Baylor College of Medicine

# MOLECULAR AND HUMAN GENETICS 2025

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# MOLECULAR AND HUMAN GENETICS

Baylor College of Medicine

BCM.EDU/GENETICS

# MESSAGE FROM THE CHAIR

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

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

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

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

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

The Baylor College of Medicine Undiagnosed Diseases Center houses our NIH Undiagnosed Diseases Network clinical site and continues to provide clinical services and genetic testing and analysis to assess patients who have not received a diagnosis for their condition. The NIH-supported Project GIVE study has also advanced in its mission to address disparity in access to genomic care for underserved families in the Rio Grande Valley and in west Texas. Both the Undiagnosed Diseases Center and Project GIVE use the Consultagene platform to provide access to genetic evaluation, peer-to-peer consultation and genetic counseling.

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

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

Best regards,

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

# CONTENTS

# ABOUT THE DEPARTMENT


*Huda Zoghbi, M.D.*


*Richard Gibbs, Ph.D.*

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

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

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

Among genetics departments at U.S. medical schools, we continue to rank highest in both the number of grants and total funding from the National Institutes of Health for 13 consecutive years. Our facilities are equipped with state-of-the-art instrumentation for research in molecular, cellular and biochemical genetics. There are several specialized research centers that galvanize collaboration among faculty at Baylor, as well. We have also extended our mission globally with a center for medical genetics at the Chinese University of Hong Kong and the joint venture diagnostic laboratory, Baylor Genetics, with H.U. Group Holdings, Inc. The Department's various research, clinical and administrative activities currently occupy over 110,000 square feet of space. Because of this rich environment, the Department continues to be a magnet for trainees interested in genetics while continuing to grow in breadth, depth and accomplishments.

# DEPARTMENT LEADERSHIP

**CHAIRMAN**

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

**DEPARTMENT ADMINISTRATOR**

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

**FACULTY ADVISORY COMMITTEE**

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

Christine Eng, M.D.

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

Kim Worley, Ph.D.
Basic & Translational

Sandesh Nagamani, M.D.
Clinical

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

Gad Shaulsky, Ph.D.
Graduate Education

Lorraine Potocki, M.D.
Undergraduate Medical Education

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

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

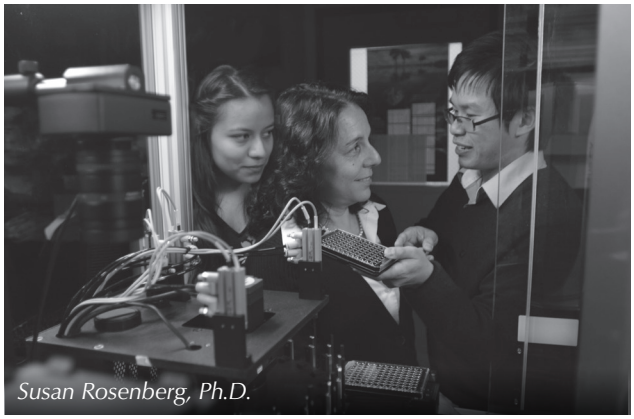
**CLINICAL AFFAIRS**
**Vice Chair**

Carlos Bacino, M.D.

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

Debra Murray, Ph.D.

Gladys Pryor, B.S.



*Susan Rosenberg, Ph.D.*

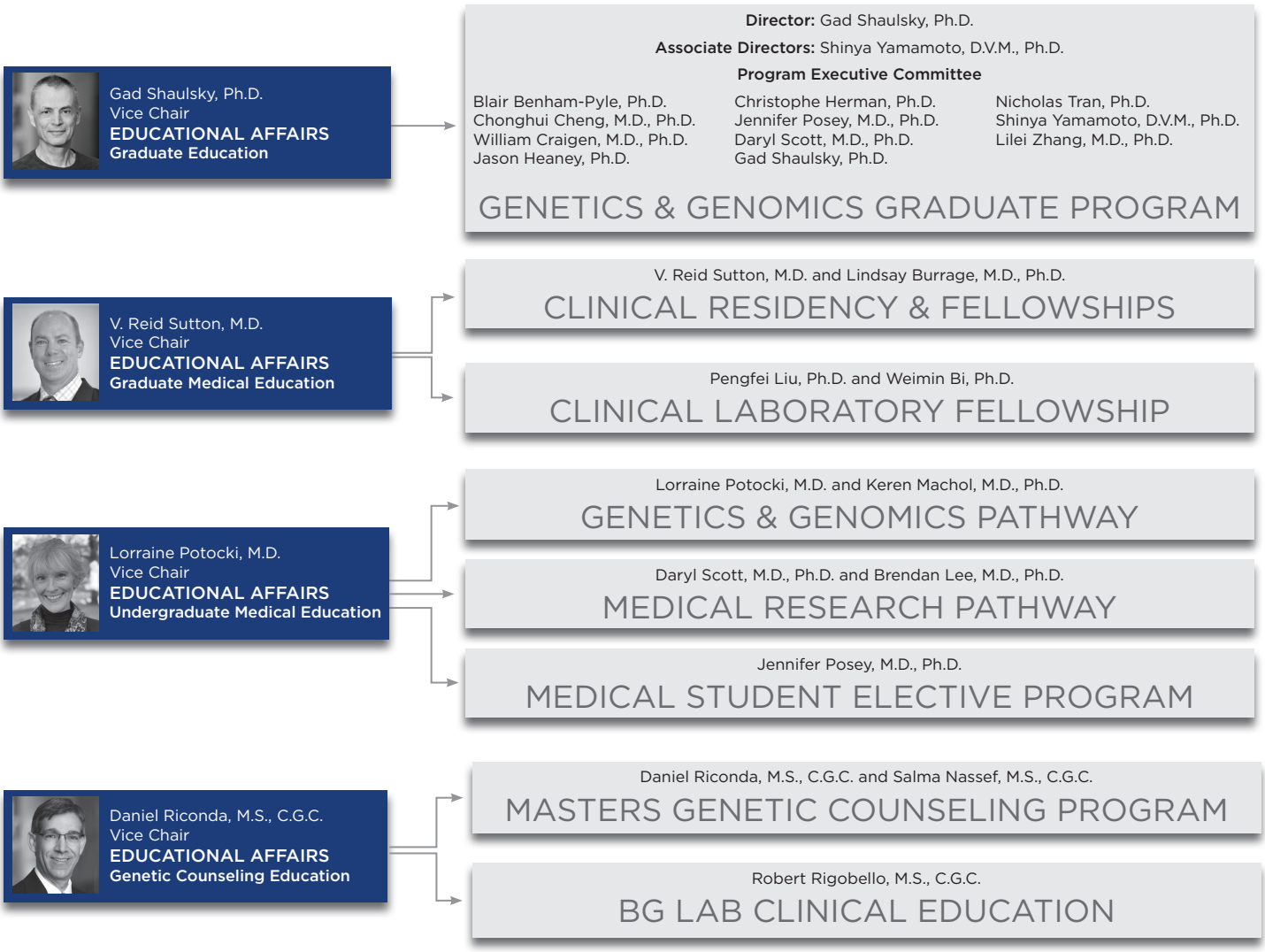

*Penelope Bonnen, Ph.D. and Alison Bertuch, M.D., Ph.D.*

*Joshua Shulman, M.D., Ph.D.*

*Ben Arenkiel, Ph.D.*

# GRADUATE AND MEDICAL EDUCATION

## DIVISION OF EDUCATIONAL AFFAIRS




## GRADUATE PROGRAM IN GENETICS & GENOMICS

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

The program requires a full-time commitment to graduate studies and research. To encourage our students to fulfill their potential and excel in their work, we provide a competitive stipend, which stretches further in Houston where the cost of living is lower than in other large U.S. cities. Students who enroll in 2025-2026 will receive $38,625 per year. Tuition, medical and dental insurance also are provided. Students who obtain funding through personal fellowships receive an additional $3,000 bonus from the Dean of the Graduate School.

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

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

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


*Gad Shaulsky, Ph.D.*

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

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

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

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

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

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

### Program Leadership
Gad Shaulsky, Ph.D., Director
Shinya Yamamoto, D.V.M., Ph.D., Associate Director

### Graduate Program Administrator
Judi Coleman

## MEDICAL STUDENT EDUCATION

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

The goals of the Genetics & Genomics Pathway include building upon the foundation of basic genetic principles provided in the pre-clerkship curriculum with additional educational experiences in medical genetics; enhancing the medical student experience to include a broad range of patients with genetic conditions; developing the student's appreciation for the nuances inherent in performing and interpreting clinical diagnostic analyses in biochemical genetics, molecular genetics and cytogenetics; providing an interface with the community and patient advocacy organizations to enhance the student's awareness of the social concerns faced by patients and families affected with genetic disorders; preparing students to author a scholarly publication and/or presentation; and providing students a means to network and discuss various topics and career paths in medical genetics.

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

## POSTDOCTORAL RESEARCH TRAINING

The faculty of the Department of Molecular and Human Genetics have broad expertise and have mentored hundreds of postdoctoral trainees. Faculty research projects range from seeking answers to basic science questions to ones that are immediately clinically applicable. Specific research interests are outlined in the profile of each faculty member. Applications for and inquiries regarding research postdoctoral training should be addressed to the specific faculty member.

## RESIDENCY AND FELLOWSHIP TRAINING PROGRAMS

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

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

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

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

*Recent graduates and incoming trainees of the Medical Genetics Residency & Clinical Laboratory Fellowship Programs*

accredited by the ACGME. Baylor offers two-year fellowship training in both programs. LGG is a specialty of the ABMGG that incorporates training in both molecular and cytogenetic techniques, clinical interpretation and laboratory management in a single 24-month program.

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

Fellows have the opportunity to participate in clinical test validations, take part in the ongoing assay developments and improvements and develop research projects that are often translational in scope. The integrated training provided by the fellowship programs prepare those who wish to become laboratory directors in academic or commercial diagnostic centers as well as those who wish to lead projects focusing on clinical genetic and genomic diagnostics.

### Program Leadership

V. Reid Sutton, M.D., Director of Clinical Residency and Fellowship Programs
Lindsay Burrage, M.D., Ph.D., Associate Program Director of Residency Programs
Chaya Murali, M.D., Assistant Program Director of Residency Programs
Pengfei Liu, Ph.D., LGG Program Director
Weimin Bi, Ph.D., LGG Associate Program Director

### ABMGG Residency & Fellowship Program Coordinator

Kara Mitchell

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

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

The aims of the Center are to design, establish and conduct professional development activities and training in medical genetics and genetic counseling to fit the increasing need in Asia; establish a leading referral center in Asia for prenatal and postnatal diagnosis and treatment for patients and families affected by genetic disorders; 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 host an annual pan-Asian symposium on state-of-the-art clinical genetics care and research.

**Center Director:** Fernando Scaglia, M.D.

*Genetic Counseling Program class of 2025*

## GENETIC COUNSELING PROGRAM

The Baylor College of Medicine Genetic Counseling Program was accredited in February 2018 and graduated its first class of eight students in June 2020. The program now admits 10 students each year. The 21-month Master of Science degree program is housed under the School of Health Professions and was founded with the financial and logistical support of the Department of Molecular and Human Genetics. The program provides students a transformative education in genomic medicine and the practice of genetic counseling. The outstanding clinical, laboratory and research faculty empower graduates to be empathic professionals with effective critical thinking skills. Clinical rotations include a variety of clinics offered both in-person and via telehealth with the following services: pediatric genetics at Texas Children's Hospital, adult genetics at the Michael E. Debakey VA Medical Center, Harris Health System and Baylor Medicine at McNair Campus, and prenatal and reproductive genetics at Texas Children's Pavilion for Women and Consultagene Clinic, among others. Program differentiators include the variant interpretation and counseling course developed in collaboration with the diagnostic laboratory, Baylor Genetics, and the diverse research opportunities available within the department and across the Texas Medical Center.

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

# DIVISION OF CLINICAL AFFAIRS

Carlos Bacino, M.D.
Vice Chair
**CLINICAL AFFAIRS**

Carlos Bacino, M.D.
Director
**Pediatrics Genetics Service**

Shweta Dhar, M.D.
Director
**Adult Genetics Service**

Igna Van den Veyver, M.D.
Director
**Prenatal and Reproductive Genetics Service**

Pilar Magoulas, M.S., C.G.C.
Director
**Genetic Counseling Service**

Sandesh Nagamani, M.D.
Director
**Clinical Research Service**

Fernando Scaglia, M.D.
Director
**BCM-CUHK Center for Medical Genetics Hong Kong**

**TEXAS CHILDREN'S HOSPITAL**

**General** - Chief: Carlos Bacino, M.D.

**Metabolic** - Chief: V. Reid Sutton, M.D.

**Neurofibromatosis & Phakomatoses** - Chief: William Craigen, M.D., Ph.D.

**Skeletal Dysplasia** - Chief: Brendan Lee, M.D., Ph.D.

**Angelman Syndrome** - Chief: Carlos Bacino, M.D.

**Renal Genetics** - Chief: Mir Reza Bekheirnia, M.D.

**Gender Medicine** - Chief: V. Reid Sutton, M.D.

**Neurogenetics** - Chief: Lisa Emrick, M.D.

**Consultagene and Consult Service** - Chief: Seema Lalani, M.D.

**Smith-Magenis Clinic** - Chief: Lorraine Potocki, M.D.

**Mitochondrial Medicine** - Co-Chiefs: Fernando Scaglia, M.D. & Lisa Emrick, M.D.

PEDIATRIC GENETICS

**BAYLOR MEDICINE**

**General** - Chief: Shweta Dhar, M.D.

**Bone** - Chief: Sandesh Nagamani, M.D.

**Cardiovascular** - Chief: Lilei Zhang, M.D.

**Cancer** - Chief: Shweta Dhar M.D., M.S.

**Neurogenetics** - Chief: Laurie Robak, M.D., Ph.D.

**Mitochondrial Medicine** - Chief: Fernando Scaglia, M.D.

**HARRIS HEALTH SYSTEM SMITH CLINIC**
Chief: Kevin Glinton, M.D., Ph.D.

**MICHAEL E. DEBAKEY VA MEDICAL CENTER**
Chief: Shweta Dhar, M.D.

ADULT GENETICS

**Texas Children's Pavilion for Women** - Lead GCs: Sandra Darilek, M.S., C.G.C. and Tamara Solomon, M.S., C.G.C.

**Baylor Medicine (Adult)** - Lead GC: Tanya Eble, M.S., C.G.C.

**Texas Children's Pediatrics** - Lead GC: Pilar Magoulas, M.S., C.G.C.

**Baylor Genetics** - Jason Chibuk, M.S., C.G.C. and Laura Andolina, M.S., C.G.C.

**Consultagene** - Lead GC: Sandra Darilek, M.S., C.G.C.

GENETIC COUNSELING

## GENETICS CLINICS

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

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

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

Specialty clinics within the Texas Children's Genetics Clinic include the metabolic clinic, neurofibromatosis clinic and the skeletal dysplasia clinic. There are many multidisciplinary team clinics like the Angelman Syndrome

Clinic, the Center for Genetic Disorders of Obesity, Mitochondrial Medicine Clinic and the Gender Medicine Program. The department's clinical and genetic counseling faculty also staff joint clinics with other departments such as oncology (cancer genetics), otolarynogology (otogenetics) and neurology (neurogenetics/tuberous sclerosis).

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

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

## CLINIC LOCATIONS

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

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

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

**Telegenetic Counseling**
Consultagene Clinic
www.consultagene.org

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

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

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

The Baylor Prenatal and Reproductive Genetics Clinic at Texas Children's Pavilion for Women contains seven Texas Children's community maternal-fetal medicine clinics that are 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 Texas Children's Fetal Center, the clinic offers world-renowned clinical and research expertise in prenatal and reproductive genetic screening, diagnostic testing and counseling. Prenatal and reproductive genetic services and counseling are offered at Ben Taub Tower Specialty Clinics and virtually through the Consultagene Clinic.

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

### Clinical Faculty

April Adams, M.D.
Carlos A. Bacino, M.D.
Mir Reza Bekheirnia, M.D.
Lindsay Burrage, M.D., Ph.D.
Sanmati Cuddapah, M.D.
William J. Craigen, M.D., Ph.D.
Shweta Dhar, M.D., M.S.
Christine M. Eng, M.D.
Kevin Glinton, M.D., Ph.D.
Seema Lalani, M.D.
Brendan Lee, M.D., Ph.D.
James R. Lupski, M.D., Ph.D.
Keren Machol, M.D., Ph.D.
Ronit Marom, M.D., Ph.D.
Yishay Ben Moshe, M.D.
Chaya Murali, M.D.
Sandesh Nagamani, M.D.
Sharon E. Plon, M.D., Ph.D.
Jennifer Posey, M.D., Ph.D.
Lorraine Potocki, M.D.
Laurie Robak, M.D., Ph.D.
Fernando Scaglia, M.D.
Daryl A. Scott, M.D., Ph.D.
V. Reid Sutton, M.D.
Ignatia B. Van den Veyver, M.D.
Michael Francis Wangler, M.D.
Monika Weisz Hubshman, M.D., Ph.D.
Lilei Zhang, M.D., Ph.D.

### Nursing Faculty

Saima Ali, M.S.N., R.N., FNP-C
Dianne Bauri, M.S., R.N., FNP-C
Alicia Turner, M.S.N., R.N., FNP-C

### Nursing Staff

Wanda Dosal, B.S.N.

## GENETIC COUNSELING

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

Prenatal genetic counselors provide services to patients throughout Houston and surrounding communities, including Katy, The Woodlands and Sugar Land, and via telegenetic counseling through Consultagene. Prenatal genetic counselors often see couples who have an increased chance of having a child with a genetic condition or birth defect; women who will be over 35 years of age at the time of delivery; couples who have had recurrent miscarriages; couples who are carriers of a genetic condition; or couples who have had abnormal genetic or prenatal screening tests, such as ultrasound or amniocentesis.

Pediatric genetic counselors often work as part of a team and evaluate children in the inpatient and outpatient setting at the Texas Children's Hospital main campus and The Woodlands campus. They evaluate children in the general genetics clinics for a variety of indications, such as developmental delay, autism spectrum disorders, intellectual disability, inborn errors of metabolism, skeletal dysplasias, hearing loss and birth defects. They see patients in many other subspecialty

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

and multidisciplinary clinics for obesity, cystic fibrosis, hematology, cardiology, neurology, allergy and immunology and pediatric oncology.

Adult and cancer genetic counselors evaluate and offer genetic counseling services to patients at the McNair campus, Michael E. DeBakey VA Medical Center, Harris Health System and the Lester and Sue Smith Breast Center. Common indications for referral to an adult genetics clinic or genetic counselor include increased risk of hereditary cancer syndromes, such as breast and ovarian cancer, colon cancer and thyroid cancer, and adults with intellectual disability or mitochondrial disorders.

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

### Genetic Counseling Faculty

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

### Genetic Counseling Staff

Benjamin Akman, M.S., C.G.C.
Darwin Argueta, M.S., C.G.C.
Erin Atkinson, M.S., C.G.C.
Grant W. Bonesteele, M.S., C.G.C.
Miavonna Craig, M.S., C.G.C.
Lauren Desrosiers-Battu, M.S., C.G.C.
Wanda Dosal, RN
Dina El Achi, M.S., C.G.C.
Serena Fleming, M.S.
Melyssa Garner, M.S., C.G.C.
Hailey Hein, M.S., C.G.C.
Nhi Ho, M.S., C.G.C.
Shontiara Johnson, M.S.
Kari Johnston, M.S., C.G.C.
Josephine Minick, M.S., C.G.C.
Bailey Mitchell, M.S.
Morgan Nutter, M.S.
Lisa Saba, M.S., C.G.C.
Meagan Siehr, M.S., C.G.C.
Emily Soludczyk, M.S., C.G.C.
Ashley Spector, M.S., C.G.C.
Mikaela Thurmond, M.S., C.G.C.
Blake Vuocolo, M.S., C.G.C.
Abigail Yesso, M.S., C.G.C..
Michelle Zelnick, M.S., C.G.C.

# DIVISION OF DIAGNOSTIC LABORATORY AFFAIRS


## BAYLOR GENETICS

Established in February 2015, Baylor Genetics, a joint venture between Baylor College of Medicine and H.U. Group Holdings, Inc., strives to continue the tradition of genetic testing innovation and operational excellence. By building on the Department of Molecular and Human Genetics' strengths in research and discovery, Baylor Genetics' mission is to provide quality genetic testing services for 21st-century precision medicine. Over the last 40 years, the laboratory has been at the forefront of introducing novel genetic testing modalities that have provided more tools to diagnose patients with genetic disorders. The innovative testing approaches developed at the laboratory include whole exome sequencing, Chromosomal Microarray Analysis (CMA), universal carrier screening, non-invasive prenatal testing for single gene disorders, metabolomics, and most recently, whole transcriptome RNA sequencing. Baylor Genetics continues to offer high-quality comprehensive diagnostic services in all areas of genetic testing including cytogenetics, biochemical genetics, cancer genetics, mitochondrial genetic testing and next-generation sequencing panels. The laboratory, located within Houston's Texas Medical Center, is staffed with more than 200 employees, has a library of over 3,000 tests, and serves clients in all 50 states and 16 countries. Baylor Genetics is well-equipped with cutting-edge diagnostic equipment, allowing it to generate the most accurate clinical genetic data. In collaboration with the Department's newly established, Medical Genetics Multi-omic Laboratory (MGML), it strives to make available both standard of care genetic testing and cutting-edge innovative tests at the leading edge of research.

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

*Laboratory technicians at Baylor Genetics*

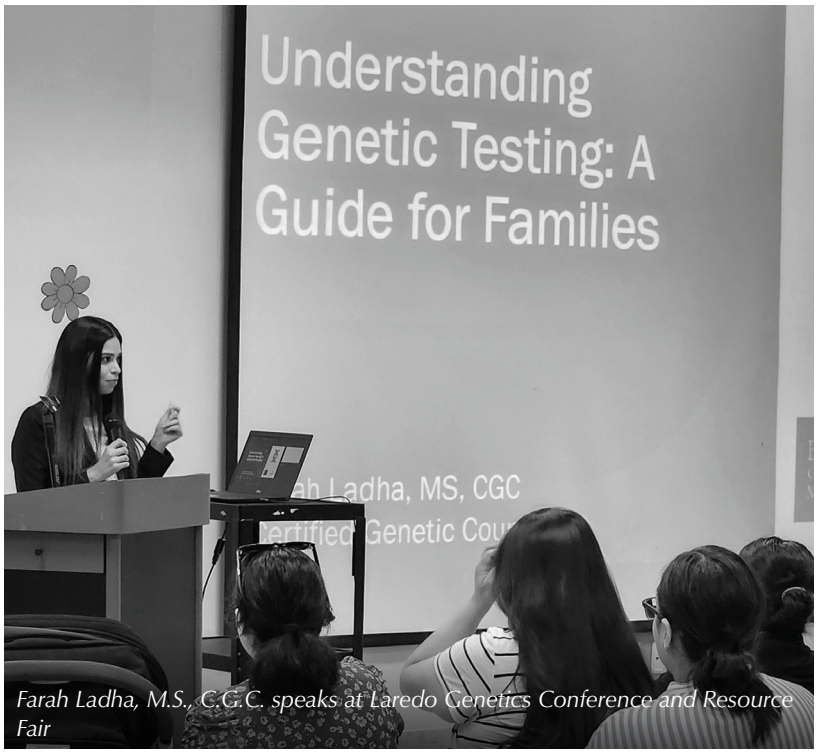
are committed to the education and training of the next generation of clinical and laboratory diagnosticians through our participation in the American Board of Medical Genetics and Genomics fellowship programs.

### Diagnostic Laboratory Faculty

Carlos Bacino, M.D.
Weimin Bi, Ph.D.
Jun Chen, Ph.D.
Hongzheng Dai, Ph.D.
Sarah Elsea, Ph.D.
Christine Eng, M.D.
Xiaoyan Ge, Ph.D.
Natalia Golardi, Ph.D.
Eric Kao, Ph.D.
Ning Liu, Ph.D.
Pengfei Liu, Ph.D.
Xi Luo, Ph.D.
Linyan Meng, Ph.D.
Nichole Owen, Ph.D.
Katharina Schulze, Ph.D.
Yue Cindy Si, Ph.D.
Teresa Santiago Sim, Ph.D.
Janice Smith, Ph.D.
Qin Sun, Ph.D.
V. Reid Sutton, M.D.
Pawel Stankiewicz, Ph.D.
Casey Thornton, P.D.
Liesbeth Vossaert, Ph.D.
Yue Wang, Ph.D.
Chung Wah Wu, Ph.D.
Fan Xia, Ph.D.
Bo Yuan, Ph.D.
Xiaonan Zhao, Ph.D.

# COMMUNITY ENGAGEMENT AND EQUITY

**The Office of Community Engagement and Equity** in the Department of Molecular and Human Genetics works alongside Baylor College of Medicine's Office of Community Engagement and Health Equity to promote an environment that fosters inclusion, education and understanding for faculty, trainees, staff and the community-at-large. The office's engagement and equity committee have established educational programs for its faculty and staff that address equity in education, research and medicine, as well as genetics outreach programs for the general public.



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

The **Evenings with Genetics series** has served the community for 18 years. The department partners with Texas Children's Hospital to offer this free seminar series to the public. A genetics faculty member paired with faculty from another specialty area, plus a parent speaker, are highlighted at each seminar. The goals of the series are to provide current genetic and genomic information in a clear, plain-language manner offer support and resources to families impacted by a genetic disorder; and foster interdepartmental collaborations. Seminars are translated to Spanish. During this past year, we celebrated our 18th anniversary with the fourth annual "Race and Genetics: Perspectives of Precision Medicine" webinar series during Black History Month. In addition, the office held its second webinar honoring Hispanic Heritage Month.

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

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

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

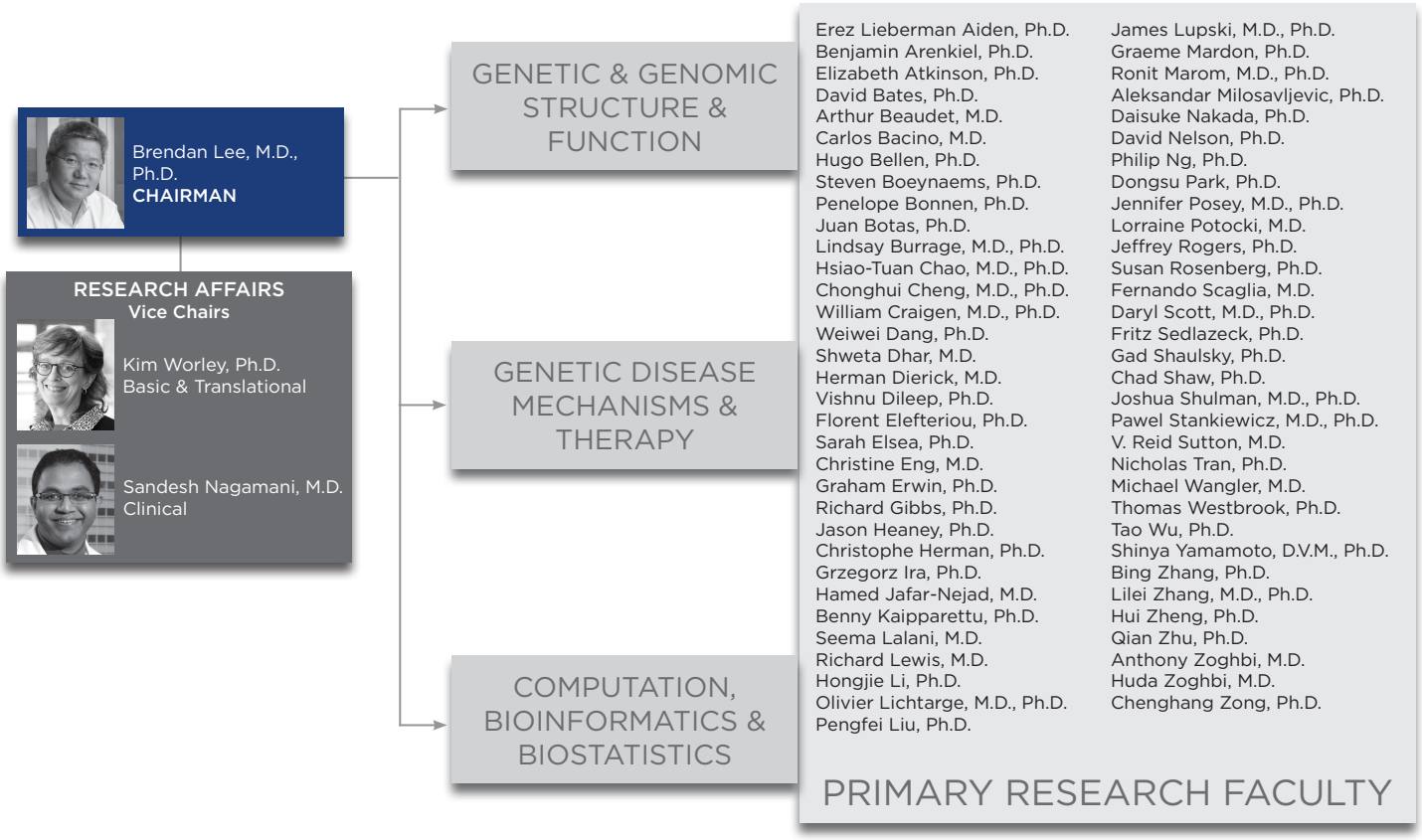
**"Let's Learn about One Another"** is a series of interactive presentations that began in 2020 to address the climate of social injustice. The "Let's Learn" program includes perspectives from the department's widely diverse members. The program has offered the "Let's Learn about One Another: Understanding the African American Experience in America" (2020), "Let's Learn about One Another: Understanding the Asian American and Pacific Islander Experience in America" (2021), "Let's Learn about One Another: Understanding the Hispanic/Latin/a/o Experience in America" (2022), and "Let's Learn about One Another: the Academic Woman's Experience" (2023) with faculty, graduate students, postdoctoral trainees and staff members sharing their experiences. The office also curates an online library of articles regarding inclusion and equity for department faculty, trainees and staff.

The office also offers "Understanding Genetic Variations" sessions at national student research meetings (Annual Biomedical Research Conference for Minoritized Scientists, Society for Advancement of Chicanos/Hispanics & Native Americans in Science) to introduce genetics and genomics and encourage participation in the field.

**Co-Directors**
Debra Murray, Ph.D.
Gladys Pryor, B.S.

# RESEARCH FACULTY

## Division of Research Affairs




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

Bioinformatics
Bacterial genetics
Cancer genetics
Cytogenetics
DNA recombination
Drosophila genetics
Functional genomics
Gene therapy
Gene structure and expression
Genome sequencing
Genomic stability, replication and repair
Mammalian development
Metabolic basis for inherited human disease
Mouse molecular genetics
Neurogenetics
Somatic cell genetics
Yeast genetics

# EREZ AIDEN, PH.D.

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

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

## RESEARCH INTERESTS

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

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

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

## SELECTED PUBLICATIONS

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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.

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# BENJAMIN R. ARENKIEL, PH.D.

## McNair Scholar

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

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

## RESEARCH INTERESTS

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

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

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

## SELECTED PUBLICATIONS


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# ELIZABETH ATKINSON, PH.D.

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

*Ph.D., Washington University in St. Louis*
*Postdoc, IRACDA fellow; Harvard Medical School – Massachusetts General Hospital & Broad Institute*

## RESEARCH INTERESTS

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

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

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

## SELECTED PUBLICATIONS

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ELIZABETH.ATKINSON@BCM.EDU @EGATKINSON

# CARLOS A. BACINO, M.D., FACMG

**Professor and Vice Chair for Clinical Affairs**, Department of Molecular and Human Genetics
**Director**, Pediatric Genetics Clinic
**Medical Director, Cytogenetics Laboratory**, Baylor Genetics
**Chief**, Genetics Service, Texas Children's Hospital

*M.D., University of Buenos Aires, Argentina*
*Intern and Resident, Pediatrics, Beth Israel Medical Center*
*Fellow, Clinical Genetics and Cytogenetics, Cedars-Sinai Medical Center, Los Angeles*

## RESEARCH INTERESTS

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

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

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

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

## SELECTED PUBLICATIONS

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# DAVID BATES, PH.D.

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

*Ph.D., University of New Mexico*
*Postdoc, University of New Mexico School of Medicine*
*Postdoc, Harvard University*

## RESEARCH INTERESTS

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

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

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

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

## SELECTED PUBLICATIONS

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# ARTHUR BEAUDET, M.D.

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

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*Resident, Pediatrics, John Hopkins Hospital*
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## RESEARCH INTERESTS

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

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

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

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

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

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

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

## March of Dimes Chair in Developmental Biology

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*Business Engineer, Solvay, University of Brussels, Belgium*
*D.V.M., Ghent University, Belgium*
*Ph.D., Genetics, University of California, Davis*
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## RESEARCH INTERESTS

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

My lab as well as the laboratories of Michael Wangler and Shinya Yamamoto here at BCM were selected by the Undiagnosed Diseases Network (UDN) as the Drosophila Model Organism Screening Center (MOSC). Through close collaborations with human geneticists and physicians, we have identified variants in numerous human genes that are associated with neurological diseases in children. We have so far participated in the discovery of the genetic causes of 50 human diseases in the past eight years. We are also studying some of these genes in depth to determine the molecular events that underlie these diseases to identify targets to develop drugs and have been successful in identifying FDA approved drugs for four diseases.

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

## WEBSITE: FLYPUSH.RESEARCH.BCM.EDU

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# STEVEN BOEYNAEMS, PH.D.

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**CPRIT Scholar in Cancer Research**
**Departmental Commercialization Officer**

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

## RESEARCH INTERESTS

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

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

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

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# PENELOPE E. BONNEN, PH.D.

**Associate Professor**, Departments of Molecular and Human Genetics and Molecular Physiology & Biophysics
**Faculty Member,** Computational and Integrative Biomedical Research Center; Graduate Programs in Quantitative & Computational Biosciences; Development, Disease Models & Therapeutics; and Genetics & Genomics

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*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.

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# JUAN BOTAS, PH.D.

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## RESEARCH INTERESTS

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

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

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

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

## SELECTED PUBLICATIONS

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

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*Medical Genetics Residency, Baylor College of Medicine*
*Biochemical Genetics Fellowship, Baylor College of Medicine*

## RESEARCH INTERESTS

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

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

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

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

## SELECTED PUBLICATIONS

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# HSIAO-TUAN CHAO, M.D., PH.D.

## McNair Scholar

**Assistant Professor**, Departments of Molecular and Human Genetics, Pediatrics-Neurology and Neuroscience
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**Investigator**, The Cain Foundation Laboratories, Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital

*M.D., Baylor College of Medicine*
*Ph.D., Baylor College of Medicine*
*Intern, Pediatrics, Texas Children's Hospital*
*Resident, Pediatric Neurology, Texas Children's Hospital*

## RESEARCH INTERESTS

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

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

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

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# CHONGHUI CHENG, PH.D.

**Professor**, Departments of Molecular and Human Genetics and Molecular and Cellular Biology; Lester and Sue Smith Breast Center
**Faculty Member**, Graduate Programs in Cancer & Cell Biology and Genetics & Genomics
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*Postdoc, Massachusetts Institute of Technology*

## RESEARCH INTERESTS

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

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

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

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

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

**Professor**, Departments of Molecular and Human Genetics, Molecular Physiology and Biophysics, and Pediatrics
**Faculty Member**, Graduate Programs in Genetics & Genomics; Development, Disease Models & Therapeutics; and the Clinical Translational Research Certificate of Added Qualification (CTR-CAQ) program
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*Fellow, Medical Genetics, Baylor College of Medicine*
*Resident, Pediatrics, Baylor College of Medicine*

## RESEARCH INTERESTS

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

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

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# WEIWEI DANG, PH.D.

**Associate Professor**, Department of Molecular and Human Genetics and Huffington Center on Aging
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**CPRIT Scholar in Cancer Research**

*Ph.D., Southern Illinois University*
*Postdoc, University of Pennsylvania*

## RESEARCH INTERESTS

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

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

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

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

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

## RESEARCH INTERESTS

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

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

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

## SELECTED PUBLICATIONS

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# HERMAN A. DIERICK, M.D.

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*Research Fellow, The Neurosciences Institute*

## RESEARCH INTERESTS

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

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

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

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# VISHNU DILEEP, PH.D.

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

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

## RESEARCH INTERESTS

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

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

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

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# FLORENT ELEFTERIOU, PH.D.

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

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

## RESEARCH INTERESTS

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

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

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

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

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# SARAH H. ELSEA, PH.D.

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

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

## RESEARCH INTERESTS

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

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

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

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# CHRISTINE M. ENG, M.D.

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

*M.D., Tulane University School of Medicine*

## RESEARCH INTERESTS

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

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

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

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# GRAHAM ERWIN, PH.D.

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

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

## RESEARCH INTERESTS

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

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

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

## SELECTED PUBLICATIONS

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# RICHARD A. GIBBS, PH.D.

## Wofford Cain Chair in Molecular and Human Genetics

**Professor**, Department of Molecular and Human Genetics
**Faculty Member**, Graduate Programs in Genetics & Genomics; Quantitative & Computational Biosciences; Integrative Molecular and Biomedical Sciences; and Translational Biology & Molecular Medicine
**Director**, Human Genome Sequencing Center

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

## RESEARCH INTERESTS

Richard Gibbs is the Founder and Director of the Human Genome Sequencing Center (HGSC), established at Baylor in 1996. The HGSC has a core mission of advancing medical care through research and translation of genomics. The group was one of the five worldwide sites to undertake and complete the Human Genome Project, culminating in the contribution of approximately ten percent of the sequence in 2003. The group subsequently collaborated to sequence many key species (*Drosophila melanogaster*, Brown Norway rat, rhesus macaque, bovine, *Dictyostelium discoideum*, sea urchin and honey bee genomes) and to generate the first comprehensive map of human genetic variation (the HapMap project). The HGSC now employs more than 120 staff, including ten 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 individuals each month. The HGSC is also part of the national program for systematic discovery of the cause of human single genome defects and has an active bioinformatics program, with research projects involving biologists and computer scientists. To advance the use of genomics in adult clinics the HGSC has developed methods for screening for cardiovascular genetic risk and has recently joined the national *All of Us* consortium. Problems under study focus on developing tools for generating, manipulating, and analyzing genome data.

## SELECTED PUBLICATIONS


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# JASON HEANEY, PH.D.

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## RESEARCH INTERESTS

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

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

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

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

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# CHRISTOPHE HERMAN, PH.D.

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## RESEARCH INTERESTS

### Transcription errors and Epigenetic Inheritance

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

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

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

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# GREGORY IRA, PH.D.

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## RESEARCH INTERESTS

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

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

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# HAMED JAFAR-NEJAD, M.D.

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## RESEARCH INTERESTS

Glycosylation is the most common post-translational modification of animal 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 multisystem 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 these enzymes and will provide a framework to identify mechanism-based therapies for them.

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

**Towards a therapy 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 generated three mouse models representing the spectrum of liver abnormalities in ALGS and have identified a number of dosage-sensitive genetic modifiers of the disease phenotypes. Published and preliminary data indicate that postnatal targeting of these modifiers can significantly improve the ALGS liver phenotypes in these models. Ongoing experiments are aimed at **using these models and their genetic modifiers to better understand the pathophysiology of ALGS, and to develop a therapy for this disease and potentially other diseases associated with bile duct paucity.** 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 global developmental delay, movement disorders, osteopenia, constipation, 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 several cell types and signaling pathways affected by the loss of NGLY1. 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 also helping us identify novel roles for *N*-glycosylation in animal development.

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# BENNY ABRAHAM KAIPPARETTU, PH.D.

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## RESEARCH INTERESTS

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

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

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

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

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

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*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 diagnostic tools such as chromosomal microarray analysis (CMA) and exome sequencing (ES) in understanding the genetic basis of birth defects. We have also studied the clinical utility of rapid ES in neonatal intensive care units. I have been involved with the Undiagnosed Diseases Network (UDN) study at Baylor College of Medicine for several years and helped characterize diagnoses in multiple undiagnosed children with rare diseases. In 2016, we first described a cohort of patients with TANGO2 deficiency disorder (TDD) and are currently recruiting families for the natural history study. I also lead project GIVE, an NIH study to reduce genomic health disparities in the Hispanic children living in the Rio Grande Valley (RGV) and El Paso in Texas. We are using an academic web-based virtual platform called Consultagene to combine virtual health delivery with genome sequencing in this pediatric population, living along the Texas-Mexico border.

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

## Robert and Janice McNair Endowed Chair in Molecular and Human Genetics

**Professor and Chair**, Department of Molecular and Human Genetics
**Faculty Member**, Graduate Programs in Genetics & Genomics; Development, Disease Models & Therapeutics
**Director**, Center for Skeletal Medicine and Biology
**Associate Director**, Medical Research Pathway, School of Medicine, Baylor College of Medicine
**Director**, Texas Children's Hospital Skeletal Dysplasia Clinic
**Director**, The Lawrence Family Bone Disease Program of Texas

*Ph.D., State University of New York Downstate Medical Center*
*M.D., State University of New York Downstate Medical Center*
*Research Fellow, Mount Sinai School of Medicine*
*Resident, Pediatrics, Baylor College of Medicine*
*Clinical Fellow, Medical Genetics, Baylor College of Medicine*
*Clinical Fellow, Clinical Biochemical Genetics, Baylor College of Medicine*

## RESEARCH INTERESTS

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

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

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

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

**Professor**, Departments of Molecular and Human Genetics, Ophthalmology, Pediatrics, and Medicine
**Member**, National School of Tropical Medicine and the Steering Committee of the Undiagnosed Disease Network at Baylor College of Medicine

*M.D., University of Michigan Medical School*
*M.S., University of Michigan*
*Residency in Ophthalmology, University of Michigan Hospitals, Ann Arbor, Michigan*
*Fellowship, Montefiore Hospital, Einstein School of Medicine, Bronx, New York*
*Fellowship, Bascom Palmer Eye Institute, University of Miami, Miami, Florida*

## RESEARCH INTERESTS

Dr. Lewis, an ophthalmologist historically affiliated with the Cullen Eye Institute, joined the Department of Molecular and Human Genetics to provide in-depth consultations and research in genetic eye disorders and ocular manifestations of systemic hereditary disorders for Texas Children's Hospital and the adult genetics services at the Baylor-affiliated hospitals. His clinical practice includes genetic eye disease and their constitutional associations. With numerous members of the Department, he and his colleagues pioneered the mapping and isolation of many X-linked ocular disorders, including X-linked Retinitis Pigmentosa, 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. Ignatia Van den Veyver and Dr. Reid Sutton continue the search for the genetic construct for Aicardi Syndrome, another distinctive phenotype in females only with extreme retinal and optic nerve malformations and profound brain and developmental consequences.

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

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

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

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# HONGJIE LI, PH.D.

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

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

## RESEARCH INTERESTS

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

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

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

## SELECTED PUBLICATIONS

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# OLIVIER LICHTARGE, M.D., PH.D.

## The Cullen Foundation Endowed Chair

**Professor**, Departments of Molecular and Human Genetics, Biochemistry & Molecular Biology, and Pharmacology
**Faculty Member**, Graduate Programs in Genetics & Genomics; Quantitative and Computational Biosciences; Developmental Biology; and Integrative Molecular and Biomedical Sciences
**Director**, Computational and Integrative Biomedical Research Center (CIBR)

*Ph.D., Stanford University*
*M.D., Stanford University*
*Residency, Internal Medicine, University of California, San Francisco*
*Fellowship, Endocrinology, University of California, San Francisco*
*Postdoc, University of California, San Francisco*

## RESEARCH INTERESTS

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

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

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

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# PENGFEI LIU, PH.D., FACMGG

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

*Ph.D., Baylor College of Medicine*

## RESEARCH INTERESTS

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

## SELECTED PUBLICATIONS

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# JAMES R. LUPSKI, M.D., PH.D., D.SC. (HON)

## The Cullen Foundation Endowed Chair in Molecular and Human Genetics

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

*Ph.D., New York University*
*M.D., New York University School of Medicine*
*Postdoc, New York University*
*Resident, Pediatrics, Baylor College of Medicine*
*Fellow, Medical Genetics, Baylor College of Medicine*
*Sabbatical, Wellcome Trust Sanger Institute*
*D.Sc., Watson School of Biological Sciences, Cold Spring Harbor Laboratory (CSHL)*

## RESEARCH INTERESTS

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

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

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

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

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# GRAEME MARDON, PH.D.

## James R. Davis Chair in Pathology

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## RESEARCH INTERESTS

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

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

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

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*Medical Genetics Residency, Baylor College of Medicine*
*Medical Biochemical Genetics Fellowship, Baylor College of Medicine*
*Postdoctoral Research Fellowship, Baylor College of Medicine*

## RESEARCH INTERESTS

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

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

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

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

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# ALEKSANDAR MILOSAVLJEVIC, PH.D.

**Professor**, Department of Molecular and Human Genetics
**Director**, Graduate Program in Quantitative and Computational Biosciences
**Faculty Member**, Graduate Program in Genetics & Genomics
**Co-Director**, Computational and Integrative Biomedical Research Center (CIBR)

*Ph.D., University of California, Santa Cruz*

## RESEARCH INTERESTS

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

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

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

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

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

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

**Professor and Vice Chair for Research Affairs - Clinical,** Department of Molecular and Human Genetics
**Director**, Baylor Intellectual and Developmental Disabilities Research Center (IDDRC)

*M.B.B.S., University of Mysore*
*M.D., Gandhi Medical College*
*Internship, Internal Medicine, Fairview Hospital*
*Residency, Clinical Genetics, Baylor College of Medicine*
*Residency, Internal Medicine, Baylor College of Medicine*
*Postdoc, Baylor College of Medicine*

## RESEARCH INTERESTS

I am an internist and a clinical geneticist who is focused on improving clinical care in individuals with genetic disorders. The focus of my research program is clinical investigation including 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 an Multiple Principal Investigator (MPI) for the NIH Rare Diseases Clinical Research Network's Urea Cycle Disorders Consortium, I am involved in conducting natural history studies and proof-of-principle pilot studies. As PI for the Pilot/Feasibility core of the consortium, I am involved in facilitating projects that will develop and validate new biomarkers for disease activity and endpoints that can be used in clinical investigation. As the PI for the Career Enhancement Core for the consortium, I am glad to be championing the career advancement of young investigators in the field of inborn errors of metabolism.

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

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

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

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

## SELECTED PUBLICATIONS

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# DAISUKE NAKADA, PH.D.

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**CPRIT Scholar in Cancer Research**
**Leukemia and Lymphoma Society Scholar**

*Ph.D., Nagoya University, Japan*
*Postdoc, University of Michigan*

## RESEARCH INTERESTS

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

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

## SELECTED PUBLICATIONS

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# DAVID L. NELSON, PH.D.

## The Cullen Foundation Professorship in Molecular Genetics

**Professor**, Department of Molecular and Human Genetics
**Director**, BCM-Michigan-Emory Fragile X Research Center
**Faculty Member**, Graduate Programs in Neuroscience and Genetics & Genomics
**Program Director**, Graduate Programs in Cancer and Cell Biology and Integrative Molecular and Biomedical Sciences

*Ph.D., Massachusetts Institute of Technology*
*Postdoc, National Institute for Neurological, Communicative Disorders & Stroke, NIH*
*Postdoc, Baylor College of Medicine*

## RESEARCH INTERESTS

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

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

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# PHILIP NG, PH.D.

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

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

## RESEARCH INTERESTS

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

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

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

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

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

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# DONGSU PARK, PH.D.

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

*Ph.D., Baylor College of Medicine*
*Postdoc, Massachusetts General Hospital & Harvard Stem Cell Institute*

## RESEARCH INTERESTS

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

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

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

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

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

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

## RESEARCH INTERESTS

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

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

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

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

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

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

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

## SELECTED PUBLICATIONS

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# LORRAINE POTOCKI, M.D., FACMG

**Professor and Vice Chair for Undergraduate Medical Education**, Department of Molecular and Human Genetics
**Director**, Genetics & Genomics Pathway, School of Medicine, Baylor College of Medicine

*M.D., Boston University School of Medicine*
*Resident, Pathology, University of Massachusetts*
*Fellow, Fetal and Perinatal Pathology, Brown University*
*Fellow, Medical Genetics, Baylor College of Medicine*

## RESEARCH INTERESTS

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

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

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

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

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

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

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# JEFFREY ROGERS, PH.D.

**Associate Professor**, Department of Molecular and Human Genetics and Human Genome Sequencing Center
**Core Scientist**, Wisconsin National Primate Research Center, Madison, WI
**Faculty Member**, Graduate Programs in Genetics & Genomics and Development, Disease Models & Therapeutics

*Ph.D., Anthropology, Yale University*

## RESEARCH INTERESTS

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

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

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

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

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# SUSAN M. ROSENBERG, PH.D.

## Ben F. Love Chair in Cancer Research

**Professor**, Departments of Molecular and Human Genetics, Biochemistry & Molecular Biology and Molecular Virology & Microbiology
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**Faculty Member**, Graduate Program in Genetics & Genomics

*Ph.D., University of Oregon*
*Postdoc, University of Paris VII*
*Postdoc, University of Utah School of Medicine*
*Postdoc, National Cancer Institute at Frederick*

## RESEARCH INTERESTS

### Genome Instability in Evolution, Antibiotic Resistance, and Cancer

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

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

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

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

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# FERNANDO SCAGLIA, M.D.

**Professor**, Department of Molecular and Human Genetics
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**Director**, Adult Mitochondrial Medicine Clinic, Baylor St Luke's Medical Center McNair Campus
**Clinical Director**, Baylor College of Medicine and Chinese University of Hong Kong Joint Center for Medical Genetics in Hong Kong

*M.D., University of La Plata School of Medicine*
*Intern, Pediatrics, Emory University School of Medicine*
*Resident, Pediatrics, Emory University School of Medicine*
*Fellow, Medical Genetics, Emory University School of Medicine*

## RESEARCH INTERESTS

My primary research interest is focused on the study of the natural history of mitochondrial disorders supported by the NIH funded North American Mitochondrial Disease Consortia (NAMDC), a registry that focuses on the longitudinal study of patients with mitochondrial disease. Furthermore, I am also involved in clinical trials in children and adults with mitochondrial disorders. One of my current areas of research includes the study of nitric oxide deficiency as the basis for stroke-like episodes in adults and children with a mitochondrial syndrome called MELAS. As a Principal Investigator on several grants that have been funded by national organizations in the U.S., I have laid the groundwork for the study of nitric oxide deficiency in MELAS syndrome and its restoration with the use of arginine and citrulline supplementation. A current NIH grant funds a phase 1 study that aims to determine the maximum tolerated dose and safety profile of citrulline supplementation in adults with MELAS syndrome. Moreover, I am involved in an international clinical trial for pediatric patients evaluating the efficacy of vatiquinone in mitochondrial refractory epilepsy and in a national multi-center trial evaluating the safety and efficacy of dichloroacetate in pyruvate dehydrogenase deficiency. In addition, I have conducted a trial to evaluate the effect of bocidelpar sulfate, a selective modulator of PPARδ in adults with primary mitochondrial myopathy. Finally, I am also involved in establishing the natural history of congenital disorders of glycosylation with the support of the NIH funded Frontiers in Congenital Disorders of Glycosylation Consortia (FCDGC).

Furthermore, I am interested in determining whether there is a specific metabolomics signature for the different mitochondrial disorders caused by mitochondrial and nuclear gene defects and whether this profile could be used to monitor their natural history and the treatment efficacy when novel therapeutic approaches are trialed. In that capacity, I am the co-chair of a CDE mitochondrial biomarker subgroup that works with NINDS.

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# DARYL A. SCOTT, M.D., PH.D.

**Professor**, Department of Molecular and Human Genetics
**Faculty Member**, Graduate Programs in Development, Disease Models & Therapeutics and Genetics & Genomics
**Director**, Medical Research Pathway, School of Medicine, Baylor College of Medicine

*M.D./Ph.D., University of Iowa*
*Resident, Pediatrics, University of Utah*
*Resident, Clinical Genetics, Baylor College of Medicine*

## RESEARCH INTERESTS

Our laboratory is dedicated to identifying and characterizing genes and genomic alterations that cause common, life-threatening birth defects and determining the molecular mechanisms by which they impact human health.

**Congenital Diaphragmatic Hernia and Cardiovascular Malformations:** Children with congenital diaphragmatic hernia (CDH) have an abnormal opening in the diaphragm that allows abdominal organs, like the liver and intestines, to enter the chest. This invasion interferes with normal lung development causing severe respiratory problems at birth. CDH affects about one in every 3,500 newborns. CDH-associated mortality and morbidity are high, particularly in the subset of individuals who have a co-existing cardiovascular malformation (CVM). We use clinical and molecular data from patients and machine learning to identify genes associated with CDH and/or CVM. Genes we have worked on include *GATA4, SOX7, ZFPM2, FREM1, FREM2, FRAS1, NONO, NR2F2, FZD2, HCCS, HEY2, FBN1, SON, TRRAP, FGFRL1,* and *FOXP1*. We are now using mouse models developed in our laboratory to discover the morphogenetic and molecular mechanisms by which a subset of these genes function during diaphragm and heart development.

**1p36 Deletion Syndrome:** Deletions of chromosome 1p36 can cause a variety of birth defects including brain anomalies, eye/vision problems, hearing loss, cardiovascular defects, cardiomyopathy and renal anomalies. Approximately one in 5,000 newborns carry either a terminal or interstitial deletion on chromosome 1p36. The *RERE* and *SPEN* genes are located on chromosome 1p36 and encode transcription factors that play important roles during embryonic development. Using a combination of animal models and data from individuals with mutations of *RERE*, we have shown that RERE plays a critical role in the development of the brain, eye, inner ear, palate, heart and kidneys. We are actively working to determine the molecular mechanisms by which RERE deficiency causes defects in each of these organs and to define the spectrum of defects caused by a lack of SPEN function. We are also searching for other genes that contribute to the medical problems seen in individuals with 1p36 deletions.

**Other Structural Birth Defects and Neurodevelopmental Phenotypes:** We work with physicians and scientists from around the world to identify genes and genomic regions that are associated with other structural birth defects and neurodevelopmental phenotypes including developmental delay, intellectual disability and autism spectrum disorder. Recently, we have used machine learning to aid us in these efforts. This has resulted in the discovery of dozens of low-penetrance genes for a variety of phenotypes.

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# FRITZ SEDLAZECK, PH.D.

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

*Dr. rer. nat, Bioinformatics, University of Vienna*
*Dipl. Ing. (FH), Bioinformatics, Upper Austria University of Applied Sciences, Hagenberg*

## RESEARCH INTERESTS

My research focuses on the identification of coding and non-coding complex variations and their impact on evolution and diseases across a multitude of organisms, with a focus on human diseases. My training in genomics started in 2008, when I started my Ph.D. in computational biology where I designed algorithms to investigate genomic variability of model and non-model organisms through the alignment of short reads. Throughout my entire career, I have been intrigued to investigate genomic variability across tissues, as well as within populations and across populations. This drove my training and investigation into the impact of such variability. To assess these, I collaborated and initiated efforts to determine which technologies or methodologies were most appropriate to discover variations of different forms, as well as the biases that they contain. This work recently led to novel insights in structural variations and their genotypic and phenotypic impact on cardiovascular, Mendelian and neurological diseases and other organisms. My group and I continue to drive the understanding around SVs and their impact on phenotypes in human diseases and across other organisms.

Over my young career as a scientist, I followed a clear path to investigate genomic variability starting with SNPs and focusing over the last 5 years on structural variations.

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# GAD SHAULSKY, PH.D.

**Professor and Vice Chair for Graduate Education**, Department of Molecular and Human Genetics
**Director**, Graduate Program in Genetics & Genomics
**Faculty Member**, Graduate Programs in Genetics & Genomics and Immunology & Microbiology
**Professor**, Department of Education, Innovation and Technology
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*Ph.D., Weizmann Institute of Science*
*Postdoc, University of California, San Diego*

## RESEARCH INTERESTS

**Allorecognition:** *Dictyostelium* cells preferentially cooperate with relatives (Ostrowski, 2008), and we are investigating the mechanisms that underlie this kin discrimination. We found two highly polymorphic cell-surface proteins, TgrB1 and TgrC1, which are required for allorecognition (Benabentos, 2009) and showed that the sequence polymorphism is sufficient to explain allorecognition in *Dictyostelium* (Hirose, 2011). This kin-recognition system protects cooperators against cheaters (Ho, 2013) and is temporally regulated, which allows it to evolve despite its essential role in development (Ho, 2015). We are investigating the mechanisms that regulate allorecognition under the hypothesis that TgrB1 and TgrC1 function as a ligand-receptor pair (Hirose, 2017), which is at the top of a signal transduction cascade that regulates development and allorecognition. We used genetic suppressor analysis to identify elements that mediate the TgrB1-C1 signal transduction (Li, 2016). We found that TgrB1 and TgrC1 are components of a greenbeard mechanism, and that activation of TgrB1 induces altruistic behavior and inactivation of TgrB1 causes cheating (Katoh-Kurasawa, 2024). We are continuing the analysis of this pathway.

**The evolution of social behavior in *Dictyostelium:*** Social organisms must deal with cheaters - individuals that reap the benefits of sociality without paying the full cost. In *Dictyostelium*, some cells sacrifice themselves and benefit others that may be genetically different, providing a fertile ground for cheating. We found over 100 genes that participate in social interactions (Santorelli, 2008), characterized some of the underlying mechanisms, and tested how cooperators resist cheating (Khare and Shaulsky, 2006; Khare, 2009; Khare and Shaulsky, 2010). We are investigating the role of the TgrB1-C1 pathway in cheating (Katoh-Kurasawa, 2024).

**Functional Genomics:** We use transcriptomes to discover gene function in *Dictyostelium* (Booth, 2005; Van Driessche, 2007). We have shown that the transcriptome is a good phenotyping tool for discovering epistatic relationships (Van Driessche, 2005). Using RNA-seq, we compared the developmental transcriptomes of *D. discoideum* and *D. purpureum*, two species that diverged ~350MYA, but whose developmental morphologies are similar. We found vast similarities between the two transcriptomes (Parikh, 2010). We analyzed many mutants, and we developed a system for analysis of transcription factors with RNA-seq and ChIP-seq (Santhanam, 2015). We found complex regulation of transcriptional activity during development (Rosengarten, 2015) and described the long-non-coding transcriptome (Rosengarten, 2017). We analyzed the major transcriptional transitions that characterize *Dictyostelium* development using RNA-seq profiles of 20 mutants (Katoh-Kurasawa, 2021). We are also developing tools for *Dictyostelium* genome exploration, including a deep coverage genomic DNA library (Rosengarten, 2015), gene discovery by chemical mutagenesis at low level and whole-genome sequencing to identify mutations (Li, 2016), and an adaptation of GoldenBraid as a synthetic biology tool for *Dictyostelium* (Kundert, 2020).

**Data Mining:** We are collaborating with Dr. Zupan's group at the University of Ljubljana, Slovenia, to develop new concepts in genetic analysis. We have developed a tool that performs automated epistasis analysis, GenePath (Demsar, 2001). We developed a gene-function prediction system that relies on compressive data fusion and chaining and demonstrated its utility in predicting the function of bacterial-recognition genes in *D. discoideum* (Zitnik, 2015). We developed dictyExpress, a web tool that can access and analyze transcriptome data (Stajdohar, 2017). We also developed scOrange, a tool for analyzing single cell RNA-seq data (Stražar, 2019) and an image analysis platform that utilizes deep models in a visual programming environment (Godec, 2019).

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# CHAD SHAW, PH.D.

**Professor**, Department of Molecular and Human Genetics
**Joint Professor of Statistics and Director of D2K Laboratory**, Rice University
**Investigator**, Jan and Dan Duncan Neurological Research Institute
**Faculty Member**, Stem Cells and Regenerative Medicine (STaR) Center and Graduate Program in Quantitative & Computational Biosciences

*Ph.D., Mathematical Statistics, Rice University*

## RESEARCH INTERESTS

Chad Shaw is trained as a mathematical statistician, and he has worked in statistical genomics and bioinformatics for approximately 20 years. He is currently a Professor at BCM and Adjunct Professor of Statistics at Rice University. He is also the Senior Director of Innovation at Baylor Genetics Laboratory.

He has experience in next-generation sequencing, variant analysis, multi-omic data integration, gene expression profiling and variant functionalization. He also has expertise in copy-number analysis and has worked in the area of mechanistic studies of structural variation, with a focus on the role of repetitive elements in new mutations.

He led the development and analysis of an applied probabilistic model for the transmission of new mutations in the context of human genetic disease, which led to the elucidation of the dependency of recurrence risk on parent of origin, parental somatic mosaicism and paternal age. This fundamental contribution to human genetics was featured in many reviews and in the New York Times as a lay press article.

He has been an author on approximately 200 peer-reviewed publications, and his work has been cited approximately 17,000 times. He has trained 5 Ph.D. students in his own laboratory and over 10 students as a thesis committee member. He serves as chairman of the qualifying exam committee for the Quantitative and Computational Biosciences program. His students have performed methodologic research in high dimensional sparse regression, statistical methods for high throughput NGS screens approaches to modifiers of Mendelian disease, eQTL analyses and software tools for variant prioritization in rare disease diagnostics.

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# JOSHUA M. SHULMAN, M.D., PH.D.

## Effie Marie Cain Chair in Alzheimer's Disease Research

**Professor**, Departments of Molecular and Human Genetics, Neurology, and Neuroscience
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*Resident in Neurology, Brigham & Women's Hospital, Massachusetts General Hospital*
*Movement/Memory Disorders Fellow, Brigham & Women's Hospital, Massachusetts General Hospital*

## RESEARCH INTERESTS

Our research integrates genetic and genomic investigation in human subjects and model organisms, with the goal of understanding brain function and aging and improving the treatment of neurologic disease. We focus on Alzheimer's disease and Parkinson's disease, two incurable neurodegenerative disorders and experimental paradigms for the age-dependent failure of brain cognitive and motor control in humans.

**Human Genetics:** The clinical manifestation of neurodegenerative disease is the culmination of a multi-tiered pathogenic cascade that evolves over decades—understanding how genetic variants impact this causal chain is essential. We are therefore investigating the impact of genomic variation on directly measured Alzheimer's and Parkinson's disease pathology and related biomarkers, including quantitative measures of motor impairment based on assessments with biosensor devices. We are also deploying whole genome sequencing in the Alzheimer's and Parkinson's disease clinics and returning results to patients and families for precision medicine applications. Lastly, we are actively exploring links between inherited pediatric lysosomal disorders and oligogenic risk for late-onset, adult neurodegenerative diseases.

***Drosophila* Genetics:** Despite the promise of current human genomic strategies, such as genome-wide association studies, next-generation sequencing, and gene expression profiling, they often fail to definitively identify disease causal genes and variants. Therefore, we are taking advantage of the rapid and powerful genetics available in the fruit fly, *Drosophila melanogaster*, in order to accelerate the validation of responsible genes and understanding of relevant mechanisms. The expression of human amyloid-beta, Tau, or alpha-synuclein proteins in the fly nervous system recapitulates many core features of Alzheimer's disease and Parkinson's disease pathogenesis. We are testing candidate human susceptibility genes for functional genetic interactions in these fly models of neurodegeneration. Implicated molecular pathways are probed in greater depth, using both *Drosophila* as well as mouse and human cellular models for translation. Current areas of interest include endolysosomal sorting, RNA metabolism/splicing, neuronal cell adhesion and synaptic mechanisms of neurodegeneration. In order to dissect the dynamic, aging-dependent gene expression changes in brains affected by Alzheimer's and Parkinson's disease, we are also generating and analyzing longitudinal, multi-scale omic datasets from fly and mouse models.

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# PAWEL STANKIEWICZ, M.D., PH.D.

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

*M.D., Medical University of Warsaw, Poland*
*Ph.D., Institute of Mother and Child, Warsaw, Poland*
*Postdoc, Baylor College of Medicine*
*Dr. Habil (D.Sc), Institute of Mother and Child, Warsaw, Poland*

## RESEARCH INTERESTS

**Genomic Disorders:** The focus of our research is pathogenetics of lung development, and particularly the role of non-coding regulatory elements. We demonstrated that haploinsufficiency of the transcriptional factor *FOXF1* gene on 16q24.1 results in a lethal neonatal diffuse developmental lung disorder, alveolar capillary dysplasia with misalignment of pulmonary veins. We described the role of the *TBX4* and *FGF10* genes in other developmental lung diseases, including acinar dysplasia and congenital alveolar dysplasia.

We found that somatic mosaicism for CNVs that also contribute to germline mosaicism is significantly more common than previously thought. We showed that a considerable number of apparently *de novo* mutations causing genomic disorders occur in the previous generation as low-level somatic mosaicism and can thus be recurrently transmitted to future offspring.

We unraveled the complexity of ancestral chromosome 2 fusion in humans, going from 48 to 46 chromosomes in hominin evolution.

We identified the causative role of the *PSMD12*, *BPTF*, *MEF2C*, and *TRIP12* genes and defined the Stankiewicz-Isidor syndrome (OMIM #617516), Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies syndrome (OMIM #617755), Chromosome 5q14.3 deletion syndrome (OMIM #613443), and Clark-Baraitser syndrome (OMIM #617752), respectively.

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# V. REID SUTTON, M.D.

**Professor and Vice Chair for Graduate Medical Education**, Department of Molecular and Human Genetics
**Director**, Medical Genetics Residency & Fellowship Programs
**Director**, Inborn Errors of Metabolism Service, Texas Children's Hospital
**Medical Director**, Biochemical Genetics Laboratory, Baylor Genetics

*M.D., University of Kentucky*
*Resident, Pediatrics, Washington University in Saint Louis*
*Fellow, Medical Genetics & Clinical Biochemical Genetics, Baylor College of Medicine*

## RESEARCH INTERESTS

I have committed myself to advance scientific knowledge and patient care by applying my clinical skills to research questions. I have employed my knowledge and expertise in the diagnosis of genetic syndromes, dysmorphology, genetic mechanisms of disease, inborn errors of metabolism and skeletal dysplasias to answer clinical research questions. I have done this in independent studies of my own design as well as many instances of collaborative research with colleagues engaged in the laboratory investigation of Mendelian diseases.

I have made contributions through gene discovery and defining the phenotypic spectrum of a number of syndromes including Uniparental Disomy for Chromosome 14, Aicardi, Goltz, Ankyloblepharon-Ectodermal Dysplasia Clefting (AEC), Robinow and White-Sutton syndromes. I am the clinical geneticist for the Baylor Center for Genomic Research to Elucidate the Genetics of Rare Disorders (GREGoR) which is an NIH/NHGRI-funded study to discover the genetic basis of Mendelian disorders.

In my role as the Medical Director of the Biochemical Genetics Laboratory at Baylor Genetics, I have overseen the development of large-scale metabolomic profiling for the screening and diagnosis of inborn errors of metabolism, and our laboratory is the first in the world to offer metabolomic profiling on a clinical basis, which has led to both advances in care and new discoveries.

I am the principal investigator for a multi-site longitudinal study of OI that is funded by the NIH (NCATS, NICHD, NIDCR, NIAMS & NIMH) as part of the Brittle Bone Disorders Consortium of the Rare Disease Clinical Research Network. I am also the clinical team liaison for this project.

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# NICHOLAS TRAN, PH.D.

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*Ph.D., Washington University in St Louis*
*Postdoc, Harvard University*

## RESEARCH INTERESTS

The brain is composed of a remarkably diverse set of neuronal cell types that each play a specific role in supporting brain function. When CNS tissues are damaged by injury or disease, this complex machine becomes dysfunctional, often with limited potential for recovery. A curious phenomenon is that in essentially all neurodegenerative conditions, certain cell types are more affected than others. My lab focuses on understanding what happens to different neuronal populations in neurodegenerative conditions using cutting-edge, single-cell genomic approaches. Our model of choice is the retina, the most accessible part of the brain, which we use both to study blinding disorders like glaucoma and to study basic mechanisms of degeneration. Our ultimate mission is to identify better targets for therapies that protect neurons from degeneration and stimulate axon regeneration.

## SELECTED PUBLICATIONS

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# MICHAEL WANGLER, M.D.

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

## RESEARCH INTERESTS

### Molecular and Developmental Mechanisms of Mendelian Disorders

Our lab studies rare human disease phenotypes to gain insight into general principles of human health. Methods include clinical studies in rare disease, genomics and model organism genetics particularly *Drosophila melanogaster*. We are currently using *Drosophila* to study Mendelian disorders and their underlying genetic and developmental mechanisms in two major efforts:

**1) Model Organisms and the Molecular Pathogenesis of Mendelian Disorders:** We use *Drosophila* models for diagnostic paradigms. We are part of the Model Organisms Screening Center (MOSC) for the Undiagnosed Diseases Network (UDN). We also use these methods in underserved populations in Texas called Community TEXOME.

**2) Mendelian Disorders of the Peroxisome and Organelle Dynamics:** Peroxisomes are fundamental sub-cellular organelles present in all eukaryotic cells. We use clinical and *Drosophila* studies in the elucidation of mechanisms of Peroxisomal Biogenesis Disorders- Zellweger Spectrum disorders (PBD-ZSD). These diseases are expanding from autosomal recessive disorders to a broad range of human diseases related to peroxisomes.

## SELECTED PUBLICATIONS

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# THOMAS F. WESTBROOK, PH.D.

**Robert A. Welch Chair in Chemistry**
**McNair Scholar**

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

*Ph.D., University of Rochester School of Medicine*
*Postdoc, Harvard Medical School*

## RESEARCH INTERESTS

Cancers are driven by genomic and epigenetic alterations that result in the activation of cellular proto-oncogenes and the inactivation of tumor suppressor genes. Although high-throughput genomic approaches have begun to establish extensive catalogs of gene alterations in human tumors, the genes that control tumor genesis, progression, and response to therapies are often concealed by the complex chromosomal instability in cancer cell genomes. This challenge is exacerbated by the lack of functional annotation for the vast majority of genes in the human genome. Thus, functional approaches are critical for identifying the genetic programs underlying cancer pathogenesis. Our laboratory applies genome-wide RNA interference (RNAi) and other technologies to the unbiased discovery of cancer genes and networks. Specifically, we focus on two areas of cancer gene discovery:

**Discovering new oncogene-induced "stress pathways" and translating these pathways into cancer therapies:** The cancer community has largely studied the effects of oncogenes and tumor suppressors and how they contribute to the "pro-tumorigenic" hallmarks of cancer cells. However, it has also become clear that oncogenes themselves induce a variety of stresses in cancer cells such as metabolic reprogramming, oxidative pressures, mitotic instability, and proteomic imbalance. These stress phenotypes, sometimes collectively referred to as ***oncogenic stress***, can serve to antagonize tumor growth and survival. The idea that oncogenes confer a highly stressed state onto cancer cells predicts that strategies to exacerbate one or more of these oncogene-induced stresses may tilt this balance in favor of killing cancer cells. We have been interested in exploiting the idea of oncogene-induced stresses for therapeutic discovery by tackling 3 poorly understood questions: **(1)** what are the molecular mechanisms by which prominent oncogenes (ex. Myc, Ras, etc.) induce these stresses? **(2)** how do cancer cells tolerate these stresses? and **(3)** are these stress support pathways different in normal and tumor cells? By using forward genetic approaches, we have made surprising discoveries about the endogenous cell pathways that are required to tolerate predominant oncogenic drivers like c-Myc (ex. Kessler *et al.*, Science 2012). We are now extending these studies by elucidating the stress support pathways that enable cancer cells to tolerate other prominent drivers.

**Identifying new oncogene / tumor suppressor networks via functional genetic screens:** With the explosion of genomic data emerging from TCGA, COSMIC, and other annotations of cancer genomes, there are fundamental challenges in **(1)** discerning which mutant genes are critical cancer drivers, **(2)** how these drivers are connected in genetic / signaling networks, and **(3)** how these cancer gene networks can be exploited for new therapies. We are addressing these important questions by developing genetic screens in human and mouse systems for new cancer gene networks. By combining new genetic technologies and engineered cell systems, we are uncovering new tumor suppressors (PTPN12, REST, INPP4B, etc.) and oncogenes (PLK1, TEX14, etc.) that control tumor initiation and progression (ex. Westbrook *et al.*, Nature 2008; Sun *et al.*, Cell 2011; Pavlova *et al.*, eLife 2013). Through orthogonal studies, we have assembled these cancer genes into interconnected networks and uncovered new entrypoints for cancer therapies. For example, our group discovered a new tumor suppressor network that is disrupted in more than 70% of aggressive triple-negative breast cancers (TNBCs), with the tyrosine phosphatase PTPN12 acting as a core component of this network. Importantly, disruption of this tumor suppressor network leads to the concerted hyper-activation of a class of receptor tyrosine kinases. These kinases work together to drive TNBC and probably other cancers. Importantly, we have shown that pharmacologic inhibition of these collaborating kinases leads to tumor regression of primary TNBCs *in vivo*. We are currently dissecting the mechanism(s) by which these signaling pathways cooperate, and translating these discoveries into new clinical trials for TNBC patients at Baylor.

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# KIM C. WORLEY, PH.D.

**Professor and Vice Chair for Research Affairs - Basic and Translational**, Department of Molecular and Human Genetics
**Faculty Member**, Human Genome Sequencing Center
**Chair,** BCM Faculty Senate

*B.S., Massachusetts Institute of Technology*
*Ph.D., Baylor College of Medicine*
*Postdoc, Baylor College of Medicine*

## RESEARCH INTERESTS

My research interests center on building, annotating, understanding and making use of genomes. I have coordinated research in large multi-institutional international research consortia, including analysis and publication of research results for the Human Genome Project, Human Microbiome Project, and comparative genomics projects for over 40 animal species. For these projects, I had a role in creating genome representations through *de novo* genome assembly, improving genome representation through targeted sequencing and structural variation analysis, and contributing to the understanding of genome function through analysis, annotation and computational methods. The number of sequenced human genomes has increased, and genomes representative of diverse humans have become available, but the challenge of interpreting the impact of personal variation and applying this knowledge in a way that serves individual patients and improves the practice of medicine remains an analytical frontier.

Ongoing research interests include:

**All of Us:** As a part of the *All of Us Evenings with Genetics* Research Education Program, led by Dr. Debra Murray, I lead data science training for researchers to study the *All of Us* data. Their research projects include gene-disease association studies using the extensive whole genome sequence, clinical records, environmental exposure and survey data. Trainees with computational experience can be trainers with the program. Early-stage investigators can apply for the program at https://www.bcm.edu/departments/molecular-and-human-genetics/engagement-and-equity/all-of-us-evenings-with-genetics-research-program.

**Alzheimer's Disease Sequencing Project Consortium (ADSP):** I work with Drs. Olivier Lichtarge, Ismael Al-Ramahi, Juan Botas and Joanna Jankowsky on projects to assess the functional impact of variants in the ADSP data. Read more about the consortium here: https://www.nia.nih.gov/research/dn/alzheimers-disease-sequencing-project-consortia.

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

**RE-JOIN (Restoring Joint Health and Function to Reduce Pain):** This consortium is mapping the network of sensory nerves that connect to the temporomandibular (TMJ) and the knee joints to understand how the types and patterns of sensory neuron networks in joints change with disease and aging. Drs. Brendan Lee, Ben Arenkiel, and Russell Ray lead the Baylor mouse knee joint project. I work with the administrative team and the 'omics working group enabling cross-project communication.

**Undiagnosed Diseases Network / Undiagnosed Diseases Center:** For this project, I lead the sequence analysis and variant interpretation group. We utilize genome sequencing as well as newer assays (RNAseq, long read sequence data, Hi-C data) to identify causal genomic variants and diagnose undiagnosed patients. Find out more about the Baylor UDC at https://www.bcm.edu/research/research-centers/undiagnosed-diseases-center.

**Other strategic initiatives:** I also work on strategic projects related to genomic data science at Baylor including the Consultagene platform (https://consultagene.org/), researcher access to genomic data and new sequencing technology implementation.

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# TAO WU, PH.D.

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**CPRIT Scholar in Cancer Research**

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*Postdoc, Yale Stem Cell Center & Department of Genetics, Yale School of Medicine, New Haven, CT*

## RESEARCH INTERESTS

The Wu Lab is dedicated to understanding how mammalian cells make dynamic decisions in response to internal and external signals in both developmental and disease models. Our long-term goal is to transfer the knowledge from the bench to the bedside. Our current central question is to unearth the molecular mechanisms underpinning cellular plasticity unlocking (CPU) and cell reprogramming. Cellular plasticity (CP) refers to the capacity of cells to transfer their state/identity (ID) and function in response to various signals and environmental stimuli. Therefore, such as the cell ID, CP is an intrinsic property and crucial in embryonic development, tissue repair, aging, and human diseases, such as cancer.

Cancer is a systems biological disease. Despite the development of powerful weapons such as chemotherapies, targeted therapies, and immunotherapies in the past decades, treatment resistance remains a pressing challenge and the leading cause of patient mortality. While acquired resistance can be partially attributed to genetic mutations induced by treatment, it could also be driven by CPU and non-mutational epigenetic reprogramming at specific stages. Epigenetic processes in mammals, such as DNA/RNA methylations and histone modifications, are pivotal for controlling cell ID and CP. The profound alterations of epigenetic markers are common signatures in most types of cancer. In 2022, "Unlocking Phenotypic Plasticity," underpinned by cancer cell aberrant CPU, has been assigned as one of the new hallmarks of cancer, along with another rising hallmark, "Nonmutational Epigenetic Reprogramming." However, the underlying molecular mechanisms by which the epigenetic mechanisms govern the CPU and drive the cancer cell adaptation/evolution remain elusive.

In my previous research, we discovered a novel non-canonical mammalian DNA modification, "N6-methyladenine" (6mA), with SMRT-ChIP (3rd-generation single-molecule real-time sequencing with native ChIP) in mouse embryonic stem cells. We also identified ALKBH1 as the major demethylase/eraser of DNA 6mA. Then, we pinpointed that the 6mA and ALKBH1 appear to regulate hypoxia response genes, which are well-known for driving drug resistance development in GBM. After I joined BCM, we developed new chemical-based sequencing methods to quantify 6mA methylation at single-base resolution. DNA 6mA's readers, writers, and erasers could be novel targets that help to bypass the resistance and boost the first-line therapies.

In addition to epigenetic factors, we also focus on the "dark matter" of the human genome, endogenous retrotransposable elements (ERE). We have found that the human endogenous retrovirus-like elements (HERVs) become aberrantly active in the chemo-treatment adaptation of triple-negative breast cancer (TNBC). Furthermore, our recent findings indicated that a subset of cells with high HERVs activity might transiently mediate the persistence of cancer cells at the early stage of the treatment, and HERVs activity coupled with whole transcriptomic and chromatin landscape reprogramming. Currently, we employ embryonic stem cell and cancer patient-derived organoid (PDO) models to investigate the functional roles of non-canonical targets like EREs in the drug-tolerant persistent (DTP) cancerous cells with holistic approaches (genomics, systems genetics, biochemistry, single-cell multi-omics, and machine learning). In the past five years, we and our multidisciplinary collaborators have been developing new technologies and defining novel yardstick to couple epigenetic mechanisms and CPU.

In other words, we are uniquely positioned to potentially uncover critical pieces of the CP puzzle and design new strategies to overcome treatment resistance. The discovery of novel factors for CP control might lead to the next paradigm-shifting in regenerative medicine and cancer biology.

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

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**Associate Director**, Graduate Program in Genetics & Genomics
**Faculty Member**, Graduate Programs in Development, Disease Models & Therapeutics and Neuroscience

*D.V.M., The University of Tokyo/Ministry of Agriculture, Forestry and Fisheries of Japan*
*Ph.D., Baylor College of Medicine*
*Postdoc, Baylor College of Medicine*

## RESEARCH INTERESTS

Many projects in the Yamamoto lab are related to rare and undiagnosed diseases. Over 25 million individuals (about the population of Texas) are affected by rare or ultra-rare diseases in the U.S. alone (>300 million worldwide), and many affected individuals experience a long and winding 'diagnostic odyssey' to try to find out the cause of their disorders. While state-of-the-art genomic technologies such as whole-exome sequencing (WES) and whole-genome sequencing (WGS) may provide answers to a subset of these individuals, many are often left with a handful of candidate genetic variants that require experimental studies to understand their functional consequences. As a co-director/leader and member of the Model Organisms Screening Center (MOSC) of the Undiagnosed Diseases Network (UDN) and Baylor College of Medicine (BCM) Center for Precision Medicine Models (CPMM), my lab utilizes the fruit fly *Drosophila melanogaster* to test whether a genetic variant identified in a patient is the cause of their disease, which is pursued in close collaboration with clinicians and human geneticists across the country and around the world. We also study functional consequences of rare variants linked to common neurological disorders such as Alzheimer's disease and autism spectrum disorders and further leverage *Drosophila* genetics to study disease mechanisms. I also lead or co-lead the development of novel computational tools such as ModelMatcher (https://www.modelmatcher.net) and MARRVEL (http://marrvel.org) through close collaboration with bioinformaticians and programmers at BCM to facilitate rare disease diagnosis, research and collaborations.

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# BING ZHANG, PH.D.

## McNair Scholar

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*Postdoctoral fellow, University of Tennessee, Knoxville*
*Postdoctoral fellow, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

## RESEARCH INTERESTS

Advances in high-throughput sequencing, mass spectrometry, and informatics have transformed cancer research. To harness these innovations, I lead an interdisciplinary research team dedicated to developing advanced data analytical methods that translate the vast amount of cancer omics data into actionable biological and clinical insights. Our work spans three strategic domains: computational proteomics, proteogenomics for precision oncology, and data democratization. Through computational proteomics, we decode the intricate dynamics of proteins and their modifications, which are essential for cellular function and the success of therapeutic interventions. In the realm of precision oncology, we use an integrated proteogenomic approach to elucidate the functional consequences of genetic variations, enhancing the personalization of available therapies and informing new treatment development. Furthermore, we simplify the complexity of cancer data through user-friendly interfaces, providing the scientific community with accessible tools to navigate the ever-expanding cancer data landscape. Our commitment in these areas has spawned data-driven hypotheses that illuminate new biological mechanisms, biomarkers, and therapeutic targets, particularly in the fields of targeted and immunotherapies. In close collaboration with cancer biologists and clinicians, we aim to turn these discoveries into tangible benefits for cancer patients.

## SELECTED PUBLICATIONS

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# LILEI ZHANG, M.D., PH.D.

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*Ph.D., Johns Hopkins University, Baltimore, Maryland*
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*Intern, University Hospitals Case Medical Center, Cleveland, Ohio*
*Resident, Internal Medicine, University Hospitals Case Medical Center, Cleveland, Ohio*
*Fellow, Medical Genetics, University Hospitals Case Medical Center, Cleveland, Ohio*
*Postdoctoral Fellow, Case Western Reserve University, Cleveland, Ohio*

## RESEARCH INTERESTS

Our overarching mission is to translate the study of genetic and epigenetic regulation of cardiovascular disease into novel therapeutic approaches. One of our research focuses is circadian gene regulation in cardiac remodeling. Our work covers the entire circadian regulatory landscape, from the core clock to the slave clock, to the effectors. We discovered that core clock factor REV-ERB is protective for cardiac pathological remodeling and pharmacological activation of REV-ERB prevents heart failure progression even in late-stages. We recently expanded this finding to both HFrEF and HFpEF models and mechanistically demonstrated that REV-ERB suppressed aberrant gene expression, which is required for heart failure development and progression. This was the first example of treating heart failure by manipulating circadian machineries and shows great promise to complement current standard of care. Our finding is now being accelerated towards IND. We also established the very first cardiac slave clock, KLF15, which controls the circadian ischemia reperfusion injury in the heart via regulating $NAD^+$.

Another focus of our laboratory is to study inherited cardiac diseases using induced pluripotent stem cell differentiated cardiomyocyte (iPSC-CM) model. We have recently demonstrated that folate can terminate otherwise lethal and recalcitrant arrhythmia in patients with TANGO2 deficiency disorder. This result corroborates what we have observed in large patient cohort and isolated case reports. Additionally, we use iPSC-CMs combined with genome editing, a battery of high throughput phenotyping and machine learning tools to answer human genetics questions in inherited cardiac diseases, including identifying novel disease genes, interpreting variants, understanding disease mechanisms, and testing novel therapeutic strategies.

## SELECTED PUBLICATIONS

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# HUI ZHENG, PH.D.

## Huffington Foundation Endowed Chair in Aging

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## RESEARCH INTERESTS

Alzheimer's disease (AD) is the most common form of neurodegenerative disorder characterized by the deposition of beta-amyloid plaques and the accumulation of tau tangles. My laboratory has a long-standing interest in basic and translational research on Alzheimer's disease. Our expertise is mouse genetics, and we are known for using sophisticated mouse models and innovative approaches to probe the biology and pathophysiology of AD. Our earlier investigation provided critical insights into the physiological functions of the amyloid precursor protein and presenilins, mutations of which are linked to early-onset AD. Our recent effort has expanded from neurons to glial cells and from amyloid pathology to tau tangles. Our overarching hypotheses are AD is caused by faulty clearance of misfolded proteins and manifested by uncontrolled neuroinflammation. Accordingly, our major projects are focused on the investigation of the autophagy-lysosomal pathway and neuron-immune interaction with the goal to understand the disease mechanisms and to identify new therapeutic targets. Along these lines, we identified a highly selective and potent role of TFEB in the clearance of tau tangles and deciphered cell-autonomous and non-cell-autonomous mechanisms in this process. Additionally, we mapped out a complement C3 and C3aR signaling axis that governs network function and innate immunity in the context of aging, AD and tauopathy. Lastly, we revealed a novel epoxy lipid metabolic pathway that becomes dysregulated in AD and show that targeting this pathway by small molecule inhibitors lead to potent anti-inflammatory and neuroprotective effects, supporting the potential of these inhibitors as AD therapy.

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## SELECTED PUBLICATIONS

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# QIAN ZHU, PH.D.

**Assistant Professor**, Department of Molecular and Human Genetics
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## RESEARCH INTERESTS

Dr. Qian Zhu is interested in studying the role of genetic elements and their chromatin interactions in developmental diseases (sickle cell disease, muscular dystrophy), and in breast cancer.

He integrates large-scale datasets such as chromatin accessibility, transcription factor binding, histone modifications, and 3D chromatin structure data to characterize changes in the chromatin and epigenome during normal cell development, and in diseases when chromatin regulators are mutated or dysfunctional. He is recently interested in the nuclear matrix protein Matrin-3, implicated in skeletal muscle dystrophy and amyotrophic lateral sclerosis. He works with biologists to characterize chromatin rewiring of several developmental loci caused by Matrin3 knockout, which can explain pathological processes seen in muscular dystrophy and ALS patients. It is expected that mutations and knockout studies of Matr3 will provide the context for better understanding the interplay between nuclear matrix organization, chromatin structure, and RNA processing.

His second interest is to characterize the role of genetic elements to breast cancer development. Treatment resistance is still a major problem among breast cancer patients. He is interested in characterizing the genetic elements that underlie treatment resistance and therapy response. Specifically, he would like to characterize the role of chromatin structure rewiring as a mechanism of treatment resistance, and the instances of enhancer hijacking and super enhancer formation seen in rearranged tumors. Variations between individual cancer patients in their chromatin accessibility profiles and epigenomes may govern individuals' response to immunotherapy. These works will require overlaying chromatin structure and epigenome profiles on top of existing database of cancer susceptibility loci to better interpret the role of these loci.

His final interest is in the informatics development for novel spatial multi-omic technologies such as spatial transcriptomics, proteomics, and epigenomics. Further integration of these technologies with images (H&E, IFs) is particularly useful in pathological diagnosis and biomarker development. In his CPRIT-funded project, he will develop methodologies to characterize morphological genes whose expression associate with morphological features extracted from images and conduct morphological-based screening for drugs that can target EMT. Ultimately, the spatial transcriptomic experiments not only can aid in disease diagnosis, but also can guide drug-screening by leveraging image features and morphology-gene associations.

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# ANTHONY WILLIAM ZOGHBI, M.D.

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*T32 Schizophrenia Research Fellowship, Columbia University Irving Medical Center, New York State Psychiatric Institute*

## RESEARCH INTERESTS

The primary goal of our lab is to understand the biological basis of neuropsychiatric disorders and translate those insights into improvements in clinical care, disease risk prediction and novel therapeutic development. To achieve this goal, we combine novel phenotyping strategies (e.g., studying severely affected patients), whole genome sequencing, proteomics, and cutting-edge bioinformatics tools development to identify clinically relevant genetic risk factors and biomarkers across psychiatric disorders.

We are also exploring the role of the immune system in psychiatric disorders. Specifically, we aim to identify autoimmune causes of neuropsychiatric disorders using state-of-the-art autoantibody profiling technologies. By integrating genomic and proteomic technologies with advanced computational and machine learning techniques, we aim to identify actionable diagnostic biomarkers and accelerate therapeutic development to improve the lives of those suffering from these disabling conditions.

## SELECTED PUBLICATIONS

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# HUDA Y. ZOGHBI, M.D.

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## RESEARCH INTERESTS

My laboratory's research is rooted in my early clinical encounters with patients suffering rare and enigmatic disorders. One memorable patient suffered Rett Syndrome; another was part of a family that suffered a neurodegenerative disease that struck each successive generation at younger ages. Our investigations into the pathogenesis of these two diseases have influenced our understanding of basic neurobiology and more common disorders such as autism and Alzheimer's disease. Conversely, our foray into fundamental neurodevelopmental processes governed by Atonal homolog 1 (Atoh 1) has had unexpected ramifications for our understanding of (and potential therapies for) several diseases, from deafness and medulloblastoma to sudden infant death syndrome.

**Polyglutamine Pathogenesis and Neurodegeneration.** We co-discovered the gene for spinocerebellar ataxia type 1 (SCA1) in 1993 with Harry Orr, Ph.D., at the University of Minnesota and have been collaborating to understand the disease mechanism. Our genetic studies in mice and (in collaboration with Juan Botas, Ph.D.) in fruit flies, led us to propose that the polyglutamine tract stabilizes Ataxin-1 increasing its levels and interactions and causing toxicity due to its enhanced function. We also discovered that the enhanced function of mutant Ataxin-1, with its native partner Capicua (CIC), drives the cerebellar ataxia. Further, we discovered that reducing Ataxin-1 in the cerebellum is a viable therapeutic strategy, but that for other vulnerable brain regions the pathogenic mechanism is distinct. Interestingly, we learned that loss of Ataxin-1 and the subsequent repressor activity loss of the Ataxin-1-CIC complex leads to upregulation of *Bace1* and increased risk of Alzheimer pathology in the forebrain. Our current studies are focused on understanding the mechanisms driving the regional vulnerability in SCA1.

Inspired by our work on SCA1 and the importance of Ataxin-1 levels for brain health, we have pursued cross-species studies to identify modulators of APP, tau, and alpha-synuclein, proteins that drive degeneration in Alzheimer's and Parkinson's disease. We have identified and validated several modulators of tau levels. Exploring the mechanisms by which such modulators regulate tau levels we have gained insight into tau biology and the key molecules involved in its degradation. We are capitalizing on our genetic and mechanistic data to develop potential therapeutic strategies that can help people with Alzheimer's and related dementias.

**Rett Syndrome and Autism Spectrum Disorders.** We discovered that Rett syndrome is caused by mutations in the X-linked methyl-CpG–binding protein 2 (*MECP2*). Our mouse model studies led to the definition of clinical phenotypes not previously appreciated in *MECP2* disorders and revealed that neurons are quite sensitive to having just slightly too much or too little MeCP2. In collaboration with Jianrong Tang, Ph.D., at Baylor, we found that forniceal deep brain stimulation restored hippocampal learning and plasticity. Using an *MECP2* duplication mouse model, we showed that normalizing MeCP2 levels using antisense oligonucleotides reverses disease symptoms including late onset seizures in adult mature animals. These findings set the stage for a clinical trial to treat patients with *MECP2* duplication syndrome. More recently, we discovered that presymptomatic training of Rett mice improved their performance, delayed disease onset by months, and improved neuronal morphology and physiology. We are now focused on understanding the molecular mechanism mediating the benefits from early training. In addition, we are developing strategies to increase MeCP2 levels as potential therapies for Rett patients with partially functioning MeCP2. Lastly, we are pursuing studies to understand the regulation and functions of MeCP2.

Beyond Rett, we are interested in understanding what drives the male sex bias of autism spectrum disorders (ASD). Based on our preliminary data, we propose that hypomorphic and non-coding mutations in X-linked genes render males more vulnerable to ASD; we are testing this hypothesis in collaboration with Evan Eichler, Ph.D., Aravinda Chakravarti, Ph.D., and Tomasz Nowakowski, Ph.D.

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# CHENGHANG (CHUCK) ZONG, PH.D.

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*Postdoc, Harvard University*

## RESEARCH INTERESTS

The research of our laboratory focuses on the development of novel single-cell technologies and their applications in biology studies. With the rapid development of next-generation sequencing technology, high-throughput sequencing has become a powerful tool for biological research. In our lab, we are interested in examining the genome at single-cell resolution, in contrast to the genome averaged from an ensemble of cells. As a demonstration of the principle, we can detect somatic mutations existing in individual cancer cells. We are particularly interested in detecting early mutations that drive tumorigenesis and the early stage of tumor heterogeneity that will influence later tumor development. The lab specifically focuses on pancreatic cancer. Supported by NIH's New Innovator's award, we have successfully developed a linear amplification-based whole-genome amplification method (LCS-WGA), which allows us to profile not only the somatic mutations existing in single cells but also the spontaneous DNA damage in single cells for the first time, which we refer to as damagenome. The successful profiling of DNA damagenome promoted us to identify the high-damage genes existing in the human genome and unveil their association with complex human diseases. Furthermore, the even genome coverage of a single cell allows to construct the single-cell tumor evolution tree at unprecedented resolution.

In addition to profiling the genome at single-cell resolution, we are also interested in developing novel methods for single-cell transcriptional profiling. We have developed the first single-cell total-RNA-seq method (MATQ-seq). MATQ-seq has been applied to characterize the early lesions of pancreatic cancer using the mice model, the heterogeneity in tumor and its microenvironment, and various biological processes through collaborations.

Recently we have developed the droplet-based high throughput platform of MATQ-seq: MATQ-drop. MATQ-Drop can process both frozen and FFPE samples, which allows authentic profiling of tumor heterogeneity. Furthermore, we have successfully applied MATQ-Drop to profile the transcriptome of individual synapses (synaptosome). The high-throughput gene expression profiling of individual synapses opens a new avenue to study various neurological processes and diseases. Our goal is to unveil the transcriptome and epigenome changes in various biological processes such as tumorigenesis, aging and neurodegeneration.

## SELECTED PUBLICATIONS

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## CHRISTIE M. BALLANTYNE, M.D.

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

**Professor**, Departments of Medicine, Molecular and Human Genetics and Molecular Physiology and Biophysics
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*Clinical Fellow, Cardiology, Baylor College of Medicine*
*American Heart Association/Bugher Foundation Fellowship, Howard Hughes Medical Institute and Institute for Molecular Genetics, Baylor College of Medicine*

### RESEARCH INTERESTS

Dr. Ballantyne's research interests include the pathophysiology of atherosclerosis, focusing on monocyte activation and adhesion. Ballantyne and his colleagues use both murine and human studies to understand the mechanisms by which hyperlipidemia and obesity influence inflammation.

Ballantyne's clinical research interests include preventive cardiology, lipids, metabolic syndrome, atherosclerosis, genetics and coronary artery disease. As director of the core laboratory for the ARIC study, Ballantyne examines the role of genetic variation combined with novel biomarkers to identify individuals at high risk for cardiovascular disease, metabolic syndrome and diabetes, using genomics and proteomics. His group also studies how genetic variation modifies the response to therapy with the goal of developing personalized diet, lifestyle and pharmacotherapy based on genetic profile and clinical phenotype.

### SELECTED PUBLICATIONS

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*Internship and Residency, Pediatrics, Baylor College of Medicine*
*Clinical Fellow in Pediatric Hematology/Oncology and Postdoc, Baylor College of Medicine*

### RESEARCH INTERESTS

Dr. Alison Bertuch's research is aimed at understanding the mechanisms of telomere structure and function and DNA double-strand break repair and their intersection. Her research uses yeast as a model system for the rapid identification and investigation of the genes that govern telomere homeostasis as well as human cell lines. In addition, Dr. Alison Bertuch's laboratory studies the role of telomere and DNA repair dysfunction in the development of bone marrow failure in children. A long-term goal is to exploit the knowledge gained from these studies to aid in the treatment of not only bone marrow failure but also cancer.

### SELECTED PUBLICATIONS

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### RESEARCH INTERESTS

Dr. Brenner's primary research interest is the use of gene transfer to augment the immune response to human tumors, using vaccines and adoptive transfer of genetically modified T cells. In neuroblastoma, Dr. Brenner and co-investigators have shown that T cells expressing a chimeric antigen receptor (CAR) for a surface marker (GD2) on neuroblastoma cells can produce tumor responses in more than half the patients with refractory or relapsed disease. The Center for Cell & Gene Therapy is also studying the benefits of T cells, including those modified with CARs, that target other tumor antigens on hematological malignancies and solid tumors and initial clinical results are promising. Efforts are being made to further increase the effectiveness of these T cells by incorporating genes that enhance T cell growth and survival and that render the T cells resistant to the inhibitory effects of many human tumors. To enhance the safety of genetically modified T cells, Dr. Brenner and colleagues have clinically developed an inducible caspase system that will rapidly cause apoptosis of T cells within minutes of administration of a small molecule dimerizing drug, allowing adverse effects from the T cells to be reversed.

### SELECTED PUBLICATIONS

Hegde M, Mukherjee, M, Grada Z, (...), **Brenner MK,** et. al. (2016). Tandem CAR T cells targeting HER2 and IL13Ra2 mitigate tumor antigen escape. **J Clin Invest**. 126: 3036-3052.

Ramos CA, Savoldo B, Torrano V, (...), **Brenner MK,** et. al. (2016). Clinical responses with T lymphocytes targeting malignancy-associated k light chains. **J Clin Invest**. 126: 2588-2604.

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

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

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## EDWARD C. COOPER, M.D., PH.D.

**Associate Professor**, Departments of Neurology, Neuroscience, and Molecular and Human Genetics; Postdoctoral Training Program in Brain Disorders and Development; Graduate Programs in Genetics & Genomics and Neuroscience

*M.D., Yale School of Medicine, Yale University, New Haven*
*Ph.D., Yale School of Medicine, Yale University, New Haven*
*Residency, Neurology, University of California, San Francisco*
*Postdoc and Adjunct Asst. Professor of Neurology and Physiology, University of California, San Francisco*

### RESEARCH INTERESTS

The Cooper Lab is focused on understanding and developing new treatments for forms of epilepsy affecting infants, children, and adults, mood disorder that often accompanies epilepsy, and related brain disease. These are complex developmental disorders that impact the whole person and the brain as a system. To gain leverage on such tough problems, we have taken clues from human and experimental genetics implicating a molecular pathway—the machinery of the action potential, the neuron's rapid long-distance signal. Of central importance, both as genes often mutated in disease and therapeutic targets, are the voltage-gated potassium and sodium ion channels that generate and conduct the action potential's electrical currents. However, channels do not function alone. Therefore, we also study the protein networks and signal paths that position, regulate, and respond to these channels.

### SELECTED PUBLICATIONS

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

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

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

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## RYAN DHINDSA, M.D., PH.D.

**Assistant Professor**, Departments of Pathology & Immunology and Molecular and Human Genetics; Graduate Programs in Genetics & Genomics and Quantitative and Computational Biology;
**Investigator**, Jan and Dan Duncan Neurological Research Institute

*M.D./Ph.D, Columbia University College of Physicians and Surgeons, New York*

### RESEARCH INTERESTS

My research program focuses on how genomic variation influences human health, particularly in neurological disorders. In my lab, we combine population genetics, human stem cell models, and functional genomics models to investigate the genetic mechanisms of complex diseases and identify novel therapeutic targets. We have led the analysis of hundreds of thousands of human genomes, which has revealed an outstanding role of rare variants in complex human diseases and uncovered new risk genes for disorders such as epilepsy, Parkinson's disease, and others. In parallel, our group develops new statistical and machine learning methods to improve the interpretation of genetic variation. We combine these computational discoveries with focused molecular biological experiments, including CRISPR-based functional genomics screens in stem cell-derived neurons. These approaches allow us to uncover key molecular and cellular events in the development of neurodevelopmental and neurodegenerative diseases at scale. Through collaborations with academia and industry, we aim to translate these insights into targeted therapies and advancing precision medicine.

### SELECTED PUBLICATIONS

**Dhindsa RS**, Burren OS, Sun BB, Prins BP, Matelska D, (...); AstraZeneca Genomics Initiative; Vitsios D, Ashley EA, Whelan CD, Pangalos MN, Wang Q, Petrovski S (2023). Rare variant associations with plasma protein levels in the UK Biobank. **Nature**. 622: 339-347.

Wang Q, **Dhindsa RS**, Carss K, Harper AR, Nag A, (...); AstraZeneca Genomics Initiative; Wasilewski S, Smith KR, March R, Platt A, Haefliger C, Petrovski S (2021). Rare variant contribution to human disease in 281,104 UK Biobank exomes. **Nature**. 597: 527-532.

**Dhindsa RS**, Zoghbi AW, Krizay DK, Vasavda C, Goldstein DB (2021). A Transcriptome- Based Drug Discovery Paradigm for Neurodevelopmental Disorders. **Ann Neurol.** 89: 199-211.

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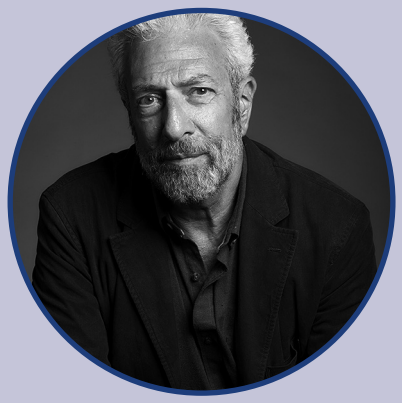
## RICHARD H. FINNELL, PH.D.

### William T. Butler, M.D., Endowed Chair for Distinguished Faculty



**Professor**, Departments of Molecular and Cellular Biology, Medicine, and Molecular and Human Genetics; Center for Precision Environmental Health; Graduate Programs in Genetics & Genomics and Development, Disease Models & Therapeutics

*Ph.D., University of Oregon Medical School*
*Postdoctoral fellow, Anatomisches Institut, Universität Zürich, Switzerland*

### RESEARCH INTERESTS

Dr. Finnell is a pediatric geneticist who has been involved in investigating genetic susceptibility to environmentally induced birth defects, applying stem cell technology to the detection of potential teratogenic compounds in efforts to prevent these birth defects utilizing genome editing technologies to create novel model systems to better understand the pathogenesis of the defects, and applying highly innovative approaches to treating these disabilities. The laboratory focuses on micronutrient transport during embryogenesis and the interaction between gene variants and one carbon metabolism as it relates to the development of birth defects. His research involves global collaborative NGS studies of complex birth defects and using precision medicine approaches to managing high-risk pregnancies.

### SELECTED PUBLICATIONS

Kim SE, Chothani PJ, Shaik R, Pollard W, **Finnell RH** (2023). Pax3 lineage-specific deletion of Gpr161 is associated with spinal neural tube and craniofacial malformations during embryonic development. **Dis Model Mech.** 16: dmm050277.

Caiaffa CD, Ambekar YS, Singh M, Lin YL, Wlodarczyk B, Aglyamov SR, Scarcelli G, Larin KV, **Finnell RH** (2024). Disruption of Fuz in mouse embryos generates hypoplastic hindbrain development and reduced cranial nerve ganglia. **Dev Dyn.** doi: 10.1002/dvdy.702. Epub ahead of print.

Iskandar BJ, **Finnell RH** (2022). Spina Bifida. **N Engl J Med.** 387: 444-450.

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## MARGARET A. GOODELL, PH.D.

### Vivian L. Smith Chair in Regenerative Medicine

**Chair and Professor**, Department of Molecular and Cellular Biology
**Professor**, Center for Cell and Gene Therapy and Departments of Pediatrics, Molecular and Human Genetics and Pathology & Immunology; Stem Cells and Regenerative Medicine (STaR) Center; Graduate Programs in Cancer & Cell Biology; Development, Disease Models & Therapeutics; and Genetics & Genomics

*Ph.D., Cambridge University*
*Postdoc, Whitehead Institute, Massachusetts Institute of Technology*
*Postdoc, Harvard Medical School*

### RESEARCH INTERESTS

**Murine and human hematopoietic stem cells; genetic and epigenetic regulation and development.**

We are interested in the basic biology of hematopoietic stem cells and how their regulation goes awry leading to leukemia development. It has been known for decades that hematopoietic stem cells reside in the bone marrow in a quiescent state and replenish the supply of differentiated cells of the peripheral blood throughout the lifetime of an animal. No other adult cell type retains the capacity for such immense proliferation and differentiation. However, little is known about the cells or factors that regulate their primitive state or control their activation. We study the behavior of these stem cells *in vivo* and *in vitro* using mouse stem cells as a model, as well as pursue the mechanisms which control their behavior on a molecular level using genome-wide profiling strategies and mouse mutants. Many of the genes that control normal stem cell behavior appear to become dysregulated in leukemia and lymphoma.

### SELECTED PUBLICATIONS

Hsu JI, Dayaram T, Tovy A, De Braekeleer E, Jeong M, (...), **Goodell MA** (2018). PPM1D Mutations Drive Clonal Hematopoiesis in Response to Cytotoxic Chemotherapy. **Cell Stem Cell**. 23: 700-713.e6.

Brunetti L, Gundry MC, Sorcini D, Guzman AG, Huang YH, (...), **Goodell MA** (2018). Mutant NPM1 Maintains the Leukemic State through HOX Expression. **Cancer Cell.** 34: 499-512.e9.

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

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

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## PHILIP J. LUPO, PH.D.

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

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

### RESEARCH INTERESTS

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

### SELECTED PUBLICATIONS

**Lupo PJ**, Schraw JM, Desrosiers TA, Nembhard WN, Langlois PH, (...), Plon SE (2019). Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births. **JAMA Oncol.** 5: 1150-1158.

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

Li H, Sisoudiya SD, *Martin-Giacalone BA, Khayat MM, Dugan-Perez S, (...), **Lupo PJ** (2021). Germline Cancer-Predisposition Variants in Pediatric Rhabdomyosarcoma: A Report from the Children's Oncology Group. **J Natl Cancer Inst.** 113: 875-883.

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# MARTIN M. MATZUK, M.D., PH.D.

## Stuart A. Wallace Chair in Pathology

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

*M.D., Ph.D., Washington University School of Medicine*
*Postdoc, Baylor College of Medicine*

### RESEARCH INTERESTS

Our laboratory is focused on 1) using functional genomics to investigate essential fertility pathways, reproductive tract cancers, and TGF-beta family signaling in mammals and 2) applying chemical biology approaches to develop lead compounds for contraception, cancer, and debilitating diseases. We have taken a discovery-based approach to first uncover genes expressed exclusively in the male or female germline and subsequently to define their roles *in vivo* using CRISPR/Cas9 technology and transgenic mouse models. In the process, we have identified novel genes involved in oocyte–somatic cell interactions during ovarian folliculogenesis, germ-cell intercellular bridge formation, acrosome formation, the piRNA pathway, etc. If a knockout results specifically in male infertility, this gene product may be a promising drug target for contraception in men, and our lab has begun to characterize small-molecule contraceptives to target male germ cells. We have successfully created unique mouse models to study ovarian cancer and to decipher the crosstalk of TGF-beta family, hormonal, and small RNA signaling pathways in normal and diseased reproductive tissues and their roles during pregnancy.

### SELECTED PUBLICATIONS

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

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

Nagashima T, Li Q, Clementi C, Lydon JP, DeMayo FJ, **Matzuk MM** (2013). BMPR2 is required for postimplantation uterine function and pregnancy maintenance. **J Clin Invest**. 123: 2539-50.

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

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# ANTHONY MUSTOE, PH.D.

**Assistant Professor**, Departments of Biochemistry and Molecular Biology and Molecular and Human Genetics; Therapeutic Innovation Center (THINC)
**CPRIT Scholar in Cancer Research**

*B.S., Washington University*
*Ph.D., University of Michigan*
*Postdoc, University of North Carolina*

### RESEARCH INTERESTS

The overarching goal of my laboratory is to define the mechanisms underpinning RNA folding and function. We seek to develop an improved, quantitative understanding of biology and human disease and to translate this knowledge into new therapeutic strategies. Our principal expertise is in developing and applying chemical probing techniques to define RNA structure and dynamics in living cells. We have used our technologies to discover novel functional structures in both non-coding RNAs and messenger RNAs (mRNAs), and to reveal transcriptome-wide roles for mRNA structure in tuning translation efficiency. We are presently applying our techniques to develop a quantitative understanding of how RNA structures modulate recognition and regulation by RNA binding proteins and microRNAs, and how RNA misfolding can lead to disease, particularly cancer. We additionally have multiple collaborations with other groups investigating the structure and function of diverse biomedically important RNAs.

### SELECTED PUBLICATIONS

Olson SW, Turner AW, Arney JW, Saleem I, Weidmann CA, Margolis DM, Weeks KM, **Mustoe AM** (2022). Discovery of a large-scale, cell-state-responsive allosteric switch in the 7SK RNA using DANCE-MaP. **Mol Cell**. 82: 1708-1723.e10.

**Mustoe AM**, Busan S, Rice GM, Hajdin CE, Peterson BK, Ruda VM, Kubica N, Nutiu R, Baryza JL, Weeks KM (2018). Pervasive Regulatory Functions of mRNA Structure Revealed by High-Resolution SHAPE Probing. **Cell**. 173: 181-195.e18.

**Mustoe AM**, Lama NN, Irving PS, Olson SW, Weeks KM (2019). RNA base-pairing complexity in living cells visualized by correlated chemical probing. **Proc Natl Acad Sci U S A.** 116: 24574-24582.

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## JEFFREY L. NOEBELS, M.D., PH.D.

### The Cullen Trust for Health Care Endowed Chair in Neurogenetics

**Professor**, Departments of Neurology, Neuroscience, and Molecular and Human Genetics; Graduate Programs in Neuroscience and Development, Disease Models & Therapeutics
**Director**, Blue Bird Circle Developmental Neurogenetics Laboratory

*Ph.D., Stanford University*
*M.D., Yale University*
*Postdoc, Harvard Medical School*

### RESEARCH INTERESTS

The principal research strategy in the Developmental Neurogenetics Laboratory is to apply mutational analysis to learn how genes regulate neuronal excitability and network synchronization within the developing central nervous system. We have linked over 40 genes with various patterns of epilepsy, and discovered hyperexcitability and synchronization defects in Alzheimer's Disease, leading to a paradigm change in understanding the basis for accelerated cognitive decline. Other current projects center on genes for absence seizures, the most common childhood epilepsy; linking epilepsy with lethal cardiac arrhythmias; and network hyperexcitability in the peritumoral cortical microenvironment of glioblastoma. We trace the biology of the mutant circuitry in mice using molecular anatomical, patch clamp, optogenetic and 2 photon imaging. These experimental studies form the basis for development of preclinical strategies to selectively correct the expression of neuronal gene errors early in development. In collaboration with the Baylor Human Genome Sequencing Center, we performed a large-scale translational genomic research study of ion channel genes in epilepsy (The Human Channelopathy Project). We also lead a multisite NIH Center without Walls focusing on risk prediction of variants in ion channel genes linked to neurocardiac phenotypes.

### SELECTED PUBLICATIONS

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

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

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

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

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

*Ph.D., Department of Pathology, Ohio State University College of Medicine*
*M.D., Ohio State University College of Medicine*
*Resident, Pediatrics, Johns Hopkins University*
*Clinical Fellow, Pediatric Hematology-Oncology, Johns Hopkins University & National Cancer Institute*
*Clinical Fellow, Neuro-Oncology, Johns Hopkins University*

### RESEARCH INTERESTS

Dr. Parsons studies the clinical application of genomic technologies in pediatric cancer care. His work has been instrumental in the characterization of the genetic landscapes of a variety of pediatric and adult cancers, including the first identification of IDH1 and IDH2 as cancer genes. Dr. Parsons has helped lead seminal studies evaluating the use of clinical sequencing for childhood cancer patients as part of the NHGRI Clinical Sequencing Evidence-Generating Research (CSER) program: the BASIC3 study (2011-2017) for newly diagnosed patients at Texas Children's Cancer Center and the Texas KidsCanSeq study (2018-) for both newly diagnosed and relapsed patients at multiple study sites across Texas. Dr. Parsons has a particular interest in development and evaluation of molecularly targeted therapies and holds a number of leadership roles in this area including serving as the study chair for the ongoing NCI-COG Pediatric MATCH trial (the first nationwide precision oncology trial for children, adolescents, and young adults with refractory cancers) and as a Steering Committee member and Genomics & Translational Biology lead for the NIH Pediatric Early Phase Clinical Trials Network.

### SELECTED PUBLICATIONS

Ting MA, Reuther J, Chandramohan R, et al (2021). Genomic analysis and preclinical xenograft model development identify potential therapeutic targets for *MYOD1*-mutant soft-tissue sarcoma of childhood. **J Pathol.** 255: 52-61.

**Parsons DW**, Janeway KA, Patton DR, et al (2022). Actionable tumor alterations and treatment protocol enrollment of pediatric and young adult patients with refractory cancers in the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. **J Clin Oncol.** 40: 2224-2234.

Eckstein OS, Allen CE, Williams PM, et al (2022). Phase II study of Selumetinib in children and young adults with tumors harboring activating mitogen-activated protein kinase pathway genetic alterations: Arm E of the NCI-COG Pediatric MATCH Trial. **J Clin Oncol.** 40: 2235-2245.


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

### Dan L. Duncan Endowed Professorship

**Professor**, Departments of Pediatrics and Molecular and Human Genetics and Human Genome Sequencing Center; Graduate Programs in Cancer & Cell Biology and Genetics & Genomics
**Assistant Dean of Dual Degree Programs and Pathways**, School of Medicine

**Director**, Cancer Genetics Clinical and Research Programs, Texas Children's Hospital

*M.D., Ph.D., Harvard University*
*Resident, Internal Medicine, University of Washington*
*Postdoc, National Cancer Institute, National Institutes of Health*
*Fellow, Medical Genetics, Fred Hutchinson Cancer Research Center, Univ. of Washington*

### RESEARCH INTERESTS

I have had a longstanding focus on the fields of cancer genetics and clinical genomics. My translational research is designed to understand mechanisms of susceptibility to pediatric cancer through large collaborative projects. We have worked closely with Dr. Philip Lupo on a landmark study of the association between birth defects and childhood cancer and are now using whole genome sequencing of these unique patients to identify novel cancer susceptibility genes as well as the hereditary basis of rhabdomyosarcoma, an often-lethal tumor in children. I serve as co-PI with Dr. Donald (Will) Parsons and Dr. Amy McGuire on the NHGRI/NCI- U01 Texas KidsCanSeq trial that studies the incorporation of CLIA clinical genome-scale exome sequencing into the care of childhood cancer patients (solid tumors and brain tumors) in the diverse patient populations across six sites in Texas. I am one of the principal investigators of the Clinical Genome Resource (ClinGen), an international effort to develop databases and websites to improve the clinical interpretation of genetic variation.

### SELECTED PUBLICATIONS

Parsons DW, Roy A, Yang Y, Wang T, Scollon S, Bergstrom K, (...), Eng CM, Gibbs RA, **Plon SE** (2016). Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. **JAMA Oncol**. 2: 616-624.

Lupo PJ, Schraw JM, Desrosiers TA, Nembhard WN, Langlois PH, (...), **Plon SE** (2019). Association Between Birth Defects and Cancer Risk Among Children and Adolescents in a Population-Based Assessment of 10 Million Live Births. **JAMA Oncol.** 5: 1150-1158.

Li H, Sisoudiya SD, Martin-Giacalone BA, Khayat MM, Dugan-Perez S, (...), **Plon SE**, Sabo A, Lupo PJ (2021). Germline Cancer Predisposition Variants in Pediatric Rhabdomyosarcoma: A Report From the Children's Oncology Group. **J Natl Cancer Inst.** 113: 875-883.

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## NOAH F. SHROYER, PH.D.

**Associate Professor**, Departments of Medicine-Gastroenterology and Hepatology and Molecular and Human Genetics; Graduate Programs in Cancer & Cell Biology and Development, Disease Models & Therapeutics
**Adjunct Associate Professor**, Department of Pediatrics-Gastroenterology, Hepatology & Nutrition, Cincinnati Children's Hospital

*Ph.D., Cell and Molecular Biology, Baylor College of Medicine*
*Postdoc, Molecular and Human Genetics, Baylor College of Medicine*

### RESEARCH INTERESTS

My laboratory is focused on understanding the mechanisms that control intestinal development and homeostasis, and translating this knowledge into novel therapeutic approaches to treat diseases of the intestine such as IBD and colorectal cancer. My laboratory has elucidated roles for epithelial transcription factors such as Atoh1 (Math1), Gfi1, and Spdef in development and differentiation of the intestine. Moreover, my laboratory has translated these findings to human diseases, by showing that Atoh1 and its target Spdef are tumor suppressors that are frequently silenced in colon cancers, and that these genes are essential targets of Notch inhibitory drugs. In addition to these mechanistic studies, we have recently developed novel organ culture methods to direct differentiation of human pluripotent stem cells into intestinal tissue to study intestinal development and disease, and we have used intestinal stem cell-derived organoids in quantitative assays to evaluate intestinal stem cell activity.

### SELECTED PUBLICATIONS

Noah TK, **Shroyer NF** (2013). Notch in the intestine: regulation of homeostasis and pathogenesis. **Annu Rev Physiol**. 75: 263-88.

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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.

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## IGNATIA B. VAN DEN VEYVER, M.D.

**Professor**, Departments of Obstetrics & Gynecology and Molecular and Human Genetics; Graduate Programs in Development, Disease Models & Therapeutics and Genetics & Genomics
**Director**, Clinical Translational Research Certificate of Added Qualification (CTR-CAQ) program
**Director of Clinical Prenatal & Reproductive Genetics**, Department of Molecular and Human Genetics

*M.D., University of Antwerp*
*Resident, Obstetrics and Gynecology, Univ. of Antwerp Affiliated Hospitals, Belgium*
*Fellow, Maternal-Fetal Medicine, Baylor College of Medicine*
*Fellow, Genetics, Baylor College of Medicine*

### RESEARCH INTERESTS

My lab studies in mice and embryonic stem cell models how maternal effect mutations in genes that code for proteins of the oocyte subcortical maternal complex, which is essential for oocytes and embryos, cause infertility due to early embryo arrest, multilocus imprinting defects that lead to recurrent pregnancy failure in particular molar pregnancies, and congenital in offspring. We also conduct research on the cause of Aicardi syndrome, an elusive likely X-linked, neurodevelopmental disorder, that affects primarily girls who have eye and brain abnormalities, severe seizures and intellectual disability. For my clinical translational research, I investigate the benefits and challenges of introducing new genomic technologies, such as arrays, non-invasive prenatal screening and genome-wide sequencing into prenatal diagnosis and care. We are conducting a multicenter NIH-funded study to evaluate the clinical and diagnostic utility of trio prenatal whole genome sequencing for pregnancies with complicated fetal structural congenital anomalies.

### SELECTED PUBLICATIONS

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

Anvar Z, Chakchouk I, Sharif M, Mahadevan S, Nasiotis ET, Su L, Liu Z, Wan YW, **Van den Veyver IB** (2023). Loss of the maternal effect gene Nlrp2 alters the transcriptome of ovulated mouse oocytes and impacts expression of histone demethylase KDM1B. **Reprod Sci.** 30: 2780-93.

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

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## JAMES VERSALOVIC, M.D., PH.D.

### Milton J. Finegold Professor of Pathology & Immunology

**Professor**, Departments of Pathology & Immunology; Pediatrics, Molecular and Human Genetics and Molecular Virology & Microbiology; Graduate Program in Immunology & Microbiology
**Co-Director**, Medical Scientist Training Program, Baylor College of Medicine
**Pathologist-in-Chief and Head of Pathology**, Texas Children's Hospital
**Director**, Texas Children's Microbiome Center, Texas Children's Hospital

*M.D., Ph.D., Baylor College of Medicine*
*Postdoc, Digestive Diseases, Baylor College of Medicine*
*Resident, Clinical Pathology, Massachusetts General Hospital*
*Clinical Fellow, Pathology, Harvard Medical School*
*Postdoc, Comparative Medicine, Massachusetts Institute of Technology*

### RESEARCH INTERESTS

The Versalovic laboratory seeks to understand the nature of the mammalian gut microbiome and how gut bacteria (and probiotics) impact mucosal immunity and intestinal inflammation. Primary clinical interests are inflammatory bowel disease and colorectal cancer. The body site of primary interest is the mammalian intestine (small and large) using mouse models, mouse and human cell lines, and human specimens. Our group links the study of bacterial genomes and metagenomes to the systems biology of the mammalian intestines.

We are actively exploring microbiome replacement and manipulation of the intestinal microbiome as models of fecal transplantation programs in humans. Our aim is to cure disease by fundamentally changing the function or composition of the intestinal microbiome to prevent or treat disease phenotypes such as IBD and cancer. We believe that this strategy represents the microbial cell and gene therapy of the future.

### 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.

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# CHERYL WALKER, PH.D.

## Margaret and Albert Alkek Presidential Chair in Environmental Health

**Director**, Center for Precision Environmental Health
**Professor**, Departments of Molecular & Cellular Biology, Medicine, and Molecular and Human Genetics; Graduate Programs in Cancer & Cell Biology and Genetics & Genomics
**Director**, NIH T32 Training Program in Precision Environmental Health

*B.A. in Molecular, Cellular and Developmental Biology, University of Colorado-Boulder, 1977*
*Ph.D. in Cell Biology, The University of Texas Southwestern Medical School, 1984*

### RESEARCH INTERESTS

Our laboratory explores molecular mechanisms of disease pathogenesis, primarily cancer and metabolic diseases, including gene:environment interactions (GxE), and how the epigenome acts as a target, and determinant, of health and disease.

**Environmental Determinants of Health and Disease.** Our lab studies how early life environmental exposures disrupt the epigenome to increase susceptibility to adult diseases (Treviño et al., 2020). This work offers the potential to develop epigenetic biomarkers of early life exposure and/or future risk of disease, as well as new targets for intervention and disease prevention (Wang et al., 2018)

**A New Function for the Epigenetic Machinery.** We have also recently discovered that the epigenetic machinery that regulates chromatin also plays a key role remodeling the cytoskeleton (Park et al., 2016; Seervai et al., 2020; Karki, et al., 2021). We are currently studying the role, and potential importance, of this new biology for the neuronal cytoskeleton, and exploring how defects in dual-function chromatin-cytoskeleton remodelers contribute to autism spectrum disorder and other neurological diseases such as Huntington's Disease (Koenning, et al., 2021).

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# ROBERT A. WATERLAND, PH.D.

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

*Ph.D., Cornell University*
*Postdoc, Duke University*

### RESEARCH INTERESTS

In the Waterland laboratory, we work to understand how nutrition and other environmental influences on developmental epigenetics affect risk of disease later in life. Epigenetic mechanisms are established during development to regulate cell type-specific gene expression. Of these we focus on DNA methylation because it is the most stable, enabling lifelong persistence. Following up on our earlier studies on early nutritional influences at the agouti viable yellow locus (a mouse metastable epiallele) we are identifying human metastable epialleles and characterizing phenotypic consequences of individual epigenetic variation at these loci.

Another focus is the role of epigenetic dysregulation in obesity. We use mouse models to study how fetal and early postnatal exposures affect developmental epigenetics in the hypothalamus to alter lifelong energy balance.

In collaboration with experts in nutrition, computational biology, developmental neuroanatomy, and epidemiology, we apply genome-wide epigenomic profiling (Bisulfite-seq, RNA-seq, etc.) and sophisticated computational analysis. Our mouse work also employs methods to study neuroanatomical and cell type-specific epigenetic alterations.

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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.

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# MINGSHAN XUE, PH.D.

**Associate Professor**, Departments of Neuroscience and Molecular and Human Genetics; Graduate Programs in Development, Disease Models & Therapeutics; Genetics & Genomics; and Neuroscience
**Investigator**, Jan and Dan Duncan Neurological Research Institute

*Ph.D., Baylor College of Medicine*
*Postdoctoral fellow, University of California, San Diego*

## RESEARCH INTERESTS

The long-term research goal of my laboratory is to understand how dysfunction of neural circuits contributes to the pathogenesis of neurodevelopmental disorders and harness this knowledge to develop therapies. Human genetic studies of neurodevelopmental disorders continue to uncover pathogenic mutations in genes encoding synaptic proteins. However, the functional roles of these proteins in neural circuits and behaviors are poorly understood because in-depth neurological and behavioral studies in animal models are often lacking. Consequently, the pathological mechanisms underlying these synaptic disorders remain elusive and the therapeutic interventions are limited. We believe that this knowledge gap can be significantly narrowed by studying a few prioritized genes that are highly penetrant and affect a broad spectrum of neurological and neuropsychiatric features common among neurodevelopmental disorders. Thus, we are currently focusing on the mechanisms underlying circuit dysfunctions in mouse models of autism and epileptic encephalopathies, and ASO or AAV-based genetic therapies for these disorders. We collaborate with scientists from both academia and industry on multiple projects.

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Kim JH, Chen W, Chao ES, Rivera A, Kaku HN, Jiang K, Lee D, Chen H, Vega JM, Chin TV, Jin K, Nguyen KT, Zou SS, Moin Z, Nguyen S, **Xue M** (2024). GABAergic/glycinergic and glutamatergic neurons mediate distinct neurodevelopmental phenotypes of STXBP1 encephalopathy. **J Neurosci.** 44: e1806232024

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# BAYLOR COLLEGE OF MEDICINE

Located in Houston, Baylor College of Medicine is internationally recognized as a premiere academic health science center. The College is known for excellence in education, research and patient care.


Baylor College of Medicine Medical Center McNair Campus

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

Baylor College of Medicine is co-owner of Baylor St. Luke's Medical Center and has affiliations with seven additional teaching hospitals, each known for medical excellence. It also ranks consistently among the top U.S. medical schools in funding for research and development. The reputation of the College's distinguished faculty attract graduate, medical and health professions students from across the United States and throughout the world.

Baylor College of Medicine's vision is to improve health through science, scholarship and innovation and its mission is to create knowledge and apply science and discoveries to further education, healthcare and community service locally and globally.

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

# TEXAS MEDICAL CENTER

*Aerial View of the Texas Medical Center*

The Texas Medical Center is the largest medical complex in the world and comprises more than 1,345 acres dedicated to biomedical research and care. The total acreage combined with $25 billion in gross domestic product makes the Texas Medical Center the eighth largest business district in the U.S. Among its components are three medical schools, 21 renowned hospitals, eight academic and research institutions, six nursing programs, three public health organizations, two universities, two pharmacy schools, a dental school and 13 support organizations.

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

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

The Texas Medical Center is home to the world's largest children's hospital, Texas Children's Hospital, and the world's largest cancer hospital, the University of Texas MD Anderson Cancer Center. The TMC has 10 million visits per year and over 106,000 people are employed at its member institutions. It has the highest concentration of life sciences professionals in the country.


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

# HOUSTON

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

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

Houston is an international city that is a leader in the arts, education and healthcare, and has a top-rated culinary scene that is continuing to gain national attention. The same vision and entrepreneurial spirit that made Houston the energy capital of the world has given rise to global companies in a wide array of industries.

Toss out any images of dusty plains, because Houston is full of trees and boasts 20,000 acres of parks, public green space and open water. The city offers an abundance of recreational activities, restaurants, shopping, cultural performances, entertainment and sporting events.

Take a quick look at what makes Houston such a great place to live, get an education and work:

**The people**: Houston is the fourth largest U.S. city. Thirty-seven percent are 24 or younger, and 32 percent are between ages 25-44. Houston has a multicultural population of more than 5.5 million and is considered to be the most diverse, large metropolitan area in the United States.

**The low cost of living**: This means affordable housing. Plus, there are no state or local income taxes. How can it get better?

**The job market**: Houston has an expanding economy in diverse industries. Have you checked out careers at Baylor?

**The weather**: In the winter, you may need a light jacket but ice or snow won't keep you from enjoying the outdoors. With an average temperature year-round of 68 degrees and average rainfall of 46 inches, you can enjoy the outdoors as much as you'd like.

**The entertainment**: Really, it's impossible to be bored here. There are entertainment options for all ages, including a permanent ballet, opera, symphony and theater companies, dozens of top-notch museums and so much more. Don't forget that Houston is home to NASA's Johnson Space Center, too.

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

**The sports**: Sports fans, you'll never wait too long for the next game. You'll find plenty of professional and college sports here.

**The shopping**: You'll save money with the low cost of living in Houston, but there's no shortage of stores, malls, boutiques and more in the city!

**The education**: Houston offers more than 40 colleges, universities and institutes.

# BAYLOR COLLEGE OF MEDICINE, AFFILIATED HOSPITALS, INSTITUTIONS AND FACILITIES

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