Eunice Kennedy Shriver National Institute of Child Health and Human Development

Pediatric Scientist Development Program

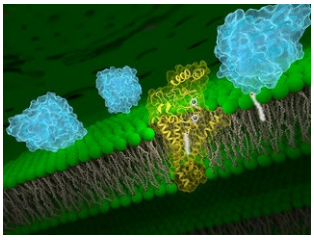
Research Opportunities in the Intramural Research Program of the
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institutes of Health

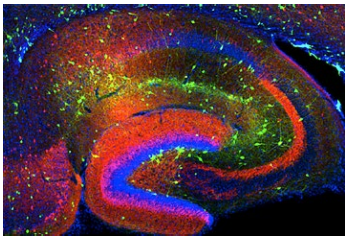
NICHD Intramural Research Program

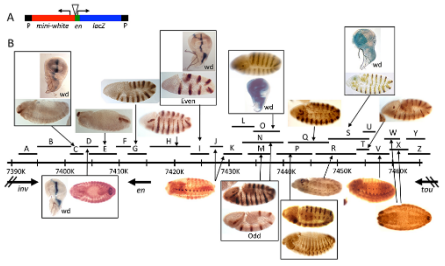
Our mission is to plan and conduct the institute's laboratory and clinical research programs to seek fundamental knowledge about the nature and behavior of living systems through basic, clinical, and population-based research and determine how to apply such knowledge to illuminate developmental origins of health and disease and help ensure that women and men have good reproductive health, that children are born healthy, and that people develop to live healthy and productive lives.

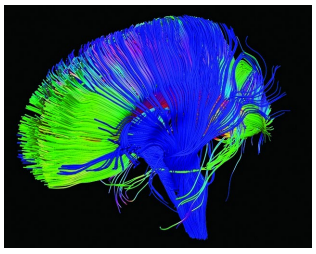
Thirteen affinity groups comprised of roughly 62 units and sections, as well as the Division of Population Health Research, constitute DIR.

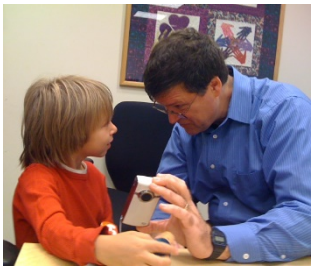
DIR conducts laboratory, clinical, epidemiological, and statistical research programs to seek fundamental knowledge about the nature and behavior of living systems through basic, clinical, and population-based research. We use this knowledge to illuminate developmental origins of health and disease and to help ensure that women and men have good reproductive health, that children are born healthy, and that people develop to live productive lives. Research efforts are focused on the acquisition of information that will enhance our understanding of the biology of development and reproduction. Our research program emphasizes the importance of fundamental investigations into the physics, chemistry, and biology of cells, their component parts, and the processes that govern and regulate their function. As part of their investigative focus, the scientific researchers of DIR accord primary importance to the transmission of new information to future generations of scientists.

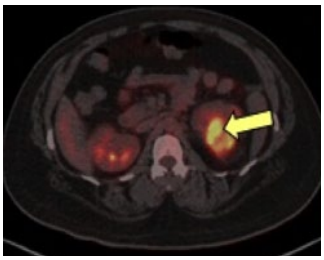


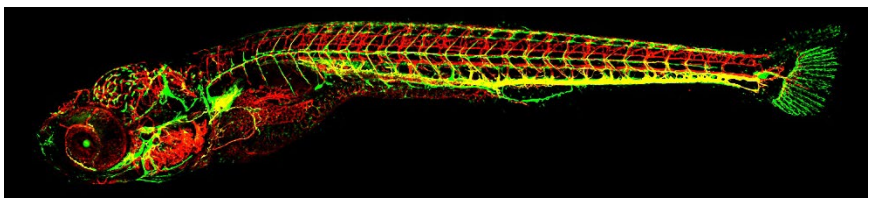












For additional information on NICHD and our 2020 Strategic Plan:

https://www.nichd.nih.gov/
https://www.nichd.nih.gov/about/org/strategicplan

For additional information on the NICHD Intramural Research Program:

https://www.nichd.nih.gov/research/atNICHD
https://annualreport.nichd.nih.gov/

For general information or questions related to NICHD Intramural Research Program participation in the Pediatric Scientist Development program please contact:

Dr. Forbes D. Porter
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For specific information related to individual NICHD intramural laboratories and research opportunities please feel free to contact the Principal Investigators directly.

NICHD Mission

NICHD's mission is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all.

Jeffrey Baron, MD
Section on Growth and Development

Laboratory Description and Research Opportunity:

Our research group investigates the cellular and molecular mechanisms governing childhood growth and development. One goal of this work is to gain insight into the many human genetic disorders that cause childhood growth failure and overgrowth. We also seek to develop new treatments for children with severe growth disorders.

Much of our work has focused on the growth plate, a thin layer of cartilage which is responsible for bone growth in children and therefore for height gain. Growth at the growth plate is controlled by multiple interacting regulatory systems, involving endocrine, paracrine, extracellular matrix-related, and intracellular pathways. Our group has studied growth plate regulation by FGFs, BMPs, C-type natriuretic peptide, retinoids, WNTs, PTHrP/IHH, IGFs, estrogens, glucocorticoids, and microRNAs. We have also investigated the mechanisms that cause bone growth to occur rapidly in early life but then to progressively slow with age and eventually cease.

For many children with disorders of growth and development, the etiology remains unknown. To discover new genetic causes of these disorders, we have used powerful genetic approaches including SNP arrays and exome sequencing. Using this approach, we have explored the roles of ACAN, QRICH1, BRF1, and CYP26A1/C1 in disorders of human growth.

Currently, treatment approaches for linear growth disorders are limited. We have undertaken a project designed to improve treatment by targeting growth-promoting endocrine and paracrine factors specifically to the growth plate by linking these factors to cartilage-binding antibody fragments. When administered systemically, these hybrid molecules are preferentially taken up by growth plate cartilage, and thus can augment the therapeutic effect on the target organ while diminishing adverse effects due to action on other tissues.

Laboratory website link: https://www.nichd.nih.gov/research/atNICHD/Investigators/baron

Selected publications:

1. Weise, M, De-Levi, S, Barnes, KM, Gafni, RI, Abad, V, Baron, J. Effects of estrogen on growth plate senescence and epiphyseal fusion. *Proc Natl Acad Sci U S A*, 98:6871-6876, 2001.
2. Lui JC, Jee YH, Garrison P, Iben JR, Yue S, Ad M, Nguyen Q, Kikani B, Wakabayashi Y, Baron J. Differential Aging of Growth Plate Cartilage Underlies Differences in Bone Length and Thus Helps Determine Skeletal Proportions, PLoS Biol, 23;16(7):e2005263, 2018
3. Lui JC, Colbert M, Cheung CS, Ad M, Lee A, Zhu Z, Barnes K, Dimitrov DS, Baron J. Cartilage-Targeted IGF-1 treatment to promote longitudinal bone growth, Mol Ther. 27:673-680, 2019.
4. Lui JC, Nguyen Q, Ad M, Garrison P, Jee YH, Nilsson O, Barnes K, Baron J. EZH1 and EZH2 promote skeletal growth by repressing inhibitors of chondrocyte proliferation and hypertrophy, *Nat Commun*, 7:13685, 2016. PMCID:PMC5477487
5. Baron J, Sävendahl L, Phillip M, De Luca F, Dauber A, Wit JM, Nilsson O. Short and tall stature: a new paradigm emerges. Nat Rev Endocrinol, 11:735-46, 2015. PMCID: PMC5002943

PI Contact information: Jeffrey.baron@nih.gov. 301-496-6312

The cell biology of cellular lipid landscape

Tamas Balla, MD, PhD
Section on Molecular Signal Transduction (SMST)

Our group studies the mechanisms by which eukaryotic cells control the lipid composition of their various membrane compartments. Almost all biological processes are controlled by protein signaling complexes that assemble on the surface of cellular membranes. Consequently, most human diseases can be traced to molecular defects that change protein function as it relates to membrane interactions. Various cellular organelles have unique lipid compositions contributing to their identity and determining the signaling modalities that are associated with them. The biochemical basis and enzymology of lipid metabolism has been mostly worked out but the cellular compartmentalization of the lipid biosynthetic machinery and the transport processes that establish and maintain the lipid composition of organelle membranes are poorly understood. Moreover, the cellular decision making whether to use lipids as energy sources, membrane building blocks or to store them is critical for the metabolic fitness of cells and hence for the whole organism. The small amount of regulatory lipids, the phosphoinositides play central roles in cellular signaling, vesicular membrane trafficking and cellular lipid homeostasis. The major focus of our group is to develop molecular tools that allow visualization and acute manipulation of phosphoinositides in living cells to better understand the molecular basis of their pivotal roles in controlling lipid distribution and organelle dynamics. Our approach relies on the use of fluorescent proteins and protein engineering and hence a variety of fluorescence microscopy applications to induce or follow lipid dynamics in live cells. Trainees joining our group can learn molecular biology and structure-instructed molecule design as well as cell culture-based genome editing and fluorescence microscopy. They are exposed to lively discussions about the scientific literature experimental design and data analysis during our weekly lab-meetings and monthly journal clubs. Trainees also have a chance to present their work and improve their writing and presentation skills and these are in addition to the rich developmental programs offered by NICHD.

https://www.nichd.nih.gov/research/atNICHD/Investigators/balla

Selected publications

1.Pemberton JG, Kim YJ, Humpolickova J, Eisenreichova A, Sengupta N, Toth DJ, Boura E, Balla T. Defining the subcellular distribution and metabolic channeling of phosphatidylinositol. J Cell Biol. 2020 Mar 2;219(3). e201906130. doi: 10.1083/jcb.201906130.

2.Baba T, Toth DJ, Sengupta N, Kim YJ and Balla T. PI(4,5)P_2 controls Rab7 and Plekhm1 membrane cycling during autophagosome-lysosome Fusion. EMBO J. 38: e100312, 2020

3.Sohn M, Korzeniowski M, Zewe JP, Wills RC, Hammond GRV, Humpolickova J, Vrzal L, Chalupska D, Veverka V, Fairn GD, Boura E, Balla T. PI(4,5)P_2 controls plasma membrane PI4P and PS levels via ORP5/8 recruitment to ER-PM contact sites. J Cell Biol. 2018 May 7;217(5):1797-1813.

4.Sohn M, Ivanova P, Brown HA, Toth DJ, Varnai P, Kim YJ, Balla T. Lenz-Majewski mutations in PTDSS1 affect phosphatidylinositol 4-phosphate metabolism at ER-PM and ER-Golgi junctions. Proc Natl Acad Sci U S A. 2016 Apr 19;113(16):4314-9.

5.Kim YJ, Guzman-Hernandez ML, Wisniewski E, Balla T. Phosphatidylinositol-Phosphatidic Acid Exchange by Nir2 at ER-PM Contact Sites Maintains Phosphoinositide Signaling Competence. Dev Cell. 33:549-61, 2015.

PI Contact information: ballat@mail.nih.gov, phone: 301-435-5637

Protein Trafficking in the Endosomal-Lysosomal System

Juan S. Bonifacino, PhD
Section on Intracellular Protein Trafficking

Our laboratory investigates the molecular mechanisms by which transmembrane proteins (referred to as "cargo") are sorted to different compartments of the endomembrane system in eukaryotic cells. This system comprises an array of membrane-enclosed organelles including the endoplasmic reticulum (ER), the Golgi apparatus, the *trans*-Golgi network (TGN), endosomes, lysosomes, lysosome-related organelles (LROs) (e.g., melanosomes, cytotoxic granules), and different domains of the plasma membrane in polarized cells such as epithelial cells and neurons. Transport of cargo between these compartments is mediated by vesicular/tubular carriers that bud from a donor compartment, translocate through the cytoplasm, and fuse with an acceptor compartment. Work in our laboratory focuses on the molecular machineries that mediate these processes, including (1) sorting signals and adaptor proteins that select cargo for packaging into transport carriers, (2) microtubule motors and organelle adaptors that drive movement of transport carriers and other organelles through the cytoplasm, and (3) tethering factors that promote fusion of transport carriers to acceptor compartments. We study these machineries in the context of different intracellular transport pathways, including endocytosis, recycling from endosomes to the plasma membrane, retrograde transport from endosomes to the TGN, biogenesis of lysosomes and LROs, autophagy, and polarized sorting in epithelial cells and neurons. Knowledge gained from this basic research is applied to the elucidation of mechanisms of disease, including congenital disorders of protein traffic such as the pigmentation and bleeding disorder Hermansky-Pudlak syndrome (HPS), hereditary spastic paraplegias (HSPs) and other neurodevelopmental disorders.

Laboratory website links: https://www.nichd.nih.gov/research/atNICHD/Investigators/bonifacino; https://irp.nih.gov/pi/juan-bonifacino

Selected publications:

Gershlick DC, Ishida M, Jones JR, Bellomo A, Bonifacino JS, Everman DB (2019) A neurodevelopmental disorder caused by mutations in the VPS51 subunit of the GARP and EARP complexes. *Hum Mol Genet*. 28:1548-1560.

Dell'Angelica EC, Bonifacino JS (2019) Coatopathies: genetic disorders of protein coats. *Annu Rev Cell Dev Biol*. 35:131-168.

Ballabio A, Bonifacino JS (2020) Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nat Rev Mol Cell Biol*. 21:101-118.

Mattera R, De Pace R, Bonifacino JS (2020) The role of AP-4 in cargo export from the *trans*-Golgi network and hereditary spastic paraplegia. *Biochem Soc Trans.* 48:1877-1888.

Saric A, Freeman SA, Williamson CD, Jarnik M, Guardia CM, Fernandopulle MS, Gershlick DC, Bonifacino JS (2021) SNX19 restricts endolysosome motility through contacts with the endoplasmic reticulum. *Nat Commun.* 12:4552.

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The zebrafish Lateral Line: a model system for understanding the self-organization of sense organ development and axon trafficking deficits in Kif1a Associated Neurological Disorder

Ajay Chitnis, MBBS, PhD
Section on Neural Developmental Dynamics

1. Understanding the development of the posterior pLL primordium: The posterior Lateral Line (pLL) primordium is a group of about a hundred cells that migrates under the skin, from the ear to the tip of the tail, periodically forming and depositing neuromasts, to spearhead formation of the zebrafish pLL sensory system. Our primary goal is to use a combination of cellular, molecular, genetic and biomechanical manipulations coupled with live imaging, image processing and the development of multi-scale computational models to understand the coordination of cell-fate, morphogenesis and collective migration of the pLL primordium. Current projects examinine how a) changes in individual cell shape and movement account for emergent behavior and organization of the primordium following specific chemical and physical manipulations, and b) how superficial cells interact with overlying basal cells to determine effective primordium migration. Data collected from these diverse studies will be integrated into expanded computational models that integrate the role chemical and mechanical interactions play in determining primordium behavior.

2. Developing a zebrafish model of Kif1a Associated Neurological Disorder (KAND):

Kif1a is microtubule associated motor protein with a role in the anterograde transport of synaptic vesicles, growth factors, peroxisomes and other essential cargo to synaptic terminals. Spontaneous mutations in the motor domain of Kif1 result in dominant inhibitory effects that interfere with anterograde transport and cause a severe progressive neurological disorder in children. We have developed transgenic fish to induce expression of such a mutant form of Kif1a and are using it to study how it affects anterograde transport. The goal of this project is to use this zebrafish model to study how problems in anterograde transport might contribute to development of neurological disorders and to use it as a platform with a network of scientists who study KAND to help them evaluate the potential efficacy of different therapeutic approaches to this devastating disease.

https://www.nichd.nih.gov/research/atNICHD/Investigators/chitnis
https://developmentalbiology.nih.gov/PI/ChitnisA.php

Selected publications:

1. **Dalle Nogare DE et al.** Line primordium migration requires interactions between a superficial sheath of motile cells and the skin. **Elife**. **2020** Nov 25;9:e58251.doi: 10.7554/eLife.58251. PMID: 33237853; PMCID: PMC7688310.
2. **Dalle Nogare D**, **Chitnis AB**. NetLogo agent-based models as tools for understanding the self-organization of cell fate, morphogenesis and collective migration of the zebrafish posterior Lateral Line primordium. **Semin Cell Dev Biol**. **2020** Apr;100:186-198. doi: 10.1016/j.semcdb.2019.12.015. Epub 2019 Dec 31.PMID: 31901312.
3. **Neelathi UM, Dalle Nogare D**, **Chitnis AB**. Cxcl12a induces *snail1b* expression to initiate collective migration and sequential Fgf-dependent neuromast formation in the zebrafish posterior lateral line primordium. **Development. 2018** Jul 30;145(14):dev162453. doi: 10.1242/dev.162453. PMID: 29945870; PMCID: PMC6078336.
4. **Dalle Nogare D**, **Chitnis AB**. A framework for understanding morphogenesis and migration of the zebrafish posterior Lateral Line primordium. **Mech Dev**. **2017** Dec;148:69-78. doi: 10.1016/j.mod.2017.04.005. Epub 2017 Apr 28. PMID: 28460893.
5. **Nogare DD**, Nikaido M, Somers K, Head J, Piotrowski T, **Chitnis AB**. In toto imaging of the migrating Zebrafish lateral line primordium at single cell resolution. **Dev Biol. 2017** Feb 1;422(1):14-23. doi: 10.1016/j.ydbio.2016.12.015. Epub 2016 Dec 11. PMID: 27965055.

Contact info: chitnisa@nih.gov 3014258262

Translational Biophotonics in Developmental Disorder Disease

PI: Amir H. Gandjbakhche, Ph.D.

We are using functional Near-Infrared Spectroscopy (fNIRS) and EEG techniques to examine as it relates to developmental level in babies, toddlers., and adults. Our studies are performed through a series of projects and collaborations at NIH and with Academia.

Currently we are having three clinical protocols: 1) Mirror Network in Infant at risk (MNN), 2) Non-invasive optical imaging, and 3) multimodal biosensor protocols.

The objective of the MNN protocol is to combine two child-friendly brain imaging techniques and stochastic modeling to determine the neural basis for the development of imitation and mimicry in human infants and to use machine learning to identify brain activation patterns that predict impairment in imitation and mimicry in infants at risk for social communication disorders. This protocol has two phases: phase 1 is a pilot study on an adult population (n = 40) and phase two will recruit typically developing infants (n=60) and infants at risk for developmental delays (n=60) from 9–12 months of age. At-risk infants will be brought in again at 24 months of age to evaluate any deviations in their social communicative development. We are completing phase 1 of this study and will soon move to phase 2.

The non-invasive optical imaging protocol aims to cross-validate our NIRS imaging system with existing fMRI and electroencephalogram (EEG) data, to investigate any significant technical issues associated with optode placement and motion artifacts, and to explore techniques that will potentially improve the feasibility and reliability of the system according to the needs of the population for whom existing imaging systems are unsuitable. This protocol is going on and we target to recruit a total of 250 healthy, adult participants.

The multimodal biosensor protocol will compare the performance of a multimodal biosensor device with commercial systems for measuring vital physiological signals including cardiac, respiratory, and tissue oxygenation in individuals at rest. This protocol was approved in Sep 2021. We are preparing to recruit a total of 40 healthy, adult participants.

Finally we have design a point of care device to assess transabdominal placental oxygenation levels non-invasively. In collaboration with Prenatal Research Branch of NICHD at Detroit our wearable device has been tested in 12 pregnant women with an anterior placenta; 5 of whom had maternal pregnancy complications. Preliminary results revealed that the placental oxygenation level is closely related to pregnancy complications and placental pathology. Women with maternal pregnancy complications were found to have a lower placental oxygenation level (69.4% ± 6.7%) than those with uncomplicated pregnancy (75.0% ± 5.8%). This device is a step in the development of a point-of-care method designed to continuously monitor placental oxygenation and to assess maternal and fetal health. We are planning to bring this technology to Howard University Ogy-Gyn branch.

https://www.nichd.nih.gov/research/atNICHD/Investigators/gandjbakhche

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Social and Behavioral Sciences Branch

Stephen Gilman, ScD and Tonja Nansel, PhD

The Social and Behavioral Sciences Branch (SBSB) conducts innovative research on the social and behavioral determinants of maternal, child, and adolescent health, and designs and tests social and behavioral interventions to improve health. The disciplinary expertise represented in our Branch spans the fields of developmental, social, and community/clinical psychology; education; nutrition; and social and psychiatric epidemiology. Our research, which is situated within the Social and Behavioral Sciences and Health Disparities focus areas in NIH's Intramural Research Program, applies social and behavioral science theories and methods to population-based research in order to understand health, development, and behavior.

Dr. Stephen Gilman leads SBSB's research on the social determinants of child development and mental health, which aims to advance our understanding of the early life origins of socioeconomic and racial/ethnic disparities in children's physical and mental development with long-term ramifications for mental well-being.

Dr. Tonja Nansel directs SBSB's research on behavioral nutrition in children and families, which uses experimental and observational methods to investigate influences on health behaviors leading to optimal growth and development. This program of research includes both experimental and observational studies on the influences of reward-related eating on diet quality and relationships of diet and nutritional status with health outcomes in youth with type 1 diabetes.

Please see https://www.nichd.nih.gov/about/org/dir/dph/officebranch/sbsb for more information about SBSB's research, and contact Dr. Stephen Gilman about SBSB at stephen.gilman@nih.gov.

Selected publications

Gilman SE, Hornig M, Ghassabian A, Hahn J, Cherkerzian S, Albert PS, Buka SL, Goldstein JM. Socioeconomic disadvantage, gestational immune activity, and neurodevelopment in early childhood. Proc Natl Acad Sci U S A. 2017;114(26):6728-33. PubMed PMID: 28607066; PMCID: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5495226

Nansel TR, Lipsky LM, Faith M, Liu A, Siega-Riz AM. The accelerator, the brake, and the terrain: associations of reward-related eating, self-regulation, and the home food environment with diet quality during pregnancy and postpartum in the pregnancy eating attributes study (PEAS) cohort. Int J Behav Nutr Phys Act. 2020;17(1):149. PubMed PMID: 33228724; PMCID: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7684737

Lipsky LM, Burger KS, Faith MS, Siega-Riz AM, Liu A, Shearrer GE, Nansel TR. Pregnant Women Consume a Similar Proportion of Highly vs Minimally Processed Foods in the Absence of Hunger, Leading to Large Differences in Energy Intake. J Acad Nutr Diet. 2021;121(3):446-57. PubMed PMID: 33109504

Yu J, Ghassabian A, Chen Z, Goldstein RB, Hornig M, Buka SL, Goldstein JM, Gilman SE. Maternal Immune activity during pregnancy and socioeconomic disparities in children's self-regulation. Brain Behav Immun. 2020;90:346-52. PubMed PMID: 32919039; PMCID: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7544646

Yu J, Patel RA, Gilman SE. Childhood disadvantage, neurocognitive development and neuropsychiatric disorders: Evidence of mechanisms. Curr Opin Psychiatry. 2021;34(3):306-23. PubMed PMID: 33587493

The biological impact of transposable elements

Henry Levin, Ph.D.
Section of Eukaryotic Transposable Elements

Transposable elements were highly active throughout evolution resulting in genome landscapes dominated by sequence repeats. The regulatory sequences contained within transposable elements have been broadly dispersed to form gene regulatory networks important for many biological functions. Our current studies focus on the integration of transposable elements and how de novo insertion modifies host biology. Experimental systems include the LTR retrotransposon of fission yeast, and HIV-1 in human cells. Recent work relies on the vast databases of human genetics to understand the role of transposable elements in human disease. Our studies of integration include inserts throughout the fission yeast genome that revealed pol II transcribed promoters are the primary targets of Tf1 integration. We adapted high throughput sequencing and developed new technology to sequence 1 million insertion sites. These experiments show that Tf1 has a preference for stress response promoters and the targeting of integration involves the DNA binding protein Sap1. We have also applied new methods to sequence 1 million integration sites of HIV-1 in cultured cells. These data led to the important discovery that the integrase of HIV-1 directs integration to highly spliced genes and interacts with splicing factors. We continue to develop novel methods for applying integration technology. As an example we developed a method called integration profiling that uses the transposon Hermes and deep sequencing to map the essential genes of fission yeast. We and other labs are using this method to identify genes with specific functions.

Laboratory website links
https://www.nichd.nih.gov/research/atNICHD/Investigators/levin
https://irp.nih.gov/pi/henry-levin

Selected publications

1. Lee SY, Hung S, Esnault C, Pathak R, Johnson KR, Bankole O, Yamashita A, Zhang H, Levin HL. Dense Transposon Integration Reveals Essential Cleavage and Polyadenylation Factors Promote Heterochromatin Formation. *Cell Rep*. 2020;30(8):2686-2698.e8.
2. Esnault C, Lee M, Ham C, Levin HL. Transposable element insertions in fission yeast drive adaptation to environmental stress. *Genome Res*. 2019;29(1):85-95.
3. Rai SK, Sangesland M, Lee M Jr, Esnault C, Cui Y, Chatterjee AG, Levin HL. Host factors that promote retrotransposon integration are similar in distantly related eukaryotes. *PLoS Genet*. 2017;13(12):e1006775.
4. Singh PK, Plumb MR, Ferris AL, Iben JR, Wu X, Fadel HJ, Luke BT, Esnault C, Poeschla EM, Hughes SH, Kvaratskhelia M, Levin HL. LEDGF/p75 interacts with mRNA splicing factors and targets HIV-1 integration to highly spliced genes.*Genes Dev*. 2015;29(21):2287-97.
5. Chatterjee AG, Esnault C, Guo Y, Hung S, McQueen PG, Levin HL. Serial number tagging reveals a prominent sequence preference of retrotransposon integration. *Nucleic Acids Res*. 2014;42(13):8449-60.

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Claire Le Pichon, PhD
Unit on the Development of Neurodegeneration
Molecular Medicine Affinity Group

Our work is dedicated to advancing our understanding of common molecular and cellular mechanisms of neurodegeneration with the ultimate goal of developing treatments for neurodegenerative diseases and even preventing them. One focus area is on mechanisms of axon damage signaling in neurons. Another lab theme is to understand fundamental differences between vulnerable and resilient populations of neurons in models of acute trauma and chronic disease.
We employ a multidisciplinary approach including mouse genetics, wide-scale imaging of whole cleared tissues, single cell transcriptomics, and cell biological studies in human iPSC-derived neurons to investigate the early events underlying the onset and progression of neurodegenerative disease. We have a particular interest in rare developmental neurodegenerative diseases that affect spinal motor neurons, such as SMA (spinal muscular atrophy) and juvenile ALS (amyotrophic lateral sclerosis).

Laboratory website links:
https://irp.nih.gov/pi/claire-le-pichon
https://www.nichd.nih.gov/research/atNICHD/Investigators/lepichon

1. Alkaslasi MR, Piccus ZE, Hareendran S, Silberberg H, Chen L, Zhang Y, Petros TJ, Le Pichon CE. Single nucleus RNA-sequencing defines unexpected diversity of cholinergic neuron types in the adult mouse spinal cord. *Nat Commun*. 2021;12(1):2471.

2. Wlaschin JJ, Gluski JM, Nguyen E, Silberberg H, Thompson JH, Chesler AT, Le Pichon CE. Dual leucine zipper kinase is required for mechanical allodynia and microgliosis after nerve injury. *Elife*. 2018;7.

3. Nguyen MQ, Le Pichon CE, Ryba N. Stereotyped transcriptomic transformation of somatosensory neurons in response to injury. *Elife*. 2019;8.

4. Le Pichon CE, Meilandt WJ, Dominguez S, Solanoy H, Lin H, Ngu H, Gogineni A, Sengupta Ghosh A, Jiang Z, Lee SH, Maloney J, Gandham VD, Pozniak CD, Wang B, Lee S, Siu M, Patel S, Modrusan Z, Liu X, Rudhard Y, Baca M, Gustafson A, Kaminker J, Carano RAD, Huang EJ, Foreman O, Weimer R, Scearce-Levie K, Lewcock JW. Loss of dual leucine zipper kinase signaling is protective in animal models of neurodegenerative disease. *Sci Transl Med*. 2017;9(403).

5. Chesler AT, Szczot M, Bharucha-Goebel D, Čeko M, Donkervoort S, Laubacher C, Hayes LH, Alter K, Zampieri C, Stanley C, Innes AM, Mah JK, Grosmann CM, Bradley N, Nguyen D, Foley AR, Le Pichon CE, Bönnemann CG. The Role of PIEZO2 in Human Mechanosensation. *N Engl J Med*. 2016;375(14):1355-1364.

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Defining the role of Metabolism in Oocyte Development

Mary Lilly, PhD
Section on Gamete Development

My laboratory uses the genetically tractable model organism *Drosophila melanogaster* to examine how meiotic progression is instructed by the developmental and metabolic program of the egg. Using a combination of molecular genetics, cell biology and biochemistry, we work to define the pathways that ensure the production and maintenance of high-quality oocytes. In mammals, studies on the early stages of oogenesis face serious technical challenges in that entry into the meiotic cycle, meiotic recombination, and the initiation of the highly conserved prophase I arrest all occur during embryogenesis. By contrast, in *Drosophila* these critical events of early oogenesis all take place continuously within the adult female. Easy access to the early stages of oogenesis, coupled with available genetic and molecular genetic tools, make *Drosophila* an excellent model for studies on the role of metabolism in oocyte development and maintenance. Chromosome mis-segregation during female meiosis is the leading cause of miscarriages and birth defects in humans. Recent evidence suggests that many meiotic errors occur downstream of defects in oocyte growth and the hormonal signaling pathways that drive oocyte differentiation. Thus, understanding how oocyte development and growth impact meiotic progression is essential to studies in both reproductive biology and medicine.

Laboratory website link
https://www.nichd.nih.gov/research/atNICHD/Investigators/lilly

Selected publications

Yang S, Zhang Y, Ting CY, Bettedi L, Kim K, Ghaniam E, Lilly MA. (2020) The Rag GTPase regulates the dynamic behavior of TSC downstream of both amino acid and growth factor restriction. *Dev. Cell.* 2020 PMID: 32898476

Wei Y, Bettedi L, Ting CY, Kim K, Zhang Y, Cai J, Lilly MA. (2019). The GATOR complex regulates an essential response to meiotic double-stranded breaks in Drosophila. *eLife*. 8:e42149. PMID: 31650955

Cai, W., Wei, Y., Jarnik, M., and M.A. Lilly (2016) The GATOR2 Component Wdr24 Regulates TORC1 Activity and Lysosome Function. PLoS Genetics. *http://dx.doi.org/10.1371/journal.pgen.1006036*

Wei, Y,. Reveal, B., Reich, J., Laursen, W., Senger, S., Akar, T., Iida-Jones, I., Cai., W., Jarnik, M., and M. A. Lilly (2014) The TORC1 regulators Iml1/GATOR1 and GATOR2 control meiotic entry and oocyte development in Drosophila. *PNAS.* 111 (52) E5670-E5677.

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Section on Mammalian Development and Evolution

Todd Macfarlan, PhD

At NICHD, our central mission is to ensure that every human is born healthy. Despite much progress in understanding the many ways the mother interacts with the fetus during development, we still know little about the genetic changes that promoted the emergence of placental mammals over 100 million years ago from our egg-laying relatives, nor those mechanisms that continue drive phenotypic differences amongst mammals. One attractive hypothesis is that retroviruses and their endogenization into the genomes of our ancestors played an important role in eutherian evolution, by providing protein coding genes like syncytins (derived from retroviral *env* genes that cause cell fusions in placental trophoblasts) and novel gene regulatory nodes that altered expression networks to allow for implantation and the emergence and continued evolution of the placenta. The primary interest of my lab is to explore the impact of these endogenous retroviruses (ERVs), that account for ~10% of our genomic DNA, on embryonic development and on the evolution of new traits in mammals. This has led us to examine the rapidly evolving Kruppel-associated box zinc finger protein (KZFP) family, the single largest family of transcription factors (TFs) in most, if not all mammalian genomes. Our hypothesis is that KZFP gene expansion and diversification has been driven primarily by the constant onslaught of ERVs and other transposable elements (TEs) to the genomes of our ancestors, as a means to transcriptionally repress them. This hypothesis is supported by recent evidence demonstrating the majority of KZFPs bind TEs and that TEs and nearby genes are activated in KZFP knockout mice. In the next several years we will continue to explore the impacts of the TE/KZFP “arms race” on the evolution of mammals. We will also begin a new phase exploring whether KZFPs play broader roles in genome regulation beyond gene silencing, and how these functions impact mammalian development.

Selected publications

Wolf G, de Iaco A, Sun MA, Bruno M, Tinkham M, Hoang D, Mitra A, Ralls S, Trono D, **Macfarlan TS**. KRAB-zinc finger protein gene expansion in response to active retrotransposons in the murine lineage. ***Elife.*** 2020 Jun 1;9:e56337. doi: 10.7554/eLife.56337.PMID: 32479262

Mahgoub M, Paiano J, Bruno M, Wu W, Pathuri S, Zhang X, Ralls S, Cheng X, Nussenzweig A, Macfarlan TS. Dual histone methyl reader ZCWPW1 facilitates repair of meiotic double strand breaks in male mice. ***Elife***. 2020 Apr 30;9:e53360. doi: 10.7554/eLife.53360.PMID: 32352380

Patel A[1], Yang P[1], Tinkham M, Pradham M, Sun MA, Wang Y, Hoang D, Wolf G, Horton JR, Zhang X, **Macfarlan T***, Cheng X*. DNA conformation induces adaptable binding by tandem zinc finger proteins. ***Cell*** 2018. Mar 22;173(1):221-233.e12 doi.org/10.1016/j.cell.2018.02.0581. PMID:29551271

Wolf G, Rebollo R, Karimi MM, Ewing AD, Kamada R, Wu W, Wu B, Bachu M, Ozato K, Faulkner GJ, Mager DL, Lorincz MC, **Macfarlan TS**. On the role of H3.3 in retroviral silencing. ***Nature*** 2017 Aug 3; 548E1-E3. doi:10.1038/nature23277. PMID:28770848

Yang P, Wang Y, Hoang D, Tinkham M, Patel A, Sun M-A, Wolf G, Baker M, Chien H-C, Lai N, Cheng X, Shen C-K J, and **Macfarlan TS***. A placental growth factor is silenced in mouse embryos by the zinc finger protein ZFP568. ***Science*** 2017 May 19;356(6339):757-759. doi: 10.1126/science.aah6895. PMID:28522536

https://www.nichd.nih.gov/research/atNICHD/Investigators/macfarlan

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Hippocampal Interneurons and Their Role in the Control of Network Excitability

Dr. Christopher J. McBain, Ph.D.
Laboratory of Cellular and Synaptic Neurophysiology

Cortical and hippocampal GABAergic inhibitory interneurons (INs) are "tailor-made" to control cellular and network excitability by providing synaptic and extrasynaptic input to their downstream targets via $GABA_A$ and $GABA_B$ receptors. The axons of this diverse cell population make local, short-range projections (although some subpopulations project their axons over considerable distances) and release the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) onto a variety of targets. Distinct cohorts of INs regulate sub- and supra-threshold intrinsic conductances, regulate Na^+- and Ca^{2+}-dependent action-potential generation, modulate synaptic transmission and plasticity, and pace both local- and long-range large-scale synchronous oscillatory activity. An increasing appreciation of the roles played by INs in several neural-circuit disorders, such as epilepsy, stroke, Alzheimer's disease, and schizophrenia, has seen this important cell type take center stage in cortical circuit research. With almost 30 years of interest in this cell type, the main objectives of the lab have been to understand: (1) the developmental trajectories taken by specific cohorts of INs as they populate the nascent hippocampus and cortex; (2) how ionic and synaptic mechanisms regulate the activity of both local circuit GABAergic INs and principal neurons (PN) at the level of small, well defined networks; and (3) how perturbations in their function alter hippocampal/neocortical networks in several neural circuit disorders. To this end, we use a variety state if the art electrophysiological, imaging, optogenetic, immunohistochemical, biochemical, molecular, genetic, and sequencing approaches in wild-type and transgenic mice using both *ex-vivo* (eg. brain slices, tissue homogenates) and *in-vivo* (awake behaving animals) experimental platforms. In addition, we have established robust pipelines to interrogate IN function and circuit participation in brain tissue from higher species such as human and non-human primate to evaluate evolutionary conservation or innovations of IN function.
https://dir.ninds.nih.gov/Faculty/Profile/chris-mcbain.html

Selected publications:

1. Pelkey KA, Chittajallu R, Craig MT, Tricoire L, Wester JC, McBain CJ. Hippocampal GABAergic inhibitory interneurons. *Physiol Rev* 2017;97:1619-1747.
2. Pelkey KA, Calvigioni D, Fang C, Vargish G, Ekins T, Auville K, Wester JC, Lai M, Mackenzie-Gray Scott C, Yuan X, Hunt S, Abebe D, Xu Q, Dimidschstein J, Fishell G, Chittajallu R, McBain CJ. Paradoxical network driven excitation by glutamate release from VGluT3+ GABAergic interneurons. *eLife* 2020;9:e51996.
3. Mahadevan V, Peltekian A, McBain CJ. Translatome analyses using ribosomal tagging in GABAergic interneurons and other sparse cell types. *Curr Protoc Neurosci* 2020;92:e93.
4. Chittajallu R, Auville K, Mahadevan V, Lai M, Hunt S, Pelkey KA, Zaghloul K, McBain CJ. Activity dependent tuning of intrinsic excitability in mouse and human neurogliaform cells. *eLife* 2020;9:e57571.
5. Wester JC, Mahadevan V, Rhodes CT, Calvigioni D, Venkatesh S, Maric D, Hunt S, Yuan X, Zhang Y, Petros TJ, McBain CJ**.** Neocortical Projection Neurons Instruct Inhibitory Interneuron Circuit Development in a Lineage-Dependent Manner. *Neuron* 102(5):960-975

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Clinical and Basic Investigations of Rare Genetic Disorder

Forbes D. Porter, M.D., Ph.D
Section on Molecular Dysmorphology

My research team combines both clinical and basic research to study the molecular, biochemical, and cellular processes that underlie genetic disorders resulting from impaired cholesterol homeostasis and lysosomal dysfunction. Our ultimate goal is to identify and test potential therapeutic interventions. The disorders currently being studied include Smith-Lemli-Opitz syndrome (SLOS), Niemann-Pick disease, type C (NPC) and CLN3 or Juvenile Batten disease. SLOS is an inborn error of cholesterol biosynthesis that results in multiple congenital malformations as well as cognitive and behavioral issue. NPC and CLN3 disease are lethal, progressive, neurodegenerative disorders due to lysosomal dysfunction. My basic research group utilizes multiple model systems including induced pluripotent stem cells, zebrafish and mouse models. Our basic research is complemented by ongoing natural history trials for all three disorders. As part of our natural history trials, we have established large cross-sectional and longitudinal collections of cell lines, urine, serum/plasma and cerebral spinal fluid from well-phenotyped patients. These biomaterials are being used to identify diagnostic, prognostic and therapeutic responsive biomarkers. We have also engaged in multiple phase 1/2a and phase 2b/3 therapeutic trials.

Laboratory website links
https://annualreport.nichd.nih.gov/porter.html

Selected publications

Francis KR et al. Modeling Smith-Lemli-Opitz syndrome with induced pluripotent stem cells reveals a causal role for Wnt/beta-catenin defects in neuronal cholesterol synthesis phenotypes. *Nat Med* 2016;22:388-396.

Ory DS et al. Intrathecal 2-hydroxypropyl-ß-cyclodextrin decreases neurological disease progression in Niemann-Pick disease, type C1: an ad-hoc analysis of a non-randomized, open-label, phase 1/2 trial. *Lancet* 2017;390(10104):1758-1768.

Cougnoux A et al. Single cell transcriptome analysis of Niemann-Pick disease, type C1 cerebella. *Int J Mol Sci* 2020;21(15):5368.

Solomon BI et al. Association of miglustat with swallowing outcomes in Niemann-Pick disease, type C1. *JAMA Neurol* 2020;77(12):1-6.

Dang Do AN Neurofilament light chain levels correlate with clinical measures in CLN3 disease. *Genet Med* 2021; 23 (4): 751-757.

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Mechanisms of synapse development and homeostasis

Mihaela Serpe, PhD
Section on Cellular Communication

Laboratory Description and Research Opportunity

Synapse development is coordinated by intercellular communication between the pre- and postsynaptic compartments, and by neuronal activity itself. Understanding this coordination is the central objective of our research. Synaptogenesis requires three key processes: (1) recruiting the components at the proper site; (2) organizing those components to build synaptic structures, and (3) maturation and homeostasis of the synapse to optimize its activity. Our studies have revealed that a handful of multi-molecular ensembles that span the synapse link all three processes into one network coordinated by bone morphogenetic proteins (BMPs) and the auxiliary protein Neto. Our long-term goal is to dissect the signaling mechanisms that play central roles in synapse development and homeostasis using the *Drosophila* NMJ as a model system for glutamatergic synapse.

The fly NMJ is a powerful genetic system to investigate mechanisms of synapse assembly and homeostasis. The fact that individual NMJs can be reproducibly identified and are easily accessible makes them uniquely suited for in vivo studies on synapse assembly, growth and plasticity. In addition, the fly NMJ relies entirely on kainate-type glutamate receptors, which impact synaptic transmission and neuronal excitability in mammalian CNS but remain poorly understood. *Drosophila* NMJ can thus be used to analyze and model defects in the structural and physiological plasticity of glutamatergic synapses that are associated with a variety of human pathophysiological disorders from learning and memory deficits to epileptic seizures and autism. In flies, the subunits that form the glutamate-gated ion channels (iGluRs) are relatively well known, but the molecular mechanisms that control the synaptic recruitment of iGluRs have remained mysterious for decades. We discovered an essential auxiliary protein, Neto, absolutely required for the recruitment of postsynaptic iGluRs and NMJ functionality. The discovery of Neto allowed us to reconstitute functional NMJ iGluRs in heterologous systems and to characterize the biophysical properties of these receptors. In recent studies we have (i) uncovered presynaptic Neto functions crucial for basal neurotransmission and synapse homeostasis and (ii) described a novel BMP signaling modality that stabilizes selective iGluRs as a function of their activity. Our genetic and biochemical screens for Neto interacting partners uncovered several novel molecules critical for synapse development, revealing a Neto-coordinated network that organizes and fine-tunes synapse structure and function. *Drosophila* has long served as a source of insight into human genetics, development, and disease, and the basic discoveries our laboratory makes in the fly will likely serve our overarching goal of understanding how chemical synapses are assembled and sculpted during development and homeostasis.

Laboratory website links: http://ucc.nichd.nih.gov/

Selected publications:

1) Han, T.H., Vicidomini, R., et al (2020) Neto-α controls synapse organization and homeostasis at the *Drosophila* neuromuscular junction. *Cell Reports* 32(1):107866.
2) Nguyen et al (2020) Selective disruption of synaptic BMP signaling by a Smad mutation adjacent to the highly conserved H2 helix. *Genetics* 216: 159-175 (Epub 2020 Jul 31).
3) Sulkowski et al (2016) A novel, noncanonical BMP pathway modulates synapse maturation at the *Drosophila* neuromuscular junction. *PLoS Genetics* 12, e1005810.

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Development of Sensory Processing

Mark Stopfer PhD
Section on Sensory Coding and Neural Ensembles

All animals need to know what is going on in the world around them. Brain mechanisms have thus evolved to gather and organize sensory information to build transient and sometimes enduring internal representations of the environment.

Using relatively simple animals and focusing primarily on olfaction and gustation, we combine electrophysiological, anatomical, behavioral, computational, optogenetic, and other techniques to examine the ways in which intact neural circuits, driven by sensory stimuli, process information. Our work reveals basic mechanisms by which sensory information is transformed, stabilized, and compared, as it makes its way through the nervous system.

We use three species of insects, each with specific and interlocking experimental advantages, as our experimental preparations: locusts, moths, and fruit flies. Compared to the vertebrate, the insect nervous system contains relatively few neurons, most of which are readily accessible for electrophysiological study. Essentially intact insect preparations perform robustly following surgical manipulations, and insects can be trained to provide behavioral answers to questions about their perceptions and memories. Ongoing advances in genetics permit targeting specific neurons for optogenetic or electrophysiological recording or manipulations of activity. And further, the relatively small neural networks of insects are ideal for tightly constrained computational models that test and explicate fundamental circuit properties.

How do the sensory capacities of animals develop? Animals often demonstrate, through their innate sensory preferences, the existence of inborn information. How is this information encoded, and how does it differ from information acquired through direct experience? This research opportunity will focus on understanding these fundamental questions.

Laboratory website:
http://stopfer.nichd.nih.gov

Selected publications:

Ray, S., Aldworth, Z., Stopfer, M. (2020) Feedback inhibition and its control in an insect olfactory circuit. *eLife*, 2020;9:e53281 DOI: 10.7554/eLife.53281.

Gupta, N., Singh, S.S., and Stopfer, M. (2016) Oscillatory integration windows in neurons. *Nature Communications*, 7, 13808 doi: 10.1038/ncomms13808.

Huston, S.J.*, Stopfer, M.*, Cassenaer, S., Aldworth, Z.N., and Laurent, G. (2015) Neural encoding of odors during active sampling and in turbulent plumes. *Neuron*, 88(2), 403–418.

Reiter, S., Campillo Rodriguez C., Sun, K., and Stopfer, M. (2015) Spatiotemporal coding of individual chemicals by the gustatory system. *Journal of Neuroscience*, 35(35), 12309 –12321.

Aldworth, Z., and Stopfer, M. (2015) Tradeoff between information format and capacity in the olfactory system. *Journal of Neuroscience*, 35(4), 1521-1529.

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NIH Distinguished Investigator
Gisela Storz, PhD
Section on Environmental Gene Regulation

The current focus of the group is identifying and characterizing genes that were missed, particularly those encoding regulatory small RNAs and small proteins.

Although small, noncoding RNAs play critical regulatory roles in all cells, the corresponding genes are not consistently annotated in genome databases, and as a result, are frequently missed in genetic screens. Small RNAs also are often ignored or missed by biochemical approaches. Thus, we have carried out several systematic screens for small RNAs, which have led to the identification of a large complement of the small RNAs expressed in *E. coli*. We have elucidated the functions of multiple small, regulatory RNAs. On-going work further is aimed at characterizing other unique base-pairing and non-base-pairing small RNAs and their evolution.

In our studies of small RNAs, we discovered that some of these RNAs actually encode small proteins. The correct annotation of the smallest proteins is one of the biggest challenges of genome annotation. Although these proteins have largely been missed, the few small proteins studied in bacterial and mammalian cells nonetheless have been found to have important functions in regulation, signaling and in cellular defenses. We initiated a project to identify the entire set of small proteins employing bioinformatic searches and, more recently, ribosome profiling. Currently, we are at the forefront of elucidating the functions of proteins of less than 50 amino acids in size. Many are single-pass transmembrane proteins act by modulating the activities or levels of transporters and other larger transmembrane proteins.

Laboratory website link: https://www.nichd.nih.gov/research/atNICHD/Investigators/storz

Selected publications:

Adams, P.P., Baniulyte, G., Esnault, C., Chegireddy, K., Singh, N., Monge, M., Dale, R.K., Storz, G. and Wade, J.T. (2020) Regulatory roles of *Escherichia coli* 5´ UTR and ORF-internal RNAs detected by 3´ end mapping, *eLife* 10, e62438.

Melamed, S., Adams, P.P., Zhang, A., Zhang, H. and Storz, G. (2020) RNA-RNA interactomes of Hfq and ProQ reveal overlapping and competing roles. Mol. Cell *77*, 411-425.

Wu Orr, M., Mao, Y., Storz, G. and Qian, S.-B. (2020) Alternative ORFs and small ORFs: shedding light on the dark proteome. Nucleic Acids Res. *48*, 1029-1042.

Du, D., Neuberger, A., Wu Orr, M., Newman, C., Hsu, P.-C., Samsudin, F., Szewczak-Harris, A., Ramos, L. M., Debela, M., Khalid, S., Storz, G. and Luisi, B. F. (2019) Interactions of a bacterial RND transporter with a transmembrane small protein in a lipid environment. Structure *28*, 625-634.

Weaver, J., Mohammad, F., Buskirk, A. R. and Storz, G. (2019) Identifying small proteins by ribosome profiling with stalled initiation complexes. mBio 10, e02819-18.

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Vascular Zebrafish

Brant M. Weinstein, Ph. D.
Section on Vertebrate Organogenesis

The Weinstein laboratory studies blood and lymphatic vascular development, meningeal development, and developmental epigenetics using a variety of molecular, cellular, genetic, transgenic, microscopic imaging, and next-generation sequencing approaches. The zebrafish is our primary research model, but we also use mice, cell culture, and Mexican cavefish *(Astyanax mexicanus)* models in our research work.

We have an active research program on vascular development, angiogenesis, and lymphangiogenesis. Our laboratory pioneered many of the key tools and resources used for vascular biology research in the fish, including numerous vascular-specific transgenic fish lines and methods for high resolution *in vivo* time-lapse imaging of zebrafish vessels. We have made a variety of seminal discoveries in the areas of vascular specification, differentiation, and patterning, including a novel pathway regulating arterial identity, a role for neuronal guidance factors in vascular patterning, a mechanism for vascular lumen formation in vivo, and identification and characterization of a lymphatic vascular system in the zebrafish.

We also study the meninges and meninges-associated cell types, and the brain neurovascular interface. The meninges are complex, multilayered, highly vascularized tissues surrounding the brain that play a critical role in brain homeostasis and protection and are involved in a variety of brain pathologies. Our laboratory recently discovered that the zebrafish has a meningeal architecture very similar to that of mammals, and we are exploiting the advantages of the fish as a powerful new model for genetic and experimental dissection of this critical tissue. We are also interested in using the zebrafish to better understand the neurovascular interface throughout the brain, using the sophisticated genetic and imaging capabilities of the zebrafish.

Our laboratory has also recently developed an interest in studying the "genetics of epigenetics." Epigenetic mechanisms such as DNA methylation and histone modifications are critical for establishing and maintaining differentiated cell and tissue identities, but the mechanisms directing this in vertebrate animals are largely unknown. We have discovered novel epigenetic mechanisms regulating hematopoietic development and eye development, and we are currently carrying out the first large-scale forward-genetic screen in a vertebrate for tissue-specific epigenetic regulators using a novel transgenic reporter. This highly successful ongoing screen has resulted in the identification of a large number of new vertebrate epigenetic regulators, which we are now in the process of further characterizing and studying.

https://www.nichd.nih.gov/research/atNICHD/Investigators/weinstein

For a listing of Weinstein Lab publications, see:

https://www.ncbi.nlm.nih.gov/sites/myncbi/brant.weinstein.1/bibliography/48861132/public/?sort=date&direction=descending

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Etiologies, Consequences, and Treatment of Obesity

Jack A. Yanovski, MD, PhD
Section on Growth and Obesity

Laboratory Description and Research Opportunity
The primary goal of the Section on Growth and Obesity (SGO) is to elucidate metabolic and behavioral endophenotypes that contribute to the development of obesity. Using an integrated program of basic and clinical translational research that takes advantage of the exceptional resources of the NIH Clinical Research Center as well as collaborations with intramural and extramural scientists, our ongoing and proposed studies of people with monogenic and polygenic obesity advance our understanding of energy balance regulation during childhood. In addition, using our longitudinal cohorts of children who have undergone intensive phenotyping, we examine genetic and phenotypic factors predictive of progression to adult obesity. Once identified as linked to obesity, genetic variants that impair gene function are studied intensively and precision medicine approaches applied to treatment. These approaches are expected to improve our ability to predict which children are at greatest risk for obesity and its comorbid conditions and to lead to more targeted, etiology-based prevention and treatment strategies for pediatric obesity.

The SGO offers excellent opportunities for young investigators to develop their basic and clinical research skills. The lab currently has 6 clinical (1 observational, 5 interventional) and 3 animal study obesity-related protocols. Dr. Yanovski works with each person within the lab to address personal goals, needed training, and individual research progress. Mentees travel to/present at national/international scientific meetings at least yearly. Dr. Yanovski has received awards for mentorship, including the 2019 Thomas A. Wadden Award for Distinguished Mentorship (The Obesity Society), a 2018 Excellence in Mentoring Award (NICHD) and the 2014 NIH Director's Ruth L. Kirschstein Mentoring Award.

Laboratory website: https://www.nichd.nih.gov/research/atNICHD/Investigators/yanovski

Selected publications:

a. Han JC … Yanovski JA. Brain Derived Neurotrophic Factor and Obesity in WAGR Syndrome. **N Engl J Med** 359:918-27, 2008. PMC2553704
b. Yanovski JA et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. **Diabetes** 60:477-85, 2011. PMC3028347
c. Yanovski SZ, Yanovski JA. Long-term Drug Treatment for Obesity: A Systematic and Clinical Review. **JAMA** 311(1): 74-86, 2014. PMC3928674
d. Lee B … Yanovski JA. A mouse model for a partially-inactive, obesity-associated human *MC3R* variant. **Nature Commun** 7: 10522, 2016. PMC4738366.
e. Demidowich AP … Yanovski JA. Effects of colchicine in adults with metabolic syndrome: A pilot randomized controlled trial. **Diabetes Obes Metab**; 21:1642–1651, 2019. PMC6570563
f. Pontzer H, … Yanovski JA, … Speakman JR. Daily Energy Expenditure through the Human Life Course. **Science** 373, 808–812, 2021. PMC8370708

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Pediatric Epidemiology

Edwina Yeung, PhD
Epidemiology Branch, Division of Population Health Research, Division of Intramural Research

Laboratory Description and Research Opportunity:

Dr. Yeung's team leads large epidemiologic studies to understand how early exposures lead to long-term health outcomes among children and adults. In particular, the Upstate KIDS study, a large exposure matched cohort from New York State, was formed to determine whether children conceived by infertility treatment differ from their peers in growth and development from birth to age 3 to 9 years. As a birth cohort, the study has served as a rich resource for understanding important aspects of child health ranging from early development to dietary patterns (see selected publications below). We are also exploring the possible mechanisms underlying associations with prenatal exposures, including DNA methylation.

Laboratory website links: Upstate KIDS Study

Selected publications:

1. Yeung EH, Sundaram R, Bell EM, Druschel C, Kus C, Ghassabian A, Bello S, Xie Y, Buck Louis GM. Examining Infertility Treatment and Early Childhood Development in the Upstate KIDS Study. *JAMA Pediatrics*. 2016; 170(3):251-258. PMID: 26746435. PMCID: PMC5000851
2. Ghassabian A, Sundaram R, Chahal N, McLain AC, Bell E, Lawrence DA, Yeung EH. Determinants of neonatal brain-derived neurotrophic factor and its association with child development. *Development and Psychopathology*. 2017; 29(4):1499-1511. PMID: 28462726 PMCID: PMC6201316
3. Trinh M, Sundaram R, Robinson S, Lin TC, Bell EM, Ghassabian A, Yeung E. Association of Trajectory and Covariates of Children's Screen Media Time. *JAMA Pediatrics* 2019 Nov 25;174(1):71-78. PMID: 31764966 PMCID: PMC6902189
4. Robinson SL, Ghassabian A, Sundaram R, Trinh MH, Lin TC, Bell EM, Yeung EH. Parental weight status and offspring behavioral problems and psychiatric symptoms. *Journal of Pediatrics* 2020 Feb 14. pii: S0022-3476(20)30029-9. doi: 10.1016/j.jpeds.2020.01.016. PMID: 32067780 PMCID: PMC7186145
5. Robinson SL, Sundaram R, Putnick DL, Gleason JL, Ghassabian A, Lin TC, Bell EM, Yeung EH. Predictors of age at juice introduction and associations with subsequent beverage intake in early and middle childhood. *Journal of Nutrition* 2021;151(11):3516-3523. PMID: 34486676 PMCID: PMC8564695

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