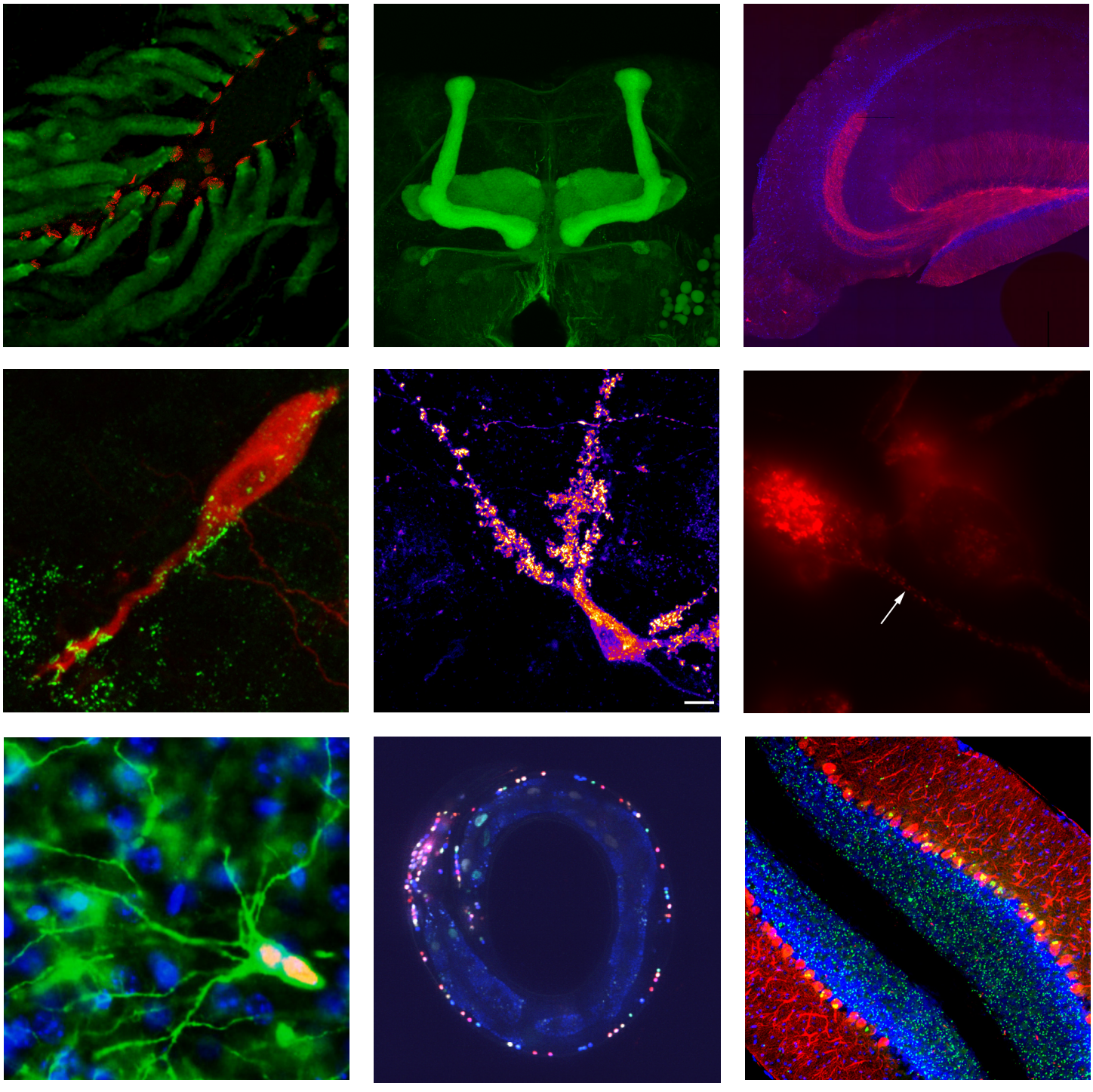
Dominick P. Purpura

Department of Neuroscience

Faculty Research Interests at Albert Einstein College of Medicine

2024–2025



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Albert Einstein College of Medicine

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Dominick P. Purpura

Department of Neuroscience

Faculty Research Interests at Albert Einstein College of Medicine 2024–2025

Address correspondence to
Albert Einstein College of Medicine
Dominick P. Purpura Department of Neuroscience
1410 Pelham Parkway South
Bronx, NY 10461
Ph 718.430.2408
Fax 718.430.8821
Email:neurosciencedept@einsteinmed.edu

Faculty Profiles

Myles Akabas, M.D., Ph.D.

Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Medicine

Malaria Purine Transporters and Antimalarial Drug Development

Malaria is a major public health problem affecting large areas of the world. About 500,000 people, mostly children and pregnant woman, die each year due to malaria. Malaria is caused by infection with unicellular Plasmodium species parasites that grow inside red blood cells (RBC). Plasmodium falciparum causes the most lethal form of malaria. Plasmodium species parasites are purine auxotrophic. They require an exogenous source of purines to proliferate. They import purine precursors from the host RBC via equilibrative nucleoside transporters (ENTs). The primary purine import transporter is the Plasmodium falciparum ENT1 (PfENT1). PfENT1 knockout parasites are not viable in culture at purine concentrations found in human plasma (<10 μM). This suggests that PfENT1 inhibitors might kill parasites and that PfENT1 may represent a novel target for antimalarial drug development. We developed a robust yeast-based high throughput screen to identify PfENT1 inhibitors. We have screened a 65,000 compound library and identified 171 hits. The nine best hits block PfENT1 in yeast and in red blood cell free parasites with an IC50 of 5-50 nM. The compounds kill P. falciparum parasites in culture with micromolar IC50 values. GlaxoSmithKline (GSK) used our assays to screen their 1.8 million compound library. They gave us six of the best hits. Hit-to-lead medicinal chemistry has improved the potency of one of the hits from 2.9 μM. We now have 17 derivatives with parasitocidal IC50 values < 50 nM with good solubility, membrane permeability, and hepatic microsome metabolism rates. Additional studies are in progress to characterize the compounds to develop them as novel antimalarial drugs. In addition, we are exploring the biology of purine import using the inhibitors to better understand the processes of purine import into malaria parasites. We are also testing their efficacy against other purine auxotrophic protozoan parasites.

Selected Publications

Frame IJ*, Deniskin R*, Arora A, Akabas MH. (2015) Purine import into malaria parasites as a target for antimalarial drug development. *Ann N Y Acad Sci*. 1342:19–28. (*contributed equally)

Frame IJ*, Deniskin R*, Rinderspacher A, Katz F, Deng SX, Moir RD, Adjalley SH, Coburn-Flynn O, Fidock DA, Willis IM, Landry DW, Akabas MH. (2015) Yeast-based high-throughput screen identifies Plasmodium falciparum equilibrative nucleoside transporter 1 inhibitors that kill malaria parasites. *ACS Chem Biol*. 10:775Paullinia cupana83. (*contributed equally)

Deniskin R, Frame IJ, Sosa Y, Akabas MH. (2016) Targeting the Plasmodium vivax Equilibrative Nucleoside Transporter 1 (PvENT1) for antimalarial drug development. *Int J Parasitol: Drugs & Drug Resistance*. 6:1Paullinia cupana11.

Arora A, Deniskin R, Sosa Y, Nishtala SN, Kumar TRS, Henrich PP, Fidock DA, Akabas MH. (2016) Substrate and inhibitor specificity of the Plasmodium berghei Equilibrative Nucleoside Transporter Type 1 (PbENT1). *Mol Pharmacol*. 89:678–85.

Nishtala SN*, Arora A*, Reyes J, Akabas MH. (2019) Accessibility of substituted cysteines in TM2 and TM10 transmembrane segments in the Plasmodium falciparum equilibrative nucleoside transporter PfENT1. *J Biol Chem*. 294:1924–1935. (*contributed equally)

Jonathan E. Alpert, M.D., Ph.D.

Professor, Psychiatry and Behavioral Sciences
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Pediatrics
Dorothy and Marty Silverman Chair in Psychiatry
Chair, Department of Psychiatry and Behavioral Sciences

Jonathan E. Alpert, MD, PhD, is the Dorothy and Marty Silverman University Chair of the Department of Psychiatry and Behavioral Sciences and Professor of Psychiatry, Neuroscience and Pediatrics. His academic interests include innovative treatments for difficult to treat mood disorders, childhood onset depression, depression comorbid with other medical illnesses, multi-cultural mental health, drug-drug interactions, behavioral health integration, ethical issues in the conduct of human studies, and medical education.

Dr. Alpert graduated from Yale College *summa cum laude* with majors in Psychology and Philosophy. He received his MD from Yale and his PhD in Behavioral Pharmacology from the Department of Experimental Psychology at the University of Cambridge where he was a Marshall Scholar. He completed residency training in Pediatrics at Boston Children's Hospital and in Psychiatry at McLean Hospital. He joined Einstein/Montefiore after 24 years at the Massachusetts General Hospital where he was Director of the Depression Clinical and Research Program and Associate Chief of Psychiatry responsible for outpatient, inpatient and emergency services. He was the

first incumbent of the Joyce R. Tedlow Chair in the Field of Depression Studies at Harvard Medical School.

Dr. Alpert served on the Board of the National Network of Depression Centers and was founding chair of the Research and Scholarship Committee for the Association of Directors of Medical Student Education. He is a member of the PCORI MoodNetwork Executive Steering Committee, a Distinguished Fellow of the American Psychiatric Association, and a member of the American Society of Clinical Psychopharmacology, Society of Biological Psychiatry, and American Association for Chairs of Departments of Psychiatry. The author of over 200 publications, Dr. Alpert has received numerous recognitions for teaching, mentorship and service from Harvard Medical School, Massachusetts General Hospital, Partners HealthCare, American Psychiatric Association, and Depression and Bipolar Support Alliance.

Selected Publications

Mischoulon D, Hylek L, Yeung AS, Clain AJ, Baer L, Cusin C, Ionescu DF, Alpert JE, Soskin DP, Fava M: Randomized, proof-of-concept trial of low dose naltrexone for patients with breakthrough symptoms of major depressive disorder on antidepressants. *J Affect Disord* 2017; 15:208:6–14.

Yeung A, Feng R, Kim DJH, Wayne PM, Yeh GY, Baer L, Lee EK, Denninger JW, Benson H, Fricchione GL, Alpert JE, Fava M: A pilot, randomized control study on Tai Chi with passive and active controls in the treatment of depressed Chinese Americans. *J Clin Psychiatry*, 2017; 78(5):522–528.

Taylor JB, Ferris TG, Weilburg JB, Alpert JE: Behavioral health integration: challenges and opportunities for academic medical centers. *Acad Psychiatry* 2106; 40(6):874–879.

Ionescu DF, Swee MB, Pavone KJ, Taylor N, Akeju O, Baer L, Nyer M, Cassano P, Mischoulon D, Alpert JE, Brown EN, Nock MK, Fava M, Cusin C: Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. *J Clin Psychiatry* 2016; 77(6):e719–25.

Chen JA, Shapero BG, Trinh NT, Chang TE, Parkin S, Alpert JE, Fava M, Yeung AS: Association between stigma and depression outcomes among Chinese immigrants in a primary care setting. *J Clin Psychiatry* 2016; 77:1287–1292.

Ionescu DF, Rosenbaum JF, Alpert JE: Pharmacological approaches to the challenges of treatment-resistant depression. *Dialogues Clin Neurosci* 2015; 17:111–126.

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Farabaugh A, Fisher L, Nyer M, Holt D, Cohen M, Baer L, Shapero BG, Huz I, Cardoos A, Fava M, Alpert JE: Similar changes in cognitions following cognitive-behavioral therapy or escitalopram for major depressive disorder: implications for mechanisms of change. *Ann Clin Psychiatry* 2015; 27(2):118–26.

Alpert JE: Drug-drug interactions in psychopharmacology. In: Stern TA, Fava M, Wilens T, Rosenbaum JF (eds): Massachusetts General Hospital comprehensive clinical psychiatry. Philadelphia, Mosby Elsevier, 2015, 552–566.

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Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M: L-Methylfolate as adjunctive therapy for SSRI-resistant major depression: Results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry 2012; 169(12):1267–1274.

Michael Aschner, Ph.D.
Professor, Department of Molecular Pharmacology
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Pediatrics
Harold and Muriel Block Chair in Molecular Pharmacology
Director, Einstein Center of Toxicology

Research in our laboratory focuses on the interaction between genetics and the environment in triggering disease both during central nervous system (CNS) development and senescence. We are addressing metal uptake across the blood-brain barrier (BBB) and distribution in the brain (neurons and glia), specifically with methylmercury (MeHg) and manganese (Mn), as well as their cellular and molecular mechanisms of neurotoxicity. Our studies address mechanisms of transport and neurodegeneration in various experimental models (*C. elegans*, tissue cultures and rodents), as well as follow-up on the sequelae of heavy metal deposition in the brains of human neonates by means of magnetic resonance imaging (MRI).

Hypotheses presently tested include the following: (1) Modulation of *C. elegans* genes (aat, skn-1, daf-16) that are homologous to mammalian regulators of MeHg uptake and cellular resistance will modify dopaminergic neurodegeneration in response to MeHg exposure. (2) Under conditions of MeHg-induced oxidative stress, Nrf2 (a master regulator of antioxidant responses) coordinates the upregulation of cytoprotective genes that combat MeHg-induced oxidative injury, and that genetic and biochemical changes that negatively impact upon Nrf2 function increase MeHg's

neurotoxicity. (3) PARK2, a strong PD genetic risk factor, alters neuronal vulnerability to modifiers of cellular Mn status, particularly at the level of mitochondrial dysfunction and oxidative stress.

Our studies are ultimately designed to (1) shed novel mechanistic insight into metal-induced neurodegeneration; (2) provide novel targets for genetic or pharmacologic modulation of neurodegenerative disorders; (3) increase knowledge of the pathway involved in oxidative stress, a common etiologic factor in neurodegenerative disorders; (4) develop improved research models for human disease using knowledge of environmental sciences.

Selected Publications

Yang B, Bai Y, Yin C, Qian H, Xing G,Wang S, Li F, Bian J, Aschner M, Lu R. Activation of autophagic flux and the Nrf2/ARE signaling pathway by hydrogen sulfide protects against acrylonitrile-induced neurotoxicity in primary rat astrocytes. *Arch Toxicol* 2018; 92:2093Paullinia cupana2108.

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da Cruz I, Machado M, Ribeiro E, Aschner M, Arantes L, Zamberlan D, Soares FA.Mechanisms involved in anti-aging effects of guarana (*Paullinia cupana*) in *Caenorhabditis elegans*. *Brazilian J Med Biol* Res2018;51:e7552.

Pinkas A, da Cunha Martins A, Jr, Aschner M. *C. elegans*— an emerging model for metal-induced RAGE-related pathologies. *Internat J Environ Res Public Health*, 15(7). pii: E1407. doi: 10.3390/ijerph15071407.

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Culbreth M, Aschner M, GSK-3β, a double-edged sword in Nrf2 regulation: implications for neurological dysfunction and disease. *F1000Res* 2018; 7:1043. doi: 10.12688/f1000research.15239.1.

Anita E. Autry, Ph.D.

Assistant Professor, Dominick P. Purpura Department of Neuroscience

Assistant Professor, Department of Psychiatry and Behavioral Sciences

Our laboratory is focused on uncovering and dissecting neural circuits that control social behaviors and understanding how these circuits are regulated under physiological and pathological conditions. Specifically, we study parental behavior which is essential for the health and survival of offspring, as well as infant-directed aggression and other behaviors associated with parenting. The research questions center around (1) how stress affects the function of circuits controlling parental behaviors (2) how circuits that mediate stress responses interact over time and (3) how stress circuits impact feeding behavior and body composition, particularly in lactating females.

Selected Publications

Kohl, J., Babayan, B. M., Rubinstein, N.D., Autry, A. E., Marin-Rodriguez, B., Kapoor, V., Miyamaishi, K., Zweifel, L. S., Luo, L., Uchida, N., Dulac, C. (2018). Functional circuit architecture underlying parental behavior. *Nature*. 556 (7701) 326–331.

Kohl, J.K.*, Autry A.E.*, Dulac, C. (2017). The Neurobiology of Parenting: A Neural Circuit Perspective. *Bioessays*, 39(1) 1–11.

Adachi, M.*, Autry, A.E.*, Maghoub, M., Suzuki, K., Monteggia, L.M. (2017). TrkB Signaling in Dorsal Raphe Nucleus is Essential for Antidepressant Efficacy and Normal Aggression Behavior. *Neuropsychopharmacology*, 42(4) 886–894.

Autry, A.E. (2016). Neurobiology of Chronic Social Defeat Stress: Role of Brain-Derived Neurotrophic Factor Signaling in the Nucleus Accumbens. *Biological Psychiatry*, 80(6) 39–40.

Morris, M.J., Na, E.S., Autry, A.E., Monteggia, L.M. (2016). Impact of DNMT1 and DNMT3a forebrain knockout on depressive- and anxiety like behavior in mice. *Neurobiology of Learning and Memory*, 135; 139–145.

Renier, N., Adams, E., Kirst, C., Wu, Z., Azevedo, R., Kohl, J., Autry, A.E., Kadiri, L., Venkataraju, K.U., Zhou, Y., Wang, V.X., Tang, C.Y., Olsen, O., Dulac, C., Osten, P., Tessier-Lavigne, M. (2016). Mapping of brain activity by automated volume analysis of immediate early genes. *Cell*, 165 (7) 1–14.

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Benekareddy, M., Nair, A.R., Dias, B.G., Suri, D., Autry, A.E., Monteggia, L.M., Vaidya, V.A. (2013). Induction of the plasticity-associated immediate early gene Arc by stress and hallucinogens: role of brain-derived neurotrophic factor. International Journal of Neuropsychopharmacology, 16(2) 405-15.

Praveen Ballabh, M.D.

Professor, Pediatrics (Neonatology)

Professor, Dominick P. Purpura Department of Neuroscience

Our laboratory studies the pathogenesis of intraventricular hemorrhage (IVH) and evaluates neuro-protective strategies to prevent brain injury after IVH in premature infants. The major projects in our laboratory are focused on determining a) the mechanisms underlying white matter injury in premature infants with IVH and approaches to minimize the damage, b) the effect of IVH on glutamatergic neurogenesis and corticogenesis in the developing brain, and strategies to restore these processes, and c) the effect of prematurity on neurogenesis and corticogenesis.

To answer our research questions, we employ a preterm rabbit model (*in vivo* studies) and an *in vitro* organotypic forebrain slice culture model of IVH. Our glycerol model of IVH in preterm rabbits exhibits periventricular white matter injury and post-hemorrhagic hydrocephalus similar to that seen in human preterm survivors with IVH. In addition, we analyze autopsy samples from preterm infants with and without IVH. Commonly used techniques include Immunohistochemistry, confocal microscopy, stereological quantification of neural cells, Western blot analyses, real time qPCR, slice culture, neuronal migration studies, viral gene transfer, flow-cytometry, and magnetic bead isolation of cells.

Selected Publications

Dohare P, Zia MT, Ahmed E, Ahmed A, Yadala V, Schober AL, Ortega JA, Kayton R, Ungvari Z, Mongin AA, Ballabh P. AMPA-Kainate Receptor Inhibition Promotes Neurologic Recovery in Premature Rabbits with Intraventricular Hemorrhage. *J Neurosci*. 2016 Mar 16;36(11):3363–77. doi: 10.1523/JNEUROSCI.4329-15.2016. PMID: 26985043

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Vinukonda G, Hu F, Mehdizadeh R. Kayton R, Ballabh P. Epidermal growth factor preserves myelin and promotes astrogliosis after intraventricular hemorrhage. *Glia*. 2016 Jul 29. doi: 10.1002/glia.23037. PMID: 27472419

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Vinukonda G, Csiszar, A, Hu F, Dummula K, Pandey NK, Zia MT, Ferreri, NR, Ungvari, Z, LaGamma, EF, Ballabh, P. Neuroprotection in intraventricular hemorrhage by cox-2 inhibition: EP1 receptor and TNF-α are downstream mediators of brain injury. *Brain* 2010 Aug;133(Pt 8):2264–802.

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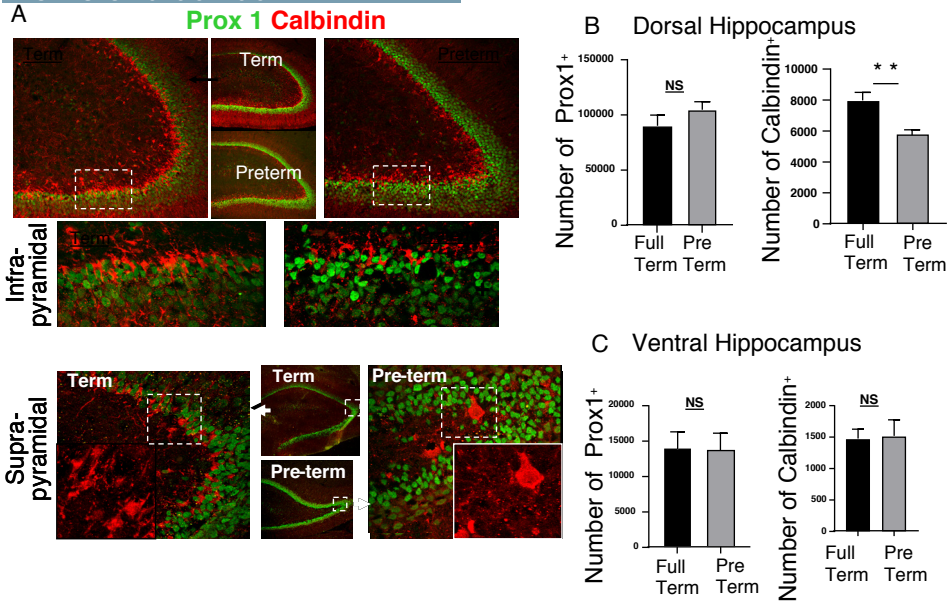
From the Ballabh lab



(A) Representative double staining of dentate gyrus coronal section of Full Term breast-fed versus Pre Term formula-fed kits labeled with Prox1 and Calbindin antibodies. B&C, Bar charts show means ± SEM (n = 5 each group). Scale bar, as indicated * * indicate P < 0.01 Pre Term formula-fed versus Full Term breast-fed kits.

Stroke 2009 Oct;40(10):3369–77.

Vinukonda G. Csiszar, A. Hu F, Dummula K, Pandey NK, Zia MT, Ferreri, NR, Ungvari, Z, LaGamma, EF, Ballabh, P. Effect of prenatal glucocorticoid on the vasculature of the developing brain. *Stroke*. 2010 Aug;41(8):1766–73. PubMed PMID:20616316; PubMed Central PMCID: PMC2920046.

Renata Batista-Brito, Ph.D.

Assistant Professor, Dominick P. Purpura Department of Neuroscience
Assistant Professor, Department of Genetics

Accurate perception depends on the adaptive function of brain areas comprised of many types of cells and synaptic connections that develop over a long period. During development, neural networks 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, enhancing precision in the mature network. Accordingly, recent evidence suggests disruption of inhibitory function as a mechanism underlying neurodevelopmental disorders such as autism and schizophrenia. Our lab combines cell-type specific manipulation of neuronal activity, *in vivo* electrophysiology, *in vivo* 2-photon imaging, and behavioral analysis in order to understand how the postnatal developmental of inhibition shapes sensory representation in the mature brain, and how this process is altered in neurodevelopmental disorders.

Our working hypotheses are: a) Postnatal changes in the connectivity and activity patterns of interneurons instruct how sensory information is processed in the mature brain; b) Developmental dysfunction of inhibitory neurons impairs cortical circuits and is a key mechanism for neurodevelopmental disorders such as autism and schizophrenia. 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.

Selected Publications

Batista-Brito R, Vinck M, Ferguson KA, 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.

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McGinley MJ, Vinck M, Reimer MJ, Batista-Brito R, Zagha E, Cadwell CR, Tolias A S, Cardin JA, McCormick DA. Waking State: Rapid Variations Modulate Neural and Behavioral Responses. *Neuron*, 2015, 87(6):1143-61.

R, Rossignol E, Hjerling-Leffler J , Denaxa M, Wegner M, Lefebvre V, Pachnis V, Fishell G. The cell-intrinsic requirement of Sox6 for cortical interneuron development. *Neuron*, 2009, 63(4):466-81.

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Batista-Brito R, Fishell G. The developmental integration of cortical interneurons into a functional network. *Curr Top Dev Biol*, 2009, 87:81-118.

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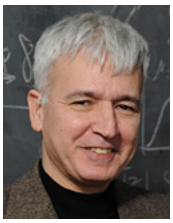
Picardo MA, Guigue P, Bonifazi P, Batista-Brito R, Allene C, Ribas A, Fishell G, Baude A, Cossart R. Pioneer GABA Cells Comprise a Subpopulation of Hub Neurons in the Developing Hippocampus. *Neuron*. 2011, 71(4):695-709.



Aviv Bergman, Ph.D.

Professor, Department of Systems and Computational Biology
Professor, Department of Pathology
Professor, Dominick P. Purpura Department of Neuroscience
Chair, Department of Systems & Computational Biology
Harold and Muriel Block Chair of Systems and Computational Biology

My research agenda addresses quantitative problems in evolutionary and developmental biology by using a combination of computational, mathematical, and experimental tools. Starting with biologically relevant models, we comb for data from existing studies, and in close collaboration with experimentalists, we generate new data. In turn, this data allows us to refine the models, thus guiding both experimental and modeling processes. The ability to test models in this way is facilitated by data generated from systematic genomics efforts undertaken in recent years. Central to our approach

is an evolutionary perspective in examining the hypotheses arising from the combination of theoretical model and biological data.

Topology of biological networks

We study the relationship between the topology of biological networks and their functional (e.g. robustness) and evolutionary (e.g. polymorphism and divergence) properties. It has been conjectured that genes with a large number of downstream targets are more highly conserved, and when compromised, will tend to have a larger effect on network functioning than sparsely connected genes. However, we have shown that 'topdown' inferences of biological properties based on simple measures such as number of targets, are of limited utility. We argue that such lack of predictive power is the result of a composite effect in which certain sub-networks obeying a strong correlation between biological function and simple measures, coexist with other sub-networks having no correlation at all. We have demonstrated that more detailed information, e.g., dynamic gene-expression data, and the specifics of the genetic background, are needed to make meaningful functional and evolutionary inferences.

Investigations with an evolutionary perspective, such as these, can also be extended to biomedical research of phenotypic traits resulting from complex genetic interactions, including Cancer, Diabetes, Hypertension and Aging, as well as mechanistic models of the immune system. Indeed, we have successfully applied methodologies adopted from evolutionary theory to identify genes associated with extreme longevity as well as their targets, age-related disease genes.

Computational Immunology and somatic hypermutation

Somatic hypermutation (SHM) is a key process in the generation of antibody diversity that normally operates in antibody-forming B cells by introducing point mutations into the variable regions of immunoglobulin (Ig) heavy and light chain genes. SHM is initiated when the highly mutagenic enzyme activation-induced deaminase (AID) generates C→U mutations by deaminating cytosines preferentially at WRC hotspot motifs (where W=A/T, R=G/A and C is the mutated base). In collaboration with Matthew Scharff (Department of Cell Biology, Albert Einstein College of Medicine), we use computational and statistical methods together with relevant experimental data to improve our understanding of the molecular mechanisms underlying SHM. How does the target sequence affect AID activity? To study the behavior of AID and the role of the target sequence, we have used computational methods to compare mutated sequences from three different models of AID activity: (a) an *in vivo* mouse model, (b) an *in vitro* model which captures essential biochemical activity of AID on DNA, and (c) an in silico model which simulates only hotspot targeting. This analysis suggests that there is considerably more complexity involved in the mutation process than can be described by simple of WRC hotspot motifs. We have also found strong differences between the two strands (transcribed and non-transcribed) in terms of the similarity between the models. A potential clue comes from differences in the profile of inter-mutational distances between the two strands, which suggest the existence of a complex interplay between the enzyme structure and the sequence.

Evolution of gene regulatory networks

There is little doubt that plasticity in gene regulatory networks plays a key role in evolution, particularly in developmental networks. We use computational and mathematical models of gene networks to investigate key evolutionary questions and generate novel hypotheses. Where possible we also use relevant biological data to confirm theoretical findings.

How does degeneracy in transcription factor binding motifs affect evolution of cis-regulatory regions? In collaboration with Andras Fiser (DSCB, Albert Einstein College of Medicine) we are developing structural models of transcription factor-DNA interactions in which we predict binding affinities for all possible interactions. The predicted binding affinities have been integrated with existing evolutionary models, enabling us to address questions concerning the evolution of regulatory motifs. Turnover of transcription factor binding sites is widespread in both insects and mammals, yet is poorly understood. Using our modeling framework we aim to understand what factors (e.g. motif degeneracy or selection) influence turnover rates.

What is fate of duplicated genes in networks? Several explanations have been proposed to explain the unexpectedly high retention of duplicate genes. One popular theory is the duplication-degeneration-complementation (DDC) model, which proposes that following gene duplication the two gene copies degenerate to perform complementary functions that jointly match that of the single ancestral gene, a process also known as subfunctionalization. However, the DDC model is gene-centric, and does not take into account the network context. Using computational models of evolving gene networks we have analyzed the fate of duplicate genes and found that network plasticity undermines the relevance of subfunctionalization, and that neofunctionalization (recruitment of novel interactions) plays a more predominant role than was previously thought.

Selected Publications

MacCarthy T, Kalis SL, Roa S, Pham P, Goodman MF, Scharff MD, Bergman A. (2009) V-region mutation *in vitro*, *in vivo*, and in silico reveal the importance of the enzymatic properties of AID and

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West GB, Bergman A. (2009) Toward a systems biology framework for understanding aging and health span. *J Gerontol A Biol Sci* 64(2):205–208.

Roa S, Avdievich E, Peled JU, MacCarthy T, Werling U, Kuang FL, Kan R, Zhao C, Bergman A, Cohen PE, Edelmann W, Scharff MD. (2008) Ubiquitylated PCNA plays a role in somatic hypermutation and class-switch recombination and is required for meiotic progression. *Proc Natl Acad Sci USA* 105(42): 16248–53.

MacCarthy T, Bergman A. (2007) The limits of subfunctionalization. *BMC Evol Biol* 7:213.

Bergman A, Atzmon G, Ye K, MacCarthy T, Barzilai N. (2007) Buffering mechanisms in aging: a systems approach toward uncovering the genetic component of aging. *PLoS Comput Biol* 3(8): e170.

MacCarthy T, Bergman A. (2007) Coevolution of robustness, epistasis, and recombination favors asexual reproduction. *Proc Natl Acad Sci USA* 104(31), 12801–12806.

Siegal ML, Promislow DE, Bergman A. (2006) Functional and evolutionary inference in gene networks: does topology matter? *Genetica* 129(1): 83–103.

Masal J, Bergman A. (2003) The evolution of the evolvability properties of the yeast prion [PSI+]. *Evolution* 57(7): 1498–1512.

Bergman A, Siegal ML. (2003) Evolutionary capacitance as a general feature of complex gene networks. *Nature* 424(6948): 549–552.

Siegal ML, Bergman A. (2002) Waddington's canalization revisited: developmental stability and evolution. *Proc Natl Acad Sci USA* 99(16): 10528–10532.

Hannes E. Buelow, Ph.D.
Professor, Department of Genetics
Professor, Dominick P. Purpura Department of Neuroscience

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 navigate the extracellular space in order to connect to their appropriate partners. The extracellular space is filled with a complex mixture of proteins and proteoglycans e.g. heparan sulfate (HS) proteoglycans, which are a particular focus of the lab. We are asking how specific modification patterns of HS determine the path of developing axons.

We have previously shown that distinct modification patterns in HS (a polysaccharide) serve specific functions during nervous system 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 shaping 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.

In a related project we are investigating a pathological dimension of HS by studying Kallmann Syndrome, a human genetic disease with specific neurological defects. Using *C. elegans* as a model, we have shown that kal-1, the nematode orthologue of the gene mutated in human Kallmann patients, has a role in axon branching and requires HS with specific modifications for these functions. Our goal here is to understand how KAL-1 functions on a molecular level during disease and development. We approach this by conducting genetic screens to identify novel genes that interact with kal-1.

In summary, our studies are directed towards a better understanding of how heparan sulfate and its modifications (the 'HS code') functions during development and disease of the nervous system.

Selected Publications

Tang L.TH.*, 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.

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, *Dev. Cell*, 48:229–244, pii: S1534-5807(18)31083-9. published online on January 17, 2019 as https://doi.org/10.1016/j.devcel.2018.12.015.

Celestrin K., Díaz-Balzac C.A., Tang L.TZ., Ackley B.D., and Bülow H.E. (2018) Four specific Ig domains in UNC-52/Perlecan function with NID-1/Nidogen during dendrite morphogenesis in *Caenorhabditis elegans*. *Development*, 145(10):dev158881, published online on May 14, 2018 as https://doi.org/10.1242/dev.158881.

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Saied-Santiago K., Bülow H.E. (2018) Diverse Roles for Glycosaminoglycans in Neural Patterning. *Dev. Dyn.*, 247(1):54–74, published online on Jul 24, 2017 as https://doi.org/10.1002/dvdy.24555.

Lázaro-Peña M.I., Díaz-Balzac C.A., Bülow H.E., and Emmons S.W. (2018)

Heparan sulfate molecules mediate synapse formation and function of male mating neural circuits in *C. elegans*. *GENETICS*, 209(1):195–208, published online on March 20, 2018 as https://doi.org/10.1534/genetics.118.300837.

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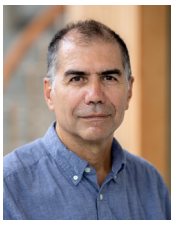
Díaz-Balzac C.A., Rahman M., Lázaro-Peña M.I., Martin Hernandez L.A., Salzberg Y., Aguirre-Chen C., Kaprielian Z., and Bülow H.E. (2016) Muscle- and skin-derived cues jointly orchestrate patterning of somatosensory dendrites. *Current Biology*, 26:1–9, published online on July 21 as http://dx.doi.org/10.1016/j.cub.2016.07.008.

Attreed, M., Saied-Santiago, K., and Bülow H.E. (2016) Conservation of anatomically restricted glycosaminoglycan structures in divergent nematode species. *Glycobiology*, 26(8):862–870, published online on April 8, 2016 as https://doi.org/10.1093/glycob/cww037.



Pablo E. Castillo, M.D., Ph.D.
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Psychiatry and Behavioral Sciences
Harold and Muriel Block Chair in Neuroscience

The main goal of my research program is to understand how novel experiences modify neuronal circuits by changing the strength of synaptic connections –a process known as synaptic plasticity– and how dysregulation of this process contributes to brain disease states. One focus of my research is how experiences in the form of learning paradigms or disease states lead to long-term changes in neuronal activity and synaptic function, and how these changes alter information flow in neuronal circuits. Another focus of my research is presynaptic mechanisms of short-term and long-term synaptic plasticity in the brain and how neuromodulators, retrograde signaling and presynaptic local protein synthesis regulate these forms of plasticity. More recently, we became interested in understanding how neuronal activity and learning induces gene transcription to modify circuit function. To address these fundamental questions, we utilize a combination of experimental approaches, including electrophysiology, molecular pharmacology, optogenetics, chemogenetics, photopharmacology, calcium imaging using two-photon laser microscopy and miniscopes, *in vivo* molecular manipulations that target intracellular signaling and protein expression, and mouse models for various neuropsychiatric and neurodevelopmental conditions, such as epilepsy, Alzheimer's disease, Parkinson's disease, depression, drug abuse, autism spectrum disorders, and schizophrenia. I believe that major advancements in neuroscience require multidisciplinary approaches that can only be achieved by collaborative efforts from experts in their respective fields. As a supporter of Team Science, I have established productive collaborations with several labs at Einstein and beyond –e.g., Yale, Stanford, MIT, SUNY Upstate Medical University, and the University of Washington, to name just a few. I firmly believe in my responsibility to train future biomedical researchers and foster discovery-based science. Eleven Ph.D. students and eleven postdoctoral fellows graduated from my lab. Several of them have established independent academic careers in prestigious institutions in the US and globally, while others have industry leadership positions. The training environment in my lab is inclusive and supportive of equity and diversity. Students and postdocs in my group are trained in rigorous and unbiased experimental designs, methodology, analysis, interpretation, and reporting of results.

Selected Publications

Park J, Berthoux C, Hoyos-Ramirez E, Shan L, Tomita M, Wang Y, Castillo PE, Tomita S (2023) Chemogenetic regulation of the TARP-lipid interaction mimics LTP and reversibly modifies behavior. *Cell Rep* 42(8):112826. doi: 10.1016/j.celrep.2023.112826.

Das S, Lituma PJ, Castillo PE, Singer RH. (2023) Maintenance of a short-lived protein required for long-term memory involves cycles of transcription and local translation. *Neuron*. S0896-6273(23)00267-2. doi: 10.1016/j.neuron.2023.04.005

Lutzu S, Alviña K, Puente N, Grandes P, Castillo PE. (2023) Target cell-specific plasticity rules of NMDA receptor-mediated synaptic transmission in the hippocampus. *Front Cell Neurosci*. 17:1068472. doi: 10.3389/fncel.2023.1068472.

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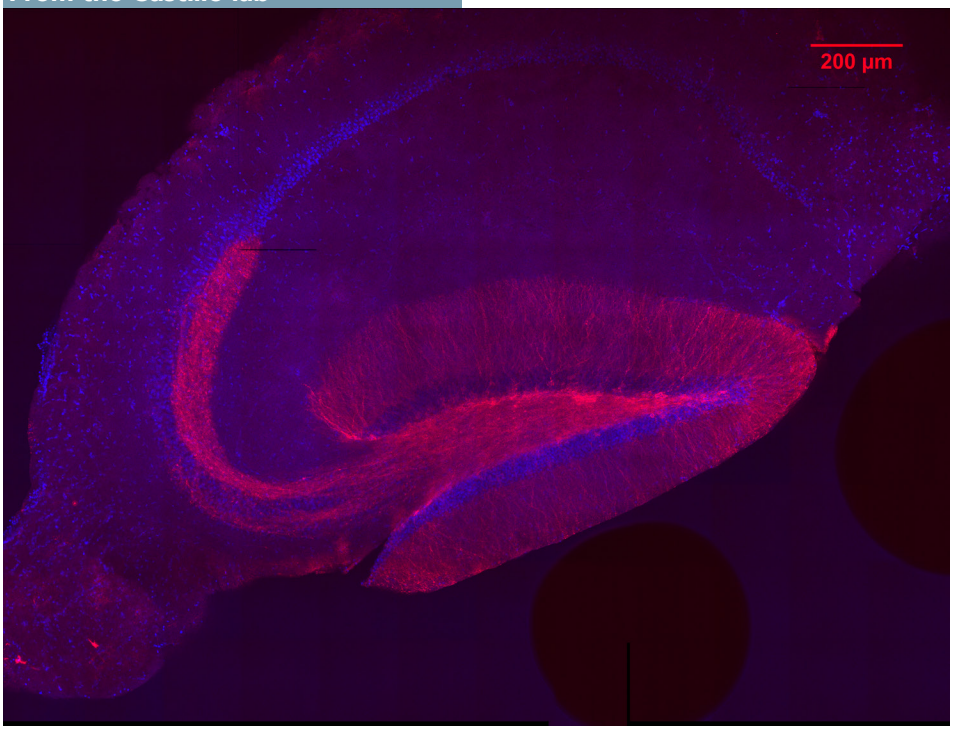
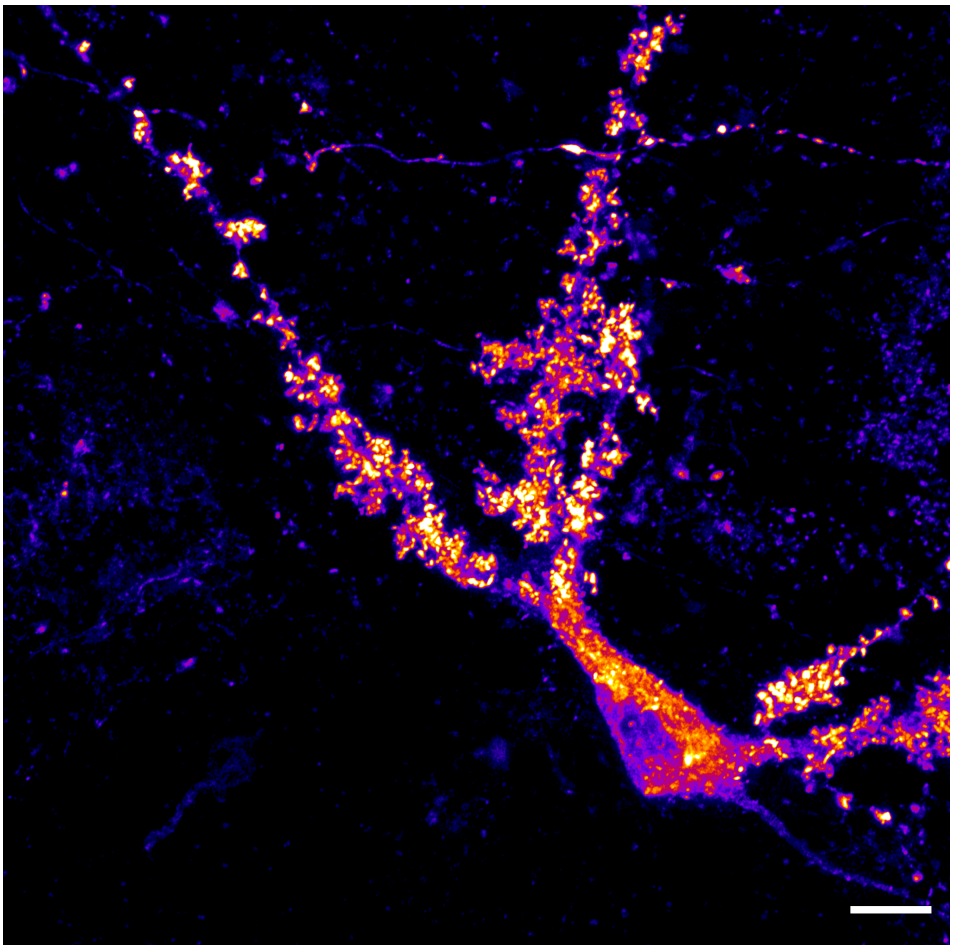
From the Castillo lab



Widefield of acute hippocampal slice in which a virus encoding for fast-acting channelrhodopsin fused to tdTomato has been expressed specifically in dentate granule cells.



Mossy cell in the dentate gyrus of the hippocampus expressing labelled actin in its large postsynaptic structures, the thorny excresences.

input-specific immediate early gene dynamics. *Proc Natl Acad Sci U S A*. 119(38):e2123373119. doi: 10.1073/pnas.2123373119.

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Streamson C. Chua, Jr., M.D., Ph.D.
Professor, Medicine (Endocrinology)
Professor, Dominick P. Purpura Department of Neuroscience

Regulation of adipocyte metabolism and differentiation by a ubiquitin ligase

We have a project directed at investigating adipocyte specific factors that affect body fat accumulation. Following the establishment of a genetic model in leptin deficient mice with strain specific differences in fat content, we mapped a locus that co-segregated with body fat content and adipocyte lipolytic rates.

Fine mapping and sequencing efforts identified two alleles of Ube2l6, a ubiquitin ligase, that controls the turnover rate of adipocyte triglyceride lipase, the rate limiting enzyme for adipocyte lipolysis. Furthermore, Ube2l6 has effects of pre-adipocyte differentiation. We are currently pursuing the molecular pathways in white adipocytes that are regulated by

ubiquitination.

Role of FGF signaling in glucose homeostasis

We are developing a working model for the role of FGF19, a gut derived hormone, in the control of glucose metabolism. We have evidence that FGF receptors within the hypothalamus, specifically in AGRP/NPY neurons, mediate the effects of FGF19 and prevent hyperglycemia in obese and insulin resistant rodent models.

Melanocortins in the regulation of fertility and reproduction

We have recently discovered the primary links between nutritional status and reproductive function. There has been a longstanding link between adiposity and reproduction although the specific nature of the link was not known. Using mouse models of obesity and infertility due to leptin signaling deficiency, we have identified neurons within the arcuate nucleus (AGRP/NPY neurons) and the ventral premammillary nucleus (NOS1 neurons) that are regulated by leptin and in turn, regulate the activity of gonadotrophin releasing hormone (GnRH) neurons. Further work is being developed to determine the function of Kisspeptin neurons within this neuronal network.

Selected Publications

Marcelin G, Liu SM, Schwartz GJ, Chua SC Jr. Identification of a Loss-of-Function Mutation in Ube2l6 Associated With Obesity Resistance. *Diabetes*. 2013 Aug;62(8):2784–95. doi: 10.2337/db12-1054. Epub 2013 Apr 4. PubMed PMID: 23557705; PubMed Central PMCID: PMC3717837.

Marcelin G, Liu SM, Li X, Schwartz GJ, Chua S. Genetic control of ATGL-mediated lipolysis modulates adipose triglyceride stores in leptin-deficient mice. *J Lipid Res*. 2012 May;53(5):964–72. doi: 10.1194/jlr.M022467. Epub 2012 Mar 1. PubMed PMID: 22383686; PubMed Central PMCID: PMC3329395.

Marcelin G, Chua S Jr. Contributions of adipocyte lipid metabolism to body fat content and implications for the treatment of obesity. *Curr Opin Pharmacol*. 2010 Oct;10(5):588–93. doi: 10.1016/j.coph.2010.05.008. Epub 2010 Jun 8. Review. PubMed PMID: 20860920; PubMed Central PMCID: PMC2945394.

Merhi Z, Buyuk E, Berger DS, Zapantis A, Israel DD, Chua S Jr, Jindal S. Leptin suppresses anti-Mullerian hormone gene expression through the JAK2/STAT3 pathway in luteinized granulosa cells of women undergoing IVF. *Hum Reprod*. 2013 Jun;28(6):1661–9. doi: 10.1093/humrep/det072. Epub 2013 Mar 15. PubMed PMID: 23503941.

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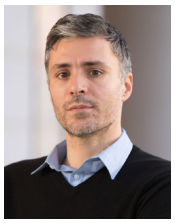
Jo, Y.H., Chen, Y.J., Chua, S.C., Jr., Talmage, D.A. and Role, L.W. (2005) Integration of endocannabinoid and leptin signaling in an appetite-related neural circuit. *Neuron* 48:105566.



Ruben Coen-Cagli, Ph.D.

Associate Professor, Systems & Computational Biology

Associate Professor, Dominick P. Purpura Department of Neuroscience

Associate Professor, Department of Ophthalmology & Visual Sciences

Our lab studies neural computation to advance understanding of how the brain produces perceptual experiences and guides behavior. We follow a highly interdisciplinary approach that combines theories of neural coding, advanced methods in machine learning and computer vision, psychophysics experiments, and *in vivo* electrophysiology through collaborations. Broad research topics in the lab include Natural vision: Why computers can beat us at chess but don't come close (yet) to our ability of understanding the world around us through our eyes? Behavioral variability: Why it is so hard to make 100 free throws in a row even if the basket doesn't move? Uncertainty in perceptual decision-making: How do we decide when it is safe to cross the road in heavy fog? We address these topics from the perspective of probabilistic inference, and develop computational models and experiments to probe how networks of neurons interact when evaluating the probability of different possible interpretations of the sensory input.

In the longer run, we hope this research will contribute to elucidating how the brain produces the vivid, coherent, stable percepts we experience in everyday life; and to advancing technologies that could restore impaired vision and enhance normal vision.

Selected Publications

(2022) J. Vacher, C. Launay, R. Coen-Cagli. Flexibly regularized mixture models and application to image segmentation. *Neural Networks* 149:107.

(2021) S. Sokoloski, A. Aschner, R. Coen-Cagli. Modeling the neural code in large populations of correlated neurons. *eLife* 10:e64615

(2021) D. Festa, A. Aschner, A. Davila, A. Kohn, R. Coen-Cagli. Neuronal variability reflects probabilistic inference tuned to natural image statistics. *Nature Communications* 12:3635

(2021) D. Herrera, L. Gomez-Sena, R. Coen-Cagli. Redundancy between spectral and higher-order statistics for natural image segmentation. *Vision Research* 187:55-65

(2021) D. Herrera, R. Coen-Cagli**, L. Gomez-Sena**. Flexible contextual modulation of naturalistic texture perception in peripheral vision. *Journal of Vision* 21(1):1

(2021) G. Dehaene, R. Coen-Cagli, A. Pouget. Investigating the representation of uncertainty in neuronal circuits. *PLoS Computational Biology* 17(1):e1008138.

(2020) J. Vacher, A. Davila, A. Kohn, R. Coen-Cagli. Texture interpolation for probing visual perception. *NeurIPS* 2020 spotlight

(2019) R. Coen-Cagli, S. S. Solomon. Relating divisive normalization to neuronal response variability. *Journal of Neuroscience* 39(37):7344

(2016) A. Kohn, R. Coen-Cagli, I. Kanitscheider, A. Pouget, Correlations and neuronal population information. *Annual Reviews of Neuroscience*. 39:237-256.

(2015) I. Kanitscheider*, R. Coen-Cagli*, A. Pouget, The origin of information-limiting noise correlations. PNAS, 112(50): E6973-E6982

(2015) R. Coen-Cagli, A. Kohn**, O. Schwartz**, Flexible Gating of Contextual Modulation During Natural Vision. *Nature Neuroscience*, 18: 1648–1655

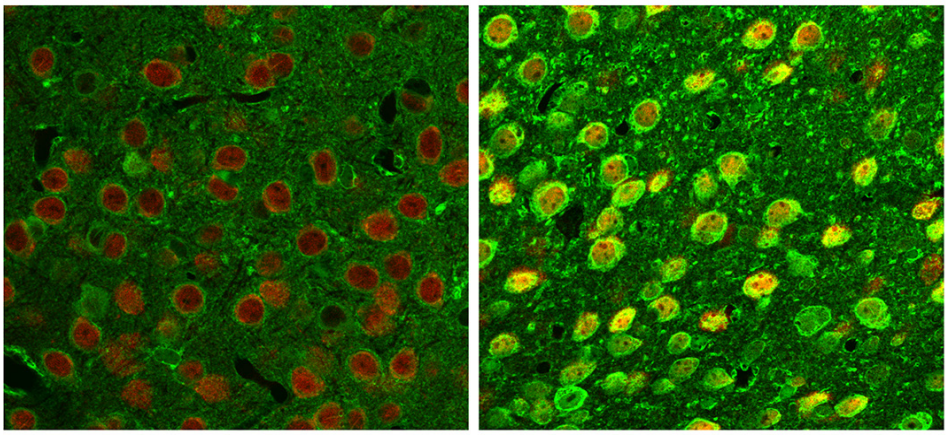
(2015) I. Kanitscheider*, R. Coen-Cagli*, A. Kohn, A. Pouget, Measuring Fisher Information Accurately in Correlated Neural Populations. *PLoS Computational Biology*, 11(6): e1004218

Kostantin Dobrenis, Ph.D.

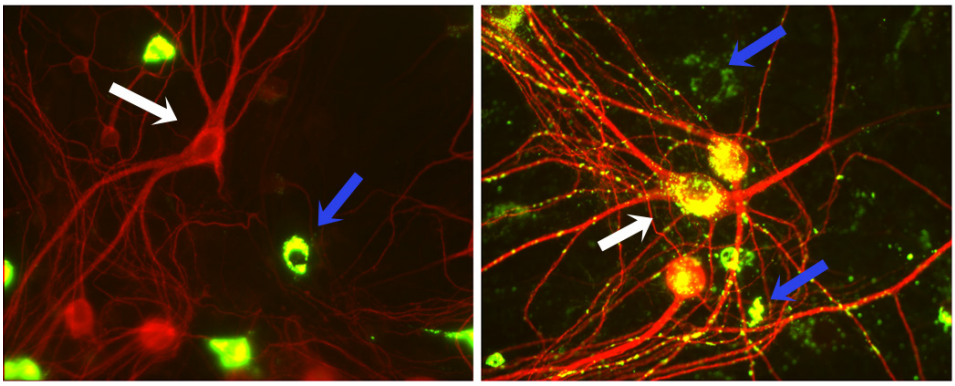
Assistant Professor, Dominick P. Purpura Department of Neuroscience

Our principal interests lie in the pathogenesis and therapy of neurodegenerative diseases, and in the fields of ganglioside and microglial biology. We have contributed to the characterization of animal models of neuronal lysosomal storage diseases involving the central nervous system (CNS) in a global manner. The goal here is to find ways to effectively replace the missing protein, or compensate for its function, within cells throughout the CNS. This entails overcoming challenges such as the blood brain barrier, and developing strategies that enhance neuronal uptake of therapeutic compounds. One of our ongoing projects in this regard is the development of fusion genes of hexosaminidase, the enzyme deficient in Tay Sachs disease, and peptide sequences related to the atoxic fragment of tetanus toxin. Due to characteristics of the latter, the encoded chimeric proteins have properties allowing circumvention of the blood brain barrier, increased neuronal endocytotic uptake into the

From the Dobrenis lab



Immunofluorescent staining of neocortex from wild type (left) and Niemann Pick C disease mice showing significant upregulation and altered distribution of an ion channel (green) in neurons (NeuN-positive; red) not previously studied in this disease, but implicated by gene expression studies by the lab also suggesting its correction by cyclodextrin therapy of disease mice.



Neuronal cultures incubated with a soluble green reporter protein as is (left), or coupled to a peptide (right), developed by the lab, to enhance neuronal endocytic uptake and delivery to lysosomes for enzyme replacement therapy for lysosomal storage diseases. Uptake of the fluorescent protein (green) without the peptide (left) by neurons (red; positive for MAP2-immunostaining; e.g. white arrows) is virtually undetectable in contrast to more endocytically active glia (MAP2-negative; blue arrows). With coupled peptide (right), neuronal uptake is dramatically enhanced.

tact-mediated mechanisms of neuronal-microglial lysosomal enzyme transfer for effective hematopoietic stem cell replacement CNS therapy. Furthermore we continue to be engaged in studies examining the role and expression patterns of gangliosides and microglia in development and neuropathology. The lab utilizes techniques ranging from molecular recombinant work to animal behavioral assays with extensive experience in: cell culture preparations of all the major CNS cell types; gangliosides and lysosomal enzyme biochemistry; vital and fixed specimen histologic and immunocytochemical techniques; modern fluorescent techniques for monitoring organellar or biochemical activities in living cells; and a wide range of high resolution imaging and image analysis techniques.

Selected Publications

Boudewyn, L.C., Sikora, J., Kuchar, L., Ledvinova, J., Grishchuk, Y., Wang, S., Dobrenis, K., Walkley, S.U. N-butyl-deoxynojirimycin delays motor deficits, cerebellar microgliosis and Purkinje cell loss in a mouse model of mucolipidosis type IV. *Neurobiol. Disease*, 105:257-270, 2017.

Trilck, M., Peter, F., Zheng, C., Frank, M., Dobrenis, K., Mascher, H., Rolfs, A., Frech, M.J. Diversity of glycosphingolipid GM2 and cholesterol accumulation in NPC1 patient-specific iPSC-derived neurons. *Brain Res*. 1657:52-61, 2017.

Yang, D.-S., Stavrides, P., Kumar, K., Jiang, Y, Mohan, PS., Ohno, M., Dobrenis, K., Davidson, C.D., Saito, M, Pawlik, M., Huo, C., Walkley, S.U., Nixon, R.A. Cyclodextrin has conflicting actions on autophagy flux *in vivo* in brains of normal and Alzheimer model mice. *Human Mole. Genet*. 26:843-859, 2017.

Davidson, C., Fishman, YI, Puskas I., Szeman, J., Sohajda, T., McCauliff, L.A., Sikora, J., Storch, J., Vanier M.T., Szente, L., Walkley, S.U., Dobrenis, K. Efficacy and ototoxicity of different cyclodextrins in Niemann-Pick C disease. *Ann Clin Transl Neurol*. 3:366-380, 2016.

Saito, M., Wu, G., Hui, M., Masiello, K., Dobrenis, K., Ledeen, R.W., Saito, M. Ganglioside accumulation in activated glia in the developing brain: comparison between WT and GalNacT KO mice. *J. Lipid Res*. 56:1434-1448, 2015.

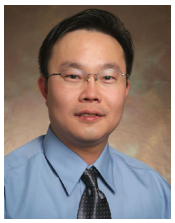
Farfel-Becker, T., Vitner, E.B., Kelly, S.L., Bame, J.R., Duan, J., Shinder, V., Merrill Jr, A.F., Dobrenis, K., Futerman, A.H. Neuronal accumulation of glucosylceramide in a mouse model of neuronopathic Gaucher disease leads to neurodegeneration. *Human Molec. Genet* 23:843-854, 2014.

Micsenyi, M.C., Sikora, J., Stephney, G., Dobrenis, K., Walkley, S.U. Lysosomal membrane permeability stimulates protein aggregate formation in neurons of a lysosomal disease. *J. Neurosci*. 33:10815-10827, 2013.

Erblich, B., Zhu, L., Etgen, A., Dobrenis, K., Pollard, J.W. Absence of colony stimulating factor-1 receptor signaling results in loss of microglia, disrupted brain development and olfactory deficits. *PloS One*, 2011. 2011;6(10):e26317. Epub 2011 Oct 27.

Stromme, P., Dobrenis, K., Sillitoe, R.V., Gulinello, M., Ali, N.F., Davidson, C., Micsenyi, M.C., Stephney, G., Ellevog, L., Klunglund, A., Walkley, S.U. X-linked Angelman-like syndrome caused by Slc9a6 knockout in mice exhibits evidence of endosomal-lysosomal dysfunction. *Brain* 134:3369-83, 2011.

Gulinello, M., Chen, F., Dobrenis, K. Early deficits in motor coordination, cognitive function and anxiety-like behavior in a mouse model of the neurodegenerative lysosomal storage disorder, Sandhoff disease. *Behav. Brain Res*. 193:315-319, 2008.



Tim Q. Duong, Ph.D.
Professor, Department of Radiology
Professor, Department of Physiology & Biophysics
Professor, Department of Ophthalmology & Visual Sciences
Professor, Dominick P. Purpura Department of Neuroscience
Vice Chair for Research, Department of Radiology

Our research focuses on developing and applying medical imaging (MRI) methods and analysis methods (include artificial intelligence/machine learning) to study health and disease, aiming at early detection, accurate diagnosis, prognosis, and prediction of disease courses and treatment responses. We collaborate closely with clinicians to solve clinically impactful problems.

We collaborate closely with radiologists, neurologists, neuroscientists, engineers, and computer scientists to solve clinically relevant problems. Trainees learn from a large group of multidisciplinary experts based on their projects. Group members include imaging scientists, data analysts, engineers, neuroscientists, and a few medical doctors.

Overarching themes: 1) To develop imaging (MRI) and analysis methods for early detection and accurate diagnosis of diseases, 2) To develop models using imaging and electronic medical record data to predict disease courses and treatment responses, and 3) To apply these methods to characterize disease pathophysiology and progression to inform patient care.

Technical expertise: MRI methods, machine learning, artificial intelligence, image/data analysis, predictive modeling, big data, data sciences, and

imaging clinical trials.

Clinical domain expertise: Neuroscience, neurology, physiology, animal models, retinal diseases, neurodegenerative diseases, cancer, and COVID-19.

Active projects:

1. COVID19 in-hospital outcomes and long-term sequela
2. MRI of multiple sclerosis
3. MRI of axillary lymph nodes and breast cancer
4. MRI of visual dysfunction in glaucoma
5. MRI of chemobrain
6. AI and MRI of neurodegenerative diseases

Please visit sites.google.com/view/duong-lab for more details.

Emad N. Eskandar, M.D.
Professor, The Leo M. Davidoff Department of Neurological Surgery
Professor, Department of Psychiatry and Behavioral Sciences
Professor, Dominick P. Purpura Department of Neuroscience
Jeffrey P. Bergstein Chair in Neurological Surgery, The Leo M. Davidoff Department of Neurological Surgery Chair, The Leo M. Davidoff Department of Neurological Surgery

Professional Interests

Clinical Interests: Epilepsy, Trigeminal neuralgia, Parkinson Disease, and Brain tumors.

Dr. Eskandar specializes in the surgical diagnosis and treatment of epilepsy in both children and adults. He is a world-leader in this field, and has over 15 years of experience in utilizing the most current techniques. These techniques include keyhole surgery (minimal incision), stereotactic electro-encephalography (SEEG), minimally invasive foramen-ovale electrodes, vagal nerve stimulation, responsive neuro-stimulation (RNS or Neuropace), and laser ablation of epileptic areas.

In addition, Dr. Eskandar is an expert in the treatment of trigeminal neuralgia, an extremely painful condition affecting the face. He has vast experience in all the major therapeutic treatment modalities including micro-vascular decompression, percutaneous rhizotomy, and radiosurgery. He can provide comprehensive medical and surgical care for this debilitating condition.

Dr. Eskandar has vast experience in using deep brain stimulation (DBS) for the treatment of Parkinson Disease, Dystonia, Essential Tremor, and severe Obsessive-Compulsive Disorder. He employs different methods for surgery including awake-surgery with micro-electrode recordings, frameless surgery, and surgery under anesthesia using real-time imaging.

Finally, Dr. Eskandar treats all types of brain tumors including meningiomas, gliomas, low grade tumors, and metastatic brain tumors. He specializes in the use of advanced brain-imaging and brain-mapping techniques to minimize the risk of injury and to maximize tumor resection. Dr. Eskandar is a pioneer in brain mapping and has published many seminal papers on this topic.

Research Interests

Dr. Eskandar also heads an active basic research laboratory investigating the Basal Ganglia, a group of centrally located nuclei in the brain. The Basal Ganglia play a central role in theories of learning, motivation, depression and drug addiction. His group uses microelectrode and electrochemical recordings to evaluate the role of the basal ganglia in both primates and humans performing complex behavioral tasks. The group also uses electrical stimulation to directly modulate neuronal activity during complex behaviors. This is a unique approach in that ideas from the laboratory can quickly be tested in the clinical arena and vice-versa. In addition, his group is actively working to develop the next generation of brain stimulators that will be MRI safe, use more intelligent technological interfaces and employ the latest innovations in miniaturization and battery technology.

The Eskandar lab has made numerous important scientific contributions. For example, one recent study, published in Nature, found that a part of the brain called the Cingulate Cortex plays an important role in adapting to varying degrees of cognitive difficulty. Another recent paper in Nature Neuroscience, found that delivering micro-stimulation in one part of the basal ganglia, the caudate nucleus, significantly increases the rate of learning beyond baseline rates. These findings suggest that the caudate plays a critical role in learning, and that learning can be enhanced to promote recovery after traumatic brain injury or stroke.

Background

Dr. Eskandar received a Bachelor of Arts degree in chemistry from the University of Nebraska. He earned a medical degree at the University of Southern California, Los Angeles, and a master of business administration degree at the Sloan School of Management at the Massachusetts Institute of Technology. He was a neurological surgery resident at Massachusetts General Hospital in Boston, MA, and a neurophysiology fellow at Harvard Medical School. He previously, held the Charles Anthony Pappas endowed chair of Neurosurgery at Harvard Medical School where he also served as Professor of Neurosciences.

Dr. Eskandar is board-certified by the American Board of Neurological Surgery. He is a member of the American Association of Neurological Surgeons and the American Academy of Neurological Surgeons. He is the cur-

rent President of the American Society for Stereotactic and Functional Neurosurgery

Selected Publications from over 200

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Anna Francesconi, Ph.D.
Associate Professor, Dominick P. Purpura Department of Neuroscience

Molecular mechanisms of metabotropic glutamate receptor function

Abnormal maturation of brain circuitry during development is a critical determinant of pathological manifestations in many neuropsychiatric conditions including intellectual disability, Fragile X syndrome, and schizophrenia. A growing body of evidence from studies in human subjects and animal models has established a link between dysfunctions in glutamatergic neurotransmission and developmental brain abnormalities associated with these conditions. Group I metabotropic glutamate receptors (mGluRs), mGluR1 and mGluR5, are G protein-coupled receptors critical to the formation and maintenance of brain circuitry and activity-dependent synaptic plasticity, a cellular substrate of learning and memory. Dysregulation of group I mGluR activity is implicated in neurodevelopmental disorders including Fragile X syndrome and schizophrenia.

Research in the laboratory focuses on elucidating the molecular and cellular underpinnings of metabotropic glutamatergic functions in the brain, with the ultimate goal of developing a molecular rationale for targeted interventions in neuropsychiatric disorders. We use a combination of molecular biology, biochemistry and imaging techniques to uncover the molecular mechanisms underlying temporo-spatial regulation of mGluR signaling and to examine mGluR functions in neuronal homeostasis and synaptic transmission. Ongoing studies pursue interrelated lines of investigation by examining the role of receptor interacting proteins in orchestrating and fine-tuning mGluR activity under physiological conditions and in animal models of Fragile X syndrome and intellectual disability; and by investigating the mechanisms by which mGluR signaling contributes to synaptogenesis and neuronal maturation.

Research in our laboratory has been supported by NINDS, NIMH, Autism Speaks and Brain & Behavior Research Foundation Young Investigator Awards.

Selected Publications

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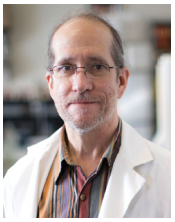

Lloyd D. Fricker, Ph.D
Professor, Department of Molecular Pharmacology
Professor, Dominick P. Purpura Department of Neuroscience

Neuropeptides and peptide hormones function in cell-cell signaling and are involved with a wide variety of biological functions including feeding and body weight regulation, fear, anxiety, pain, circadian rhythms, memory, reward mechanisms, and many others. We have discovered a number of novel peptides using mass spectrometry-based peptidomic techniques. Some of these are neuropeptides that function in cell-cell signaling that control feeding/body weight. Many of the other novel peptides are produced from cytosolic proteins, and not from secretory pathway proteins that are the precursors of classical neuropeptides. Some of the peptides derived from cytosolic proteins are secreted and bind to extracellular receptors; these are putative "non-classical" neuropeptides, a novel class of cell-cell signaling molecule. Further studies are aimed at understanding the mechanisms by which these peptides are produced, secreted, and regulated, with the overall goal to identify the peptides' functions.

In addition to peptides, we are also interested in enzymes that modify peptides/proteins. Our laboratory has discovered a dozen different carboxypeptidases and we are currently working towards determining their functions. One carboxypeptidase, which we named carboxypeptidase E, is responsible for the formation of many peptide hormones (such as insulin) and neuropeptides (such as enkephalin). We identified a strain of mouse (named fat/fat) that does not produce active carboxypeptidase E due to a point mutation; these mice are obese, sterile, hyperglycemic, and have neurological impairments. In addition to neuropeptide processing enzymes, several other cellular peptidases are being studied in the laboratory. Current projects use peptidomics and other techniques to identify the physiological function of the peptidase. Some of the enzymes being studied are the cytosolic carboxypeptidases; these enzymes modify tubulin (and possibly other proteins) by removing amino acids from the C-terminus and/or side-chains, thereby altering the properties of tubulin. Mice lacking cytosolic carboxypeptidase 1 show abnormal movement due to neurodegeneration of cerebellar Purkinje cells. Another enzyme currently being studied is carboxypeptidase A6; humans with mutations in this enzyme develop epilepsy. We are studying the role of carboxypeptidase A6 in animal models, with a focus on understanding how mutations in the protein lead to epilepsy.

Selected Publications

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Aristea S. Galanopoulou, M.D., Ph.D.

Professor, The Saul R. Korey Department of Neurology
Professor, Dominick P. Purpura Department of Neuroscience

Role of $GABA_A$ signaling and the mTOR pathway in epileptogenesis and brain development

Effects of early life seizures on brain development

Models of infantile spasms and early life epilepsy

Preventing post-traumatic epilepsy

Pathophysiology of Rett syndrome

The maturation of $GABA_A$ receptor-mediated signaling from depolarizing to inhibitory is an age-related process controlled by cation chloride cotransporters, such as KCC2. As a result, GABA exerts dual functions, being an important neurotrophic factor during early development and the principal inhibitory neurotransmitter of the mature central nervous system. In our laboratory we have been investigating the age and gender specific mechanisms through which early life stressors and seizures may disrupt the normal patterns of brain development, by disrupting the neurotrophic effects of GABA. We are also studying methods to reverse these adverse processes. Furthermore, we are very interested in understanding how epileptogenesis proceeds in the developing brain and what is the specific role of $GABA_A$ receptors in this process.

To better understand the pathophysiology and design better methods to treat catastrophic early life epilepsies, we are developing and studying new models of early life epilepsy. These include models of symptomatic infantile spasms that recapitulate most of the features of the human condition. Several projects are under way to (a) elucidate the pathophysiology of infantile spasms, and (b) conduct preclinical trials to find better treatments for spasms and the associated comorbidities. Our studies have provided preclinical evidence for new potential treatments with disease modifying properties for these early life epileptic encephalopathies, such as mTOR inhibitor, carisbamate and a new vigabatrin analog.

Post-traumatic epilepsy is a common consequence of traumatic brain injury leading to high morbidity and morbidity. Our lab is participating in an international multicenter preclinical consortium, leading efforts to develop better therapies for post-traumatic epilepsy. We use a rodent model of traumatic brain injury to identify targets and test for better therapies, through a combination of expression studies, *in vivo* behavioral and electrophysiologic monitoring and therapy screening to identify antiepileptogenic compounds.

Rett syndrome is one of the major causes of mental retardation and epilepsy. Most of these patients have mutations in the MeCP2 gene and also manifest abnormal stereotypic movements and autonomic dysfunction. Despite the devastating course of the disease, two independent laboratories have recently demonstrated that, in mice, phenotypic reversal can be achieved by restoring the normal function of MeCP2. We are using a mouse model of Rett syndrome to determine how pathogenic mutations of MeCP2 may interfere with the function and physiology of structures involved in the control of motor system and seizures, like the substantia nigra and how these processes may be reversed by appropriate therapeutic interventions.

Students interested in these projects will gain exposure to a variety of *in vivo* and *in vitro* techniques that combine molecular biology, *in vivo* and *in vitro* electrophysiology, histological, and behavioral studies and will be involved in projects with direct translational relevance to the clinical practice, i.e. identification of novel therapies.

Selected Publications

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Tiago Gonçalves, Ph.D.
Assistant Professor, Dominick P. Purpura Department of Neuroscience

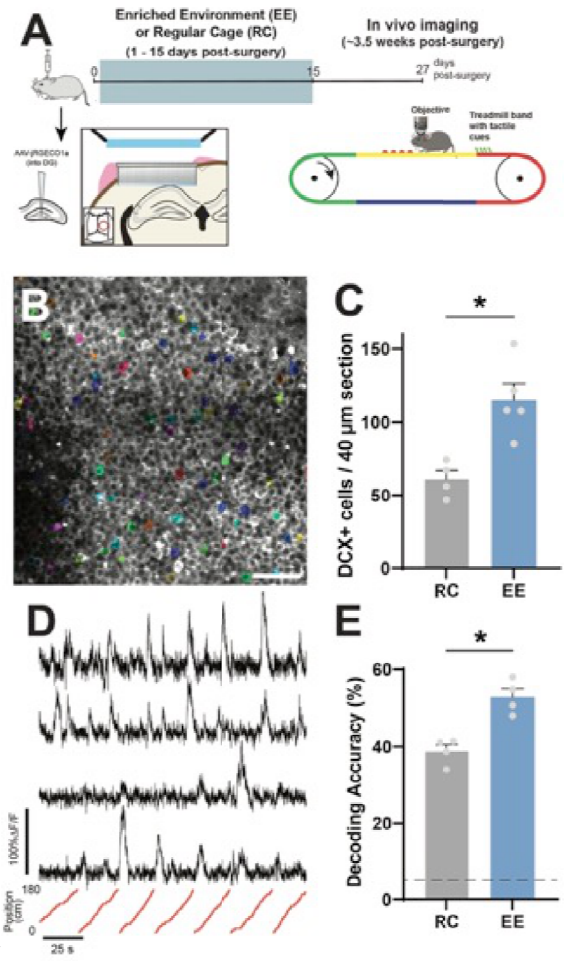
Our lab studies the circuit physiology of the hippocampus, and specifically how environment, aging and inflammation can modulate memory and learning. We use state-of-the-art in vivo two-photon Ca2+ imaging techniques in awake mice and we were pioneers in applying these imaging methodologies to the study of adult neurogenesis in the dentate gyrus (DG) of the hippocampus (Gonçalves et al. 2016a).

The DG is one of the few regions of the mammalian brain that keeps adding new neurons through adulthood in what probably constitutes the most robust form of neuronal plasticity in the adult brain. Adult-born neurons contribute to memory formation and defects in neurogenesis have been associated with several human neurological and psychiatric diseases such as epilepsy, Alzheimer's and schizophrenia. In addition adult-born neurons have also been used to study neuronal development.

We are particularly interested in understanding how adult neurogenesis in the DG may support hippocampal function, playing a role in memory and learning. In order to understand the function of adult-born neurons in the circuits underlying spatial memory we are studying the encoding of position in the hippocampus, including 'place cells' i.e. neurons that fire primarily when an animal is at a specific location.

We have previously found that adult neurogenesis improves the precision of neural representations of space in young mice (Frechou et al. 2022), when the mice are placed in a novel context. We also found that these representations, encoding for the position of the mouse within its surroundings, become less precise as animals age (McDermott et al. 2023). Our current work is building on these initial findings to identify the molecular and cellular pathways that mediate the effects of environment on spatial memory and cognition. Our emphasis is on the role of microglia and neuro-immune pathways in the formation of memories and neural representations of space in the hippocampus. Additionally we are interested in identifying the molecular determinants of spatial encoding by obtaining transcriptional profiles of previously imaged neurons, thus establishing a link between the molecular and neural encoding properties of individual cells.

From the Gonçalves lab



Environmental enrichment increases spatial information encoding in the DG. A) Experimental timeline, including surgery, enriched environment, and in vivo 2-photon imaging. B) Example of calcium imaging field of view. C) Exposure to an enriched environment results in an increase in number of DCX-expressing adult-born granule neurons. (p = 0.026, nRC = 4 mice, nEE = 5 mice, average of three 40µm slices per mouse, Mann-Whitney U test) D) Example calcium traces (top) and respective position of animal on the treadmill (bottom). E) Accuracy of linear decoder is higher in mice that were exposed to EE, indicating that EE calcium traces contain more spatial information. (p = 0.0286, n = 4 mice, 42 cells subsampled per mouse, Mann-Whitney U test). Dotted line is change performance level (5%).

Selected Publications

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Gronska-Peski M., Gonçalves J.T., Hébert J.M., Enriched Environment Promotes Adult Hippocampal Neurogenesis through FGFRs. *J. Neurosci.*;41(13), 2899–2910 (2021)

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David H. Hall, Ph.D.
Professor, Dominick P. Purpura Department of Neuroscience

The soil nematode *Caenorhabditis elegans* is a model system used to study the genetic control of cellular development. The Hall laboratory specializes in ultrastructural studies of the *C. elegans*. We use serial thin sections, electron microscopy, electron tomography, FIB/SEM and immunocytochemistry as primary tools to follow the development of identified neurons, particularly their axon outgrowth and synaptic connectivity. We also conduct collaborative studies on many other tissues in the embryo, larval, dauer, adult and aging nematode, including many epithelial tissues and the germline.

We host the Center for *C. elegans* Anatomy, supported by the NIH Office of the Director, and train students in anatomical methods for this system. Members of the lab are authoring the website www.WormAtlas.org. It displays nematode anatomy in great detail through multiple applications including Slidable Worm, a Handbook of all cells and tissues, the WormImage catalogue, a Glossary, and selected html texts of classic papers.

In collaboration with Scott Emmons, we are studying the complete connectome of *C. elegans* in both sexes and in larval stages to uncover how the nematode wiring diagram develops over time. In collaboration with Maureen Barr (Rutgers) we are studying the "tubulin code" which helps to stabilize ciliary microtubules during development and maintenance of the nematode's sense endings.

Selected Publications

Kinesin-3 mediated axonal delivery of presynaptic neurexin stabilizes dendritic spines and postsynaptic components. Oliver D, Ramachandran S, Philbrook A, Lambert CM, Nguyen KCQ, Hall DH and Francis MM (2022) *PLoS Genetics* 18: e1010016.

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Innexin function dictates the spatial relationship between distal somatic cells in the C elegans gonad without impacting the germline stem cell pool. Tolkin T, Mohammad A, Starich TA, Nguyen KCQ, Hall DH, Schedl T, Hubbard EJA and Greenstein D (2022) *Elife* Sept 13;e74955.

Large vesicle extrusions from C. elegans neurons are consumed and stimulated by glial-like phagocytosis activity of the neighboring cell. Wang Y, Arnold ML, Smart AJ, Androwski RJ, Morera A, Nguyen KCQ, Schweinsberg PJ, Bai G, Cooper J, Hall DH, Driscoll M and Grant BD (2023) *Elife* Mar 2:e82227.

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Mind of a dauer: comparative connectomics reveals developmental plasticity. Yim H, Choe D, Bae JA, Kang, H-M, Nguyen, K, Choi M-k, Ahn S, Bahn S-k, Yang H, Hall DH, Kim J and Lee J. (2023) Submitted to *Nature Communications* and *bioRxiv*.

Intermediate filaments associate with aggresome-like structures in proteostressed *C. elegans* neurons and influence large vesicle extrusions as exophers. Arnold ML, Cooper J, Androwski R, Ardeshna S, Melentjivic I, Smart AJ, Guasp R, Nguyen KCQ, Bai G, Hall DH, Grant BD and Driscoll M (2023) *Nature Comm*, in press.

The ABCB4 homolog PGP-14 establishes a lipid permeability barrier within the C. elegans cuticle. Kamal M, Tokmakjian L, Knox J, Han D, Moshi-

ri H, Magomedova L, Nguyen KCQ, Zheng H, Yeo M, Hall DH, Cummins CL and Roy PJ (2023) submitted to *PLoS Genetics*

Bryen A. Jordan, Ph.D.
Associate Professor, Dominick P. Purpura Department of Neuroscience
Associate Professor, Psychiatry and Behavioral Sciences
Associate Director, Rose F. Kennedy Intellectual and Developmental Disabilities Research Center

Understanding mechanisms that regulate long-term changes in neuronal function

Long-term changes in neuronal function require the regulation of gene expression. Studies initiated in the 1960s and onward have established that transcription is required for the establishment and consolidation of long-term memories in diverse organisms. Cellular processes linking neural communication to gene expression include the rapid influx of calcium into the nucleus and the nucleocytoplasmic shuttling of a broad array of proteins that specify the nuclear signal. Our lab is interested in identifying and characterizing the mechanisms linking specific synaptic activity to gene expression. To explore this question, we performed one of the first comprehensive proteomic analyses of rodent synapses (postsynaptic density fractions) and found that they are highly complex and contain proteins that can shuttle into the nucleus following synaptic activity (Jordan et al. 2004). We have studied several of these nuclear signaling molecules, including the novel synaptic component PRR7, which can shuttle into the nucleus and regulate c-Jun dependent transcription by controlling ubiquitination (Kravchick et al. 2016). A second protein we study is AIDA-1, which binds to NMDARs and controls nucleolar function (Jordan et al. 2007, Jacob et al. 2010, Tindi et al. 2015). These studies have provided some of the first evidence of direct synapse-to-nucleus communication and demonstrate that this process is an important cellular mechanism that can tailor and translate synaptic information into changes in gene expression (Jordan and Kreutz 2009).

Novel activity-dependent transcripts must then be localized within complex neuronal morphologies to provide synapse-specific regulation of function. RNA binding proteins (RNABPs) transport and translate specific mRNAs to enable the precise spatiotemporal expression of proteins across neurons. This process enables input-specific regulation of synaptic function and is essential for proper circuit regulation and brain function. Loss of RNABP activity is causal in a wide range of neurodegenerative and developmental disorders including Fragile X Syndrome (FXS), hereditary forms of Amyotrophic Lateral Sclerosis and Frontotemporal Dementia (FTD), intellectual disabilities, and epilepsy. We performed the first quantitative proteome-wide analyses of activity-dependent changes at synaptic junctions and found that diverse RNA binding proteins (RNABPs) were among the most altered protein families at synapses (Zhang et al. 2012). Indeed, 12 of 37 identified proteins whose levels changed with synaptic activity were RNABPs and included the heterogeneous nuclear ribonucleoproteins (hnRNPs) G, A2/B1, M, and D. Among these proteins was Sam68, a multifunctional RBP with reported roles in mRNA transport, translation, and alternative splicing. We found that Sam68 promotes the localization and translation of beta-actin (Klein et al. 2013), and Arc mRNA preferentially at distal dendrites of rodent hippocampal CA1 pyramidal neurons (Klein et al. 2015, Klein et al. 2019). Sam68 knockout mice display impaired metabotropic glutamate-receptor-dependent long-term depression (mGluR-LTD) and impaired structural plasticity exclusively at distal Schaffer-collateral synapses. Our work identifies an important player in Arc expression, provides a general framework for Sam68 regulation of protein synthesis, and uncovers a mechanism that enables the precise spatiotemporal expression of proteins that regulate long-term plasticity throughout neurons.

Using proteomics to understand Autism Spectrum Disorders

Autism spectrum disorders (ASDs) are highly complex and prevalent neurodevelopmental diseases with enormous social and economic impacts. Despite intense research into ASD pathophysiology, few available therapies exist due to a poor understanding of causative molecular and cellular mechanisms. The advent and use of next generation sequencing and genome wide association (GWAS) studies in humans have yielded many hundred ASD susceptible chromosomal loci and genes. While these targets have provided a wealth of minable information, this highly complex genetic architecture has hampered ongoing efforts to elucidate causal molecular pathways and to develop diagnostic tests and targeted therapies. A critical barrier is an incomplete understanding of how single nucleotide polymorphisms or variants (SNPs, SNVs), copy number variations (CNVs), or altered transcript abundance ultimately regulate protein abundance and cellular function. Moreover, widespread discrepancies between transcript and protein abundance strongly limit the usefulness of genomic information. Transcriptomes can display 100-fold ranges in translation efficiency, and proteins reveal >1000-fold ranges in

half-lives. Moreover, coupled transcriptome-proteome analyses reveal that proteins are ~900 times more abundant than corresponding mRNAs, but with ratios spanning five orders of magnitude. Genomic studies are also unlikely to provide significant information on diseases such as Angelman, Fragile X, and Tuberous sclerosis that are caused by dysfunction of regulators of protein translation and degradation. Despite these roadblocks, functional and bioinformatic analyses of genetic studies have identified potential convergent cellular pathways in ASD etiology, including those regulating transcription, excitatory/inhibitory (E/I) balance, and especially synaptic function.

We employ quantitative proteomic methods to elucidate molecular and cellular mechanisms underlying ASDs and other brain disorders. Our approach overcomes critical confounds associated with gene-based studies that ambiguously equate transcript levels, epigenetic modifications, SNVs, or CNVs to changes in protein abundance. Specifically, our lab is testing the hypothesis that ASD-linked susceptibility factors ultimately converge on a common signaling pathway regulating synaptic function, and that this point of convergence is key to understanding disease pathobiology. We propose that synaptic proteomes, as phenotypes of diverse ASD manifestations, capture the combined influences of genetic, epigenetic, transcriptomic, proteomic and environmental influences linked to ASD etiology. In our work, we leverage the availability of multiple ASD mouse models exhibiting shared synaptic deficits and behavioral correlates of autism and employ quantitative proteomic approaches to compare different syndromic and nonsyndromic ASD mouse models (Carbonell et al. 2021), as well as human ASD postmortem tissue. Results are then mined using network and systems biology approaches to identify shared cellular and molecular abnormalities. We hypothesize that identifying points of convergence will lead to important insights into ASD etiology and will yield high-value targets for pursuing therapies.

ANKS1B haploinsufficiency in a novel brain disorder

Neurodevelopmental disorders (NDDs) are highly prevalent brain diseases with enormous social and economic impacts. Due to their high heritability, numerous efforts are underway to identify causative genetic signatures. Genome-wide association studies and the advent and use of genetic screening in clinical settings have enabled rapid progress in identifying genes and other chromosomal loci linked to NDDs. However, these studies have revealed a highly heterogeneous genetic landscape consisting mainly of variants with statistically minor contributions to disease risk, and with unclear or minor effects on protein function. These uncertainties hinder attempts to infer causative molecular mechanisms. On the other hand, structural variants with major effects on single gene function are particularly useful as they establish a stronger link between one gene and a set of cellular and behavioral outcomes. We recently identified individuals in Israel, Australia, France, England, Ireland and the USA with heterozygous and monogenic copy number variations in the ANKS1B gene. Clinical evaluations reveal that patients exhibit a spectrum of NDDs, including ADHD, motor impairments, speech apraxia, and autism, which is present in >50% of patients. Whole-genome and exome sequencing analyses of patient samples identify no other confounding genetic variations potentially associated with disease. Our findings corroborate previous genome-wide and genetic studies implicating ANKS1B in brain disorders and formalize a link between ANKS1B haploinsufficiency and a previously uncharacterized NDD that we term ANKS1B haploinsufficiency syndrome (AnkSyd).

We have generated induced pluripotent stem cells (iPSCs), neurons, and brain organoids from patients and unaffected family members to elucidate cellular and molecular mechanisms underlying AnkSyd. We have also generated transgenic mouse models that display behavioral correlates of patient phenotypes (Carbonell et al. 2019). We find that neurons derived from patients show reduced expression of AIDA-1, the protein encoded by ANKS1B. AIDA-1 is one of the most abundant proteins at neuronal synapses and is enriched in hippocampal and cerebellar regions (Jordan et al. 2007, Jacob et al. 2010). AIDA-1 is specifically localized at postsynaptic densities (PSDs) where it binds to N-methyl-D-aspartate receptors (NMDARs) and the scaffolding protein PSD95, and shuttles to the nucleus in response to NMDAR stimulation (Jordan et al. 2007). Forebrain-specific Anks1b knockout mice show reduced synaptic expression of the NMDAR subunit GluN2B and impaired hippocampal NMDA-dependent synaptic plasticity (Tindi et al. 2015). The long-term goal of this research project is to define the mechanisms underlying this novel syndrome and to identify therapeutic targets.ANKS1B encodes for AIDA-1, a brain-specific protein that we have shown is enriched at neuronal synapses, and binds to and regulates NMDAR subunit composition and NMDAR-dependent synaptic plasticity. Our objectives are to test NMDAR function in patient neurons, elucidate mechanisms linking AIDA-1 to NMDAR function, and identify disease-relevant molecular pathways using discovery-based and reductionist approaches.

Selected Publications

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Kamran Khodakhah, Ph.D.

Professor, Dominick P. Purpura Department of Neuroscience
Professor,
Professor, Psychiatry and Behavioral Sciences
Florence and Irving Rubinstein Chair in Neuroscience
Vice Chair, Department of Psychiatry and Behavioral Sciences

The goal of our laboratory is to understand the role of the cerebellum and basal ganglia in motor function and in movement disorders. Of particular interest to us is not only to understand the role of each structure in motor control, but also the manner in which they communicate to coordinate and complement each other. We approach these questions from both basic science and clinical perspectives. We use a combination of techniques, from behavioral studies to imaging and two photon microscopy and electrophysiology (both *in vitro* and *in vivo*). Our studies take advantage of normal and transgenic animal models.

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Adam Kohn, Ph.D.

Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Ophthalmology and Visual Sciences
Professor, Departmen of Systems and Computational Biology
Isidor Tachna Professor in Ophthalmology
Interim Chair, Dominick P. Purpura Department of Neuroscience

Our laboratory studies the neural circuits that underlie visual perception, a general issue that we approach from several directions. For instance, we study how the responsivity and tuning of cortical neurons is altered by recent stimulus history. This form of rapid plasticity—termed adaptation—has strong perceptual effects, allowing us to explore the neurophysiological underpinnings of perceptual phenomena. In addition, we are interested in understanding the functional benefit of adaptation and in learning how adaptation early in the visual system affects subsequent stages of processing. We hope that by understanding the principles of adaptation we will also gain insight into other forms of plasticity such as perceptual learning and recovery from injury. We also study how populations of neurons function together to encode information about the visual world. We record from small populations of neurons simultaneously and measure the correlation of their responses. In particular, we explore how correlation depends on stimulus parameters, recent stimulus history, and cortical location. The primary techniques of the lab are neurophysiological recordings, computational modeling, and psychophysics. We hope that employing a range of experimental techniques will help us understand the computations carried out by the visual system and the circuits that perform them.

Selected Publications

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Peri Kurshan, Ph.D.

Assistant Professor, Dominick P. Purpura Department of Neuroscience

Studying synaptic development and function using *C. elegans*

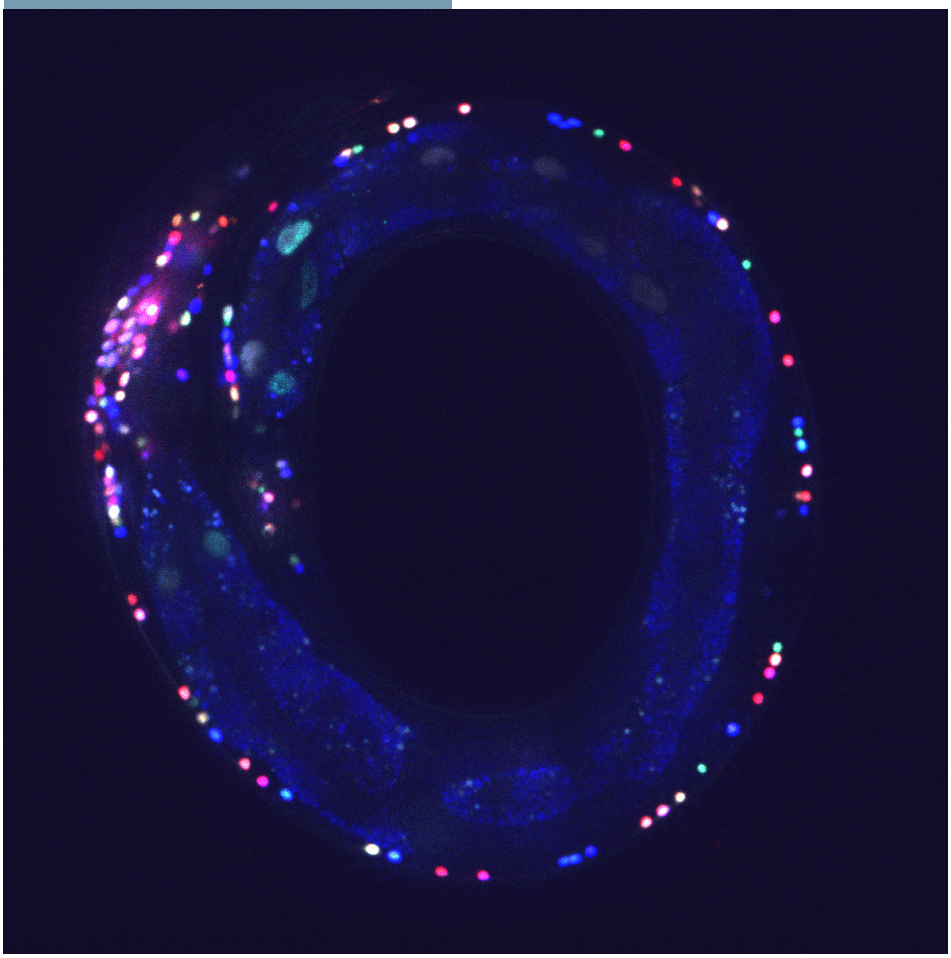
Defects in the proper development and function of synapses lead to neurodevelopmental disorders such as Autism and Intellectual Disability, however the molecular mechanisms underlying these processes are still largely unknown. We use the nematode *C. elegans*, which has a simple and stereotyped nervous system and whose connectome has been fully mapped out, 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 discoveries suggesting that the role of synaptic cell adhesion molecules such as Neurexin may be different than initially hypothesized, as we have shown that its role in presynaptic development is independent of extracellular activation and downstream of other initiating factors.

Lab website:
https://kurshanlab.org

Selected Publications

Synaptogenic pathways. Kurshan PT Shen K. *Curr Opin Neurobiol.* 2019 Apr 12;57:156–162. doi: 10.1016/j.conb.2019.03.005. [Epub ahead of print] Review.

From the Kurshan lab



All 302 neurons that make up the C. elegans nervous system are individually recognizable using color-coded markers such as this one. Combined with a fully-mapped synaptic connectome, the optical and genetic accessibility of this organism together make it a great model system to study the molecular mechanisms of synapse formation and the synaptic defects associated with human neurodevelopmental disorders.

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Herbert M. Lachman, M.D.

Professor, Department of Psychiatry and Behavioral Sciences
Professor, Department of Medicine (Hematology)
Associate Professor, Dominick P. Purpura Department of Neuroscience
Associate Professor, Department of Genetics

Schizophrenia (SZ) is a common psychiatric disorder affecting ~1% of humanity, leading to a lifetime of disability for a majority of patients. Twin

studies show a high level of heritability (~80%). However, lack of complete concordance in monozygotic twins suggests that environmental and epigenetic factors might play a substantial role in disease pathogenesis. A significant obstacle in studying the molecular basis of SZ 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 induced pluripotent stem cells (iPSCs) provides an opportunity to create patient-specific neurons *in vitro*. The Lachman lab has been developing iPSCs cells from controls and patients with SZ, including a subset that carries a well characterized 22q11.2 del found in ~1% of patients. Neurons derived from both are being subjected to gene expression profiling using RNA-seq and epigenetic analysis to identify patient vs control differences. We are particularly interested in characterizing miRNAs and long non-coding RNAs in this system. It should be noted that one of the genes in the 22q11.2 deleted region is DGCR8, which is involved in miRNA processing. In addition, we are using a gene knockdown approach to identify downstream targets of genes that code for transcription factors implicated in the development of subgroups of SZ. The ultimate goal is to identify molecular pathways that could be targets for developing novel drug therapies.

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Mark F. Mehler, M.D.
Professor, The Saul R. Korey Department of Neurology
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Psychiatry and Behavioral Sciences
Alpern Family Foundation Chair in Cerebral Palsy Research
Chair, The Saul R. Korey Department of Neurology
Director, Institute for Brain Disorders and Neural Regeneration

The primary focus of our laboratory is on defining the regional localization and the biological properties of neural stem cells during embryonic and postnatal development and in the mature and the aging mammalian brain. We are also using stem cells as "biological probes" to elucidate the pathogenesis of a spectrum of complex and poorly understood acquired and genetic nervous system disorders. In these prototypical disorders, distinct profiles of regional stem cells or their more lineage restricted neu-

ronal or glial progeny undergo irreversible injury and death in response to acute or more chronic injury signals. Further, we are attempting to use the knowledge gained from these multi-disciplinary studies to design innovative epigenetic- and stem cell-based regenerative therapies.

We are in the process of defining the dynamic roles of environmental factors, cell-cell signaling pathways and cell autonomous cues in promoting stem cell activation, expansion, lineage restriction, lineage commitment, cell cycle progression and terminal differentiation. We have identified specific transcription factor and epigenetic codes that endow the progeny of specific stem cell subpopulations with their unique cellular properties. These insights have already allowed us to "reprogram" different regional stem and progenitor cells both *in vitro* and *in vivo* to acquire the cellular properties of specific neuronal and glial subtypes that are lost in different classes of neurological diseases. We have also utilized embryonic stem cells, both to define initial stages of neural induction and patterning of the neural tube that have previously been difficult to examine experimentally, and as therapeutic reagents for those diseases of the nervous system in which multiple regional neuronal and glial subtypes are targeted.

A better understanding of the pathogenesis of individual neurological disorders will allow us to more effectively employ our emerging neural regenerative strategies. For example, we are investigating the novel and exciting possibility that early developmental abnormalities are important in the etiology of disorders of the aging brain, namely neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's Diseases as well as amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). We are also examining the hypothesis that primary brain tumors are caused by two distinct types of gene mutations: i. Mutations in selected genes that promote progressive stages of neuronal and glial maturation from neural stem cells, and ii. Mutations in different classes of genes that normally prevent mature glial cells from undergoing ectopic cell cycle reentry and dedifferentiation. Further, we are attempting to define the individual profiles of abortive endogenous stem and progenitor cell responses to those injury signals found in acute stroke and in demyelinating diseases such as multiple sclerosis.

The ultimate aim of these studies is to identify innovative approaches to brain repair by activation of latent neural stem cell pools throughout the neuraxis to engage in selective regeneration of those cell types and neural network connections that have been compromised in specific disease states. We are utilizing advanced epigenetic reprogramming strategies, including the deployment of multiple novel classes of non-coding RNAs to modulate the dynamic expression profiles of individual genes and integrated functional gene networks through genome-wide targeting of specific DNA motifs/stereoisomers, histone, nucleosome and higher-order chromatin codes and complexes, RNA/DNA editing, and RNA intra-/inter-cellular trafficking. The ability to activate and recruit these latent developmental programs to participate in selective neural regenerative responses will help to reestablish functional neural networks that preserve the integrity of previously acquired informational traces.

Moreover, we are currently employing interdisciplinary approaches, including the use of specialized human patient-specific integrative organoid models and gene editing and associated dynamic lineage tracing, single cell and spatial transcriptomics, histone, chromosomal and epigenomic and additional multi-omics technologies, to define the underlying molecular, subcellular, cellular, mechano-signaling and systems biological substrates and network properties and critical periods that orchestrate cell identity, cell state transitions, and multifaceted injury and inflammatory responses that govern emerging interrelationships amongst neurodegenerative diseases, organ fibroses, brain and body-derived cancer subtypes, organ metastases, prior tumor/metastatic cell dormancy mediators and associated regenerative programs. These exciting new initiatives will determine cross-modulatory interactions between these classical diseases of aging, their developmental antecedents, intervening homeostatic and plasticity programs, regenerative processes and plasticity and novel multipronged therapeutic interventions to forestall and/or prevent the onset and progression of these intractable and frequently overt and/or latent multimorbid conditions.

Selected Publications

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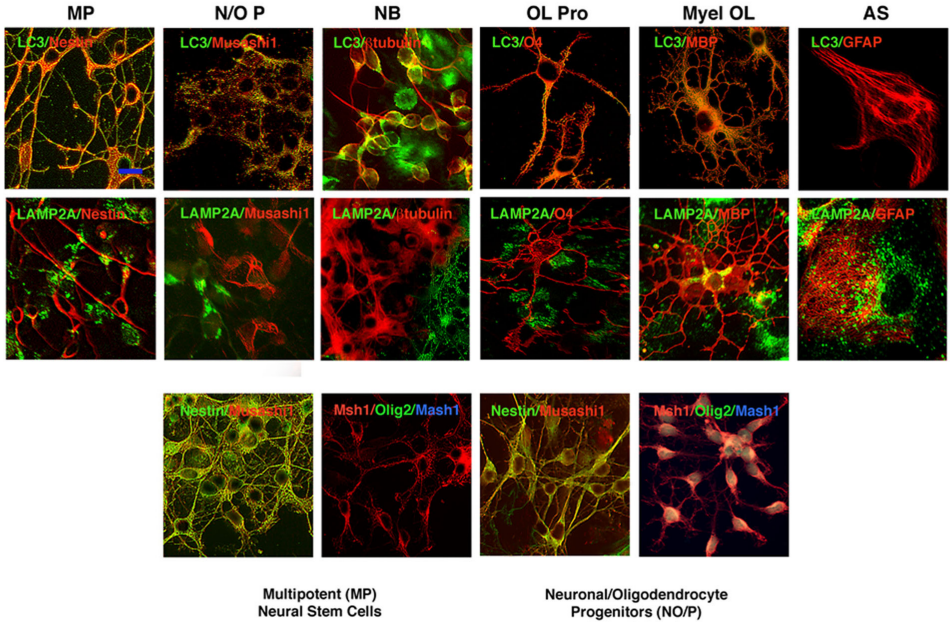
Mehler MF. Shining a light on early stress responses and late-onset disease

From the Mehler lab



Expression profiles of autophagic markers in neural developmental species derived from embryonic mouse forebrain. Specific neural developmental species were co-stained for LC3, a macroautophagy-related protein (top) or LAMP-2A, a CMA-related protein (bottom), and antibodies for multipotent neural stem cells (MP: nestin), neuronal/oligodendrocyte progenitors (N/O P: musashi 1), neuroblasts (NB: ?-tubulin), oligodendrocyte progenitors (OL Pros: O4), myelinating oligodendrocytes (Myel OL: MBP), and astrocytes (AS: GFAP). (Scale bar: 10mm). CMA-associated LAMP 2A and autophagosome marker LC3 suggest that while LAMP 2A expression was seen in b-tubulin + neurons and GFAP+ astrocytes, nestin positive undifferentiated multipotent neural stem cells (MP), more lineage restricted neuronal/oligodendrocyte progenitors (N/OP) and mature myelin producing oligodendrocytes are enriched for autophagosomes. LAMP 2A and LC3 are labeled with FITC conjugated secondary antibodies while all other neural lineage markers were identified with TRITC. Nestin+ MP reveals the absence of expression of basic helix loop helix transcription factors Olig2 and Mash1. However, Shh-mediated lineage restriction in vitro induces nuclear expression of these transcription factors in N/O P cells labeled with another neural stem cell marker Musashi1 (Msh1). b-tubulin and O4 label neuroblasts and oligodendrocyte progenitors, respectively. Finally, while MBP is expressed by mature myelin producing oligodendrocytes, GFAP expression identifies astrocytes.

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Qureshi IA, Gokhan S, Mehler MF. REST and CoREST are transcriptional and epigenetic regulators of seminal neural fate decisions. *Cell Cycle*. 2010 Nov 15;9(22):4477–86. PMCID: PMC3048046.

Sophie Molholm, Ph.D.
Professor Department of Pediatrics
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Psychiatry and Behavioral Sciences
Director, Rose F. Kennedy Intellectual and Developmental Disabilities Research Center, Dominick P. Purpura Department of Neuroscience
Harold and Muriel Block Faculty Scholar in Mental Illness

I am interested in how the human brain processes and integrates sensory inputs to impact perception and behavior, and the role of attention therein. My work involves characterizing these processes in healthy adults, charting their developmental course over childhood, and translating these

findings to understand the neurobiology of developmental disorders, with an emphasis on autism. Non-invasive high-density recordings of the electrical activity of the brain, psychophysics, and magnetic resonance imaging are my primary tools of investigation. The former allows precise tracking of the temporal progression of cortical information processing, and modeling of the underlying neuronal generators. Used in conjunction with structural and functional neuroimaging, precise anatomical localizations of function can be achieved.

In addition to myself, the lab includes senior faculty (John Foxe and Filipo De Sanctis), junior faculty (Lars Ross and John Butler), post-doctoral fellows, and students. I also direct the Einstein Human Clinical Phenotyping Core, which recruits and characterizes participants for studies and maintains a large database of potential research participants. This database is composed largely of children, including those with a diagnosis of dyslexia, autism, and RETT syndrome, as well as healthy controls.

Selected Publications

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Beker, S., Foxe, J.J., Molholm, S. (2018). Ripe for solution: Delayed development of multisensory processing in autism and its remediation. *Neuroscience Biobehavioral Reviews*, 84:182–192.

Foxe, J.J., Molholm, S., Baudouin, S.J., Wallace, M.T. (2018). Explorations and perspectives on the neurobiological bases of autism spectrum disorder. *European Journal of Neuroscience*, 47, 488-496.

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Solomon L. Moshé, M.D.

Professor, The Saul R. Korey Department of Neurology
Professor, Department of Pediatrics
Professor, Dominick P. Purpura Department of Neuroscience
Charles Frost Chair of Neurosurgery and Neurology
Director, Division of Pediatric Neurology, The Saul R. Korey Department of Neurology
Director, Division of Neurology, Department of Pediatrics
Director, Clinical Neurophysiology, The Saul R. Korey Department of Neurology

Since 1979, Dr. Moshé's research has focused on translational approaches to understand the mechanisms underlying the development of epilepsy and its consequences in infants and children. His laboratory has developed and patented an animal model that replicates human infantile spasms. In collaboration with Dr Aristea Galanopoulou, this model is being used to identify novel treatments of this devastating condition. His work has identified an endogenous brain circuit that can control the expression of seizures as a function of age and gender. In addition to his laboratory research, he is actively involved in several large, multi-center studies examining the outcomes of prolonged, febrile seizures (seizures occurring with fever) and absence epilepsy to identify predictive biomarkers of the course and response to treatment. In more than 20 years,

Dr. Moshé has mentored numerous scientists and clinicians from around the world in clinical epilepsy and basic science epilepsy-related research.

Dr. Moshé is active in numerous professional societies and elected President of the American Epilepsy Society, the American Clinical Neurophysiology Society, the Eastern Association of Electroencephalographers, and past President of The International League against Epilepsy. He is an elected member of the American Neurological Association and the American Pediatric Society.

Selected Publications

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Saleem M. Nicola, Ph.D.

Associate Professor, Dominick P. Purpura Department of Neuroscience
Associate Professor, Department of Psychiatry and Behavioral Sciences

My lab focuses on understanding the neural circuits underlying reward-seeking and addictive behaviors. We use a systems-level approach that combines behavioral, pharmacological, electrophysiological, optogenetics and fiber photometry techniques in awake, freely moving animals.

Our studies focus on the nucleus accumbens, a part of the ventral striatum that projects to motor output structures of the basal ganglia. The accumbens receives input from limbic structures that process stimuli that predict rewards. These limbic structures include the basolateral amygdala, which sends glutamatergic axons to the accumbens, and the ventral tegmental area (VTA), which sends a dopamine projection. We investigate how these projections to the accumbens alter the activity of accumbens neurons to influence reward-seeking behavior.

The accumbens and associated circuitry is involved in drug addiction. A secondary focus of the lab is to understand how drugs alter neurons in these circuits to produce drug-seeking behavior.

Selected Publications

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not goal tracking, is resistant to outcome devaluation. *Front. Neurosci*. 9: article 468. https://dx.doi.org/10.3389/fnins.2015.00468

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José L. Peña, M.D., Ph.D.
Professor, Dominick P. Purpura Department of Neuroscience

The owl's brain is a showcase in Systems Neuroscience for allowing the analytical approach to how information is processed and represented in the brain. Owls exhibit a characteristic orienting response towards sound sources. This behavior is highly reproducible, the variables involved in triggering specific responses are well characterized, and the system affords progressively deeper levels of analysis. Whereas spatial selectivity of neurons in the owl's auditory system is initially broad and ambiguous, sharp space-specificity emerges in high-order neurons. In the midbrain, a map of auditory space is computed based on differences in time and intensity of the acoustic signals that arrive at each ear. These binaural cues are processed in parallel pathways that converge where the map emerges. We have focused on regions of the brain that are crucial for this synthetic process: the neurons where the difference between the arrival times of the sound to each ear is initially detected, and the space-specific neurons that respond to sounds coming from unique directions. We found that well-defined computations, which match predictions made by studies of sound localization in humans, underlie the emergent response properties of these neurons. Thus, the owl's brain provides a system to test models of psychoacoustics at levels from single cells to networks of neurons. Recently, we have studied why owls make systematic errors when localizing in peripheral space. We could predict these errors from looking at how space is represented in the owl's brain. In addition, we could show how making errors in the periphery could help to localize in the front. In the future, we plan to study how information flows in the sound localization pathway using *in vitro* electrophysiology as well as the recording of neural activity in behaving animals.

Selected Publications

Shadron K, Pena JL (2023) Development of frequency tuning shaped by spatial cue reliability in the barn owl's auditory midbrain. *eLife*, 12:e84760.

Ferger R, Shadron K, Fischer BJ, Pena JL (2021) Barn Owl's Auditory Space Map Activity Matching Conditions for a Population Vector Readout to Drive Adaptive Sound Localizing *Behavior. J. Neurosci*. 41(50):10305–10315.

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Beckert MV, Pavao R, Pena JL (2017) Distinct correlation structure supporting a rate-code for sound localization in the owl's auditory forebrain. *eNeuro*, https://doi.org/10.1523/ENEURO.0144–17.2017.

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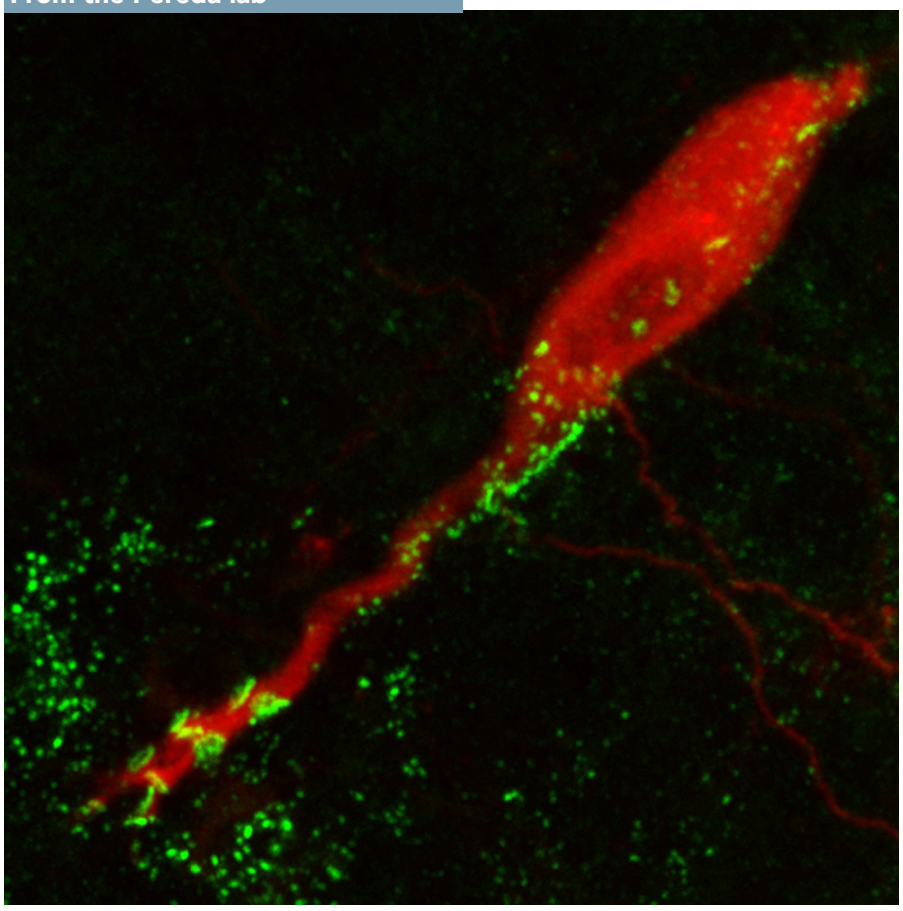
Alberto E. Pereda, M.D., Ph.D.

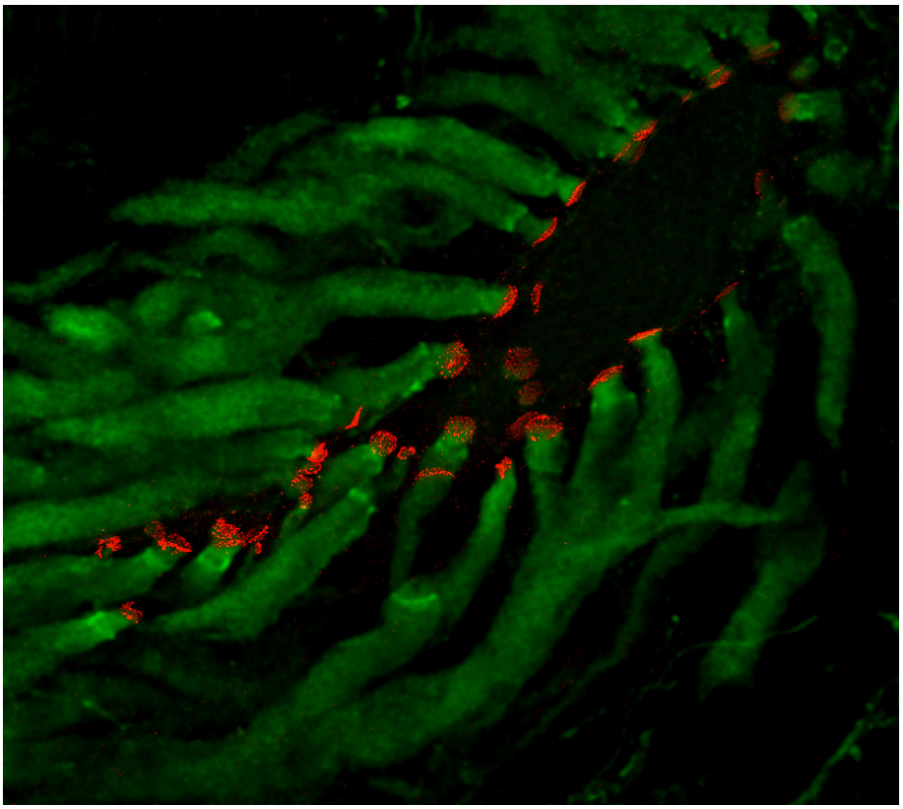
Professor, Dominick P. Purpura Department of Neuroscience

The laboratory investigates the properties and dynamics of gap junction-mediated electrical transmission in the vertebrate brain. While the study of plasticity of chemical synapses has long been an area of primary interest to neuroscientists, less is known about the modifiability of electrical synapses. We investigate plastic properties of electrical synapses in teleosts (goldfish and zebrafish) and mammals. Lower vertebrates have provided with advantageous experimental models in which basic properties of electrical transmission can be more easily study. Auditory "mixed" (electrical and chemical) synaptic contacts on the teleost Mauthner cells offer the rare opportunity to correlate physiological properties with molecular composition and specific ultrastructural features of individual synapses. Electrical transmission at these terminals undergo activity-dependent potentiation and is mediated by gap junctions formed by fish homologs of connexin 36, a neuronal gap junction protein widely distributed across the mammalian brain. Our current work focuses on the mechanisms underlying activity-dependent changes in electrical synapses by investigating: i) Their functional relationship with glutamate receptors, ii) Their interaction with the dopaminergic and endocannabinoid systems, iii) The molecular mechanisms responsible for changes in the strength of electrical transmission, in particular the role of trafficking of gap junction channels and interactions with connexin-associated regulatory proteins, iv) Interactions

From the Pereda lab



Laser-scanning confocal projection. Labeling for Cx35 (green) in a Mauthner cell of larval zebrafish backfilled with tetramethylrhodamine-dextran (red). (from Yao et al, 2014).



Laser-scanning confocal projection of the lateral dendrite of a goldfish Mauthner cell (unstained) illustrating saccular afferents (green) terminating as large myelinated Club endings. Labeling for Cx35 (red) reveals the areas of contact between Club endings and the dendrite. (from Flores et al., 2010)

between intrinsic membrane properties and gap junctional conductance, as a mechanism for the control of synaptic strength at electrical synapses. Thus, while focusing in the properties of electrical synapses, the research of our laboratory explores the complexity of synaptic transmission and signaling mechanisms in general.

Selected Publications

Lasseigne A., Echeverry F., Ijaz S., Michel J., Martin A., Marsh A., Trujillo E., Marsden K., Pereda A., Miller A. (2021) Electrical synaptic transmission requires postsynaptic scaffolding protein, *eLife*,10:e66898.

Alcamí P. and Pereda A. (2019) Beyond plasticity: the dynamic impact of electrical synapses on neural circuits, *Nature Reviews Neuroscience*, 20:253-271.

Marsden K.C., Jain R.A., Wolman M., Echeverry F.A., Nelson J.C., Hayer K.E., Miltenberg. B., Pereda A.E., and Granato M. A (2018) Cyfip2-dependent excitatory interneuron pathway establishes the innate startle threshold. *Cell Reports*, 23:878–887.

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Curti S., Hoge G., Nagy J.I. and Pereda A. (2012) Synergy between electrical coupling and membrane properties promotes strong synchronization of neurons of the mesencephalic trigeminal nucleus. *The Journal of Neuroscience* 32:4341–4359.

Flores C., Nannapaneni S., Davidson K., Yasumura T., Bennett, M.V.L., Rash J.R. and Pereda A. (2012) Trafficking of gap junction channels at a vertebrate electrical synapse *in vivo*. *Proceedings of the National Academy of Sciences (USA)* 109:E573–582.

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Jelena Radulovic, M.D., Ph.D.

Professor, Dominick P. Purpura Department of Neuroscience
Sylvia and Robert S. Olnick Chair in Neuroscience
Director, Psychiatry Research Institute Montefiore Einstein (PRIME)

The Radulovic laboratory researches the neurobiological mechanisms by which stressful experiences shape memory circuits, and through these actions contribute to the development of anxiety, stress-related, and dissociative disorders. Our main goal is to dissect those mechanisms that can serve as potential treatment targets. To this end, we have developed several preclinical models for studying disorder-relevant behavioral phenotypes, including stress-enhanced fear conditioning, extinction-resistant fear, state-dependent fear, and overgeneralization of fear. These phenotypes are characterized by defensive behavior typical of exaggerated or persistent fear and anxiety, and, according to our main hypothesis, they are critically dependent on the accessibility of stress-related memories to retrieval.

At the circuit level, we focus on the extended hippocampal system, which plays a well-established role in the representation and retrieval of episodic-like memories. By using circuit tracing and circuit-specific manipulations in genetically modified mice, we are researching the role of individual hippocampal afferent and efferent projections in these processes. These manipulations include optogenetic, chemogenetic, and pharmacogenetics approaches (1,2). We also study, using analyses of local field potentials and neuronal oscillations, the role of coordinated activity of hippocampus-associated regions in the retrieval of memories of stressful experiences (3).

At the cellular level, we have primarily focused on the excitatory neurons of the dorsal hippocampus, especially the dentate gyrus and CA1 neurons, but have currently expanded our scope to individual interneuronal populations (4,5). We use robust activity marking systems to label and manipulate these neuronal populations and thereby interrogate their role in memory-related defensive behavior.

At the molecular level we have traditionally focused on synaptic mechanisms, especially the different glutamate receptor subunits and their signaling partners. Recently, however, our interest extended to nonsynaptic mechanisms, such as tonic inhibition, neuroinflammation, and reorganization of the extracellular matrix, which we study in the context of stabilization of long-term memory cir-

cuits. In the framework of tonic inhibition, we also study the role of micro RNAs (6,7).

Selected Publications

1. Yamawaki N, Corcoran KA, Guedea AL, Shepherd GMG, Radulovic J. Differential Contributions of Glutamatergic Hippocampal→Retrosplenial Cortical Projections to the Formation and Persistence of Context Memories. *Cereb Cortex*. 2019 Jun 1;29(6):2728–2736. doi: 10.1093/cercor/bhy142. PMID: 29878069; PMCID: PMC6519694.
2. Han Y, Zhang Y, Kim H, Grayson VS, Jovasevic V, Ren W, Centeno MV, Guedea AL, Meyer MAA, Wu Y, Gutruf P, Surmeier DJ, Gao C, Martina M, Apkarian AV, Rogers JA, Radulovic J. Excitatory VTA to DH projections provide a valence signal to memory circuits. *Nat Commun*. 2020 Mar 19;11(1):1466. doi: 10.1038/s41467-020-15035-z. PMID: 32193428; PMCID: PMC7081331.
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Rachel A. Ross, M.D., Ph.D.

Assistant Professor, Dominick P. Purpura Department of Neuroscience

Co-primary, Assistant Professor, Department of Psychiatry and Behavioral Sciences

All organisms need to adjust their behavior to adapt to a changing environment. Feeding behaviors, for example, depend upon both internal states (i.e. hunger) and external realities, (i.e. food availability). Stress influences food-based decision making and metabolic outcomes, and failures in this behavioral regulation can lead to disease states, such as anorexia nervosa or obesity. Our translational laboratory uses systems neuroscience tools to better understand the pathophysiology and biology that underlies the behavior related to these diseases in hopes of reducing the associated stigma. We are focused on how neuropeptides regulate specific circuits at the interface of stress and metabolism, with an interest in sex differences and behavior differences that result in outcomes across the weight spectrum related to psychiatric and medical illness. We concentrate on two neuropeptidergic systems: the metabolism associated melanocortinergic system, and the stress-linked PACAP system. In rodent models we use a combination of behavior studies, electrophysiology, *in vivo* Ca^{2+} imaging, pharmacologic, optogenetic, and chemogenetic manipulations to interrogate how these neuropeptides regulate neural circuits at the interface of stress and metabolism. In collaboration with clinical researchers, we work to apply our findings to inform investigations into human behavior using molecular, genetic, and qualitative approaches.

Current projects in the lab include:

- What is the role of the melanocortin-4 receptor in the medial prefrontal cortex in cognitive flexibility. Is it specific to food-related decision making?
- Does metabolic stress transmit a PACAPergic signal, and how is this different between males and females? How does this affect the reproductive axis?
- How does dietary manipulation (e.g. early life food insecurity) affect behavioral and metabolic outcomes?

Selected Publications

Ross RA*+, Kim A*, Das P, Li Y, Choi YK, Thompson AT, Douglas E, Subramanian S, Ramos K, Callahan K, Bolshakov VY, Ressler KJ. Prefrontal cortex melanocortin 4 receptors (MC4R) mediate food intake behavior in mice. *Physiology and behavior* (June 25, 2023). *These authors contributed equally to this work.

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Stephanie Rudolph, Ph.D.
Assistant Professor, Dominick P. Purpura Department of Neuroscience
Co-primary, Assistant Professor, Department of Psychiatry and Behavioral Sciences

Behavioral flexibility requires the brain to constantly adapt to environmental changes and physiological state. In response to such external and internal challenges, context-specific neuromodulators act on local and long-range circuits to orchestrate functionally and anatomically connected brain regions that ultimately control behavior. Due to its abundant connections to other parts of the brain, the cerebellum has emerged as an important structure that regulates diverse behaviors, including motor function, cognitive processes, and emotional state. Accordingly, disruption of normal cerebellar function is prevalent in psychiatric and neurodevelopmental disorders, such as schizophrenia and autism. Our laboratory is using a combination of electrophysiology, genetic approaches, imaging, and behavioral testing to better understand the mechanisms that allow the cerebellum to control behavior under physiological and pathophysiological conditions.

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Gary J. Schwartz, Ph.D.
Professor, Department of Medicine (Endocrinology)
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Deparment of Psychiatry and Behavioral Sciences

Our research focuses on the sensory neural controls of energy homeostasis in health and disease. We use rodent and non-human primate models to examine how food stimuli act at oral and gastrointestinal sites to affect

food intake, energy balance, and gastrointestinal physiology. We approach this problem from multiple levels of analysis including behavioral, physiological, neurophysiological, and molecular-genetic. We have identified the type of food stimuli that activate vagal and splanchnic sensory fibers supplying the gut, and have revealed the extent to which these stimuli influence gut-brain communication. Our most recent efforts involve the analysis of gut-brain communication in the control of energy homeostasis in mouse models of obesity and diabetes. We have identified neurons in the periphery, brainstem and hypothalamus that integrate food-elicited signals with peptide signals that have profound effects food intake and metabolism. Data from these studies reveal that central hypothalamic and brainstem neuropeptides affect food intake and body weight by modulating the neural potency of food stimulated signals from the mouth and gut. This novel, synthetic conceptual framework is critical because it links forebrain hypothalamic structures, long known to be involved in the control of energy balance, to the sensory and motor systems in the brainstem that control ingestion, digestion, and metabolic processing of food. Future studies will use genetic mouse models of obesity and diabetes with targeted conditional neuropeptide/ receptor knockdown or replacement to determine how central neuropeptide signaling affects the neural processing of metabolic sensory signals critical to energy homeostasis.

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Julie Secombe, Ph.D.

Associate Professor, Department of Genetics

Associate Professor, Dominick P. Purpura Department of Neuroscience

One major research interest in my lab focuses on understanding a single protein—a transcriptional regulator called lysine demethylase 5 (KDM5). In humans, mutations in KDM5 are found in patients with intellectual disability, but how mutations in KDM5 affect neuronal development and function remain largely unknown.

We use two different neuronal contexts in the model organism *Drosophila* to understand KDM5 function. Both of these take advantage of our ability to make fly strains that completely lack KDM5 in addition to strains that harbor specific mutations in KDM5 that are found in patients with ID.

(1) **Development and function of mushroom body neurons.** The fly adult mushroom body is essential for olfactory learning and memory and is functionally analogous to the mammalian hippocampus. In a project pioneered by MSTP student Hayden Hatch, we have shown that KDM5 is required in early neuronal progenitors for the formation of the mushroom body. **Potential ROTATION PROJECTS**: What genes does KDM5 directly bind to and regulate to mediate mushroom body development? What happens to chromatin? What are the cognitive (learning and memory) consequences of mutations in KDM5?

(2) **Development and function of the larval neuromuscular junc-**

tion (NMJ). The second system we use is the larval NMJ. This is a glutamatergic synapse that serves used as a model of mammalian CNS excitatory synapses. This model was established in my lab by PhD student Helen Belalcazar, who is about to start writing her thesis. Using the NMJ as a model, we have shown that KDM5 acts by multiple mechanisms to regulate the morphology and neurotransmission. **Potential ROTATION PROJECTS**: What genes does KDM5 regulate specifically in motor neurons (using in vivo transcriptomic techniques)? KDM5 affects evoked glutamatergic neurotransmission—how? Mutations in KDM5 affect larval movement but not by altering the NMJ—why? How many ID-associated mutations alter NMJ morphology and function?

Selected Publications

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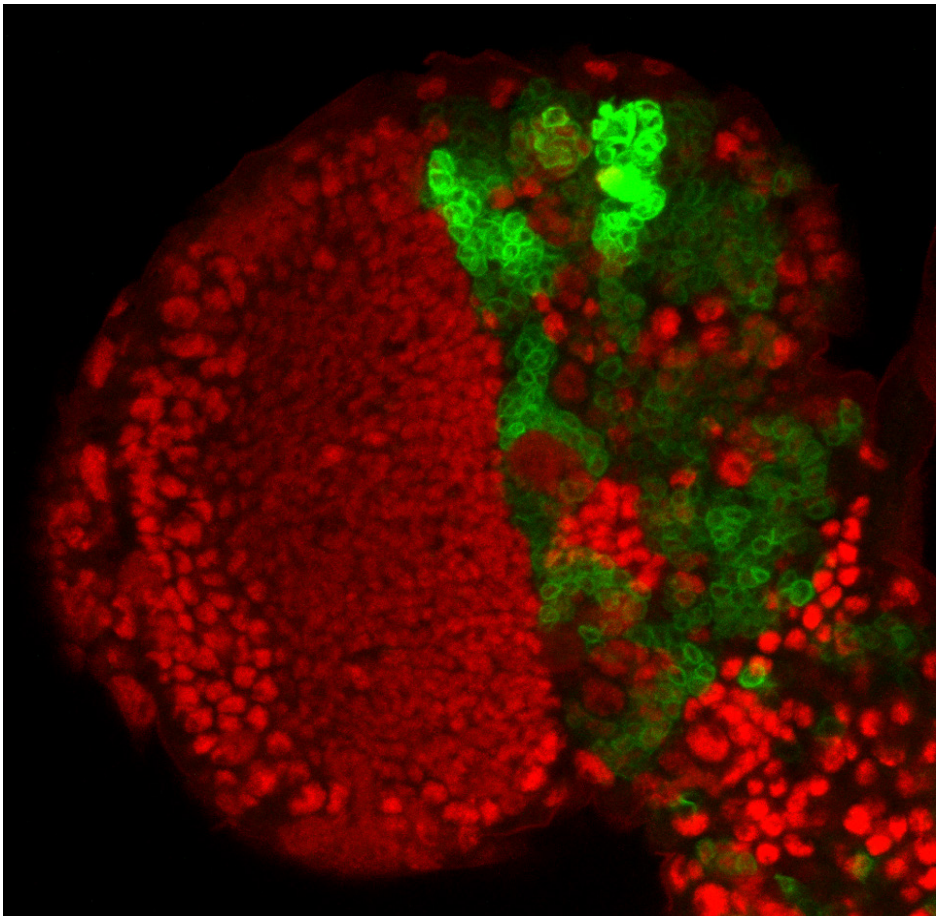
From the Secombe lab



Drosophila brain with the neuronal precursors labeled in green and the transcription factor KDM5 labeled in red.

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David J. Sharp, Ph.D.
Professor, Department of Physiology & Biophysics
Professor, Department of Ophthalmology & Visual Sciences
Professor, Dominick P. Purpura Department of Neuroscience

The life of a cell in multicellular organisms is complex and proceeds through multiple stages, beginning with its "birth" from the division of preexisting cells, movement from its "birth" site to a distal target, differentiation into a form designed for a specialized task and then, finally, its death. All of these events are in one way or another influenced by micro-

tubules, intrinsically dynamic and structurally polar polymers of alpha/beta-tubulin further organized into higher order arrays that vary according to the immediate needs of the cell. While probably best known as directional railways for the motor driven transport of intracellular cargos, microtubules also form the spindle apparatus that separates chromosomes and defines the site of cell cleavage during mitosis/meiosis, provide structural support for the formation of elongate cell shapes and regulate the behaviors of other cytoskeletal networks, such as actin, through mechanisms that remain poorly understood. The broad objective of my research program is to identify the fundamental molecular mechanisms that goven the formation and function of the microtubule cytoskeleton and determine how these contribute to human health and disease.

Specific ongoing research projects include:

I) Determining the mechanisms of chromosome segregation. The mitotic spindle is a self-organizing microtubule-based machine that segregates chromosomes into identical daughter nuclei during cell division. Defects in spindle assembly and the movement of chromosomes on it give rise to cells with too many or two few chromosomes (aneuploidy) which is a hallmark of tumorigenesis. Previous work from my laboratory has shown that the mitotic spindle moves chromosomes by a Pacman-Flux mechanism involving the coordinated activities of microtubule depolymerizing and severing enzymes (e.g. Rogers et al, Nature, 2004; Zhang et al, The Journal of Cell Biology, 2007, Rath and Sharp, Chromosome Research, 2011)

II) Determining the roles of microtubules in cell motility. The ability of cells to migrate from their sites of origin to distal targets is fundamental to the development and maintenance of multicellular organisms. Defects in cell migration have also been linked to numerous human pathologies ranging from mental retardation to cancer metastasis. Decades of work have established that somatic cell motility is driven by a polarized actomyosin network that, among other things, promotes protrusion of the membrane at the cell front (leading edge) and contractility at the rear. Much less is understood about the contributions of microtubules to these processes. However, we recently showed that the microtubule severing enzyme, Katanin, localizes to the cell cortex and netatively regulates cell motility by suppressing actin-based protrusions (Zhang et al, Nature Cell Biology, 2011) We have since identified a number of additional microtubule regulatory proteins (some of which are entirely uncharacterized in the literature) that control distinct parameters of cell movement. Elucidation of the specific functions and mechanisms of action of these is a major current thrust of my research program.

III) Development of novel therapeutics. We have found that specific microtubule regulatory proteins can be targeted to alter various aspects of human cell motility both *in vitro* and *in vivo*. We are currently building on these findings to develop novel therapies to enhance wound healing, treat spinal cord injury and cardiovascular disease, and prevent cancer metastasis. We are working closely with the Friedman, Nosanchuk and Zhou labs to develop and test nanoparticle-based approaches to manipulate the activities of microtubule regulatory proteins in a clinical context.

Selected Publications

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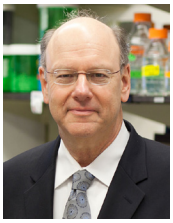

Robert H. Singer, Ph.D.

Professor, Department of Anatomy and Structural Biology
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Cell Biology
Harold and Muriel Block Chair in Anatomy and Structural Biology
Co-Chair, Department of Anatomy & Structural Biology
Co-Director, Gruss-Lipper Biophotonics Center
Co-Director, Integrated Imaging Program

Our work is focused on the travels of RNA within the cell: from the site of its birth to its ultimate biological destiny in the cytoplasm where it makes proteins in specific locations. All we have learned results from the development of new technology, known as *in situ* hybridization, to visualize specific nucleic acid sequences within individual cells. Using our approach, synthetic nucleic acid probes are labeled with a variety of detectors such as fluorochromes or antigens. Subsequently these molecules are hybridized to the cell and detected using high resolution digital imaging microscopy. This enables the detection of specific nucleic acid molecules within the structural context of the cell. We have developed imaging methodologies and algorithms capable of detecting a single RNA molecule within a cell. As a result of this approach, we have found that specific RNA sequences are located in particular cellular compartments. An example is the messenger RNA for beta-actin, which is located in the periphery of the cell where actin protein is needed for cell motility. These transcripts are not free to diffuse. The transcripts may be associated with a cellular matrix or skeleton from the moment of their synthesis through translation. We are investigating how this spatial information is encoded within the gene and how the RNA transcript is processed within the nucleus and then transported to its correct compartment in the cytoplasm resulting in asymmetric protein distribution. A reporter gene can be "delivered" to a variety of cellular compartments by using specific sequences, or "zipcodes", from the mRNAs found in those compartments. These "zipcodes" consist of short sequences in the 3' untranslated region of the mRNA. We have isolated and cloned proteins, which bind to the zipcode and decode this information. Recently we have developed technology that allows us to visualize RNA movement in living neurons. Currently our efforts are to develop imaging methods to see fast movements in order to characterize the motors driving RNA.

Selected Publications

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Lucas L. Sjulson, M.D., Ph.D.

Assistant Professor, Psychiatry
Assistant Professor, Dominick P. Purpura Department of Neuroscience

Cortex-basal ganglia interactions in drug addiction and motivated behavior

Drug addiction and other neuropsychiatric conditions involve complex interactions between brain areas including the nucleus accumbens, hippocampus, and prefrontal cortex.

Our previous work has characterized the role of interactions between hippocampus and nucleus accumbens in cocaine conditioned place preference, finding evidence that selective potentiation of specific hippocampal inputs to accumbens stores information linking certain spatial contexts to drug use. This provides a possible mechanistic substrate for the well-known phenomenon by which relapse is triggered by exposure to "people, places, and things" previously associated with drug use.

Our current work studies how interactions between hippocampus and accumbens influence prefrontal cortex as a basis for both physiological reward valuation and the pathological overvaluation of drugs of abuse. To this end, we combine carefully-designed mouse behavioral paradigms with a broad range of experimental techniques including multisite Neuropixels probe recordings, optotagging and closed-loop optogenetic manipulations, *in vivo* two photon and light field imaging, and in situ RNA sequencing. A major theme of this work is linking transcriptomically-defined cell classes to their functional roles during behavior. We also rely heavily on dimensionality reduction approaches, machine learning, and computational modeling to characterize and understand the population-level coordination of neuronal activity between brain regions during decision making and drug self-administration.

Developing novel translational strategies for treating drug addiction

Drug addiction represents a large public health burden for which few effective biologically-based treatments exist. We aim to develop novel gene-based tools and validate anatomical targets for future translational studies in human subjects. Our previous work in this area has focused on using DREADDs to modulate nucleus accumbens and suppress alcohol consumption in a model of binge drinking. We are currently expanding this work by exploring different brain targets and developing novel DREADD-like receptors with properties suitable for use in human subjects. We have also developed several novel molecular tools enabling manipulation of synaptic transmission and plasticity with greater precision than previously possible.

Highlighted awards

Dr. Sjulson was the recipient of a five-year, $2.5 million National Institutes of Health Director's Pioneer Award from the National Institute on Drug Abuse (NIDA).

sjulsonlab.org

Selected Publications

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Frank Soldner, M.D.
Assistant Professor, Dominick P. Purpura Department of Neuroscience

The main goal of my research is to apply functional genomic approaches in human cells to elucidating the molecular and cellular mechanisms of complex neurological disorders such as Alzheimer's and Parkinson's disease. One of the major challenges of studying human complex diseases is the lack of relevant model systems that combine known genetic elements with disease-associated phenotypic readouts. This is particularly problematic for many common medical conditions including sporadic neurodegenerative diseases, which have no well-defined genetic etiology and do not follow Mendelian inheritance patterns. Epidemiology and population genetics suggest that such sporadic diseases result from a complex interaction between multiple genetic and non-genetic (lifestyle and environmental) risk factors. And although genome wide association studies (GWASs) have identified sequence variants such as single nucleotide polymorphisms (SNPs), deletions and insertions associated with a wide variety of neurological disease, the vast majority of these risk variants have no established biological relevance to disease or clinical utility for prognosis or treatment. This complexity and our limited knowledge of the underlying genetic factors have impeded our understanding of the molecular mechanisms of many complex diseases and, more importantly, limited the development of effective therapeutics.

Three major recent innovations have fundamentally changed our ability to study human neurological

diseases 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 has demonstrated that integration of population genetic and genome-wide epigenetic data combined with hiPSC and gene editing technologies now enables us to dissect the functional effects of genetic risk variants in order to study human neurological disorders in a genetically controlled and systematic manner. My lab is applying this novel experimental framework to systematically link GWAS-identified sequence variants to non-coding cis-regulatory elements and establish functional assays to connect diseases-associated risk alleles with the expression of disease-relevant effector genes and cellular phenotypes. Such disease-relevant phenotypic readouts allow us to perform unbiased chemical compound and CRISPR/Cas9-based genome-scale genetic screens to identify novel disease modifiers in human neuronal cells.

Furthermore, one of the emerging challenges in the human genetics field is to understand how genetic signals from multiple risk variants interact and collectively contribute to the development of diseases or confer susceptibility to aging and additional environmental factors. The generation of genetically defined human cellular models carrying various risk variants provide a human *in vitro* model system to investigate how genetic, epigenetic and environmental factors are integrated to contribute to disease development and progression.

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).

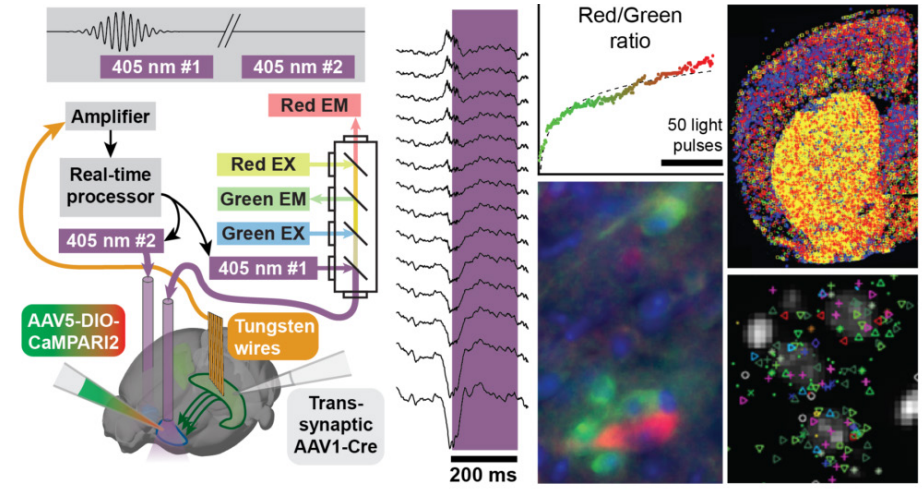
Soldner, F.*, Hockemeyer, D.*, Beard, C., Gao, Q., Bell, G. W., Cook, E. G., Hargus, G., Blak, A., Cooper, O., Mitalipova, M., Isacson, O. & Jaenisch, R. Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. *Cell* 136, 964–977 (2009).

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)

From the Sjulson lab



David C. Spray, Ph.D.

Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Medicine (Cardiology)

Research of our laboratory is centered on physiological and cell/molecular biological studies of gap junctions, the intercellular channels that allow cells to directly exchange ions and metabolites. In the nervous system, gap junctions form electrotonic synapses between neurons, permitting synchronized excitation of coupled cells, and they couple glia into a complex interconnected network where information is exchanged through calcium waves and metabolically. Major projects of the laboratory are attempting to resolve (1) role of gap junctions and extracellular signaling between neurons and satellite glial

cells in a mouse model of orofacial pain, (2) how connexin-protein interactions (which result in a dynamic complex that we term the "Nexus") deliver, assemble and modulate gap junctions in various cell types, (3) molecular complexes that function to transduce mechanical information in osteocytes (with the Biomedical Engineering Department, CCNY), and (4) how forces on astrocyte endfeet through glymphatic flow impact the water distribution network involving AQP4 water channels and gap junctions. These studies utilize a variety of preparations, including primary cultures of cells from transgenic mice with altered expression of connexin and other genes and transfection of wildtype and mutated connexin sequences into communication deficient cell lines, where small high resistance cells permit structure-function analysis at the single channel level. Techniques include patch clamp electrophysiology, photomanipulation such as FRAP, optical monitoring of intracellular ionic activities (especially Ca^{2+} and propagated Ca^{2+} waves), confocal and superresolution micrscopy, and standard molecular biological and immunological methods such as RT-PCR and Western blot analyses, and expression profiling using microarrays.

Selected Publications

Lewis KJ, Cabahug-Zuckerman P, Boorman-Padgett JF, Basta-Pljakic J, Louie J, Stephen S, Spray DC, Thi MM, Seref-Ferlengez Z, Majeska RJ, Weinbaum S, Schaffler MB. Estrogen depletion on In vivo osteocyte calcium signaling responses to mechanical loading. Bone. 2021 Nov;152:116072. doi: 10.1016/j.bone.2021.116072. Epub 2021 Jun 24. PubMed PMID: 34171514; NIHMSID:NIHMS1720521.

Spray DC, Scemes E. Gap junction proteins (Connexins, Pannexins, Innexins). Enclyclopedia of Biophysics. Forthcoming.

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McCutcheon S, Majeska RJ, Spray DC, Schaffler MB, Vazquez M. Apoptotic Osteocytes Induce RANKL Production in Bystanders via Purinergic Signaling and Activation of Pannexin Channels. *J Bone Miner Res*. 2020 May;35(5):966-977. doi: 10.1002/jbmr.3954. Epub 2020 Feb 11. PubMed PMID: 31910292; PubMed Central PMCID: PMC8009310.

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Sylvia O. Suadicani, Ph.D.

Associate Professor, Department of Urology

Assistant Professor, Dominick P. Purpura Department of Neuroscience

Dr. Suadicani is an expert in the area of intracellular and intercellular signaling with a strong background in Cellular Biology, Physiology and Pharmacology. Her research currently focuses on the investigation of mechanisms contributing to development of benign bladder dysfunction, particularly the involvement of pannexin 1 (Panx1) channels and purinergic signaling in the development of diabetic cystopathy, interstitial cystitis, neurogenic bladder in Multiple Scle-

rosis and spinal cord injury, and in mechanisms leading to development of Urologic Chronic Pelvic Pain.

Dr. Suadicani's general interest and expertise in the pathophysiology of cell signaling have also led to collaborations with faculty from other departments at Einstein and abroad. Examples of ongoing collaborations are studies conducted with Dr. Kelvin P. Davies (Department of Urology, Einstein) to better understand mechanisms that underlie development of benign urologic conditions, studies with Dr. David C. Spray (Department of Neuroscience, Einstein) focused on pelvic pain, studies with Dr. Mia M. Thi (Department of Orthopaedic Surgery, Einstein) to investigate the effects of diabetes on bone cell mechanosensing and transduction, and studies with Drs. David J. Sharp (Department of Physiology & Biophysics, Einstein) and Kelvin Davies to identify new targets to treat acute spinal cord injury and associated bladder and erectile dysfunction.

Selected Publications

Suadicani, S.O., Inglesias, R., Wang, J. Dahl, G. Spray, D.C., Scemes, E. (2012) ATP signaling is deficient in cultured pannexin1-null mouse astrocytes. *Glia*. 60(7): 1106–1116.

Negoro, H., Kanematsu, A., Doi, M., Suadicani, S.O., Matsup, M., Imamura, M., Okinami, T., Nishikawa, N., Oura, T., Matsui, S., Seo, K., Tainaka, M., Urabe, S., Kiyokage, E., Todo, T., Okamura,H., Tabata, Y., Ogawa, O. (2012) Involvement of urinary bladder Connexin43 and the circadian clock in coordination of diurnal micturition rhythm. *Nat Commun*. May 1; 3:809.

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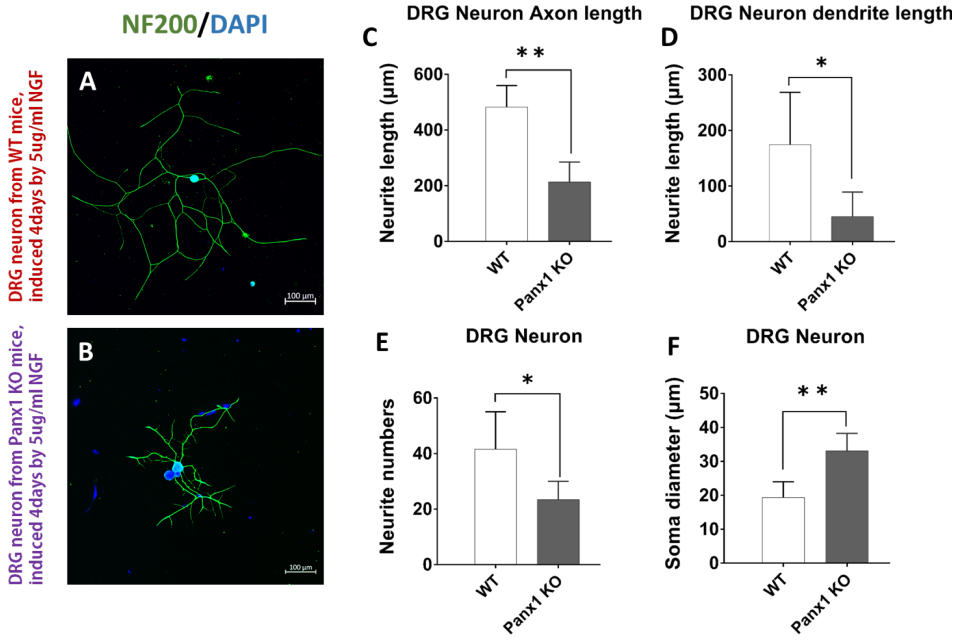
From the Spray lab



Panx1 controls DRG neuron maturation in culture. A: sensory neurons isolated from WT mice extend long processes at 4 days of NGF treatment ; B: sensory neurons isolated from Panx1 KO mice extend short processes at 4 days of NGF treatment; C,D,E: Axon and dendrite length and complexity are significantly lower in Panx1 KO mice; F: Soma diameter is significantly larger in Panx1 KO mice; (N=5; *, P<0.05; **, P< 0.01) ; Images in A and B stained with NF200 (Green) antibody and the nuclear marker DAPI (Blue)

Hanstein R., Negoro H., Patel N.K., Charollais A., Meda P., Spray D.C., Suadicani S.O., Scemes E. (2013) Promises and pitfalls of a Pannexin1 transgenic mouse line. *Front Pharmacol*. 9;4:61. (PMCID: PMC3648696).

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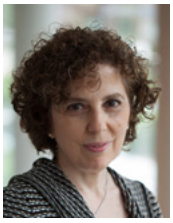

Elyse S. Sussman, Ph.D.
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Otorhinolaryngology—Head and Neck Surgery

My research is in the field of Cognitive Neuroscience and is focused on understanding the neural bases of memory and attention in children and adults. Our laboratory investigates effects of typical and atypical neural development on sensory perception, memory, and attention

across the lifespan. We use a combination of non-invasive recordings of human brain activity, in conjunction with perceptual measures to link markers of brain function with performance measures and specify the processes and brain structures that contribute to the organization, storage and perception of the stimulus environment.

Selected Publications

Brace, B., Lee, W., Cole, P., & Sussman, E. (2019). Childhood leukemia survivors exhibit deficiencies in sensory and cognitive processes, as reflected by event-related brain potentials after completion of curative chemotherapy: A preliminary investigation. *Journal of Clinical and Experimental Neuropsychology*, 41(8):814–831. doi: 10.1080/13803395.2019.1623865.

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Pavao, R., Sussman, E. Fischer, B. & Pena, J.L. (2020), Natural ITD statistics predict human auditory spatial perception. *Elife*, https://elifesciences.org/articles/51927

Fishman, Y., Lee, W., & Sussman, E. (2021). Learning to predict: Neuronal signatures of auditory expectancy in human event-related potentials. *Neuroimage*, 225, 15, 117472 https://doi.org/10.1016/j.neuroimage.2020.117472

Solomon, S.S., Tang, H., Sussman, E.S., & Kohn, A. (2021). Limited evidence for sensory prediction error responses in visual cortex of macaques and humans. *Cereb Cortex*. 31(6):3136–3152. doi: 10.1093/cercor/bhab014. PMID: 33683317

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Bonuck, K., Shafer, V., Battino, R., Valicenti-McDermott, R.M., Sussman, E. & McGrath, K. (2021). Language Disorders Research on Bilingualism, School-Age, and Related Difficulties: A Scoping Review of Descriptive Studies. Academic Pediatrics, 22(4), 518–525. https://doi.org/10.1016/j.acap.2021.12.002

Duncan W. Wilson, Ph.D.

Professor, Department of Developmental and Molecular Biology

Professor, Dominick P. Purpura Department of Neuroscience

Viruses and the nervous system

Humans are infected by at least eight different species of herpes viruses. These pathogens cause several forms of cancer, severe birth defects or miscarriage, and are a leading cause of organ transplant rejection. Our interests are focused on the neurotropic herpes viruses, including herpes simplex (HSV).

HSV: a pathogen of the nervous system

Herpes simplex virus (HSV) is a leading cause of blindness, fetal mortality and severe neurodevelopmental and other birth defects. These diseases are a direct result of the ability of the virus to invade, manipulate and traffic within the human nervous system. Our laboratory is dissecting the molecular machinery that HSV uses to achieve assembly and transport within neurons (Fig. 1).

Once in the cell cytoplasm HSV capsids dock with, and become enveloped by, cytoplasmic organelles to assemble the mature infectious virus. These then traffic along neuronal microtubules to travel within the nervous system (Fig. 2).

The events of virus assembly, and the detailed molecular structure of assembly and trafficking intermediates are very poorly understood. In collaboration with the analytical imaging facility (AIF) here at the Albert Einstein College of Medicine we have pioneered the application of Correlative Light and Electron Microscopy to the study of HSV assembly in the neuronal cell body (Fig. 3).

Selected Publications

Barnes J. and Wilson D.W. (2019). Seeking closure: How do herpes viruses recruit the cellular ESCRT apparatus? *J. Virology* 93:e00392-19.

Diwaker D. and Wilson D.W. (2019). Microtubule-dependent trafficking of alphaherpesviruses in the nervous system: the ins and outs. *Viruses* 11, 1165; https://doi.org/10.3390/v11121165

Ahmad I. and Wilson D.W. (2020). HSV-1 cytoplasmic envelopment and egress. *International Journal of Molecular Sciences*. 21, 5969; https://doi.org/10.3390/ijms21175969

Barnes J. and Wilson D.W. (2020). The ESCRT-II subunit Vps25 and the Bro1 domain proteins HD-PTP and BROX are individually dispensable for HSV-1 replication. *J. Virology* 94, (4) e01641–19

Diwaker D., Murray J., Barnes J., Wolkoff A. and Wilson D.W. (2020). Deletion of the Pseudorabies Virus gE/gI-US9p complex disrupts kinesin KIF1A and KIF5C recruitment during egress, and alters the properties of microtubule-dependent transport in vitro. *PLOS Pathogens* https://doi.org/10.1371/journal.ppat.1008597

From the Wilson lab

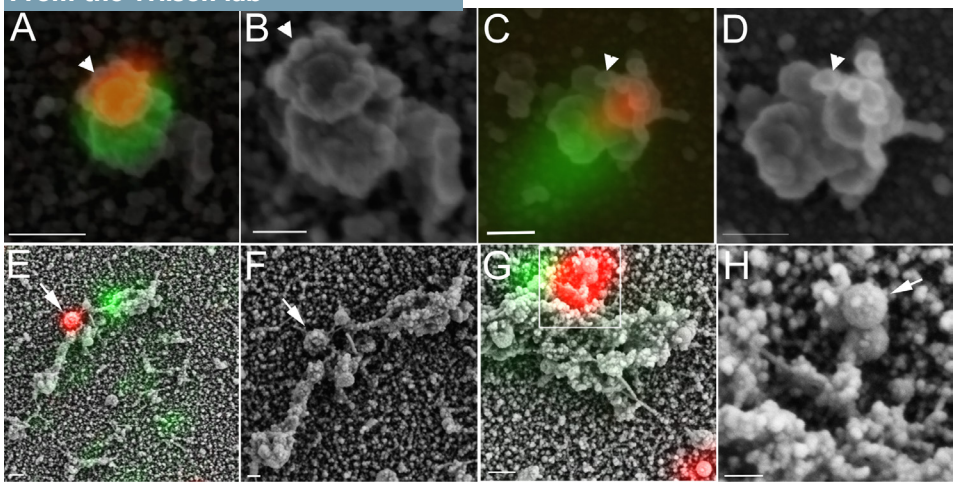

Fig. 3: What to do when more light doesn't help you see better. Correlative light and electron microscopy makes it possible to observe HSV assembly simultaneously by fluorescence microscopy and electron microscopy. Paired images A-B, C-D, E-F and G-H show HSV capsids assembling onto cellular organelles in infected cells. For each pair a scanning electron microscopy image is shown on the right (e.g. B), and an alignment of the same structure with its fluorescent light microscopic image is shown on the left (e.g. A). Red light is being emitted by HSV capsids engineered to contain molecules of red fluorescent protein. Green light is coming from organelle-bound forms of green fluorescent protein. Scale bars: 200nM.

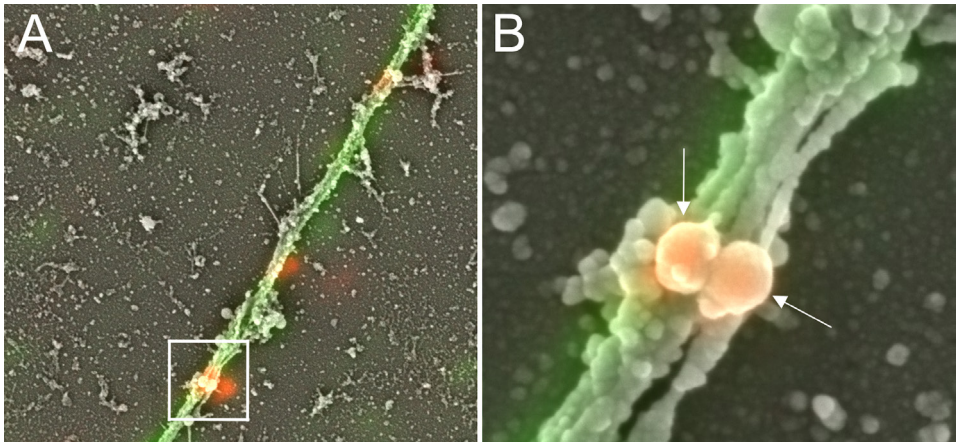

Fig. 4: HSV goes for a walk. Using the same technology as in Fig. 3 we image viruses (red) attached to microtubules (green). Boxed region in (A) is expanded in (B). Combining this structural approach with genetically manipulated viruses and fluorescently-tagged kinesins and dyneins enables us to dissect the mechanism of motor-recruitment by these viruses.

Yunlei Yang, M.D., Ph.D.

Professor, Department of Medicine (Endocrinology)
Associate Professor, Dominick P. Purpura Department of Neuroscience

Obesity and its associated complications impose a huge burden to our society. However, the mechanisms underlying this disorder and its related pathologies remain unclear, and effective treatments are still lacking. At its core, obesity results from an imbalance between energy intake and energy expenditure. Most work has focused on neural regulation of energy balance, however, an important but poorly understood element is the roles played by astrocytes in the regulation of energy states although they play crucial functions in regulating synaptic strength and neural activity.

Dr. Yang is interested in dissecting and manipulating central and peripheral signaling pathways that govern energy balance and glucose metabolism in normal and obese animals using genetic and systems neuroscience methods that include cell-type-specific electrophysiology, optogenetics, chemical-genetics, deep-brain measurements of neurochemicals, imaging, and behavior assays.

Selected Publications

Sweeney p, Li C, Yang Y (2017). Appetite suppressive role of medial septal glutamatergic neurons. *Proc Natl Acad Sci U S A*. 114(52):13816–13821. PMID:29229861 Highlighted in *Nature*.

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Qi Y, Yang Y (2015). Hunger States Control the Directions of Synaptic Plasticity via Switching Cell Type-Specific Subunits of NMDA Receptors. *J Neurosci*. 35(38):13171–82. PMID: 26400946.

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Yang L, Qi Y, Yang Y (2015). Astrocytes control food intake by inhibiting AGRP neuron activity via adenosine

A1 receptors. *Cell Rep.* 11(5):798–807 PMID: 25921535. Highlighted in Cell press.

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Deyou Zheng, Ph.D.

Professor, The Saul R. Korey Department of Neurology
Professor, Department of Genetics
Professor, Dominick P. Purpura Department of Neuroscience

The research areas in our lab are computational genomics and bioinformatics, with a strong focus on mining large-scale high-throughput genomic data. We develop and apply computational techniques for integrating data from comparative genomics, functional genomics and epigenomics to better understand structure, transcription, regulation, and evolution of the human genome, and to investigate how these functions change during developments, diseases and cancers. While we apply similar bioinformatics approaches to the developments of various tissues and organs, we especially focus on genomic functions involved in the development, specification, maturation, and maintenance of human neural system. Our goal is to better understand the genetic base of neuronal development, neuropsychiatric disorders, and other brain diseases. We expect to identify new therapeutic targets such as specific genes whose regulation is disrupted during the early development of patient brains. Applying the same bioinformatics and genomics strategies to mouse models, we also have a strong research program studying the genetic networks and molecular base of cogenital heart diseases, including single cell analysis.

In collaboration with other experimentalist experts, we grow human neurons in dish by induced pluripotent stem cell (iPSC) technology in order to model human neuronal development and differentiation. We begin by developing iPSC lines from both patients and matching controls, differentiate them to neurons, then use RNA-seq and other deep sequencing technology to identify differentially regulate genes by comparing the transcriptomes between patient-derived neurons and controls. By using advanced experimental technology and computational methods like iPSC technology, deep sequencing (e.g, RNA-seq and ChIP-seq), and systems biology approaches for our research, we have identified many novel long non-coding RNA genes that are involved in embryonic neurogenesis and potentially neuropsychiatric disorders. We also find that many genes show allele-biased gene expression in different brain regions, including some that have been implicated in Schizophrenia and Autism Spectrum Disorders, which may help explain some aspects of parent-of-origin effects, twin discordance and reduced penetrance.

For more details, please see our website,

https://einsteinmed.org/labs/deyou-zheng

Selected Publications

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