Bejjani BA, Shaffer LG, Cheung SW, Lupski JR, Stankiewicz P, **Scaglia F** (2012). Novel 9q34.11 gene deletions encompassing combinations of four Mendelian disease genes: *STXBP1*, *SPTAN1*, *ENG*, and *TOR1A*. *Genet Med.* 14: 868-76.

Tavyev Asher YJ, **Scaglia F** (2012). Molecular bases and clinical spectrum of early infantile epileptic encephalopathies. *Eur J Med Genet.* 55: 299-306.

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.

El-Hattab AW, Hsu JW, Emrick LT, Wong LJ, Craigen WJ, Jahoor F, **Scaglia F** (2012). Restoration of impaired nitric oxide production in MELAS syndrome with citrulline and arginine supplementation. *Mol Genet Metab.* 105: 607-14.

**Scaglia F** (2012). Nuclear gene defects in mitochondrial disorders. *Methods Mol Biol.* 837: 17-34. Review.

Schaaf CP, Blazo M, Lewis RA, Tonini RE, Takei H, Wang J, Wong LJ, **Scaglia F** (2011). Early-onset severe neuromuscular phenotype associated with compound heterozygosity for *OPA1* mutations. *Mol Genet Metab.* 103: 383-7.

Kamdar KY, Krull KR, El-Zein RA, Brouwers P, Potter BS, Harris LL, Holm S, Dreyer Z, **Scaglia F**, Etzel CJ, Bondy M, Okcu MF (2011). Folate pathway polymorphisms predict deficits in attention and processing speed after childhood leukemia therapy. *Pediatr Blood Cancer.* 57: 454-60.

Marini JC, Lanpher BC, **Scaglia F**, O'Brien WE, Sun Q, Garlick PJ, Jahoor F, Lee B (2011). Phenylbutyrate improves nitrogen disposal via an alternative pathway without eliciting an increase in protein breakdown and catabolism in control and ornithine transcarbamylase-deficient patients. *Am J Clin Nutr.* 93: 1248-54.

Hanchard NA, Shchelochkov OA, Roy A, Wiszniewska J, Wang J, Poppek EJ, Karpen S, Wong LJ, **Scaglia F** (2011). Deoxyguanosine kinase deficiency presenting as neonatal hemochromatosis. *Mol Genet Metab.* 103: 262-7.

## DARYL A. SCOTT, MD, PhD

Associate 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

MD/PhD, 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 (CDH):** Children with congenital diaphragmatic hernia (CDH) have an abnormal opening in the diaphragm that allows abdominal organs, like the liver and intestines, to enter into the chest. This invasion interferes with normal lung development causing severe respiratory problems at birth. CDH affects about one in every 2,500 newborns. To date, we have identified over 20 genomic regions that are recurrently deleted or duplicated in individuals with CDH. It is likely that each of these regions harbors one or more dosage-sensitive CDH genes. Using a combination of molecular cytogenetic data and mouse modeling, we have identified and characterized several genes that cause CDH in humans including *HCCS*, *FZD2*, *FREM1* and *ZFPM2*. We have also developed novel mouse models for CDH that carry mutations in *Sox7*, *Frem1*, *Frem2*, and *Fras1*. We are now using these models to learn how diaphragmatic hernias form and how various CDH genes interact *in vivo*.

**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 carries 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 presently using array-based copy number detection assays and whole exome sequencing to identify genes that cause these disorders.

**Novel Gene Discovery:** We also work with physicians and scientists from around the world to identify genes and genomic regions that are associated with a variety of other phenotypes including congenital heart defects, cardiomyopathy, developmental delay, intellectual disability and autism.

E-mail: [dscott@bcm.edu](mailto:dscott@bcm.edu)



### SELECTED PUBLICATIONS

Sewani M, Nugent K, Blackburn PR, Tarnowski JM, Hernandez-Garcia A, Amiel J, Whalen S, Keren B, Courtin T, Rosenfeld JA, Yang Y, Patterson MC, Pichurin P, McLean SD, **Scott DA** (2020). Further delineation of the phenotypic spectrum associated with hemizygous loss-of-function variants in *NONO*. **Am J Med Genet A**. 182: 652-658.

Scott TM, Guo H, Eichler EE, Rosenfeld JA, Pang K, Liu Z, Lalani S, Bi W, Yang Y, Bacino CA, Streff H, Lewis AM, Koenig MK, Thiffault I, Bellomo A, Everman DB, Jones JR, Stevenson RE, Bernier R, Gilissen C, Pfundt R, Hiatt SM, Cooper GM, Holder JL, **Scott DA** (2020). *BAZ2B* haploinsufficiency as a cause of developmental delay, intellectual disability, and autism spectrum disorder. **Hum Mutat**. 41: 921-925.

Gibson S, Azamian MS, Lalani SR, Yen KG, Sutton VR, **Scott DA** (2020). Recessive *ACO2* variants as a cause of isolated ophthalmologic phenotypes. **Am J Med Genet A**. 182: 1960-1966.

Rossetti LZ, Grinton K, Yuan B, Liu P, Pillai N, Mizerik E, Magoulas P, Rosenfeld JA, Karaviti L, Sutton VR, Lalani SR, **Scott DA** (2019). Review of the phenotypic spectrum associated with haploinsufficiency of *MYRF*. **Am J Med Genet A**. 179: 1376-1382.

Jordan VK, Fregeau B, Ge X, Giordano J, Wapner RJ, (...), **Scott DA** (2018). Genotype-phenotype correlations in individuals with pathogenic *RERE* variants. **Hum Mutat**. 39: 666-675.

Jordan VK, Beck TF, Hernandez-Garcia A, Kundert PN, Kim BJ, (...), **Scott DA** (2018). The role of *FREM2* and *FRAS1* in the development of congenital diaphragmatic hernia. **Hum Mol Genet**. 27: 2064-2075.

Callaway DA, Campbell IM, Stover SR, Hernandez-Garcia A, Jhangiani SN, Punetha J, Paine IS, Posey JE, Muzny D, Lally KP, Lupski JR, Shaw CA, Fernandes CJ, **Scott DA** (2018). Prioritization of Candidate Genes for Congenital Diaphragmatic Hernia in a Critical Region on Chromosome 4p16 using a Machine-Learning Algorithm. **J Pediatr Genet**. 7: 164-173.

Kim BJ, Zaveri HP, Jordan VK, Hernandez-Garcia A, Jacob DJ, Zamora DL, Yu W, Schwartz RJ, **Scott DA** (2018). *RERE* deficiency leads to decreased expression of *GATA4* and the development of ventricular septal defects. **Dis Model Mech**. 11. pii: dmm031534.

Fregeau B, Kim BJ, Hernández-García A, Jordan VK, (...), **Scott DA\***, Sherr EH\* (2016). De Novo Mutations of *RERE* Cause a Genetic Syndrome with Features that Overlap Those Associated with Proximal 1p36 Deletions. **Am J Hum Genet**. 98: 963-70. (\*Authors contributed equally)

**Scott DA**, Hernandez-Garcia A, Azamian MS, Jordan VK, Kim BJ, Starkovich M, Zhang J, Wong LJ, Darilek SA, Brennan AM, Yang Y, Lupski JR, Jiwanji AK, Das B, Lalani SR, Iglesias AD, Rosenfeld JA, Xia F (2016). Congenital heart defects and left ventricular non-compaction in males with loss-of-function variants in *NONO*. **J Med Genet**. 54: 47-53.

## GAD SHAULSKY, PHD

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

PhD, Weizmann Institute of Science

Postdoc, University of California, San Diego

### RESEARCH INTERESTS

**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.

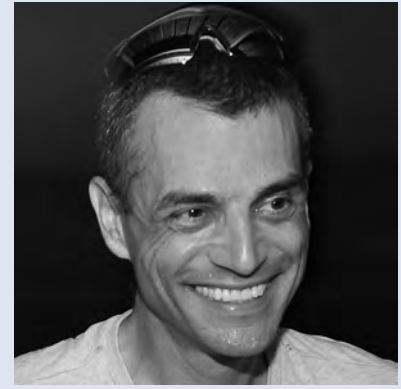
We are developing new tools for exploration of the *Dictyostelium* genome. Recent tools include a deep coverage genomic DNA library (Rosengarten, 2015), a method for gene discovery by chemical mutagenesis at low level and whole-genome sequencing to identify mutations (Li, 2016), and an adaptation of the GoldenBraid system as a synthetic biology tool for *Dictyostelium* (Kundert, 2020).

**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).

**Allorecognition:** We found that *Dictyostelium* cells preferentially cooperate with relatives (Ostrowski, 2008), possibly reducing their exposure to cheaters. We are investigating the molecular mechanisms that underlie kin discrimination. We found two cell-cell adhesion genes, *tgrB1* and *tgrC1*, that are highly polymorphic in natural populations and are required for allorecognition (Benabentos, 2009). Gene replacement experiments have shown that the sequence polymorphism in these genes is sufficient to explain allorecognition in this system (Hirose, 2011). This kin-recognition system protects cooperators against cheaters (Ho, 2013) and it 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. Some signal transduction genes were found using a genetic suppressor screen (Li, 2016) and we are continuing the characterization and identification of additional signaling elements.

**Data Mining:** We are collaborating with Dr. Zupan and his group at the University of Ljubljana in 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 (Codec, 2019).

E-mail: [gadi@bcm.edu](mailto:gadi@bcm.edu)



### SELECTED PUBLICATIONS

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.

Santhanam B, Cai H, Devreotes PN, **Shaulsky G**, Katoh-Kurasawa M (2015). The GATA transcription factor *GtaC* regulates early developmental gene expression dynamics in *Dictyostelium*. **Nat Commun.** 6: 7551.

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, Sugang R, Chen R, Zupan B, Loomis WF, Kuspa A, **Shaulsky G** (2010). Conserved developmental transcriptomes in evolutionarily divergent species. **Genome Biol.** 11: R35.

Khare A, Santorelli LA, Strassmann JE, Queller DC, Kuspa A, **Shaulsky G** (2009). Cheater-resistance is not futile. **Nature.** 461: 980-2.

Benabentos R, Hirose S, Sugang R, Curk T, Katoh M, Ostrowski EA, Strassmann JE, Queller DC, Zupan B, **Shaulsky G**, Kuspa A (2009). Polymorphic members of the lag gene family mediate kin discrimination in *Dictyostelium*. **Curr Biol.** 19: 567-72.

Santorelli LA, Thompson CRL, Villegas E, Svez J, Dinh C, Parikh A, Sugang R, Kuspa A, Strassmann JE, Queller DC, **Shaulsky G** (2008). Facultative cheater mutants reveal the genetic complexity of cooperation in social amoebae. **Nature.** 451: 1107-10.

## CHAD SHAW, PHD

**Professor**, Department of Molecular and Human Genetics  
**Faculty Member**, Stem Cells and Regenerative Medicine (STaR) Center and  
 Graduate Program in Quantitative & Computational Biosciences

*PhD, 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 Head of Statistical Genetics at Baylor Genetics Diagnostic Laboratory.

Chad 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 on new mutations.

Chad 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.

Chad has been an author on approximately 200 peer reviewed publications, and his work has been cited approximately 17,000 times. He has trained five PhD students in his own laboratory and over 10 students as a thesis committee member.

**E-mail:** [cashaw@bcm.edu](mailto:cashaw@bcm.edu)



### 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, MD, PhD

Associate Professor, Departments of Molecular and Human Genetics, Neurology, and Neuroscience

Faculty Member, Graduate Programs in Genetics & Genomics and Neuroscience

PhD, University of Cambridge

MD, Harvard Medical School

Resident in Neurology, Brigham & Women's Hospital, Massachusetts General Hospital

Movement/Memory Disorders Fellow, Brigham & Women's Hospital, Massachusetts General Hospital

Postdoc, Neurogenetics, Brigham And Women's Hospital, Massachusetts General Hospital

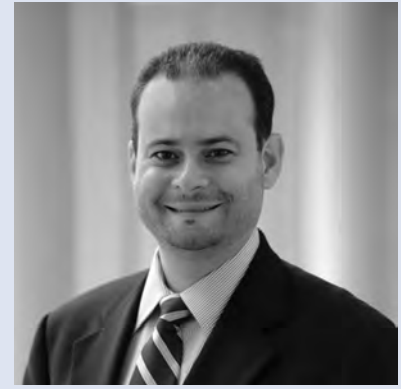
### RESEARCH INTERESTS

Recent advances have made the discovery of genetic susceptibility loci for complex human phenotypes a reality, including nervous system disorders. The critical next step will be to definitively identify the responsible genes and understand their functions in both health and disease. 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 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 relevant mechanisms in nervous system health and disease. 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.

E-mail: [Joshua.Shulman@bcm.edu](mailto:Joshua.Shulman@bcm.edu)



### SELECTED PUBLICATIONS

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

Johnson ECB, Dammer EB, Duong DM, Ping L, Zhou M, (...), **Shulman JM**, Lah JJ, Levey AI, Seyfried NT (2020). Large-scale Proteomic Analysis of Alzheimer's Disease Brain and Cerebrospinal Fluid Reveals Early Changes in Energy Metabolism Associated with Microglia and Astrocyte Activation. **Nat. Med.** 26: 769-780.

Hsieh Y-C, Guo C, Yalamanchili HK, Abreha M, Al-Ouran R, Li Y, Dammer EB, Lah JJ, Levey AI, Bennett DA, De Jager PL, Seyfried NT, Liu Z, **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, Duraine L, Zuo Z, Petyuk V, De Jager PL, Bennett DA, Arenkiel BR, Bellen H, **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.

Guo C, Jeong HH, Hsieh YC, Klein HU, Bennett DA, De Jager PL, Liu Z, **Shulman JM** (2018). Tau Activates Transposable Elements in Alzheimer's Disease. **Cell Rep.** 23: 2874-2880.

Robak LA, Jansen IE, van Rooij J, Uitterlinden AG, Kraaij R, Jankovic J, International Parkinson's Disease Genetics Consortium (IPDGC), Heutink P, **Shulman JM** (2017). Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease. **Brain.** 140: 3191-3203.

Jansen IE, Ye H, Heetveld S, Lechler MC, (...), International Parkinson's Disease Genetics Consortium (IPDGC), Morris HR, Brice A, Singleton AB, David DC, Nollen EA, Jain S, **Shulman JM**, Heutink P (2017). Discovery and functional prioritization of Parkinson's disease candidate genes from large-scale whole exome sequencing. **Genome Biol.** 18: 22.

Jakobsdottir J, van der Lee SJ, Bis JC, Chouraki V, Li-Kroeger D, Yamamoto S, (...), Seshadri S, **Shulman JM**, Gudnason V, van Duijn CM (2016). Rare Functional Variant in *TM2D3* is Associated with Late-Onset Alzheimer's Disease. **PLoS Genet.** 12: e1006327.

**Shulman JM** (2015). *Drosophila* and experimental neurology in the post-genomic era. **Exp Neurol.** 274(Pt A): 4-13.



## PAWEŁ STANKIEWICZ, MD, PhD

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

MD, Medical University of Warsaw, Poland

PhD, Institute of Mother and Child, Warsaw, Poland

Postdoc, Baylor College of Medicine

Dr. Habil (DSc), Institute of Mother and Child, Warsaw, Poland

### RESEARCH INTERESTS

**Genomic Disorders:** The main areas of focus in 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). Recently, 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 the 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 a 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 are particularly interested in elucidating the role of higher-order genomic architectural features such as low-copy repeats (LCRs) and repetitive elements (LINEs, *Alus*, HERVs) in genomic instability. Recently, we reported the role of *BPTF*, *PSMD12*, and *TRIP12* in neurodevelopmental disorders.

E-mail: [pawels@bcm.edu](mailto:pawels@bcm.edu)



### SELECTED PUBLICATIONS

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.

Szafranski P, Liu Q, Karolak JA, (...), **Stankiewicz P** (2019). Association of rare non-coding SNVs in the lung-specific *FOXF1* enhancer with a mitigation of the lethal ACDMPV phenotype. **Hum Genet.** 138: 1301-11.

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.

Zhang J, Gambin T, (...), Xia F, **Stankiewicz P** (2017). Haploinsufficiency of the E3 ubiquitin-protein ligase gene *TRIP12* causes intellectual disability with or without autism spectrum disorders, speech delay, and dysmorphic features. **Hum Genet.** 136: 377-86.

Gambin T, Yuan B, (...), Shaw CA, **Stankiewicz P** (2017). Identification of novel candidate disease genes from *de novo* exonic copy number variants. **Genome Med.** 9: 83.

Szafranski P, Gambin T, Dharmadhikari AV, (...), **Stankiewicz P** (2016). Pathogenetics of alveolar capillary dysplasia with misalignment of pulmonary veins. **Hum Genet.** 135: 569-86.

## V. REID SUTTON, MD

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

MD, University of Kentucky

Resident, Pediatrics, Washington University

Fellow, Medical Genetics, Baylor College of Medicine

### RESEARCH INTERESTS

I have committed myself to advancing 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 (Focal Dermal Hypoplasia), Ankyloblepharon-Ectodermal Dysplasia Clefing (AEC) and Robinow and White-Sutton syndrome. I am the clinical geneticist for the Baylor-Hopkins Center for Mendelian Genomics 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) as part of the Brittle Bone Disorders Consortium of the Rare Disease Clinical Research Network and am also the administrative PI for this project.

E-mail: [vrsutton@texaschildrens.org](mailto:vrsutton@texaschildrens.org)



### SELECTED PUBLICATIONS

Tosi LL, Floor MK, Dollar CM, Gillies AP; Members of the Brittle Bone Disease Consortium, Hart TS, Cuthbertson DD, **Sutton VR**, Krischer JP (2019). Assessing disease experience across the life span for individuals with osteogenesis imperfecta: challenges and opportunities for patient-reported outcomes (PROs) measurement: a pilot study. **Orphanet J Rare Dis.** 14: 23.

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.

Romere C, Duerschmid C, Bourmat J, Constable P, Jain M, Xia F, Saha PK, Del Solar M, Zhu B, York B, Sarkar P, Rendon DA, Gaber MW, LeMaire SA, Coselli JS, Milewicz DM, **Sutton VR**, Butte NF, Moore DD, Chopra AR (2016). Asprosin, a Fasting-Induced Glucogenic Protein Hormone. **Cell.** 165: 566-79.

White J, Beck CR, Harel T, Posey JE, Jhangjani SN, (...), **Sutton VR** (2016). POGZ truncating alleles cause syndromic intellectual disability. **Genome Med.** 8: 3.

Bostwick B, Fang P, Patel A, **Sutton VR** (2016). Phenotypic and molecular characterization of focal dermal hypoplasia in 18 individuals. **Am J Med Genet C Semin Med Genet.** 172C: 9-20.

Miller MJ, Kennedy AD, Eckhart AD, Burrage LC, Wulff JE, (...), **Sutton VR**, Elsea SH (2015). Untargeted metabolomic analysis for the clinical screening of inborn errors of metabolism. **J Inherit Metab Dis.** 38: 1029-39. Erratum in: **J Inherit Metab Dis.** (2016) 39: 757

Patel RM, Nagamani SC, Cuthbertson D, Campeau PM, Krischer JP, (...), **Sutton VR** (2015). A cross-sectional multicenter study of osteogenesis imperfecta in North America - results from the linked clinical research centers. **Clin Genet.** 87: 133-40.

Miller MJ, Soler-Alfonso CR, Grund JE, Fang P, Sun Q, Elsea SH, **Sutton VR** (2014). Improved standards for prenatal diagnosis of citrullinemia. **Mol Genet Metab.** 112: 205-9.

Wang X\*, **Reid Sutton V\***, Omar Peraza-Llanes J, Yu Z, Rosetta R, Kou YC, Eble TN, Patel A, Thaller C, Fang P, Van den Veyver IB (2007). Mutations in X-linked PORCN, a putative regulator of Wnt signaling, cause focal dermal hypoplasia. **Nat Genet.** 39: 836-8. \*These authors contributed equally to this work

## MENG WANG, PHD

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

PhD, 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/lipidomics, 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.

E-mail: [wmeng@bcm.edu](mailto:wmeng@bcm.edu)



### 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, MD

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

MD, 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. Our overall goal is to improve our understanding of the molecular pathogenesis of Mendelian disease by merging clinical observations, genomics and studies in model organisms 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). Similar efforts are underway related to the Centers for Mendelian Genomics (CMG) and the Simon's Foundation for Autism Research Initiative (SFARI).

**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 disease related to peroxisomes.

E-mail: [michael.wangler@bcm.edu](mailto:michael.wangler@bcm.edu)



### SELECTED PUBLICATIONS

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, Baglaj 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

Schoch K, Meng L, Szelinger S, Bearden DR, Stray-Pedersen A, (...) **Wangler MF\***, Shashi V\* (2017). A Recurrent de novo Variant in NACC1 Causes a Syndrome Characterized by Infantile Epilepsy, Cataracts and Profound Developmental Delay. **Am J Hum Genet.** 100: 343-351. \*Corresponding Authors

**Wangler MF\***, Chao YH, Bayat V, Giagtzoglu N, Putluri N, (...), Bellen HJ. (2017) Peroxisomal biogenesis is genetically and biochemically linked to carbohydrate metabolism in *Drosophila* and mouse. **PLoS Genet.** 13: e1006825. \*Corresponding Author

## THOMAS F. WESTBROOK, PHD

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

PhD, 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.

E-mail: [thomasw@bcm.edu](mailto:thomasw@bcm.edu)



### 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.

**LEE-JUN C. WONG, PhD**

**Professor**, Department of Molecular and Human Genetics  
**Faculty Member**, Graduate Programs in Genetics & Genomics  
**Senior Laboratory Director**, Baylor Genetics

*PhD, Ohio State University*  
*Postdoc, Princeton University*

**RESEARCH INTERESTS**

My primary research interest lies in the understanding of mitochondrial genetics and function in disease, cancer, and aging. For many years, our laboratory has had its major contribution to the improvement of the molecular diagnosis of the complex dual genome mitochondrial disorders. This includes the development of various molecular technologies to detect and quantify single nucleotide variants (SNVs) and copy number changes (CNVs) in both mitochondrial and nuclear genomes. We have developed a dense exon targeted oligonucleotide arrays CGH for coding exons for various mitochondrial, metabolic, and genetic disorders for the detection of various sizes of exonic CNVs. We invented back-to-back primers to amplify the intact circular mitochondrial genome followed by deep massively parallel sequencing to accurately detect and quantify mtDNA point mutations at any nucleotide positions of the mitochondrial genome without the interference of nuclear mitochondrial DNA homologous sequences. In addition, the breakpoints of mtDNA single and multiple deletions can be unequivocally determined. Using target gene capture and deep next generation sequencing (NGS) technology, we have validated a series of NGS-based panel testing for clinical diagnostic utilities. These include groups of genes involved in specific metabolic pathways, such as glycogen storage disease (GSD) and congenital disorders of glycosylation (CDG); disease with defined clinical phenotype (eg Usher syndrome); genetically heterogeneous diseases involved a particular organ (eg eye, bone); various cancers, genetically and clinically heterogeneous mitochondrial disorder, in addition to complex neuromuscular disorders. We developed analytical pipeline to simultaneously detect point mutations (SNVs) and exonic deletions (CNVs), as well as balanced translocations and Alu mediated chromosomal rearrangement involving captured regions using deep NGS sequence data. Most recently, we apply sophisticated molecular barcoding technologies to cell free DNA based noninvasive prenatal screening and liquid biopsies for cancers.

Reprogramming of energy metabolism is one of the hallmarks of cancer. In proliferating cancer cells, the rates of glycolysis, lactate production, and biosynthesis of lipids and other macromolecules are increased. This Warburg effect is attributed to defective or re-programmed mitochondrial energy metabolism in cancer cells. My research interest is to investigate the mechanism of the interplay between the nuclear and mitochondrial genomes and to identify key modulators in the dual genome cross-talk that impact cellular energetics. We established transmitochondrial cybrids with a defined nuclear background containing mitochondria derived from cancer cell lines with various degrees of tumorigenicity and metastatic potency to investigate the functional effect of cancer mitochondria on nuclear gene expression and to provide insight into the mechanism of mitochondrial-nuclear cross-talk as well as the relationship between energy metabolism and cancer development.

**E-mail:** [ljwong@bcm.edu](mailto:ljwong@bcm.edu)

**SELECTED PUBLICATIONS**

Yu H, Zhang VW, (...), **Wong LJ** (2016). Rapid molecular diagnostics of severe primary immunodeficiency determined by using targeted next-generation sequencing. **J Allergy Clin Immunol.** 138: 1142-1151.

Qin L, Wang J, Tian X, Yu H, Truong C, Mitchell JJ, Wierenga KJ, Craigen WJ, Zhang VW, **Wong LJ** (2016). Detection and Quantification of Mosaic Mutations in Disease Genes by Next-Generation Sequencing. **J Mol Diagn.** 18: 446-53.

Li J, Tang J, Feng Y, Xu M, Chen R, Zou X, Sui R, Chang EY, Lewis RA, Zhang VW, Wang J, **Wong LJ** (2016). Improved Diagnosis of Inherited Retinal Dystrophies by High-Fidelity PCR of ORF15 followed by Next-Generation Sequencing. **J Mol Diagn.** 17: 545-53.

Park JH, (...), **Wong LJ**, Kaiparettu BA (2016). Fatty Acid Oxidation-Driven Src Links Mitochondrial Energy Reprogramming and Oncogenic Properties in Triple-Negative Breast Cancer. **Cell Rep.** 14: 2154-65.

Wang J, Yu H, Zhang VW, Tian X, Feng YM, Wang G, Gorman E, Wang H, Lutz RE, Schmitt ES, Peacock S, **Wong LJ** (2016). Capture based high coverage NGS: a powerful tool to uncover a wide spectrum of mutation types. **Genet Med.** 18: 513-21.

Tian X, Liang WC, Feng YM, Wang J, Zhang VW, Chou CH, (...), **Wong LJ**, Jong YJ (2015). Expanding genotype/phenotype of neuromuscular diseases by comprehensive target capture/NGS. **Neurol Genet.** 1: e14.

Li J, Dai H, Feng Y, Tang J, Chen S, Tian X, Gorman E, Schmitt ES, Hansen T, Wang J, Plon SE, Zhang VW, **Wong LJ** (2015). A comprehensive strategy for accurate mutation detection of the highly homologous PMS2 gene. **JMD** 17: 545-553.

Gargis AS, Kalman L, Bick DP, da Silva C, Dimmock DP, Funke BH, ..., Lubin IM (2015). Good laboratory practice for clinical next-generation sequencing informatics pipelines. **Nat Biotechnol.** 33: 689-93.

Feng Y, Chen D, Wang GL, Zhang VW, **Wong LJ** (2015). Improved molecular diagnosis by the detection of exonic deletions with target gene capture and deep sequencing. **Genet Med.** 17: 99-107.

Zhou S, Hertel PM, Finegold MJ, Wang L, Kerker N, Wang J, **Wong LJ**, Plon SE, Sambrotta M, Foskett P, Niu Z, Thompson RJ, Knisely AS (2015). Hepatocellular carcinoma associated with tight-junction protein 2 deficiency. **Hepatology.** 62: 1914-6.

Tannour-Louet M, York B, Tang K, Stashi E, Bouguerra H, Zhou S, Yu H, **Wong LJ**, Stevens RD, Xu J, Newgard CB, O'Malley BW, Louet JF (2014). Hepatic SRC-1 activity orchestrates transcriptional circuitries of amino acid pathways with potential relevance for human metabolic pathogenesis. **Mol Endocrinol.** 28: 1707-18.

## KIM C. WORLEY, PHD

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

BS, Massachusetts Institute of Technology  
PhD, 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 creating genome representations through *de novo* genome assembly, improving genome representation through targeted sequencing and structural variation analysis, and contributing to the understanding 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.

E-mail: [kworley@bcm.edu](mailto:kworley@bcm.edu)



### SELECTED PUBLICATIONS

International Human Genome Sequencing Consortium (2001). Initial sequencing and analysis of the human genome. **Nature**. 409: 860-921.

International Human Genome Sequencing Consortium (2004). Finishing the euchromatic sequence of the human genome. **Nature**. 431: 931-45.

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.

Human Microbiome Project Consortium (2012). Structure, function and diversity of the healthy human microbiome. **Nature**. 486: 207-14.

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.

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.

Bovine Genome Sequencing and Analysis Consortium (2009). Elsik CG, Tellam RL, **Worley KC** corresponding authors. The genome sequence of taurine cattle: a window to ruminant biology and evolution. **Science**. 324: 522-8.

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

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.

Honeybee Genome Sequencing Consortium (2006). Insights into social insects from the genome of the honeybee *Apis mellifera*. **Nature**. 443: 931-49.

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.

## TAO WU, PHD

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 our lab wants to answer is how the epigenetic factors dynamically regulate the cell fate decision and the response to external stimulation. Our final goal is to apply the fundamental knowledge for curing human diseases, such as cancer. 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, the cancer treatment resistance is still the 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. Recently, using 2nd generation high-throughput sequencing, about 50% of human cancers were found to harbor mutations in the epigenetic regulatory enzymes which are involved in chromatin organization. Meanwhile, the 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, a DNA methylation that had never been detected in mammals before) with SMRT-ChIP (3rd generation single-molecule real-time sequencing with native ChIP samples) in mouse ES cells. We also identified ALKBH1 as the major demethylase of DNA 6mA. Very recently, we pinpointed that 6mA level is ultra-high in glioblastoma stem cells and high-grade glioblastoma (GBM) patient's samples. In contrast, the 6mA's abundance is much lower in the differentiated 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, I hypothesize that DNA 6mA might be a driver epigenetic mutation and its regulators could constitute an essential pathway which manipulates cancer treatment resistance. The DNA 6mA's readers, writers, or erasers, could be defined as new cancer dependencies which could be targeted to bypass the resistance and enhance the cancer 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 optimized CRISPR/Cas9 screening approaches, we will explore new cancer dependencies with the novel DNA or histone modifications in different model systems.

E-mail: [Tao.Wu@bcm.edu](mailto:Tao.Wu@bcm.edu)



### SELECTED PUBLICATIONS

Wu TP, Wang T, et al. (2016). DNA methylation on N(6)-adenine in mammalian embryonic stem cells. **Nature**. 532: 329-33.

Xie Q\*, Wu TP\*, Gimple RC\*, et al. (2018). N(6)-methyladenine DNA Modification in Glioblastoma. **Cell**. 175: 1228-1243.e20.

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.

Buganim Y, Markoulaki S, van Wietmarschen N, Hoke H, Wu T, et al. (2014). The developmental potential of iPSCs is greatly influenced by reprogramming factor selection. **Cell Stem Cell**. 15: 295-309.

Dan J, Liu Y, Liu N, Chiourea M, Okuka M, Wu T, et al. (2014). *Rif1* maintains telomere length homeostasis of ESCs by mediating heterochromatin silencing. **Dev Cell**. 29: 7-19.

Zhang B\*, Chen B\*, Wu T\*, Tan Y, et al. (2011). Estimating the quality of reprogrammed cells using ES cell differentiation expression patterns. **PLoS One**. 6: e15336. (\*First Author)

Zhang B, Chen B, Wu T, Xuan Z, et al. (2011). Estimating developmental states of tumors and normal tissues using a linear time-ordered model. **BMC Bioinformatics**. 12: 53.

Shi B\*, Guo X\*, Wu T\*, et al. (2009). Genome-scale identification of *Caenorhabditis elegans* regulatory elements by tiling-array mapping of DNase I hypersensitive sites. **BMC Genomics**. 10: 92. (\*First Author)

Tan Y, Zhang B, Wu T, Skogerbø G, et al. (2009). Transcriptional inhibition of *Hoxd4* expression by miRNA-10a in human breast cancer cells. **BMC Mol Biol**. 10: 12.

He H, Wang J, Liu T, Liu XS, Li T, Wang Y, Qian Z, Zheng H, Zhu X, Wu T, et al. (2007). Mapping the *C. elegans* noncoding transcriptome with a whole-genome tiling microarray. **Genome Res**. 17: 1471-7.

Wu T\*, Wang J, Liu C, et al. (2006). NPInter: the noncoding RNAs and protein related biomacromolecules interaction database. **Nucleic Acids Res**. 34: D150-2. (\*First Author)



## SHINYA YAMAMOTO, DVM, PhD

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

DVM, Ministry of Agriculture, Forestry and Fisheries of Japan  
PhD, Baylor College of Medicine  
Postdoc, Baylor College of Medicine

### RESEARCH INTERESTS

Many pediatric diseases and conditions are caused by mutations found in the patients' genomic DNA. Genetic mutations responsible for some of these disorders have been successfully identified which have opened up new doors for researchers to develop better diagnostic tools and new treatments. However for most neurological and psychiatric diseases, the causes are yet to be identified.

The human genome contains ~25,000 genes, yet the biological functions of more than 80% of them are not well characterized. Yamamoto lab aims to bridge this gap using powerful genetic tools available in the model organism, *Drosophila melanogaster* (fruit flies) that allow for rapid discovery and functional elucidation of genes that play key roles in the development and maintenance of nervous system.

Using the information obtained from large-scale fly screens and combining this with large whole exome sequence (WES) datasets from thousands of patients with undiagnosed diseases (in collaboration with Drs. Jim Lupski, Richard Gibbs, Michael Wangler and the Baylor-Hopkins Center for Mendelian Genomics), we have identified a number of new human disease causing genes. Furthermore, by extensively studying the function of the fly homologs of these diseases genes, we have revealed molecular mechanisms by which mutations in these genes cause certain disease conditions.

We are especially interested in classes of genes that regulate cell-cell communication in development and disease. Notch signaling is a key pathway in the development of almost all organs, and defects in Notch signaling leads to different congenital disorders, stroke and cardiovascular diseases, as well as in many types of cancer in both children and adults. Dopamine signaling, on the other hand, regulates diverse aspects of neuronal function, and its dysfunction is seen in diverse neurodevelopmental (e.g. autism spectrum disorders, ADHD/ADD), neurological (e.g. dystonia, restless legs syndrome), psychiatric (e.g. schizophrenia, mood disorders, addiction), as well as neurodegenerative conditions (e.g. Parkinson's disease).

We aim to identify and characterize novel genes in these pathways and understand their precise functions *in vivo* using genetic, cell/molecular biological, biochemical, and electrophysiological methodologies. Our goal is to provide a better understanding of the molecular mechanisms underlying these diseases, allowing researchers to explore novel drug targets and potential therapies towards a cure.

E-mail: [yamamoto@bcm.edu](mailto:yamamoto@bcm.edu)



### SELECTED PUBLICATIONS

**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.

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.

**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.

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

David-Morrison G, Xu Z, Rui YN, Charng WL, Jaiswal M, **Yamamoto S**, Xiong B, Zhang K, Sandoval H, Duraine L, Zhang S, Bellen HJ (2016). WAC regulates mTOR activity through the TTT-Pontin/Reptin complex. **Dev Cell**. 36: 139-51.

Jaiswal M, Haelterman NA, Sandoval H, Xiong B, Donti T, Kalsotra A, **Yamamoto S**, Cooper TA, Graham BH, Bellen HJ (2015). Impaired mitochondrial energy production causes light induced photoreceptor degeneration independent of oxidative stress. **PLoS Biol**. 13: e1002197.

Sandoval H, Yao CK, Chen K, Jaiswal M, Donti T, Lin YQ, Bayat V, Xiong B, Zhang K, David G, Charng WL, **Yamamoto S**, Duraine L, Graham BH, Bellen HJ (2014). Mitochondrial fusion but not fission regulates larval growth and synaptic development through steroid hormone production. **ELife**. 3: e03558.

Haelterman NA, Jiang L, Li Y, Bayat V, Sandoval H, Ugur B, Tan KL, Zhang K, Bei D, Xiong B, Charng WL, Busby T, Jawaid A, David G, Jaiswal M, Venken KJ, **Yamamoto S**, Chen R, Bellen HJ (2014). Large-scale identification of chemically induced mutations in *Drosophila melanogaster*. **Genome Res**. 24: 1707.

Charng WL, **Yamamoto S**, Jaiswal M, Bayat V, Xiong B, Zhang K, Sandoval H, David G, Gibbs S, Lu HC, Chen K, Giagtzoglou N, Bellen HJ (2014). *Drosophila Tempura*, a novel protein prenyltransferase  $\alpha$  subunit, regulates notch signaling via Rab1 and Rab11. **PLoS Biol**. 12: e1001777.

## JIHYE YUN, PhD

**Assistant Professor**, Department of Molecular and Human Genetics and USDA/ARS Children's Nutrition Research Center

**Faculty Member**, Graduate Programs in Genetics & Genomics, Cancer & Cell Biology, and Chemical, Physical & Structural Biology

**Member**, Gulf Coast Center for Precision Environmental Health

**CPRIT Scholar in Cancer Research**

**V Scholar for Cancer Research**

**Pew-Stewart Scholar for Cancer Research**

*PhD, Johns Hopkins School of Medicine, Baltimore, Maryland*

*Postdoctoral fellow, Weill Cornell Medicine, New York, New York*

*Instructor, Weill Cornell Medicine, New York, New York*

### RESEARCH INTERESTS

Colorectal cancer is the second leading cause of cancer-related deaths in developed countries. Epidemiological studies strongly suggest that diet is the most important environmental factor in colorectal cancer development. Indeed, diet is known to affect many important aspects of cancer development such as epigenetics, metabolism, immune systems and gut microbiota. As such, if we can identify and understand the mechanisms by which dietary factors can prevent or facilitate cancer development, we will be able to control cancer initiation, progression and metastasis more effectively. Unfortunately, the field connecting diet to cancer has been difficult to study experimentally in humans. The main challenge is the difficulty to perfectly control or restrict an individual's diet or life style, which can confound the dietary factors in question. Furthermore, it is difficult to dissect the molecular mechanisms of complex relationship between diet and pathogenesis of cancer in human subjects.

The goal of our laboratory is to identify dietary factors that can affect tumorigenesis and understand the molecular basis for the relationship between diet and colorectal cancer using preclinical model systems. In this regard, we will use genetically engineered mouse models of intestinal cancer, *ex vivo* intestinal organoid co-culture systems, and patient or mouse-derived organoid transplantation models. Furthermore, we have the integrative and systematic '-omics' approaches using state-of-the-art techniques such as metabolomics and next-generation sequencing to untangle the complex but important relationship between dietary factors, genetics, and cancer pathogenesis. Ultimately, our laboratory seeks to develop and discover novel strategies to prevent and treat colorectal cancer as well as other types of cancer by understanding the role of diet in cancer, which we believe can have a positive impact on society directly and immediately.

**E-mail:** [Jihye.Yun@bcm.edu](mailto:Jihye.Yun@bcm.edu)



### SELECTED PUBLICATIONS

Ngo B, Van Riper JM, Cantley LC, **Yun J** (2019). Targeting cancer vulnerabilities with high-dose vitamin C. **Nat Rev Cancer**. 19: 271-282.

Goncalves MD, Lu C, Tutnauer J, Hartman TE, Hwang SK, Murphy CJ, Pauli C, Morris R, Taylor S, Bosch K, Yang S, Wang Y, Van Riper J, Lekay HC, Roper J, Kim Y, Chen Q, Gross SS, Rhee KY, Cantley LC, **Yun J** (2019). High-fructose corn syrup enhances intestinal tumor growth in mice. **Science**. 363: 1345-1349.

**Yun J**, Mullarky E, Lu C, Bosch KN, Kavalier A, Rivera K, Roper J, Chio II, Giannopoulou EG, Rago C, Muley A, Asara JM, Paik J, Elemento O, Chen Z, Pappin DJ, Dow LE, Papadopoulos N, Gross SS, Cantley LC (2015). Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. **Science**. 350: 1391-6.

**Yun J**, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, Willson JK, Markowitz S, Zhou S, Diaz LA Jr, Velculescu VE, Lengauer C, Kinzler KW, Vogelstein B, Papadopoulos N (2009). Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. **Science**. 325: 1555-9.

## BING ZHANG, PHD

**Professor**, Department of Molecular and Human Genetics and Lester and Sue Smith Breast Center

**Faculty Member**, Graduate Program in Quantitative and Computational Biosciences

*PhD, Chinese Academy of Sciences, Shanghai, China*

*Postdoctoral fellow, University of Tennessee, Knoxville*

*Postdoctoral fellow, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

### RESEARCH INTERESTS

The long-term goal of my research is to develop computational and statistical methods and tools that help translate cancer omics data into better diagnosis, prognosis, and treatment of human cancer. Current work in my laboratory focuses on the integrative analysis of cancer proteomics and genomics data, a new research field named cancer proteogenomics. Proteins are the functional units in the cell and primary drug targets, however, we know very little about cancer proteomes. Through participating in the National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC), my lab has developed several novel methods and tools for the integrative analysis of cancer genomic and proteomic data (Wang et al., 2012; Shi et al., 2013; Wang et al., 2017; Vasaikar et al., 2018; Wen et al., 2019). We led two CPTAC colon cancer studies (Zhang et al., 2014; Vasaikar et al., 2019), demonstrating the power of proteogenomics in revealing new cancer drivers and vulnerabilities inaccessible from genomic assessment alone. Our methods have also been used in the CPTAC breast and ovarian cancer studies (Mertins et al., 2016; Zhang et al., 2016).

Success of these studies have led to the expansion of the CPTAC program to more cancer types. I am now leading a CPTAC data analysis center at BCM, with first-hand access to all genomics and proteomics data generated on these new cancer types. We also have close collaboration with cancer biologists and clinicians to experimentally validate our computational predictions in cell lines, patient-derived xenografts (PDXs), and clinical trials.

With access to these data and collaborations, my group is working on three key challenges. First, can we use these data to better predict cancer patient survival and treatment response? Second, can we use these data to find more effective treatment strategies? Third, can we make these data easily accessible and useful to cancer researchers without programming skills?

**E-mail:** [bing.zhang@bcm.edu](mailto:bing.zhang@bcm.edu)



### SELECTED PUBLICATIONS

Vasaikar S, Huang C, Wang X, Petyuk VA, Savage SR, Wen B, Dou Y, Zhang Y, Shi Z, Arshad OA, Gritsenko MA, Zimmerman LJ, McDermott JE, Clauss TR, Moore RJ, Zhao R, Monroe ME, Wang YT, Chambers MC, Slebos RJC, Lau KS, Mo Q, Ding L, Ellis M, Thiagarajan M, Kinsinger CR, Rodriguez H, Smith RD, Rodland KD, Liebler DC, Liu T, **Zhang B**; Clinical Proteomic Tumor Analysis Consortium.(2019). Proteogenomic Analysis of Human Colon Cancer Reveals New Therapeutic Opportunities. **Cell**. 177: 1035-1049.e19.

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.

Wang J, Vasaikar S, Shi Z, Greer M, **Zhang B** (2017). WebGestalt 2017: a more comprehensive, powerful, flexible and interactive gene set enrichment analysis toolkit. **Nucleic Acids Res**. 45: W130-W137.

Wang J, Ma Z, Carr SA, Mertins P, Zhang H, Zhang Z, Chan DW, Ellis MJ, Townsend RR, Smith RD, McDermott JE, Chen X, Paulovich AG, Boja ES, Mesri M, Kinsinger CR, Rodriguez H, Rodland KD, Liebler DC, **Zhang B** (2017). Proteome profiling outperforms transcriptome profiling for co-expression based gene function prediction. **Mol Cell Proteomics**. 16: 121-134.

Mertins P, Mani DR, Ruggles KV, Gillette MA, Clauser KR, Wang P, Wang X, Qiao JW, Cao S, Petralia F, Kawaler E, Mundt F, Krug K, Tu Z, Lei JT, Gatza ML, Wilkerson M, Perou CM, Yellapantula V, Huang KL, Lin C, McLellan MD, Yan P, Davies SR, Townsend RR, Skates SJ, Wang J, **Zhang B**, Kinsinger CR, Mesri M, Rodriguez H, Ding L, Paulovich AG, Fenyö D, Ellis MJ, Carr SA; NCI CPTAC (2016). Proteogenomics connects somatic mutations to signalling in breast cancer. **Nature**. 534: 55-62.

Zhang H, Liu T, Zhang Z, Payne SH, Zhang B, (...), **Zhang B**, Snyder MP, Levine DA, Smith RD, Chan DW, Rodland KD; CPTAC Investigators (2016). Integrated proteogenomic characterization of human high-grade serous ovarian cancer. **Cell**. 166: 755-765.

**Zhang B**, Wang J, Wang X, Zhu J, Liu Q, Shi Z, Chambers MC, Zimmerman LJ, Shaddock 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.

Wang X, Slebos RJ, Wang D, Halvey PJ, Tabb DL, Liebler DC, **Zhang B** (2012). Protein identification using customized protein sequence databases derived from RNA-Seq data. **J Proteome Res**. 11: 1009-17. Erratum in: **J Proteome Res**. 2012 Sep 7; 11: 4764.

## LILEI ZHANG, MD, PhD

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

MD, Peking University Health Science Center, Beijing, China

PhD, 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

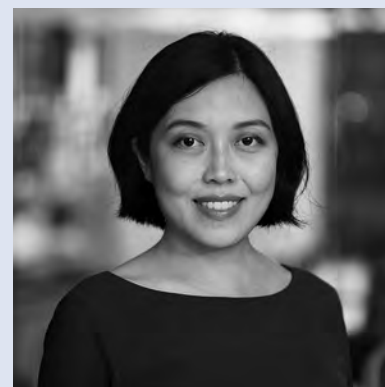
### RESEARCH INTERESTS

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.

E-mail: [Lilei.Zhang@bcm.edu](mailto:Lilei.Zhang@bcm.edu)



### 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<sup>+</sup> 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-ERB $\alpha$  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, Collier 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, Stampler 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 PPAR $\alpha$  Cooperate to Regulate Cardiomyocyte Lipid Gene Expression and Oxidation. **PPAR Res**. 2015: 201625.

## HUI ZHENG, PhD

### HUFFINGTON FOUNDATION ENDOWED CHAIR IN AGING

Professor, Departments of Molecular and Human Genetics, Molecular & Cellular Biology, and Neuroscience

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

Director, Huffington Center on Aging

PhD, 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 neurofibrillary tangles (NFT). Besides the pathological hallmarks, AD is accompanied by profound neuroinflammation marked by reactive astrogliosis and microgliosis. The overarching goals of the laboratory are to understand the fundamental mechanisms underlying AD pathogenesis and identify key pathways for therapeutic targeting. There are two major ongoing projects in the lab: one is to investigate the role of the autophagy-lysosomal pathway (ALP) in NFT pathology; the other is to interrogate the neuron-immune interaction in AD.

NFTs are composed of misfolded tau proteins. The ALP has been implicated in the degradation of protein aggregates. We found that TFEB, a master regulator of autophagy and lysosomal biogenesis, exhibits a potent and selective effect in clearing the pathological tau species and rescuing neurodegeneration in mouse models of tauopathy and our results implicate both cell-autonomous and non-cell-autonomous effects of TFEB in this process. Building on these observations, we are interested to a) probe the intraneuronal mechanisms underlying TFEB-mediated NFT clearance; b) decipher the role of astroglial and microglial TFEB in the cell-to-cell spreading of tau/NFT pathology; c) screen for small molecule TFEB and selective autophagy activators as potential therapy for AD.

Neuroinflammation has long been considered a non-specific and secondary effect in neurodegenerative diseases. However, recent genetic evidence supports a causal role of neuroinflammation in AD pathogenesis. We mapped out a complement-mediated neuron-glia and glia-glia signaling pathway whereby astroglial complement factor C3 interacts with both neuronal and microglial C3aR to modulate spine morphology and phagocytosis and neuroinflammation, respectively. Significantly, the C3-C3aR pathway is prominently elevated in both AD mouse models and human AD brains and our results show that inactivation of C3aR attenuates AD pathology. We have developed tools to isolate different cell types in the brain and we seek to dissect the neuron-immune interaction by a) creating cell-type specific mouse mutants and b) performing cell-type specific molecular and functional analyses. Specific to the astrocytes, we are interested in cataloging the astrocyte subpopulations and determining the role of the diverse astrocyte populations in aging and AD.

E-mail: [huiz@bcm.edu](mailto:huiz@bcm.edu)

Website: [www.bcm.edu/research/labs/hui-zheng/](http://www.bcm.edu/research/labs/hui-zheng/)



### SELECTED PUBLICATIONS

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.

Xu Y, Zhang S, **Zheng H** (2018). The cargo receptor SQSTM1 ameliorates neurofibrillary tangle pathology and spreading through selective targeting of pathological MAPT (microtubule associated protein tau). **Autophagy**. 5: 1-16.

Martini-Stoica H, Cole AL, Swartzlander DB, Chen F, Wan YW, Bajaj L, Bader DA, Lee VMY, Trojanowski JQ, Liu Z, Sardiello M, **Zheng H** (2018). TFEB enhances astroglial uptake of extracellular tau species and reduces tau spreading. **J Exp Med**. 215: 2355-2377.

Swartzlander DB, Propson NE, Roy ER, Saito T, Saido T, Wang B, **Zheng H** (2018). Concurrent cell type-specific isolation and profiling of mouse brains in inflammation and Alzheimer's disease. **JCI Insight**. 3(13). pii: 121109.

Wang B, Li H, Mutlu SA, Bowser DA, Moore MJ, Wang MC, **Zheng H**. The Amyloid Precursor Protein Is a Conserved Receptor for Slit to Mediate Axon Guidance. **eNeuro**. 2017 Jun 15; 4(3). pii: ENEURO.0185-17.2017.

Lian H, Litvinchuk A, Chiang A, Aithmitti N, Jankowsky JL, **Zheng H** (2016). Astrocyte-microglia crosstalk through complement activation modulates amyloid pathology in mouse models of Alzheimer's disease. **J Neurosci**. 36: 577-89.

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, Tagliatela 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.

Justice NJ, Huang L, Tian JB, Cole A, Pruski M, Hunt AJ Jr, Wang B, Wang Z, Sun L, Yang L, Li H, Cole A, Rodriguez-Rivera J, Lu H-C, **Zheng H** (2014). The amyloid precursor protein controls adult hippocampal neurogenesis through GABAergic interneurons. **J Neurosci**. 34: 13314-25.

Polito VA, Li H, Martini-Stoica H, Wang B, Yang L, Xu Y, Swartzlander DB, Palmieri M, di Ronza A, Lee VM, Sardiello M, Ballabio A, **Zheng H** (2014). Selective clearance of aberrant tau proteins and rescue of neurotoxicity by transcription factor EB. **EMBO Mol Med**. 6: 1142-60.

## HUDA Y. ZOGHBI, MD

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

MD, 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. (We co-discovered the gene for spinocerebellar ataxia type 1 (SCA1) in 1993 with Dr. Harry Orr at the University of Minnesota.) Our investigations into the pathogenesis of these two diseases have influenced our understanding of basic neurobiology. 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 to medulloblastoma.

**Polyglutamine Pathogenesis and Neurodegeneration.** 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 (due to haploinsufficiency of its negative regulator, Pum1) causes cerebellar degeneration and ataxia in mice; moreover, we found that haploinsufficiency of *PUM1* causes childhood ataxia and developmental disabilities in humans. We recently discovered that the enhanced function of mutant Ataxin-1 with its native partner Capicua drives the cerebellar ataxia. Thus, to reduce the toxicity of Ataxin-1 and develop therapeutics for SCA1 we have embarked on cross-species genetic screens to identify potentially druggable modulators of Ataxin-1 levels. We have also adapted a similar strategy to find modulators of other disease driving proteins like alpha-synuclein and tau and identified modulators of the levels of these proteins.

**Atoh1 (aka Math1) and Neurodevelopment.** We identified the mouse homolog of the *Drosophila* gene *atonal*, which controls the development and function of the fly's chordotonal organs. *Atoh1* null mice lack cerebellar granule neurons, pontine neurons, hair cells in the vestibular and auditory systems, the D1 interneurons of the spinocerebellar tracts, and Merkel cells. This single gene controls the genesis and/or differentiation of multiple components of the conscious and unconscious proprioceptive pathway and the neurons critical for interoception, neonatal breathing and chemosensitivity. We identified *Atoh1*'s transcriptional targets and revealed its critical role in regulating proliferation and differentiation of granule neuron precursors and how this regulation might go awry in sonic hedgehog-induced medulloblastoma. We are currently focused on identifying the specific roles of certain *Atoh1*-dependent neurons in the hindbrain.

**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 fornical 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. We are now pursuing additional network studies to gain insight into the network dysfunction in Rett syndrome model and how we might manipulate that to improve function. We are also carrying out genetic screens to gain better insight into *MeCP2* regulation and molecular functions, and potentially identify modifiers that might impact the pathogenesis of Rett syndrome and *MECP2* duplication syndrome.

E-mail: [hzoghbi@bcm.edu](mailto:hzoghbi@bcm.edu)



### SELECTED PUBLICATIONS

Suh J, Romano DM, Nitschke L, Herrick SP, DiMarzio BA, Dzhala V, Bae JS, Oram MK, Zheng Y, Hooli B, Mullin K, Gennarino VA, Wasco W, Schmammann JD, Albers MW, **Zoghbi HY**, Tanzi RE (2019). Loss of Ataxin-1 Potentiates Alzheimer's Pathogenesis by Elevating Cerebral BACE1 Transcription. *Cell*. 178: 1159-1175.e17.

Van der Heijden ME, **Zoghbi HY** (2018). Loss of *Atoh1* from neurons regulating hypoxic and hypercapnic chemoresponses causes neonatal respiratory failure in mice. *ELife*. 7. pii: e38455.

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)

Pohodich AE, Yalamanchili H, Raman AT, Wan YW, Gundry M, Hao S, Jin H, Tang J, Liu Z, **Zoghbi HY** (2018). Fornical deep brain stimulation induces gene expression and splicing changes that promote neurogenesis and plasticity. *ELife*. 7. pii: e34031.

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). Fornical deep brain stimulation rescues hippocampal memory in Rett syndrome mice. *Nature*. 526: 430-445. \*Corresponding author. This paper was the subject of a Nature News and Views commentary by Cobb SR., Oct 15; 526: 331-332.

Park J, Al-Ramahi I, Tan Q, Mollema N, Diaz-Garcia JR, Gallego-Flores T, Lu HC, Lagalwar S, Duvick L, Kang H, Lee Y, Jafar-Nejad P, Sayegh LS, Richman R, Liu X, Gao Y, Shaw CA, Arthur JS, Orr HT, Westbrook TF, Botas J, **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, Yoo J, Neul JL, Gong S, Heintz N, Ekker M, Rubenstein J, Noebels JL, Rosenmund C, **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, PHD

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

PhD, University of California, San Diego

Postdoc, University of Illinois at Urbana-Champaign

Postdoc, Harvard University

### RESEARCH INTERESTS

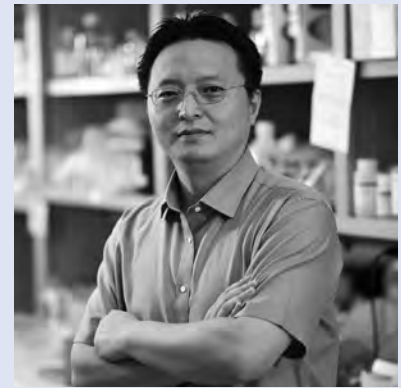
The research of our laboratory lies in the interface between novel single cell technologies and quantitative biology. We pursue the development of new quantitative and high-throughput methods for characterizing **genomic, epigenetic and transcriptional variations at single cell resolution**.

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 the demonstration of the principle, we are able to detect the genomic variations between individual cancer cells. We are interested in detecting early events that drive tumorigenesis as well as the early stage of tumor heterogeneity that will influence later tumor development. The lab will focus on pancreatic cancer in particular.

In addition to the genome, we are also interested in developing novel methods for single cell transcriptional and epigenetic profiling. The goal is to capture the development in action, particularly adult stem cell differentiation. Much finer temporal and spatial resolution will allow us to unveil the early signature transcriptome and epigenome changes, which are often buried among downstream responses by late stage and ensemble profiling. The modeling of complex cellular decision-making processes at multiple layers of pathways and regulatory networks will also be pursued in the lab with the enriched heterogeneous and dynamic information extracted from single cells.

For translational research, we will actively pursue clinical applications of single cell techniques, including prenatal genetic testing as well as early cancer diagnosis.

E-mail: [Chenghang.Zong@bcm.edu](mailto:Chenghang.Zong@bcm.edu)



### SELECTED PUBLICATIONS

Zong CC (2017). Single-cell RNA-seq study determines the ontogeny of macrophages in glioblastomas. **Genome Biol.** 18: 235.

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.

Tian L, Goldstein A, Wang H, Ching Lo H, Sun Kim I, Welte T, Sheng K, Dobrolecki LE, Zhang X, Putluri N, Phung TL, Mani SA, Stossi F, Sreekumar A, Mancini MA, Decker WK, Zong C, Lewis MT, Zhang XH (2017). Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming. **Nature.** 544: 250-254.

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.

So LH, Ghosh A, Zong C, Sepúlveda LA, Segev R, Golding I (2011). General properties of transcriptional time series in *Escherichia coli*. **Nat Genet.** 43: 554-60.

Zong C, So LH, Sepúlveda LA, Skinner SO, Golding I (2010). Lysogen stability is determined by the frequency of activity bursts from the fate-determining gene. **Mol Syst Biol.** 6: 440.

Zeng L, Skinner SO, Zong C, Sippy J, Feiss M, Golding I (2010). Decision making at a subcellular level determines the outcome of bacteriophage infection. **Cell.** 141: 682-91.

**KJERSTI AAGAARD, MD, PHD****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

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

PhD, Mayo Graduate School of Medicine

MD, University of Minnesota Medical School

MSci, 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 Wellcome 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.

E-mail: [aagaardt@bcm.edu](mailto:aagaardt@bcm.edu)

**CHRISTOPHER I. AMOS, PH.D.****J. S. ABERCROMBIE CHAIR - ATHEROSCLEROSIS AND LIPOPROTEIN RESEARCH**

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

PhD, Louisiana State University Medical Center, New Orleans

FACMG, Interinstitute 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 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 for disease.

E-mail: [chrisa@bcm.edu](mailto:chrisa@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.

**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.



## CHRISTIE M. BALLANTYNE, MD

J. S. ABERCROMBIE CHAIR - ATHEROSCLEROSIS AND LIPOPROTEIN RESEARCH

Professor and Vice Chair of Research, Department of Medicine  
Professor, Departments of 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  
Faculty Member, Graduate Program in Development, Disease Models & Therapeutics

MD, 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 pathophysiology of atherosclerosis, focusing on monocyte activation and adhesion. Dr. Ballantyne and his colleagues use targeted homologous recombination to develop mice deficient in particular cell adhesion molecules to study myocardial ischemia-reperfusion injury, vascular injury, and mechanisms by which hyperlipidemia and obesity influence inflammation.

Dr. 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, Dr. 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 response to therapy with the goal of developing personalized diet, lifestyle, and pharmacotherapy based on genetic profile and clinical phenotype.

E-mail: [cmb@bcm.edu](mailto:cmb@bcm.edu)

## ALISON A. BERTUCH, MD, PhD

Associate Professor, Departments of Pediatrics-Hematology/Oncology and Molecular and Human Genetics  
Faculty Member, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics

MS, MD, and PhD, 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.

E-mail: [abertuch@bcm.edu](mailto:abertuch@bcm.edu)

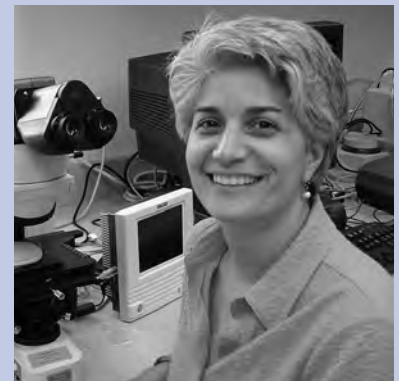


### SELECTED PUBLICATIONS

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

Pokharel Y, Sun W, Polfus LM, Folsom AR, Heiss G, Sharrett AR, Boerwinkle E, **Ballantyne CM**, Hoogeveen RC (2015). Lipoprotein associated phospholipase A2 activity, apolipoprotein C3 loss-of-function variants and cardiovascular disease: the Atherosclerosis Risk In Communities Study. **Atherosclerosis**. 241: 641-8.

Hoogeveen RC, Gaubatz JW, Sun W, Dodge RC, Crosby JR, Jiang J, Couper D, Virani SS, Kathiresan S, Boerwinkle E, **Ballantyne CM** (2014). Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study. **Arterioscler Thromb Vasc Biol**. 34: 1069-77.



### 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.

**MALCOLM BRENNER, MD, PhD****FAYEZ SAROFIM CHAIR**

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

**Founding Director**, Center for Cell & Gene Therapy

**Faculty Member**, Stem Cells and Regenerative Medicine (STaR) Center

*MBChB, University of Cambridge*

*PhD, 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.

**E-mail:** [mbrenner@bcm.edu](mailto:mbrenner@bcm.edu)

**EDWARD C. COOPER, MD, PhD**

**Associate Professor**, Departments of Neurology, Neuroscience, and Molecular and Human Genetics

**Faculty Member**, Postdoctoral Training Program in Brain Disorders and

Development; Graduate Programs in Genetics & Genomics and Neuroscience

*MD, Yale School of Medicine, Yale University, New Haven*

*PhD, 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.

**E-mail:** [ecc1@bcm.edu](mailto:ecc1@bcm.edu)

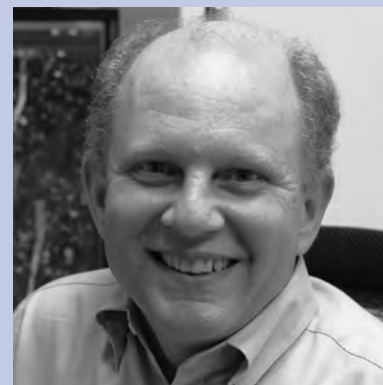
**SELECTED PUBLICATIONS**

Hegde M, Mukherjee, M, Grada Z, (...), **Brenner MK**, et al. (2016). Tandem CAR T cells targeting HER2 and IL13Rα2 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 κ light chains. *J Clin Invest*. 126: 2588-2604.

Papadopoulou A, Gerdemann U, Katari UL, (...), **Brenner MK**, et al. (2014). Activity of Broad-Spectrum T Cells as Treatment for AdV, EBV, CMV, BKV, and HHV6 Infections after HSCT. *Sci Transl Med*. 6: 242-248.

Di Stasi A, Tey SK, Dotti GP, (...), Rooney CM, **Brenner MK** (2011). Inducible Apoptosis as a Safety Switch for Adoptive Cell Therapy. *N Engl J Med*. 365: 1673-83.

**SELECTED PUBLICATIONS**

Millichap JJ, Miceli F, De Maria M, Keator C, Joshi N, Tran B, Soldovieri MV, Ambrosino P, Shashi V, Mikati MA, **Cooper EC**, Tagliatela M (2017). Infantile spasms and encephalopathy without preceding neonatal seizures caused by *KCNQ2* R198Q, a gain-of-function variant. *Epilepsia*. 58: e10-e15.

Lopez AY, Wang X, Xu M, Maheshwari A, Curry D, Lam S, Adesina AM, Noebels JL, Sun QQ, **Cooper EC** (2017). Ankyrin-G isoform imbalance and interneuronopathy link epilepsy and bipolar disorder. *Mol Psychiatry*. 22: 1464-1472.

Millichap JJ, Park KL, Tsuchida T, Ben-Zeev B, Carmant L, (...), Venkatesan C, Weckhuysen S, **Cooper EC** (2016). *KCNQ2* encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. *Neurol Genet*. 2: e96.

**MAURO COSTA-MATTIOLI, PHD****CULLEN FOUNDATION ENDOWED CHAIR**

Associate Professor, Departments of Neuroscience, Molecular and Human Genetics and Molecular and Cellular Biology  
Faculty Member, Graduate Programs in Genetics & Genomics and Neuroscience

PhD, University of Nantes  
Postdoc, McGill University

**RESEARCH INTERESTS**

Memory is essential for the survival of all organisms: for humans, it forms the core of our identity. My laboratory's primary aim is to understand the neurobiological basis of long-term memory formation. We seek to understand what happens in the brain when a memory is formed and more specifically how a labile short-term memory becomes a stable long-term memory. Disorders of learning and memory can strike the brain of individuals during development (e.g., Autism Spectrum Disorder or Down syndrome), as well as during adulthood (e.g., Alzheimer's disease). We are also interested in understanding the specific circuits and/or molecular pathways that are primarily targeted in cognitive disorders and how they can be restored. To tackle these questions, we use a multidisciplinary, convergent and cross-species approach that combines mouse and fly genetics, molecular biology, electrophysiology, imaging, stem cell biology, optogenetics and behavioral techniques.

E-mail: [costamat@bcm.edu](mailto:costamat@bcm.edu)

**SELECTED PUBLICATIONS**

Di Prisco GV, Huang W, Buffington SA, Hsu CC, Bonnen PE, Placzek AN, Sidrauski C, Krnjevic K, Kaufman RJ, Walter P, **Costa-Mattioli M** (2014). Translational control of hippocampal mGluR-dependent long-term depression and object-place learning by eIF2. *Nat Neurosci*. 8: 1073-82.

Buffington S, Huang W, **Costa-Mattioli M** (2014). Translational regulatory mechanism in synaptic plasticity and memory storage. *Ann Rev Neurosci*. 37: 17-38.

**Costa-Mattioli M**, Monteggia LM (2013). mTOR complexes in neurodevelopmental and neuropsychiatric disorders. *Nat Neurosci*. 16: 1537-43.

Huang W, Zhu PJ, Zhang S, Zhou H, Stoica L, Galiano M, Krnjevic K, Roman G, **Costa-Mattioli M** (2013). mTORC2 controls actin polymerization required for consolidation of long-term memory. *Nat Neurosci*. 16: 441-8.

**MARY E. DICKINSON, PHD****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  
Faculty Member, Graduate Program in Genetics & Genomics

BS, Vanderbilt University  
PhD, 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.

E-mail: [mdickins@bcm.edu](mailto:mdickins@bcm.edu)

**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.

## RICHARD H. FINNELL, PHD

**Professor**, Departments of Molecular and Cellular Biology, Medicine, and Molecular and Human Genetics

**Faculty Member**, Center for Precision Environmental Health; Graduate Programs in Genetics & Genomics and Development, Disease Models & Therapeutics

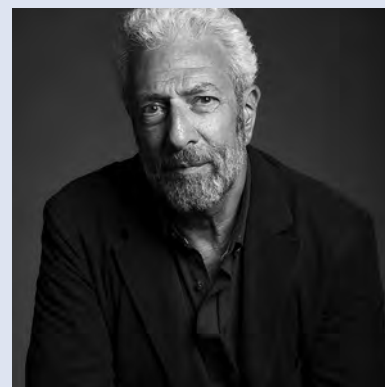
*PhD, University of Oregon Medical School*

*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.

**E-mail:** [finnell@bcm.edu](mailto:finnell@bcm.edu)



### SELECTED PUBLICATIONS

Taiwo TE, Cao X, Cabrera RM, Lei Y, **Finnell RH** (2020). Approaches to studying the genomic architecture of complex birth defects. **Prenat Diagn.** 40: 1047-1055.

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.

Lu HC, Tan Q, Rousseaux MW, (...), **Finnell RH**, (...), Schaaf CP, Zoghbi HY (2017). Disruption of the ATXN1-C1C complex causes a spectrum of neurobehavioral phenotypes in mice and humans. **Nat Genet.** 49: 527-536.

Wallingford JB, Niswander LA, Shaw GM, **Finnell RH** (2013). The continuing challenge of understanding, preventing, and treating neural tube defects. **Science.** 339: 1222002.

## MARGARET A. GOODELL, PHD

**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

**Faculty Member**, Stem Cells and Regenerative Medicine (STaR) Center; Graduate Programs in Cancer & Cell Biology; Development, Disease Models & Therapeutics; and Genetics & Genomics

*PhD, 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.

**E-mail:** [goodell@bcm.edu](mailto:goodell@bcm.edu)



### SELECTED PUBLICATIONS

Hsu JI, Dayaram T, Tovy A, De Braekeleer E, Jeong M, (...), Donehower LA, Takahashi K, **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, (...), Martelli MP, Falini B, **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, (...), 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.

Yang L, Rodriguez B, Mayle A, Park HJ, Lin X, (...), Rau R, Li W, **Goodell MA** (2016). DNMT3A Loss Drives Enhancer Hypomethylation in FLT3-ITD-Associated Leukemias. **Cancer Cell.** 30: 363-365.

## KENDAL D. HIRSCHI, PHD

**Professor**, Departments of Pediatrics and Molecular and Human Genetics  
**Faculty Member**, 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

*PhD, 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.

**E-mail:** kendalh@bcm.edu

## MARTIN M. MATZUK, MD, PHD

### STUART A. WALLACE CHAIR IN PATHOLOGY

**Professor**, Departments of Pathology & Immunology, Molecular & Cellular Biology, Molecular and Human Genetics, and Pharmacology  
**Faculty Member**, Graduate Programs in Cancer & Cell Biology; Chemical, Physical & Structural Biology; and Genetics & Genomics  
**Director**, Center for Drug Discovery

*MD, PhD, 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.

**E-mail:** mmatzuk@bcm.edu



### SELECTED PUBLICATIONS

Pizzio GA, **Hirschi KD**, Gaxiola RA (2017). Conjecture Regarding Posttranslational Modifications to the *Arabidopsis* Type I Proton-Pumping Pyrophosphatase (AVP1). **Front Plant Sci.** 8:1572.

Spinler JK, Karri V, **Hirschi KD** (2019). Planting the Microbiome. **Trends Microbiol.** 27: 90-93.

Primo C, Pizzio GA, Yang J, Gaxiola RA, Scholz-Starke J, **Hirschi KD** (2019). Plant proton pumping pyrophosphatase: the potential for its pyrophosphate synthesis activity to modulate plant growth. **Plant Biol (Stuttg).** 21: 989-996.

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<sup>+</sup> gradient to synthesize pyrophosphate. **J Biol Chem.** 294: 1290-1299.



### SELECTED PUBLICATIONS

Miyata H, Castaneda JM, Fujihara Y, (...), Ikawa M, **Matzuk MM** (2016). Genome engineering uncovers 54 evolutionarily conserved and testis-enriched genes that are not required for male fertility in mice. **Proc Natl Acad Sci U S A.** 113: 7704-10.

Castaneda J, **Matzuk MM** (2015). Toward a rapid and reversible male pill. **Science.** 350: 385-6.

Nagashima T, Li Q, Clementi C, Lydon JP, DeMayo FJ, **Matzuk MM** (2013). BMP2 is required for postimplantation uterine function and pregnancy maintenance. **J Clin Invest.** 123: 2539-50.

Peng J, Li Q, Wigglesworth K, Rangarajan A, Kattamuri C, Peterson RT, Eppig JJ, Thompson TB, **Matzuk MM** (2013). Growth differentiation factor 9: bone morphogenetic protein 15 heterodimers are potent regulators of ovarian functions. **Proc Natl Acad Sci U S A.** 110: E776-85.

**DAVID D. MOORE, PHD**

THE R. P. DOHERTY, JR. WELCH CHAIR IN SCIENCE

Professor, Departments of Molecular &amp; Cellular Biology and Molecular and Human Genetics

Faculty Member, USDA/ARS Children's Nutrition Research Center; Graduate Program in Genetics &amp; Genomics

PhD, University of Wisconsin-Madison

Postdoc, University of California, San Francisco

**RESEARCH INTERESTS****Nuclear Hormone Receptors Regulate Metabolism and Cancer**

The 48 nuclear hormone receptors function as ligand-dependent or, in some cases, ligand-independent transcription factors. The major goal of this laboratory is to understand the impact of these receptors on metabolic and oncogenic pathways in the liver.

One major focus is on CAR, which regulates the response of the liver to xenobiotics, potentially toxic foreign compounds. CAR activation increases the liver's ability to metabolize and eliminate xenobiotics. CAR-dependent responses are generally protective, but chronic CAR activation results in liver tumors due to direct effects of CAR on hepatocyte proliferation and apoptosis. We are pursuing both the mechanism of this tumor promotion and therapeutic approaches that block it.

The fasted liver oxidizes fatty acids and makes glucose, while the fed liver utilizes glucose and makes fatty acids. PPAR $\alpha$  activation in the fasted liver promotes fatty acid oxidation, and FXR activation in the fed liver represses both pathways. We recently found that PPAR $\alpha$  and FXR also have mutually antagonistic impact on autophagy. We are extending this to assess the broader roles of these two nutrient sensitive nuclear receptors in liver energy balance.

E-mail: [moore@bcm.edu](mailto:moore@bcm.edu)**ANTHONY MUSTOE, PHD**

Assistant Professor, Departments of Biochemistry and Molecular Biology and Molecular and Human Genetics

Faculty Member, Therapeutic Innovation Center (THINC)

CPRIT Scholar in Cancer Research

BS, Washington University

PhD, 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 the structures of mRNA untranslated regions modulate targeting by microRNAs and RNA binding proteins. We are further interested in how mRNA misfolding can lead to dysregulation and disease, particularly cancer. We additionally have ongoing collaborations with a number of groups investigating the structure and function of diverse biomedically important RNAs.

E-mail: [Anthony.Mustoe@bcm.edu](mailto:Anthony.Mustoe@bcm.edu)**SELECTED PUBLICATIONS**

Gomez-Ospina N, Potter CJ, Xiao R, Manickam K, (...), **Moore DD** (2016). Mutations in the nuclear bile acid receptor FXR cause progressive familial intrahepatic cholestasis. *Nat Commun.* 7: 10713.

Wooton-Kee CR, Jain AK, Wagner M, Grusak MA, Finegold MJ, Lutsenko S, **Moore DD** (2015). Elevated copper impairs hepatic nuclear receptor function in Wilson's disease. *J Clin Invest.* 125: 3449-60.

Lee JM, Martin Wagner M, Xiao R, Kim KH, Feng D, Lazar MA, **Moore DD** (2014). Nutrient Sensing Nuclear Receptors Coordinate Autophagy. *Nature.* 516: 112-5.

Lee JM, Lee YK, Mamrosh JL, Busby SA, Griffin PR, Pathak MC, Ortlund EA, **Moore DD** (2011). A nuclear-receptor-dependent phosphatidylcholine pathway with antidiabetic effects. *Nature.* 474: 506-10.

**SELECTED PUBLICATIONS**

**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.

**Mustoe AM**, Brooks CL, AHashimi HM (2014). Hierarchy of RNA functional dynamics. *Annu Rev Biochem.* 83: 441-66.

## JEFFREY L. NOBELS, MD, PhD

### THE CULLEN TRUST FOR HEALTH CARE ENDOWED CHAIR IN NEUROGENETICS

Professor, Departments of Neurology, Neuroscience, and Molecular and Human Genetics

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

Director, Blue Bird Circle Developmental Neurogenetics Laboratory

PhD, Stanford University

MD, 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 monogenic hyperexcitability and synchronization defects in Alzheimer's Disease, heralding a paradigm change in understanding the basis for cognitive decline. Two other current projects center on genes linking epilepsy with lethal cardiac arrhythmias, and peritumoral epilepsy in glioblastoma. We trace the biology of the mutant circuitry 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.

E-mail: [jnoebels@bcm.edu](mailto:jnoebels@bcm.edu)

## PAUL A. OVERBEEK, PhD

Professor, Departments of Molecular & Cellular Biology, Molecular and Human Genetics, and Neuroscience

Faculty Member, Graduate Programs in Cancer & Cell Biology

PhD, University of Michigan

MBA, University of Chicago

Postdoc, National Institute of Child Health and Human Development, NIH

### RESEARCH INTERESTS

My laboratory studies the molecular pathways of cell fate determination. Two different strategies are used. Both strategies make use of transgenic mice. In the first strategy, differentiation decisions are studied and altered in a model organ, the eye. In the second system, random insertional mutations are used to identify novel genes that are required for normal embryogenesis.

For our studies of ocular development, we use cell-specific promoters to alter the patterns of expression of growth factors, growth factor receptors, signal transduction proteins, transcription factors, and cell cycle regulatory proteins during ocular development. Recently, we have analyzed the epigenetic regulation of lens induction. We are currently using the CRISPR/Cas9 system to alter the cis-acting sequences that regulate expression of Pax6 and BMP-4, two genes that are essential for lens induction.

We also generate and characterize mice with novel developmental mutations. We have generated and analyzed mutations that affect left-right asymmetry, sex determination, hair follicle induction, CNS morphogenesis, craniofacial development, skin maturation, growth, fertility, and social behavior.

E-mail: [overbeek@bcm.edu](mailto:overbeek@bcm.edu)



### SELECTED PUBLICATIONS

Klassen T, Davis C, Goldman A, Burgess D, Chen T, Wheeler D, McPherson J, Bourquin T, Lewis L, Villasana D, Morgan M, Muzny D, Gibbs R, **Noebels J** (2011). Exome sequencing of ion channel genes reveals complex profiles confounding personal risk assessment in epilepsy. *Cell*. 145: 1036-48.

John Lin CC, Yu K, Hatcher A, Huang TW, Lee HK, Carlson J, Weston MC, Chen F, Zhang Y, Zhu W, Mohila CA, Ahmed N, Patel AJ, Arenkiel BR, **Noebels JL**, Creighton CJ, Deneen B (2017). Identification of diverse astrocyte populations and their malignant analogs. *Nat Neurosci*. 20: 396-405.

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

Meyer J, Maheshwari A, **Noebels J**, Smirnakis S (2018). Asynchronous suppression of visual cortex during absence seizures in stargazer mice. *Nat Commun*. 9: 1938.



### SELECTED PUBLICATIONS

Fu C, Begum K, Jordan PW, He Y, **Overbeek PA** (2016). Dearth and Delayed Maturation of Testicular Germ Cells in Fanconi Anemia E Mutant Male Mice. *PLoS One*. 11: e0159800.

Badal SS, Wang Y, Long J, Corcoran DL, Chang BH, Truong LD, Kanwar YS, **Overbeek PA**, Danesh FR (2016). miR-93 regulates Msk2-mediated chromatin remodelling in diabetic nephropathy. *Nat Commun*. 7: 12076.

Wolf L, Harrison W, Huang J, Xie Q, Xiao N, Sun J, Kong L, Lachke SA, Kuracha MR, Govindarajan V, Brindle PK, Ashery-Padan R, Beebe DC, **Overbeek PA**, Cvekl A (2013). Histone posttranslational modifications and cell fate determination: lens induction requires the lysine acetyltransferases CBP and p300. *Nucleic Acids Res*. 41: 10199-10214.

## DONALD W. (WILL) PARSONS, MD, PHD

Associate Professor, Departments of Pediatrics - Hematology-Oncology and Molecular and Human Genetics; Pathology & Immunology; Human Genome Sequencing Center  
Faculty Member, Graduate Program in Genetics & Genomics

*PhD, Department of Pathology, Ohio State University College of Medicine*  
*MD, 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.

E-mail: [dwpanson@bcm.edu](mailto:dwpanson@bcm.edu)

## SHARON E. PLON, MD, PHD

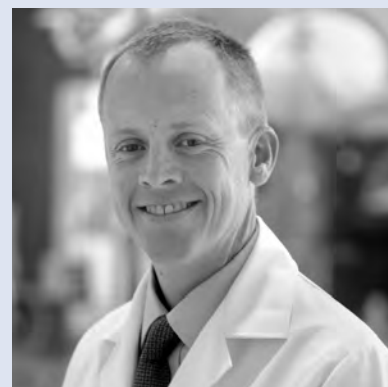
Professor, Departments of Pediatrics and Molecular and Human Genetics and Human Genome Sequencing Center  
Faculty Member, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics  
Director, MD/PhD Medical Scientist Training Program  
Director, Cancer Genetics Clinical and Research Programs, Texas Children's Hospital

*MD, PhD, 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

The overall goal of my laboratory is to understand the underlying genomic mechanisms that result in tumor development and the genetic predisposition to cancer. We have carried out whole genome and exome sequencing analyses through a collaboration with the Human Genome Sequencing Center on families with radiation sensitivity and/or unusual patterns of childhood cancer. We recently identified a new recessive disorder due to mutations in the *NSMCE3* gene that impacts chromosome segregation. With regard to clinical research, we are completing a clinical trial investigating the impact of adding whole exome sequencing of tumor and blood into the care of newly diagnosed childhood cancer patients. I am also one of the principal investigators of the Clinical Genome Resource (ClinGen) which is developing databases and websites to improve the clinical interpretation of genetic variation.

E-mail: [splon@bcm.edu](mailto:splon@bcm.edu)



### 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.



### SELECTED PUBLICATIONS

van der Crabben SN, Hennis MP, McGregor G, Ritter DJ, Nagamani SC, (...), Pearl LH, **Plon SE\***, Murray JM\*, van Haafden G\* (2016). Destabilized SMC5/6 complex leads to chromosome breakage syndrome with severe lung disease. **J Clin Invest.** 126: 2881-92. \*Co-corresponding authors

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.

Rehm HL, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, Ledbetter DH, Maglott DR, Martin CL, Nussbaum RL, **Plon SE**, Ramos EM, Sherry ST, Watson MS (2015). ClinGen: The Clinical Genome Resource. **N Engl J Med.** 372: 2235-42.



## NOAH F. SHROYER, PHD

Associate Professor, Departments of Medicine-Gastroenterology and Hepatology and Molecular and Human Genetics

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

Adjunct Associate Professor, Department of Pediatrics-Gastroenterology, Hepatology & Nutrition, Cincinnati Children's Hospital

PhD, 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.

E-mail: [noah.shroyer@bcm.edu](mailto:noah.shroyer@bcm.edu)

## IGNATIA B. VAN DEN VEYVER, MD

Professor, Departments of Obstetrics & Gynecology and Molecular and Human Genetics

Director of Clinical Prenatal Genetics, Department of Molecular and Human Genetics

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

MD, 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. We collect clinical data on girls paired with genome-wide sequencing to find the mutation that causes AIC. For my clinical translational research, I investigate benefits and challenges of introducing new genomic technologies, such as arrays, non-invasive screening, and genome-wide sequencing into prenatal diagnosis and care.

E-mail: [iveyver@bcm.edu](mailto:iveyver@bcm.edu)



### 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  $\beta$ -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.



### SELECTED PUBLICATIONS

Crossland RF, Balasa A, Ramakrishnan R, Mahadevan SK, Fiorotto ML, **Van den Veyver IB** (2017). Chronic Maternal Low-Protein Diet in Mice Affects Anxiety, Night-Time Energy Expenditure and Sleep Patterns, but Not Circadian Rhythm in Male Offspring. *PLoS One.* 12: e0170127.

Wong BK, Sutton VR, Lewis RA, **Van den Veyver IB** (2017). Independent variant analysis of TEAD1 and OCEL1 in 38 Aicardi syndrome patients. *Mol Genet Genomic Med.* 5: 117-21.

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.

**JAMES VERSALOVIC, MD, PHD****MILTON J. FINEGOLD PROFESSOR OF PATHOLOGY & IMMUNOLOGY**

Vice Chair of Molecular Pathology and Omics, Department of Pathology &amp; Immunology

Professor, Departments of Pediatrics, Molecular and Human Genetics and Molecular Virology &amp; 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

Faculty Member, Graduate Program in Immunology &amp; Microbiology

MD, PhD, 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.

E-mail: [jamesv@bcm.edu](mailto:jamesv@bcm.edu)**CHERYL WALKER, PHD****MARGARET AND ALBERT ALKEK PRESIDENTIAL CHAIR IN ENVIRONMENTAL HEALTH**

Director, Center for Precision Environmental Health

Professor, Departments of Molecular &amp; Cellular Biology, Medicine, and Molecular and Human Genetics

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

Director, NIH T32 Training Program in Precision Environmental Health

BA in Molecular, Cellular and Developmental Biology, University of Colorado-Boulder, 1977

PhD 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 (Walker and Ho Nature Reviews Cancer 2012, Walker et. al. Nature Reviews in Endocrinology 2018). 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.

**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 Cell 2016). 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.

E-mail: [cheryl.walker@bcm.edu](mailto:cheryl.walker@bcm.edu)**SELECTED PUBLICATIONS**

Hemarajata P, Spinler JK, Balderas MA, **Versalovic J** (2014). Identification of a proton-chloride antiporter (EriC) by Himar1 transposon mutagenesis in *Lactobacillus reuteri* and its role in histamine production. **Antonie Van Leeuwenhoek**. 105: 579-92.

Thomas CM, Hong T, van Pijkeren JP, Hemarajata P, Trinh DV, Hu W, Britton RA, Kalkum M, **Versalovic J** (2012). Histamine derived from probiotic *Lactobacillus reuteri* suppresses TNF via modulation of PKA and ERK signaling. **PLoS One**. 7: e31951.

Preidis GA, Saulnier DM, Blutt SE, Mistretta TA, Riehle KP, Major AM, Venable SF, Barrish JP, Finegold MJ, Petrosino JF, Guerrant RL, Conner ME, **Versalovic J** (2012). Host Response to Probiotics Determined by Nutritional Status of Rotavirus-infected Neonatal Mice. **J Pediatr Gastroenterol Nutr**. 55: 299-307.

**SELECTED PUBLICATIONS**

Chiang YC, Park IY, Terzo EA, (...), Dere R, **Walker CL**, Rathmell WK (2018). *SETD2* Haploinsufficiency for Microtubule Methylation Is an Early Driver of Genomic Instability in Renal Cell Carcinoma. **Cancer Res**. 78: 3135-3146.

Foulds CE, Treviño LS, York B, **Walker CL** (2017). Endocrine-disrupting chemicals and fatty liver disease. **Nat Rev Endocrinol**. 13: 445-457.

Wang Q, Trevino LS, Wong RL, (...), **Walker CL** (2016). Reprogramming of the Epigenome by MLL1 Links Early-Life Environmental Exposures to Prostate Cancer Risk. **Mol Endocrinol**. 30: 856-71.

Park IY, Powell RT, Tripathi DN, Dere R, Ho TH, Blasius TL, Chiang YC, Davis IJ, Fahey CC, Hacker KE, Verhey KJ, Bedford MT, Jonasch E, Rathmell WK, **Walker CL** (2016). Dual Chromatin and Cytoskeletal Remodeling by *SETD2*. **Cell**. 166: 950-62.

## ROBERT A. WATERLAND, PHD

Professor, Departments of Pediatrics and Molecular and Human Genetics  
Faculty Member, USDA/ARS Children's Nutrition Research Center; Graduate Program in Genetics & Genomics

PhD, 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.

E-mail: [waterland@bcm.edu](mailto:waterland@bcm.edu)

## MINGSHAN XUE, PHD

Assistant Professor, Departments of Neuroscience and Molecular and Human Genetics

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

Investigator, Jan and Dan Duncan Neurological Research Institute

PhD, 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 different classes of neurons in the mammalian cortical circuits interact with one another through the synapses and how dysfunction or abnormal development of these circuits contributes to the pathogenesis of neurodevelopmental disorders. 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, our current research focuses on the mechanisms underlying circuit dysfunctions in mouse models of autism and epileptic encephalopathies, and gene therapies for these disorders.

E-mail: [mxue@bcm.edu](mailto:mxue@bcm.edu)



### SELECTED PUBLICATIONS

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.

Van Baak TE, Coarfa C, Dugué PA, Fiorito G, Laritsky E, (...), **Waterland RA** (2018). Epigenetic supersimilarity of monozygotic twin pairs. **Genome Biol.** 19: 2.

Eclarinal JD, Zhu S, Baker MS, Piyarathna DB, Coarfa C, Fiorotto ML, **Waterland RA** (2016). Maternal exercise during pregnancy promotes physical activity in adult offspring. **FASEB J.** 30: 2541-8.

Kessler NJ, Van Baak T, Baker MS, Laritsky E, Coarfa C, **Waterland RA** (2016). CpG methylation differences between neurons and glia are highly conserved from mouse to human. **Hum Mol Genet.** 25: 223-32.



### SELECTED PUBLICATIONS

Chen W, Cai ZL, Chao ES, (...), Zoghbi HY, Tang J, Swann JW, **Xue M** (2020). Stxbp1/Munc18-1 haploinsufficiency impairs inhibition and mediates key neurological features of STXBP1 encephalopathy. **ELife.** 9: e48705.

Messier JE, Chen H, Cai ZL, **Xue M** (2018). Targeting light-gated chloride channels to neuronal somatodendritic domain reduces their excitatory effect in the axon. **ELife.** 7: e38506.

Yin J, Chen W, Chao ES, Soriano S, Wang L, Wang W, Cummock SE, Tao H, Pang K, Liu Z, Pereira FA, Samaco RC, Zoghbi HY, **Xue M**, Schaaf CP (2018). Otud7a knockout mice recapitulate many neurological features of 15q13.3 microdeletion syndrome. **Am J Hum Genet.** 102: 296-308.

Meng X, Wang W, Lu H, (...), Tang J, **Xue M**, Zoghbi HY (2016) Manipulations of MeCP2 in glutamatergic neurons highlight their contributions to Rett and other neurological disorders. **ELife.** 5: e14199.

# BAYLOR COLLEGE OF MEDICINE

Located in Houston, Baylor College of Medicine is the only private medical school in the Greater Southwest. Since its founding in 1900, The College has grown into a health science university that is internationally recognized as a premiere academic health science center. The College is known for excellence in education, research and patient care.

In 1903, the medical school began an affiliation with Baylor University that lasted until 1969, when Baylor College of Medicine became an independent institution. Originally located in Dallas, the College moved to Houston in 1943 to become the educational cornerstone of the Texas Medical Center.

Baylor College of Medicine is co-owner of Baylor St. Luke's Medical Center and has affiliations with seven additional teaching hospitals, each known for medical excellence. It also ranks consistently among the top U.S. medical schools in funding for research and development. Baylor College of Medicine received **\$426 million** in total funding from 2,409 sponsored project awards in fiscal year 2016.



*Baylor College of Medicine Medical Center McNair Campus*

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.

Although the member institutions of the TMC operate under independent direction, there is considerable inter-institutional cooperation and scientific collaboration. Frequent seminars permit students and faculty of the many institutions to benefit from the broad base of local scientific expertise.

The Texas Medical Center is home to the World's largest children's hospital, Texas Children's Hospital, and the World's largest cancer hospital, the University of Texas MD Anderson Cancer Center. The TMC has 10 million visits per year and over 106,000 people are employed at its

member institutions. It has the highest concentration of life sciences professionals in the country.

Adjacent to the Museum District, The Texas Medical Center is located in one of the most attractive areas in Houston. The TMC adjoins the trees and ponds of Hermann Park, with its zoo, golf course, fountains, hike-and-bike trails, and children's areas such as playgrounds, ponds, and a miniature railroad. Both the nearby University of Houston and Rice University add to the youthful, academic ambience of this section of the city. There are many cafés, bookstores, music and theater groups, film series, and art exhibits.



*Texas Children's Pavilion for Women and Texas Children's Hospital*

# HOUSTON

**W**hen you think about Houston, do you envision cowboys and tumbleweeds? Well, forget those ideas. Contrary to these preconceived notions, Houston – the fourth most populous city in the United States – boasts modern industries, a thriving intellectual and cultural environment, lush vegetation, and much more.

Houston is an international city that is a leader in the arts, education, 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 to.



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

**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.

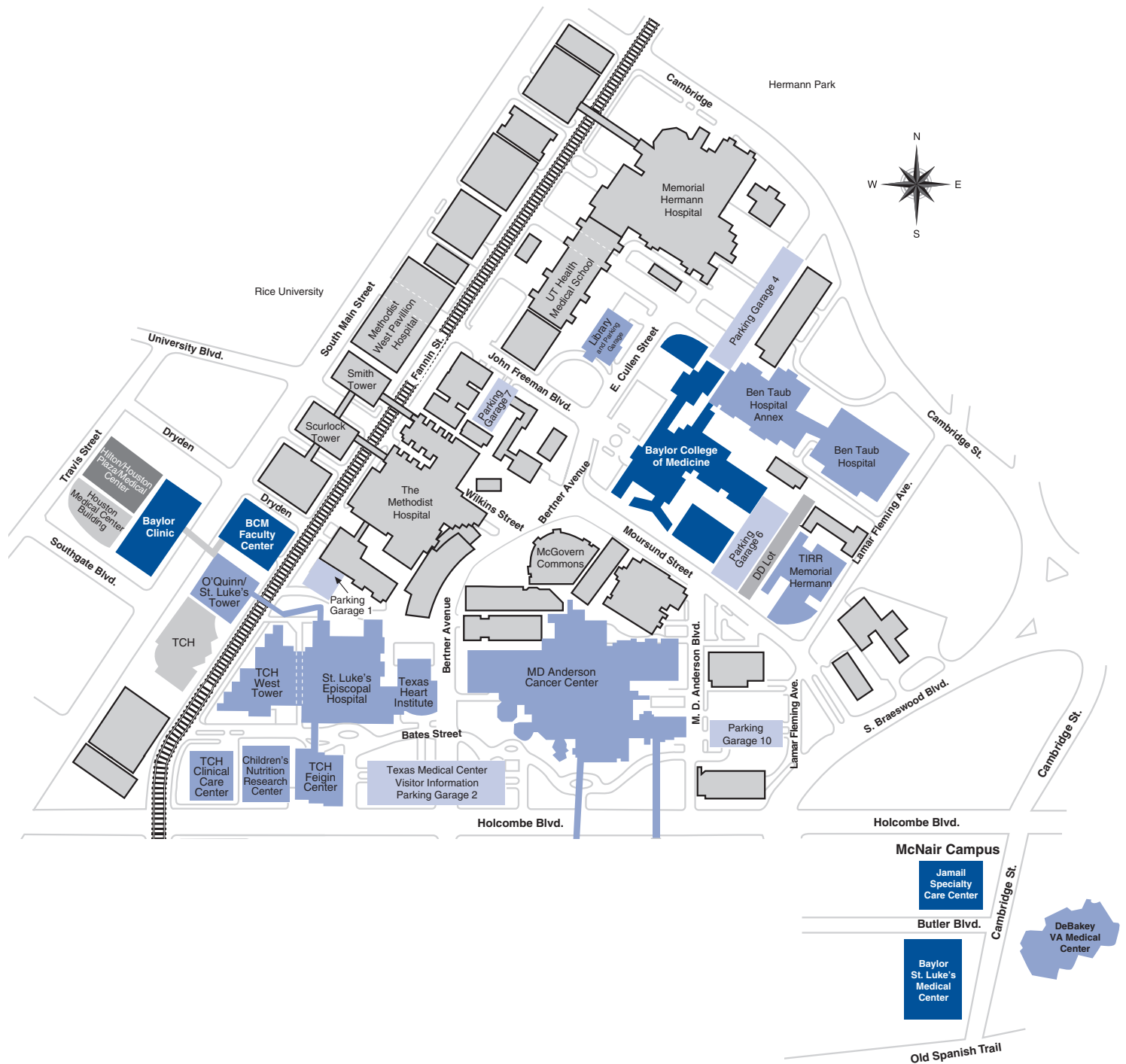
**The food:** Houston has 11,000 restaurants (and counting!), which serve every type of cuisine you could think of, both brick-and-mortar establishments and food trucks. It's not just BBQ and Tex-Mex (though you're missing out if you haven't tried these cuisines here).

**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](http://bcm.edu/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 link to our website or visit [bcm.edu/genetics](http://bcm.edu/genetics)