

Department of Genetics
2022-2023

GENETICS FACULTY

2022-2023

	<u>Room</u>	<u>Building</u>	<u>Phone</u>
Gil Atzmon , Associate Professor (primary appointment, Medicine/Endocrinology)	502C	Golding	430-3628
Nicholas E. Baker , Professor (secondary appointment, Developmental and Molecular Biology) (tertiary appointment, Ophthalmology and Visual Sciences)	805	Ullmann	430-2854
Nir Barzilai , Professor (primary appointment, Medicine/Endocrinology)	701A	Belfer	430-3144
Renata A. Batista-Brito , Assistant Professor (primary appointment, Neuroscience)	203	Kennedy	430-8507
Hannes Buelow , Professor (secondary appointment, Neuroscience)	709	Ullmann	430-3621
Ching-Pin Chang , Professor	414	Price	678-1067
Roy S. Chuck , Professor (primary appointment, Chair, Ophthalmology and Visual Sciences)	3332 Rochambeau Ave., MMC		920-6665
Ales Cvekl , Professor (primary appointment, Ophthalmology and Visual Sciences)	123	Ullmann	430-3217
Meelad Dawlaty , Associate Professor (secondary appointment, Developmental and Molecular Biology and Stem Cell Institute)	419	Price	678-1224
Winfried Edelmann , Professor (primary appointment, Cell Biology)	277	Price	678-1086
Scott Emmons , Professor (secondary appointment, Neuroscience)	703	Ullmann	430-3130
John Greally , Professor (secondary appointment, Pediatrics)	322	Price	678-1234
Jean Hébert , Professor (primary appointment, Neuroscience)	237	Kennedy	430-3494
William R. Jacobs, Jr. , Professor (primary appointment, Microbiology & Immunology)	577	Price	678-1075
Andreas Jenny , Professor (primary appointment, Developmental and Molecular Biology)	503	Chanin	430-4183
Ganjam V. Kalpana , Professor (secondary appointment, Microbiology & Immunology)	823	Ullmann	430-2354
Peri Kurshan , Assistant Professor (primary appointment, Neuroscience)	810	Kennedy	430-3631

Herb Lachman , Professor (primary appointment, Psychiatry and Behavioral Sciences) (secondary appointment, Medicine/Hematology) (tertiary appointment, Genetics) (tertiary appointment, Neuroscience)	103	Forchheimer	430-2428
Jack Lenz , Professor (secondary appointment, Microbiology & Immunology)	717	Ullmann	430-3715
Wei Liu , Associate Professor (primary appointment, Ophthalmology and Visual Sciences)	117A	Ullmann	839-7926
Sridhar Mani , Professor (primary appointment, Medicine/Oncology)	302D-1	Chanin	430-2871
Sofiya Milman , Associate Professor (primary appointment, Medicine/Endocrinology)	702B	Belfer	430-3462
Parsa Mirhaji , Research Associate Professor (primary appointment, Clinical Research Informatics)	538	Block	430-2916
Cristina Montagna , Adjunct Professor	Department of Radiation Oncology Rutgers Cancer Institute of New Jersey Room 3557 195 Little Albany Street New Brunswick, NJ 08901		732-235-6430
Bernice Morrow , Professor (secondary appointment, Obstetrics & Gynecology and Women's Health) (tertiary appointment, Pediatrics)	475	Price	678-1121
Srilakshmi Raj , Assistant Professor	422A	Price	678-1245
Michael G. Rosenfeld , Adjunct Professor	UCSD 9500 Gilman Drive #0648 La Jolla, CA 92093		858-534-5858
Jayanta Roy-Chowdhury , Professor (primary appointment, Medicine/Liver Diseases)	523	Ullmann	430-2265
Namita Roy-Chowdhury , Professor (primary appointment, Medicine/Liver Diseases)	523	Ullmann	430-2254
Julie Secombe , Professor (secondary appointment, Neuroscience)	809	Ullmann	430-2698
Milan Sen , Associate Professor (primary appointment, Orthopaedic Surgery)	Jacobi Medical Center 1400 Pelham Parkway South Building 1, Room 218 Bronx, New York 10461		718-918-4921
Frank Soldner , Assistant Professor (primary appointment, Neuroscience) (secondary appointment, Genetics)	235	Kennedy	839-7770
Simon D. Spivack , Professor (primary appointment, Medicine/Pulmonary Medicine) (secondary appointment, Epidemiology & Population Health) (tertiary appointment, Genetics)	301	Price	678-1040

Yousin Suh , Adjunct Professor	630 West 168 th Street Room 10-518 New York, NY 10032		212-305-6832
Masako Suzuki , Assistant Professor	477	Price	678-1202
Anne Van Arsdale , Associate Professor (primary appointment, Obstetrics & Gynecology and Women's Health (Gynecological Oncology) (secondary appointment, Genetics)	1695 Eastchester Road Room 601 Bronx, New York 10461		718-405-8086
	469	Price	678-1159
Vladislav Verkhusha , Professor (Co-Director of the Gruss-Lipper Biophotonics Center)	1217	Ullmann	430-8591
Jan Vijg , Professor and Chair (secondary appointment, Ophthalmology & Visual Sciences)	450	Price	678-1151
David Q.-H. Wang , Professor (primary, Medicine/Gastroenterology & Liver Diseases) (secondary, Genetics)	611	Ullmann	430-8865
Tao Wang , Professor (primary, Epidemiology & Population Health) (secondary, Genetics)	1303A	Belfer	430-4007
Melissa Wasserstein , Professor (primary appointment, Pediatrics) (secondary appointment, Genetics)	3411 Wayne Avenue, MMC		718-741-2318
Daniel Weiser , Associate Professor (primary appointment, Pediatrics)	813	Ullmann	430-2181
Zhengdong Zhang , Professor	353A	Price	678-1139
Deyou Zheng , Professor (primary appointment, Genetics and Neurology) (tertiary appointment, Neuroscience)	320	Price	678-1217
Bin Zhou , Professor (secondary appointment, Pediatrics) (tertiary appointment, Medicine/Cardiology)	402	Price	678-1067

RESEARCH FACULTY

Department of Genetics

2022-2023

<u>Name (Mentor)</u>	<u>Title</u>	<u>Room</u>	<u>Building</u>	<u>Phone</u>
Mikhail Baloban (Verkhusha)	Associate	1217	Ullmann	430-2127
Wei Cheng (Chang)	Associate	414	Price	676-1551
Robert Dubin (Greally)	Associate	553	Price	678-1226
Xuhui Feng (Chang)	Associate	408	Price	678-1551
Amit Kumar (Baker)	Associate	805	Ullmann	430-2855
Jhieh-Rong Lin (Zhang)	Associate	353	Price	678-1147
Pengfei Lu (Zhou)	Associate	408	Price	678-1551
Shahina Maqbool (Greally)	Research Assoc. Prof.	157	Price	678-1163
Alexander Maslov (Vijg)	Research Assoc. Prof.	468	Price	678-1135
Nha Nguyen (Zhang)	Associate	353	Price	678-1147
David Reynolds (Morrow)	Associate	1203	Ullmann	929-246-6735
Daria Shcherbakova (Verkhusha)	Research Asst. Prof.	1217	Ullmann	430-2127
Jidong Shan (Montagna)	Research Assoc. Prof.	401	Price	678-1155
Roman Sidorov (Baker)	Associate	805	Ullmann	430-2855
Shixiang Sun (Vijg)	Associate	478	Price	678-1135
Leo Tsz-Ho Tang (Buelow)	Associate	709	Ullmann	430-3622
Bingruo Wu (Zhou)	Research Assoc. Prof.	402	Price	678-1551
Yingjie Zhao (Morrow)	Associate	469	Price	678-1122

POSTDOCTORAL FELLOWS

Department of Genetics

2022-2023

<u>Name (Mentor)</u>	<u>Telephone</u>	<u>Lab Location</u>
Natalia Barykina (Verkhusha)	430-2127	1217 Ullmann
Christopher DeBono (Morrow)	678-1122	469 Price
Reza Jabal Ameli Forooshani (Zhang)	678-1147	353 Price
Johanna Heid (Vijg)	678-1135	468 Price
Zhenqiu Huang (Vijg)	678-1135	468 Price
Mariko Isshiki (Raj)	678-1245	420 Price
Ludmila Kasatkina (Verkhusha)	430-2127	1217 Ullmann
Kyrylo Manoilov (Verkhusha)	430-2127	1217 Ullmann
Yuta Matsuno (Suzuki)	678-1159	469 Price
Rohan Misra (Zheng)	678-1166	320 Price
Rajiv Pathik (Kalpana)	430-2404	823 Ullmann
Lijie Shi (Morrow)	678-1122	469 Price
Sviatlana Smokskaya (Verkhusha)	430-2127	1217 Ullmann
Bethany Terry (Secombe)	430-4463	809 Ullmann
ZarChi Thent (Zhou)	678-1551	408 Price
Ying Hong Tham (Emmons)	430-2249	703 Ullmann

GRADUATE STUDENTS

Department of Genetics

2022-2023

<u>Name (Mentor)</u>	<u>Telephone</u>	<u>Lab Location</u>
Olivia Albert (Vijg/Montagna)	678-1135)	468 Price
Jesse Barnes (Lachman)	430-2491	103 Forchheimer
Zipporah Bush (Soldner)	839-7770	235 Kennedy
Michael Camerino (Cvekl)	430-3219	123 Ullmann
Melissa Castiglione (Secombe)	430-4463	809 Ullmann
Ronald Cutler (Vijg/Sidoli)	678-1135	468 Price
Blake Ebert* (Dawlaty)	678-1210	413 Price
Alexander Ferrera (Zheng)	678-1166	353 Price
Elisha Fogel (Morrow)	678-1122	469 Price
Julio Flores* (Dawlaty)	678-1210	413 Price
Jenna Freund (Buelow)	430-3622	709 Ullmann
Kevyn Jackson (Morrow)	678-1122	469 Price
Harmony Ketchum (Dawlaty)	678-1210	413 Price
Garrett Alexander Lee* (Buelow)	430-3622	709 Ullmann
Ian MacArthur* (Dawlaty)	678-1210	413 Price
Roshan Mathews (Kalpana)	430-2404	823 Ullmann
Daniella Miller (Morrow)	678-1122	469 Price
Michael Rogers* (Secombe)	430-4463	809 Ullmann
Megan Russell (Zhou)	678-1551	408 Price
Christopher Salazar (Buelow)	430-3622	709 Ullmann
Blair Schneider (Secombe)	430-4463	809 Ullmann
Hansoo Song (Morrow)	678-1122	469 Price
Jada Summerville (Kurshan)	430-3646	810 Kennedy
Meera Trivedi* (Buelow)	430-3622	709 Ullmann
David Yang (Raj/Greally)	678-1570	314 Price
Matanel Yheskel* (Secombe)	430-4463	809 Ullmann
Xiang Yu Zheng (Zheng)	678-1166	353 Price

*M.D./Ph.D. Students

Epigenetic Profiling in Healthy Aging and Exceptional Longevity

Examples of epigenetic regulation of genome architecture and gene expression are paved across the evolutionary lineage. Even if only a small proportion of human genes are subject to similar effects, they may still play a major role in the phenotypic variation and susceptibility to diseases. My long-term research goal is to investigate changes in the epigenetic control of gene expression which may be one of the central mechanisms by which aging predisposes to many age-related diseases and therefore lifespan.

Despite some early work, the role of epigenetics in human life span and age related diseases has remained unexplored. Discovering that methylated loci are involved in the genetic control of cellular existence, modify the risk for age-related disease and influence mortality is a novel and extremely important concept that would significantly enhance our understanding of the biology of aging. In addition, accumulating evidence supports the notion that major age-associated diseases (such as diabetes, metabolic syndrome and cancer) are regulated by epigenetic alterations. Epigenetic changes may provide information on the pivotal points between healthy and sick stages in the lifespan of an individual. Hence, epigenetic changes could serve as landmarks of events such as onset of disease and these events can be tracked long after its occurrence (forms of epimutation and the Barker theory).

To test our hypothesis, we employed a novel high-throughput genome-wide methylation assay, HELP-tag and EPIC arrays (Illumina). Additionally, we utilized a combination of large-scale epigenomic analysis (EWAS) to identify the most distinctive epigenetic loci that show greatest differential methylation. We then performed Multi-locus validation for methylation status using MassARRAY. We tested expression of candidate loci to explore possible mechanisms of methylation regulation. We combined these results with whole genome sequences to assess the interaction between the genetic blueprint and the environment as it manifested through epigenetic changes.

This research furthered our understanding of the complexity of healthy lifespan process by identifying loci that when altered epigenetically have important ramifications for age-related diseases and lifespan. Validating the genes whose function is modulated epigenetically could lead to interventions to delay or even prevent the development of age-associated diseases.

Recent Publications:

Aleksic S et al. Integrity of hypothalamic-pituitary-testicular axis in exceptional longevity. *Aging Cell*. 2022, 13656.

Hindy G, Rare coding variants in 35 genes associate with circulating lipid levels-A multi-ancestry analysis of 170,000 exomes. *Am J Hum Genet*. 2022, 109(1):81-96.

Longchamps RJ, et al. Genome-wide analysis of mitochondrial DNA copy number reveals loci implicated in nucleotide metabolism, platelet activation, and megakaryocyte proliferation. *Hum Genet*. 2022 141(1):127-146.

Halvorsen M, et al. Elevated common variant genetic risk for Tourette Syndrome in a densely-affected pedigree. *Mol Psychiatry*. 2021 26(12):7522-7529,

Cell competition, ribosomopathy, and neuronal development

Cell-cell communication is the key process that makes complex life possible, enabling cells to follow different fates. We use *Drosophila* and more recently mice to identify and characterize new genes involved in these crucial processes. Currently we study novel molecular mechanisms of signaling and regulation in three main areas.

Cell competition and aneuploidy Competition is a process that can occur when cells within tissues differ. A specific pathway of cell competition selectively removes cells that have become aneuploid, or acquired other large-scale genetic changes. This is thought to suppress tumorigenesis and promote healthy aging. We have begun to identify the molecular pathways involved. Our current goals include understanding how differences in genome content between cells are recognized., how cell competition participates in tumor suppression, including the potential cell competition roles of p53, one of the most important human tumor suppressors, and how changes in cell competition might increase or be exploited to decrease cancer incidence, both in fruitflies and in mammals.

Ribosomopathy Ribosomes are essential for growth. Their biogenesis and assembly are elaborate, regulated processes. Ribosome biogenesis and function is affected during growth and in neurodegenerative diseases. Ribosomal proteins are affected in several human diseases, and mutations in ribosomal protein genes unexpectedly seem to be causal in many cancers. We are interested in the molecular signaling mechanisms activated by ribosomes, and their roles in cancer and neurological diseases.

Neural cell fate determination Commitment to neural development requires the expression of particular transcriptional master regulatory genes, of which the proneural basic helix-loop-helix (bHLH) proteins are most important. Their activities appear to be highly regulated. Our studies use genetic screening, modern genome resequencing methods and multidisciplinary studies to characterize how proneural bHLH proteins are regulated.

recent publications and preprints

- Khan, C. and N.E. Baker, The DNA damage response and cell competition are p53- and Xrp1-dependent processes that suppress hyperplastic aneuploidy. *bioRxiv*. <https://doi.org/10.1101/2022.06.06.494998>.
- Folgado-Marco, V., Ames, K., Chuen, J., Gritsman, K., and Baker, N.E. Haploinsufficiency of the essential gene RpS12 causes defects in erythropoiesis and hematopoietic stem cell maintenance. *Elife*, under revision. *BioRxiv* <https://doi.org/10.1101/2021.05.04.442585>
- Kiparaki, M., Khan, C., Folgado Marco, V., Chuen, J., and Baker, N.E. (2022) The transcription factor Xrp1 orchestrates both reduced translation and cell competition upon defective ribosome assembly or function. *Elife*, **11**: e71705.
- Ji, Z., Chuen, J. Kipakai, M., and Baker, N.E. (2021) Cell competition removes segmental aneuploid cells from *Drosophila* imaginal disc-derived tissues based on ribosomal protein gene dose. *Elife*, **10**:e61172.
- Quiquand, M., Rimesso, G., Qiao, N., Suo, S., Zhou, C., Slattery, M., White, K.P., Han, J.J., and Baker, N.E. (2021) New regulators of *Drosophila* eye development identified from temporal transcriptome changes. *Genetics*, **217(4)**: iyab007.doi: 10.1093/genetics/iyab007.
- Baker, N.E. Emerging mechanisms of cell competition. (2020) *Nature Reviews Genetics*, **21**; 683-697.
- Blanco, J., Cooper, J.C., and Baker, N.E. (2020) Roles of C/EBP class bZip proteins in the growth and cell competition of Rp ("Minute") mutants in *Drosophila* (2020). *Elife*, **9** 9:e50535
- Ji, Z., Kiparaki, M., Folgado, V., Kumar, A., Blanco, J. Rimesso, G., Liu, Y., Zheng, D., and Baker, N.E. (2019) *Drosophila* RpS12 controls translation, growth, and cell competition through Xrp1. *PLoS Genetics*, **15(12)**:e1008513.
- Wang, L.-H. and Baker, N.E. (2019) Salvador-Warts-Hippo pathway regulates sensory organ development via caspase-dependent non-apoptotic signaling. *Cell Death & Disease* **10** 669.
- Li, K. and Baker, N.E. (2019) Transcriptional and post-transcriptional regulation of *extra macrochaetae* during *Drosophila* adult peripheral neurogenesis. *Dev Biol* **449**: 41-51.
- Baker, N.E., Kiparaki, M., and Khan, C. (2019) A potential link between p53, cell competition and ribosomopathy in mammals and in *Drosophila*. *Dev Biol* **446**: 17-19.
- Lee, C.H., Kiparaki, M., Blanco, J., Folgado, V., Ji, Z., Kumar, A., Rimesso, G., and Baker, N.E. (2018) A regulatory response to ribosomal protein mutations controls translation, growth, and cell competition. *Dev Cell*, **46**, 456-469.
- Baker, N.E., and Brown, N.L. (2018) All in the family: neuronal diversity and proneural bHLH genes. *Development*, **145**: dev159426.
- Li, K., and Baker, N.E. (2018) Regulation of the *Drosophila* ID protein Extra Macrochaetae by proneural dimerization partners. *Elife* **7**: e33967.
- Kale, A., Ji, Z., Kiparaki, M., Rimesso, G., Flibotte, S., and Baker, N.E. (2018) Ribosomal protein S12e has a distinct function in cell competition. *Dev Cell* **44**, 42-55.

NIR BARZILAI, M.D.

Searching for Longevity Genes in Humans

Why do some people live much longer than others? What allows these individuals to escape age-associated diseases that contribute to mortality in the elderly? Is this a result of favorable genes or merely a healthy life style? If the genome does play a role, what are the mechanisms?

To address these questions, we recruited over 1500 Ashkenazi Jews. The Ashkenazi Jewish population is unique as it is derived from a small number (several thousands) of founders and therefore it is genetically homogeneous. This population has been utilized for identification of several genes, a prominent example being the breast cancer gene. The subjects fall into three groups; probands, subjects with exceptional longevity (1:10000 in the general population); their offspring; and a control group consisting of spouses of the offspring and other Ashkenazi Jewish people recruited from the Einstein Aging Study.

Studying the clinical and metabolic phenotype, revealed certain physiological characteristics in the centenarians and their offspring such as high levels of high-density lipoprotein (HDL), high adiponectin levels, and high IGF-1 levels. In collaboration with Dr. Atzmon and Suh, we showed that each of those phenotype is now associated with a genotype that has a functional meaning, and each of those genotypes have been validated independently in at least one other population of centenarians. One of the genotypes is also specifically protective from cognitive decline, and this was also validated as an Alzheimer's protective gene. We studied telomere length demonstrating longer telomeres in our longest living subjects and their offspring compared to control. These findings may indicate longer telomeres at birth or slower attrition rate in their length, and this was associated with a specific haplotype of the telomere gene. Most important, since the trait of longer telomeres is associated with protective lipoprotein profile and less age-related disease, this test may be used as a predictor for longevity.

Using an un-biased approach, we have employed an Affimetrix 6.0 platform with almost 2MM markers and across the genome. Comparing the centenarian genotype to a younger un-related control, we established 35 genotypes that increase monotonically with aging (from age 60 to 112) and were linked significantly ($p < 10^{-6}$) to genes that have not been previously linked to aging. In collaboration with Drs. Greally and Atzmon, we have used high throughput methylation assay (HELP) to demonstrate that centenarians methylation pattern across the genome is significantly different than in younger un-related subjects.

Our lab has trained many graduates and post-docs, and the latest graduate, Reid Thompson, MD/Ph.D. student, can be a reference. We offer a clinical platform for variety of genomic studies in collaboration with many of the Einstein faculty.

Recent Publications:

Kato K, Zweig R, Schechter CB, Verghese J, Barzilai N, Atzmon G. Personality, self-rated health, and cognition in centenarians: Do personality and self-rated health relate to cognitive function in advanced age? Aging (Albany NY). 2013 Mar 23. PMID: 23524310

Han J, Ryu S, Moskowitz DM, Rothenberg D, Leahy DJ, Atzmon G, Barzilai N, Suh Y. Discovery of novel nonsynonymous SNP variants in 988 candidate genes from 6 centenarians by target capture and next-generation sequencing. Mech Ageing Dev. 2013 Jan 31. doi:pii: S0047-6374(13)00020-1. PMID: 23376243

Barzilai N and Ferrucci L. Insulin Resistance and Aging: A Cause or a Protective Response? J Gerontol A Biol Sci Med Sci. August 2012; PMID: 22859390

Gombar S, Jung HJ, Dong F, Calder B, Atzmon G, Barzilai N, Tian XL, Pothof J, Hoeijmakers JH, Campisi J, Vijg J, Suh Y. Comprehensive microRNA profiling in B-cells of human centenarians by massively parallel sequencing. BMC Genomics. 2012 Jul 31;13(1):353 PMID: 22846614

Barzilai N, Guarente L, Kirkwood TB, Partridge L, Rando TA, Slagboom PE. The place of genetics in ageing research. Nat Rev Genet. 2012 Jul 10;13(8):589-94. doi: 10.1038/nrg3290. PMID: 22777128

Huffman DM, Deelen J, Ye K, Bergman A, Slagboom EP, Barzilai N, Atzmon G. Distinguishing Between Longevity and Buffered-Deleterious Genotypes for Exceptional Human Longevity: The Case of the MTP Gene. J Gerontol A Biol Sci Med Sci. 2012 Apr 10. PMID: 22496539

Conneely KN, Capell BC, Erdos MR, Sebastiani P, Solovieff N, Swift AJ, Baldwin CT, Budagov T, Barzilai N, Atzmon G, Puca AA, Perls TT, Geesaman BJ, Boehnke M, Collins FS. Human longevity and common variations in the LMNA gene: a meta-analysis. Aging Cell. 2012 Feb 16. PMID: 22340368

Rajpathak SN, Liu Y, Ben-David O, Reddy S, Atzmon G, Crandall J, Barzilai N. Lifestyle Factors of People with Exceptional Longevity. J Am Geriatr Soc. 2011 Aug 3. PMID: 2181276

The Batista-Brito lab investigates how inhibitory circuits shape sensory representation and perception at critical developmental ages. We use a powerful combination of methods, including single-cell genetic profiling, mouse genetics, cell-type specific manipulation of neuronal activity, *in vivo* electrophysiology, *in vivo* 2-photon imaging, and behavioral analysis, in order to functionally dissect the developmental impact of specific sources of inhibition on cortical processing and perception. This research illuminates how cortical functions are altered in neurodevelopmental disorders, with particular focus on schizophrenia and autism.

We investigate how postnatal development of inhibitory function shapes the way sensory information is processed in the brain in the context of health and disease. Perception depends on the adaptive function of brain areas comprised of many types of cells and synaptic connections that develop on a long timescale. During development, neural networks must grow from a state of zero connectivity to the precisely interconnected circuits characteristic of the adult brain. The activity of GABAergic inhibitory neurons during postnatal development is likely to mediate synaptic refinement, reducing synchrony and enhancing precision in the mature network. Accordingly, dysregulation of GABAergic interneurons has been linked to several neurodevelopmental disorders. Addressing these questions will identify key developmental processes, elucidate fundamental mechanisms by which sensory information guides behavior, and potentially provide new biomarkers for neuropsychiatric diseases.

We investigate the mechanisms by which contextual modulations are implemented within local cortical circuits and impact behavior. Contextual influences of global behavioral/arousal state (e.g. how alert am I?), sensory predictions (e.g. which stimuli do I expect?), and top-down attention (what is relevant to me?) are implemented throughout sensory cortices and have massive impact on perception. Such contextual influences are mediated by excitatory and inhibitory local circuits, however the specific nature of those circuits remain largely unknown. In this line of research we ask the basic science question - what are the essential neuron classes responsible for translating neuromodulatory signals into changes in sensory processing and perception? We hope that investigating the circuit mechanisms of contextual modulation operations, we will not only shift current research paradigms by opening new avenues for studying the role of inhibition in sensory behavior, but will also enhance our understanding of how mutations in GABAergic inhibitory neurons and alterations in neuromodulatory signaling lead to specific deficits of information processing in neuropsychiatric diseases.

Papers:

1. **Batista-Brito R**, Vinck M, Ferguson KA, Chang JT, Laubender D, Lur G, Mossner JM, Hernandez VG, Ramakrishnan C, Deisseroth K, Higley MJ, Cardin JA. Developmental dysfunction of VIP interneurons impairs cortical circuits. *Neuron*, 2017, 95(4):884-895. PMID: PMC5595250.
2. **Batista-Brito R, Mujandar A, Nuno A, Cardin JA. Developmental loss of EbbB4 in PV interneurons disrupts state-dependent cortical circuit dynamics. *BioRxiv*, 2020. doi: 10.1101/2020.12.09.418590. Under evaluation in *Molecular Psychiatry*.**
3. Mayer C, Hafemeister C, Bandler RC, Machold R, **Batista Brito R**, Jaglin X, Allaway K, Butler A, Fishell G, Satija R. [Developmental diversification of cortical inhibitory interneurons](#). *Nature*. 2018 Mar 22; 555(7697):457-462. PMID: 29513653.
4. Vormstein-Schneider DC, Lin JD, Pelkey KA, Chittajallu R, Guo B, Arias Garcia M, Sakopoulos S, Stevenson O, Schneider G, Zhang Q, Sharma J, Franken TP, Smith J, Vogel I, Sanchez V, Ibrahim LA, Burbridge T, Favuzzi E, Saldi GA, Xu Q, Guo L, Yuan X, Zaghoul KA, Sabri E, Goldberg EM, Devinsky O, **Batista-Brito R**, Reynolds J, Feng G, Fu Z, McBain CJ, Fishell GJ, Dimidschstein J. Viral manipulation of functionally distinct neurons from mice to humans. *Nature Neuroscience*, 2020, 23, 1628-1636.
5. Mossner J, **Batista-Brito R**, Pant R, Cardin JA. Developmental loss of MeCP2 from VIP interneurons impairs cortical function and behavior. *eLife*, 2020; Apr 28;9:e55639. PMID: 32343226.
6. Munguba H, Chattopadhyaya B, Nilsson S, Carriço JN, Memic F, Oberst P, **Batista-Brito R**, Munoz-Manchado AB, Wegner M, Fishell G, Di Cristo G, Hjerling-Leffler. Postnatal Sox6 regulates synaptic function of cortical parvalbumin-expressing neurons. *Journal Neuroscience*, 2021 Sep 9:JN-RM-0021-21. doi: 10.1523/JNEUROSCI.0021-21.2021. Online ahead of print.PMID: 34503995
7. Ratliff J, & **Batista-Brito, R**. The interneuron class struggle. *Cell*, 2020, 183(4), 845–847.
8. **Batista-Brito R**, Fishell G. Interneurons: Learning on the Job. *Neuron*. 2019, 102(5):905-907. PMID: 31170396
9. **Batista-Brito R**, Vinck M, Zagha E, Ratliff J. Top down modulation of cortical circuits in health and disease. *Current Opinion in Neurobiology*, issue 52. 2018.

For full paper list see:

<http://batista-britolab.com/index.php/papers-2/>

Genetics of Nervous System Development and Function

My lab uses the small nematode *C. elegans* with its simple and well characterized nervous system as a genetic model. We are trying to understand how growing axons and dendrites navigate the extracellular space to connect to their partners and be appropriately patterned. In addition, we are investigating how an animal's experience affects connectivity, i.e. hardwiring of its nervous system.

In one project we are studying the development of dendrites in polymodal multidendritic neurons of *C. elegans*. We are aiming to understand how the complex dendritic arbors that resemble menorah-like candelabras are patterned. Of particular interest are the mechanisms and molecules that promote or restrict the growth of dendrites both cell-autonomously and non-cell-autonomously. In a second project, we are investigating development and function of the connectome, i.e. the hardwiring of the nervous system. Specifically, we are interested in how an animal's experience can influence and change connectivity. To this end, we have developed methods to visualize cell-specific synaptic connections. We are now using a combination of genetic, behavioral, and imaging approaches to test how specific connections change in response to the environment and which genes mediate these processes. In a final project, we are studying the role of proteoglycans, e.g. heparan sulfate (HS) proteoglycans in development and disease. We are asking how specific modification patterns of the polysaccharide HS determine the path of developing axons. For instance, we have shown that distinct modification patterns in HS serve specific and instructive functions during neural development leading us to formulate the 'HS code' hypothesis. We propose that defined combinations of modifications in the sugars of HS contain information and generate a molecular map that helps shape the nervous system. Our goal is to decipher the information contained in HS, determine the factors that create and modulate it and describe the genes that respond to it. We are also investigating a pathological dimension of HS by studying Kallmann Syndrome, a human genetic disease with specific neurological defects in which we have identified mutations in HS genes. In summary, we are using genetic coupled with biochemical and advanced imaging approaches to understand the function of genes involved in development, function, and disease of the nervous system.

Selected Recent Publications:

Tornberg J., Sykiotis G.P., Keefe K., Plummer L., Hoang X, Hall J.E., Quinton R., Seminara S.B., Hughes V., Van Vliet G., Van Uum S., Crowley, Jr W.F., Habuchi H., Kimata K., Pitteloud N.*, Bülow H.E.* (2011) *Heparan sulfate 6-O-sulfotransferase 1*, a gene involved in extracellular sugar modifications, is mutated in patients with idiopathic hypogonadotropic hypogonadism. ***Proc Natl Acad Sci USA***, 108(28):11524-11529, published online June 23, 2011 as [doi:10.1073/pnas.1102284108](https://doi.org/10.1073/pnas.1102284108), * contributed equally.

Attreed M., Desbois M., van Kuppevelt T.H., and Bülow H.E. (2012) Direct visualization of specifically modified extracellular glycans in living animals. ***Nat. Methods***, 9(5):477-479, published online April 1, 2012 as [doi:10.1038/nmeth.1945](https://doi.org/10.1038/nmeth.1945).

Salzberg Y., Diaz-Balzac C.A., Ramirez-Suarez N.J., Attreed M., Tecle E., Desbois M., Kaprielian Z., and Bülow H.E. (2013) Skin-derived cues control arborization of sensory dendrites in *Caenorhabditis elegans*. ***Cell***, 155(2): 308–320, published online on October 10 as <http://dx.doi.org/10.1016/j.cell.2013.08.058>.

Díaz-Balzac C.A., Lázaro-Peña M.I., Ramos-Ortiz G.O., Bülow H.E. (2015) The Adhesion molecule KAL-1/anosmin-1 regulates Neurite Branching through a SAX-7/L1CAM–EGL-15/FGFR Receptor Complex. ***Cell Reports***, 11:1–8, published online on May 21 as <http://dx.doi.org/10.1016/j.celrep.2015.04.057>.

Díaz-Balzac C.A., Rahman M., Lázaro-Peña M.I., Martin Hernandez L.A., Salzberg Y., Aguirre-Chen C., Kaprielian Z., and Bülow H.E. (2016) Muscle- and skin-derived cues jointly orchestrate patterning of somatosensory dendrites. ***Current Biology***, 26:1-9, published online on July 21 as <http://dx.doi.org/10.1016/j.cub.2016.07.008>.

Ramirez-Suarez N.J., Belalcazar H.M., Salazar C.J., Beyaz B., Raja B., Nguyen K.C.Q., Celestrin K., Fredens J., Færgeman N.J., Hall D.H., and Bülow H.E. (2019) Axon-dependent patterning and maintenance of somatosensory dendritic arbors, ***Developmental Cell***, 48:229-244, published online on January 17, 2019 as <https://doi.org/10.1016/j.devcel.2018.12.015>.

Tang L.T.H.*, Díaz-Balzac C.A.*, Rahman M., Ramirez-Suarez N.J., Salzberg Y., Lázaro-Peña M.I., and Bülow H.E. (2019) TIAM-1/GEF can shape somatosensory dendrites independently of its GEF activity by regulating F-actin localization. ***eLife***; 8:e38949 DOI: [10.7554/eLife.38949](https://doi.org/10.7554/eLife.38949).

Tang L.T.*, Trivedi M.*, Freund J., Salazar C.J., Lee G.L., Ramirez-Suarez N.J., Rahman M., Wang Y., Grant, B.D., Bülow H.E. (2021) The CATP-8/P5A-type ATPase is required for multiple aspects of neuronal patterning, ***PLoS Genetics***, Jul 1, 17(7):e1009475, published online July 1, 2021 as <https://doi.org/10.1371/journal.pgen.1009475>.

Rahman M., Ramirez-Suarez N.J., Diaz-Balzac C.A., and Bülow H.E. (2022) Specific N-glycans regulate an extracellular adhesion complex during somatosensory dendrite patterning, ***EMBO Reports***, July 5, 23(7):e54163, published online on May 19, 2022 as e54163, <https://doi.org/10.15252/embr.202154163>.

Epigenetics and Noncoding RNA Mechanisms of Cardiomyopathy

Area of interests: Heart failure, Genetics, Epigenetics, RNA. The laboratory employs techniques of molecular biology, cell biology, developmental biology, and mouse genetics to determine the fundamental mechanisms of cardiovascular diseases. Our goal is to define the molecular mechanisms underlying cardiomyopathy and heart failure and translate bench findings to clinical applications. We established an epigenetic framework by which cardiac stress activates epigenomic changes in the heart to reprogram gene expression, causing cardiomyopathy. We identified several new chromatin regulators that are stress-regulated to control cardiac hypertrophy and failure. These regulators include chromatin-remodeling factors, histone and DNA modifying enzymes, transcription co-factors, and long non-coding RNAs. Those studies shed new lights on chromatin biology and epigenetic responses to environmental stress. It also led us to discover Myheart—a long noncoding RNA (lncRNA) that disrupts the Brg1-centered epigenetic network to protect the heart from hypertrophy and failure. Our chromatin and RNA work revealed a new mechanistic paradigm of how gene expression is controlled under different pathophysiological conditions (Nature 2010, Nature 2014). The lab continues to focus on in-depth mechanisms of cardiomyopathy, with an aim to better understand the stress-activated epigenetic and RNA mechanisms of heart failure.

List of Published Work in MyBibliography: <http://www.ncbi.nlm.nih.gov/sites/myncbi/ching-pin.chang.1/bibliography/41156584/public/?sort=date&direction=descending>

- Chang CP**, Neilson JR, Bayle JH, Gestwicki JE, Kuo A, Graef IA, Crabtree GR. A field of myocardial-endocardial NFAT signaling underlies heart valve morphogenesis. *Cell* 2004; 118(5):649-663. [Cover Story], [Editorial commentary]: Lambrechts D, Carmeliet P. Sculpting heart valves with NFAT and VEGF. *Cell* 2004;118(5):532
- Stankunas K, Hang CT, Tsun ZY, Chen H, Lee NV, Wu JI, Shang C, Bayle JH, Shou W, Iruela-Arispe ML, **Chang CP**. Endocardial Brg1 represses ADAMTS1 to maintain the microenvironment for myocardial morphogenesis. *Dev Cell* 2008 Feb;14(2):298-311.
- Kao SC, Wu H, Xie J, **Chang CP**, Ranish JA, Graef IA, Crabtree GR. Calcineurin/NFAT signaling is required for neuregulin-regulated Schwann cell differentiation. *Science* 2009 Jan; 323(5914):651-654.
- Stankunas K, Shang C, Twu KY, Kao SC, Jenkins NA, Copeland NG, Sanyal M, Selleri L, Cleary ML, **Chang CP**. Pbx/Meis deficiencies demonstrate multigenetic origins of congenital heart disease. *Circ Res* 2008; 702-9. [Cover Story]
- Bajpai R, Chen DA, Rada-Iglesias A, Zhang J, Xiong Y, Helms J, **Chang CP**, Zhao Y, Swigut T, Wysocka J. CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature* 2010;463: 958-962.
- Hang CT, Yang J, Han P, Cheng HL, Shang C, Ashley E, Zhou B, **Chang CP**. Chromatin regulation by Brg1 underlies heart muscle development and disease. *Nature* 2010 Jul; 466(7302):62-67. [Highlighted as Article, Press-released]
- Wu B, Zhang Z, Lui W, Chen X, Wang Y, Chamberlain A, Moreno-Rodriguez RA, Markwald RR, O'Rourke RP, Sharp DJ, Zheng D, Lenz J, Baldwin HS, **Chang CP**, Zhou B. Endocardial cells form coronary arteries by angiogenesis through myocardial to endocardial VEGF signaling. *Cell* 2012; 21;151(5):1083-96.
- Li W, Xiong Y, Shang C, Twu KY, Hang CT, Yang J, Han P, Lin CY, Lin CJ, Tsai FC, Stankunas K, Meyer T, Bernstein D, Pan MG, **Chang CP**. Brg1 governs distinct pathways to direct multiple aspects of mammalian neural crest cell development. *Proc Natl Acad Sci USA*. 2013; 110 (5): 1738-43. [Highlighted by CHARGE syndrome foundation]
- Han P, Li W, Lin CH, Yang J, Chang C, Jin KK, Xu W, Yang J, Lin CY, Lin CJ, Xiong Y, Zhou Bin, Ashley E, Chen PS, Chen V, Quertermous T. **Chang CP**. A long non-coding RNA protects the heart from pathological hypertrophy. *Nature* 2014; 514(7520):102-6.
- [NIH commentary]: NIH Research Matters: Molecule Protects Against Heart Failure in Mice. Sept. 15, 2014. <http://www.nih.gov/researchmatters/september2014/09152014heart.htm/>
- [Cell commentary]: An Epigenetic "LINK(RNA)" to Pathological Cardiac Hypertrophy. *Cell Metabolism*. 2014;20(4):555-557
- [AHA commentary]: Dawn of Epi-LncRNAs, New Path from Myheart. *Circ Res*. 2015;116: 235-236
- [Circulation Special Report]: Top Advances in Functional Genomics and Translational Biology for 2014. *Circ Cardiovasc Genet*. 2015; 8:207-210
- [Circulation Commentary]: Long Noncoding Mhrt RNA: molecular crowbar unravels insights into heart failure treatment, *Circ Cardiovasc Genet*. 2015; 8:213-215
- Yang J, Feng X, Zhou Q, Cheng W, Shang C, Han P, Lin C-H, Chen V, Quertermous T, **Chang CP** Pathological Ace/Ace2 switch in the stressed hearts is transcriptionally controlled by the endothelial Brg1–FoxM1 complex. *Proc Natl Acad Sci USA*. 2016 Sep 20;113(38): E5628-35
- Yang J, Savvatis K, Kang JS, Fan P, Zhong H, Schwartz K, Barry V, Mikels-Vigdal A, Karpinski S, Korniyev D, Adamkewicz J, Feng X, Zhou Q, Shang C, Kumar P, Phan D, Kasner M, Lopez B, Diez J, Wright KC, Kovacs RL, Chen P-S, Quertermous T, Smith V, Yao L, Tschope C, **Chang CP**. Targeting LOXL2 for cardiac interstitial fibrosis and heart failure treatment. *Nature Communications* 2016 Dec.14: DOI: 10.1038/ncomms13710
- Zhang D, Wang Y, Lu P, Wang P, Yuan X, Yan J, Cai C, **Chang CP**, Zheng D, Wu B, Zhou B. [REST regulates the cell cycle for cardiac development and regeneration.](#) *Nature Communications* 2017 Dec 7;8(1):1979.

Genetic and Epigenetic Regulatory Mechanisms in Mammalian Eye Development and Diseases

We are studying mammalian eye as a model system to elucidate basic molecular mechanisms of tissue-specific gene expression during cell type specification, determination and cellular differentiation. Gene control is regulated a) at the level of *cis*-regulatory grammar of promoters and enhancers mediated by sequence-specific DNA-binding transcriptional factors (TFs), b) at the level of *cis*-sites in 5'- and 3'-UTRs in mRNAs mediated by RNA-binding proteins (RBPs) and microRNAs, and c) 3D-organization of chromatin regulated by promoter-enhancer interactions and formation of topologically associated domains (TADs) involving DNA-binding protein CTCF and cohesin complex.

PAX6 encodes a sequence-specific DNA-binding TF that plays pivotal roles in the earliest stages of lens and retinal development. Mutations in PAX6 cause aniridia, characterized by the absence of iris, as well as early onset cataract, corneal abnormalities, foveal hypoplasia and glaucoma. Genetic data of the microphthalmia-anophthalmia-coloboma (MAC) human syndrome identified prominent roles of TFs PAX6 and SOX2 and retinoic acid (RA) signaling. Pax6 directly regulates expression of DNA-binding TFs c-Maf and Prox1. Together, these genes form gene regulatory networks (GRNs) comprised of multiple feed-forward loops governing crystallin gene expression in the lens. These GRNs represent excellent models to study principles of tissue morphogenesis. Pax6 recruits multiple chromatin remodeling complexes, including BAF, ISWI, NuRD, Mll1/Set1 and CBP/p300. Mutations in these genes are also linked to human congenital eye diseases. Pax6 also plays important roles in the formation of other organs, including brain and pancreas.

We study enhancers via their genomic deletions coupled with analyses of transgenic EGFP reporters. We examine interactions of PAX6 and BAF complexes with chromatin at single molecule resolution using super-resolution microscopy. We employ isogenic human iPS cells carrying both heterozygous and homozygous mutations in PAX6 to generate *in vitro* lens and retinal organoids to elucidate the cellular and molecular mechanisms underlying aniridia. The unbiased multi-omics approaches used in the lab include RNA-seq, scRNA-seq, ATAC-seq, ChIP-seq/CUT&RUN and 4C-seq/Hi-C. Nascent transcription/transcriptional bursting, mRNA splicing and transport, crystallin mRNA stability control, and their translational regulation via RBPs are probed via RNA FISH and MCP-MS2 system to visualize mRNAs at single molecule levels. All these projects are highly collaborative and involve computational biology and bioinformatics.

Our interest in age-related ocular diseases is focused on age-related macular degeneration, cataract, and glaucoma. Using eye, retinal, retinal pigmented epithelium and lens organoids differentiated from human ES/iPS cells we aim to develop human models to understand disease mechanisms through CRISPR-based genome engineering and use these systems for discovery of novel therapeutic interventions.

Recent Publications:

Xie, Q. and A. Cvekl. 2011. The orchestration of mammalian tissue morphogenesis through a series of coherent

feed-forward loops. *J. Biol. Chem.* **286**:43259-43271.

Wolf, L., W. Harrison, J. Huang, Q. Xie, N. Xiao, J. Sun, L. Kong, S.A. Lachke, M.R. Kuracha, V. Govindarajan, P.K. Brindle, R. Ashery-Padan, D.C. Beebe, P.A. Overbeek, and A. Cvekl. 2013. Histone posttranslational modifications and cell fate determination: Lens induction requires the lysine acetyltransferases CBP and p300. *Nucleic Acids Res.* **41**:101989-10214.

Sun, J., S. Rockowitz, Q. Xie, D. Zheng, and A. Cvekl. 2015. Identification of *in vivo* DNA-binding mechanisms of Pax6 and reconstruction of Pax6-dependent gene regulatory networks during forebrain and lens development. 2015. *Nucleic Acids Res.* **43**:6827-6846.

Xie, Q., R. McGreal, R. Harris, C.Y. Gao, W. Liu, L. Reneker, L.S. Musil and A. Cvekl. 2016. Regulation of c-Maf and α A-crystallin by FGF signaling in lens. *J. Biol. Chem.* **291**:3947-3958.

Esteban-Martinez, L., E. Sierra-Filardi, R.S. McGreal, M. Salazar-Roa, G. Marino, E. Seco, S. Durand, D. Enot, O. Grana, M. Malumbres, A. Cvekl, A.M. Cuervo, G. Kroemer, and P. Boya. 2017. Programmed mitophagy is essential for the glycolytic switch during cell differentiation. *EMBO J.* **36**:1688-1706.

Limi, S., A. Senecal, R. Coleman, M. Lopez-Jones, P. Guo, C. Polumbo, R.H. Singer, A.I. Skoultchi, and A. Cvekl. 2018. Transcriptional dynamics during lens fiber cell differentiation and novel insights into the denucleation process. *J. Biol. Chem.* **293**:13176-13190.

Zhao, Y., D. Zheng, and A. Cvekl. 2019. Profiling of chromatin accessibility and identification of *cis*-regulatory mechanisms that control two ocular lens differentiation pathways. *Epigenetics Chromatin* **12**:27.

Cvekl, A. and C. Eliscovich. 2021. Crystallin gene expression: Insights from studies of transcriptional bursting. *Exp. Eye Res.* 207:108564.

Diacou, R., Nandigrami, P., Fiser, A., Liu, W., Ashery-Padan, R., and A. Cvekl. 2022. Cell fate decisions, transcription factors and signaling during early retinal development. *Prog. Retinal Eye Res.* **89**:in press.

Epigenetic regulation of stem cells, development and cancer

We seek to understand the epigenetic mechanisms governing the biology of stem cells, development and cancer. We study how the DNA methylation and demethylation machineries reshape the epigenome and regulate stem cell biology during development and in disease. We integrate mouse genetics with cellular, molecular, biochemical and bioinformatics approaches to define epigenetic pathways and mechanisms regulating stem cell specification, self-renewal, pluripotency and multipotency. We focus on the Tet family of DNA dioxygenases (Tet1, Tet2 and Tet3) which promote DNA demethylation by converting 5-methylcytosine (5mC) to 5-hydroxy-methylcytosine (5hmC) and other derivatives. Tet enzymes also partner with chromatin regulatory complexes to promote gene activation and repression independent of their catalytic activity. We study how these dual functions of Tets regulate gene expression, and define their molecular and biological requirements in development and their implications in human diseases like cancer.

- *Embryonic stem cell (ESC) biology:* We study the enzymatic dependent and independent roles of Tets in gene regulation in ESCs and dissect their biological significance in pluripotency and development. We have identified noncatalytic roles of Tet1 in partnering with Sin3a and PRC2 for H3K27 modification. This is essential for establishing bivalency at developmental genes and is critical for silencing mesodermal and trophoctodermal genes as well as cell cycle progression in ESCs.
- *Embryonic lineage specification and development:* We study how Tet enzymes regulate lineage specification and organogenesis during post gastrulation development with an interest in the hematopoietic and neural lineages. We have implicated Tets in activating hematopoietic and neural genes during embryogenesis.
- *Hematopoietic stem cells (HSCs) and cancer:* We investigate how Tet2, which is commonly mutated in human blood malignancies, regulates HSCs. We have identified enzymatic and nonenzymatic requirements for Tet2 in regulating the myeloid and lymphoid lineages, respectively.

Our work defines novel mechanisms of epigenetic regulation by Tet enzymes and 5hmC in development. It has implications in identifying new markers and targets for stem cell applications and for treatment of diseases.

For more details on our research please visit our lab website: <https://www.dawlatylaboratory.com>

Selected publications:

1. Chrysanthou S*, Tang Q* (co-first authors), Lee J, Taylor SJ, Zhao Y, Steidl U, Zheng D, **Dawlaty MM**, The DNA dioxygenase Tet1 regulates H3K27 modification and embryonic stem cell biology independent of its catalytic activity, *Nucleic Acid Research*, February (2022), PMID:35150568 PMCID: [PMC8989540](https://pubmed.ncbi.nlm.nih.gov/35150568/)
2. Ma L, Tang Q, Gao X, Lee J, Lei R, Suzuki M, Zheng D., Ito K, Frenette PS, and **Dawlaty MM.**, Tet-mediated DNA demethylation regulates specification of hematopoietic stem and progenitor cells during mammalian embryogenesis, *Science Advances*, March (2022), PMID:35235365 PMCID: [PMC8890710](https://pubmed.ncbi.nlm.nih.gov/35235365/)
3. Ito Ky*, Lee J*, (co-first author), Chrysanthou S, Zhao Y, Josephs K, Sato H, Teruya-Feldstein J, Zheng D, **Dawlaty M.M.****, Ito K**, Non-catalytic roles of Tet2 are essential to regulate hematopoietic stem and progenitor cell homeostasis, *Cell Reports*, September (2019), PMID: 31484061 PMCID: [PMC6750732](https://pubmed.ncbi.nlm.nih.gov/31484061/)
4. Ravichandran M*, Lei R*(co-first author), Tang Q, Zhao Y, Lee J, Ma L, Chrysanthou S, Lorton B, Cvekl A, Shechter D, Zheng D, and **Dawlaty M.M.**, Rinf regulates pluripotency network genes and Tet enzymes in embryonic stem cells, *Cell Reports*, August (2019), PMID: 31433977 PMCID: [PMC6716522](https://pubmed.ncbi.nlm.nih.gov/31433977/)
5. Abou-Jaoude A, Huang C, Flores JC, Ravichandran M, Lei R, Chrysanthou S, and **Dawlaty MM**, Idax and Rinf facilitate expression of Tet enzymes to promote neural and suppress trophoctodermal programs during differentiation of embryonic stem cells, *Stem Cell Research*, March (2022), PMID:35390758
6. MacArthur I.C. and **Dawlaty M.M.**, TET enzymes and 5-hydroxymethylcytosine in neural progenitor cell biology and neurodevelopment, *Front. in Cell & Dev. Biology*, February (2021) PMID: 33681230 PMCID: [PMC7930563](https://pubmed.ncbi.nlm.nih.gov/33681230/)
7. **Dawlaty M.M.**, Breiling A., Le T., Barrasa I.M., Raddatz G., Gao Q., Powell B.E., Cheng A.W., Faull K.F., Lyko F., and Jaenisch R., Loss of Tet enzymes compromises proper differentiation of embryonic stem cells, *Developmental Cell*, April (2014)

Genomic Instability and Cancer in Murine Models

The maintenance of genomic integrity in all organisms requires multiple DNA repair pathways that are involved in the processes of DNA replication, repair and recombination. Perturbations in these pathways can lead to increased mutation rates or chromosomal rearrangements that ultimately result in cancer. DNA mismatch repair (MMR) is one of the repair systems that mammalian cells employ to maintain the integrity of its genetic information by correcting mutations that occur during erroneous replication. Mutations in MMR genes are linked to one of the most prevalent human cancer syndromes, Lynch syndrome and a significant number of sporadic colorectal cancers. At the molecular level tumors that develop in these patients display increased genomic mutation rates as indicated by increased mutations at microsatellite repeat sequences (termed microsatellite instability, MSI). MMR in eukaryotes is complex and involves several homologs of the bacterial MutS and MutL proteins. In mammals, the initiation of the repair process requires two complexes formed by three different MutS homologs (MSH): A complex between MSH2-MSH6 for the recognition of single base mismatches and a complex between MSH2-MSH3 for the recognition of insertion/deletions. The repair reaction also requires a complex between the two MutL homologs MLH1 and PMS2 that interacts with the MSH complexes to activate subsequent repair events which include the excision of the mismatch carrying DNA strand and its re-synthesis. In addition to correcting DNA mismatches, the MMR system mediates an apoptotic response to DNA damage and both of these functions are thought to be important for genome maintenance and tumor suppression. We have generated gene targeted mouse lines with inactivating mutations in all the different MutS and MutL homologs, and also in genes that function in the later MMR steps to study their roles in genome maintenance and tumor suppression. In addition, we have generated knock-in mouse lines with missense mutations and conditional knockout mouse lines that inactivate specific MMR functions and/or model mutations found in humans. Our studies indicate that specific MMR functions play distinct roles in maintaining genome stability and that defects in these functions have important consequences for tumorigenesis. These studies have also revealed that MMR proteins play essential roles in class switch recombination and somatic hypermutation during antibody maturation and the control of meiotic recombination in mammals. We are currently studying the functions of MMR in intestinal stem cells (ISCs) and cancer stem cells (CSCs) in preclinical mouse models and how loss of MMR in stem cells affects tumorigenesis and the response of tumors to novel anticancer treatments including immune therapeutic approaches.

Selected References:

Lee K, Tosti E and Edelman W. 2016. Mouse Models of DNA Mismatch Repair in Cancer Research.

DNA Repair (Amst). 2016 Feb;38:140-146. doi: 10.1016/j.dnarep.2015.11.015. PMID: 26708047

Milano CR, Holloway JK, Zhang Y, Jin B, Smith C, Bergmann A, Edelman W* and Cohen PE. 2019. Mutation of the ATPase Domain of MutS Homolog-5 (MSH5) Reveals a Requirement for a Functional MutSy Complex for All Crossovers in Mammalian Meiosis. *G3* (Bethesda). **g3**.400074.2019. doi: 10.1534/g3.119.400074. PMID: 30944090 (*corresponding author).

Loss of MMR and TGFBR2 increases the susceptibility to microbiota-dependent inflammation-associated colon cancer. Tosti E, Almeida AS, Tran TT, Barbachan e Silva M, Ó Broin P, Dubin R, Beck AP, Mclellan AS, Golden A, O'Toole PW and Edelman W. 2022. *Cell Mol Gastroenterol Hepatol*. 2022 Jun 7:S2352-345X(22)00095-9. doi: 10.1016/j.jcmgh.2022.05.010. Online ahead of print. PMID: 35688320.

Role of EXO1 nuclease activity in genome maintenance, the immune response and tumor suppression in *Exo1^{D173A}* mice. Wang S, Lee K, Gray S, Zhang Y, Tang C, Morrish RB, Pesenti E, Tosti E, van Oers J, Cohen PE, MacCarthy T, Roa S, Scharff M, Edelman W* and Chahwan R. *Nucleic Acid Research* 2022 Jul 18: gkac616. doi: 10.1093/nar/gkac616. Online ahead of print. PMID: 35849338. (*corresponding author).

Genetic Encoding of Neural Circuits, Connectomics

How complex neural circuits form and how they function are major unsolved problems in neurobiology. We use the nematode *Caenorhabditis elegans* to study these questions at the cellular and molecular levels. Connectivity in the *C. elegans* nervous system is assayed by serial section electron microscopy. *C. elegans* is the only animal species for which the complete nervous system wiring diagram, now available for both male and hermaphrodite adults, is known, providing an unprecedented foundation for *C. elegans* neuroscience research.

The *C. elegans* nervous system is a complex neural network that is genetically specified. To investigate how the patterns of connectivity are encoded in the genome, we make use of transgenes that express fluorescent proteins targeted to specific classes of synapses. We use these synapse-specific labels to identify mutants and genes that affect formation of particular cellular synaptic contacts. We are determining the expression patterns of genes that encode neural cell adhesion proteins in the neural network that governs the mating behavior of the adult male. This class of transmembrane proteins is thought to include the molecular cell labels by which appropriate pre- and post-synaptic cells recognize each other. By correlating the expression of these molecules with connectivity, we hope to uncover the molecular code that determines the wiring diagram of the nervous system.

Visit our websites: <http://worms.aecom.yu.edu>. <http://wormwiring.org>

Selected Publications:

Jarrell, T. A., Wang, Y., Bloniarz, A. E., Brittin, C. A., Xu, M., Thomson, J. N., Albertson, D. G., Hall, D. H., and Emmons, S. W. (2012) The connectome of a decision-making neural network. *Science* 337, 437-444. **This paper was awarded the 2012-2013 AAAS NEWCOMB CLEVELAND PRIZE for the Most Outstanding Research Article Published in Science.**

Barrios, A., Ghosh, R., Fang, C., Emmons, S.W., and Barr, M.M. (2012) PDF-1 neuropeptide signaling modulates a neural circuit for mate-searching behavior in *C. elegans*. *Nature Neuroscience* 15, 1675-1682.

Emmons, S.W. (2015). The beginning of connectomics: a commentary on White et al. (1986) 'The structure of the nervous system of the nematode *Caenorhabditis elegans*'. *Phil Trans R Soc Lond B* 370.

Sammut, M., Cook, S.J., Nguyen, K.C.Q., Felton, T., Hall, D.H., Emmons, S.W., Poole, R.J., and Barrios, A. (2015). Glia-derived neurons are required for sex-specific learning in *C. elegans*. *Nature* 526, 385-390.

Kim, B., Suo, B. & Emmons, Scott W. (2016) Gene Function Prediction Based on Developmental Transcriptomes of the Two Sexes in *C. elegans*. *Cell Reports* 17, 917-928, doi:<https://doi.org/10.1016/j.celrep.2016.09.051>.

Kim, B. & Emmons, S. W. (2017) Multiple conserved cell adhesion protein interactions mediate neural wiring of a sensory circuit in *C. elegans*. *eLife* 6, e29257, doi:10.7554/eLife.29257.

Emmons, S. W. (2018) Neural Circuits of Sexual Behavior in *Caenorhabditis elegans*. *Annual review of neuroscience* 41, 349-369.

Lázaro-Peña, M. I., Díaz-Balzac, C. A., Bülow, H. E. & Emmons, S. W. (2018) Synaptogenesis Is Modulated by Heparan Sulfate in *Caenorhabditis elegans*. *Genetics* 209, 195-208. HIGHLIGHTED ARTICLE

Cook, S. J., Jarrell, T. A., Brittin, C., Wang, Y., Bloniarz, A. E., Yakovlev, M. A., Nguyen, K. C. Q., Tang, L. T.-H., Bayer, E. A., Duerr, J. S., Buelow, H., Hobert, O., Hall, D. H., and Emmons, S. W. (2019) Whole-animal connectomes of both *C. elegans* sexes. *Nature* 571, 63–71.

Molina-García, L., Lloret-Fernández, C., Cook, S.J., Kim, B. Bonnington R.C., Sammut, M., O'Shea, J.M., Gilbert, S.P.R. Elliott, D.J., Hall, D.H., Emmons, S.W., Barrios, A., and Poole, R.J. (2020) A direct glia-to-neuron transdifferentiation ensures nimble male mating. *eLife* 2020;9:e48361 DOI: 10.7554/eLife.48361

Brittin, C.A., Cook, S.J., Hall, D.H., Emmons, S.W., and Cohen, N. (2021). A multi-scale brain map derived from whole-brain volumetric reconstructions. *Nature* 91, 105-110. <https://doi.org/10.1038/s41586-021-03284-x>

JOHN M. GREALLY, D.Med., Ph.D.

Medical Genomics

The Greally lab combines interests in both basic science and clinical research focused on the human genome. Our goal is to use genomic information to understand human diseases. Typical disease diagnostics involve understanding sequence variants at coding regions of the genome. Our interest extends beyond the ~3% of the genome encoding genes, and focuses instead on DNA sequence variability at *cis*-regulatory loci, and DNA sequence-independent processes involving reprogramming of transcription and cell fate changes.

To make progress in these areas sometimes requires developing new assays and analytical techniques. Our group has a long track record and ongoing interests in genome-wide assays and software development. Lab members typically combine both wet bench and programming approaches in their projects.

Specific examples of ongoing projects include a cohort study of human T lymphocyte ageing, a functional genomics study of myalgic encephalopathy/chronic fatigue syndrome, and studies of clonal haematopoiesis, obesogenic endocrine-disrupting chemicals, and stem cell-based systems for studying hepatic fibrosis and normal osteogenesis.

We work in the most diverse county in the US, and include as part of our research mission the goal to provide better health care to Bronx residents through genomic information. The basic science studies supporting this are focused on studying the effects of genetic polymorphism on transcriptional regulation, developing these new approaches on diverse Asian populations in collaboration with Singaporean colleagues. We describe this research program, co-developed with Departmental colleague Dr. Srilakshmi Raj, as Population Epigenetics. We are also involved with a Bronx Cancer Genomics initiative, and are beginning to work with the community to understand how to develop responsible and ethical genomic studies of the Bronx population served by the Montefiore Health System.

Dr. Greally is a clinical geneticist specializing in dysmorphology, seeing patients at Montefiore Medical Center. He has led the development of clinical software tools like MADSEQ (to identify mosaic aneuploidies from sequencing data) and GenomeDiver (to enhance genomic diagnostics). His clinical goal is to improve rare disease diagnostics in patients of all genetic ancestries.

Recent Publications:

Pearson NM, Stolte C, Shi K, Beren F, Abul-Husn NS, Bertier G, Brown K, Diaz GA, Odogis JA, Suckiel SA, Horowitz CR, Wasserstein M, Gelb BD, Kenny EE, Gagnon C, Jobanputra V, Bloom T, Greally JM. GenomeDiver: a platform for phenotype-guided medical genomic diagnosis. *Genet Med*. 2021 Oct;23(10):1998-2002. doi: 10.1038/s41436-021-01219-5. Epub 2021 Jun 10. PMID: 34113009; PMCID: PMC8488006.

Johnston AD, Simões-Pires CA, Thompson TV, Suzuki M, Greally JM. Functional genetic variants can mediate their regulatory effects through alteration of transcription factor binding. *Nat Commun*. 2019 Aug 2;10(1):3472. doi: 10.1038/s41467-019-11412-5. PMID: 31375681; PMCID: PMC6677801.

Sato H, Wu B, Delahaye F, Singer RH, Greally JM. Retargeting of macroH2A following mitosis to cytogenetic-scale heterochromatic domains. *J Cell Biol*. 2019 Jun 3;218(6):1810-1823. doi: 10.1083/jcb.201811109. Epub 2019 May 20. PMID: 31110057; PMCID: PMC6548134.

Kong Y, Berko ER, Marcketta A, Maqbool SB, Simões-Pires CA, Kronn DF, Ye KQ, Suzuki M, Auton A, Greally JM. Detecting, quantifying, and discriminating the mechanism of mosaic chromosomal aneuploidies using MAD-seq. *Genome Res*. 2018 Jul;28(7):1039-1052. doi: 10.1101/gr.226282.117. Epub 2018 May 17. PMID: 29773658; PMCID: PMC6028128.

Lappalainen T, Greally JM. Associating cellular epigenetic models with human phenotypes. *Nat Rev Genet*. 2017 Jul;18(7):441-451. doi: 10.1038/nrg.2017.32. Epub 2017 May 30. PMID: 28555657.

JEAN HÉBERT, Ph.D.

Regenerating the Neocortex

The neocortex is the part of our brain that performs our highest cognitive functions. In recent years, the mechanisms underlying how stem cells in the embryo generate the neocortex have become better understood. Armed with this knowledge, the Hébert Lab is developing approaches to replace and repair adult neocortical tissue after age-related degeneration.

The lab's projects fall into two groups. In the first, we use the mouse neocortex as a platform for testing the ability of multi-cell type grafts (increasingly resembling normal neocortex) to integrate with host tissue. In the second, we are testing the ability of genetically engineered microglia that disperse throughout the adult neocortex to bolster neocortical function.

These are highly collaborative projects requiring multidisciplinary methods, which include molecular genetics, human embryonic stem cell biology, omics analyses, surgery, electrophysiology, live brain imaging, and behavioral tests, among others. Thus the Hébert Lab offers its members excellent opportunities for acquiring diverse and cutting-edge skill sets in an up-and-coming research area.

Selected Recent Publications

Krzyspiak J, Khodakhah K, Hébert JM. (2022). Potential variables for improved reproducibility of neuronal cell grafts at stroke sites. *Cells* 11:1656.

Krzyspiak J, Yan J, Ghosh HS, Galinski B, Lituma P, Alvina K, Quezada A, Kee S, Grońska-Pęski M, Tai YD, McDermott K, Gonçalves JT, Zukin RS, Weiser DA, Castillo P, Khodakhah K, Hébert JM. (2021). Donor-derived vasculature supports neocortical cell grafts after stroke. *Stem Cell Research* 59:102642. PMID: 34971934.

Mohammad S, Bellampalli R, Ghosh V, Krishna S, Dwivedi A, Nruthyathi, Sahasrabudhe, V, Cheramangalam R, Radha S, Ceribelli M, Reizis B, Hébert JM, Ghosh H. (2021). Adult neural stem cells have latent inflammatory potential, kept in check by Tcf4. *Science Advances* 7:eabf5606. PMID: 34020954 PMCID: PMC8139598..

Gronska-Peski M, Gonçalves JT, Hébert JM. (2021). Enriched environment acts through FGFRs to increase adult hippocampal neurogenesis. *J. Neurosci.* 41:2899-2910. PMID 33637561 PMCID: PMC8018882

Gronska-Peski M, Mowrey W, Hébert JM. (2020). FGFR regulation of dendrite elaboration in adult-born granule cells depends on intracellular mediator and proximity to the soma. *Neuroscience* 453:148-167. PMID: 33246055

Gronska-Peski M, Schachner M, Hébert JM. (2020). *L1cam* curbs the differentiation of adult-born hippocampal neurons. *Stem Cell Research* 48:101999. PMID 32971459.

Hébert JM. (2020). Replacing Aging. Science Unbound Press, New York, New York.

Kamatkar N, Levy M, Hébert JM. (2019). Development of a monomeric inhibitory RNA aptamer specific for FGFR3 that acts as an activator when dimerized. *Mol. Ther. Nuc. Acids* 17:530-339..

Kang W, Nguyen KCQ, Hébert JM. (2019). Transient redirection of SVZ-stem cells to oligodendrogenesis by FGFR activation promotes remyelination. *Stem Cell Reports* 12:1223-1231.

Hébert JM, Vijg J. (2018). Cell replacement to reverse brain aging: challenges, pitfalls, and opportunities. *Trends Neurosci.* 41: 267-279.

Antoine MW, Zhu X, Dieterich M, Brandt T, Vijayakumar S, McKeehan N, Arezzo J, Zukin RS, Borkholder D, Jones SM, Frisina R, Hébert JM. (2018). Early uneven ear input induces long-lasting differences in left-right motor function. *PLoS Biology* 16: e2002988.

Sterilizing Chemotherapies and Immunotherapies against Tuberculosis, Herpes, and Influenza

Tuberculosis:

Tuberculosis (TB) was the single leading infectious cause of death in the world in 2018, causing over 10 million new cases per year and accounting for 1.5 million deaths annually. The onset of the HIV epidemic worsened the TB global health burden leading to increases in incidences, reactivated disease, and the emergence of drug resistance. The worsening problem of TB is surprising because both a vaccine and sterilizing chemotherapy exist to treat this disease. A major reason for the ineffectiveness of these therapies, is TB's ability to persist; persistence is the capacity of *Mycobacterium tuberculosis* (*Mtb*) to survive sterilization in animals and humans. Persistence is also an epigenetic process found in all bacteria and cancer cells. Recently, the Jacobs Lab demonstrated populations of *Mtb* have a subpopulation of *Mtb* cells that are phenotypically resistant to bactericidal antibiotics. They have identified specific transcriptional patterns that regulate phenotypic resistance and developed dual reporter mycobacteriophages to rapidly identify this subpopulation of cells. Moreover, they discovered the addition N-acetylcysteine or Vitamin C to cultures of *Mtb* prevent the formation of persisters and allow for rapid sterilization in the presence of bactericidal drugs. Current efforts are focused on characterizing the mechanisms by which persisters are formed and identifying relevant targets to eliminate these persisters.

Herpes and Influenza:

In collaboration with Dr. Betsy Herold, the Jacobs lab has generated a precise deletion of the gene encoding *gD* of Herpes Simplex Virus (HSV) 2, termed $\Delta gD-2$, that upon immunization in mice elicits sterilizing immunity against challenge with HSV-1 and HSV-2. This unprecedented protection results from the induction of a special type of antibodies that mediate antibody dependent cell mediated killing (ADCK) of herpes infected cells. They have subsequently found that many pathogens do not elicit ADCK antibodies but they hypothesized that by cloning genes encoding important antigens into our herpes viral vector, they could elicit protection against other pathogens such as influenza. Recently, the Jacobs lab generated recombinant $\Delta gD-2$ herpes virus expressing genes encoding flu antigens and demonstrated that we can confer complete protection against the homologous influenza challenge. This proof of principle suggests that by cloning antigens from other pathogens, such as *Mtb*, it is possible to make novel vaccines and elicit ADCK antibodies. Thus, other efforts in the Jacobs lab focus on characterizing the mechanisms by which ADCK antibodies facilitate the collaboration of innate immunity with adaptive immune responses.

Lab Website: <http://williamrjacobs.org/>

Select Publications:

- **Saranathan R, Levi MH, Wattam AR, Malek A, Asare E, Behin DS, Pan DH, Jacobs WR Jr, Szymczak WA.** (2020). "Helicobacter pylori Infections in the Bronx, New York: Surveying Antibiotic Susceptibility and Strain Lineage by Whole Genome Sequencing". *J Clin Microbiol.* 24;58(3) e01591-19. PMID: PMC7041580
- **Vilcheze, C., Hartman, T., Weinrick, B., Jain, P., Weisbrod, T.R., Leung, L.W., Freundlich, J.S. and Jacobs, W.R., Jr.** (2017). "Enhanced respiration prevents drug tolerance and drug resistance in *Mycobacterium tuberculosis*." *Proc Natl Acad Sci U S A.* 114(17):4495-4500. PMID: PMC5410800
- **Jain P, Weinrick BC, Kalivoda EJ, Yang H, Munsamy V, Vilcheze C, Weisbrod TR, Larsen MH, O'Donnell MR, Pym A, Jacobs WR Jr.** (2016). Dual-Reporter Mycobacteriophages ($\Phi 2DRMs$) Reveal Preexisting *Mycobacterium tuberculosis* Persistent Cells in Human Sputum." *MBio.* (5). pii: e01023-16. PMID: PMC5080378
- **Petro, C., González, P.A., Cheshenko, N., Jandl, T., Khajjouinejad, N., Bénard, A., Sengupta, M., Herold, B.C., Jacobs, W.R., Jr.** (2015) Herpes simplex type 2 virus deleted in glycoprotein D protects against vaginal, skin and neural disease. *eLife.* PMID PMC4352706

A genetic model for Endosomal Microautophagy

Aging-associated diseases are an increasing socio-economic burden despite efforts to improve healthspan. Pathologies that cause degeneration of the nervous system are particularly devastating, and in many cases are associated with decline in proteostasis and lysosomal malfunction. Prime examples are Parkinson and Alzheimer's disease that are characterized by accumulation of insoluble protein aggregates that lead to neuronal decay. Autophagy delivers cytosolic components to lysosomes for degradation and is thus essential for cellular homeostasis and to cope with different stressors. Macroautophagy (MA) can selectively degrade organelles or aggregated proteins, but selective degradation of single proteins has only been described for Chaperone-mediated autophagy (CMA) and endosomal Microautophagy (eMI). These two autophagic pathways, described to date only in mammals, are specific for proteins containing KFERQ-related targeting motifs. In collaboration with the Cuervo lab, we have established a genetic model for eMI in *Drosophila in vivo*. We are thus for the first time able to perform genetic screens for regulatory components of eMI, this only recently identified form of autophagy about which barely anything is known.

Lysosomes are also important regulatory hubs that integrate nutritional signals and participate in lipid metabolism. We have recently characterized *Drosophila* Lamp1, a bona fide homolog of the mammalian LAMP1/2. *Lamp1* deficiency results in an increase in the number of acidic organelles in the fat body, strongly suggesting defects in the regulation of the pH of the endolysosomal system. Furthermore, *Lamp1* mutant larvae have elevated levels of sterols and diacylglycerols, indicating functions of Lamp1 in lipid transport beyond sterols. Significantly, these phenotypes are similar to loss of glucocerebrosidase, the gene causing Gaucher disease and a major risk factor for Parkinson.

Rho kinase and its effector Cmb in spermiogenesis

During development, genetic and molecular programs control the differentiation of various cell types and orchestrate their morphogenetic behaviors to form organs with specific functions. Organogenesis requires the coordination of cell polarity, cellular movement, and cell shape, driven by intercellular signaling and the tissue-specific interpretations of these signals. Traditionally, Rho kinase (Rok) functions as effector of the non-canonical Wnt/Frizzled PCP pathway during gastrulation and neural tube formation. In a systematic, genome-wide screen, we have identified the previously uncharacterized Comover, an intrinsically disordered protein as novel Rok substrate. Significantly, our follow up studies have identified a novel and unanticipated role of Rok and Cmb during spermiogenesis. We currently address how, downstream of Rok, Comover orchestrates the transition between axoneme elongation and sperm individualization by coordinating the actin and microtubule cytoskeletons with the plasma membrane, thus ensuring proper resolution of the syncytial spermatids into functional sperm that are encapsulated by their own plasma membrane. The biomedical significance of sperm individualization is further exemplified by the presence of multiciliate spermatozoa and spermatids with unresorbed cytoplasm in infertile men.

It is our goal to use *Drosophila* as model system to address fundamental questions that are relevant for development and disease in general.

Lab homepage: <https://www.jenny-lab.org>

Selected References:

- Rodan, A.R., Jenny, A. (2017) WNK kinases in development and disease. Edited by Jenny, A. [Curr. Top. Dev. Bio. 123:1-47.](#)
- Steinhauer, J., Statman, B, Fagan, J., Borck, J., Surabhi, S., Yarikipati, P., Edelman, D., Jenny, A. (2019) Comover interacts with the axonemal component Rsp3 and is required for sperm individualization. [Development. 146\(17\). pii: dev179275. doi: 10.1242/dev.179275](#)
- Domingos, P. M., Jenny, A., Combie, K.F., Del Alamo, D., Mlodzik, M., Steller, H., Mollereau, B. (2019) Regulation of Numb during planar cell polarity establishment in the *Drosophila* eye. [Mech Dev, doi: 10.1016/j.mod.2019.103583.](#)
- Mukherjee, A., Koga, H., Cuervo, AM., Jenny, A. (2016) Selective endosomal microautophagy is starvation inducible in *Drosophila*. [Autophagy. 12 \(11\). 1984-1999.](#)
- Mesquita, A., Glenn, J., Jenny, A. (2020) Differential activation of eMI by distinct forms of cellular stress. [Autophagy, doi: 10.1080/15548627.2020.1783833.](#)
- Chaudhry, N.*, Sica, M.*, Surabhi, S.*, Sanchez Hernandez, D., Mesquita, A., Selimovic, A., Riaz, A. Lescat, L., Bai, H., Macintosh, G, C.*, Jenny, A*. (2022) Lamp1 mediates lipid transport, but is dispensable for autophagy in *Drosophila*. [Autophagy 10.1080/15548627.2022.2038999](#)

Molecular Genetic Analysis of INI1/hSNF5 in HIV-1 Replication, HIV-1 latency and Cancer: Single molecule analysis to Organismal studies

INI1/hSNF5/SMARCB1/BAF47 is a component of the chromatin remodeling SWI/SNF complex. This complex influence replication of HIV-1 and SARS Corona Virus-2. *INI1/SMARCB1* was discovered as a HIV-1 IN binding protein and is a tumor suppressor biallelically mutated/deleted in many human cancers. The goal of our laboratory is to determine how INI1 affects viral replication, tumor suppression, and in general cellular function.

(i) RNA mimicry of IN-binding Rpt1 domain and Implications for HIV-1 replication and novel anti-HIV therapies: INI1/hSNF5 plays multiple roles during HIV-1 replication. By solving the NMR structure of IN-binding INI1 Rpt1 domain we have discovered that this domain structurally mimics TAR RNA. Using this information, we identified an alpha helix region of INI1 that binds to IN. Using this alpha helix at the IN-INI1 interface, we have generated stapled peptides that potently inhibit HIV-1 replication. These stapled peptides are “first-in-class” inhibitors that target IN-INI1 interaction and can be used to inhibit actively and latently reactivated HIV-1.

(ii) Application of a single cell and single molecule RNA-FISH and IF method to study HIV-1 latency and SARS-CoV2 replication: A final hurdle to eradicate HIV-1 is the persistence of the virus in latent reservoirs, which are transcriptionally suppressed and low in number. We have developed a Single Cell Single Molecule Immunofluorescence and RNA-FISH assay (SMIRA) in collaboration with Dr. Robert Singer to study latency. This novel assay will be applied to characterize latent reservoirs in various reservoirs in blood, brain, gut etc.. and the effect of various Latency Reversing Agents (LRA, that are in clinical trials) and drugs of abuse.

(iv) Mechanism of tumor suppression by *INI1/hSNF5* and developing novel and effective therapeutic strategies to combat INI1-deficient tumors: By using a series of genetic systems developed in our laboratory (knock-out, knock-in mouse models, cell culture models), we are dissecting the mechanism of INI1-mediated tumor suppression and are developing molecularly targeted therapies. Previously we discovered that INI1 harbors a masked nuclear export signal. Recently, in collaboration with international team of neuropathologists, we have found that mutations that affect the regulated nuclear export is a tumorigenic event that it offers a novel therapeutic target. In addition, we are investigating novel downstream targets of INI1, i.e. FoxM1 and GBP1, and their effect on senescence and their therapeutic potential.

Selected Publications:

1. **Dixit U, Bhutoria S, Wu X, Qiu L, Spira M, Mathew S, Harris R, Adams LJ, Cahill S, Pathak R, Rajesh Kumar P, Nguyen M, Acharya SA, Brenowitz M, Almo SC, Zou X, Steven AC, Cowburn D, Girvin M, Kalpana GV.** INI1/SMARCB1 Rpt1 domain mimics TAR RNA in binding to integrase to facilitate HIV-1 replication. *Nat Commun.* 2021 May 12;12(1):2743. doi: 10.1038/s41467-021-22733-9. PMID: 33980829. (Highlighted in Einstein Research Brief <https://einsteinmed.edu/research-briefs/2601/a-novel-strategy-for-inhibiting-hiv-1-replication/>)
2. **Pathak R, Zin F, Thomas C, Bens S, Gayden T, Karamchandani J, Dudley RW, Nemes K, Johann PD, Oyen F, Kordes U, Jabado N, Siebert R, Paulus W, Kool M, Frühwald MC, Albrecht S, Kalpana GV***, Hasselblatt M*. Inhibition of nuclear export restores nuclear localization and residual tumor suppressor function of truncated SMARCB1/INI1 protein in a molecular subset of atypical teratoid/rhabdoid tumors. *Acta Neuropathol.* 2021 Aug;142(2):361-374. doi: 10.1007/s00401-021-02328-w. Epub 2021 May 18. PMID: 34003336; PMCID: PMC8270878. *equal correspondence. (Highlighted in Einstein Research Brief <https://www.einsteinmed.edu/research-briefs/2626/change-in-proteins-location-may-cause-aggressive-cancers/>)
3. **David A., Rao V. R., Wu, W., Ramasamy, S., Pujato, M., Ruiz, A. P., Fiser, A., Bresnick, A., Kalpana, G. V., Prasad, V. R.** (2019) CCL2 Mobilizes ALIX to Facilitate 1 Gag-p6 Mediated HIV-1 Virion Release. *eLife*;8:e35546
4. **La Porte, A., Cano, J., Wu, X., Mitra, D., Kalpana, G. V.** (2016) An essential role of INI1/hSNF5 chromatin remodeling protein in HIV-1 post-transcriptional events and Gag/GagPol stability. *J Virol.* 2016 Oct 14;90(21):9889-9904 (PMID:27558426 PMCID:[PMc5068538](https://pubmed.ncbi.nlm.nih.gov/27558426/))
5. **Bhutoria, S., Kalpana G. V.*, and Acharya, S.*** (2016) Computational Modeling of Repeat1 region of INI1/hSNF5: An evolutionary link with Ubiquitin. *Equal corresponding authors. *Protein Sci.* (PMID:[27261671](https://pubmed.ncbi.nlm.nih.gov/27261671/))
6. **Mathew, S., Nguyen, M., Wu, X., Pal, A., Shah, V. B., Aiken, C., and Kalpana, G. V.** (2013) INI1/hSNF5-interaction defective HIV-1 IN mutants exhibit impaired particle morphology, reverse transcription and integration *in vivo*. *Retrovirology.* 10:66. [Epub ahead of print] PMID:23799881
7. **Smith, ME, Cimica V, Chinni S, Jana S, Koba W, Yang Z, Fine E, Zagzag D, Montagna C, Kalpana GV.** (2011). Therapeutically targeting Cyclin D1 in primary tumors arising from loss of *Ini1*. *Proc Natl Acad Sci U S A.* 108:319-24. Epub 2010 Dec 20. PMID: 21173237

PERI KURSHAN, PH.D.

Towards a molecular understanding of synapse development

Defects in the proper development and function of synapses lead to neurodevelopmental disorders such as Autism and Intellectual Disability, however the molecular mechanisms underlying these processes are still largely unknown. We use the nematode *C. elegans*, which has a simple and stereotyped nervous system, to investigate the conserved molecular mechanisms of synapse development. In particular, we study how presynaptic components including cell adhesion molecules, active zone scaffold proteins, calcium channels and synaptic vesicles arrive at the synapse and form a mature and fully functional presynaptic compartment. We combine the power of worm genetics with high resolution imaging and optical physiology readouts to elucidate the role of key molecules. These approaches have led to the discovery that the role of the synaptic cell adhesion molecule neurexin may be different than initially hypothesized.

For more information on the lab and current projects visit: www.KurshanLab.org

Selected publications:

1. **Kurshan PT**, Shen K. Synaptogenic pathways. *Curr Opin Neurobiol.* 2019 Aug;57:156-162. *Review.*
2. **Kurshan PT**, Merrill SA, Dong Y, Ding C, Hammarlund M, Bai J, Jorgensen E, Shen K. α -Neurexin and Frizzled mediate parallel synapse assembly pathways antagonized by receptor endocytosis. *Neuron* 2018 Oct 10;100(1):150-166.
Previewed in: Ramesh N and Sigrist SJ. The long and short of it: A dwarf neurexin suffices for synapse assembly. *Neuron* 2018 Oct 10;100(1):6-8.
3. Xuan Z, Manning L, Nelson J, Richmond JE, Colón-Ramos D, Shen K, and **Kurshan PT**. Clarinet (*cla-1*), a novel active zone protein required for synaptic vesicle clustering and release. *eLife* 2017 Nov 21;6.
4. San-Miguel A, **Kurshan PT**, Crane MM, Zhao Y, McGrath PT, Shen K, Lu H. Deep Phenotyping Unveils Hidden Traits and Genetic Relations in Subtle Mutants. *Nat Commun.* 2016 Nov 23;7:12990.
5. **Kurshan PT**, Phan AQ, Wang GJ, Crane MM, Lu H, Shen K. Regulation of synaptic extracellular matrix composition is critical for proper synapse morphology. *J Neurosci.* 2014 Sep 17;34(38):12678-89.
6. Crane MM, Stirman JN, Ou CY, **Kurshan PT**, Rehg JM, Shen K, Lu H. Autonomous screening of *C. elegans* identifies genes implicated in synaptogenesis. *Nature Methods.* 2012 Oct;9(10):977-80
7. **Kurshan PT**, Oztan Matos A, Schwarz TL. Presynaptic $\alpha 2\delta$ -3 is required for synaptic morphogenesis independent of its Ca^{2+} -channel functions. *Nature Neurosci.* 2009 Nov: 12(11):1415-23.
Previewed in: Sigrist SJ and Plested AJR. How to button a bouton with $\alpha 2\delta$ s. *Nature Neurosci.* 2009 Nov:12(11) 1357-1358.
8. Dickman DK*, **Kurshan PT***, Schwarz TL. Mutations in a Drosophila alpha-2-delta voltage-gated calcium channel subunit reveal a crucial synaptic function. *J Neurosci.* 2008 Jan 2;28(1):31-8. (*co-first authors)
9. Pack-Chung E, **Kurshan PT**, Dickman DK, Schwarz TL. A Drosophila kinesin required for synaptic bouton formation and synaptic vesicle transport. *Nature Neurosci.* 2007 Aug;10(8):980-9.

Induced pluripotent stem (iPS) cells for disease modeling in schizophrenia and autism

A significant obstacle in studying the molecular basis of schizophrenia (SZ), autism spectrum disorders (ASD) and other neuropsychiatric disorders is the inaccessibility of the human brain, which has restricted molecular studies, such as gene expression profiling and epigenetic analysis, to autopsy samples. While some interesting findings have been made using postmortem brain, interpreting the data is associated with numerous confounding factors. In addition, since SZ is believed to be a developmental disorder, studying molecular events in postmortem samples is limiting. The discovery of iPS cells, which essentially allows investigators to reprogram somatic cells into pluripotent stem cells capable of differentiating into neurons and other cell types, provides an opportunity to create patient-specific neurons *in vitro*. The Lachman lab develops patient-specific iPS cells from controls and patients with SZ who have 22q11.2 deletions, which is found in ~1% of patients. Recently, an iPS cell model has been generated for Lowe Syndrome, a rare X-linked disorder that is associated with learning disability and epilepsy. In addition, an iPS cell model relevant to neuropsychiatric disorders is being generated using CRISPR-Cas9 gene editing targeting the ASD candidate gene CHD8. Gene expression profiling using RNA-seq showed that CHD8 haploinsufficiency leads to an increase in expression of genes involved in GABAergic differentiation in cerebral organoids, a property shared with another ASD candidate gene, FOXP1. CHD8 haploinsufficiency also leads to alterations in WNT/ β -catenin signaling. Both GABAergic differentiation and WNT/ β -catenin signaling are druggable targets; translating basic science findings into novel drug treatments for SZ and ASD is a major objective of the Lachman lab.

Selected Recent Publications:

Mingyan Lin, Erika Pedrosa, Abhishek K. Shah, Anastasia Hrabovsky, Shahina Maqbool, Deyou Zheng, Herbert M. Lachman. Deep sequencing transcriptome analysis of human neurons derived from induced pluripotent stem cells identifies candidate long non-coding RNAs involved in neurogenesis and neuropsychiatric disorders. *PLoS One*. 2011;6(9):e23356.

Mingyan Lin, Anastasia Hrabovsky, Erika Pedrosa, Tao Wang, Deyou Zheng, Herbert M. Lachman. Allele-biased expression in differentiating human neurons: implications for neuropsychiatric disorders. *PLoS One*. 2012;7(8):e44017. Epub 2012 Aug 30

Mingyan Lin, Dejian Zhao, Anastasia Hrabovsky, Erika Pedrosa, Deyou Zheng, Herbert M. Lachman. *PLoS One*. 2014 Apr 15;9(4):e94968. doi: 10.1371/journal.pone.0094968. eCollection 2014. Gene expression profiling in an induced pluripotent stem cell model of the developing human telencephalon: effects of heat shock and its potential consequences in the development of neuropsychiatric disorders.

Jian Chen, Mingyan Lin, Anastasia Hrabovsky, Erika Pedrosa, Jason Dean, Swati Jain Deyou Zheng, Herbert M. Lachman ZNF804A transcriptional networks in differentiating human neurons derived from induced pluripotent stem cells. *PLoS One*. 2015 Apr 23;10(4):e0124597.2015.

Zhao D, Lin M, Chen J, Pedrosa E, Hrabovsky A, Fourcade HM, Zheng D, Lachman HM. *PLoS One*. 2015 Jul 14;10(7):e0132387. doi: 10.1371/journal.pone.0132387. eCollection 2015. PMID: 26173148 MicroRNA Profiling of Neurons Generated Using Induced Pluripotent Stem Cells Derived from Patients with Schizophrenia and Schizoaffective Disorder, and 22q11.2 Del.

Wang P, Lin M, Pedrosa E, Hrabovsky A, Zhang Z, Guo W, Lachman HM, Zheng D. CRISPR/Cas9-mediated heterozygous knockout of the autism gene CHD8 and characterization of its transcriptional networks in neurodevelopment. *Mol Autism*. 2015 Oct 19;6:55. doi: 10.1186/s13229-015-0048-6. eCollection 2015.

Nebel RA, Zhao D, Pedrosa E, Kirschen J, Lachman HM, Zheng D, Abrahams BS. Reduced CYFIP1 in Human Neural Progenitors Results in Dysregulation of Schizophrenia and Epilepsy Gene Networks. *PLoS One*. 2016 Jan 29;11(1):e0148039. doi: 10.1371/journal.pone.0148039. eCollection 2016.

Mingyan Lin, Erika Pedrosa, Ryan Mokhtari, Anastasia Hrabovsky, Jian Chen, Benjamin R. Puliafito, Stephanie R Gilbert, Deyou Zheng, Herbert M. Lachman. Integrative Transcriptome Network Analysis of iPSC-derived Neurons from Schizophrenia and Schizoaffective Disorder Patients with 22q11.2 Deletion. *BMC Syst Biol*. 2016 Nov 15;10(1):105.

Ping Wang, Ryan Mokhtari, Erika Pedrosa, Michael Kirschenbaum, Can Bayrak, Deyou Zheng, Herbert M. Lachman. CRISPR-Cas9 mediated knockout of the autism gene CHD8 and characterization of its transcriptional networks in cerebral organoids derived from iPS cells. *Mol Autism*. 2017 Mar 20;8:11. doi: 10.1186/s13229-017-0124-1

Dejian Zhao, Ryan Mokhtari, Erika Pedrosa, Rayna Birnbaum, Deyou Zheng, Herbert M. Lachman. *Mol Autism*. 2017 Mar 29;8:17. doi: 10.1186/s13229-017-0134-z. Transcriptome analysis of microglia in a mouse model of Rett Syndrome: differential expression of genes associated with microglia/macrophage activation and cellular stress

JACK LENZ, Ph.D.

Molecular Genetics of Viruses in Cancer and Evolution

Viruses have etiological roles in about 12% of human cancers and in many other instances throughout nature. Viral tumorigenesis entails a variety of molecular genetic mechanisms. Some viruses encode genes that evolved to support virus replication that can also drive host cell proliferation, manipulate host cell survival, and evade host immune responses. Others lack genes that directly drive oncogenic processes, but instead cause tumors by insertion of their DNA into the host cell genome resulting in transcriptional activation of host oncogenes that flank viral DNA insertion sites, most commonly by an enhancer mechanism. Some viruses use all of these mechanisms. Current research efforts are focused on insertional oncogenesis by human papillomaviruses (HPVs) in collaboration with Drs. Cristina Montagna and Anne Van Arsdale. Key issues being addressed include identification of host oncogenes targeted by these viruses, mechanisms underlying transcriptional effects on flanking oncogenes, genetic interactions between viral and host oncogenes in tumorigenesis, and mechanisms of virus induced instability in host genomes.

Retrovirus DNA comprises about 8% of the genome. Human endogenous retrovirus K (HERV-K) is the most recent of all the retroviruses to enter the germline DNA of humans that is transmitted from parents to children. All humans are born with about 20 distinct, full-length HERV-K proviruses (i.e. integrated retroviral DNA) in their germline DNA, although all of these have mutations that inactivate their infectivity. We were the first to show that most of these proviruses formed relatively recently in human evolution, long after the divergence of the human and chimpanzee lineages approximately 6 million years ago, including some that formed so recently that they are not yet fixed in the human genome. Current interests are under what circumstances HERV-K proviruses are transcribed, whether human cells can recognize HERV-K transcripts, and whether infectious HERV-K ever regenerates from the proviruses in the human genome today.

References:

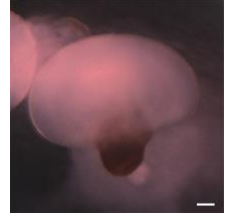
Agoni, L., Lenz, J, and Guha, C. Influence of ionizing radiation on transcription of Human Endogenous Retrovirus K (HERV-K) in cancer cell lines. PLoS One. 2013 8(10):e76472. doi: 10.1371/journal.pone.0076472.

Lenz J. HERV-K HML-2 diversity among humans. Proc Natl Acad Sci USA. 2016 Apr 19;113(16):4240-2. doi: 10.1073/pnas.1603569113.

Van Arsdale A, Patterson N, Maggi E, Agoni L, Van Doorslaer K, Harmon B, Nevadunsky N, Kuo DSY, Einstein MH, Lenz J and Montagna C. Insertional oncogenesis by HPV70 revealed by multiple genomic analyses in a clinically HPV-negative cervical cancer. Genes Chromosomes Cancer. 2020 Feb; 59(2): 84–95.

Retinal differentiation, inherited degenerations, and regeneration

- Elucidate the molecular and cellular mechanisms of retinal differentiation using engineered mice
- Model human retinal differentiation and inherited degenerations using pluripotent stem cells



The neuroretina, retinal pigment epithelium (RPE), ciliary body, and iris are structurally and functionally connected in the human adult retina. Inherited degenerations of any tissue will affect the others, leading to blinding retinal disease such as retinitis pigmentosa, age-related macular degenerations, and glaucoma. Macular degenerations affect vision the most, since the macula is responsible for central vision and visual acuity. Human adult neuroretina does not naturally regenerate. Regenerative medicine of the retina holds a promise to save and restore vision.

Elucidating the mechanisms of retinal differentiation is a prerequisite for retinal regeneration. Embryonic development of the neuroretina, RPE, ciliary body, and iris is an integrated process under the regulation of transcription factors and signal transduction molecules. In mice, morphogenesis of optic-cups leads to the specification of neuroretinal and RPE progenitor cells in the inner and outer layer of optic cups at E10.5, respectively. Neuroretina is continuous with RPE via epithelial sheet bending. Close to the bending region, peripheral neuroretina gradually reduces its thickness to form a tapered zone, which is subsequently specified as ciliary margin at E12.5. Neuroretinal progenitor cells are multipotent, producing all retinal neurons and Müller glial cells. Ciliary margin differentiates into ciliary body and iris. How multipotent retinal progenitor cells are regulated in coordination with ciliary margin specification is underexplored. We address the critical knowledge gap by dissecting the molecular functions of homeodomain transcription factors and signaling transduction molecules in retinal differentiation using engineered mice.

The macula is enriched for cone photoreceptors and is unique to primates. The availability and high cost of non-human primates limit their use in retinal disease studies. Macular degenerations are often not closely recapitulated in mouse models because mice do not have the macula. Notably, we recently generated and characterized cone-rich human retinal organoids reminiscent of the macula based on the ratio of cones to rods and single-cell transcriptomes. As a recognition by the field, we recently received an [NEI prize](#) for progress toward developing lab-made retinas. We now utilize retinal organoids to model human retinal differentiation and inherited degenerations.

Current projects in my lab:

- To elucidate the mechanisms underlying the regulation of multipotent neuroretinal progenitor cells;
- To determine the mechanisms of photoreceptor cell differentiation;
- To model human retinal differentiation and inherited degenerations using human embryonic stem cells.

Our studies will decipher the mechanisms of retinal differentiation and inherited degenerations, leading to therapeutic development for blinding retinal disease.

Recent publications

Kim S, Lowe A, Dharmat R...Zhou Z, Chen R, Liu W (2019). **Proc Natl Acad Sci U S A**, 116(22):10824-10833.
Diacou R, Zhao Y, Zheng D, Cvekl A, Liu W (2018). **Cell Reports**, 25: 2510-2523.
Liu W[†], Cvekl A (2017). **Dev Biol**, 428(1):164-175. [†] Corresponding author.
Lowe A, Harris R, Bhansali P, Cvekl A, Liu W (2016). **Stem Cell Reports**, 6(5):743-756.
Liu W, Lagutin O, Swindell E, Jamrich M and Oliver G (2010). **J of Clin Invest**, 120: 3568-77.

Host-Microbial genetics, orphan nuclear receptors, metabolites, and disease

Pregnane X Receptor (PXR) [a.k.a the Steroid and Xenobiotic Receptor (SXR)] is a master nuclear receptor regulator of host xenobiotic/endobiotic metabolism, detoxification and inflammation. More recently, we have shown that the receptor plays a major role in relaying host microbial signals in the intestines with innate immunity. Specifically, we have shown that microbial metabolites of L-tryptophan, indoles and indole propionates, activate PXR in intestinal epithelial cells to promote intestinal immune homeostasis via a TLR4 specific pathway^{*}. This discovery has led our laboratory into new directions primarily focused on molecular mechanisms governing host-microbial and microbial-microbial relationships in the intestines (similar approaches could be used elsewhere or for other physiologic-pathophysiologic conditions).

1. Discovery of endobiotic PXR ligands and use of microbial metabolite mimicry to design drugs combating intestinal inflammation and cancer. Here we are investigating how different microbial metabolites bind and activate and/or antagonize PXR function in the intestines with the hopes of establishing a physiologic role for microbial metabolites in mammals. In parallel, we have embarked on chemical biological approaches to discovery of indole propionate analogs as potent PXR ligand agonists, with the eventual hope of designing small molecule drugs (microbial metabolite mimicry) combating intestinal inflammation and inflammation-induced cancer^{**}. More recently, the role for indole metabolites connect the gut microbes to neuronal function partly via PXR^{***}. We are also interested in covering all other human receptors in regards to microbial metabolite effects.

2. Discovery of new (novel) microbes and mechanisms governing its regulation of innate immunity. Here we are interested in deciphering molecular mechanisms of indole metabolites as well as small molecule indole mimics as they interact with the host microbiome (e.g., biofilms, drug resistance etc.) in conditions of homeostasis and intestinal stress. These types of investigations have led to the identification of a novel bacterial strain with a unique community phenotype that alters intestinal inflammation. We have diversified our interests to the study of how and why these novel bacterial strains arise during inflammation, what regulates their swarming behavior, and how they execute a phenotype in mice[§]. Finally, our goal is to derive probiotic approaches, harnessing our internal microbiome, for the treatment of a variety of health conditions. These projects have led to multidisciplinary approaches of designing probiotic drug delivery systems using physics of bacterial spreading, molecular microbiology and host biology^{§§}. We are also interested in bar coded recording of transcriptional events in probiotics and pathogens.

Selected Publications:

^{*} Venkatesh M, Mukherjee S, Wang H, Li H, Sun K, Benechet AP, Qiu Z, Maher L, Redinbo MR, Phillips RS, Fleet JC, Kortagere S, Mukherjee P, Fasano A, Le Ven J, Nicholson JK, Dumas ME, Khanna KM, Mani S. Symbiotic Bacterial Metabolites Regulate Gastrointestinal Barrier Function via the Xenobiotic Sensor PXR and Toll-like Receptor 4. *Immunity* 41(2): 296-310 (2014)

^{**} Dvorak Z et al (40 authors), Mani S. Targeting the Pregnane X Receptor Using Microbial Metabolite Mimicry. *EMBO Molecular Medicine* (Cover Page Citation) 12(4):e11621(2020)

^{**} Dvorak Z, Sokol H, Mani S. Drug Mimicry: Promiscuous Receptors PXR and AhR, and Microbial Metabolite Interactions in the Intestine. *Trends Pharm Sci* (Cover Page Citation) 41(12): 900-908 (2020)

^{***} Serger E et al (primary work from the Giovanni lab, Imperial College, London). The gut metabolite indole-3 propionate promotes nerve regeneration and repair. *Nature* Jun 22 doi:10.1038/s41586-022-04884-x (online ahead of print 2022)

[§] De A, Chen W, Li H, Wright JR, Lamendella R, Lukin DJ, Szymczak WA, Sun K, Kelly L, Ghosh S, Kearns DB, He Z, Jobin C, Luo X, Byju A, Chatterjee S, San Yeoh B, Vijay-Kumar M, Tang JX, Prajapati M, Bartnikas TB, Mani S. Bacterial Swarms Enriched During Intestinal Stress Ameliorate Damage. *Gastroenterology* 161(1):211-224. doi: 10.1053/j.gastro.2021.03.017 (2021)

^{§§} Chen W, Mani N, Karani H, Li H, Mani S, Tang JX. Confinement discerns swimmers from planktonic bacteria. *Elife* 10:e64176 (2021)

Genetic Regulation of Endocrine Axes in Human Aging and Longevity

Our research focuses on a unique population of centenarians and their families who are generally free of age-related diseases. Healthy longevity runs in most of these families, suggesting a heritable basis for this phenomenon. Our team conducts translational research focused on the discovery of genomic mechanisms that regulate endocrine and metabolic pathways that protect against common age-related diseases, like diabetes, cardiovascular disease and Alzheimer's disease.

Many of the discovered longevity genes and phenotypes are related to hormonal pathways. Changes in most hormones are observed throughout the human lifespan, but it remains unknown whether the observed changes cause aging, are associated with age but are not the cause of aging, or are protective for the aging body. Identification of protective endocrine parameters will inform our understanding of the mechanisms of healthy aging and lead to the discovery of interventions that protect from age-related diseases.

A biological pathway that has been repeatedly implicated in aging is the somatotrophic axis that involves signaling via growth hormone and insulin-like growth factor-I (IGF-I). Substantial evidence exists that diminished signaling via this pathway delays aging, resulting in longer lifespan and health-span, not only in animal models, but also in humans. We demonstrated that lower IGF-I levels were associated with longer survival, better cognitive function, and protection from multi-morbidity in older adults and people with exceptional longevity. Our team uses computational approaches to integrate genetic data with rich phenotypic data in families with inherited longevity to understand the genetic and molecular mechanisms that lead to protective effects of low IGF-I.

Selected Publications:

1. Aleksic S, Desai D, Ye K, Duran S, Gao T, Crandall J, Atzmon G, Barzilai N, Milman S. Integrity of Hypothalamic-Pituitary-Testicular Axis in Exceptional Longevity. *Aging Cell* 2022, *in press*
2. Lin JR, Sin-Chan P, Napolioni V, Torres GG, Mitra J, Zhang Q, Jabalameli MR, Wang Z, Nguyen N, Gao T, Regeneron Genetics Center, Laudes M, Görg S, Franke A, Nebel A, Greicius MD, Atzmon G, Ye K, Gorbunova V, Ladiges WC, Shuldiner A, Niedernhofer LJ, Robbins PD, Milman S, Suh Y, Vijg J, Barzilai N, Zhang ZD. Rare genetic coding variants associated with human longevity and protection against age-related diseases. *Nat Aging* 2021; *in press*
3. Zhang WB, Ye K, Barzilai N, Milman S. The antagonistic pleiotropy of insulin-like growth factor 1. *Aging Cell* 2021; 20(9), e13443; PMID: PMC8441393
4. Gutman D, Lidzbarsky G, Milman S, Gao T, Sin-Chan P, Gonzaga-Jauregui C, Regeneron Genetics Center, Deelen J, Shuldiner AR, Barzilai N, Atzmon G. Similar burden of pathogenic coding variants in extremely long-lived individuals and individuals without exceptional longevity. *Aging Cell* 2020, *in press*
5. Zhang ZD, Milman S, Lin J, Barzilai N, Gorbunova V, Ladiges WC, Niedernhofer LF, Suh Y, Robbins PD, Vijg J. Genetics of extreme human longevity to guide drug discovery for healthy ageing. *Nat Metab* 2020, *in press*
6. Zhang WB, Aleksic S, Gao T, Weiss EF, Demetriou E, Verghese J, Holtzer R, Barzilai N, Milman S. Insulin-like Growth Factor-1 and IGF Binding Proteins Predict All-Cause Mortality and Morbidity in Older Adults. *Cells* 2020; 9(6):E1368
7. Lehallier B, Gate D, Schaum N, Nanasi T, Lee SE, Yousef H, Moran Losada P, Berdnik D, Keller A, Verghese J, Sathyan S, Franceschi C, Milman S, Barzilai N, Wyss-Coray T. Undulating changes in human plasma proteome profiles across the lifespan. *Nat Med* 2019; 25(12):1843-1850
8. Gubbi S, Quipildor GF, Barzilai N, Huffman DM, Milman S. 40 Years of IGF-1: IGF-1: the Jekyll and Hyde of the aging brain. *J Mol Endocrinol* 2018; 61(1):T171-T185. PMID: PMC598899
9. Gubbi S, Schwartz E, Crandall JP, Verghese J, Holtzer R, Atzmon G, Braunstein R, Barzilai N, Milman S. Effect of Exceptional Parental Longevity and Lifestyle Factors on Prevalence of Cardiovascular Disease in Offspring. *Am J Cardiol* 2017; 120(12):2170-2175. PMID: PMC5698168
10. Milman S, Huffman DM, Barzilai N. The Somatotrophic Axis in Human Aging: Framework for the Current State of Knowledge and Future Research. *Cell Metab* 2016; 23(6):980-9. PMID: PMC4919980
11. Milman S, Atzmon G, Huffman DM, Wan J, Crandall JP, Cohen P, Barzilai N. Low Insulin-like Growth Factor-1 Level Predicts Survival in Humans with Exceptional Longevity. *Aging Cell* 2014; 13(4):769-71

PARSA MIRHAJI, Ph.D.

In my positions as the Director of the ICTR Health Informatics Core and the Director of the Montefiore-Einstein Center for Health Data Innovations I oversee and coordinate for strategic planning, investment and implementation, integration of our research informatics, big-data analytics, and data science infrastructure with operational and clinical systems and processes for learning healthcare, and coordinate with other ICTR leaders and core directors to provision and support researchers across all levels of clinical and translational spectrum institution-wide. I represent ICTR and the CTSA research community in enterprise data governance board and participate in enterprise-wide strategic planning and governance of Montefiore Health System Information and Data infrastructure in support of research and collaboration.

I have been the chair of Informatics committee of 6 NYC-CTSA hubs (2015-present) overseeing construction and deployment of NYC-CDRN (aka INSIGHT Network) clinical data warehouse, to be leveraged for local real-world data research collaborations across the CTSA hubs, and for participation in national PCORnet. I have led ICTR collaborations and participation in NIH:National Covid Cohort Consortium (N3C), and our participation in regional open science collaborations with other CTSA hubs (e.g. Einstein PI: Tri-Con Multi-state COVID Collaborative) for Covid research through large scale information sharing and informatics research. Presently I am the informatics lead and Einstein PI for our NIH:RECOVER EHR based studies award (2021) to develop real-world data (RWD) infrastructure to be shared nationally with NIH:RECOVER-Covid consortium.

My research focuses on computational understanding of clinical text, semantic modeling and ontological representation of complex biomedical datasets, model-driven and ontology based reasoning and logic systems, cognitive engineering and human computer interaction design for clinical decision support systems, designing artificial intelligence and deep learning models inspired by neuroscience and cognitive science, and alternate methods to train machine intelligence and artificial intelligence to solve complex clinical prediction and recommendation problems using real-world data. I have years of experience developing secured, and scalable platforms for management, harmonization, and integration of multi-source, heterogenous, and diverse data sets pertaining to individual patients and patient populations, developing agile, web-enabled, and secured health information management platforms based on open-source frameworks, the Semantic Web family of technologies for data modeling and ontology design, and design and development of large scale automated and intelligent services for biosurveillance, bioterrorism preparedness, and public health preparedness for disease outbreaks and emerging infectious diseases using real-world clinical data.

Selected Patents

Method and system for ontology driven data collection and processing

US8429179B1, Parsa Mirhaji, Board Of Regents, The University Of Texas System
Priority 2009-12-16 • Filed 2010-12-13 • Granted 2013-04-23 • Published 2013-04-23

Persistence and linking of analytic products in big data environments

WO, EP, CA WO2018013954A1 Parsa Mirhaji, Albert Einstein College Of Medicine, Inc.
Priority 2016-07-15 • Filed 2017-07-14 • Published 2018-01-18

Semantic indexing engine

US10803088B2, Parsa Mirhaji, Franz, Inc.
Priority 2014-12-22 • Filed 2017-06-10 • Granted 2020-10-13 • Published 2020-10-13

Method and system for text understanding in an ontology driven platform

US8433715B1 Parsa Mirhaji, Board Of Regents, The University Of Texas System
Priority 2009-12-16 • Filed 2010-12-13 • Granted 2013-04-30 • Published 2013-04-30

Method and system for an ontology, including a representation of unified medical language system (UMLS) using simple knowledge organization system (SKOS)

US10838971B2, Parsa Mirhaji, Board Of Regents, The University Of Texas System
Priority 2009-12-16 • Filed 2016-10-11 • Granted 2020-11-17 • Published 2020-11-17

System and method for medical observation system located away from a hospital

US20030050538A1 Parsa Mirhaji Morteza Naghavi.
Priority 2001-05-29 • Filed 2002-05-29 • Published 2003-03-13

System and method for a personal computer medical device based away from a hospital

(US20030050539A1) Parsa Mirhaji, Morteza Naghavi.
Priority 2001-05-29 • Filed 2002-05-29 • Published 2003-03-13

Health hub system and method of use

US20020184415A1, Parsa Mirhaji.
Priority 2001-05-29 • Filed 2002-05-29 • Published 2002-12-05

Link to Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/parsa.mirhaji.1/bibliography/public/>

CRISTINA MONTAGNA, Ph.D.

Genetic, epigenetic and ploidy changes during cell differentiation in development and disease.

Project 1- Role of Septin 9 in Breast Carcinogenesis.

A comparative cytogenetic approach aimed to identify recurrent DNA copy number variations in a panel of murine models for breast cancer resulted in the identification of Septin 9 (Sept9) as potential novel oncogene. The septin family of genes codes for a highly redundant and conserved family of GTP-binding proteins that assemble into filaments and bind to microfilaments and microtubules. At the locus of genomic amplification deregulation of Sept9 expression occurs by a complex pattern of genetic and epigenetic alterations affecting several Sept9 isoform variants. Our hypothesis is that during malignant transformation, breast epithelial cells undergo genomic amplification of the Sept9 locus and over-express Sept9 mRNA and protein. Additionally, aberrant cytosine methylation occurs at specific alternative promoters within the Sept9 locus resulting in an abnormal pattern of Sept9 isoform variants. We are currently studying how the expression of various Sept9 isoforms is regulated in normal and cancer cells and the functional differences between these isoforms.

Project 2- Stage- and Cell Subtype-Specific Epigenetic Regulation of Mammary Gland Development and breast tumorigenesis.

We are interested in investigating the DNA methylation changes occurring in the development of the normal mammary gland during puberty, adult age, pregnant, lactating and undergoing mammary gland involution. This approach has the final goal of dissecting the molecular processes that mediate methylation changes in the morphogenesis and differentiation of the normal breast and to identify "hot spot" loci for gene silencing in breast carcinogenesis.

Project 3- Aneuploidy in aging.

Polyploidy and aneuploidy are the most frequent cytogenetic events observed in mammalian cells. Polyploidization is a widely accepted mechanism for increasing genetic variation in unicellular organisms and for the acquisition of new properties in a variety of cell types (e.g., osteoclast fusion in bone resorption and myoblast fusion in muscle development) and is considered a physiological process. Aneuploidy on the contrary is linked to pathological states. It is a hallmark of spontaneous abortions and birth defects and is observed virtually in every human tumor. While the catastrophic consequence of high levels of aneuploidy observed in abortions is self-explanatory, the role of aneuploidy under physiological conditions is a question waiting for answers. The major goal of this project is to explore a possible correlation between age-associated genome instability in a variety of tissues and functionality of these cells.

Recent Publications:

- Acosta, D., M. Suzuki, D. Connolly, R. F. Thompson, M. J. Fazzari, J. M. Greally and C. Montagna (2011). "DNA methylation changes in murine breast adenocarcinomas allow the identification of candidate genes for human breast carcinogenesis." *Mammalian genome : official journal of the International Mammalian Genome Society* 22(3-4): 249-259.
- Connolly, D., I. Abdesselam, P. Verdier-Pinard and C. Montagna (2011). "Septin roles in tumorigenesis." *Biological chemistry* 392(8-9): 725-738.
- Connolly, D., Z. Yang, M. Castaldi, N. Simmons, M. H. Oktay, S. Coniglio, M. J. Fazzari, P. Verdier-Pinard and C. Montagna (2011). "Septin 9 isoform expression, localization and epigenetic changes during human and mouse breast cancer progression." *Breast cancer research: BCR* 13(4): R76.
- Downing, T. E., M. H. Oktay, M. J. Fazzari and C. Montagna (2010). "Prognostic and predictive value of 16p12.1 and 16q22.1 copy number changes in human breast cancer." *Cancer genetics and cytogenetics* 198(1): 52-61.
- Faggioli, F., M. G. Sacco, L. Susani, C. Montagna and P. Vezzoni (2008). "Cell fusion is a physiological process in mouse liver." *Hepatology* 48(5): 1655-1664.
- Faggioli, F., P. Vezzoni and C. Montagna (2011). "Single-cell analysis of ploidy and centrosomes underscores the peculiarity of normal hepatocytes." *PloS one* 6(10): e26080.
- Faggioli, F., J. Vijg and C. Montagna (2011). "Chromosomal aneuploidy in the aging brain." *Mechanisms of ageing and development* 132(8-9): 429-436.
- Weaver, B. A., A. D. Silk, C. Montagna, P. Verdier-Pinard and D. W. Cleveland (2007). "Aneuploidy acts both oncogenically and as a tumor suppressor." *Cancer Cell* 11(1): 25-36.

BERNICE E. MORROW, Ph.D.

Understanding genetic risk factors for birth defects on a single cell level

Our lab is interested in discovering genes required for human embryonic development to understand the cause of birth defects. Our research begins with collecting DNA samples from affected individuals with genetic disorders having known chromosomal gains or losses, and moves to looking at gene function in vertebrate model organisms. The reason for studying chromosomal disorders is that affected regions in the genome will pinpoint the location of causative genes whose function in organogenesis is sensitive to copy number.

Our main focus is on a disorder termed chromosome 22q11.2 deletion syndrome (22q11DS). Most affected individuals have a similar sized 3 million base pair (Mb) deletion encompassing 60 genes. The deletion occurs by a mistake during meiosis in forming the egg or sperm. Individuals with the syndrome have learning disabilities, psychiatric illness, cleft palate, hearing loss and cardiovascular defects. Many of these defects occur commonly in the general population in non-syndromic forms. This is why molecular genetic studies of this syndrome are particularly relevant to human health and disease.

One key gene in the 22q11.2 region is termed *TBX1* and it encodes a transcription factor that is responsible for many of the defects in patients with the syndrome. Using knockout and gain-of-function mutant mice, we have made headway to understand its function. Since it's a transcription factor, we are interested in genes it can regulate. Part of our mission is to understand the role of *Tbx1* in making cell fate decisions in mammalian embryos. We are doing this by taking single cell RNA-sequencing, chromatin accessibility and chromatin immunoprecipitation followed by genome sequencing from microdissected tissues from wildtype and mutant embryos followed by bioinformatics analysis.

Although most individuals with 22q11DS have the same sized deletion, the severity of malformations varies dramatically. For example, 60% have heart defects, many requiring surgery, while the rest have a normal heart. We hypothesize that the 22q11.2 deletion is the first hit in the genome and it uncovers other mutations that act as second hits to modify the overall phenotype of the disorder. We are taking candidate gene and unbiased whole genome sequencing approaches to identify genetic "modifiers" in subjects with 22q11DS. We are identifying common and rare, copy number and single nucleotide variants. In order to interpret the genomic data, we are taking systems biology approaches. In this way, we will extract biologically important gene networks in a holistic sense. At the same time, genes in the networks will be tested for functional significance in mouse models.

Recent Publications:

Racedo SE, Hasten E, Lin M, Devakanmalai GS, Guo T, Ozbudak EM, Cai C, Zheng D, Morrow BE. (2017) Reduced dosage of *β-catenin* provides significant rescue of cardiac outflow tract anomalies in a *Tbx1* conditional null mouse model of 22q11.2 deletion syndrome. *PLoS Genetics*, 13(3):e1006687. PMID: 28346476

Hasten E, McDonald-McGinn DM, Crowley TB, Zackai E, Emanuel BS, Morrow BE, Racedo SE. (2018) Dysregulation of *TBX1* dosage in the anterior heart field results in congenital heart disease resembling the 22q11.2 duplication syndrome. *Hum Mol Genet.* 27(11):1847-1857. PMID: 29509905

Zhao Y, Guo T, Fiksinski A, Breetvelt E, McDonald-McGinn DM, Crowley TB, Diacou A, Morrow BE. (2018) Variance of IQ is partially dependent on deletion type among 1,427 22q11.2 deletion syndrome subjects. *Am J Med Genet A.* 176(10):2172-2181. PMID:30289625

Hasten E, Morrow BE. (2019) *Tbx1* and *Foxi3* genetically interact in the pharyngeal pouch endoderm in a mouse model for 22q11.2 deletion syndrome. *PLoS Genet.* 15(8):e1008301. PMID: 31412026.

Zhao Y, Diacou A, Johnston HR, Musfee FI, McDonald-McGinn DM, McGinn D, Crowley TB, Morrow BE. (2020) Complete sequence of the 22q11.2 allele in 1,053 subjects with 22q11.2 deletion syndrome reveals modifiers of conotruncal heart defects. *Am J Hum Genet.* 106(1):26-40. PMID: 31870554

SRILAKSHMI RAJ, Ph.D.

Human Population Genetics

Our work involves leveraging the genetic and environmental variation among humans to understand variation in phenotype, disease risk and outcome. We use genetics to understand population structure and history, and use this information to investigate variation in genetic architecture of diseases among populations.

Our research is centered around using human population genetics to understand the role of genetics in human health outcomes. We are strongly interested in leveraging population differences in the genetic architecture of rare and common disorders to serve community health.

This type of research involves understanding both the environmental and clinical contexts in which genetics contributes to phenotype in different populations. We employ three main strategies to carry out this research. The first is evolutionary genetic approaches to understanding why humans vary, where in the genome this may occur, and how this may affect disease risk. The second is using population genetic approaches to address epidemiological questions, such as predicting who might be at highest risk for a particular disease and understanding the genetic architecture underlying this. Lastly, we use anthropological genetics approaches to understand the genetic variation and environmental contexts which may predispose an individual to disease. This involves extensive fieldwork to understand the contribution of human genetic and local environmental variation to phenotypic variation among specific populations.

This multi-pronged approach enables us to apply population genetic principles and approaches broadly to understand the genetic contribution to community health outcomes, which can be multifaceted and vary among populations and disease contexts.

Website: <https://srirajlab.com>

Select Publications:

1. Myer PA, Lee JK, Madison R, Pradhan K, Newberg J, Isasi CR, Klempner SJ, Frampton G, Ross JS, Venstrom J, Schrock AB, Das S, Augenlicht L, Verma A, Grealley JM, **Raj SM**, Goel S, Ali SM (2022) The Genomics of Colorectal Cancer in Populations with African and European Ancestry. *Cancer Discovery* 12 (5): 1282-1293.
2. **Raj SM**, R Ekanayake, M Bhat, J Kadandale, P Pingali. Multiple risk factors contributing to stunting in Karnataka state, India. *Current Science* 121(3):360-64.
3. **Raj SM**, R Ekanayake, K Crowley, M Bhat, J Kadandale, P Pingali. Risk factors in childhood stunting in Karnataka state vary by geography. *Current Science* 121(4):502-10.
4. Yu F*, Lu J*, Liu X*, Gazave E, Chang D, **Raj S**, Hunter-Zinck H, Blekhman R, Arbiza L, Van Hout C, Morrison A, Johnson AD, Bis J, Cupples LA, Psaty BM, Muzny D, Yu J, Gibbs RA, Keinan A, Clark AG, Boerwinkle E. 2015. A population genetic analysis of 962 whole genome sequences reveals natural selection in non-coding regions of the human genome. *PLoS One* 10, e0121644.
5. Cardona, A., Pagani L, Antao T, Lawson DJ, Eichstadt CA, Yngvadottir B, Shwe MTT, Wee J, Tyler-Smith C, Gallego Romero I, **Raj S**, Metspalu M, Vilems R, Nielsen R, Willerslev E, Malyarchuk BA, Derenko MV, Kivisild T. (2014) Genome-wide analysis of cold adaptation in indigenous Siberian populations *PLoS One* 9:e98076.
6. **Raj SM**, Pagani L, Romero IG, Kivisild T, Amos W (2013). A general linear model based approach for inferring selection to climate. *BMC Genetics* 14: 87.
7. Ye K, Lu J, **Raj SM**, Gu Z (2013). Human expression QTLs are enriched in signals of environmental adaptation. *Genome Biol Evol* 5:1689-701.
8. **Raj SM**, Halebeedu P, Iliescu FM, Romero IG, Kadandale, J, Thangaraj, K, Chandra HS, Muniyappa, K, Kivisild, T. Patterns of variation at diabetes and obesity-associated loci mirror neutral patterns of human population diversity and diabetes prevalence in India. *Annals of Human Genetics* 77(5): 392-408.

MICHAEL G. ROSENFELD

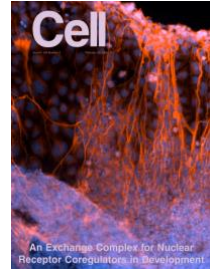
Investigator, Howard Hughes Medical Institute

Professor, UCSD School of Medicine
National Academy of Sciences (1994)
Lab location: CMM-West, Room 353

Phone: 858.534.5858

Email: mrosenfeld@ucsd.edu

Website: investigators/rosenfeld_bio.html



Lab Composition and Activities: Two graduate students from different programs, a talented group of enthusiastic (and helpful) postdoctoral fellows and a full-time laboratory manager. We have one full laboratory meeting, one graduate student-only meeting, and one individual meeting each week. We also have joint lab meetings with another lab biweekly.

Research Interests: Our central laboratory focus is to:

1. Understand the molecular mechanisms of the transcriptional and chromosomal architectural programs that underlie development, regulation and disease, focusing on enhancer networks. We utilize diverse global genomic and single cell real time imaging approaches to uncover and investigate the “enhancer code” controlled by new, previously unappreciated pathways that integrate the genome-wide response to permit proper homeostasis and that also function in aging/senescence, in disorders of the CNS, including neurodegeneration, and in specific cancers.
2. These studies have led to identification of phase separation event in acute ligand/signal activation of enhancer-dependent transcriptional programs, the discovery of the role of RNA shape in mediating the functions of promoter antisense RNAs and enhancer RNAs, and the mechanisms by which enhancers “choose” their cognate promoters. These observations are rapidly altering our concepts of homeostasis and disease.
3. We are applying these principles and simultaneous single nuclei RNA-seq and ATAC-seq analyses to uncover the early events in Alzheimer’s disease, distinguishing aging-dependent events in each CNS cell type and cellular senescence, and cancer metastasis, and studying events in learning and memory.

Current projects for potential rotations include:

- Using single nuclear RNA-seq, ATAC-seq, and ChIP-seq approaches to investigate the potential causative events leading to Alzheimer’s disease. This will require delineating the trajectory trees and heat diffusion maps for all CNS cell types and identification of the transcription factors driving normal aging vs. disease-associated alterations and the regulatory enhancers during aging and in sporadic AD. Proof of hypotheses.
- Linking phase separation events of cell type-specific enhancers in determining chromosomal architecture and long distance cooperative enhancer interactions to an unexpected requirement for signal/ligand-dependent activation of topoisomerase 1 at enhancers, which is “read” by a specific component of the DNA damage repair machinery, but here functioning as an obligatory co-activator; identification of additional novel required factors and RNAs in regulated enhancer activation events .
- Developing new methods for real time, single cell imaging to explore regulation of enhancer networks, interactions with subnuclear structures, and enhancer bursting to understand the relation of enhancer/ subnuclear structural interactions in the 4D nucleome.

15 Representative Publications (2014-2021):

- Yang F, Tanasa B, et al. Shape of promoter antisense RNAs regulates ligand-induced transcription activation. *Nature*. 2021 Jul;595(7867):444-449. doi: 10.1038/s41586-021-03589-x. Epub 2021 Jun 30. PMID: 34194047
- Oh S, et al. Enhancer release and retargeting activates disease-susceptibility genes. *Nature*. 2021 May 26. doi: 10.1038/s41586-021-03577-1. Online ahead of print. PMID: 34040254
- Alexanian M, et al. A transcriptional switch governs fibroblast activation in heart disease. *Nature*. 2021 Jul;595(7867):438-443. doi: 10.1038/s41586-021-03674-1. Epub 2021 Jun 23. PMID: 34163071
- Nott A, et al. Brain cell type-specific enhancer-promoter interactome maps and disease-risk association. *Science*. 2019 Nov 29;366(6469):1134-1139. doi: 10.1126/science.aay0793. Epub 2019 Nov 14. PMID: 31727856
- Nair SJ, et al. Phase separation of ligand-activated enhancers licenses cooperative chromosomal enhancer assembly. *Nature Struct Mol Biol*. 2019;26(3):193-203
- Kim HS, et al. Pluripotency factors functionally premark cell-type-restricted enhancers in ES cells. *Nature*. 2018 Apr;556(7702):510-514.
- Tan Y, et al. Dismissal of RNA Polymerase II Underlies a Large Ligand-Induced Enhancer Decommissioning Program. *Mol Cell*. 2018 Aug 16;71(4):526-539.e8. doi: 10.1016/j.molcel.2018.07.039.
- Yang, F, et al. Glucocorticoid receptor: MegaTrans Switching Mediates the Repression of an ER α -Regulated transcriptional Program. *Mol Cell*. 2017 May 4;66(3):321-331
- Wang J, et al. LSD1n is an H4K20 demethylase regulating memory formation via transcriptional elongation control. *Nat Neurosci*. 2015 Sep;18(9):1256-64. doi: 10.1038/nn.4069. Epub 2015 Jul 27.
- Telese F, et al. LRP8-Reelin-Regulated Neuronal Enhancer Signature Underlying Learning and Memory Formation. *Neuron*. 2015 May 6;86(3):696-710. PMID:2589230
- Li W, et al. Condensin I and II Complexes License Full Estrogen Receptor α -Dependent Enhancer Activation. *Mol Cell*. 2015 Jul 16;59(2):188-202. PMID:26166704.

Puc J, et al. Ligand-dependent enhancer activation regulated by topoisomerase-I activity. **Cell**. 2015 Jan 29;160(3):367-80. PMID:25619691.

Skowronska-Krawczyk, D., et al. Required Interactions of Enhancers with Matrin-3 Nuclear Architecture for Transcriptional Activation by Homeodomain Factor. **Nature** 2014;514(7521):257-61. PMID:25119036.

Basnet H, et al. Tyrosine phosphorylation of histone H2A by CK2 regulates transcriptional elongation. **Nature**. 2014 Dec 11;516(7530):267-71. PMID:25252977.

Liu Z, et al. Enhancer activation requires trans-recruitment of a mega transcription factor complex. **Cell**. 2014 Oct 9;159(2):358-73. PMID:25303530.

Please feel free to [email](#) me or call @534-5858 for questions and if you would like to meet/Zoom and discuss projects. Thanks, Geoff

JAYANTA ROY-CHOWDHURY, MBBS, MRCP, AGAF, FAASLD

Our current focus is on developing cell and gene-based therapies for monogenic liver diseases, such as inherited hyperbilirubinemia (Crigler-Najjar syndrome, CN-1), α_1 antitrypsin (AAT) deficiency, dyslipidemias and hemophilias A and B.

Subproject 1. Hepatocyte-based therapies for genetic liver diseases. To develop a minimally invasive alternative to liver transplantation, we are developing strategies to repopulate the liver by transplanted hepatocytes. To overcome the hurdles of inefficient hepatocyte engraftment and failure of transplanted hepatocytes to proliferate, we are evaluating targeted hepatic irradiation and mitotic stimulation of the transplanted hepatocytes. Regiospecific conformal hepatic irradiation (HIR) is being used to transiently disrupt the sinusoidal endothelial barrier, thereby enhancing initial engraftment. HIR makes the host hepatocytes in the irradiated region less mitotically competent. We are exploring different types of mitotic agents to stimulate the proliferation of the engrafted hepatocytes, which can competitively repopulate the host liver. We are also evaluating whether co-transplantation of liver sinusoidal endothelial cells can augment liver repopulation by hepatocytes. Our work was translated into the first successful hepatocyte transplantation in a CN-1 patient, and more recently in two patients with urea cycle disorders and one with phenyl ketonuria.

AAT deficiency (ATD) is one of the most common potentially lethal monogenic liver disorders in the West. In classic ATD, a mutant misfolded AAT (ATZ) is secreted inefficiently and is retained within hepatocytes. Circulatory AAT deficiency leads to unrestrained neutrophil elastase activity in the lung, causing pulmonary emphysema, whereas ATZ accumulation within hepatocytes results liver disease. We showed that wildtype hepatocytes transplanted into transgenic mice expressing human ATZ competitively replace the host hepatocytes. Our current focus is to disrupt ATZ expression in a fraction of the hepatocyte mass by DNA break-enhanced homologous recombination *in vivo*, so that the gene-edited hepatocytes can repopulate the liver, thereby providing normal AAT and correcting the liver disease.

Subproject 2. Transplantation of endothelial cells to repopulate mutant liver endothelial cells (LSEC): LSECs are highly specialized endothelial cells that are important in maintaining liver architecture, as well as hepatocyte regeneration and function. In addition, these cells express coagulation factor VIII (the deficiency of which causes hemophilia A) and Von Willebrand factor. In ongoing work, we have found that intravenous infusion of LSECs following regional HIR results in engraftment of LSECs in the liver. Subsequent pharmacological stimulation of the LSECs results in regional liver repopulation by the transplanted cells. This procedure has cured the bleeding disorder in Factor VIII-deficient hemophilic mice.

In ongoing studies we are correcting the genetic lesions in mutant hepatocytes and LSECs, using CRISPR-cas or zinc finger nuclease-enhanced homologous recombination to generate phenotypically corrected for transplantation into animal models of inherited human liver diseases.

Recent Publications:

Ding J, Yannam GR, Roy-Chowdhury N, Hidvegi T, Basma H, Rennard SI, Wong RJ, Avsar Y, Guha C, Perlmutter DH, Fox IJ, **Roy-Chowdhury J**. Spontaneous hepatic repopulation in transgenic mice expressing mutant human alpha 1-anti-trypsin by wildtype donor hepatocytes. *J. Clin. Invest.* 121:1930-4, 2011.

Chen Y, Li Y, Wang X, Zhang W, Sauer V, Chang CJ, Han B, Tchaikovskaya T, Avsar Y, Tafaleng E, Madhusudana Girija S, Tar K, Stephen S, Bouhassira E, Guha C, Fox IJ, **Roy-Chowdhury J** and **Roy-Chowdhury N**. Amelioration of hyperbilirubinemia in Gunn rats after transplantation of hepatocytes derived from human induced pluripotent stem cells. *Stem Cell Reports* 5:1-9, 2015.

Sauer V, Tchaikovskaya T, Wang X, Li Y, Zhang W, Tar K, Polgar Z, Ding J, Guha C, Fox IJ, **Roy-Chowdhury N**, **Roy-Chowdhury J**. Human urinary epithelial cells as a source of engraftable hepatocyte-like cells using stem cell technology. *Cell transplant*, 2016, 25:2221-2243.

Roy-Chowdhury N, Wang X, Guha C, **Roy-Chowdhury J**. Hepatocyte-like cells derived from induced pluripotent stem cells. *Hepatology International*, 2017, 11:54-69, 2017.

Soltys KA, Setoyama K, Tafaleng EN, et al. Host conditioning and rejection monitoring in hepatocyte transplantation in humans. *J Hepatol.* 66:987-1000, 2017. doi: 10.1016/j.jhep.2016.12.017. PMID: 28027971.

Peterson EA, Polgar Z, Devakanmalai GS, Li Y, Jaber FL, Zhang W, Wang X, Iqbal NJ, Murray JW, Roy-Chowdhury N, Quispe Tintaya W, Maslov AY, Tchaikovskaya TL, Sharma Y, Rogler LE, Gupta S, Zhu L, **Roy-Chowdhury J**, Shafritz DA. Genes and pathways promoting long-term liver repopulation by ex vivo hYAP-ERT2 transduced hepatocytes and treatment of jaundice Gunn rats. *Hepatology Communications* 2019; 3:129-146

Barahman M, Zhang W, Harris HY, Aiyer A, Kabarriti R, Kinkhabwala M, Roy-Chowdhury N, Beck AP, Scanlan TS, **Roy-Chowdhury J**, Asp P, Guha C. Radiation-primed hepatocyte transplantation in murine monogenic dyslipidemia normalizes cholesterol and prevents atherosclerosis. *J Hepatol.* 2019 70:1170-1179.

I. Inherited Disorders of Bilirubin Glucuronidation

UGT1A1 is a member of UDP-glucuronosyltransferases (UGT) family of enzymes, which is concentrated in the hepatic endoplasmic reticulum (ER). UGT1A1, which mediates the glucuronidation of bilirubin and estrogens, is required for biliary excretion of bilirubin. We showed that the genetic lesions in any one of the five exons encoding UGT1A1 can abolish or reduce bilirubin glucuronidation, causing potentially lethal Crigler-Najjar syndrome type I (CN-I), or its less severe variant, Crigler-Najjar syndrome type II (CN-II). We also showed that Gilbert syndrome, a milder form of inherited hyperbilirubinemia, is caused by a promoter polymorphism. We have been studying the regulation of UGT1A1 gene expression. Our current objective is to develop novel gene and cell-based therapies to cure this disease. Fibroblasts or renal tubular epithelial cells present in urine of CN1 patients will be reprogrammed to iPSC cells, genetically corrected, differentiated into hepatocytes and transplanted into jaundice Gunn rat model of CN1.

II. Primary Hyperoxaluria Type 1 (PH1)

PH1 is an autosomal recessive disease caused by mutations in the alanine:glyoxylate aminotransferase gene (AGXT). In humans, insufficient AGXT activity in liver peroxisomes leads to increased oxalate production that causes calcium oxalate stones in the kidney and then in blood, heart, bones, etc. It is a lethal disease unless combined liver and kidney transplantation is performed. We have developed a mouse model of PH1. Our plan is to cure this disease by (a) gene therapy (b) transplantation of adult primary hepatocytes or (c) hepatocytes derived from human embryonic (hESC) or induced pluripotent stem cell (iPSC). For the latter, fibroblasts from the skin of normal volunteers or patients with PH1 are used to generate iPSC. Initially we used viral vectors to generate the iPSCs, but now use non-DNA integrating approaches to generate iPSC cells. The cells are differentiated to hepatocyte-like iHep cells for transplantation into our mouse model of PH1

Publications:

- Salido E, Li Xiao, Lu Y, Wang X., Santana A., **Roy-Chowdhury N**, Torres A, Shapiro L, Roy-Chowdhury J (2006) Alanine-glyoxylate aminotransferase deficient mice, a model for primary hyperoxaluria that responds to adenoviral gene transfer. *Proc. Natl. Acad. Sci., USA*, 103:18249-18254.
- Jiang J, Salido EC, Guha C, Wang X, Moitra R, Liu L, Roy-Chowdhury J, **Roy-Chowdhury N**. (2008) Correction of Hyperoxaluria by liver repopulation with hepatocytes in a mouse model of primary hyperoxaluria type -1. *Transplantation* 85,1253-1260..
- Ding J, Yannam GR, **Roy-Chowdhury N**, Hidvegi T, Basma H, Rennard SI, Wong RJ, Avsar Y, Guha C, Perlmutter DH, Fox IJ, Roy-Chowdhury J. (2011) Spontaneous hepatic repopulation in transgenic mice expressing mutant human alpha 1- antitrypsin by wild-type donor hepatocytes. *J Clin Invest.*121(5): 1930-1934.
- Roy-Chowdhury N**, Roy-Chowdhury J. (2015) Liver physiology and energy metabolism. In *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th edition. Feldman M., Friedman LS, Brandt LJ, editors. Saunders-Elsevier, Philadelphia. Page 1223-1232.
- Chen Y, Li Y, Wang X, Zhang W, Sauer V, Chang CJ, Han B, Tchaikovskaya T, Avsar Y, Tafaleng E, Madhusudana Girija S, Tar K, Stephen S, Bouhassira E, Guha C, Fox IJ, Roy-Chowdhury J, **Roy-Chowdhury N**. (2015) Amelioration of hyperbilirubinemia in Gunn rats after transplantation of hepatocytes derived from human induced pluripotent stem cells. *Stem Cell Reports* 5:1-9.
- Sauer V, Tchaikovskaya T, Wang X, Li Y, Zhang W, Tar K, Polgar Z, Ding J, Guha C, Fox IJ, **Roy-Chowdhury N**, Roy-Chowdhury J (2016). Human urinary epithelial cells as a source of engraftable hepatocyte-like cells using stem cell technology. *Cell transplant*, 25:2221-2243.
- Polgar Z, Yanfeng Li Y, Wang X, Guha C, **Roy-Chowdhury N**, Roy-Chowdhury J (2017). Gunn rats as a surrogate model for evaluation of hepatocyte transplantation-based therapies of Crigler-Najjar syndrome type 1. *Meth Mol Biol* 1506:131-147.
- Peterson EA, Polgar Z, Devakanmalai GS, Li Y, Jaber FL, Zhang W, Wang X, Iqbal NJ, Murray JW, **Roy-Chowdhury N**, Quispe Tintaya W, Maslov AY, Tchaikovskaya TL, Sharma Y, Rogler LE, Gupta S, Zhu L, Roy-Chowdhury J, Shafritz DA. Genes and pathways promoting long-term liver repopulation by ex vivo hYAP-ERT2 transduced hepatocytes and treatment of jaundice Gunn rats. *Hepatology Communications* 2019; 3:129-146
- Roy-Chowdhury N**, Wang X, Roy-Chowdhury J. Bile pigment metabolism and its disorders. *Emery and Rimoin's Principle and Practice of Medical Genetics*, 7th edition, Rimoin DL, Connor JM, Pyeritz RE, Korf BR, editors. Churchill-Livingstone-Elsevier, Philadelphia. 2019
- Roy Chowdhury N, Li Y, Roy Chowdhury J. Chapter 20. Disorders of bilirubin metabolism. In *The Liver: Biology and Pathobiology*, Sixth edition, Arias, IM, editor in chief. Wiley-Blackwell, Oxford, U.K. 2019

JULIE SECOMBE, Ph.D.

Transcriptional Regulation of Neuronal Function and Aging

In my lab, we are interested in understanding the transcriptional regulatory mechanisms that regulate the development and function of neurons in addition to those that mediate the aging process. To do this, we take advantage of the many genetic tools available by using the model organism *Drosophila melanogaster*.

There are currently two main projects in the lab:

(1) Defining the transcriptional and cellular defects caused by KDM5 mutations that result in intellectual disability. While many mutations in human KDM5 family genes have been found in intellectual disability patients, the link between KDM5 dysfunction and cognitive impairment remains unknown. Based on the hypothesis that intellectual disability-associated mutations in KDM5 are caused by aberrant transcription, we have generated fly strains harboring disease alleles. These alleles show defective learning and memory, in addition to morphological defects in several types of neurons. We are currently examining these fly strains for transcriptional defects and alterations to the recruitment of KDM5 to its target genes. We expect that this first *Drosophila* model of KDM5-induced intellectual disability will dramatically enhance our understanding of human intellectual disability.

(2) Activation of Endogenous Transposable Elements by Myc During Aging. A poorly explored potential contributor to aging is the mobilization of endogenous transposable elements (TEs), which can be highly mutagenic and promote genomic instability. We showed that increasing or decreasing levels of the oncoprotein Myc in *Drosophila* reduces or extends lifespan, respectively. More recently, we have shown Myc activates the expression of a subset of endogenous TEs. Because mobilization of TEs can cause insertional mutagenesis, genome rearrangements and DNA damage, they have been proposed to contribute to tumorigenesis and other phenotypes associated with aging. We are combining single cell analyses with strategies to attenuate or activate specific TEs to define their effect on normal and Myc-induced aging.

Recent Publications:

- Belalcazar, H.M., Hendricks, E.L., Zamurrad, S., Liebl, F.L.W., and Secombe J** (2021) The histone demethylase KDM5 is required for synaptic structure and function at the *Drosophila* neuromuscular junction. *Cell Reports*, 34(7):108753. DOI:10.1016/j.celrep.2021.108753. PMID:33596422
- Hatch, H.A.M., Belalcazar H.M., Marshall O.J., and Secombe J** (2021) A KDM5-Prospero transcriptional axis functions during early neurodevelopment to regulate mushroom body formation. *eLife* doi.org/10.7554/eLife.63886 PMID: 33729157
- Hatch, H.A.M., O'Neill, M.H., Marion, R.W., Secombe, J.#, and L.H. Shulman#** (2021) Caregiver-reported characteristics of children diagnosed with pathogenic variants in KDM5C. *American Journal of Medical Genetics - Part A*, doi:10.1002/amjg.a.62381 PMID:34089235
co-corresponding authors.
- Drelon, C., Belalcazar, H.M. and J. Secombe** (2019) The histone demethylase KDM5 controls developmental timing by promoting prothoracic gland endocycles. *Development*, 146:dev182568 doi: 10.1242/dev.182568. PMID:31862793
- Chen, K., Luan, X., Liu, Q., Wang, J., Chang X., Snijders A. M., Mao J-H., Secombe J., Dan Z, Chen J-H., Wang Z., Dong X., Qiu C., Chang X., Zhang D., Celniker S. E., and Xingyin Liu** (2019) *Drosophila* KDM5 regulates social behavior through immune control and gut microbiota maintenance. *Cell Host & Microbe* 25, 1-16. PMID:30902578
- Zamurrad, S., Hatch, H.A.M., Drelon, C., Belalcazar, H.M, and J. Secombe** (2018) A *Drosophila* model of intellectual disability caused by mutations in the histone demethylase KDM5. *Cell Reports* 22, 2359-2369.
- Drelon, C., Belalcazar, H.M. and J. Secombe** (2018) The histone demethylase KDM5 is essential for larval growth in *Drosophila*. *Genetics*. pii: genetics.301004.2018. doi: 10.1534/genetics.118.301004.
- Navarro-Costa, P., McCarthy, A., Prudêncio, P., Greer, C., Guilgur, L.G., Becker J., Secombe, J., Rangan, P and R. Martinho** (2016). Early programming of the oocyte epigenome temporally controls late prophase I transcription and chromatin remodeling. *Nat. Comms.*, 10;7:12331. PMID:PMCID:PMC4987523..
- Liu, X., and Secombe, J#** (2015) KDM5 recognizes chromatin context to activate genes essential for mitochondrial function. *Cell Reports*, 13, 2219-2231.
- Liu, X., Greer, C., and Secombe, J#** (2014). KDM5 interacts with Foxo to modulate cellular levels of oxidative stress. *PLoS Genetics*, 10(10):e1004676.

MILAN SEN, M.D., C.M.

Hip fractures represent a major cause of morbidity and mortality among the elderly population, with a 1-year mortality rate estimated to be 30%. This rate has remained stable in the literature over the past 40 years. To date, efforts to develop a biological measure of mortality risk in this population have not resulted in meaningful methods of risk assessment, nor have they elucidated novel areas of potential intervention aimed at mortality reduction.

The purpose of my current research with Professor Vijg is to establish a predictive relationship between pre-operative DNA methylation levels in the blood, and post-operative mortality in the geriatric hip fracture population. We hypothesize that in geriatric patients with an isolated acute hip fracture, elevated pre-operative DNA methylation levels will be associated with a higher risk of all-cause mortality at 1 year follow-up. If we are able to identify the high risk group using the DNA methylation clock, we hope to study a targeted pharmacological intervention in this select group.

Selected Publications:

- Z Sharfman, A Parsikia, TN Rocker, MD Kahn, S Sokol, ME Stone Jr., J McNelis, MK Sen, A Dimitroulias. Increased Morbidity and Mortality in Elderly Patients with Lower Extremity Trauma and Associated Injuries: A Review of 420,066 Patients from the National Trauma Database. *Injury*, 2021 Apr;52(4):757-766
- R Yang, D Murphy, A Goch, J Wang, V Charubhumi, J Fox, M Sen, B Hoang, D Geller. A Novel Tripod Percutaneous Reconstruction Technique in Peri-Acetabulum Lesion Caused by Metastatic Cancer. *J Bone Joint Surg Am*. 2020 Apr 1;102(7):592-599
- WB Cohen-Levy, J Liu, M Sen, SH Teperman, ME Stone. Prophylactic Inferior Vena Cava Filters for Operative Pelvic Fractures: A 12 Year Experience. *Int Orthop*. 2019 Aug 7.
- MK Sen, N Sama, M Raglan, C Bircher, M Bircher, DL Helfet. Treatment of Acetabular Fractures in Adolescents. *Am J Orthop*. 2015 Oct;44(10):465-70.
- JM Aho, MK Sen, M Saint-Cyr. Free and Pedicle Flaps in Lower-Extremity Trauma. *Eur. J Plast Surg*, June 2015, Vol. 38, No. 3:171-182.
- MR Brinker, BD Hanus, M Sen, DP O'Connor. The Devastating Effects of Tibial Nonunion on Health-Related Quality of Life. *J Bone Joint Surg Am*. 2013 Dec 18;95(24):2170-6.
- Kang Y, Scully A, Young DA, Kim S, Tsao H, Sen M, Yang Y. Enhanced mechanical performance and biological evaluation of a PLGA coated β -TCP composite scaffold for load-bearing applications. *Eur Polym J*. 2011 Aug 1;47(8):1569-1577.

FRANK SOLDNER, M.D.

Novel approaches to investigate the genetic, cellular, and molecular basis of complex neurological disorders

Our laboratory focuses on modeling human brain development and function in a cell culture dish to understand the molecular and cellular basis of complex disorders such as Parkinson's and Alzheimer's disease. A significant challenge of studying complex human diseases is the lack of relevant model systems that combine known genetic elements with disease-associated phenotypic readouts. This is particularly problematic for sporadic neurodegenerative diseases that have no well-defined genetic etiology and do not follow Mendelian inheritance patterns. Epidemiology and population genetics suggest that such diseases result from a complex interaction between multiple risk factors, both genetic and non-genetic (lifestyle and environmental). Although genome wide association studies (GWAS) have identified genomic variations, such as single nucleotide polymorphisms (SNPs), deletions, and insertions associated with a higher risk to develop specific neurological disorders, the vast majority of such sequence variants have no established biological relevance to disease or clinical utility to prognosis or treatment.

Three major recent innovations have fundamentally changed our ability to study human neurological disorders in a cell culture dish: (i) Reprogramming of somatic cells into human induced pluripotent stem cells (hiPSCs) to generate patient-derived disease-relevant neuronal cells, (ii) the development of genome engineering technologies such as the CRISPR/Cas9 system to modify the genome in human cells, and (iii) the availability of tissue-type and disease-specific genome-scale genetic and epigenetic information. Our previous work demonstrated that an interdisciplinary approach, integrating these technologies, enables us to study neurological disorders in a genetically controlled and systematic manner in human neuronal cells. Using these previously unavailable molecular and cellular tools, we were able to dissect the functional role of disease-associated sequence variations in non-coding regulatory elements such as distal enhancer sequences in the pathogenesis of Parkinson's disease. My lab is extending this novel experimental framework in human pluripotent stem cell (hPSC)-derived two-dimensional (2D) monolayer and three-dimensional (3D) organoid neuronal culture systems to systematically investigate the genetic, cellular, and molecular basis of neurodegenerative disorders. We are establishing robust disease-relevant phenotypic readouts to perform unbiased compound and CRISPR/Cas9-based genome-scale genetic screens and will exploit these approaches to understand how genetic, epigenetic, and environmental factors contribute to the development and progression of neurological diseases.

Selected publications

Soldner, F. & Jaenisch, R. Stem Cells, Genome Editing, and the Path to Translational Medicine. *Cell*, 175, 615-632 (2018)

Soldner, F., Stelzer, Y., Shivalila, C. S., Abraham, B. J., Latourelle, J. C., Barrasa, M. I., Goldmann, J., Myers, R. H., Young, R. A. & Jaenisch, R. Parkinson-associated risk variant in distal enhancer of α -synuclein modulates target gene expression. *Nature* 533, 95–99 (2016).

Soldner, F., Laganière, J., Cheng, A. W., Hockemeyer, D., Gao, Q., Alagappan, R., Khurana, V., Golbe, L. I., Myers, R. H., Lindquist, S., Zhang, L., Guschin, D., Fong, L. K., Vu, B. J., Meng, X., Urnov, F. D., Rebar, E. J., Gregory, P. D., Zhang, H. S. & Jaenisch, R. Generation of Isogenic Pluripotent Stem Cells Differing Exclusively at Two Early Onset Parkinson Point Mutations. *Cell* 146, 318–331 (2011).

Soldner, F.*, Hockemeyer, D.*, Beard, C., Gao, Q., Bell, G. W., Cook, E. G., Hargus, G., Blak, A., Cooper, O., Mitalipova, M., Isacson, O. & Jaenisch, R. Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. *Cell* 136, 964–977 (2009).

Hockemeyer, D.*, Soldner, F.*, Beard, C., Gao, Q., Mitalipova, M., Dekelver, R. C., Katibah, G. E., Amora, R., Boydston, E. A., Zeitler, B., Meng, X., Miller, J. C., Zhang, L., Rebar, E. J., Gregory, P. D., Urnov, F. D. & Jaenisch, R. Efficient targeting of expressed and silent genes in human ESCs and iPSCs using zinc-finger nucleases. *Nat Biotechnol* 27, 851–857 (2009).

Hockemeyer, D.*, Soldner, F.*, Cook, E. G., Gao, Q., Mitalipova, M. & Jaenisch, R. A drug-inducible system for direct reprogramming of human somatic cells to pluripotency. *Cell Stem Cell* 3, 346–353 (2008).

(* Equally contributing authors)

Epigenetic Variability and Functional Impact on Gene Regulation in the Lung

The goal of the Spivack laboratory is to understand differences in gene regulation in the lung among individuals, using genetic and epigenetic techniques. The mechanistic goal is to understand the subtleties of how specific high-resolution patterns of DNA methylation and microRNA expression regulate gene expression. We have developed several new functional genetic technologies to examine epigenetic function. We have recently completed initial genome-wide searches of the transcriptome, methylome, and microRNAome of lung cancers, and recently of epithelial progenitor cells that give rise to lung cancers. The translational goal is to use these functionally sifted epigenetic, genetic (and metabolomic and proteomic) features, and detect them non-invasively, to identify individuals at particularly high risk for lung cancer and other common lung disorders (asthma/COPD), to enhance prevention and early detection efforts for each disorder.

Mechanistically, the role of promoter sequence and epigenetic variation in the regulatory region of carcinogenesis and oxidant pathway genes is being explored *in vitro*. We've developed techniques in the lab, such as human genomic methyl-DNA reporter constructs, and now CAS9-based methylome writing, in addition to studying native gene regulation models. Unique technologies include the laboratory's microRNA:mRNA binding assay, and modelling the functional consequence of DNA methylation patterns reproduced in reporter constructs, and in native chromatin.

Translationally, epigenetic and other biomarkers are being established in laser capture microdissected human lung and several unique, non-invasively collected surrogate specimens developed in the laboratory, such as mRNA expression signatures from brush-exfoliated buccal mucosa cells, and microRNA, analyses from exhaled breath condensate, which are first reports for a new airway biomarker class. These airway-derived specimens continue to accrue from our sampling (currently n>1000) of a lung cancer case-control study. The specimens are being studied for quantitative gene expression, and their regulatory substrates listed above, in multiple pathways. These expression, genetic, and epigenetic data are being linked to put a real metric to gene-environment interaction.

Selected Recent Publications/Manuscripts:

Batbayar Khulan, Kenny Ye, Spencer Waldman, Ava Marsh, Miao Kevin Shi, Taha Siddiqui, Will Liao (NYGC), Masako Suzuki, Aditi Desai, Dhruv Patel, Jaiminkumar Patel, Jay Dobkin, Ali Sadoughi, Chirag Shah, Jan Vijg, Yakov Peter, Simon D. Spivack. Bronchial field progenitor basal cells show methylome-wide signatures reflective of smoking status of the donor. [*submission fall 2022*]

Shi M, Han W, Loudig O, Shah C, Dobkin J, Keller S, Sadoughi A, Patel D, Desai A, Gombar S, Suh Y, Fernandez MK, DeLaRosa L, Wang T, Hosgood D, Pradhan K, Ye K, Spivack SD. (2022) An exhaled microRNA panel interrogated for lung cancer case-control discrimination. [*submitted*].

Zhenqiu Huang, Alex Maslov, Xiao Dong, Shixiang Sun, Moonsook Lee, Chirag Shah, Ali Sadoughi, Aditi Desai, Dhruv Patel, Taha Siddiqui, Jaiminkumar Patel, Miao Shi, Spencer Waldman, Ava Marsh, Yakov Peter, *Simon D Spivack, *Jan Vijg (*co-senior authors). Somatic Mutations At Single Base Resolution in Single Bronchial Progenitor Cells Collected From Human Lung. [*Nature Genetics*, 022 Apr;54(4):492-498. doi: 10.1038/s41588-022-01035-w. Epub 2022 Apr 11].

Cleven KL, Ye K, Zeig-Owens R, Hena KM, Montagna C, Shan J, Hosgood HD 3rd, Jaber N, Weiden MD, Colbeth HL, Goldfarb DG, Spivack SD++, Prezant DJ++ (++)co-senior authors). Genetic Variants Associated with FDNY WTC-Related Sarcoidosis. *Int J Environ Res Public Health*. 2019 May 23;16(10). pii: E1830. doi: 10.3390/ijerph16101830. PMID:31126090.

Dong X, Shi M, Lee M, Toro R, Gravina S, Han W, Yasuda S, Vijg J, Suh Y, Spivack SD. Global, integrated analysis of methylomes and transcriptomes from laser capture microdissected bronchial and alveolar cells in human lung. [*Epigenetics*, 10.1080/15592294.2018.1441650 2018].

Mullapudi N, Ye B, Suzuki M, Fazzari M, Han W, Shi M, Marquardt G, Lin J, Wang T, Keller S, Zhu C, Locker J, Spivack SD. (2015) Genome-wide methylome alterations in lung cancer. *PLoS ONE* 18;10(12):e0143826. PMID:26683690.

Lin J, Marquardt G, Mullapudi N, Wang T, Han W, Shi M, Keller S, Zhu C, Locker J, Spivack SD. Lung cancer transcriptomes refined with laser capture microdissection. *Am J Pathol* 06.028. PMID25128906, 2014.

Han W, Shi M, Spivack SD. Site-specific methylated reporter constructs for functional analysis of DNA Methylation. *Epigenetics*. 4;8(11). PMID: 24004978, 2013.

Shi M, Han W, Spivack SD. A quantitative method to identify microRNAs that target a messenger RNA using a 3'UTR RNA affinity technique *Anal. Biochem*. 1;443(1):1-12. PMID: 23938772, 2013.

YOUSIN SUH, Ph.D.

Functional Genomics of Aging

We have been taking human genetics and functional genomics approaches to understand the fundamental mechanisms of aging in humans. Aging is the single largest risk-factor for most chronic diseases such as Alzheimer's disease, cancer, cardiovascular disease, and type 2 diabetes and is emerging as a major component in basic, translational and clinical research. Our long-term research goals are to investigate the (epi)genetic component that underlies the interface of intrinsic aging and disease. To gain insight into the (epi)genetic link between aging and disease, we focus on the identification of functional (epi)genetic variation in human populations and the assessment of their potential functional impact on aging and disease. We take an integrated approach to study the connection between disease and aging at different levels, i.e., from (epi)genetic determinants in the form of (epi)genetic variants, through cell type- and tissue-specific regulated gene expression, to molecular and cellular endpoints in the tissues, leading to new targets for interventions as well as (epi)genetic markers for aging and its associated diseases. To achieve translation of genetic association into clinical benefits, it is critical to assess the functional impact of associated (epi)genetic variants. Such functionalization of observed associations is now the main knowledge gap in human disease genetics.

To discover functional (epi)genetic variants associated with aging or diseases of aging, we have been conducting systematic multidisciplinary studies of human genetic data from whole genome sequencing (WGS), whole exome sequencing (WES), and genome wide association studies (GWAS), which are prioritized through integrative analyses of human genetic, functional genomic, and epigenomic data. We then use the paradigm of CRISPR/Cas9-mediated genome engineering of human pluripotent stem cells followed by differentiation of the genome-edited stem cells into multiple cell lineages in order to elucidate cell type-specific and combinatorial effects of functional variants. For top candidate functional variants, we generate mouse models to understand their in vivo roles in aging and aging-related diseases. Our approach is unique and important because it ascertains the biological significance and the causality of human genetic association data, uncovering the fundamental mechanisms underlying human aging and potential targets for intervention against aging.

We have relocated to Columbia University in the Departments of OB/GYN and Genetics & Development as of October 1, 2019. Dr. Suh leads a new program on Reproductive Aging and Women's Health with the goal of bridging basic aging biology and clinical medicine. While the female reproductive system is the first to age in the human body, very little is known about the basic biology of reproductive aging. We are leveraging our expertise in human genetics, functional genomics, molecular and cellular biology, and stem cell engineering to address key unanswered questions on reproductive aging in women. We focus on how the fundamental biology of aging influences reproductive aging and its sequelae in women and if geroprotectors can delay their onset and progression.

Selected Publications:

Suh, Y., Atzmon, G., Cho, M.-O., Hwang, D., Liu, B., Barzilai, N., Cohen, P. Functional insulin-like growth factor-I receptor mutations in centenarians. *Proc. Natl. Acad. Sci.* 105: 3438-3442. 2008.

G. Atzmon, M. Cho, R.M. Cawthon, T.. Budagov, M. Katz, X. Yang, G. Siegel, A. Bergman, D.M. Huffman, C.B. Schechter, W.E. Wright, J.W. Shay, N. Barzilai, D.R. Govindaraju, and **Y. Suh**. Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians. *Proc. Natl. Acad. Sci.* 107 Suppl(1):1710-1717. 2010

Tazearslan, C., Huang, J., Barzilai, N., and **Suh, Y.** Impaired IGF1R signaling in cells expressing longevity associated human IGF1R alleles. *Aging Cell.* 10(3):551-4. 2011

Suh, Y. and Kennedy, B.K. Dialing down SUN1 for laminopathies. *Cell.* 149(3):509-10. 2012

Park, C., **Suh, Y***, and Cuervo*, A.C. Regulated degradation of Chk1 by chaperone-mediated autophagy in response to DNA damage. *Nature Communications.* 6:6823. 2015.

Johnson, S.C., Dong, X., Vijg, J., **Suh, Y.** Genetic evidence for common pathways in human age-related diseases. *Aging Cell.* 4(5):809-17. 2015

Lau CH, **Suh Y.** In vivo epigenome editing and transcriptional modulation using CRISPR technology. *Transgenic Research.* PMID: 30284145. 2018

Ryu, S., Han, J., Norden-Krichmar, T., Zhang, Q., Lee, S., Zhang, Z., Atzmon, G., Niedernhofer, L.J., Robbins, P.D., Barzilai, N., Schork, N.J., **Suh, Y.** Genetic signature of human longevity in PKC and NF- κ B signaling. *Aging Cell* e13362. 2021

Jin, C, Wang, X., Hudgins, AD, Gamliel, A, Pei, M, Kim, S, Contreras, D, Hoeijmakers, J, Campisi, J, Lobo, RA, Williams, SZ, Rosenfeld, MG, **Suh, Y.** The regulatory landscapes of human ovarian ageing. 2022.
<https://www.biorxiv.org/content/10.1101/2022.05.18.492547v1> (Preprint)

MASAKO SUZUKI, D.V.M., Ph.D.

Long-term memory of adverse prenatal micronutrient environment of offspring

The long-term research goal of the Suzuki lab is to identify mechanisms of how the offspring memorize their environmental exposure status throughout life. The health conditions of the mother during pregnancy critically contribute to the pregnancy outcome as well as the health of the baby. It has been reported that adverse intrauterine environment exposure is associated with susceptibility to many diseases such as cardiovascular diseases, asthma, diabetes, and obesity. Therefore, health throughout the life of the baby would be attributed to the health of the mother during pregnancy. However, the mechanisms of how the adverse prenatal environment causes long-term effects of offspring, which increases the risk of disease later in life, is not elucidated.

Our research focuses on the effects of in utero micronutrient deficiencies on cell subtype proportions and cell memory in offspring, and the association with developing diseases later in life. We hypothesize that this adverse prenatal exposure changes the repertoire of cell subtypes that comprise the mature organs of offspring that confers much of the risk of developing the disease phenotype. We believe this will open a new paradigm for epigenetic studies of the Developmental Origins of Health and Diseases (DOHaD).

In our community, we have many understudied populations prone to these micronutrient deficiencies. For instance, vitamin D deficiency/insufficiency is much higher in Hispanic (23%) and Black (non-Hispanic) populations (46%) than White (non-Hispanic) subjects (6.6%). Moreover, while the current national prevalence rate of vitamin A deficiency in the United States is reported to be very low (<1%), our recent study in the Bronx showed close to 60% of Hispanic pregnant females we studied were vitamin A deficient (Suzuki et al., *Nutrients* 2021).

We are currently studying the effects of fat-soluble micronutrients, vitamins A and D, deficiency during development on offspring as this may be informative for our community. The prenatal vitamin A deficiency project focuses on identifying the molecular mechanisms of how prenatal vitamin A deficiency status alters the pulmonary disease risks in adulthood (R01, PI Suzuki, NHLBI). The prenatal vitamin D deficiency project focuses on the molecular mechanism of how prenatal deficiency conditions affect the hematopoiesis of the offspring in adulthood. In addition, we are expanding our research interest to macro and micronutrient imbalance (hidden hunger).

Select Publications:

Lundy K, Greally JF, Essilfie-Bondzie G, Olivier JB, Doña-Termine R, Greally JM, **Suzuki M***. Vitamin D deficiency during development permanently alters liver cell composition and function. *Frontiers Endocrinology* 2022 May 12; 13:860286. PMID: 35634491

Suzuki M*, Tomita M. Genetic Variations of Vitamin A-Absorption and Storage-Related Genes, and Their Potential Contribution to Vitamin A Deficiency Risks Among Different Ethnic Groups. *Front Nutr.* 2022; 9:861619. Review. PMID: 35571879

Cwiek A, **Suzuki M**, deRonde K, Conaway M, Bennett KM, El Dahr S, Reidy K, Charlton JR. Premature differentiation of nephron progenitors and dysregulation of gene pathways critical to kidney development in a model of preterm birth. *Scientific Reports.* 2021 Nov 4;11(1):21667. DOI: 10.1038/s41598-021-00489-y. PMID: 34737344

Suzuki M*, Wang T, Garretto D, Isasi CR, Cardoso WV, Greally JM, Quadro L. Disproportionate Vitamin A Deficiency in Women of Specific Ethnicities Linked to Differences in Allele Frequencies of Vitamin A-Related Polymorphisms. *Nutrients.* 2021; 13(6):1743.

Kong Y, Rastogi D, Seoighe C, Greally JM, **Suzuki M***. Insights from deconvolution of cell subtype proportions enhance the interpretation of functional genomic data. *PLOS ONE.* 2019 14: e0215987. PMID: 31022271.

*corresponding authors

ANNE VAN ARSDALE, M.D./Ph.D.

Pathogenic role of Human Papillomavirus (HPV) DNA integration in HPV-associated dysplasias and carcinomas

Infection with high-risk Human Papillomavirus (hrHPV) is a necessary, key event in cervical carcinoma. A major advance in understanding cervical cancer was the recognition that HPV DNA is integrated into the human genome in almost all advanced cervical tumors. Human genome integration of HPV DNA 1) stably associates the viral oncogenes with a host cell, 2) potentially drives expression of host oncogenes that flank the sites of HPV DNA insertions, and 3) also causes human genome rearrangements. Cervical cancer develops through a series of progressive, dysplastic lesions termed cervical intraepithelial neoplasia (CIN1 through CIN3) that occur within the epithelial cells at the surface of the cervix. Interestingly, premalignant lesions in the vast majority of HPV infected women, including most high-grade lesions, do not progress to fully invasive carcinomas. Current clinical management of cervical cancer relies on early detection of premalignant lesions when treatment can be highly effective at preventing cancer, but entails high morbidity risks, causes significant anxiety, and incurs substantial financial costs. In collaborations with Dr. Cristina Montagna (CINJ), Dr. Jack Lenz (Albert Einstein) and Dr. Brian Haas (The Broad Institute/MIT), we have developed a research program to detect and map HPV-human DNA junctions at single nucleotide resolution using a hybridization capture and next generation sequencing approach along with a comprehensive bioinformatics pipeline that is now generalizable to any virus that causes oncogenesis. Current research efforts and key issues being addressed include: harnessing the unique molecular signatures of individual integration sites as personalized biomarkers in dysplasia and carcinoma, evaluation of integration sites in patient-derived histologic samples, and the evaluation of molecular, functional and spatio-temporal consequences of HPV integration on clonal expansion.

References:

Van Arsdale A, Patterson N, Maggi E, Agoni L, Van Doorslaer K, Harmon B, Nevadunsky N, Kuo DSY, Einstein MH, Lenz J and Montagna C. Insertional oncogenesis by HPV70 revealed by multiple genomic analyses in a clinically HPV-negative cervical cancer. *Genes Chromosomes Cancer*. 2020 Feb; 59(2): 84–95.

Engineering fluorescent proteins, biosensors and optogenetic tools

Non-invasive optical imaging, monitoring and manipulation of metabolic processes in living mammals is more feasible within the near-infrared (NIR) optical transparency window (650-900 nm) where hemoglobin and melanin absorbance significantly decreases, and water absorbance is still low. The most red-shifted fluorescent proteins (FPs) of the GFP-like family have excitation and emission spectra outside of the NIR region and suffer from low brightness and modest photostability. Natural bacterial phytochrome photoreceptors (BphPs) utilize an enzymatic product of heme, low-molecular-weight biliverdin, as a chromophore.

BphPs provide many advantages over other natural chromophore-containing proteins. Unlike the chromophores of non-bacterial phytochromes, biliverdin is ubiquitous in mammals. This makes BphP applications in mammalian cells, tissues and whole mammals as easy as conventional GFP-like FPs, without supplying chromophore through an external solution. BphPs exhibit NIR absorbance and fluorescence, which are red-shifted relative to that of any other phytochromes, and lie within the NIR optical window. This makes BphPs spectrally complementary to other existing optical probes and optogenetic tools based on the GFP, flavoprotein and rhodopsin-like protein families. Independent domain architecture and pronounced conformational changes upon biliverdin photoisomerization make BphPs attractive templates to design various photocontrollable genetically-encoded probes.

In our laboratory, we engineer new BphP-based FPs, biosensors and optogenetic tools. These include bright and spectrally resolvable permanently fluorescent NIR FPs, photoactivatable with non-phototoxic NIR light FPs, and reversibly photoswitchable FPs. We also focus on designing NIR reporters for protein interactions and biosensors for intracellular ions and metabolites. Lastly, we engineer BphPs into optogenetic elements allowing us to noninvasively regulate intracellular processes *in vivo* with NIR light.

We apply various directed protein evolution approaches based on rational structure-based design and random mutagenesis of template BphPs, high-throughput flow cytometry and multiwell plate spectroscopy. These conventional techniques allow screening for standard properties of genetically encoded probes, such as excitation and emission wavelengths, brightness, photostability, pH stability and folding efficiency. We also develop new protein engineering and high-throughput approaches to specifically optimize BphP-based constructs. These include time-resolved fluorescence lifetime measurements, expression in bacterial periplasmic space, screening of mutant libraries in yeast and mammalian cells using shuttle vectors and inducible somatic hypermutations.

The resulting NIR probes and molecular tools are tested in mouse models and applied to various *in vivo* studies. These NIR constructs extend optical methods to multicolor deep-tissue imaging, cell and tissue labeling, photoactivation and tracking, and detection of enzymatic activities and protein interactions in cells, tissues and whole mammals. The NIR optogenetic tools allow light-manipulations of cellular processes directly through the skin of living animals.

Selected Publications

- Oliinyk O.S., Baloban M., Clark C.L., Carey E., Pletnev S., Nimmerjahn A., and Verkhusha V.V. Single-domain near-infrared protein provides a scaffold for antigen-dependent fluorescent nanobodies. ***Nature Methods* 2022**, 19: 740-750.
- Kasatkina L.A., Ma C., Matlashov M.E., Vu T., Li M., Kaberniuk A.A., Yao J., and Verkhusha V.V. Optogenetic manipulation and photoacoustic imaging using a near-infrared transgenic mouse model. ***Nature Communications* 2022**, 13: 2813.
- Shemetov A.A., Monakhov M.V., Zhang Q., Canton-Josh J.E., Kumar M., Chen M., Matlashov M.M., Li R., Yang W., Nie L., Shcherbakova D.M., Kozorovitskiy Ye., Yao J., Ji N., and Verkhusha V.V. A near-infrared genetically encoded calcium indicator for *in vivo* imaging. ***Nature Biotechnology* 2021**, 39: 368-377.
- Kaberniuk A.A., Baloban M., Monakhov M.V., Shcherbakova D.M. and Verkhusha V.V. Single-component near-infrared optogenetic systems for gene transcription regulation. ***Nature Communications* 2021**, 12: 3859.
- Manoilov K.Y., Verkhusha V.V., and Shcherbakova D.M. A guide to the optogenetic regulation of endogenous molecules. ***Nature Methods* 2021**, 18: 1027–1037.
- Redchuk T.A., Karasev M.M., Donnelly S.K., Hülsemann M., Virtanen J., Moore H.M., Vartiainen M.K., Hodgson L. and Verkhusha V.V. Optogenetic regulation of endogenous proteins. ***Nature Communications* 2020**, 11: 605.
- Matlashov M.E., Shcherbakova D.M., Alvelid J., Baloban M., Pennacchiotti F., Shemetov A.A., Testa I. and Verkhusha V.V. A set of monomeric near-infrared fluorescent proteins for multicolor imaging across scales. ***Nature Communications* 2020**, 11: 239.
- Leopold A.V., Chernov K.G., Shemetov A.A. and Verkhusha V.V. Neurotrophin receptor tyrosine kinases regulated with near-infrared light. ***Nature Communications* 2019**, 10: 1129.
- Yang J., Li L., Shemetov A.A., Lee S., Zhao Y., Liu Y., Shen Y., Li J., Oka Y., Verkhusha V.V., and Wang L.V. Focusing light inside live tissue using reversibly switchable bacterial phytochrome as a genetically encoded photochromic guide star. ***Science Advances* 2019**, 5: eaay1211.
- Oliinyk O.S., Shemetov A.A., Pletnev S., Shcherbakova D.M. and Verkhusha V.V. Smallest near-infrared fluorescent protein evolved from cyanobacteriochrome as a versatile tag for spectral multiplexing. ***Nature Communications* 2019**, 10: 279.
- Shcherbakova D.M., Cammer N.C., Huisman T.M., Verkhusha V.V. and Hodgson L. Direct multiplex imaging and optogenetics of Rho GTPases enabled by near-infrared FRET. ***Nature Chemical Biology* 2018**, 14: 591-600.
- Li L., Shemetov A.A., Baloban M., Hu P., Zhu L., Shcherbakova D.M., Zhang R., Shi J., Yao J., Wang L.V. and Verkhusha V.V. Small near-infrared photochromic protein for photoacoustic multi-contrast imaging and detection of protein interactions *in vivo*. ***Nature Communications* 2018**, 9: 2734.
- Redchuk T.A., Omelina E.S., Chernov K.G., and Verkhusha V.V. Near-infrared optogenetic pair for protein regulation and spectral multiplexing. ***Nature Chemical Biology* 2017**, 13: 633-639.

Genome Dynamics in Aging

Aging is a universal process that brings life to a close at a rate that is specific for the species. In humans, life span has a limit of about 115 years. One process that has been implicated as a causal factor in the aging process is genome instability. Exactly how loss of genome integrity in normal somatic cells may lead to tissue degeneration, functional decline and increased risk of diseases, such as cancer, remains unknown. The main challenge in this respect is the lack of technology to analyze various types of DNA mutations in normal somatic cells. In the past we developed transgenic reporter systems in mouse and fruit fly, which allowed us to determine tissue-specific frequencies of various forms of genome instability, e.g., point mutations, deletions, translocations, as a function of aging. More recently, we developed new, single-cell whole genome sequencing methods to analyze these same types of mutations directly in normal cells. These and other methods, e.g., single-cell DNA methylomics and single-cell multi-omics, are now being used to comprehensively characterize the landscape of mutations and epimutations in relation to the aging process.

Selected Publications:

Bahar R, Hartmann CH, Rodriguez KA, Denny AD, Busuttill RA, Dollé MET, Calder RB, Chisholm GB, Pollock BH, Klein CA, Vijg J. Increased cell-to-cell variation in gene expression in aging mouse heart. *Nature* 2006;441:1011-1014.

Vijg J, Campisi J. Puzzles, promises and a cure for ageing. *Nature* 2008;454: 1065.

Gundry M, Li W, Maqbool SB, Vijg J. Direct, genome-wide assessment of DNA mutations in single cells. *Nucleic Acids Res.* 2012;40:2032-2040.

White RR, Milholland B, de Bruin A, Curran S, Laberge RM, van Steeg H, Campisi J, Maslov AY, Vijg J. Controlled induction of DNA double-strand breaks in the mouse liver induces features of tissue ageing. *Nat Commun.* 2015;6:6790.

Gravina S, Dong X, Yu B, Vijg J. Single-cell genome-wide bisulfite sequencing uncovers extensive heterogeneity in the mouse liver methylome. *Genome Biol.* 2016;17:150.

Dong X, Milholland B, Vijg J. Evidence for a limit to human lifespan. *Nature* 2016; 538:257–259. PMID:27706136.

Dong X, Zhang L, Milholland B, Lee M, Maslov AY, Wang T, Vijg J. Accurate identification of single-nucleotide variants in whole-genome-amplified single cells. *Nat Methods* 2017;14:491-493. PMC5408311

Zhang L, Dong X, Lee M, Maslov AY, Wang T, Vijg J. Single-cell whole-genome sequencing reveals the functional landscape of somatic mutations in B lymphocytes across the human lifespan. *Proc Natl Acad Sci USA* 2019;116:9014-9019. PMC650011

Brazhnik K, Sun S, Alani O, Kinkhabwala M, Wolkoff AW, Maslov AY, Dong X, Vijg J. Single-cell analysis reveals different age-related somatic mutation profiles between stem and differentiated cells in human liver. *Sci Adv.* 2020;6:eaax2659. PMC6994209

Vijg J, Dong X. Pathogenic Mechanisms of Somatic Mutation and Genome Mosaicism in Aging. *Cell* 2020;18:12-23.

Zhang L, Dong X, Tian X, Lee M, Ablaeva J, Firsanov D, Lee S-G, Maslov AY, Gladyshev VN, Seluanov A, Gorbunova V, Vijg J. Maintenance of genome sequence integrity in long- and short-lived rodent species. *Sci Adv* 2021;7:eabj3284. PMC8550225

Huang Z, Sun S, Lee M, Maslov AY, Shi M, Waldman S, Marsh A, Siddiqui T, Dong X, Peter Y, Sadoughi A, Shah C, Ye K, Spivack SD, Vijg J. Single-cell analysis of somatic mutations in human bronchial epithelial cells in relation to aging and smoking. *Nat. Genet.* 2022;54:492-498.

Lipid Metabolism and Lipid-related Metabolic Diseases

Professional Interests: Dr. Wang has an active research interest in the molecular and genetic mechanisms of cholesterol homeostasis and the pathophysiology of cholesterol-related metabolic diseases. The long-term objectives of his research are (i) to identify gallstone (*LITH*) genes and investigate their genotypes and phenotypes in mice and humans, as well as to elucidate the molecular, cellular, genetic and physical-chemical mechanisms of cholesterol gallstone disease at a fundamental level; (ii) to investigate molecular, cellular, genetic and physical-chemical factors determining intestinal absorption efficiency of cholesterol and fatty acids; and (iii) to study the pathophysiology of the metabolic syndrome with a special focus on the relationship between insulin resistance and nonalcoholic fatty liver disease, and to examine the pathogenesis of alcoholic liver disease and obesity, as well as to explore novel approaches for the prevention and the treatment of these lipid-related hepatobiliary and gastrointestinal diseases.

Selected Publications:

Wang DQ, Afdhal NH. Chapter 65. Gallstone disease. In Sleisenger and Fordtran's Gastrointestinal and Liver Disease, the 11th Edition. Editors by Feldman M, Friedman LS, Brandt LJ, Chung RT, Rubin DT, and Wilcox CM. Elsevier. 2021; 1016-1046.

Xu Y, Jadhav K, Li Y, Pan X, Zhu Y, Hu S, Chen S, Chen L, Tang Y, Wang HH, Yang L, **Wang DQ**, Yin L, Zhang Y. Hepatocyte ATF3 protects against atherosclerosis by regulating HDL and bile acid metabolism. *Nature Metabolism*. 2021; 3: 59-74.

Wei G, Cao J, Huang P, An P, Badlani D, Vaid KA, Zhao S, **Wang DQ**, Zhuo J, Yin L, Frassetto A, Markel A, Presnyak V, Gandham S, Hua S, Lukacs C, Finn PF, Giangrande PH, Martini PGV, Popov YV. Synthetic human ABCB4 mRNA therapy rescues severe liver disease phenotype in a BALB/c.Abc4^{-/-} mouse model of PFIC3. *Journal of Hepatology*. 2021; 74: 1416-1428.

Wang HH, de Bari O, Arnatt CK, Liu M, Portincasa P, **Wang DQ**. Activation of a novel estrogen receptor GPR30 enhances cholesterol cholelithogenesis in female mice. *Hepatology*. 2020; 71: 2077-2089.

Wang DQ, Portincasa P (Editors). Gallstones: Recent advances in epidemiology, pathogenesis, diagnosis and management. The first edition. Nova Science Publishers. New York, NY. 2017. pp. 1-676.

Wang HH, Li X, Patel SB, **Wang DQ**. Evidence that the ABCG5/G8-independent pathway plays a determinant role in cholesterol gallstone formation in mice. *Hepatology*. 2016; 64: 853-864.

Portincasa P, **Wang DQ**. Chapter 89. Gallstones. In Yamada's Textbook of Gastroenterology, 2 Volume Set, 6th Edition. Editors by Podolsky DK, Camilleri M, Fitz JG, Kalloo AN, Shanahan F, Wang TC. Wiley-Blackwell. Hoboken, NJ. 2015; pp. 1808-1834.

Lammert F, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, **Wang DQ**. Gallstones. *Nature Review Disease Primers*. 2016; 2: 16024-16040.

Wang DQ, Cohen DE. Absorption and excretion of intestinal cholesterol and other sterols. In Clinical Lipidology: A Companion to Braunwald's Heart Disease. The 2nd Edition. Editor by Ballantyne CM. Elsevier Saunders. 2015; pp. 25-42.

de Bari O, Wang TY, Liu M, Portincasa P, **Wang DQ**. Estrogen induces two distinct cholesterol crystallization pathways by activating ER α and GPR30 in female mice. *Journal of Lipid Research*. 2015; 56: 1691-1700.

Wang HH, Portincasa P, Afdhal NH, **Wang DQ**. *Lith* genes and genetic analysis of cholesterol gallstone formation. *Gastroenterol. Clin. North Am.* 2010; 39: 185-207.

Wang HH, Portincasa P, Mendez-Sanchez N, Uribe M, **Wang DQ**. Effect of ezetimibe on the prevention and dissolution of cholesterol gallstones. *Gastroenterology*. 2008; 134: 2101-2110.

TAO WANG, Ph.D.

Statistical Genetics and Genomics

The research field of my group is statistical genetics and genomics, with a strong focus on the analysis of genetic and genomic data from large-scale population based studies. Our research is focused on two highly related areas: the development of statistical genetics/genomics methodology and the application of statistical genetics/genomics methods to understand the complex genetic basis of common human diseases. Specifically, we are interested in developing statistical methods for multi-locus association analysis, multivariate genetic association analysis, family-based genetic association analysis, gene-gene and gene-environment analysis, genetic meta-analysis, and the estimation of genetic heritability and co-heritability between traits. Moreover, we have collaborated with scientists in many genetic/epigenetic studies of a variety of diseases, which include but are not limited to, congenital heart defects, aging, autism, cardiovascular diseases and cancers.

Recent publications:

Wang T, Lin CY, Rohan TE, Ye K. Resequencing of pooled DNA for detecting disease associations with rare variants. *Genetic epidemiology*. 2010; 34(5):492-501. NIHMSID: NIHMS587140 PubMed [journal] PMID: 20578089, PMCID: PMC4096227

Wang T, Pradhan K, Ye K, Wong LJ, Rohan TE. Estimating allele frequency from next-generation sequencing of pooled mitochondrial DNA samples. *Frontiers in genetics*. 2011; 2:51. PubMed [journal] PMID: 22303347, PMCID: PMC3268604

Wang T, Rohan TE, Gunter MJ, Xue X, Wactawski-Wende J, Rajpathak SN, Cushman M, Strickler HD, Kaplan RC, Wassertheil-Smoller S, Scherer PE, Ho GY. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2011; 20(5):971-7. NIHMSID: NIHMS279677 PubMed [journal] PMID: 21415362, PMCID: PMC3096873

Ahn S, Wang T. A powerful statistical method for identifying differentially methylated markers in complex diseases. *Pacific Symposium on Biocomputing*. Pacific Symposium on Biocomputing. 2013; :69-79. NIHMSID: NIHMS441925 PubMed [journal] PMID: 23424113, PMCID: PMC3621641

Wang T, Zhou B, Guo T, Bidlingmaier M, Wallaschofski H, Teumer A, Vasani RS, Kaplan RC. A robust method for genome-wide association meta-analysis with the application to circulating insulin-like growth factor I concentrations. *Genetic epidemiology*. 2014; 38(2):162-71. NIHMSID: NIHMS592219 PubMed [journal] PMID:24446417, PMCID: PMC4049273

Guo T, Chung JH, Wang T, McDonald-McGinn DM, Kates WR, Hawula W, Coleman K, Zackai E, Emanuel BS, Morrow BE. Histone Modifier Genes Alter Conotruncal Heart Phenotypes in 22q11.2 Deletion Syndrome. *American journal of human genetics*. 2015; 97(6):869-77. PubMed [journal] PMID: 26608785, PMCID: PMC4678435

Agalliu I, Wang T, Burk RD. β - and γ -Human Papillomavirus Types and Smoking in Head and Neck Cancer-Reply. *JAMA oncology*. 2016; 2(5):687-8. PubMed [journal] PMID: 27244681

Loudig O, Wang T, Ye K, Lin J, Wang Y, Ramnauth A, Liu C, Stark A, Chitale D, Greenlee R, Multerer D, Honda S, Daida Y, Spencer Feigelson H, Glass A, Couch FJ, Rohan T, Ben-Dov IZ. Evaluation and Adaptation of a Laboratory-Based cDNA Library Preparation Protocol for Retrospective Sequencing of Archived MicroRNAs from up to 35-Year-Old Clinical FFPE Specimens. *International journal of molecular sciences*. 2017; 18(3). PubMed [journal] PMID: 28335433, PMCID: PMC5372640

Dong X, Zhang L, Milholland B, Lee M, Maslov AY, Wang T, Vijg J. Accurate identification of single-nucleotide variants in whole-genome-amplified single cells. *Nature methods*. 2017; 14(5):491-493. NIHMSID: NIHMS855609 PubMed [journal] PMID: 28319112, PMCID: PMC5408311

MELISSA WASSERSTEIN, Ph.D.

Clinical Research on Rare Genetic Disorders

As a clinical biochemical geneticist, my research focuses on optimizing the outcome of individuals with rare genetic disorders through expanded newborn screening, natural history studies, therapeutic clinical trials, and implementation of genomic diagnostics in diverse populations.

I am the Principal Investigator of ScreenPlus, the largest consented pilot newborn screening program in country. ScreenPlus will screen 175,000 consented infants for an additional 14 disorders on top of the routine newborn screening panel, utilizing a novel multi-tiered assay that may enhance accuracy, reduce false positives, and perhaps help with phenotypic severity prediction. ScreenPlus also includes an exploration of the ethical issues associated with newborn screening for complex conditions.

In addition, I have been studying the natural history of acid sphingomyelinase deficiency with a focus on defining endpoints for therapeutic clinical trials. We are now in clinical trial to assess the safety and effectiveness of recombinant human acid sphingomyelinase in adults with this rare disorder.

Another research interest is evaluating the implementation of genomic medicine in underserved populations through my role as an MPI in NYCKidSeq, a multi-site project in the CSER Consortium. In collaboration with partners at Mount Sinai and the New York Genome Center, NYCKidSeq is focused on implementing diagnostic whole genome sequencing in a diverse population of children with rare disorders, evaluating the utility of a novel educational tool for genetic counseling, and utilizing bioinformatic tools to allow improved diagnostic yield.

Selected Recent Publications

- **Wasserstein M**, Lachman R, Hollak C, Arash-Kaps L, Barbato A, Gallagher RC, Giugliani R, Guelbert NB, Ikezoe T, Lidove O, Mabe P, Mengel E, Scarpa M, Senates E, Tchan M, Villarrubia J, Chen Y, Furey S, Thurberg BL, Zaher A, Kumar M. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase (ASMD) in adults: One-year results. *Genet Med.* 2022 Jul;24(7):1425-1436.
- **Wasserstein MP**, Orsini JJ, Goldenberg A, Caggana M, Levy PA, Breilyn M, Gelb MH. The future of newborn screening for lysosomal disorders. *Neurosci Lett.* 2021 Jun 22;760:136080.
- Huizing M, Hackbarth ME, Adams DR, **Wasserstein M**, Patterson MC, Walkley SU, Gahl WA; FSASD Consortium, Adams DR, Dobrenis K, Foglio J, Gahl WA, Gasnier B, Hackbarth M, Huizing M, Lek M, Malicdan MCV, Paavola LE, Patterson MC, Reimer R, Walkley SU, Wasserstein M, Wang RY, Zoncu R. Mini-Review Free Sialic Acid Storage Disorder: Progress and Promise. *Neurosci Lett.* 2021 Apr 13:135896
- Pearson NM, Stolte C, Shi K, Beren F, Abul-Husn NS, Bertier G, Brown K, Diaz GA, Odgis JA, Suckiel SA, Horowitz CR, **Wasserstein M**, Gelb BD, Kenny EE, Gagnon C, Jobanputra V, Bloom T, Grealley JM. GenomeDiver: a platform for phenotype-guided medical genomic diagnosis. *Genet Med.* 2021 Jun 10.
- **Wasserstein M**, Dionisi-Vici C, Giugliani R, Hwu WL, Lidove O, Lukacs Z, Mengel E, Mistry PK, Schuchman EH, McGovern M. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). [Mol Genet Metab.](#) 2019 Feb;126(2):98-105
- Suckiel SA, Odgis JA, Gallagher KM, Rodriguez JE, Watnick D, Bertier G, Sebastin M, Yelton N, Maria E, Lopez J, Ramos M, Kelly N, Teitelman N, Beren F, Kaszemacher T, Davis K, Laguerre I, Richardson LD, Diaz GA, Pearson NM, Ellis SB, Stolte C, Robinson M, Kovatch P, Horowitz CR, Gelb BD, Grealley JM, Bauman LJ, Zinberg RE, Abul-Husn NS, **Wasserstein MP**, Kenny EE. GUÍA: a digital platform to facilitate result disclosure in genetic counseling. *Genet Med.* 2021 Feb 2.

DANIEL A. WEISER, MD

Childhood Cancer Translational Research

Our laboratory is focused on childhood cancer research with a goal of elucidating the underlying biology of the most aggressive malignancies. In such patients with typically incurable cancer, we are striving to identify new approaches to and types of treatment. We have multiple ongoing projects:

+ Identification of biologic drivers of neuroblastoma at ultra-high risk for treatment failure. Neuroblastoma is one of the most common and deadly childhood cancers. Despite intensive research, there are limited therapeutic strategies for patients with *de novo* chemotherapy resistance that leads to particularly poor outcomes. We have been studying neuroblastoma since 2009 and are identifying additional biologic drivers of highly lethal tumors. We assess features (genetic, transcriptomic, proteomic, histologic) from patients with early death from tumor progression compared with tumor features from those with a maintained complete response. This guides our workup of potential oncogenic targets and discovery of novel therapies for patients, including selinexor, a pharmacologic Exportin-1 (XPO1) inhibitor that limits nuclear export of key regulatory proteins in cancer cells.

+ Evaluation of novel combinatorial targeted therapeutic approaches in neuroblastoma. With expected outcomes lagging behind those of more common childhood cancers, children with neuroblastoma require new approaches to treatment. Our lab works with multiple international clinical and research consortium groups to perform preclinical studies that substantiate human clinical trials.

+ Repurposing of tenofovir, a reverse transcriptase inhibitor used in HIV, for treatment of neuroblastoma. We are exploring novel ways to target telomerase, the enzyme that maintains telomere length, for treatment of the most highly aggressive neuroblastoma. We are recruiting a post-doc to take the lead on this work and build upon our exciting preliminary data.

+ Detection of circulating tumor DNA in osteosarcoma. With no reliable non-invasive approach for disease monitoring during and after treatment, we are applying next-generation sequencing and bioinformatics approaches to identify solid tumors with blood-based “liquid” biopsies. This will allow clinicians to assess tumor responsiveness to chemotherapy and predict likelihood of recurrence.

+ Prevention of cisplatin-induced ototoxicity in children with cancer. Chemotherapy has many untoward effects on healthy cells, and sensorineural hearing loss can be severely debilitating. We have developed a proprietary acetophenone compound that provides otoprotection without compromising the anti-tumor activity of cisplatin, a commonly used chemotherapeutic. Pre-clinical testing is ongoing.

Lab website: <https://sites.google.com/view/weiserlab/>

Select publications:

- Galinski B, Luxemburg M, Landesman Y, Pawel B, Johnson KJ, Master SR, Freeman KW, Loeb DM, Hebert JM, **Weiser DA**. [XPO1 inhibition with selinexor synergizes with proteasome inhibition in neuroblastoma by targeting nuclear export of IκB](#). *Translational Oncology*. 2021 May 8;14(8):101114. PMID 33975179.
- Niazi MKK, Chung JH, Heaton-Johnson KJ, Martinez D, Castellanos R, Irwin M, Master S, Pawel BR, Gurcan MN, **Weiser DA**. [Advancing clinicopathologic diagnosis of high-risk neuroblastoma using computerized image analysis and proteomic profiling](#). *Pediatric and Developmental Pathology*. 2017 Sep-Oct;20(5):394. PMID 28420318.
- Bresler SC*, **Weiser DA***, Huwe PJ*, Park JH, Krytska K, Ryles H, Laudenslager M, Rappaport EF, Wood AC, McGrady PW, Hogarty MD, London WB, Radhakrishnan R, Lemmon MA, Mossé YP. [ALK mutations confer differential oncogenic activation and sensitivity to ALK inhibition therapy in neuroblastoma](#). *Cancer Cell*. 2014 Nov 10;26(5):682-94. PMID: 25517749.
- Rybinski B, Wolinsky T, Brohl A, Moerdler S, Reed DR, Ewart M, **Weiser DA**. [Multifocal primary neuroblastoma tumor heterogeneity in siblings with co-occurring PHOX2B and NF1 genetic aberrations](#). *Genes, Chromosomes and Cancer*. 2020 Feb;59(2):119-124. PMID 31515834.
- Barris DM, Weiner SB, Dubin RA, Fremed M, Zhang X, Piperdi S, Zhang W, Maqbool S, Gill J, Roth M, Hoang B, Geller D, Gorlick R, **Weiser DA**. [Detection of circulating tumor DNA in osteosarcoma](#). *Oncotarget*. 2018 Jan 18;9(16):12695. PMID 29560102.
- Geohagen B, **Weiser DA**, Loeb DM, Nordstroem LU, LoPachin RM. [Enolate-forming compounds provide protection from platinum neurotoxicity](#). *Chemico-Biological Interactions*. 2020 Feb 1;317:108961. PMID 31978392.
- Rybinski B, Hosgood HD, Weiner SL, **Weiser DA**. [Preclinical metrics correlate with drug activity in phase II trials of targeted therapies for non-small cell lung cancer](#). *Frontiers in Oncology*. 2020 Nov 5; 10:587377. PMID 33251146.

ZHENG DONG ZHANG, Ph.D.

Computational and Systems Biology of Cancer Metastasis and Human Aging

With recent resource and technology development, biology has entered a new data-driven phase in the 21st century. The research interest of my lab is computational biology and bioinformatics, focusing on algorithm development, data integration, and software implementation. With the advent of new DNA sequencing technologies, it is a particularly challenging and exciting time now to do such computational work, as more and more biological data are being generated at an ever-accelerating speed.

Gene expression in living cells is under strict spatial and temporal control, and its dysregulation is the direct cause of many human diseases. The primary focus of research in my lab is gene expression and its regulation, for which we take an integrated approach to study the following aspects on the whole genome scale:

- Gene expression profiles
- Transcriptional regulation of gene expression
- Epigenetic mechanisms and long range control of gene expression
- Gene copy number variation

The biological systems currently under investigation are breast cancer metastasis and human aging.

- Breast cancer metastasis is a complex multi-step process during which tumor cells spread from the primary tumor mass to distant organs. To study the genetic and biochemical determinations of this deadly aspect of cancer progression, we analyze various microarray and sequencing profiles to discover its regulatory sub-networks, DNA binding of key regulators, and copy number variations during the progression. This research project is supported by a grant from NIH/NLM.
- For reasons significant to individuals and the society as a whole, human aging is of great interest not only to the academic community but also to medicine and the public in general. However, despite much research progress made over the years, it still remains a poorly understood biological process. To gain novel insights, we use a systems-biology approach to analyze aging-related genes in the context of biological networks. This research project is supported by a New Scholar Award from the Ellison Medical Foundation.

Lab web site: www.zdzlab.org

Recent Publications:

- MacArthur DG, Balasubramanian S, Frankish A, Huang N, Morris J, Walter K, Jostins L, Habegger L, Pickrell JK, Montgomery SB, Albers CA, Zhang ZD, et al** (2012) A systematic survey of loss-of-function variants in human protein-coding genes. *Science*, **335**:806-807.
- Zhang ZD, Du J, Lam H, Abyzov A, Urban A, Snyder M, Gerstein M** (2011) Identification of genomic indels and structural variations using split reads. *BMC Genomics*, **12**:375.
- Zhang ZD, Gerstein MB** (2010) Detection of copy number variation from array intensity and sequencing read depth using a stepwise Bayesian model. *BMC Bioinformatics*, **11**:539
- Zhang ZD, Frankish A, Hunt T, Harrow J, Gerstein M.** (2010) Identification and analysis of unitary pseudogenes: historic and contemporary gene losses in humans and other primates. *Genome Biol.*, **11**, R26
- Du J, Bjornson RD, Zhang ZD, Kong Y, Snyder M, Gerstein MB.** (2009) Integrating Sequencing Technologies in Personal Genomics: Optimal Low Cost Reconstruction of Structural Variants. *PLoS Comput Biol.*, **5**, e1000432.
- Zhang ZD, Nayar M, Ammons D, Rampersad J, Fox GE.** (2009) Rapid in vivo exploration of a 5S rRNA neutral network. *J. Microbiological Methods*, **76**, 181-187.
- Zhang ZD, Cayting P, Weinstock G, Gerstein M.** (2008) Analysis of Nuclear Receptor Pseudogenes in Vertebrates: How the Silent Tell Their Stories. *Mol Biol Evol.*, **25**, 131-143.
- Zhang ZD, Weinstock G, Gerstein M.** (2008) Rapid Evolution by Positive Darwinian Selection in T-Cell Antigen CD4 in Primates. *J. Mol. Evol.*, **66**, 446-456.
- Zhang ZD, Rozowsky J, Snyder M, Chang J, Gerstein M.** (2008) Modeling ChIP Sequencing In Silico with Applications. *PLoS Comput Biol.*, **4**, e1000158.

Bioinformatics and Computational Genomics

The research field of my group is Computational Genomics and Bioinformatics, with a strong focus of mining large-scale experimental genomic data to decipher the function of the human genome and the genomes of other model organisms. We develop and apply computational techniques for integrating data of comparative genomics and functional genomics (and epigenomics) to decode the structure, function, and evolution of the human genome. More generally, we are interested in bioinformatic and statistical approaches for exploiting novel and biologically significant patterns in big genomic data. Recently, we have become more focused on the expression, regulation, and evolution of human genes (both coding or non-coding) that are involved in the development, specification, maturation, and maintenance of human neural systems and hearts. Working extensively with experimentalists and by deep sequencing of the transcriptomes in human neurons or mouse hearts, our study has led to many interesting findings and will contribute important information to heart development, neuronal development, neurodegenerative diseases and other brain diseases. Please visit this for more: <https://einstein.pure.elsevier.com/en/persons/deyou-zheng>

Recent publications:

- Zheng, D***, Zhao, K and Mehler, M. (2009) Profiling RE1/REST-mediated histone modifications in the human genome. *Genome Biol* 10:R9. (*corresponding author)
- Guo X, Zhang Z, Gerstein MB, Zheng D.** (2009). Small RNAs originated from pseudogenes: cis- or trans-acting? *PLoS Comput Biol* 5(7): e1000449.
- Goldberg AD, Banaszynski LA, Noh KM, Lewis PW, Elsaesser SJ, Stadler S, Dewell S, Law M, Guo X, Li X, Wen D, Chappier A, DeKelver RC, Miller JC, Lee YL, Boydston EA, Holmes MC, Gregory PD, Greally JM, Rafii S, Yang C, Scambler PJ, Garrick D, Gibbons R, Higgs DR, Cristea IM, Urnov FD, Zheng D*, Allis CD*** (2010). Distinct factors control histone variant H3.3 localization at specific genomic regions. *Cell* 140:678-691. (*co-corresponding authors)
- Guo X, Freyer L, Morrow B, Zheng D.** (2011) Characterization of the past and current duplication activities in the human 22q11.2 region. *BMC Genomics* 12:71
- Lin M, Pedrosa E, Shah A, Hrabovsky A, Maqbool S, Zheng D, Lachman HM.** (2011). RNA-Seq of human neurons derived from iPS cells reveals candidate long non-coding RNAs involved in neurogenesis and neuropsychiatric disorders. *PLoS ONE* 6: e23356.
- Guo X, Lin M, Rockowitz S, Lachman HM, Zheng D.** (2014) Characterization of Human Pseudogene-derived Non-coding RNAs for Functional Potential. *PLoS One* 9: e93972
- Adam RC, Yang H, Rockowitz S, Larsen SB, Nikolova M, Oristian DS, Polak L, Kadaja M, Asare A, Zheng D, Fuchs E.** (2015). Pioneer factors govern super-enhancer dynamics in stem cell plasticity and lineage choice. *Nature* 521:366-370
- Rockowitz S, Zheng D.** (2015). Significant expansion of the REST/NRSF cistrome in human versus mouse embryonic stem cells: potential implications for neural development. *Nucleic Acids Res.* 43:5730-5743.
- Wang P, Lin M, Pedrosa E, Hrabovsky A, Zhang Z, Guo W, Lachman HM*, Zheng D*.** (2015). CRISPR/Cas9-mediated heterozygous knockout of the autism gene CHD8 and characterization of its transcriptional networks in neurodevelopment. *Mol Autism* 6:55. (*co-corresponding authors)
- Lin M, Lachman HM, Zheng D.** (2016). Transcriptomics Analysis of iPSC-derived Neurons and Modeling of Neuropsychiatric Disorders. *Mol Cell Neurosci* 73:32-42
- Zhao D, Lin M, Pedrosa E, Lachman HM, Zheng D.** (2017). Characteristics of allelic gene expression in human brain cells from single cell RNA-seq data analysis. *BMC Genomics* 18:860
- Zhang D, Wang Y, Lu P, Wang P, Yuan X, Yan J, Cai C, Chang CP, Zheng D, Wu B, Zhou B.** (2017) REST regulates the cell cycle for cardiac development and regeneration. *Nat Commun* 8:1979.
- Wang P, Zhao D, Lachman HM, Zheng D.** (2018). Enriched expression of genes associated with autism spectrum disorders in human inhibitory neurons. *Transl Psychiatry* 8:13.
- Liu Y, Lu P, Wang Y, Morrow BE, Zhou B, Zheng D.** (2019) Spatiotemporal Gene Coexpression and Regulation in Mouse Cardiomyocytes of Early Cardiac Morphogenesis. *J Am Heart Assoc.* 8(15):e012941.
- Liu Y, Singh VK, Zheng D.** (2020) Stereo3D: using stereo images to enrich 3D visualization. *Bioinformatics* 36:4189-4190.
- Galbo PM, Zang X*, Zheng D*.** (2021) Molecular features of cancer-associated fibroblast subtypes and their implication on cancer pathogenesis, prognosis, and immunotherapy resistance. *Clin Cancer Res.* 27:2636-2647. (*co-corresponding authors)
- Liu Y, Wang T, Zhou B, Zheng D.** (2021) Robust integration of multiple single-cell RNA sequencing datasets using a single reference space. *Nat Biotechnol.* 39: 877-884.

BIN ZHOU, M.D., Ph.D.

Heart Development, Aging, Disease, and Repair

We study factors and mechanisms that control heart development to understand the pathogenesis of congenital heart disease as well as to gain insights into potential repairing mechanisms to combat heart disease. We use mice, mouse and human stem cells as model systems in our research. We apply an integrated approach of genetics, developmental, molecular and systems biology and advanced single cell technologies and CRISPR gene editing to address three major questions: (1) How individual cardiac cells and lineages are specified, maintained, or diversified during cardiac development, disease, aging, or regeneration? (2) How cell-cell, or cell-environment communications are modulated to control cardiac functions under these conditions? (3) How fetal cardiac gene program is controlled during development and reactivated in the diseased heart?

For more details, please visit (<https://einsteinmed.org/faculty/11217/bin-zhou>).

Selected Publications:

- Lu P, Wang Y, Wu B, Liu Y, Wang Y, Liu Y, Cheng W, Feng X, Yuan X, Atteya MM, Ferro H, Sugi Y, Rydquist G, Esmaily M, Butcher JT, Chang CP, Lenz J, Zheng D, Zhou B. (2022) A SOX17-PDGFB signaling axis regulates aortic root development. *Nat Commun* Jul 13;13(1):4065. doi: 10.1038/s41467-022-31815-1
- Lu P, Wu B, Feng X, Cheng W, Kitsis RN, Zhou B. (2022) Cardiac Myosin Heavy Chain Reporter Mice to Study Heart Development and Disease. *Circ Res* <https://doi.org/10.1161/CIRCRESAHA.122.321461> *Circulation Research*. 2022;0:10.1161/CIRCRESAHA.122.321461
- Lu P, Wang Y, Liu Y, Wang Y, Wu B, Zheng D, Harvey RP, Zhou B. (2021) Perinatal angiogenesis from preexisting coronary vessels via DLL4/NOTCH1 signalling. *Nat Cell Biol* 2021 Sep;23(9):967-977. doi: 10.1038/s41556-021-00747-1. Epub 2021 Sep 8
- Wang Y, Lu, P, Jiang Liping, Wu B, Zhou B. (2020) Control of sinus venous valve and sinoatrial node development by endocardial NOTCH1. *Cardiovasc Res* 116(8):1473-1486
- del Monte-Nieto G, Ramialison M, Cherian AV, Wu B, Aharonov A, D'Uva G, Bourke LM, Pitulescu ME, Chen H, Shou W, Adams RH, Harten SK, Tzahor E, Zhou B, Harvey RP. (2018) Extracellular matrix dynamics reveals the building plan for cardiac trabeculation. *Nature* 557(7705):439-445
- Wang Y, Lu P, Wu B, Riascos-Bernal DF, Sibinga NES, Valenta T, Basler K, Zhou B. (2018) Myocardial β -Catenin-BMP2 signaling promotes mesenchymal cell proliferation during endocardial cushion formation *J Mol Cell Cardiol* 123:150-158
- Wang Y, Lu P, Wu B, Morrow BE, Zhou B. (2018) NOTCH maintains developmental cardiac gene network through WNT5A *J Mol Cell Cardiol* 125:98-105
- Zhang D, Wang Y, Lu P, Wang P, Xinchun Yuan X, Yan J, Cai C, Chang CP, Zheng D, Wu B, Zhou B. (2017) REST regulates the cell cycle for cardiac development and regeneration. *Nat Commun* 8(1):1979.
- Wang Y, Wu B, Lu P, Zhang D, Wu B, Varshney S, Del Monte-Nieto G, Zhuang Z, Charafeddine R, Kramer AH, Sibinga NE, Frangogiannis NG, Kitsis RN, Adams RH, Alittalo K, Sharp DJ, Harvey RP, Stanley P, Zhou B. (2017) Uncontrolled angiogenic precursor expansion causes coronary artery anomalies in mice lacking Pofut1. *Nat Commun* 18;8(1):578
- Wu B, Wang Y, Xiao F, Butcher JT, Yutezy KE, Zhou B. (2017) Developmental mechanisms in aortic valve malformation and disease. *Annu Rev Physiol* 79:21-41
- Zhang D, Wu B, Wang P, Wang Y, Nechiporuk T, Floss T, Grealley JM, Zheng D, Zhou B. (2017) Non-CpG methylation by DNMT3B facilitates REST binding and gene silencing in developing mouse hearts. *Nucleic Acids Res* 45:3102-3115
- Wang, Y, Wu B, Farrar E, Alfieri CM, Lui, W, Lu P, Zhang D, Mao K, Chu M, Yang D, Xu D, Rauchman M, Taylor V, Yutzey KE, Butcher JT, Zhou B. (2017) Notch-Tnf signaling is required for development and homeostasis of arterial valves. *Eur Heart J* 38:675-686
- Wu B, Zhang Z, Lui W, Chen X, Moreno-Rodriguez RA, Wang Y, Chamberlain A, Markwald RA, O'Rourke B, Sharp DJ, Lenz J, Baldwin HS, Chang CP, Zhou B. (2012) Endocardial Cells Form the Coronary Arteries by Angiogenesis through Myocardial to Endocardial VEGF Signaling. *Cell* 151:1083-1096.
- Wu B, Wang Y, Lui W, Langworthy M, Tompkins KL, Hatzopoulos AK, Baldwin, HS, Zhou B. (2011) *Nfatc1* Coordinates valve endocardial cell lineage development required for heart valve formation. *Circ Res* 109:183-192.