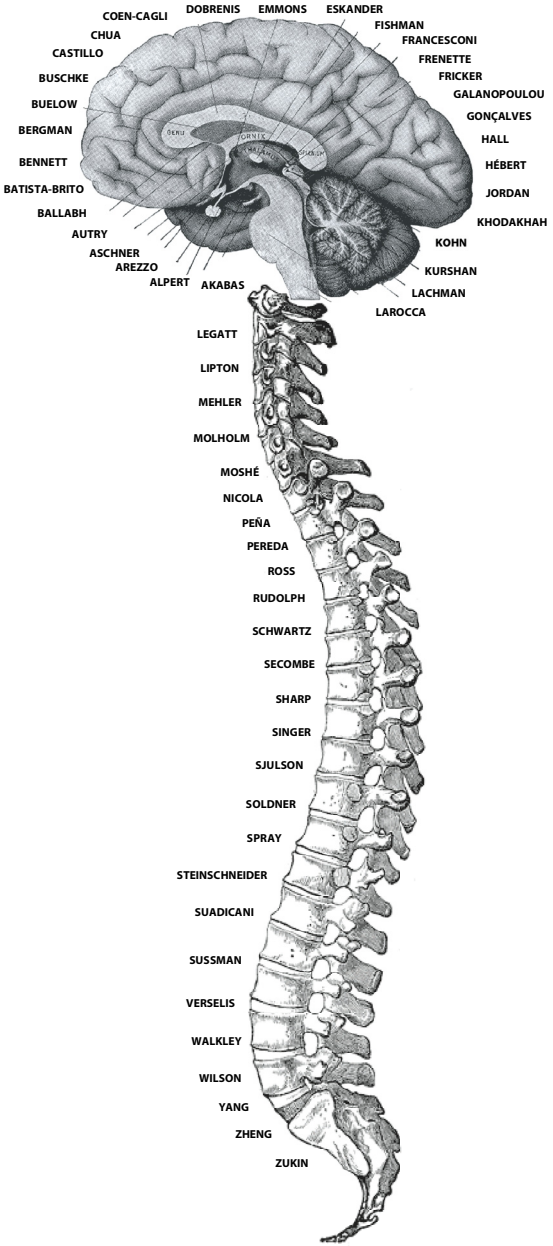
Dominick P. Purpura

Department of Neuroscience

Faculty Research Interests at the Albert Einstein College of Medicine 2019–2020



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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.

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

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Joseph C. Arezzo, Ph.D.

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

Our laboratory applies a variety of neurophysiologic techniques to explore normal and altered function in animal models and human clinical research. Experimental procedures include EEG, evoked potentials, ensemble and single unit recordings, current source density, and measures of whole nerve conduction velocity. Recently we have focused on developing sensitive biomarkers for the onset and progression of toxic neuropathies and seizure disorders. We have studied transgenic and mutant mice, models of diabetic neuropathy, compound-induced seizures, and demyelinating and iatrogenic deficits of central and peripheral nerve function. In parallel, we have participated in the "translation" of basic neuroscience principles to human clinical studies. We are currently involved in the design and conduct of multicenter Phase 1–4 clinical trials of experimental therapies intended to reduce or prevent diabetic and chemotherapy-induced neuropathies, to improve the treatment of chronic inflammatory demyelinating polyneuropathy, to explore treatment for ALS, and to monitor the modulation of pain. In this latter capacity, we have worked with the Centers for Disease Prevention and Control, the Environmental Protection Agency, the National Institute of Occupational Safety and Health and numerous pharmaceutical and biotechnology companies.

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Michael Aschner, Ph.D.

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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.

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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.

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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.

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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.

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Areas of investigation include: molecular and cellular physiology of glutamatergic transmission, mechanisms of delayed neurodegeneration induced by global ischemia, neuroprotection after ischemia or other insult and gap junction mediated intercellular communication.

Glutamatergic transmission is the primary mode of excitation in the nervous system. Modifications of synaptic efficacy underlie development and learning and also play important roles in disease processes. NMDA receptors, one class responding to glutamate, mediate forms of long term potentiation and depression, which can underlie memory. Protein kinases and phosphatases modify single channel properties and trafficking, i.e., movement out from the cell body, dendritic synthesis, insertion into the surface membrane, removal, and recycling or degradation. Delayed neuronal death in the hippocampal CA1 following global ischemia and in CA3 following kainate induced status epilepticus results from down regulation of GluR2, the AMPA receptor subunit that limits calcium permeability of these receptors. Increased Ca^{2+} influx in response to endogenous glutamate then triggers cell death by Ca^{2+} overload. GluR2 downregulation is mediated by REST(RE-1 silencing transcription factor), which is upregulated after ischemia. In ischemic preconditioning a brief period of ischemia leads to tolerance of a longer lasting and otherwise injurious ischemic episode. We are identifying changes in gene expression responsible for ischemic tolerance after preconditioning.

Electrical synapses formed by gap junctions synchronize many types of inhibitory interneurons in the mammalian brain. Gap junction channels are formed by a hemichannel from each of the coupled cells; because of their high conductance and permeability, it was thought that hemichannels were closed until docking with another hemichannel. Now it there is evidence that hemichannels not apposed to another hemichannel can open under physiological as well as pathological conditions. We are investigating the controlling mechanisms at the level of single (hemi) channels. Hemichannels mediate intercellular signaling by secreted molecules, such as ATP, and may be involved in propagation of damage (or protection) at boundaries between normal and injured tissue. Several human diseases are caused by connexin mutations, including X-linked Charcot-Marie-Tooth disease, one type of non-syndromic deafness, one type of epilepsy, two types of cataract, and oculodentodigital dysplasia (ODDD). We are analyzing how the altered biophysics of the mutations leads to the pathology.

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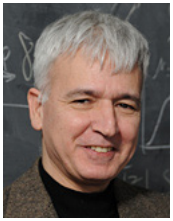

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My research agenda addresses quantitative problems in evolutionary and developmental biology by using a combination of computational, mathematical, and experimental tools. Starting with biologically relevant models, we comb for data from existing studies, 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 de-

aminase (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.

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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.

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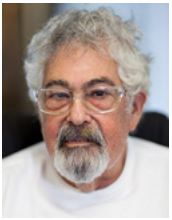

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He is the Principal Investigator of Project 2 of the Einstein Aging Study (Program Director: Dr. Richard B. Lipton). The primary objective of this project is to distinguish between normative and pathological cognitive aging by modeling intraindividual cognitive variability and change in older adults. His research will extend knowledge about the relationship among performance variability and cognitive impairment in aging in several important ways.

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Pablo E. Castillo, M.D., Ph.D.

Professor, Dominick P. Purpura Department of Neuroscience
Harold and Muriel Block Chair in Neuroscience

Synaptic transmission underlies every aspect of nervous system function. How we think, feel, act and learn, all rely on information transfer between nerve cells. In addition, synapses are extremely dynamic, and activity-dependent changes in synaptic strength are essential to most forms of learning. It is becoming increasingly clear that synaptic dysfunction is central to the etiology and progression of a wide range of neuropsychiatric and neurodevelopmental disorders. The main goal of my research program is to understand the cellular and molecular basis of activity-dependent changes in synaptic strength at both excitatory and inhibitory connections, and how such changes are modified during pathological conditions. In our studies we use brain slice electrophysiology and pharmacology, two-photon laser microscopy, optogenetics and a wide-range of molecular manipulations. To gain insights into the mechanisms of synaptic function, we include in our studies functional analyses of transgenic mice for several synaptic proteins, as well as mouse models for various neuropsychiatric conditions, including Alzheimer's disease, autistic spectrum disorders and schizophrenia.

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Streamson C. Chua, Jr., M.D., Ph.D.

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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.

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Ruben Coen-Cagli, Ph.D.

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Assistant Professor, Dominick P. Purpura Department of Neuroscience

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.

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Kostantin Dobrenis, Ph.D.

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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 including Tay-Sachs/Sandhoff disease, Niemann Pick C (NPC) disease, mucopolysaccharidosis (MPS) IIIA, and mucolipidosis IV, and more recently to understanding the pathogenesis of Christianson Syndrome, a sodium/hydrogen exchanger deficiency that displays features of storage disorders. Much of our work has been directed at developing rational therapeutic strategies for these and related genetic diseases which affect 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 lysosomal compartment, and transneuronal transsynaptic trafficking for wider dissemination of the needed protein. Additional projects include: exploring the efficacy and delineating the mechanisms of action of small molecule therapies such as miglustat, related analogs, and cyclodextrin for storage diseases, now seeing human application, in cellular, biochemical, gene expression and behavioral assays; and investigation of novel contact-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.

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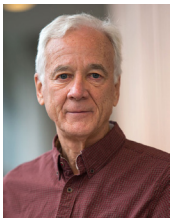

Scott W. Emmons, Ph.D.

Professor, Department of Genetics
Professor, Dominick P. Purpura Department of Neuroscience
Siegfried Ullmann Chair in Molecular Genetics

How complex neural circuits form and how they function are major unsolved problems in neurobiology. We use the nematode *Caenorhabditis elegans* to study these questions at the cellular and genetic levels. We are currently completing a comprehensive description of the synaptic interactions in the nervous system of the *C. elegans* adult male—the male connectome. We identify synapses and the trajectories of neurons in serial section electron micrographs and construct neural maps using a novel software platform. Our male wiring diagram, together with that of the adult hermaphrodite, which was published in 1986, completes the description of nervous system connectivity for the adults of this species, the only animal species for which this information is available.

We are now investigating how the male circuits generate the male's behavior and how the circuits are genetically specified. The *C. elegans* male nervous system contains a set of circuits located in its tail that generates the male's copulatory behavior. The neural network containing these circuits consists of the processes of some 185 neurons and around 8,000 synapses. We analyze the patterns of connectivity within this network using computational methods to identify pathways that subserve particular steps of behavior. Hypotheses regarding neuron function are experimentally tested by cell killing techniques. We probe the functions of classical and peptide neurotransmitters, their receptors, and gap junctions by genetic methods.

To determine how the network is genetically specified, we make use of transgenes that express fluorescent proteins targeted to specific synapses. We plan to use these synapse-specific labels to identify mutants and genes that affect formation of particular cellular synaptic contacts. In these experiments we hope to uncover the still elusive class of proteins that encode the molecular determinants of synaptic specificity.

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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 current President of the American Society for Stereotactic and Functional Neurosurgery.

Selected Publications from over 200

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Research in our laboratory examines neural mechanisms underlying auditory perception of speech, music, and other complex sounds at the cortical level. Of particular interest are the neural processes that allow the brain to perceptually segregate spectrally and temporally overlapping sounds in complex acoustic environments, e.g., speakers' voices at a cocktail party. These neural mechanisms are studied via electrophysiological recordings of neural activity in auditory cortex of awake, behaving non-human primates. Parallel interests include translational research involving both non-invasive and intracranial electrophysiological recordings in humans which is aimed at bridging explanatory gaps between neurophysiology of complex sound processing in animal models and humans.

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Molecular mechanisms of metabotropic glutamate receptor function.

Research in the laboratory focuses on elucidating the molecular and cellular underpinnings of metabotropic glutamate receptor function in the brain, with the ultimate goal of developing a molecular rationale for targeted interventions in neuropsychiatric disorders. 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 intellectual disability, autism and schizophrenia. Group I metabotropic glutamate receptors, mGlu1 and mGlu5, 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 mGlu receptor activity is implicated in neurodevelopmental disorders including Fragile X syndrome and schizophrenia.

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 plasticity. Ongoing studies pursue interrelated lines of investigation by examining the role of adaptor proteins in orchestrating and fine-tuning mGluR activity under physiological conditions and in animal models of Fragile X syndrome; and by investigating the cellular mechanisms by which mGluR signaling contributes to synaptogenesis and neuronal maturation.

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Our laboratory is interested in understanding how hematopoietic stem cells (HSCs) and mature blood cells traffic in vivo. We have uncovered a key role for the nervous system in regulating HSC trafficking, and are evaluating its role in the inflammatory response in diseases such as sickle cell disease. In addition, we are also exploring whether the traffic paradigms uncovered for healthy stem cells applies to cancer cell migration and metastasis.

Molecular and cellular constituents of the stem cell niche. HSCs continuously traffic from the bone marrow to the blood compartment (and vice-versa) under homeostasis. Recent studies have focused on the role of the nervous system in the regulation of the HSC niche in the bone marrow. This effort is based on our observations suggesting a critical function of adrenergic signals emerging from the sympathetic nervous system (SNS) in HSC egress. While investigating further the mechanisms by which HSCs were mobilized, we have found that exposure to constant light significantly reduced mobilization efficiency following the administration of the hematopoietic cytokine G-CSF. G-CSF is the most commonly used HSC mobilizer in the clinic to harvest stem cells for transplantation. This finding prompted us to assess how HSC are released from the bone marrow under steady-state conditions. We have described the phenomenon and its mechanisms. These studies revealed that stromal cells in the bone marrow are subjected to circadian adrenergic signals transmitted by the beta3 adrenergic receptor that lead to the degradation of the transcription factor Sp1 and diurnal changes in the expression of the chemokine Cxcl12. Recent investigations are focused on the identification and regulation of the stromal target for the SNS. These studies have led to the identification of a Nestin+ mesenchymal stem cell as a candidate niche cell required for HSC maintenance in the bone marrow. We have developed a novel imaging approach to assess native HSC in the bone marrow using whole-mount confocal analyses which have revealed distinct vascular niches, arteriolar and sinusoidal, that are conferred by subsets of Nestin+ cells. Ongoing studies are dissecting further the stromal subsets that form the bone marrow microenvironment.

Mechanisms of sickle cell vaso-occlusion. This project emerged from our intravital microscopy observations suggesting that sickle cell vaso-occlusion was mediated by the direct interaction between sickle erythrocytes and adherent leukocytes in small venules. Further analyses using novel high-speed multichannel fluorescence microscopy techniques have revealed that E-selectin-mediated activating signals emanating from the inflamed endothelium led to the activation of specific micro-

domains on the leading edge of adherent neutrophils, which then induce intravascular heterotypic interactions between erythrocytes or platelets with adherent leukocytes. Ongoing studies dissect further the molecular basis of this phenomenon.

Role of the nervous system in cancer. We are exploring the role of the autonomic nervous system in cancer formation and metastasis using xenogeneic and transgenic models of prostate cancer. These studies have led to the indeitification of novel functions for the sympathetic (adrenergic) and parasympathetic (cholinergic) nervous system in the initiation and metastasis, respectively, of prostate cancer. Further studies will analyze in more detail the mechanisms and to obtain new insight on the cellular and molecular cues that regulate the tumour microenvironment and allow cancer cells to spread.

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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.

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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.

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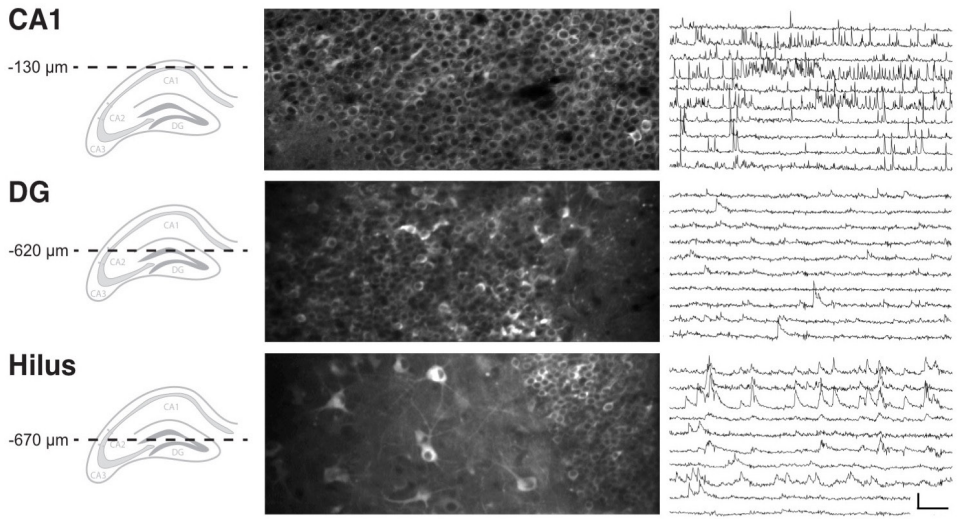
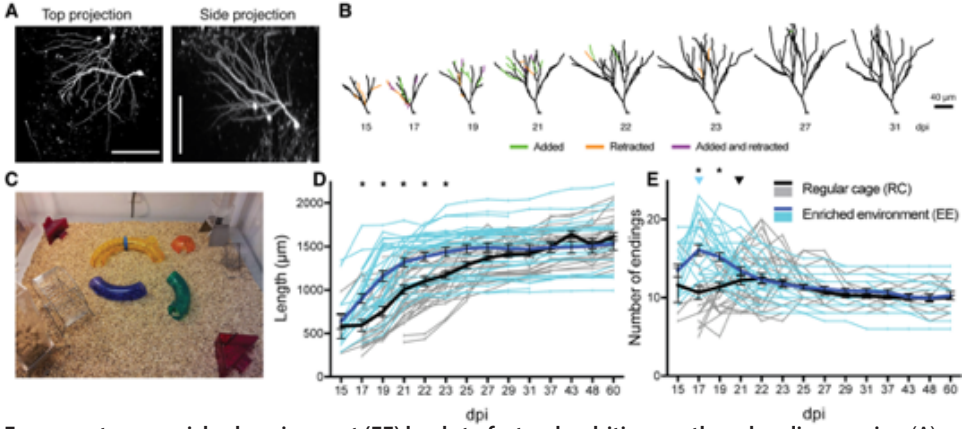
The dentate gyrus (DG) is the main input region of the hippocampus. As such, it plays a crucial role in hippocampal function, including learning and memory. Additionally, the DG is one of only two regions of the mammalian brain that continuously add new neurons through adulthood, and there is increasing evidence that these adult-born neurons play a role in specific learning tasks: particularly, the ability to distinguish between similar memories. Adult neurogenesis constitutes an unusual mode of plasticity in the brain, with specific stimuli such as environmental enrichment and voluntary exercise modulating the number of neurons integrating DG networks. In addition, adult-born neurons have been used to study neuronal development, and defects in neurogenesis have been associated with several human neurological and psychiatric diseases. The main focus of my research interests is to understand how enrichment and activity regulate the proliferation of adult neural stem cells and shape nascent adult-born neurons during their integration into DG circuits.

Experience and the activity it elicits are powerful modulators of neuronal development. As the brain matures it undergoes several critical periods where specific behavioral experiences (for example environmental enrichment and exercise) are



In vivo Ca^{2+} imaging of different hippocampal areas 3-photon images and Ca^{2+} traces of neurons expressing a genetically encoded Ca^{2+} sensor in CA1, DG granule layer and hilus/sub-granular layer. Note differences in morphology and activity patterns betwen cells in these layers. Scale bars: 100% ΔF/F 20 s.



Exposure to an enriched enviroment (EE) leads to faster dendritic growth and earlier pruning (A) In vivo 2-photon images of RV-GFP labeled cells in the DG imaged 60 days post-infection (dpi). Scale bar = 100 µm. (B) Representative reconstructions of the dendrites of two newborn DGCs, branches added and retracted between imaging time points are highlighted. (C) EE cage is large (91x91) cm) and contains running wheels. (D) Individual and mean (bold) plot of dendrite length. (D) Branching of EE dendrites peaks earlier and maximum number of endings is higher than in RC dendrites (adapted from Gonçalves et al. 2016)

needed for correct circuit formation. In the adult brain, behavioral experience has been shown to influence the proliferation of neural stem cells in the subgranular layer of the DG, their differentiation into glia and neurons, the maturation of these adult-born neurons, and their connectivity and incorporation into hippocampal circuits. Yet many aspects of the effects of experience on adult neurogenesis and hippocampus networks remain poorly understood. In our lab we study the effects of activity and experience at different phases of neuronal development ranging from the neural precursor stage to full maturity. The ability to track individual cells over their maturation period is crucial for our experiments. We use in vivo 2-photon imaging as a powerful tool to study of neuronal development since it allows for the recurrent probing of individual cells and circuits while keeping sensory input, neuronal activity patterns, and the physiological environment intact.

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The soil nematode *Caenorhabdidis 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.

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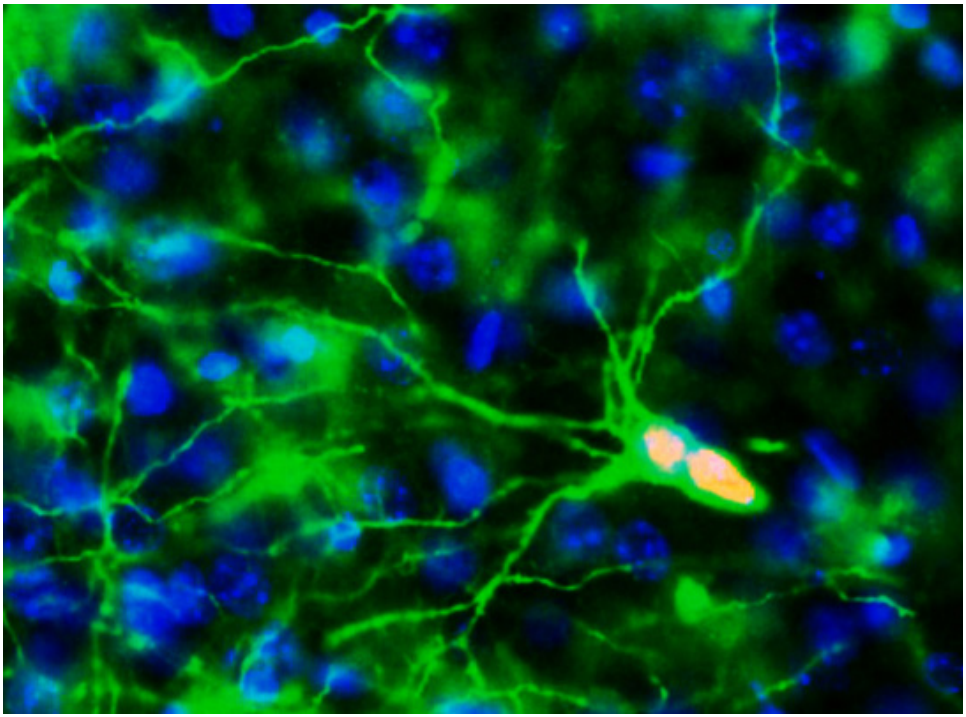
Generating and regenerating the neocortex

The Hébert lab has traditionally studied how the forebrain develops using conditional genetic methods in mice. Recently, the focus of the lab has transitioned to two new areas of interest. First, we are studying how homeostasis is maintained in the adult forebrain using primarily molecular genetic techniques to manipulate the expression of regulatory genes in neural stem and progenitor cells. Specifically, we are examining how neurogenesis is maintained in the hippocampus, how the myelination of axons is maintained through continuous oligodendrogenesis, and how cells become reactive to brain damage.



Second, we are devising novel methods to regenerate the damaged neocortex, the part of our brains that we use for our highest cognitive and perceptual functions. Neocortical damage can be local, due for example to stroke or trauma, or widespread, due for example to neurodegeneration or aging. Among the approaches we are taking, we are developing ways of replacing the principle neurons of the adult

neocortex without significantly disrupting the function of existing neural circuits. These approches involve the use of mixed cell populations for transplantation and for widespread damage the use of cells that can disperse throughout the neocortex to repopulate and bolster existing neural circuits with new cells.

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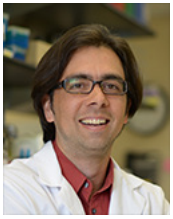

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Exploring synaptic function and activity-dependent synapse-to-nucleus signaling

An important question in neuroscience is how does neuronal activity alter neuronal connectivity. This question is critically important since changes in connectivity and transmission underlie higher order brain functions such as learning and memory and likely play a role in the cognitive deficits observed in many neurological diseases. To explore this question, we employ proteomics and mass spectrometry, which provide us with a global overview of synaptic and nuclear complexity and allow us to explore their dynamics. Using these methods, we found that a number of synaptic components can shuttle to the neuronal nucleus in response to synaptic activity. These include PRR7 and AIDA-1, which binds to NMDA receptors (NMDAR) and links synaptic activity to nuclear functions. Recent studies implicate AIDA-1 in diverse psychiatric and developmental disorders including schizophrenia and Autism spectrum disorders. A single nucleotide polymorphism (SNP) in the AIDA-1 gene (ANKS1b) is associated with response to antipsychotics, suggesting AIDA-1 may play a role in schizophrenia. Moreover copy number variations (CNVs) and SNPs of AIDA-1 have been identified in patients with autism and correlate positively with impaired play skills in ASD. Moreover we have recently found that AIDA-1 can regulate the metabolism of the Amyloid Precursor Protein (APP) in neurons. AIDA-1 can promote the generation of amyloid beta peptides by regulating APP internalization, and may therefore it may play an important role in Alzheimer's disease.

Moreover we found that certain RNA binding proteins (RNABPs) shuttle back into synaptic junctions in response to neuronal activity. We have recently shown that one of these proteins, Sam68, regulates the synaptic and dendritic expression of beta-actin and is crucial for proper spine morphology and synaptic function. Sam68 has been recently implicated in Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), which is a neurodegenerative disorder caused by mutations upstream of the FMR1 gene. We are therefore investigating if Sam68-dependent protein translation of cytoskeletal components can affect synaptic function and plasticity and ultimately behavior. We believe Sam68 plays a role in the generation and refining of neuronal networks. Understanding precisely how neurons regulate specific connections amongst their many thousand inputs is a central question in neuroscience. Therefore our lab employs broad-based proteomics methods to understand how synapses relay fast synaptic information to the nucleus and back, what are the key players in this process, and what role do these molecules play in brain pathologies.

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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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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.

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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.

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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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The overall aim of our research is to study the signalling mechanisms that participate in the regulation of myelin biogenesis. The myelin sheath is a highly specialized membranous structure that surrounds axons of the central and peripheral nervous systems and is essential for normal saltatory axonal conduction. The disruption of this membrane, for example in multiple sclerosis, leads to irreparable consequences. Myelin in the central nervous system (CNS), arises from the cellular processes that extend from the oligodendrocyte perikaryon to wrap a segment of axon in a spiral manner. Myelin biogenesis is a highly regulated process that requires the coordination of several oligodendrocytic events including lipid and protein synthesis, intracellular membrane trafficking and changes in cell shape. Intracellular vesicle transport plays a major role in the formation and maintenance of myelin. Individual myelin components are synthesized in different cellular compartments, sorted out and transported to the site of myelin formation by several different mechanisms. Some of the myelin protein including proteolipid protein (PLP) and myelin associated glycoprotein (MAG), are synthesized in the endoplasmic reticulum and transported via intracellular vesicles first to the Golgi and then to myelin. The fundamental importance of intracellular vesicular transport is further indicated by the occurrence of endocytosis in oligodendrocyte processes and myelin. Strict control of this traffic is necessary for preserving the structural and functional organization of oligodendrocytes and myelin. Our research is oriented toward: 1) Defining the intracellular membrane transport pathways in the oligodendrocytes. 2) Dissecting the molecular mechanisms that regulate the different trafficking pathways. 3) Understanding how the different routes of intracellular trafficking are integrated. 4) Determining how intracellular transport of vesicles is related to the regulation of other cellular events, such as protein and lipid synthesis, and organization of the cytoskeleton. We demonstrated the presence in the oligodendrocytes of several GTP-binding proteins including members of the Rab, Arf and Rho families. Evidence showed that Rab proteins are key components of the mechanisms that regulated intracellular traffic of membranes. Each Rab family member is located in a specific region (exocytic, endocytic, or transcytotic) and regulates a particular step of vesicular traffic. In our current studies, the different intracellular membrane trafficking pathways in living cells are visualized by fluorescent microcopy analysis of oligodendrocytes expressing fusion proteins of Rab proteins with EYFP (a fluorescent protein). The involvement of the different pathway in the myelin formation is assess by co-expression of Rab-EYFP and myelin proteins such as myelin associated glycoprotein (MAG) tagged with ECFP, and by comparing the distribution

of ECFP-tagged myelin proteins co-expressed with dominant negative mutants of Rab proteins. In addition, to define the molecular mechanisms in which the oligodendrocyte Rab proteins participate, we are using molecular cloning in a two-hybrid system for identification of the proteins that interact with the oligodendrocyte Rab proteins.

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- Intraoperative neurophysiologic monitoring.
- Topographic analysis of evoked potentials and identification of evoked potential generators.
- Studies of seizures and EEG spikes recorded during longterm monitoring in patients with epilepsy.

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My major research interest is in the application of quantitative functional and structural imaging techniques to the delineation of brain substrates of cognitive and behavioral impairment, with focus on the effects of mild traumatic brain injury (mTBI). An important pathologic and clinical feature of mTBI is the fact that the full severity of injury seems to evolve during the post-injury period; both initial injury and secondary host responses are likely required for full expression of mTBI lesions. It follows that a therapeutic window of opportunity may exist following injury, during which silencing host responses to injury could abort the evolution of mTBI pathology and improve outcomes. However, we also know that most patients recover following mTBI and only a minority proceed to long-term impairment and disability. Thus, understanding the temporal evolution of injury AND identifying the subgroup of patients likely to suffer adverse outcomes are both important research priorities. My laboratory utilizes high-resolution diffusion tensor MRI, detailed cognitive assessments and genetic assays in a longitudinal design. To date we have demonstrated, both at the time of injury and in chronic cognitively impaired patients, multifocal low fractional anisotropy (FA) in a pattern consistent with the distribution of axonal pathology in diffuse axonal injury. Measures derived from diffusion tensor imaging (DTI), such as FA, allow us to infer the relative organization of white matter structure at the cellular and subcellular levels. Although such DTI "lesions" are touted as evidence of disruption of microscopic white matter structure, an intuitive "fit" for the expected axonal pathology of mTBI, it is not clear that these "lesions" in fact reflect important axonal injury. No robust animal model of cognitive dysfunction following mTBI exists and it is unlikely that pathologic correlation will ever be achievable in humans. Thus, correlation of DTI with functional measures is needed to validate its predictive value. To this end, we have reported correlation of the magnitude of decline in FA in dorsolateral prefrontal cortex with performance on specific aspects of executive function that depend on the integrity of this brain region (Lipton, et al. 2009). Furthermore, the laboratory is amassing a growing body of longitudinal data which demonstrates change in white matter anisotropy that parallels changes in cognitive performance, suggesting that the imaging measures may in fact differentiate progressive and recovering loci of injury in TBI. These first structure-function connections in the setting of impairment due to mTBI set the stage for our ongoing studies addressing potential approaches to forecast long-term impairment and monitor progression/repair of injury in follow-up. In parallel with my study of human TBI, we are implementing parallel animal experiments to better validate the imaging measures as proxy mark-

ers for injury. We will also begin to examine molecular mechanisms of injury evolution using MRI-detectable molecular probes and transgenic animal strains. These approaches will also allow us to evaluate novel therapeutic approaches to minimize the expression of mTBI pathology.

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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 neuronal 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 multidisciplinary 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 exit 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.

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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.

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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.

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Neural circuits underlying reward-seeking behavior

My lab focuses on understanding the neural circuits responsible for reward-seeking and addictive behaviors. We use a systems-level approach that combines behavioral, pharmacological and electrophysiological techniques in awake, freely moving animals. We begin by identifying a hypothesis regarding the neural circuits underlying a particular behavior. For example, the nucleus accumbens (part of the ventral striatum) projects to motor output structures of the basal ganglia. The accumbens also receives input from limbic structures that have been suggested to process stimuli that predict events of consequence to the animal's well-being. 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. Therefore, we hypothesized that the amygdala and VTA projections to the accumbens are part of the neural circuit that controls the animal's response to reward-predictive stimuli.

To test this hypothesis, we designed a behavioral task that requires rats to respond, by pressing a lever, to an auditory stimulus that predicts sucrose reward. We then determined that the dopamine projection to the accumbens is required for this behavior by demonstrating that dopamine receptor antagonists microinjected directly into the animals' nucleus accumbens caused animals to cease responding to the stimulus. We also showed that transient inactivation of the amygdala had the same effect. Next, we used multiple simultaneous single-unit recordings of neurons in the accumbens and amygdala to demonstrate that subpopulations of neurons were excited or inhibited by the reward-predictive stimulus. Finally, we established that stimulus-evoked excitations and/or inhibitions in the accumbens are required for the reward-seeking behavior instigated by the stimulus. We did this by inactivating either the dopaminergic VTA neurons or amygdala neurons while recording from accumbens neurons during the stimulus-evoked reward seeking task. Inactivation of either structure selectively abolished the firing of accumbens neurons responsive to reward-predictive stimuli. These experiments established that the convergence of the excitatory projection from the amygdala and dopaminergic projection from the VTA in the accumbens is an important part of the neural circuits that underlie stimulus-evoked reward-seeking behavior. Ongoing experiments seek to determine the nature of the information encoded by the firing of accumbens neurons driven by the amygdala and dopamine projections.

Drugs of abuse can also serve as rewards, often to the extent that drug-seeking

(sometimes in response to drug-predictive stimuli) becomes excessive and harmful. A long-term goal of these experiments is to use our increasing knowledge of the neural circuits that control reward-seeking to ask how these circuits produce aberrant behavior (excessive drug-seeking) in addiction.

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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.

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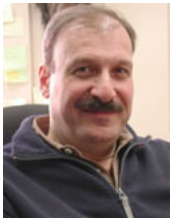

Alberto E. Pereda, M.D., Ph.D.

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Properties and plasticity of electrical synapses

Our laboratory is interested in the properties and dynamics of gap junction-mediated electrical transmission in the vertebrate brain. Perhaps because of the relative simplicity of transmission, electrical synapses are generally perceived as passive intercellular channels that lack dynamic control. Thus, 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.

In contrast with mammalian electrical synapses that generally have limited experimental access, lower vertebrates have provided with advantageous experimental models in which basic properties of electrical transmission can be more easily study. This is the case of identifiable auditory afferents terminating on teleost Mauthner cells known as "Large Myelinated Club endings". These endings are "mixed" (electrical and chemical) synaptic contacts that offer the rare opportunity to correlate physiological properties with molecular composition and specific ultrastructural features of individual synapses. Gap junctions at these model synapses undergo activity-dependent potentiation and are mediated by connexin35, the fish ortholog of connexin 36, which is widely distributed across the mammalian brain.

Our current work focuses on the mechanisms underlying activity-dependent changes in gap junction-mediated electrical synapses by investigating:

- Their functional relationship with glutamate receptors in fish (goldfish and zebrafish) and mammals.
- Their interaction with dopaminergic and endocannabinoid systems.
- The molecular mechanisms responsible for changes in electrical transmission, in particular the identification of connexin-associated regulatory proteins.
- The interaction between membrane and synaptic properties, as a mechanism for the control of the synaptic strength.

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.

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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 affect behavioral outcomes?

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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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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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My lab has a long-term interest in understanding the function of the KDM5 family of transcriptional regulators. KDM5 proteins have a unique combination of chromatin modifying and recognition domains that are likely to regulate gene expression through distinct mechanisms. In addition, an ever-growing body of evidence links their dysregulation to human pathologies. Of the four human KDM5 paralogs (KDM5A-D), three are clinically significant. KDM5A or KDM5B are overexpressed in a large number of cancers, and loss of function mutations in KDM5C are found in patients with X-linked intellectual disability.

To-date, however, no effective therapies exist to treat disorders caused by KDM5 protein dysfunction, primarily because we do not have a comprehensive knowledge of KDM5 target genes, nor of the mechanisms by which KDM5 proteins regulate gene expression. To dissect KDM5 function we use Drosophila since it encodes a single, essential, KDM5 ortholog thereby overcoming the complication of functional redundancy among the four mammalian paralogs.

We currently have a number of projects going on in the lab:

- Determining how KDM5 acts with the oncoprotein Myc to regulate cell growth, as this is likely to be directly relevant to understanding how KDM5A/B causes cancer in humans.
- Defining KDM5 target genes in larvae and in adults and defining the different mechanisms used by KDM5 to activate and repress gene expression.
- Examining neuronal phenotypes of kdm5 mutant flies to gain insight into how loss of human KDM5C results in intellectual disability.
- Generating and characterizing mutant fly strains harboring mutations that are analogous to those found in intellectual disability patients. Significantly, all missense mutations in KDM5C found in affected patients occur in evolutionarily conserved residues.

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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 microtubules, 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 Pac-man-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 ac-

tin-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.

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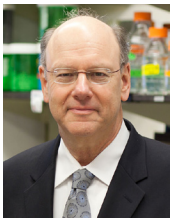

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Our work is focused on the travels of RNA within the cell: from the site of its birth to its ultimate biological destiny in the cytoplasm where it makes proteins in specific locations. All we have learned results from the development of new technology, 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.

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The long-term goal of our work is to develop novel tools and strategies for clinical neuromodulation to treat drug addiction and other neuropsychiatric disorders. To this end, efforts in the lab are focused in two primary areas:

1) Understanding dysregulation of frontolimbic circuits in drug addiction-related behaviors. Our previous work studied interactions between hippocampus and nucleus accumbens in cocaine conditioned place preference, providing the first evidence that cocaine preferentially strengthens connections arising from hippocampal place cells encoding the location where the animal received the drug. We are currently studying interactions between nucleus accumbens and prefrontal cortex in the prediction of reward value, a process whose dysregulation contributes to cravings and relapse in drug addiction. We approach these questions in rodent models using a combination of behavior, high-channel count silicon probe recordings, in vivo light field and two photon imaging, optogenetic and chemogenetic manipulations, and computational approaches.

2) Developing and validating new technologies and targets for gene-based clinical neuromodulation. Our prior work focused on validating the nucleus accumbens as a target for DREADD-based modulation in alcohol use disorders, providing a possible alternative to more invasive modalities such as lesioning or deep brain stimulation. We are currently extending these studies to other targets and disease models. In parallel, we are developing and validating improved technologies for chemogenetic and optogenetic manipulation that will be suitable for future clinical use.

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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.

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Roles of gap junctions in excitable and inexcitable cells

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 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) the role of gap junctions in stem cell therapy in a mouse model of Chagas disease (with H.B. Tanowitz, Dept Pathology), (4) endothelial cell and astrocyte mechanotransduction and cell polarization in a blood-brain-barrier model (with members of the Biomedical Engineering Department, CCNY). 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 intracellular recordings with conventional and ion-selective microelectrodes, photomanipulation such as FRAP, optical monitoring of intracellular ionic activities (especially Ca^{2+} and propagated Ca^{2+} waves), patch clamp recording of single channels and whole cell currents and standard molecular biological and immunological methods such as Northern and Western blot analyses, immunostaining and RT-PCR and expression profiling using microarrays.

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Mitchell Steinschneider, M.D., Ph.D.

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The broad objective of this program is to elucidate neural mechanisms associated with complex sound processing relevant for the perception of speech, music and auditory scene analysis. The main laboratory project focuses on defining neural mechanisms by examining electrophysiological responses within monkey auditory cortex. There are many similarities between monkeys and humans in their auditory cortex organization and in their ability to perform phonetic and complex sound discriminations, highlighting the utility of primates as a reasonable electrophysiological model. Direct recordings in monkey auditory cortex offer the opportunity to investigate neural bases of complex sound encoding with a detail that is unobtainable by studies in the human. Our studies will clarify normal mechanisms of speech and other complex sound encoding, and serve as a benchmark for evaluating hypotheses regarding dysfunctional processes associated with abnormal speech and hearing development. Studies in the monkey are complemented by collaborative work examining complex sound processing in humans. Current collaborations examine human sound processing through direct, intracranial recordings of auditory cortex in patients undergoing surgical evaluation for medically intractable epilepsy and developmental aspects of complex sound processing through non-invasive scalp recordings in children.

Recent speech-related work has focused on the cortical processes involved in the encoding of the voice onset time and place of articulation phonetic parameters. Music-related studies have concentrated on auditory cortical encoding of pitch and timbre, as well as the neural response features associated with consonance and dissonance of musical intervals. Mechanisms responsible for sequential and simultaneous features of auditory scene analysis are a major focus of our current NIH-funded monkey grant, as this basic analysis allows one to hear isolated speakers in real-world, complex sound environments. Cortical responses in the monkey are described using 4 complementary, concurrently recorded measures of neuronal ensemble activity; multiunit activity (MUA), auditory evoked potentials (AEPs) and the derived current source density (CSD) and spectral EEG analysis. CSD analysis characterizes the temporal and laminar distributions of current sources and sinks that reflect net synaptic activation and inhibition, whereas phasic MUA patterns determine changes in the net firing rate of neuronal ensembles. These recording procedures yield stable measures of the synchronized neuronal activity required for complex sound encoding. Through their relationship with the EEG and AEP, monkey intracortical responses can be directly linked with homologous

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Sylvia O. Suadicani, Ph.D.

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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 Sclerosis 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.

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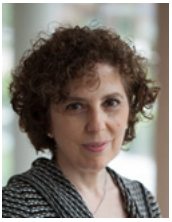

Elyse S. Sussman, Ph.D.

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My research is in the field of Cognitive Neuroscience and is focused on understanding the neural bases of auditory information processing in adults and children. Our laboratory's research uses a combination of non-invasive recordings of human brain activity, in conjunction with behavioral performance measures, to specify the processes and brain structures that contribute to the organization, storage and perception of a coherent sound environment.

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Connexins and Syndromic Sensorineural Deafness

Our work is focused on investigating the mechanistic basis of cochlear dysfunction in syndromic deafness caused by missense mutations in the GJB2 gene that encodes the human connexin 26 (Cx26) gap junction (GJ) protein. Mutations in GJB2 are one of the most common causes of inherited, non-syndromic deafness in the human population. A subset of Cx mutations leads to syndromes in which deafness is accompanied by a heterogeneous array of cutaneous manifestations. Keratitis-Ichthyosis-Deafness (KID) syndrome is one of the more severe syndromes associated with GJB2 mutations and is characterized by profound, pre-lingual sensorineural hearing loss, vascularizing keratitis, skin lesions that can be fatal due to uncontrollable sepsis and predisposition to squamous cell carcinomas. GJs, which are formed by the docking of two, so-called hemichannels (HCs), one from each of two contacting cells, are abundant between keratinocytes and between cochlear support cells and serve as pathways for direct intercellular electrical and chemical signaling. However, it is now evident that undocked Cx26 HCs can function, thereby providing a signaling role across the plasma membrane. Our principal hypothesis is that the pathogenesis of KID syndrome is the result of a new type of channelopathy, specifically mediated by Cx26 HCs that function aberrantly leading to cell dysfunction and even cell death. We use a combination of molecular, biophysical and imaging approaches to investigate the mechanisms by which hemichannels are dysfunctional in KID syndrome. We have identified a number of aberrant HC properties including altered permeability, impaired regulation by extracellular Ca^{2+} and pH and shifted voltage-dependent gating. Our current focus is on altered permeability to Ca^{2+} and ATP, two important signaling molecules in cochlea and skin. To that end we are examining the effects of expressing hCx26 mutants in exogenous expression systems and in support cells of the Organ of Corti using cochlear tissue explants. Parallel efforts are aimed at developing a mouse model for KID syndrome using a proof-of-principle 2-plasmid, Tet-On inducible expression system in cochlea developed to express mutant GJB2 transgenes in keratinocytes. Finally we plan to screen for selective blockers of Cx26 HCs, initially using a small library of compounds enriched in known ion channel pharmacophores. Lead compounds will be followed-up through medicinal chemistry approaches to increase affinity and selectivity.

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Training in Comparative Medicine and Neuroscience provided the basis for my career interests in neurogenetic disease, particularly those disorders impacting neuronal homeostatic mechanisms and resulting in intellectual disability and related neurobehavioral abnormalities. My lab has published extensively in the area of pathogenic cascade analysis in lysosomal disease, defining key changes in neuronal structure and function as a consequence of lysosomal compromise. Current studies include: (i) the causes and consequences of ectopic dendritogenesis and neuroaxonal dystrophy, (ii) altered synaptic function underlying intellectual compromise, (iii) involvement of mTOR and TFEB/TFE3 in homeostatic dysregulation following lysosomal compromise and its impact on endosomal and autophagasomal function, and (iv) the importance of metabolite salvage in lysosomal processing.

Diseases of current focus include the lysosomal diseases Niemann-Pick types A and C, mucolipidosis IV, cystinosis, GM1 and GM2 gangliosidosis, Sanfilippo type A (MPS IIIA), Batten disorders (CLN2 and CLN3) and a newly discovered endosomal disorder known as Christianson syndrome.

My lab is also significantly involved in therapy development for genetic brain disease. We were the first to show essentially complete correction of CNS disease in the lysosomal disorder known as alpha-mannosidosis through the use of bone marrow transplantation and this treatment approach is now the standard of care for children diagnosed with this rare disorder. A disease of current focus toward therapy is Niemann-Pick type C (NPC), a fatal cholesterol-glycosphingolipid lysosomal storage disorder of children. Based on our studies of glycosphingolipid processing abnormalities in NPC disease we developed the first and presently only approved (by EMEA; FDA pending) therapy for this disorder. This is the imino sugar known as N-butyldeoxynojirimycin, or miglustat, which is a partial inhibitor of glycosphingolipid synthesis.

More recently we discovered that the FDA-approved excipient known as hydroxypropyl beta-cyclodextrin is efficacious in limiting intraneuronal accumulation of both unesterified cholesterol and glycosphingolipids, and dramatically extends the lifespan in animal models of NPC disease. Research and clinical trial development was subsequently pursued through a unique scientist/clinician/parent consortium known as SOAR (Support Of Accelerated Research) for NPC disease (SOAR-NPC) and through collaboration with TRND (Therapeutics for Rare and Neglected Diseases) and NCATS (National Center for Advancing Translational Sciences) at NIH.

Phase 1 trials of this compound in NPC patients began in February, 2013, followed by the Phase 2/3 trial, with outcome analysis now in progress. To see a short video related to the trial development, go to:

https://www.youtube.com/watch?v=EE9kh6OTTSY&feature=youtu.be&app=desktop

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Professor, Dominick P. Purpura Department of Neuroscience

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).

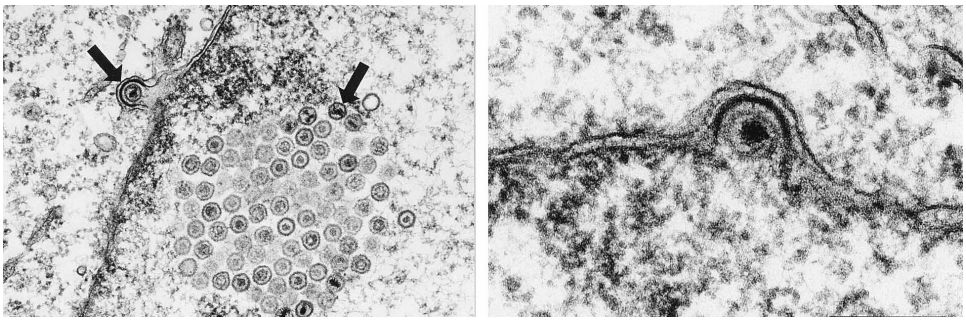

Fig. 1: HSV makes a break for it. Left hand image: HSV initially assembles clusters of capsids in the cell nucleus. These then fill with viral DNA, visible as a dense core (arrow at right). They then traffic to, and bud into, the nuclear membranes (left hand arrow) to enter the cytoplasm and cell body. Right hand image: Similar to left hand but at higher magnification, showing a DNA-containing HSV capsid punching through the nuclear membranes.

Once in the cell cytoplasm HSV capsids dock with, and become enveloped by, cytoplasmic organelles to assemble

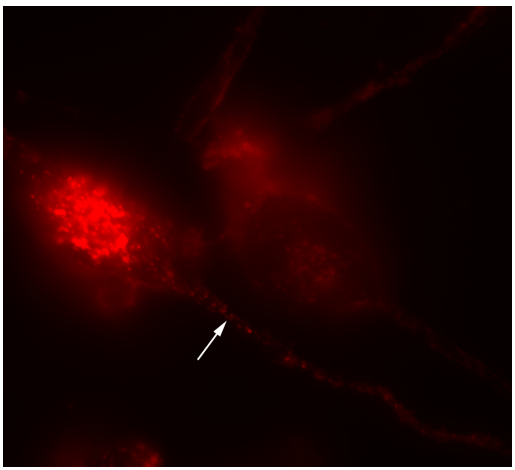

Fig. 2: HSV steals motors and traffics down the axon. HSV particles (labeled with red fluorescent protein fused to a viral structural subunit) recruit molecular motors (kinesins) then stream down the axon of neurons (white arrow) to invade adjacent epithelia and spread to the next host. (Image courtesy of Jenna Barnes in our laboratory).

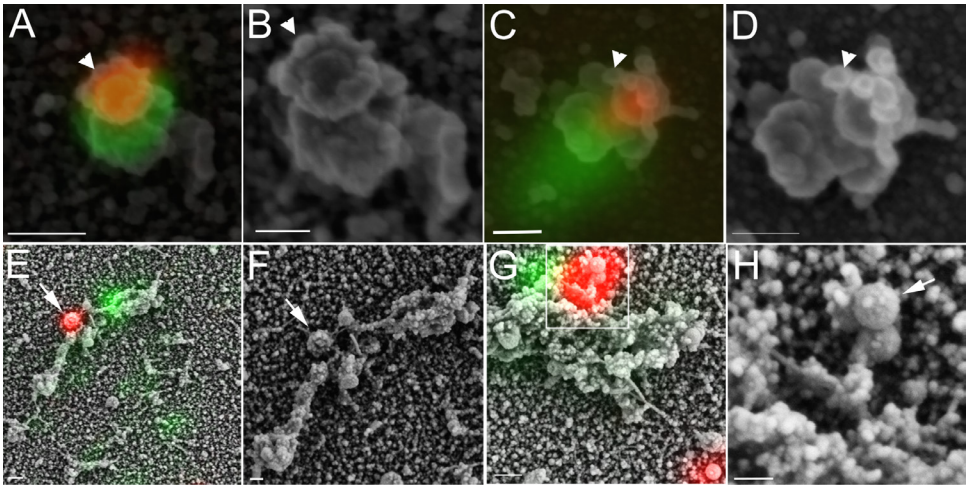

Fig. 3: What to do when more light doesn't help you see better. Correlative light and electron microscopy makes it possible to observe HSV assembly simultaneously by fluorescence microscopy and electron microscopy. Paired images A-B, C-D, E-F and G-H show HSV capsids assembling onto cellular organelles 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.

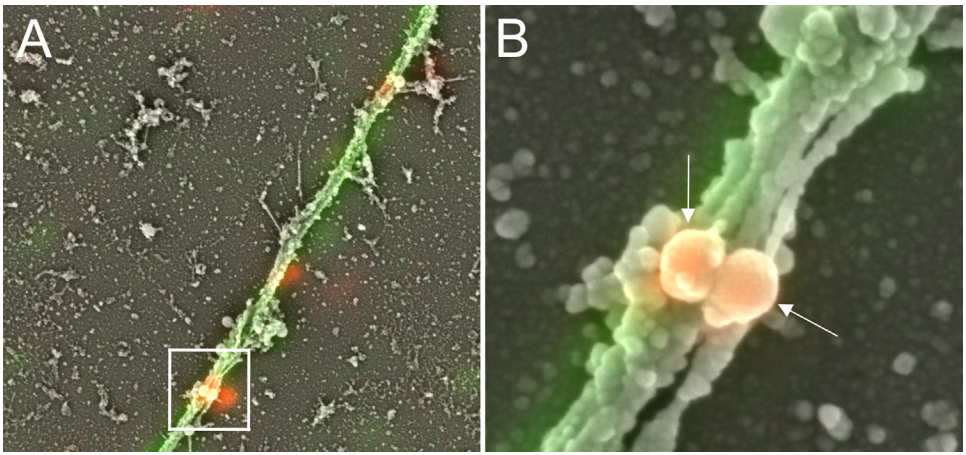

Fig. 4: HSV goes for a walk. Using the same technology as in Fig. 3 we image viruses (red) attached to microtubules (green). Boxed region in (A) is expanded in (B). Combining this structural approach with genetically manipulated viruses and fluorescently-tagged kinesins and dyneins enables us to dissect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

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).

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

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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.

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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 http://www.einstein.yu.edu/labs/deyou-zheng/.

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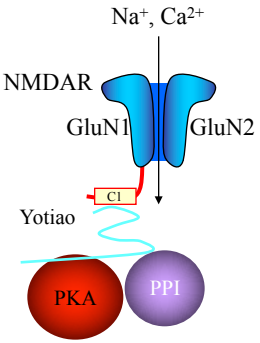
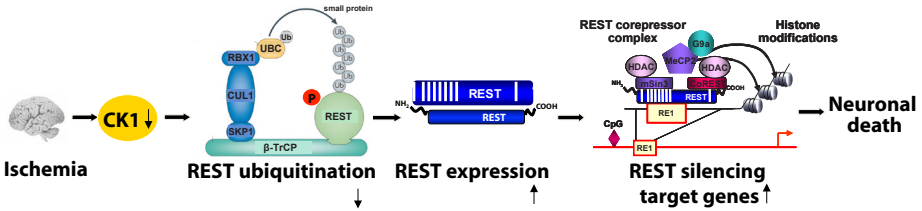
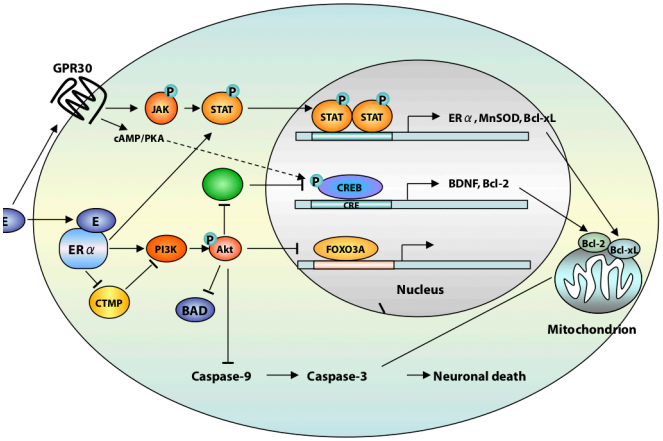
There are four major lines of ongoing research in the Zukin lab. First, we are studying the molecular and cellular mechanisms that regulate N-methyl-D-aspartate-type glutamate receptor (NMDA receptor) expression at synapses in the brain. We discovered that the switch in NMDA receptor phenotype at hippocampal synapses during normal brain development is regulated by epigenetics in an experience-dependent manner. In normal brain, the gene silencing transcription factor REST is activated during a brief window of time in differentiated neurons of the hippocampus, a brain center implicated in learning and memory, and drives the switch from immature to mature NMDA receptors. Remarkably, depriving pups of maternal access for brief periods of time during the first postnatal week prevents activation of REST and epigenetic modifications essential to acquisition of mature NMDA receptors and normal brain development. These findings have striking implications for treatment of anxiety, post-traumatic stress and other disorders associated with early maternal separation. New questions are: What is the mechanism by which REST is activated during brain development? Do other forms of stress regulate the switch in NMDA receptors? What are the consequences of blocking the switch? Our interest stems from the fact that NMDA receptors play a central role in cognitive functions such as learning and memory, synaptic plasticity and formation of neural circuitry. NMDA receptor dysregulation is implicated in Alzheimer's disease, Huntington's disease, AIDS dementia, stroke and schizophrenia.



Second, we are studying the molecular and cellular mechanisms that underlie the neuronal death associated with stroke and epilepsy. We discovered that neuronal insults activate REST in selectively vulnerable adult hippocampal neurons. Upon activation, REST orchestrates epigenetic reprogramming of neuronal genes in differentiated neurons. We further showed that prolonged activation of REST is caus-





ally related to neuronal death in a clinically-relevant model of ischemic stroke. A key downstream target of REST in insulted CA1 neurons is the gene encoding the AMPA receptor subunit GluA2. This is of interest because the GluA2 subunit governs calcium permeability, channel conductance and AMPA receptor trafficking to and from synaptic sites. GluA2-lacking AMPA receptors are highly permeable to calcium and zinc, which rise to toxic levels in insulted neurons. Objectives are: 1) to understand how REST is activated in insulted neurons; 2) to examine epigenome-wide dysregulation of REST targets in stroke, Huntington's disease and Alzheimer's disease; and 3) to identify novel strategies to protect the human brain from neurodegeneration. Our interest stems from the known role of AMPA receptors in neuronal death arising in stroke, epilepsy, ALS and spinal cord injury.

A third area of interest is that of estrogen neuroprotection in animal models of stroke, including global ischemia. Recently, we found that long-term treatment with estrogen at physiological levels ameliorates death of hippocampal neurons and cognitive deficits associated with global ischemia. We showed that ischemia and estrogen act synergistically to activate the transcription factor STAT3 and promote transcription of survivin, an inhibitor of apoptosis protein and gene target of STAT3, in insulted CA1 neurons. In experiments in which we employ direct delivery of shRNA constructs into the hippocampal CA1 of living animals, we found that STAT3 and survivin are essential to estrogen neuroprotection. These findings identify STAT3 and survivin as therapeutic targets in a clinically-relevant model of stroke. Objectives are to identify epigenetic mechanisms by which estrogen rescues neurons. Our interest stems from data that estrogen reduces the risk of cardiac arrest and stroke in animal models.

A fourth area of interest is that of RNA trafficking and targeting to dendrites and local protein synthesis in Fragile X syndrome. We found that mTOR signaling is overactivated in hippocampal neurons of Fragile X mice and causally related to aberrant synaptic plasticity. We also found that targeting of AMPAR mRNAs to synapses under basal conditions and in response to mGluR signaling is dysregulated in Fragile X neurons. We are using a combination of high resolution imaging of individual mRNA molecules (in collaboration with the Singer lab), molecular biology, and electrophysiology to examine AMPAR mRNA trafficking, local translation,

synaptic plasticity and spine structure in Fragile X mice. Objectives are to identify novel signaling pathways that play a role in synaptic dysfunction. We believe that understanding the mechanisms responsible for abnormal function at the synapse will advance novel therapeutic strategies to ameliorate cognitive deficits in Fragile X syndrome and unlock doors for treating other autism spectrum disorders.

Positions for graduate students and post-doctoral fellows are available in all four areas of the laboratory's research. Independent researchers and ideas are welcome, while well-defined and achievable projects are waiting for motivated, young investigators.

(From a total of 194 peer-reviewed papers and 41 book chapters)

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