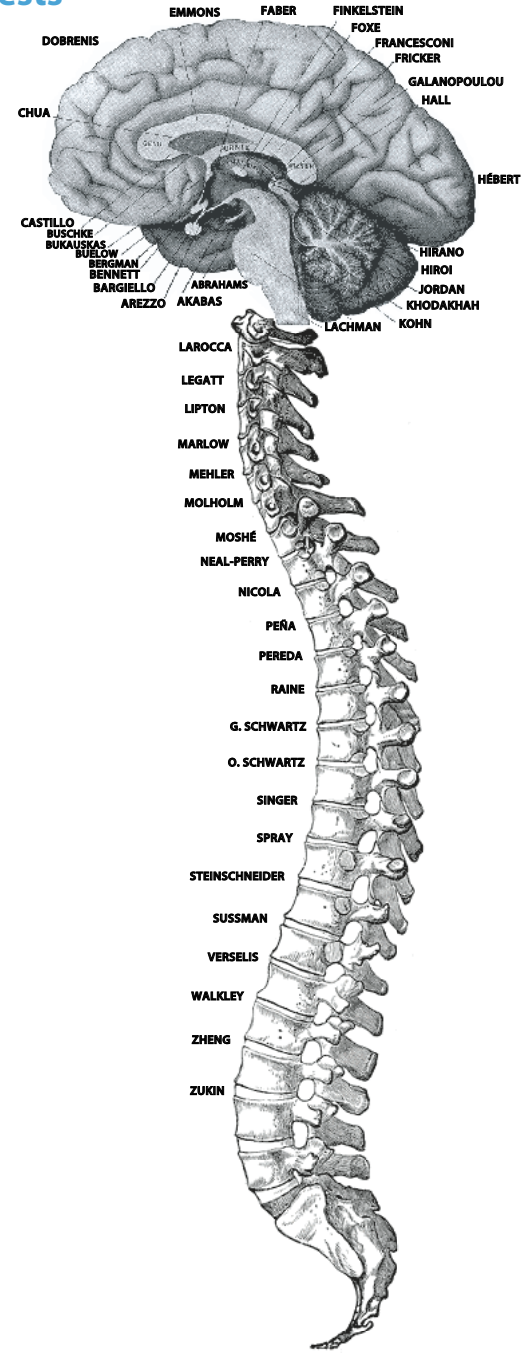
Dominick P. Purpura

Department of Neuroscience

Faculty Research Interests at the Albert Einstein College of Medicine 2014–2015



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Brett Abrahams

Genetics/Neuroscience

Assistant Professor

My work is aimed towards understanding how disorders of human cognition, and the Autism Spectrum Disorders (ASDs) in particular, are influenced by genetic variation. Defined entirely in terms of behavior, the ASDs represent a unique class of clinical conditions involving deficits in language use, impaired social behavior, and a circumscribed range of interests.

Work in my lab employs a blend of molecular genetics and developmental neurobiology to identify disease-related genes and understand how they operate functionally. Drawing on both hypothesis-based and discovery-driven methodologies, we have multiple studies directed focusing on Contactin-Associated Protein-like 2 (CNTNAP2). In addition to the potential importance of this molecule to ASD biology, we and others have obtained data to support a role for this gene in related disorders of cognition including specific language impairment, intellectual disability, and schizophrenia. And so our findings from cell, mouse, and human-based systems are likely to be of broad interest.

Looking forward, we will direct substantial effort towards understanding how individual molecular variants work alongside one another to modulate risk. New insights around how seemingly distinct molecules converge to shape disease-related processes will prove important in the development of potential therapeutics.

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Myles Akabas

Physiology & Biophysics/Neuroscience

Professor

Neurotransmitter-gated ion channels are essential components in synaptic transmission. Our work focuses on the $GABA_A$ receptor and related members of the Cys-loop receptor neurotransmitter-gated ion channel superfamily.

$GABA_A$ receptors are members of a gene superfamily that includes receptors for glycine, acetylcholine, and serotonin. $GABA_A$ receptors are the major inhibitory post-synaptic neurotransmitter receptor in the central nervous system. They are targets for drugs used clinically in the treatment of anxiety and epilepsy, and for general anesthesia. Our goals are to understand the structural bases for the functional properties of this channel superfamily and to understand the molecular interactions by which drug binding modulates structure and channel activity. We use a combination of techniques including site-directed mutagenesis, heterologous expression, covalent chemical modification and electrophysiology. These studies have identified the residues lining the channel, the location of channel blocker binding sites and identified conformational changes occurring during channel gating and modulation by drugs including valium and propofol. Recent work has focused on the role of the large intracellular loop between the M3 and M4 transmembrane segments in channel function and trafficking.

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Joseph Arezzo

Neuroscience/Neurology

Professor

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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Thaddeus Bargiello

Neuroscience

Professor

Structure function relations of gap junctions

We are investigating the structure-function relationships of voltage dependent gap junctions encoded by the vertebrate connexin gene family. Recently we have identified several amino acid residues that form part of the transjunctional voltage sensor in two closely related members of the connexin gene family; Cx26 andCx32 and have identified amino acid residues that form the physical gate of a second gating mechanism termed loop-gating. We are further examining the structural implications and operation of voltage dependent gating by site directed mutagenesis, expression of in vitro synthesized RNA in Xenopus oocytes, Molecular Dynamics simulations of connexin hemichannels imbedded into model membranes and with the solution structure of peptides with NMR. A major objective of our recent work is the creation of models of voltage-gated closed state and their validation. Atomic models of open and closed states allows the use of computational methods to describe the transition pathway. We are extending the results obtained from our investigations of Cx26 and Cx32 to other, more distantly related members of the connexin gene family to determine the generality of the gating mechanisms we have described.

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Michael V.L. Bennett

Neuroscience

Professor

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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Aviv Bergman

Systems and Computational Biology/Neuroscience

Professor and Chairman of Systems and Computational Biology

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

Topology of biological networks

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

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

Computational Immunology and somatic hypermutation

Somatic hypermutation (SHM) is a key process in the generation of antibody diversity that normally operates in antibody-forming B cells by introducing point mutations into the variable regions of immunoglobulin (Ig) heavy and light chain genes. SHM is initiated when the highly mutagenic enzyme activation-induced deaminase (AID) generates C→U mutations by deaminating cytosines preferentially at WRC hotspot motifs (where W=A/T, R=G/A and C is the mutated base). In collaboration with Matthew Scharff (Department of Cell Biology, Albert Einstein College of Medicine), we use computational and statistical methods

together with relevant experimental data to improve our understanding of the molecular mechanisms underlying SHM. How does the target sequence affect AID activity? To study the behavior of AID and the role of the target sequence, we have used computational methods to compare mutated sequences from three different models of AID activity: (a) an in vivo mouse model, (b) an in vitro model which captures essential biochemical activity of AID on DNA, and (c) an in silico model which simulates only hotspot targeting. This analysis suggests that there is considerably more complexity involved in the mutation process than can be described by simple of WRC hotspot motifs. We have also found strong differences between the two strands (transcribed and non-transcribed) in terms of the similarity between the models. A potential clue comes from differences in the profile of inter-mutational distances between the two strands, which suggest the existence of a complex interplay between the enzyme structure and the sequence.

Evolution of gene regulatory networks

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

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

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

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Hannes E. Buelow

Genetics/Neuroscience

Associate Professor

My lab uses the small nematode *C. elegans* with its simple and well characterized nervous system as a genetic model. We are trying to understand how growing axons and dendrites navigate the extracellular space to connect to their partners and be appropriately patterned.

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 the polysaccharide HS determine the path of developing axons. For instance, we have shown that distinct modification patterns in HS serve specific and instructive functions during neural development leading us to formulate the 'HS code' hypothesis. We propose that defined combinations of modifications in the sugars of HS contain information and generate a molecular map that helps shape the nervous system. Our goal is to decipher the information contained in HS, determine the factors that create and modulate it and describe the genes that respond to it. We are also investigating a pathological dimension of HS by studying Kallmann Syndrome, a human genetic disease with specific neurological defects in which we have identified mutations in HS genes.

In another project we are studying the development of dendrites in polymodal multidendritic neurons of *C. elegans*. We are aiming to understand how the complex dendritic arbors that resemble menorah-like candelabras are patterned. In summary, we are using genetic approaches coupled with biochemical and advanced imaging approaches to understand the function of genes involved in development and disease of the nervous system.

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Feliksas F. Bukauskas

Neuroscience

Professor

Our major goals are to study de-novo formation, gating and regulation of gap junction (GJ) channels and unapposed/nonjunctional hemichannels formed by connexin (Cx) proteins. GJ channels mediate direct cell-cell exchange of cytosolic ions and molecules. By combining electrophysiological, imaging and computational modeling methods, we examine electrical cell-cell coupling and metabolic communication under normal conditions and changes of intracellular pH, $[Ca^{2+}]_i$, $[Mg^{2+}]_i$ and other reagents in living cells that express different types of wild type Cxs, their mutants and Cxs fused with color variants of green fluorescent protein (Cx-GFP). We demonstrated that in each hemichannel of the GJ channel there are two distinct types of gating mechanisms, fast and slow/loop, and that the fast gate can serve as a selective filter that preserves electrical cell-cell signaling but restricts metabolic communication and chemical signaling. We developed a stochastic multi-state model describing voltage-gating of homotypic and heterotypic GJ channels combined with methods of global coordinate optimization for automated characterization of fast and slow gates from experimental measurements of voltage gating. We propose that clustering of GJ channels into junctional plaques (JPs) is central to their ability to function. We reported that depending on Cx isoform, only ~0.003–0.15 of GJ channels clustered in JPs are functional and this fraction can be significantly modulated by pHi, $[Ca^{2+}]_i$, $[Mg^{2+}]_i$, arachidonic acid, long chain alkanols, albumin and other factors. Furthermore, we demonstrated that heterotypic junctions can exhibit nearly unidirectional electrical signaling and may function as rectifying electrical synapses and that the transjunctional flux of metabolites is affected by ionophoresis and voltage-sensitive gating, which can synergistically or antagonistically affect metabolic communication. Furthermore, we study the role of Cxs in the spread of apoptosis and Cx mutants related to deafness, oculodentodigital dysplasia (ODDD), X-linked Charcot-Marie-Tooth disease, cardiac arrhythmia and other hereditary diseases.

For more details, please see our website connexons.aecom.yu.edu.

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Herman Buschke

Neurology/Neuroscience

Professor

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Pablo E. Castillo

Neuroscience

Professor

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 Chua

Medicine/Endocrinology/Neuroscience

Professor

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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Kostantin Dobrenis

Neuroscience

Assistant Professor

Our principal interests lie in the therapy of neurologic diseases and in the field of microglial biology. Much of our work is focused on developing rational therapeutic strategies for genetic diseases that affect the central nervous system (CNS) in a global manner, in particular neuronal storage disorders such as Tay-Sachs disease. The goal here is to find ways to effectively replace the missing lysosomal enzyme within cells throughout the CNS. Towards this, our research has been and is directed to satisfying three important conditions necessary for successful treatment. One is to overcome the blood:brain barrier (BBB) and deliver normal enzymes or genes into the CNS parenchyma in a widespread manner. A strategy for this is the use of appropriately specialized cell lines to serve as vectors able to cross the BBB. These lines would upon introduction into circulation target to and enter the CNS via the vasculature, and release macromolecular therapeutic agents locally. We have derived subpopulations of the monocyte/microglial lineage from unique transgenic animals and have found these cells can enter all major regions of the CNS following intravenous injection into normal mice. We are now employing strategies to enhance efficiency of entry and longevity within the brain. Cell lines efficient in circumventing the BBB could prove invaluable towards treatment of a variety of diseases with global CNS involvement for which current delivery modalities are inadequate. The second and related requirement is to provide sufficient levels of normal exogenous enzyme in the extracellular fluid for subsequent uptake by deficient CNS cells. We have shown that normal microglia and our cell lines do secrete lysosomal enzymes and are now investigating how gene overexpression, cytokine modulation and endosomal pathways can be used to enhance secretion. The third condition is to obtain efficient endocytosis of compounds from the interstitial fluid by neurons. We have previously shown that polylysine or penta-mannosyl-phosphate conjugates of b-hexosaminidase (the enzyme deficient in Tay Sachs disease) could enhance neural cell uptake of enzyme. Most effective for neurons was enzyme derivatized with the atoxic fragment of tetanus toxin (TTC). This resulted in 40-fold enhancement of uptake relative to native enzyme and successful degradation of storage compounds in disease neurons. We are now pursuing genetic modification of enzymes in our cells lines including a fusion gene incorporating neuronal binding fragments and the retrograde trans-synaptic transfer properties of TTC.

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Scott Emmons

Genetics/Neuroscience

Professor

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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Donald Faber

Neuroscience

Professor Emeritus

Mechanisms of synaptic transmission and regulation of neuronal excitability

Our research activities focus on basic mechanisms of synaptic transmission in the central nervous system, factors involved in the regulation of the strength of the synaptic connections between neurons, and intrinsic mechanisms that modulate neuronal firing patterns. We are particularly interested in the short and long term plasticity of these fundamental properties and their consequences for the operation of neural networks.

The laboratory uses a number of experimental models, focusing most recently on transgenic mouse models of neurodegenerative diseases, such as Huntington's Disease.

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Mirjany M, Preuss T, Faber DS. (2011) Role of the lateral line mechanosensory system in directionality of goldfish auditory evoked escape response. *J Exp Biol.* 214:3358–67.

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Alan Finkelstein

Physiology and Biophysics/Neuroscience
Professor

For the past several years we have been studying the voltage-dependent channels formed in planar phospholipid bilayer membranes by diphtheria toxin, colicin Ia and anthrax toxin. The remarkable finding we have discovered with the former two channels is that in association with their opening and closing there is a massive translocation of material back and forth across the membrane. In the case of diphtheria toxin, this consists of the N-terminal 270 residues, and in the case of colicin Ia, a region of at least 70 residues. Moreover, we have shown with the colicin that foreign epitopes inserted in this region are also translocated. Thus these molecules appear to be capable of translocating "any" sequence of polar residues. Our research is directed at deducing the channel structure, identifying the voltage sensor, and determining the mechanism and pathway of protein translocation.

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Yonatin Fishman

Neurology/Neuroscience

Assistant Professor

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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John Foxe

Pediatrics/Neuroscience

Professor & Director of Research of the Children's Evaluation and Rehabilitation Center

Our laboratory employs an integrated multi-methodological approach to issues in the cognitive neurosciences, using structural and functional neuroimaging, high-density electrophysiology, imaging genomics, eye tracking, psychophysics and virtual reality to understand the neural basis of basic sensory-perceptual and cognitive functions. Our work is translational at its core in that we employ an equal mix of basic-science projects in healthy individuals with clinical studies in patient groups. Our approach is to first develop novel assays of a given cognitive function in healthy individuals, which are then deployed in populations of interest. The mission of the lab is to understand the underlying neurobiology of developmental disorders, as a means to develop more effective treatments and interventions, and we have worked extensively in adolescent Schizophrenia, Autism Spectrum Disorder, ADHD and Aging. With a $2.8 million grant awarded by the National Institutes of Health, we are examining whether multisensory integration (i.e., the brain's processing of information from different senses) is impaired in people with autism. Another area of major focus for us is the basic neurobiology of attention, with more than 60 of our over 150 papers concentrating on the mechanisms of attentional control. This latter work is supported by a grant from the National Science Foundation (NSF).

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Anna Francesconi

Assistant Professor

Neuroscience

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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Lloyd Fricker

Molecular Pharmacology/Neuroscience
Professor

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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Aristea S. Galanopoulou

Neurology/Neuroscience

Professor/Associate Professor

- Models of infantile spasms and early life epilepsy
- Identification of new treatments for infantile spasms
- Role of inflammation in early life epilepsies
- Optimization of preclinical epilepsy research
- Role of $GABA_A$ signaling and the mTOR pathway in epileptogenesis and brain development
- Effects of early life seizures on brain development
- Pathophysiology of Rett Syndrome

West syndrome is one of the catastrophic epileptic encephalopathies of infancy that usually have poor outcome. The characteristic seizures in this syndrome are called infantile spasms and the available treatments are not always effective. To better understand their pathophysiology and design better methods to treat catastrophic early life epilepsies, we are developing and studying new models of early life epilepsy, in collaboration with Solomon Moshé. These include models of infantile spasms due to structural or other insults (e.g., inflammatory) that recapitulate most of the features of the human condition. Several projects are underway 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 inhibitors and carisbamate. Two of the candidate new treatments evaluated in our lab have already been designated orphan drugs for infantile spasms by FDA.

There is an international concern about the translatability of discoveries made in animal studies to clinically relevant discoveries. Our lab's investigators have played leadership roles in an international effort (ILAE, AES supported) to optimize preclinical epilepsy research and form infrastructure that will allow across-study comparisons of available data, standardization of protocols and design of new protocols that may advance epilepsy therapy discovery to address the clinical gaps and needs.

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.

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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David Hall

Neuroscience

Professor

The soil nematode *Caenorhabdidis elegans* is a model system used to study the genetic control of cellular development. Our laboratory specializes in ultrastructural studies of the nervous system. 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 host the Center for C. elegans Anatomy, 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, a glossary, and selected html texts of classic papers.

Worm Wiring is a project aiming to complete the wiring diagram for the male adult and L1 stage nematode, working with Scott Emmons (Molecular Genetics). See www.wormwiring.org.

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Jean Hébert

Neuroscience

Professor

Generating and regenerating the neocortex

The Hébert lab is interested in two broad questions: how the forebrain develops and how parts of it can be regenerated in the adult. In particular, we are interested in understanding how a simple sheet of neuroepithelial cells early in embryogenesis can develop into the adult neocortex, the part of our brains that we use for our highest cognitive and perceptual functions. Essential to this understanding is the identification of the signals that pattern the early forebrain and regulate the fate of neural stem cells and progenitor cells throughout development and in the adult.

The primary approach we are using to test the roles of candidate signaling molecules in embryos, postnatal animals, and adults is a conditional genetic approach in the mouse. This approach, which uses CRE/loxP technology, allows us to test the function of particular factors by deleting or overexpressing the genes that encode them specifically in the neocortex. In addition, studies in the adult also require approaches including stem cell transplants and viral delivery of genes to evaluate the feasibility of using genetically modified neural progenitor cells, alone or in combination with modified cellular environments, to achieve regeneration of damaged neocortices.

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Asao Hirano

Pathology/Neuroscience

Professor

Current interest is cytopathology of motor neuron disease.

Kusaka H, Hirano A. (1999) chapter 7: Cytopathology of the motor neuron. In younger DS, ed *The Motor Disorders*. Lippincott-Raven Publishers, New York; pp 93–101.

Nakano I, Hirano A. (1999) Ultrastructural changes in dementing illnesses. In, Jones EG, Peters A, eds. *Neurodegenerative and Age-Related Changes in Cerebral Cortex, Cerebral Cortex*, volume 14. Plenurn Publishing Corporation, New York pp 399–431.

Hirano A. (1998) Astrocyte: Neuropathologia View Point. In, Ikuta F., ed. *Glia Cell*. Kubapuro, Tokyo 1998; pp 111–131.

Noboru Hiroi

Psychiatry/Neuroscience

Professor

Molecular and Cellular Bases of Developmental Neuropsychiatric Disorders

The primary aim of this laboratory is to more fully understand the molecular and cellular bases of developmental neuropsychiatric disorders. The human genome includes many variations, ranging from duplications and deletions of full chromosomes to single nucleotide polymorphisms. In particular, a large number of kilo- to mega-base copy number variations (CNVs) are associated with autism spectrum disorder, mental retardation, and schizophrenia. Children and adolescents with 22q11.2 duplications and deletions consistently exhibit these neuropsychiatric disorders, along with associated cognitive and intellectual impairments during development. However, because duplications and deletions of 22q11.2 encompass 1.5 Mb or larger regions, it is not possible to determine whether segments or single genes are responsible for specific phenotypes in humans. To circumvent this obstacle, our laboratory examines the role of individual 22q11 genes in distinct aspects of behavior in genetically engineered mice. We have identified two small human 22q11.2 segments of which over-expression during development causes behavioral phenotypes consistent with neuropsychiatric disorders. Our current work examines the role of each of the genes encoded in the segments in behavioral, neuronal and synaptic phenotypes relevant to neuropsychiatric disorders in mice.

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Bryen Jordan

Neuroscience/ Psychiatry and Behavioral Sciences

Assistant Professor

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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Kamran Khodakhah

Neuroscience

Professor and Interim Chair

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

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Adam Kohn

Neuroscience

Associate Professor

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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Herb Lachman

Psychiatry and Behavioral Sciences/Medicine/Neuroscience
Professor

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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Jorge LaRocca

Neurology/Neuroscience

Associate Professor

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 microscopy 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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Alan D. Legatt

Neurology/Neuroscience

Professor/Assistant Professor

- 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.

Fried SJ, Legatt AD (2012) The utility of a forehead-to-inion derivation in recording the subcortical far-field potential (P14) during median nerve somatosensory evoked potential testing. Clin EEG Neurosci, 43:121–126.

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Michael Lipton

Radiology/Neuroscience

Associate Professor

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 markers 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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Florence Marlow

Developmental and Molecular Biology/Neuroscience
Associate Professor/Assistant Professor

Polarity in the Zebrafish Ovary

Every animal starts out as a single fertilized cell, yet we do not fully understand the events that are essential for producing that cell because they take place within the ovary of the mother. Failure to form an egg that is capable of embryonic development can result in profound birth defects or miscarriage. In addition, cancers of the ovary can arise from uncontrolled proliferation of the germ cells, those cells that can become eggs, or the somatic cells, the cells that do not develop as eggs, of the ovary. In normal ovaries, these two types of cells communicate with one another to regulate the growth and survival of both cell populations. In most animals, the germ line stem cells undergo an asymmetric division to generate daughter cells that will remain stem cells and others, cystoblasts that divide and eventually form eggs. The divisions of the cystoblasts are unique because the cells do not completely separate from one another, but instead remain attached to each other. Studies in mammals show that the connections between cystoblasts prevent too many cells from becoming oocytes, and in humans uncontrolled and complete separation of cystoblasts correlates with germ cell neoplasias. However, since these events occur before or at the time of fertilization we understand little about how the genes that are involved. Therefore, understanding how the growth and survival of these cells is regulated has important consequences to both fertility and cancer formation.

To study relationships between interacting cells within adjacent tissues, such as germline and somatic follicle cells, we need to analyze an animal system in which we can manipulate genes and study early development. The zebrafish system has advantages that allow us to use embryological, biochemical, and genetic techniques to access maternally controlled processes during vertebrate animal development. Our studies exploit the powerful genetics and cell biological access in the zebrafish system to unravel the mechanisms that regulate oocyte polarization and follicle cell fate in a vertebrate. Many features of primary oocyte development are evolutionarily conserved, including humans; thus this architecture is likely fundamental for germline development and fertility.

Our genetic and biochemical studies of oocyte polarity have led us to genes involved in mRNA localization and polarized transport, including motor and RNA binding proteins. Like oocytes, neurons are highly polarized cells, which rely on trafficking and post-transcriptional regulation of mRNAs to ensure that gene products are only expressed in discrete locations. Inappropriate accumulation of proteins and organelles due to failed trafficking and post-transcriptional regulation is associated with neuronal loss underlying devastating neurodegenerative diseases. The rapid development, optical clarity, and ease of generating transgenic and mutant zebrafish strains make it an ideal system for live cell tracking and visualization of fluorescently labeled organelles, motor proteins, mRNA cargos, and

the cytoskeleton in the living animal. To better understand how trafficking is regulated in distinct polarized cell types, we are also using the zebrafish model system to examine the cellular and molecular basis of transport in neurons. Knowledge of how the individual transport mechanisms operating in neurons contribute to their function has potential to uncover novel pathological mechanisms underlying neurodegenerative diseases.

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Mark Mehler

Neurology/Neuroscience/Psychiatry

Professor and Chairman of The Saul R. Korey Department of Neurology

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 theknowledge 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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Sophie Molholm

Pediatrics/Neuroscience

Associate Professor; Muriel and Harold Block Faculty Scholar in Mental Illness

I am interested in how the human brain processes and integrates sensory inputs to impact perception and behavior, and the role of attention therein. My work involves characterizing these processes in healthy adults, charting their developmental course over childhood, and translating these findings to understand the neurobiology of developmental disorders, with an emphasis on autism. Non-invasive high-density recordings of the electrical activity of the brain, psychophysics, and magnetic resonance imaging are my primary tools of investigation. The former allows precise tracking of the temporal progression of cortical information processing, and modeling of the underlying neuronal generators. Used in conjunction with structural and functional neuroimaging, precise anatomical localizations of function can be achieved.

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

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Solomon L. Moshé

Neurology/Pediatrics/Neuroscience

Professor and Vice Chairman of Neurology and Charles Frost Chair of Neurosurgery and Neurology

Director, Division of Neurology, Department of Pediatrics and Director, Divisions of Clinical Neurophysiology and Pediatric Neurology, The Saul R. Korey Department of Neurology

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

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

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Genevieve Neal-Perry

Ob/Gyn and Neuroscience
Associate Professor

One area of particular interest is the role of the neuroendocrine axis in female reproductive aging, especially the cellular events that alter the brain's responsiveness to ovarian steroids. Reproductive senescence in female rodents and humans is heralded by reduced responsive of the hypothalamus to estrogen positive feedback, resulting in abnormal luteinizing hormone surges, ovarian failure, and infertility. There are several candidate neurotransmitter systems and neurotrophic factors that might contribute to age-related LH surge failure and subsequent ovarian exhaustion. Our research suggests that age-related changes in the hypothalamic response to ovarian hormones and the LH surge mechanism are causally related to reduced excitatory neurotransmission mediated by the excitatory neuropeptide kisspeptin. Additional studies have suggested that decreased kisspeptin availability results in an imbalance in excitatory (glutamatergic; decreased) and inhibitory (GABAergic; increased) neurotransmission within the hypothalamus. We have recently demonstrated that reduced brain insulin growth factor-1 (IGF-1) signaling in the aging brain impairs hypothalamic responsiveness to estrogen positive feedback conditions. We also have evidence that hypogonadism in young females trigger a response that is similar to nutrient deprivation and consistent with disruption of autophagic pathways. The hypothalamus is a primary site of convergence and integration for nutrient-related feedback. Moreover hypothalamic IGF-1 receptor signaling regulates female reproductive function, hypothalamic kisspeptin expression and nutrient sensing through cellular mechanisms that rely upon autophagy. Future experiments in our lab are designed to determine whether reduced hypothalamic IGF-1 receptor signaling observed in reproductively aging females gives rise to altered neuronal nutrient sensing and abnormal autophagic cellular processes which then affect estrogen responsiveness in the brain.

Vitamin D receptors are located in the central nervous system, gonads and uterus. Vitamin D_3 is hypothesized to be important for fertility and reproductive success. The mechanism by which vitamin D_3 deficiency affects the hypothalamic-pituitary-gonadal axis is unknown. Our lab is interested in the role of vitamin D_3 in female reproductive physiology and how vitamin D_3 deficiency disrupts fertility. We are investigating the impact of vitamin D_3 deficiency on hypothalamic-pituitary physiology and subsequent effects on ovarian physiology, embryo cleavage, fertilization and implantation rates.

Our research relies upon expertise in multiple microsurgical techniques, intracerebral microdialysis, intracerebral drug infusion, HPLC, controlled ovarian hyperstimulation, immunohistochemistry, immunoassays, serial blood sampling, in vitro fertilization, and a number of molecular biochemistry techniques.

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Saleem Nicola

Psychiatry/Neuroscience

Assistant Professor

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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José L. Peña

Neuroscience

Professor

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 Pereda

Neuroscience

Professor

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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Cedric S. Raine

Pathology/Neurology/Neuroscience

Professor Emeritus

This investigator is a retired neuropathologist/neuroimmunologist whose career involved the pathogenesis and neuroimmunology of multiple sclerosis and its animal models. Trained in the U.K. where he obtained a PhD in Medicine in 1967, a D.Sc. in Medicine in 1975 and was made a Fellow of the Royal College of Pathologists in 1988. He has an office in the Forchheimer Building (1st floor) and continues to collaborate and write scientific reports. The majority of his research was targeted towards the molecular and immunologic analysis of the MS plaque and the testing of therapeutic strategies in the animal model for MS, experimental autoimmune encephalomyelitis (EAE). His list of trainees includes numerous PhD graduates and postdoctoral fellows as well as many Neurology and Pathology residents from the US and abroad who have spent research electives and/or postdoctoral fellowships in his lab and have then moved on to careers both in clinical and research disease-related Neuroscience.

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Gary J. Schwartz

Medicine/Neuroscience; Diabetes Research & Training Center
Professor

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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Odelia Schwartz

Neuroscience

Assistant Professor

We continually interact with stimuli, such as images and sounds, and make inferences about a complex world. How our brain represents and processes the information internally is an intriguing and fundamental issue at the interface of neuroscience and computation. Our lab employs tools of computational and theoretical neuroscience, to study systems from the neural level and through to perception and behavior.

We develop computational models of sensory neural processing based on the hypothesis that images and sounds have predictable and quantifiable regularities to which the brain is sensitive. The models are constructed through interplay with physiological and psychophysical data, and posit functional roles about neural processing. Additionally, a critical way to make progress is utilizing computational tools directly in experimental design and analysis. For example, we have worked extensively on spike-triggered approaches, leading to richer, non-linear characterization of neurons in retina and cortex.

Current specific interests include: (1) how neurons and percepts are affected by contextual information: spatially, what surrounds a given feature or object; temporally, what we have observed in the past, i.e., adaptation; (2) how neurons and percepts represent information under conditions of uncertainty such as visual fog; (3) how neurons represent information hierarchically from one level of neural processing to the next; (4) how populations of neurons work together to achieve perception and behavior; and (5) how we decide where to look next in images.

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Robert H. Singer

Anatomy and Structural Biology/Cell Biology/Neuroscience
Professor and Co-Chair of Anatomy and Structural Biology

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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David Spray

Neuroscience/Medicine

Professor

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

Neurology/Neuroscience

Professor

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 responses in humans.

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Elyse S. Sussman

Neuroscience/ Otorhinolaryngology-HNS

Professor

My research is in the field of Cognitive Neuroscience and is focused on understanding how auditory cognition changes across the lifespan (from infancy to aging) and how it breaks down in individuals with developmental disorders (e.g., autism, language impairments, attention deficit disorder), and hearing impairments. Our laboratory's research uses a combination of non-invasive recordings of human brain activity (event-related potentials [ERPs]), and functional magnetic resonance imaging (fMRI), in conjunction with measures of behavioral performance to specify the processes and brain structures that contribute to the organization, storage and perception of a coherent sound environment.

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Vytautas Verselis

Neuroscience

Professor

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 $Ca2^{+}$ and pH and shifted voltage-dependent gating. Our current focus is on altered permeability to $Ca2^{+}$ and ATP, two important signaling molecules in cochlea and skin. To that end we are examining the effects of expressing *h*Cx26 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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Steve Walkley

Neuroscience/Pathology/Neurology
Professor
Director, Rose F. Kennedy Intellectual and Developmental Disabilities Research Center
Head, Sidney Weisner Laboratory of Genetic Neurological Disease

Pathobiology and treatment of lysosomal disorders of brain

The research interests of my laboratory are concerned with analysis of pathogenic cascades and development of therapeutic strategies for genetic disorders of the endosomal-lysosomal system. Examples of primary lysosomal diseases include Tay-Sachs, Hurler, Sanfilippo, Niemann-Pick, and Batten disorders, all of which are characterized by insidious onset and progression of neurological dysfunction, including severe intellectual disability, following an initial period of normal development. Primary proteins implicated in these diseases include not only lysosomal hydrolases but also soluble and membrane-associated proteins often of unknown function. Animal models include both spontaneous conditions in a variety of species and gene knockout models in mice, both of which are used in our studies. Neurons affected by storage diseases often display remarkable abnormalities, including growth of ectopic dendrites, neuroaxonal dystrophy, abnormalities in autophagy and salvage systems, and selective vulnerability

to premature death. Our studies are focused on the link between the primary protein defect and the abnormal accumulation of substrate (gangliosides, glycosaminoglycans, cholesterol, etc.) and with the subsequently induced changes in trafficking and signaling events within affected neurons. Therapeutic strategies are presently focused on small molecule therapy directed at reducing substrate storage. To date our work has led to development of two new therapies for the lysosomal disease known as Niemann-Pick type C.

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Deyou Zheng

Neurology/Neuroscience and Genetics

Associate Professor

Bioinformatics and Computational Genomics

The research field of my group is Computational Genomics and Bioinformatics, with a strong focus of mining large-scale experimental genomic data to decipher the function of the human genome and the genomes of other model organisms. We develop and apply computational techniques for integrating data of comparative genomics and functional genomics (and epigenomics) to decode the structure, function, and evolution of the human genome. More generally, we are interested in bioinformatic and statistical approaches for exploiting novel and biologically significant patterns in high-throughput genomic data. Recently, we have become highly interested in the expression, regulation, and evolution of human genes (coding or non-coding) that are involved in the development, specification, maturation, and maintenance of human neural systems. Working extensively with experimentalists, our study will contribute important information to neurodegenerative diseases and many other brain diseases.

For more details, please see our website dain.aecom.yu.edu/zhenglab.

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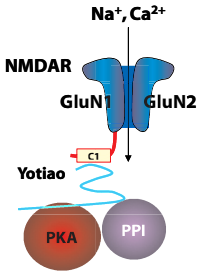
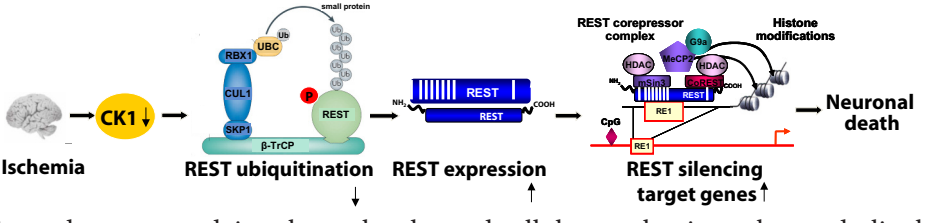
R. Suzanne Zukin

Neuroscience
F.M. Kirby Professor of Neural Repair and Protection
Director, Neuropsychopharmacology Center

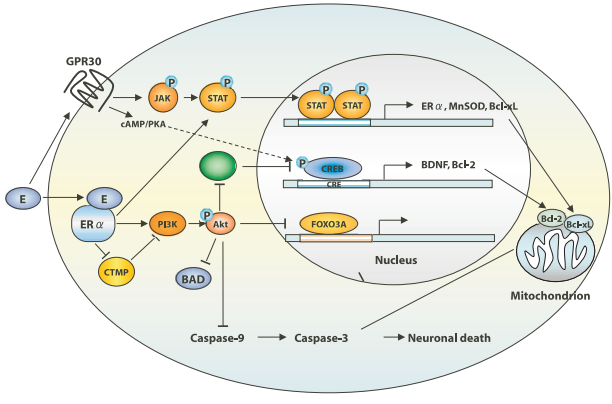


There are four major lines of ongoing research in the Zukin lab. First, we are studying the molecular and cellular mechanisms that regulate N-methyl-D-aspartate-type glutamate receptor (NMDA receptor) expression at synapses in the brain. We discovered that the switch in NMDA receptor phenotype at hippocampal 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 causally 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 perme-

able 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.

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