Baylor
College of
Medicine

MOLECULAR
AND HUMAN
GENETICS
2023

ACCREDITATION

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BAYLOR COLLEGE OF MEDICINE DIVERSITY AND INCLUSION POLICY

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

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

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

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

NOTICE OF NONDISCRIMINATION

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

MOLECULAR AND HUMAN GENETICS

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MESSAGE FROM THE CHAIR

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

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

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

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

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

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

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

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

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

Best regards,

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

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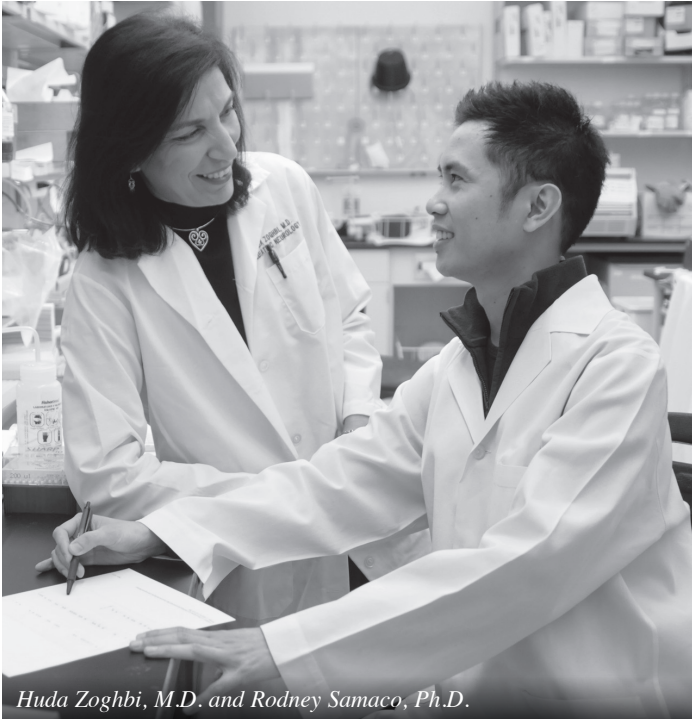
Huda Zoghbi, M.D. and Rodney Samaco, Ph.D.
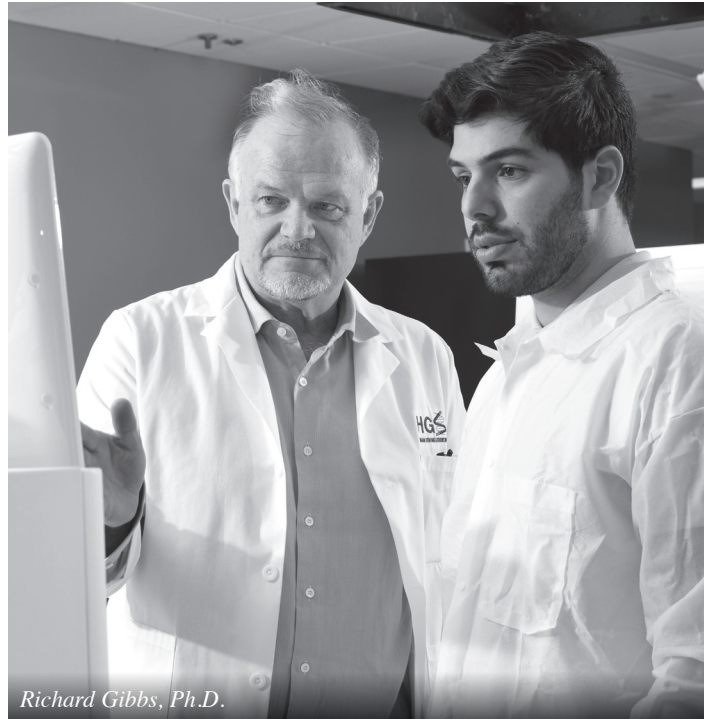
Richard Gibbs, Ph.D.

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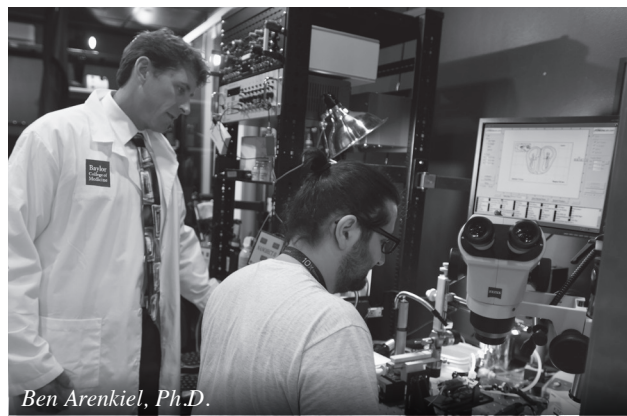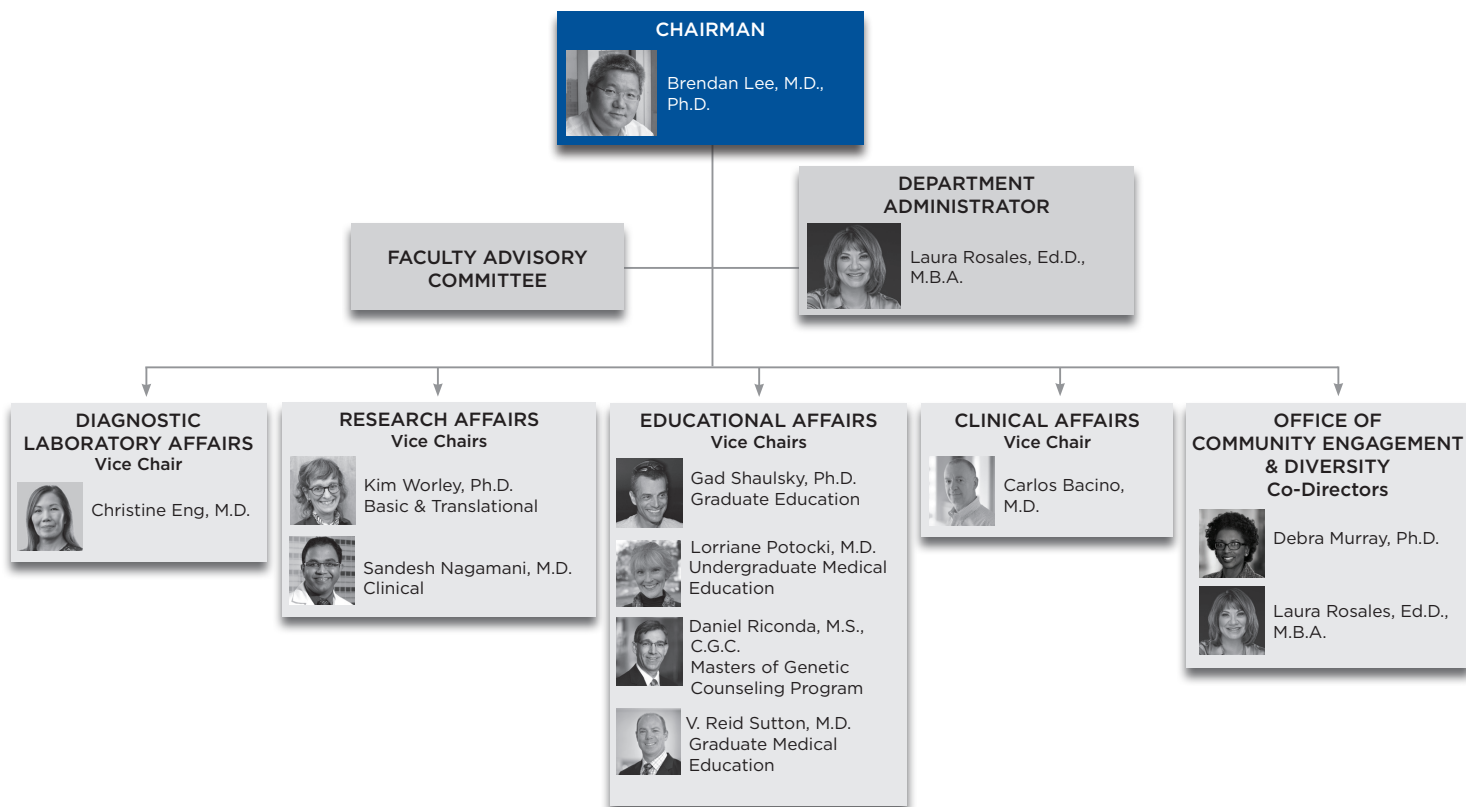mics to graduate students, medical students, postdoctoral research fellows and medical genetics residents. The Department integrates basic research in genetic and genomic mechanisms; translational research in disease models; observational and therapeutic clinical trials in rare and common genetic diseases;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

We have more than 530 faculty, trainees and staff in the Department. Our research faculty are joined by clinical, genetic counseling and diagnostic laboratory faculty in our mission to transform medicine with the science and practice of genetics. Our faculty include three members of the National Academy of Sciences, seven members of the National Academy of Medicine and nine fellows of the American Association for the Advancement of Science.

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

Among genetics departments at U.S. medical schools, we continue to rank highest in both the number of grants and total funding from the National Institutes of Health. Our facilities are equipped with state-of-the-art instrumentation for research in molecular, cellular and biochemical genetics. There are also several specialized research centers that galvanize collaboration among faculty at Baylor within the department. We also have extended our mission globally with a clinical center at The Chinese University of Hong Kong and the joint venture diagnostic laboratory, Baylor Genetics, with H.U. Group Holdings, Inc. The Department's various research, clinical and administrative activities currently occupy about 175,000 square feet of space. Because of this rich environment, the Department continues to be a magnet for trainees interested in genetics while continuing to grow in breadth, depth and accomplishments.

DEPARTMENT LEADERSHIP

CHAIRMAN

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

DEPARTMENT ADMINISTRATOR

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

FACULTY ADVISORY COMMITTEE

DIAGNOSTIC LABORATORY AFFAIRS
Vice Chair

Christine Eng, M.D.

RESEARCH AFFAIRS
Vice Chairs

Kim Worley, Ph.D.
Basic & Translational

Sandesh Nagamani, M.D.
Clinical

EDUCATIONAL AFFAIRS
Vice Chairs

Gad Shaulsky, Ph.D.
Graduate Education

Lorriane Potocki, M.D.
Undergraduate Medical Education

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

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

CLINICAL AFFAIRS
Vice Chair

Carlos Bacino, M.D.

OFFICE OF COMMUNITY ENGAGEMENT & DIVERSITY
Co-Directors

Debra Murray, Ph.D.

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

Susan Rosenberg, Ph.D.

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

Andy Groves, Ph.D.

Ben Arenkiel, Ph.D.

DIVISION OF EDUCATIONAL AFFAIRS
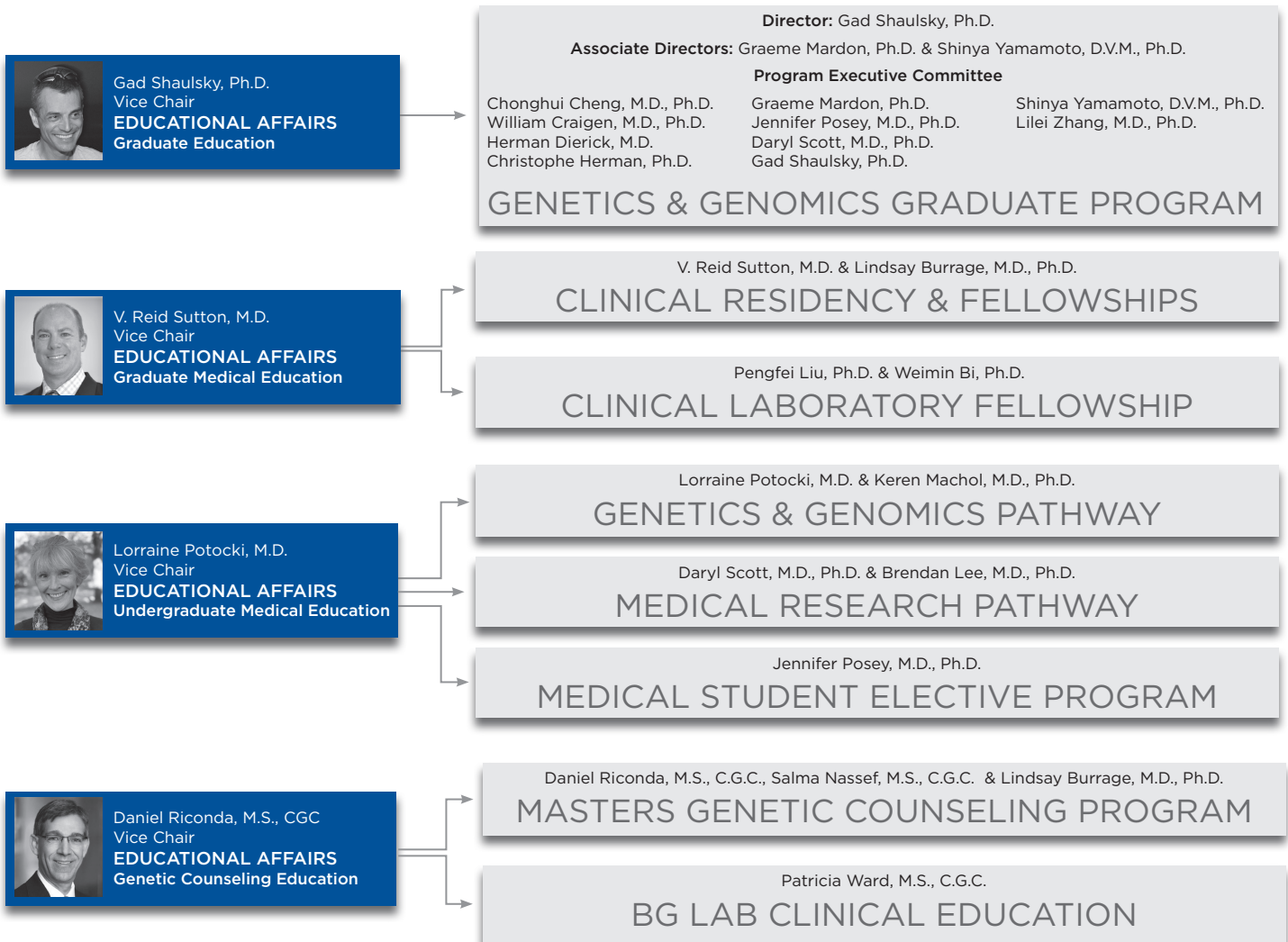
Gad Shaulsky, Ph.D.
Vice Chair
EDUCATIONAL AFFAIRS
Graduate Education

Director: Gad Shaulsky, Ph.D.
Associate Directors: Graeme Mardon, Ph.D. & Shinya Yamamoto, D.V.M., Ph.D.
Program Executive Committee

Chonghui Cheng, M.D., Ph.D.	Graeme Mardon, Ph.D.	Shinya Yamamoto, D.V.M., Ph.D.
William Craigen, M.D., Ph.D.	Jennifer Posey, M.D., Ph.D.	Lilei Zhang, M.D., Ph.D.
Herman Dierick, M.D.	Daryl Scott, M.D., Ph.D.	
Christophe Herman, Ph.D.	Gad Shaulsky, Ph.D.	

GENETICS & GENOMICS GRADUATE PROGRAM

V. Reid Sutton, M.D.
Vice Chair
EDUCATIONAL AFFAIRS
Graduate Medical Education

V. Reid Sutton, M.D. & Lindsay Burrage, M.D., Ph.D.
CLINICAL RESIDENCY & FELLOWSHIPS

Pengfei Liu, Ph.D. & Weimin Bi, Ph.D.
CLINICAL LABORATORY FELLOWSHIP

Lorraine Potocki, M.D.
Vice Chair
EDUCATIONAL AFFAIRS
Undergraduate Medical Education

Lorraine Potocki, M.D. & Keren Machol, M.D., Ph.D.
GENETICS & GENOMICS PATHWAY

Daryl Scott, M.D., Ph.D. & Brendan Lee, M.D., Ph.D.
MEDICAL RESEARCH PATHWAY

Jennifer Posey, M.D., Ph.D.
MEDICAL STUDENT ELECTIVE PROGRAM

Daniel Riconda, M.S., CGC
Vice Chair
EDUCATIONAL AFFAIRS
Genetic Counseling Education

Daniel Riconda, M.S., C.G.C., Salma Nassef, M.S., C.G.C. & Lindsay Burrage, M.D., Ph.D.
MASTERS GENETIC COUNSELING PROGRAM

Patricia Ward, M.S., C.G.C.
BG LAB CLINICAL EDUCATION

GRADUATE PROGRAM IN GENETICS & GENOMICS

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

The program requires a full-time commitment to graduate studies and research. To encourage our students to fulfill their potential and excel in their work, we provide a competitive stipend, which stretches considerably further in Houston where the cost of living is considerably lower than in other large U.S. cities. Students who enroll in 2023-2024 will receive $35,500 per year. Tuition, medical and dental insurance are also provided. Students who obtain funding through personal fellowships receive an additional $3,000 bonus from the Dean of the Graduate School.

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

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

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

Gad Shaulsky, Ph.D.

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

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

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

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

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

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

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

Graduate Program Administrator
Judi Coleman

MEDICAL STUDENT EDUCATION

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

The goals of the Genetics & Genomics Pathway include (1) building upon the foundation of basic genetic principles provided in the pre-clerkship curriculum with additional educational experiences in medical genetics,

(2) enhancing the medical student experience to include a broad range of patients with genetic conditions, (3) developing the student's appreciation for the nuances inherent in performing and interpreting clinical diagnostic analyses in biochemical genetics, molecular genetics and cytogenetics, (4) providing an interface with the community and patient advocacy organizations to enhance the student's awareness of the social concerns faced by patients and families affected with genetic disorders, (5) preparing students to author a scholarly publication and/or presentation, and (6) providing students a means to network and discuss various topics and career paths in medical genetics.

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

POSTDOCTORAL RESEARCH TRAINING

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

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

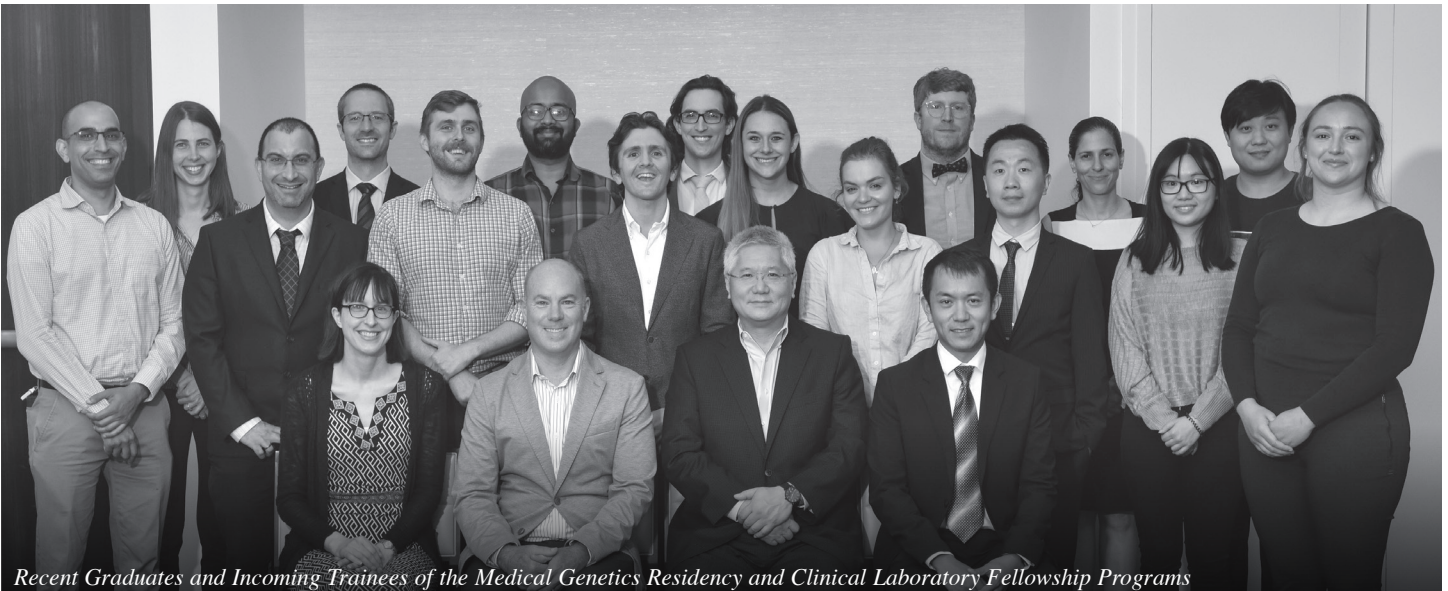## RESIDENCY AND FELLOWSHIP TRAINING PROGRAMS

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

The clinical experience is both thorough and extensive because of the availability of the department's large clinical services and clinical faculty; the comprehensive

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

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

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

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

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

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

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

Program Leadership
V. Reid Sutton, M.D., Director of Clinical Residency and Fellowship Programs
Lindsay Burrage, M.D., Ph.D., Associate Program Director of Residency Programs

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

ABMGG Residency & Fellowship Program Coordinator
Kara Mitchell

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

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

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

Center Director: Fernando Scaglia, M.D.

Genetic Counseling Program Students and Alumni

GENETIC COUNSELING PROGRAM

The Baylor College of Medicine Genetic Counseling Program was accredited in February of 2018 and graduated its first class of eight students in June of 2020. The program now admits 9 students and has plans to increase enrollment further in the future. The 22-month Master of Science degree program is housed under the School of Health Professions and was founded with the financial and logistical support of the Department of Molecular and Human Genetics. The program provides students a transformative education in genomic medicine and the practice of genetic counseling. The outstanding clinical, laboratory and research faculty empower graduates to be empathic professionals with effective critical thinking skills. Clinical rotations include a variety of clinics offered both in-person and via telehealth with the following services: p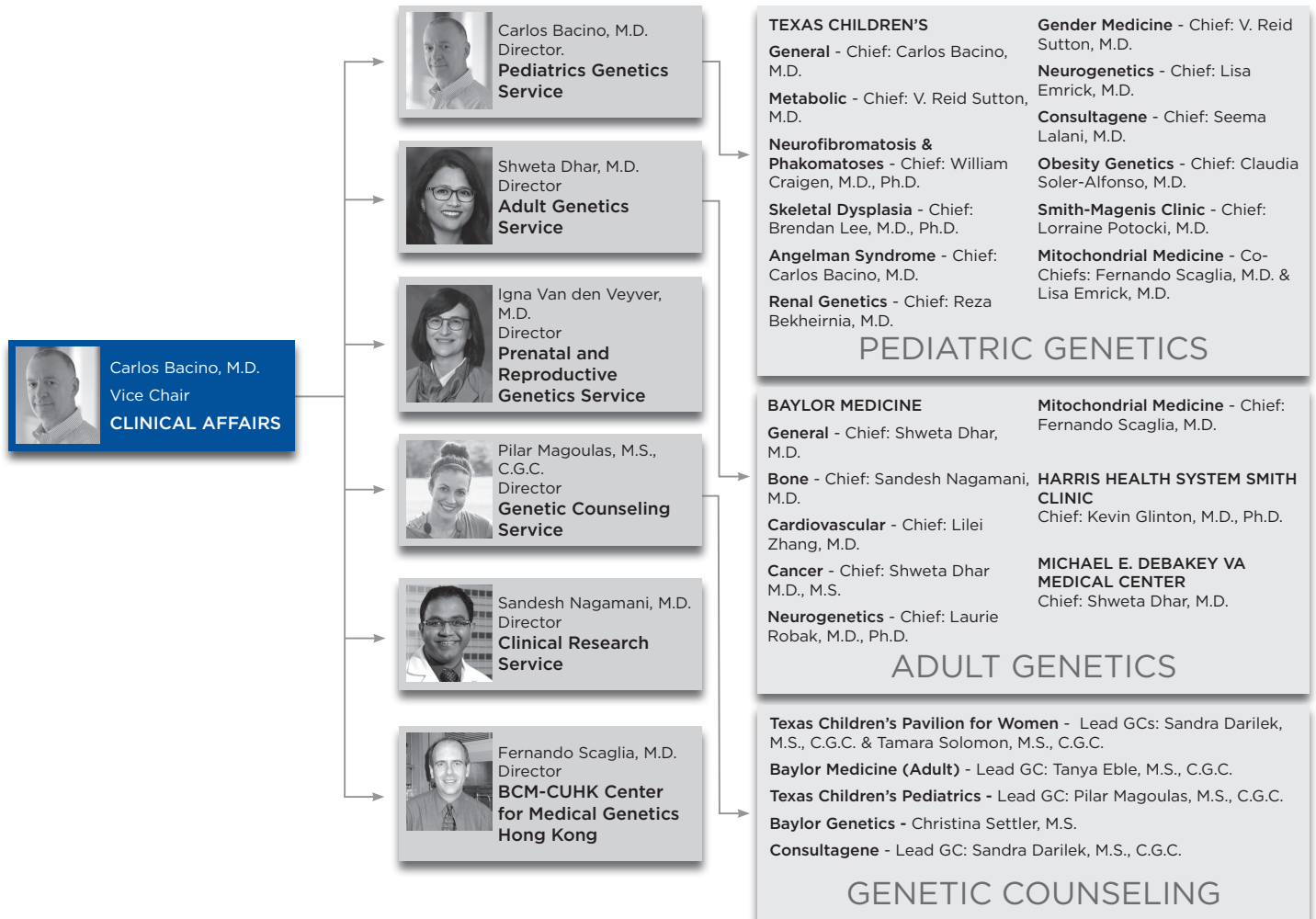ediatric genetics at Texas Children's Hospital and the Children's Hospital of San Antonio, adult genetics at the Michael E. Debakey VA Medical Center, Harris Health System, and Baylor Medicine at McNair Campus, and prenatal and reproductive genetics at Texas Children's Pavilion for Women and Consultagene Clinic, among others. Program differentiators include the variant interpretation and counseling course developed in collaboration with the diagnostic laboratory, Baylor Genetics, and the diverse research opportunities available within the department and across the Texas Medical Center.

Program Leadership:
Daniel Riconda, M.S., C.G.C., Director
Salma Nassef, M.S., C.G.C., Associate Director
Lindsay Burrage, M.D., Ph.D., Medical Director

DIVISION OF CLINICAL AFFAIRS

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

Carlos Bacino, M.D.
Vice Chair
CLINICAL AFFAIRS

TEXAS CHILDREN'S
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: Reza Bekheirnia, M.D.

Gender Medicine - Chief: V. Reid Sutton, M.D.
Neurogenetics - Chief: Lisa Emrick, M.D.
Consultagene - Chief: Seema Lalani, M.D.
Obesity Genetics - Chief: Claudia Soler-Alfonso, 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. & 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 - Christina Settler, M.S.
Consultagene - Lead GC: Sandra Darilek, M.S., C.G.C.

GENETIC COUNSELING

GENETICS CLINICS

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

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

Specialty clinics within the Texas Children's Genetics Clinic include the metabolic clinic, neurofibromatosis clinic, skeletal dysplasia clinic and the cancer genetics clinic. We also have many multidisciplinary team clinics like the Angelman Syndrome Clinic, the Center for Genetic Disorders of Obesity, Mitochondrial Medicine Clinic, and the Gender Medicine Program. The Department of Molecular and Human Genetics clinical and genetic counseling faculty also staff joint clinics with other departments such as otolarynogology (otogenetics) and neurology (neurogenetics/tuberous sclerosis).

The Adult Genetics Clinic is also one of the largest genetics clinics in the country, providing inpatient and outpatient care exclusively for adult patients in four different

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

As the largest of its kind in the U.S., the

Sandesh C.S. 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 - Clinical Care Center
6701 Fannin St., 16th Floor
Houston, TX 77030

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

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

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

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

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

Clinical Faculty (cont.)
Brendan Lee, M.D., Ph.D.
James R. Lupski, M.D., Ph.D.
Keren Machol, M.D., Ph.D.
Ronit Marom, M.D., Ph.D.
Chaya Murali, M.D.
Sandesh C.S. Nagamani, M.D.
Sharon E. Plon, M.D., Ph.D.
Jennifer Ellen Posey, M.D., Ph.D.
Lorraine Potocki, M.D.
Laurie Robak, M.D., Ph.D.
Fernando Scaglia, M.D.
Daryl A. Scott, M.D., Ph.D.
Claudia Soler-Alfonso, M.D.

V. Reid Sutton, M.D.
Ignatia B. Van den Veyver, M.D.
Michael Francis Wangler, M.D.
Lilei Zhang, M.D., Ph.D.

Nursing Faculty
Saima Ali, M.S.N., R.N., FNP-C
Dianne Bauri, M.S., R.N., FNP-C
Susan Fernbach, B.A., R.N.
Alicia Turner, M.S.N., R.N., FNP-C

Nursing Staff
Wanda Dosal, B.S.N.

GENETIC COUNSELING

The Department of Molecular and Human Genetics is home to approximately 50 genetic counselors that cover a wide range of clinical subspecialties, as well as research and laboratory positions. Genetic counselors communicate complex genetics information to families in a way that is understandable and practical to them, while supporting patients and their family members throughout the genetics evaluation and testing process.

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

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

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

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

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

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BAYLOR GENETICS

Established in February 2015, Baylor Genetics, a joint venture between Baylor College of Medicine and H.U. Group Holdings, Inc., strives to continue the tradition of genetic innovation and operational excellence. By building on the Department of Molecular and Human Genetics's strengths in research and discovery, Baylor Genetics' mission is to provide quality genetic testing services relevant to twenty-first-century precision medicine. Over the last 40 years, the laboratory has been at the forefront of introducing novel genetic testing modalities that have provided more tools to diagnose patients with genetic disorders. The innovative testing approaches developed at the laboratory include whole exome sequencing, Chromosomal Microarray Analysis (CMA), universal carrier screening, non-invasive prenatal testing for single gene disorders, metabolomics and most recently, COVID-19. In addition, Baylor Genetics continues to offer high-quality comprehensive diagnostic services in all areas of genetic testing including cytogenetics, biochemical genetics, cancer genetics, mitochondrial genetic testing and next-generation sequencing panels. The laboratory is located in Houston's Texas Medical Center with over 200 employees, over 3,000 tests available and clients in all 50 states and in 16 countries. Baylor Genetics is well-equipped with cutting-edge diagnostic equipment, allowing it to efficiently generate the most accurate clinical genetic data.

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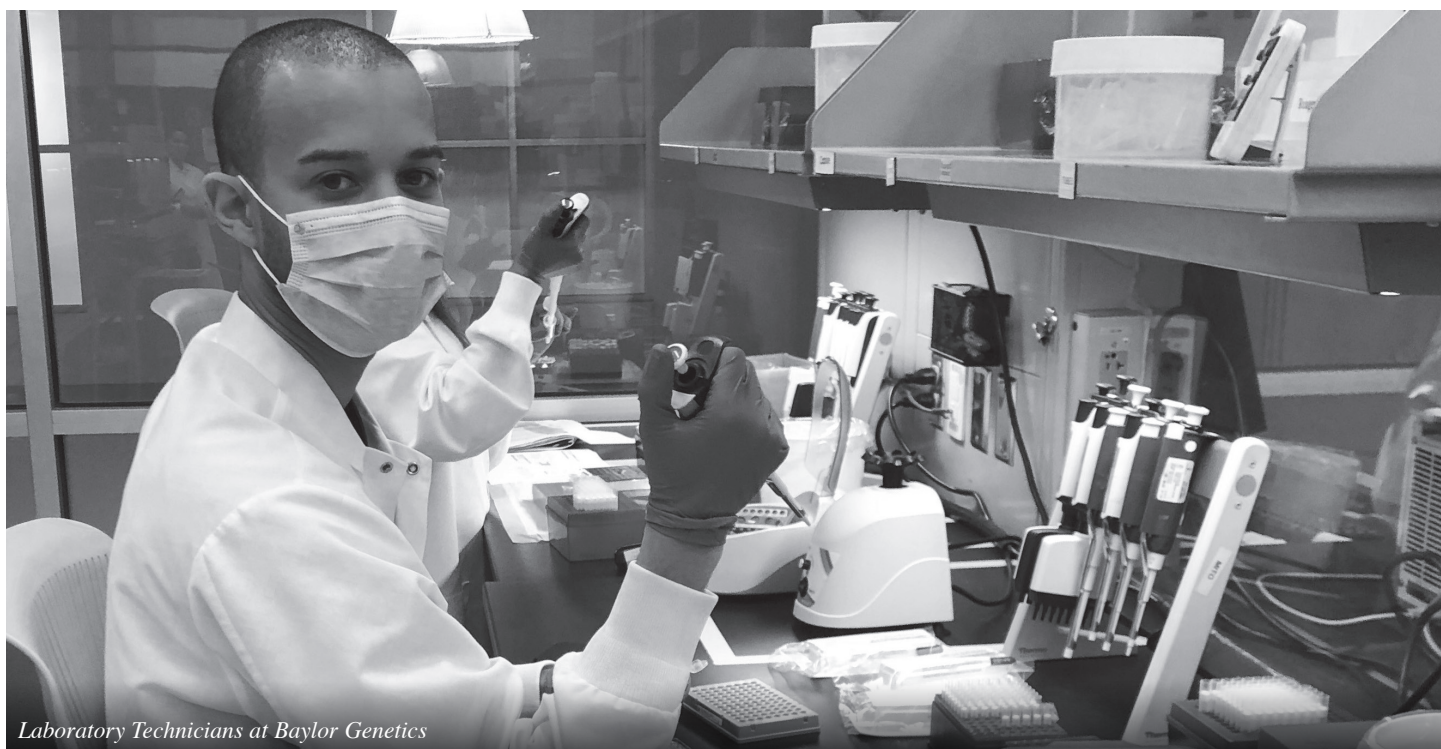
Laboratory Technicians at Baylor Genetics

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

Diagnostic Laboratory Faculty
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Ning Liu, Ph.D.
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Janice Smith, Ph.D.
Qin Sun, Ph.D.
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Liesbeth Vossaert, Ph.D.
Yue Wang, Ph.D.
Fan Xia, Ph.D.
Xiaonan Zhao, Ph.D.

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

Baylor TCH Rare Disease Day

The **Evenings with Genetics series** has served the community for 16 years. The department partners with Texas Children's Hospital to offer this free seminar series open to the public. A genetics faculty member paired with faculty from another specialty area, plus a parent expert speaker are highlighted at each seminar. The goals of the series are to provide current genetic and genomic information in a clear, plain-language manner, offer support and resources to families impacted by a genetic disorder and foster interdepartmental collaborations. Seminars include simultaneous translation to Spanish. During this past year, we celebrated our 16th anniversary with the second annual "Race and Genetics: Perspectives of Precision Medicine" webinar series during Black History Month.

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

The **Careers in Genetics and Genomics series** (virtual) is provided annually to present the genetics and genomics career path to high school and undergraduate students. The office will offer "Understanding Genetic Variations" sessions at national student research meetings (Annual Biomedical Research Conference for Minority Students, Society for Advancement of Chicanos/Hispanics & Native Americans in Science) to introduce genetics and genomics and encourage participation in the field.

The **Medical Genetics Diversity Visiting Students Program** was developed by the office to provide underrepresented fourth-year medical students a 4-week clinical rotation beginning in 2022. In 2021, we began the **Clinical Research Education Training Program (CRETP)** to introduce underrepresented first and second-year medical students to the field of medical genetics. The virtual program, **A White Coat and Genes: The Life of a Medical Geneticist**, offers third and fourth-year medical students the opportunity to learn about careers in medical genetics from department faculty and students.

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

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

Diversity and Inclusion Strategic Planning Committee

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

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Basic & Translational

Sandesh Nagamani, M.D.
Clinical

GENETIC & GENOMIC STRUCTURE & FUNCTION

GENETIC DISEASE MECHANISMS & THERAPY

COMPUTATION, BIOINFORMATICS, & BIOSTATISTICS

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Elizabeth Atkinson, Ph.D.
Steven Boeynaems, Ph.D.
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Hui Zheng, Ph.D
Anthony Zoghbi, M.D.
Huda Zoghbi, M.D.
Chenghang Zong, Ph.D

PRIMARY RESEARCH FACULTY

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.

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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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BENJAMIN R. ARENKIEL, PHD

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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.

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ELIZABETH ATKINSON, PH.D.

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RESEARCH INTERESTS

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

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

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

SELECTED PUBLICATIONS

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

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CARLOS A. BACINO, M.D., FACMG

Professor and Vice Chair for Clinical Affairs, Department of Molecular and Human Genetics
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Chief, Genetics Service, Texas Children's Hospital

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

RESEARCH INTERESTS

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

Epigenetics and Disorders of Imprinting: I have worked in Angelman syndrome clinical research for 20 years. We have followed a large group of Angelman syndrome patients at Texas Children's Hospital for developmental, clinical and EEG evaluations on a yearly basis (Natural History study). This study has allowed us to understand progression, complications and co-morbidities associated with this condition. We have also concluded two different clinical trials using betaine, creatine and folic acid/metafolin to promote methylation and revert silencing of the paternal allele. Our group is participating in a phase II clinical research trial through a pharmaceutical company using a locked nucleic acid RO7248824 (antisense oligonucleotide drug) given intrathecally to establish dosage and safety. Our group is also involved in another antisense Phase II trial sponsored by IONIS (ION582) administered intrathecally. These antisense drugs attempt to activate the paternal UBE3A gene and ameliorate the symptoms of Angelman syndrome by altering patterns of imprinting. We currently run a multidisciplinary clinic for patients with Angelman syndrome that started with the support of the Angelman Syndrome Foundation.

Skeletal dysplasias: Through the sponsorship of several pharmaceutical companies, I am involved in different studies offering treatments in achondroplasia This includes a phase 3 clinical research trial using a recombinant cartilage natriuretic peptide (CNP) also known as vosoritide (BMN-111), a drug we anticipate will promote linear and more proportionate skeletal growth in these patients. This drug was recently approved by the FDA for 5 years and older. We continue with studies on children under 5 years of age. We are part of two other trials, one using a long-acting recombinant CNP, and the last using an FGFR3 decoy therapy agent.

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

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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.

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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 and John Postlethwhait and Monte Westerfield at the University of Oregon were selected by the Undiagnosed Diseases Network (UDN) to direct the Model Organism Screening Center (MOSC) for the UDN of the U.S. Through close collaborations with human geneticists and physicians, we have identified variants in human genes that are associated with neurological diseases in children. We have so far participated in the discovery of the genetic causes of 35 human diseases in the past five years. We are also studying some of these genes in depth to determine the molecular events that underlie these diseases to identify targets to develop drugs and have been successful in identifying drugs for four diseases.

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

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

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RESEARCH INTERESTS

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

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

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

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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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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.

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RESEARCH INTERESTS

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

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

Our clinical study of hepatic complications complements our laboratory-based work in the murine model of argininosuccinate lyase deficiency (ASLD). We are using an ASL-deficient mouse model to investigate mechanisms underlying the chronic hepatic complications observed in our patients. The ASL-deficient mice model the human disorder with urea cycle dysfunction, nitric oxide (NO) deficiency, and chronic hepatocellular injury with hepatomegaly. In addition, as in human patients with the disorder, we have recently discovered hepatic glycogen accumulation and impaired hepatic glycogenolysis in these mice. We are currently dissecting the role of altered energy metabolism and hepatic glycogen accumulation in ASL-deficient mice. We are also exploring molecular and biochemical mechanisms by which ASL deficiency causes chronic liver disease using in vitro and in vivo models.

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

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RESEARCH INTERESTS

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

Our goal is to determine the role of cerebro-cerebellar excitatory and inhibitory neuronal dysfunction in the pathogenesis of neurodevelopmental and neuropsychiatric disorders by deciphering how genetic alterations perturb neurotransmission in the brain, impact neural development and lead to abnormal neurologic output. In the Chao Lab, we integrate cross-species approaches in humans to uncover the genetic etiologies of neurodevelopmental disorders, fruit flies to elucidate the molecular pathways and mice to explore the cascade of events in the mammalian brain and develop pre-clinical studies. A variety of approaches and techniques are employed in our laboratory including genetically engineered mouse and fruit fly models, functional analyses with electrophysiology, imaging, transcriptomics, molecular and cellular assays and behavioral profiling.

In addition to the laboratory research activities, I am a member of the Undiagnosed Diseases Network (UDN) and focus clinical studies on developmental epileptic encephalopathies and *EIF2AK2*-related and *EBF3*-related autism spectrum and neurodevelopmental disorders. In 2017, we established a multidisciplinary *EBF3*-HADDS clinic at TCH. We now follow the largest group of *EBF3*-related HADDS and 10q26 deletion syndrome patients to date in a single institution. Through the clinic, we conduct developmental, clinical and genetic evaluations on a yearly basis. This natural history study allows us to expand our understanding of the genotype-phenotype correlations, progression, complications and co-morbidities associated with this condition. The findings from the clinical study also inform our laboratory research efforts to understand how gene disruptions alter inhibitory and excitatory neuronal development, perturb neural network activity and lead to cognitive and behavioral abnormalities in neurodevelopmental and psychiatric disorders.

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RESEARCH INTERESTS

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

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

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

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

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

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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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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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RESEARCH INTERESTS

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

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

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

SELECTED PUBLICATIONS

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

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RESEARCH INTERESTS

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

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

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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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RESEARCH INTERESTS

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

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

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

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

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RESEARCH INTERESTS

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

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

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

Current projects also include: (1) investigating the role of NAD kinase in both Alzheimer's disease and pancreatic cancer toward developing personalized approaches to treatment and prevention of disease. These studies use cell culture and conditional mouse models to improve our understanding of the underlying etiology of the associated neurodegenerative and neoplastic mechanisms; (2) developing an expanded newborn screening disorder panel to improve early screening for treatable genetic conditions, reducing health disparities associated with delayed diagnosis of these rare but treatable disorders; and (3) improving genomic variant curation and interpretation to facilitate earlier diagnosis for rare disease.

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CHRISTINE M. ENG, M.D.

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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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RESEARCH INTERESTS

Richard Gibbs is the Founder and Director of the Human Genome Sequencing Center (HGSC), established at BCM in 1996. The HGSC has a core mission of advancing medical care through research and translation of genomics. The group was one of the five worldwide sites to undertake and complete the Human Genome Project, culminating in the contribution of approximately ten percent of the sequence in 2003. The group subsequently collaborated to sequence many key species (*Drosophila melanogaster*, Brown Norway rat, rhesus macaque, bovine, *Dictyostelium discoideum*, sea urchin and honey bee genomes) and to generate the first comprehensive map of human genetic variation (the HapMap project). The HGSC now employs more than 180 staff, including eighteen faculty.

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

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RESEARCH INTERESTS

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

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

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RESEARCH INTERESTS

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

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

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

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

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

Characterizing gene and variant contribution to Mendelian diseases. Up to 70% of patients with suspected genetic disease remain undiagnosed likely because their disease-causing variant(s) has yet to be discovered or the clinical significance of identified variants remains unclear. Precision model organisms are important tools aiding in the interpretation of these variants of uncertain clinical significance and are critical for testing therapeutic paradigms. The Center for Precision Medicine Models leverages the expertise, infrastructures, and established collaborations between the Mendelian disease clinical and gene discovery programs; animal modeling programs; and database infrastructure programs within the Department of Molecular and Human Genetics. The Center supports local, national, and international programs and individual researchers in the development of precision models that will end the diagnostic odyssey of patients with undiagnosed, rare, and Mendelian diseases and serve as resources for pre-clinical studies investigating personalized medicine approaches to their care.

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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, but our work challenge this idea by showing that transient alteration of autocatalytic systems can have profound heritable consequences. Thus, our work suggests that transient errors in information transfer may be an important mechanism of epigenetic change and should be considered as the causative agent for many human diseases ranging from the progression of AIDS to devastating neurodegenerative diseases.

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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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RESEARCH INTERESTS

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

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

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

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

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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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RESEARCH INTERESTS

My work has focused on understanding the molecular basis of neurodevelopmental and cardiovascular disorders in the pediatric population. We have used molecular cytogenetic diagnostic tools such as chromosomal microarray analysis (CMA) and exome sequencing (ES) in understanding the genetic basis of birth defects. We have also studied the clinical utility of rapid ES in neonatal intensive care units. I have been involved with the Undiagnosed Diseases Network (UDN) study at Baylor College of Medicine for several years and helped characterize diagnoses in multiple undiagnosed children with rare diseases. Using ES, we have identified several novel Mendelian disorders responsible for neurodevelopmental disorders in the pediatric population. In 2016, we first described a cohort of patients with TANGO2 disease and are currently recruiting families for the natural history study. We are also using an academic web-based virtual platform called Consultagene to combine virtual health delivery with genome sequencing in a medically underserved pediatric population with rare diseases, living along the Texas-Mexico border.

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RESEARCH INTERESTS

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

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

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

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

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M.D., University of Michigan Medical School
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Fellowship, Montefiore Hospital, Einstein School of Medicine, Bronx, New York
Fellowship, Bascom Palmer Eye Institute, University of Miami, Miami, Florida

RESEARCH INTERESTS

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

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

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

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

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

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RESEARCH INTERESTS

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

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

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

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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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RESEARCH INTERESTS

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

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

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

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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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RESEARCH INTERESTS

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

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

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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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RESEARCH INTERESTS

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

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

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

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

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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.

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RESEARCH INTERESTS

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

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

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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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RESEARCH INTERESTS

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

Proper maintenance of the bone and marrow cavity is essential for skeletal and immune cell integrity. However, which BM populations regulate medullary cavity maintenance is largely unknown. We recently identified that a subset of Cxcl12+ cells appear in the tibial and femoral diaphysis, coinciding with the development of the medullary cavity. Surprisingly, upon bone injury, these cells readily respond and proliferate within the internal fracture callus and suppress bone-forming cells with the recovery of the BM cavity. Bone marrow also provides a specialized microenvironment (niche) for HSC function. To understand how stress signals control endogenous HSCs and their niche interaction, we generated novel animal models to selectively label endogenous HSCs and SSCs and found a clear displacement of HSCs away from CXCL12-expressing niche cells upon interferon treatment. We are now elucidating the identity of unique stromal progenitor cells with anti-osteogenic function and their regulation mechanism for BM medullary cavity maintenance and normal bone repair. We are also studying the mechanisms by which niche cells regulate HSCs and understanding how perturbations to these interactions can promote disease states such as hematopoietic aging and malignancies.

My laboratory is also interested in the identity and function of stem cell populations in non-skeletal tissues such as muscle and tendon. Our recent studies demonstrated that the adult muscles and tendons contain a discrete population of stem cells that appear postnatally and undergo clonal expansion under severe stress and injury. However, their cellular origin and mechanisms that govern tendon and connective tissue regeneration and repair remain unknown. We work on these important questions using a variety of genetic, immunologic, and microscopic technologies with the goal of identifying molecules and mechanisms that regulate stem cells of different tissue origins. These studies will elucidate fundamental aspects of skeletal tissue regeneration and may lead to the development of new regenerative medicine strategies.

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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.

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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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RESEARCH INTERESTS

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

My laboratory is working on various aspects of primate genomics, including both basic comparative analyses and targeted research using primate models of human disease. As a member of the Human Genome Sequencing Center, I plan and execute various studies of nonhuman primate genomes. Working with other HGSC faculty and staff, as well as people outside BCM, we have produced *de novo* whole genome assemblies for several primates, including baboons (*Papio anubis*), sooty mangabeys (*Cercocebus atys*), marmosets (*Callithrix jacchus*), gibbons (*Nomascus leucogenys*), mouse lemurs (*Microcebus murinus*), owl monkeys (*Aotus nancymaae*) and other species. These projects involve deep whole genome sequencing of one individual per species, and computational assembly of the sequence data to produce a reference genome sequence that will be a resource for all future genetic analyses of that species. These projects also include the sequencing of additional individuals to identify intra-species genetic variation and RNA sequencing to characterize gene expression. The result is high-quality genomic information that facilitates both disease-related research and analyses of genome evolution (Rogers and Gibbs, 2014; Warren et al. 2020; Thomas et al. 2018). We have also conducted an extensive survey of genomic variation in the most widely studied nonhuman primate, the rhesus macaque (*Macaca mulatta*). By sequencing the genomes or exomes of more than 2,000 rhesus macaques from various research colonies we have discovered hundreds of thousands of functionally significant genetic variants that can be used to examine the effects of specific genes on various disease-related phenotypes. Information regarding genetic variation, including changes in protein-coding sequences and putative regulatory sequences, in combination with other genomic data, makes all these primate species more useful for future biomedical research projects.

The second major line of research in my laboratory is the targeted analysis of particular nonhuman primate models of human genetic diseases. In collaboration with psychiatrists and neurobiologists, we have studied individual variation in behavior among macaques and baboons (Rogers, 2018; Fox et al. 2021) and explored the underlying neurobiological mechanisms. The multifaceted behavior of primates, including their capacity for complex social interactions, makes them outstanding subjects for behavioral and neurogenetic investigation (Oler et al., 2010; Rogers et al., 2013; Fawcett et al., 2014; Gunter et al., 2022). The primate models point us to genetic mechanisms that may influence susceptibility to psychiatric disorders in people (Rogers et al., 2013; Fox et al. 2021). We are also analyzing primate models of inherited susceptibility to cancer (Dray et al., 2018), retinal disorders and early onset progressive vision loss (Moshiri et al., 2019), endometriosis (Tapmeier et al. 2021) and others.

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

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RESEARCH INTERESTS

Genome Instability in Evolution, Antibiotic Resistance, and Cancer

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

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

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

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

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RESEARCH INTERESTS

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

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

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RESEARCH INTERESTS

My primary research interest is focused on the study of the natural history of mitochondrial disorders supported by NAMDC (North American Mitochondrial Disease Consortia), an NIH-funded registry that focuses on the longitudinal study of patients with mitochondrial disease. Furthermore, I am also involved in clinical trials in children and adults with mitochondrial disorders. One of my current areas of research includes the study of nitric oxide deficiency as the basis for stroke-like episodes in adults and children with a mitochondrial syndrome called MELAS.

As a PI on several grants that have been funded by national organizations in the United States, I have laid the groundwork for the study of nitric oxide deficiency in MELAS syndrome and its restoration with the use of arginine and citrulline supplementation. A current NIH grant funds a phase 1 study that aims to determine the maximum tolerated dose and safety profile of citrulline supplementation in adults with MELAS syndrome. Moreover, I am involved in an international clinical trial for pediatric patients evaluating the efficacy of vatiquinone in mitochondrial refractory epilepsy. In addition, I also conduct a trial to evaluate the effect of ASP0367, a selective modulator of PPARδ in adults with primary mitochondrial myopathy.

Furthermore, I am interested in determining whether there is a specific metabolomics profile for the different mitochondrial disorders caused by mitochondrial and nuclear gene defects and whether this profile could be used to monitor their natural history and the treatment efficacy when novel therapeutic approaches are trialed.

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RESEARCH INTERESTS

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

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

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

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

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

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RESEARCH INTERESTS

Allorecognition: *Dictyostelium* cells preferentially cooperate with relatives (Ostrowski, 2008), and we are investigating the mechanisms that underlie this kin discrimination. We found two cell-cell adhesion genes, *tgrB1* and *tgrC1*, that are highly polymorphic in natural populations and required for allorecognition (Benabentos, 2009), and showed that the sequence polymorphism in these genes is sufficient to explain allorecognition in *Dictyostelium* (Hirose, 2011). This kin-recognition system protects cooperators against cheaters (Ho, 2013) and is temporally regulated, which allows it to evolve despite its essential role in development (Ho, 2015). We are investigating the mechanisms that regulate allorecognition under the hypothesis that TgrB1 and TgrC1 function as a ligand-receptor pair (Hirose, 2017), which is at the top of a signal transduction cascade that regulates development and allorecognition. The TgrB1-C1 system replaces cAMP as the central signaling system during tissue integration (Hirose, 2021), and we are investigating the downstream signal transduction mechanisms that were initially found using a genetic suppressor screen (Li, 2016).

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

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

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

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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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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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RESEARCH INTERESTS

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

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

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

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Resident, Pediatrics, Washington University in Saint Louis
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RESEARCH INTERESTS

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

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

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

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

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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.

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RESEARCH INTERESTS

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

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

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

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RESEARCH INTERESTS

Molecular and Developmental Mechanisms of Mendelian Disorders

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

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

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

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RESEARCH INTERESTS

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

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

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

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RESEARCH INTERESTS

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

Ongoing research interests include:

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

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

Alzheimer's Disease Sequencing Project Consortium (ADSP): I lead the structural variant working group seeking to assess and interpret the impact of structural variants with Fritz Sedlazeck, Richard Gibbs and Anita DeStefano. I also work with Olivier Lichtarge, Ismael Al-Ramahi, Juan Botas and Joanna Jankowsky on projects to assess the functional impact of variants in the ADSP data. Read more about the consortium here: https://www.nia.nih.gov/research/dn/alzheimers-disease-sequencing-project-consortia.

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

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

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RESEARCH INTERESTS

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

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

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

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RESEARCH INTERESTS

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

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

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RESEARCH INTERESTS

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

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

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

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RESEARCH INTERESTS

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

One of our research focuses is circadian gene regulation in cardiac remodeling. Our work covers the entire circadian regulatory landscape, from the core clock, to the slave clock, to the effectors. We discovered that core clock factor REV-ERB is protective for cardiac pathological remodeling and pharmacological activation of REV-ERB prevents heart failure progression even in late-stages. This was *the first example of treating heart failure by manipulating circadian machineries*. We also established the very first cardiac slave clock, KLF15, which controls the circadian ischemia reperfusion injury in the heart. Recently, we *discovered the first circadian lncRNA, Circa*. Circa is uniquely expressed in the adult cardiomyocytes and protects the heart during pressure overload and myocardial infarction through global regulation of alternative splicing via interaction with hnRNP A1. Our goal is to gain knowledge on circadian gene regulation in the heart and ultimately hope to use this information to design novel therapeutics for heart failure.

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

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

RESEARCH INTERESTS

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

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

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

SELECTED PUBLICATIONS

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

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Zoghbi AW, Lieberman JA (2018). Alive but Not Well: The Limited Validity but Continued Utility of the Concept of Schizophrenia. **Psychological Medicine** 2: 245-246.

Girgis, RR, **Zoghbi AW**, Javitt DC, Lieberman JA (2018). The Past and Future of Novel Therapeutics for Schizophrenia: A Critical and Comprehensive Review. **Journal of Psychiatric Research** 108: 57-83.

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HUDA Y. ZOGHBI, M.D.

Ralph D. Feigin M.D. Endowed Chair

Professor, Departments of Molecular and Human Genetics, Pediatrics - Neurology and Developmental Neuroscience
Faculty Member, Graduate Programs in Genetics & Genomics and Neuroscience
Director, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital
Investigator, Howard Hughes Medical Institute

M.D., American University of Beirut/Meharry Medical College
Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

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

Polyglutamine Pathogenesis and Neurodegeneration. We co-discovered the gene for spinocerebellar ataxia type 1 (SCA1) in 1993 with Dr. Harry Orr at the University of Minnesota and have been collaborating to understand the disease mechanism. Our genetic studies in mice and, in collaboration with Juan Botas, in fruit flies led us to propose that the polyglutamine tract stabilizes Ataxin-1 increasing its levels and interactions and causing toxicity due to its enhanced function. Consistent with this we discovered that a 30-50% increase in wild-type Ataxin-1 causes cerebellar degeneration and ataxia in mice. We also discovered that the enhanced function of mutant Ataxin-1 with its native partner Capicua drives the cerebellar ataxia. Further, we discovered that reducing Ataxin-1 in the cerebellum is a viable therapeutic strategy, but that for other vulnerable brain regions the pathogenic mechanism is distinct. Interestingly, we learned that loss of Ataxin-1 and subsequently the repressor activity of the Ataxin-1-CIC complex leads to upregulation of *Bace1* and increased risk of Alzheimer pathology in the forebrain. Our current studies are focused on understanding the mechanisms driving the regional vulnerability in SCA1. Inspired by our work on SCA1 and the importance of Ataxin-1 levels for brain health, we have pursued cross-species studies to identify modulators of APP, tau, and alpha-synuclein, proteins that drive degeneration in Alzheimer and Parkinson disease.

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

Rett Syndrome. We discovered that Rett syndrome is caused by mutations in the X-linked methyl-CpG–binding protein 2 (*MECP2*). Our mouse model studies led to the definition of clinical phenotypes not previously appreciated in MeCP2 disorders and revealed that neurons are quite sensitive to having just slightly too much or too little MeCP2. In collaboration with Jianrong Tang (BCM), we found that forniceal deep brain stimulation restored hippocampal learning and plasticity. Using a *MECP2* duplication mouse model, we found that normalizing MeCP2 levels using antisense oligonucleotides reverse the symptoms including late onset seizures in adult mature animals. More recently, we discovered that presymptomatic training of Rett mice improved their performance, delayed disease onset by months, and improved neuronal morphology and physiology. Our work is now focused on three main areas: the identification of a biomarker that serves as a proxy for MeCP2 levels, understanding of MeCP2 regulation, and the network dysfunction in Rett syndrome, with the ultimate goal of targeting regulators of MeCP2 levels as well as network modulation as potential therapies.

SELECTED PUBLICATIONS

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Gennarino VA, Palmer EE, McDonell LM, (...), Boycott KM, Holder JL Jr, **Zoghbi HY** (2018). A Mild PUM1 Mutation Is Associated with Adult-Onset Ataxia, whereas Haploinsufficiency Causes Developmental Delay and Seizures. **Cell**. 172: 924-936.

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

Amir R, Van den Veyver IB, Wan M, Tran C, Francke U, **Zoghbi HY** (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. **Nat Genet.** 23: 185-8.

CHENGHANG (CHUCK) ZONG, PH.D.

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

Ph.D., University of California, San Diego
Postdoc, University of Illinois at Urbana-Champaign
Postdoc, Harvard University

RESEARCH INTERESTS

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

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

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

SELECTED PUBLICATIONS

Niu Y, Zhu Q, **Zong C** (2022). Single-cell Damagenome Profiling by Linear Copying and Splitting based Whole Genome Amplification (LCS-WGA). **Bio-protocol.** 12: e4357.

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

Henry and Emma Meyer Chair in Obstetrics and Gynecology

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

RESEARCH INTERESTS

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

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SELECTED PUBLICATIONS

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

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

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

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

CHRISTOPHER I. AMOS, PH.D.

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

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

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

RESEARCH INTERESTS

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

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

SELECTED PUBLICATIONS

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

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

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

CHRISTIE M. BALLANTYNE, M.D.

J. S. Abercrombie Chair - Atherosclerosis and Lipoprotein Research

Professor, Departments of Medicine, Molecular and Human Genetics and Molecular Physiology and Biophysics
Chief, Cardiology and Cardiovascular Research, Department of Medicine
Director, The Maria and Alando J. Ballantyne, M.D., Atherosclerosis Clinical Research Laboratory and Center for Cardiometabolic Disease Prevention

M.D., Baylor College of Medicine
Resident, Internal Medicine, The University of Texas Southwestern Medical School
Clinical Fellow, Cardiology, Baylor College of Medicine
American Heart Association/Bugher Foundation Fellowship, Howard Hughes Medical Institute and Institute for Molecular Genetics, Baylor College of Medicine

RESEARCH INTERESTS

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

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

SELECTED PUBLICATIONS

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

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

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

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ALISON A. BERTUCH, M.D., PH.D.

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M.S., M.D., and Ph.D., Biology, University of Rochester
Internship and Residency, Pediatrics, Baylor College of Medicine
Clinical Fellow in Pediatric Hematology/Oncology and Postdoc, Baylor College of Medicine

RESEARCH INTERESTS

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

SELECTED PUBLICATIONS

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Emerson CH, Lopez CR, Ribes-Zamora A, Polleys EJ, Williams CL, Yeo L, Zaneveld JE, Chen R, **Bertuch AA** (2018). Ku DNA End-Binding Activity Promotes Repair Fidelity and Influences End-Processing During Nonhomologous End-Joining in Saccharomyces cerevisiae. **Genetics**. 209: 115-128.

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MALCOLM BRENNER, M.D., PH.D.

Fayez Sarofim Chair

Professor, Departments of Medicine, Pediatrics, and Molecular and Human Genetics; Stem Cells and Regenerative Medicine (STaR) Center
Founding Director, Center for Cell & Gene Therapy

MBChB, University of Cambridge
Ph.D., University of Cambridge
FRCPath, FRCP

RESEARCH INTERESTS

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

SELECTED PUBLICATIONS

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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.

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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.

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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.

MARY E. DICKINSON, PH.D.

Kyle and Josephine Morrow Endowed Chair in Molecular Physiology and Biophysics

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

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

RESEARCH INTERESTS

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

SELECTED PUBLICATIONS

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

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

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

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

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RICHARD H. FINNELL, PH.D.

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

RESEARCH INTERESTS

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

SELECTED PUBLICATIONS

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

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

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

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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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KENDAL D. HIRSCHI, PH.D.

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

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

RESEARCH INTERESTS

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

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

SELECTED PUBLICATIONS

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

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

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

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

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

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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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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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CPRIT Scholar in Cancer Research

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

RESEARCH INTERESTS

Dr. Parsons' research program focuses on the clinical application of genomic technologies in pediatric cancer care. His work has been instrumental in the characterization of the genetic landscapes of a variety of pediatric and adult cancers, including the first identification of IDH1 and IDH2 as cancer genes. His group is currently engaged in a number of projects seeking to genomically characterize pediatric cancers in order to identify potential molecular targets for therapy and facilitate the pre-clinical testing of novel therapeutics. Dr. Parsons was one of the principal investigators of the BASIC3 study, an NHGRI and NCI-funded U01 Clinical Sequencing Exploratory Research (CSER) program project involving clinical exome sequencing of tumor and blood specimens from children with newly diagnosed solid tumors, and is now helping to lead the KidsCanSeq study (which includes multimodal clinical genomic analysis of patients from multiple Texas institutions) as part of that same consortium. He is also the Children's Oncology Group (COG) study chair for the NCI-COG Pediatric MATCH trial, the first nationwide precision oncology clinical trial for children with relapsed and refractory cancers.

SELECTED PUBLICATIONS

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

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

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

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

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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.

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

RESEARCH INTERESTS

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

SELECTED PUBLICATIONS

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

Noah TK, Lo YH, Price A, Chen G, King E, Washington MK, Aronow BJ, **Shroyer NF** (2013). SPDEF functions as a colorectal tumor suppressor by inhibiting β-catenin activity. **Gastroenterology**. 144: 1012-1023.

Spence JR, Mayhew CN, Rankin SA, (…), **Shroyer NF**, Wells JM (2011). Directed differentiation of human pluripotent stem cells into intestinal tissue *in vitro*. **Nature**. 470: 105-9.

Kazanjian A, Noah T, Brown D, Burkart J, **Shroyer NF** (2010). Atonal homolog 1 is required for growth and differentiation effects of notch/gamma-secretase inhibitors on normal and cancerous intestinal epithelial cells. **Gastroenterology**. 139: 918-28.

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

RESEARCH INTERESTS

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

SELECTED PUBLICATIONS

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

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

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

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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.

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

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

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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).

SELECTED PUBLICATIONS

Wang T, et al. (2018). The NIEHS TaRGET II Consortium and environmental epigenomics. **Nat Biotechnol.** 36: 225-227.

Treviño LS, et al. (2020). Epigenome environment interactions accelerate epigenomic aging and unlock metabolically restricted epigenetic reprogramming in adulthood. **Nat Commun.** 11: 2316.

Park IY, et al. (2016). Dual Chromatin and Cytoskeletal Remodeling by SETD2. **Cell.** 166: 950-962.

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

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

Koenning M, et al. (2021). Neuronal SETD2 activity links microtubule methylation to an anxiety-like phenotype in mice. **Brain.** 144: 2527-2540.

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ROBERT A. WATERLAND, PH.D.

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Postdoc, Duke University

RESEARCH INTERESTS

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

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

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

SELECTED PUBLICATIONS

Gunasekara CJ, Hannon E, MacKay H, Coarfa C, McQuillin A, Clair DS, Mill J, **Waterland RA** (2021). A machine learning case-control classifier for schizophrenia based on DNA methylation in blood. **Transl Psychiatry.** 11:412.

MacKay H, Scott CA, Duryea JD, Baker MS, Laritsky E, Elson AE, Garland T, Fiorotto ML, Chen R, Li Y, Coarfa C, Simerly RB, **Waterland RA** (2019). DNA methylation in AgRP neurons regulates voluntary exercise behavior. **Nat Commun.** 10: 5364.

Gunasekara CJ, Scott CA, Laritsky E, Baker MS, MacKay H, (...), **Waterland RA** (2019). A genomic atlas of systemic interindividual epigenetic variation in humans. **Genome Biol.** 20: 105.

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

RESEARCH INTERESTS

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

SELECTED PUBLICATIONS

Lee D, Chen W, Kaku HN, Zhuo X, Chao ES, Soriano A, Kuncheria A, Flores S, Kim JH, Rigo F, Jafar-Nejad P, Beaudet AL, Caudill MS, **Xue M**. Antisense oligonucleotide therapy rescues disturbed brain rhythms and sleep in juvenile and adult mouse models of Angelman syndrome. **bioRxiv**. 2022; doi: 10.1101/2022.06.18.496687. (preprint)

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

Chen W, Cai ZL, Chao ES, (...), Zoghbi HY, Tang J, Swann JW, **Xue M** (2021). Stxbp1/Munc18-1 haploinsufficiency impairs inhibition and mediates key neurological features of STXBP1 encephalopathy. **ELife**. 9: e48705.

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

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

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

Baylor College of Medicine Medical Center McNair Campus

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.

Aerial View of the Texas Medical Center

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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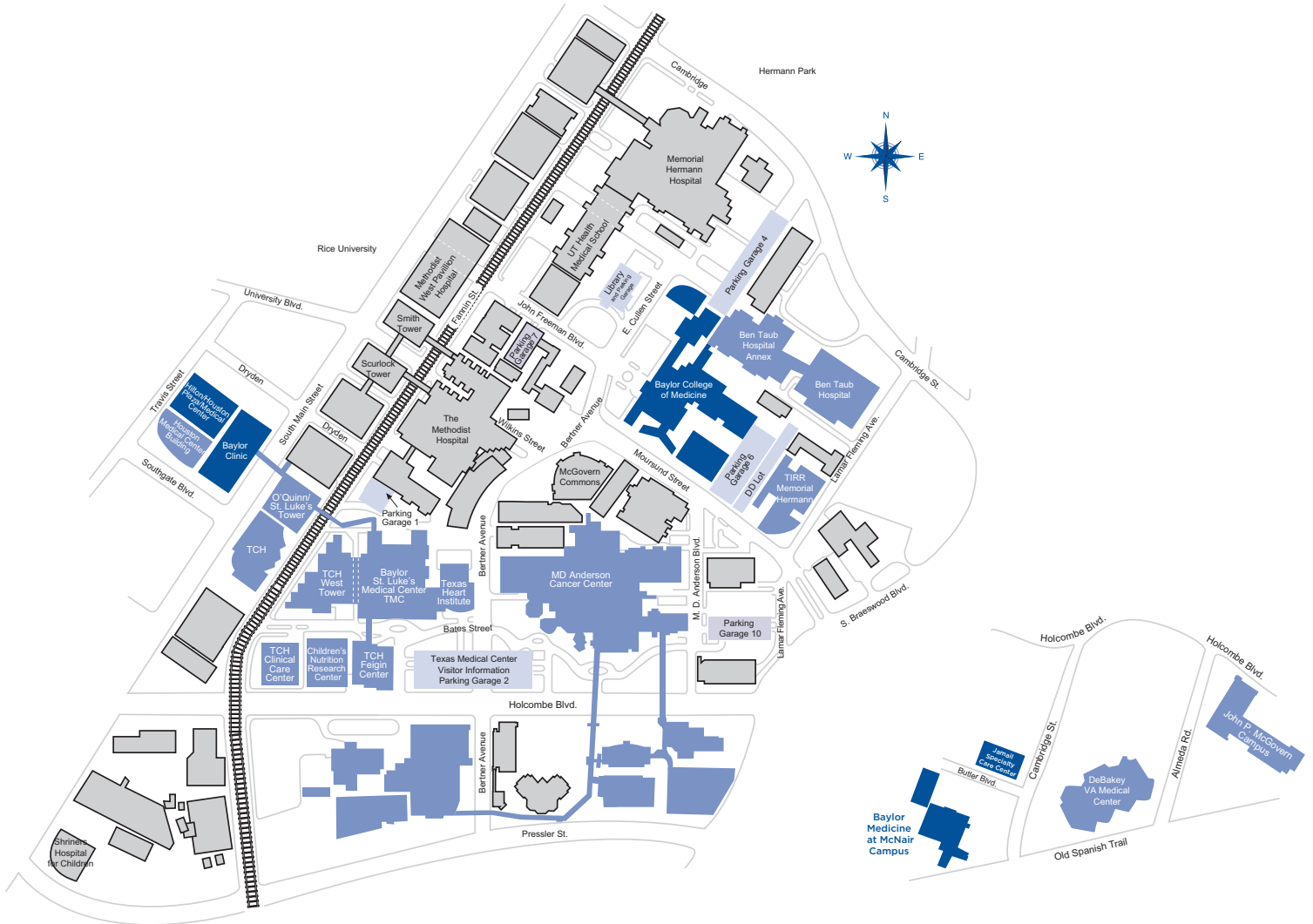
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