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.


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.


**Joseph Arezzo**  
Neuroscience/Neurology  
Professor

Neurophysiologic techniques to explore normal and altered function in animal models and human clinical research

Our laboratory uses a variety of neurophysiologic techniques to explore normal and altered function in both the peripheral and central nervous systems. Experimental procedures include EEG, evoked potentials, ensemble and single unit recordings, current source density, and conduction velocity. For the past several decades, we have focused on the timing and spatial distribution of neuromagnetic events in the neocortex of behaving monkeys. Current studies explore the complex auditory processing of components of speech and music in primary auditory cortex. In addition to our “basic science” studies, we have examined biomarkers of nerve damage in a variety of animal models, including transgenic and mutant mice, diabetic neuropathy, seizure disorders, neurotoxic insult and iatrogenic deficits of central and peripheral nerve function. Finally, 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 and to monitor the treatment-related CNS effects of compounds targeting HIV infection, cancer and depression. 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.


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 and Cx32 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. 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.


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.


**Aviv Bergman**

Systems and Computational Biology/Neuroscience  
Professor & Chairman

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.

Topography 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.


Hannes E. Buelow
Genetics/Neuroscience
Assistant 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 navigate the extracellular space in order to connect to their appropriate partners. The extracellular space is filled with a complex mixture of proteins and proteoglycans e.g. heparan sulfate (HS) proteoglycans which are a particular focus of the lab. We are asking how specific modification patterns of the polysaccharide HS determine the path of developing axons. We have previously shown that distinct modification patterns in HS serve specific and instructive functions during nervous system development leading us to formulate the 'HS code' hypothesis. We propose that defined combinations of modifications in the sugars of HS contain information and generate a molecular map that helps shaping the nervous system. Our goal is to decipher the information contained in HS, determine the factors that create and modulate it and describe the genes that respond to it.

In a related project we are investigating a pathological dimension of HS by studying Kallmann Syndrome, a human genetic disease with specific neurological defects. Using C. elegans as a discovery platform, we have found that mutations in a gene involved in introducing the HS modifications, i.e. the 'HS code' are associated with Kallmann Syndrome. Our longterm goal is to understand Kallmann Syndrome on molecular level. We approach this by conducting genetic screens to identify novel genes that are associated with Kallmann Syndrome.

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


**Feliksas F. Bukauskas**

Neuroscience
Professor

Our research interests are related to the analysis of intercellular communication. Direct cell-to-cell exchange ions and cytosolic molecules is organized via gap junction (GJ) channels assembled from connexins (Cx), members of a large family of membrane proteins.

The main goal of our studies is to elucidate the underlying mechanisms that control GJ channel formation and gating. These mechanisms are ultimately necessary for determining the role of intercellular communication in normal and diseased states. We perform experiments in living cells expressing wild type connexins and Cxs fused with fluorescent proteins (EGFP, CFP and YFP) by using imaging and electrophysiological methods. We are focusing on: 1) De novo channel formation. We examine the dynamics of cell-cell coupling formation starting from GJ channels aggregation into junctional plaques (JP), their maturation and internalization. We study the correlation between the size of JPs and functional coupling. We demonstrated that channels can be functional only when clustered into JPs. 2) Mechanisms of GJ channel gating. We raised the hypothesis that GJs contain two distinct gating mechanisms, ‘fast’ and ‘slow’. During the past several years, this hypothesis was broadly supported by studies performed in different laboratories and for different members of connexin family. We proceed in this direction by studying ionic selectivity and rectification of open and residual states that is important in providing fundamental insights into mechanisms of ionic permeation through channels. Recently, we showed that the ‘fast’ gate can serve as a selectivity filter which preserves electrical cell-to-cell signaling but restrict metabolic communication. We are testing the hypothesis that the slow gate, which fully closes GJ channel, contains a "common" gating element that can be activated by transjunctional voltage as well as by different chemical uncouplers. 3) Conditions at which heterotypic junctions exhibit unidirectional electrical cell-cell signalling and serve as voltage-sensitive valves for metabolic communication. We demonstrated that some heterotypic junctions formed between cells expressing different Cxs can function as rectifying electrical synapses by utilizing the asymmetry in voltage gating and channel rectification. Recently, we demonstrated that a small difference in resting potentials of coupled cells can effectively regulate the function of heterotypic junctions by switching it from bi-directional to unidirectional and modulate metabolic cell-cell communication and chemical signaling (Palacios-Prado and Bukauskas, 2009).
Human genetic disorders that have been linked to connexins dysfunction include X-linked Charcot-Marie-Tooth disease (CMTX), viscerotrial heterotaxia, sensorineural deafness and skin disease. Abnormalities in GJ channels may play a key role in generating cardiac arrhythmias, uterine malfunction, epileptic seizures and malignant cell growth. We study biophysical properties of Cx32 (Abrams et al., 2006), Cx26 (Bicego et al., 2006), and Cx43 Dobrowolski et al., 2008) mutants that are involved in development of CMTX syndrome, sensorineural deafness and hereditary oculodentodigital dysplasia, respectively.


**Herman Buschke**

Neurology/Neuroscience

Professor

Human Memory and Cognition: Aging, dementia, Alzheimer’s disease, memory impairment, development, cross-sectional and longitudinal change.


Our lab studies the molecular mechanisms regulating synaptic transmission in the central nervous system. We are interested in understanding how changes in neuronal activity can cause the long-lasting modifications in the strength of synaptic connections that are believed to be important for neuronal development, learning, and memory formation. In order to develop a complete picture of the events involved in such synaptic plasticity, the lab employs a combination of techniques including whole cell electrophysiology, microscopy, biochemistry and molecular biology. The focus of our efforts is on investigating how the regulated redistribution of key signaling components, particularly neurotransmitter receptors modulates synaptic strength. Our research has identified a number of cellular mechanisms which couple synaptic activity to the regulation of neuronal excitability through the insertion and removal of both AMPA-type glutamate and GABA_A receptors.

In one series of investigations, we have focused on the expression of two developmentally regulated forms of synaptic depression: one activated by NMDA-type glutamate receptors, which is believed to be critical for learning, and the other mediated by metabotropic glutamate receptors, which is dysregulated in models of Fragile X mental retardation. As such, these forms of plasticity are promising targets for therapeutic intervention relevant to cognitive deficiencies associated with mental retardation. While these two forms of plasticity similarly regulate synaptic transmission through the removal of synaptic AMPA receptors, their physiological impact seems to be distinct. We have undertaken studies to identify key molecular components for each form of plasticity and to elucidate how these forms of plasticity may differentially impact information processing in hippocampal neurons.

A second area of investigation examines the role of trafficking of GABA_A receptors in modulating inhibition. We have characterized a form of CaMKII-dependent plasticity in hippocampal neurons expressed as a result of the insertion of GABA receptors into inhibitory synapses. Related studies have demonstrated that neuronal activity is able to drive the potentiation of inhibitory transmission through the translocation of CaMKII to GABAergic synapses. We further have found that different stimulus conditions enable CaMKII to be targeted selectively either to inhibitory or excitatory synapses providing neurons with a powerful mechanism by which activity can specifically potentiate either excitation or inhibition through a single kinase mediator.

Our continuing studies aim to examine in depth the mechanisms that modulate receptor localization at the synapse with an interest in understanding how these play a role in synaptogenesis, plasticity, and neurotoxicity in the brain.


We have developed a genetically tractable mouse model to map modifier genes of diabetes (Lepr db). In a novel congenic mouse strain carrying a leptin receptor mutant allele (FVB-Lepr db), we identified a novel phenotype of continual pancreatic beta cell mass expansion during chronic hyperglycaemia. Extensive phenotypic analysis of obese mice (obese due to defective leptin signaling) of several congenic strains has determined that this is a genetically modulated trait. Analysis of obese (db/db) F1 progeny between the FVB and C57BL/6 strains suggested that the trait of pancreatic beta cell mass expansion during hyperglycaemia is a recessive trait and provided strong guidance in determining the required genetic crosses. A genome scan of N2 Lepr-null progeny (backcrossed to FVB) indicated that Chromosome 5 contained allelic variants that modified the diabetes phenotype and regulated beta cell mass expansion. We have generated Chromosome 5 congenic and subcongenic lines on the FVB strain carrying various contributions of Chr 5 from the C57BL/6 genome.

By comparison of several different congenic lines, we have defined a critical interval of ~15 million base pairs (Mbp) in the telomeric end of mouse Chr 5 that contains one of the diabetes modifier gene. Our panel of subcongenic lines indicates that there are other diabetes modifier genes on mouse Chr. 5 but their locations are less narrowly defined. We have two pairs of subcongenic lines that differ in the region and
there is a consistent difference in the degree of insulinemia and pancreatic beta cell mass wherein the lines carrying the FVB interval have higher concentrations of circulating insulin and increased beta cell mass compared to the lines carrying the C57BL/6 interval. Indeed, there is a consistent increase in insulin concentrations and beta cell mass over one month for the lines carrying the FVB interval whereas the lines with the C57BL/6 interval show either no increase or a decrement in insulin and beta cell numbers. The lines carrying the FVB interval also have an increased mitotic index (Ki67 positive beta cells) relative to the lines with the C57BL/6 interval. The ultimate aim of the project is to identify the gene and the responsible allelic variants that control beta cell mass.


**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, and 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 molecular basis of activity-dependent changes in synaptic strength at both excitatory and inhibitory connections, and how such changes are modified during pathological conditions. While most of our studies use the hippocampal formation, a brain area critically involved in memory formation, we have also analyzed synaptic function and
plasticity in the amygdala, cerebellum and prefrontal cortex. In our studies we use a combination of electrophysiological, pharmacological and molecular biological techniques. To gain insights into the mechanisms of synaptic plasticity, we also 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.


**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 polylsine 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.


**Scott Emmons**
Genetics/Neuroscience
Professor

**Connectomics: Structure, Function and Development of Neural Circuits**

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 over 5,000 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.


The laboratory uses a number of experimental models, including identified neurons in the goldfish midbrain studied in vivo and transgenic mouse models of neurodegenerative diseases, such as Huntington’s Disease.


**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.


John Foxe
Pediatrics/Neuroscience
Professor & Director of Research

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).


**Anna Francesconi**

Associate Professor

Neuroscience

Molecular Cell Biology of Metabotropic Neurotransmission

Research in the laboratory focuses on elucidating the molecular and cellular underpinnings of metabotropic glutamatergic neurotransmission in the brain, with the ultimate goal of developing a molecular rationale for targeted interventions in neuropsychiatric disorders. Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors enriched at excitatory synapses throughout the brain where they act both pre- and postsynaptically to regulate glutamatergic neurotransmission. Signaling by mGluRs is critical to synaptic circuitry formation during development and to forms of activity-dependent synaptic plasticity. Dysregulation of mGluR signaling is implicated in neurological and psychiatric disorders linked to abnormal neurodevelopment, including schizophrenia and Fragile X Syndrome, the most common inherited form of...
mental retardation. We use a combination of molecular biology, biochemistry and imaging techniques to pursue two principal lines of research. First, we are investigating the molecular mechanisms underlying the temporospatial regulation of mGluR signaling: current projects examine the role of adaptor proteins and specialized membrane compartments in orchestrating and fine-tuning mGluR activity under physiological conditions and in animal models of Fragile X Syndrome. Second, we are investigating the mechanisms underlying mGluR transport to and from synaptic sites during neuronal differentiation and in response to activity-dependent changes in synapse composition. Current projects examine the role of recently identified mGluR-interacting proteins in supporting receptor trafficking to synaptic sites.


Lloyd Fricker
Molecular Pharmacology/Neuroscience
Professor

This laboratory works on three related projects involving peptides and peptidases.

1) Peptide hormones and neurotransmitters are an important class of extracellular messengers that 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. One project in the laboratory is focused on neuropeptides and the enzymes that are involved with their post-translational processing. We are studying the various peptide processing enzyme by examining the levels and molecular forms of peptides in mice lacking peptidase activity (knock-out mice or naturally occurring mutations); peptides are being measured using a quantitative peptidomics technique. The goal of these studies is to define the physiological role of each neuropeptide processing enzyme.

2) 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. One of the enzymes being studied is cytosolic carboxypeptidase 1 (CCP1, also called Nna1), which when mutated in a mouse causes neurodegeneration of Purkinje cells and several other cell types. Another enzyme currently being studied is carboxypeptidase A6, which has been implicated in axonal guidance during development and in epilepsy. A third enzyme under analysis in our laboratory is carboxypeptidase D; this enzyme functions in the processing of growth factors and in Drosophila is necessary for animals to survive beyond the intermediate larval stage.

3) Another area of research is on novel peptides, including classical neuropeptides that are secreted from cells via the regulated secretory pathway, non-classical neuropeptides that are secreted from cells independently of the secretory pathway, and cytosolic peptides that may have functions in regulating cellular
function. The goal of these studies is to identify peptides, understand how they are produced and regulated, and finally to determine their function.


**Aristea S. Galanopoulou**

Neurology/Neuroscience

Associate Professor

- Pathophysiology and treatment of Infantile Spasms
- The role of cation chloride cotransporters and GABA<sub>A</sub> receptors in seizure susceptibility of the neonatal brain and sexual differentiation of the brain.
- Consequences of neonatal seizures.
- Pathophysiology of Rett syndrome.

The maturation of GABA<sub>A</sub> receptor-mediated signaling from excitatory 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<sub>A</sub> receptors in this process.

To better understand the pathophysiology and design better methods to treat catastrophic early life epilepsies, we are developing and studying new models of early life epilepsy. These include models of symptomatic infantile spasms that recapitulate most of the features of the human condition. Several projects are under way to elucidate the pathophysiology of infantile spasms. Furthermore, we are conducting preclinical trials to find better treatments.

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.


**David Hall**  
Neuroscience  
Professor  

The soil nematode Caenorhabditis 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, 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, supported by NIH RR grant, 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 Slideable Worm, a Handbook of all cells and tissues, a Glossary, and selected html texts of classic papers.

Wired Worm is a project aiming to complete the wiring diagram for the male adult nematode, working with Scott Emmons (Molecular Genetics).


**Jean Hebert**  
Neuroscience  
Associate 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.


Asao Hirano
Pathology/Neuroscience
Professor

Current interest is cytopathology of motor neuron disease.


Noboru Hiroi
Psychiatry/Neuroscience
Professor

The primary aim of this laboratory is to more fully understand the genetic bases of nicotine dependence and 22q11 syndrome.

Nicotine dependence: Among those who initiate smoking, only one-third develop dependence and addiction. Individuals who develop dependence often exhibit pre-existing behavioral traits. There are many genes that likely contribute, in complex ways, to individual variations in the development of nicotine dependence. Identification of such genes has been difficult in humans. Nicotine dependence includes tolerance, withdrawal, cue reactivity, and many other elements. These elements are likely to have distinct neural and genetic substrates. Additionally, it is thought that multiple genes affect nicotine dependence in a complex way. Mouse models provide a unique opportunity to examine the precise ways that individual genes alter different elements of nicotine dependence. We use diverse behavioral paradigms to examine how specific genes contribute to elements of nicotine dependence in genetically engineered mice. Our studies have revealed that the transcription factor FosB, monoamine oxidase A, and cGMP-dependent protein kinase (PKG) are required for nicotine cue reactivity and stress-related behavioral traits. We are currently using lentiviral vectors to identify specific brain regions in which genes mediate the expression of nicotine cue reactivity.

22q11 and neuropsychiatric disorders: The human genome includes many variations, ranging from duplications and deletions of full chromosomes to single nucleotide polymorphisms. Moreover, a large number of kilo- to mega-base copy number variations (CNVs) are associated with autism spectrum disorder, mental retardation, and schizophrenia. Human chromosome 22q11.2 contains CNVs. Children and adolescents with 22q11.2 duplications and deletions consistently exhibit these neuropsychiatric disorders, along with associated cognitive and intellectual impairments during development. However, the diagnosis of these neuropsychiatric disorders is challenged by variations in diverse cognitive and intellectual capacities. Thus, patients with the same diagnosis may vary greatly in specific symptoms. Moreover, 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 these obstacles, 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 whose 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 phenotypes relevant to neuropsychiatric disorders in mice.


**Dumitru Iacobas**

Neruoscience

Assistant Professor

Our laboratory uses a variety of molecular and computational biology techniques to identify and characterize the transcellular, connexin-dependent transcriptomic networks that control essential processes such as myelination, heart rhythm, and inflammatory response. Experimental data are then used to develop mathematical models and computer simulation programs of intercellular signaling in complex structures. The connexins (Cx) comprise a family of topologically similar transmembrane proteins that can assemble to form gap junction channels between cells within vertebrate animals. Such intercellular channels provide cytoplasmic continuity between the interconnected cells and play crucial roles in cell growth, differentiation and synchronous activity within specialized tissues. Through extensive microarray studies we found that, regardless of subtype or tissue or cell line, connexins are transcriptomic hubs whose expression modulates not only the expression level, but also the strength of the transcription control and expression interlinkages of numerous other genes. Moreover, the regulomes of connexin deficient tissues are largely predictable from the corresponding connexin expressomes of the wildtypes. Together with the highly significant overlap between transcriptomic alterations in connexin knockout and knockdown cells, these results suggest that the widespread changes more likely reflect Connexin-Dependent Gene Regulatory Networks rather than developmental compensation for the missing gene. In such networks, linkage partners are rearranged and strengths modified in both transgenic and diseased animals, in response to pathologic or stressful conditions, as well as during development. The observed profound remodeling of the web of transcription factors and components of the polymerase III gene cluster in connexin deficient tissues may provide a molecular explanation for the downstream and parallel "ripples" of phenotypic change resulting from single gene manipulations.


Bryen Jordan  
Neuroscience/ Psychiatry and Behavioral Sciences  
Assistant Professor  

Exploring synaptic function and activity-dependent synapse-to-nucleus signaling  
One of the principal questions in neuroscience is how does neuronal activity alter synaptic transmission. This question is critically important since activity-dependent changes in neurotransmission regulate higher order brain functions such as learning and memory. Our lab is interested in understanding how do transient changes in synaptic neurotransmission become long-term. Specifically we are interested in exploring activity-dependent synapse-to-nucleus signaling in neurons. The activity-dependent regulation of nuclear functions is essential for the long-term maintenance of synaptic strengthening and the long-term storage of memories. While the nature of this signaling pathway is widely debated, it is well known that neuronal activity results in the rapid nuclear accumulation of many proteins, including AIDA-1, Jacob, NFATc4 and NF-kB, suggesting that the nucleocytoplasmic shuttling of proteins is a mechanism in nuclear signaling. We
seek to understand how synapses relay fast synaptic information to the nucleus and specifically what are
the key players in this process, what signals they respond to and what are their nuclear functions. To study
this, we use proteomics and mass spectrometry to explore the composition and dynamics of excitatory
synapses and nuclei. These methods provide us with a global view of synaptic complexity as well as help us
identify novel components of synapse-to-nucleus signaling mechanisms, which we can then further study
using reductionist methods in cell and molecular biology as well as biochemistry and imaging analysis.
Using these methods we found that a number of synaptic components can shuttle to the nucleus in
response to synaptic activity. We also found that a number of nuclear proteins are incorporated into the
synapse in response to synaptic activity suggesting that the reverse pathway, nucleus-to-signaling pathway
also affects synaptic transmission. Our immediate goal is to study these novel synapse to nucleus signaling
messengers and to explore their synaptic and nuclear functions.


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**Zaven Kaprielian**

Pathology/Neuroscience

Professor

Axon guidance and dendrite branching in the developing nervous system

The research in my laboratory is aimed at identifying mechanisms that establish stereotyped patterns of connectivity in the developing vertebrate and invertebrate central nervous system (CNS). Our vertebrate studies are aimed at understanding how growing axons navigate through intermediate targets/choice points and ultimately connect with their appropriate targets, and how axons, which leave the CNS, choose the appropriate exit point. The invertebrate studies are directed toward identifying molecular mechanisms that control dendrite branching. To achieve these goals, we work with both well-studied and understudied classes of vertebrate spinal interneurons and motor neurons and a unique *C. elegans* neuron that extends highly branched dendrites. Our main focus is on understanding mechanisms that control the pathfinding of spinal commissural axons, a major class of midline-crossing axons in the developing CNS. In these studies, we use novel *in vitro* assay systems, chick *in ovo* electroporation and a large array of transgenic reporter, as well as, mutant mice to identify guidance cues and their corresponding receptors, which regulate the pathfinding of genetically distinct populations of spinal commissural axons. By manipulating guidance receptor expression in mouse and chick embryos, we are also investigating how dynamic changes in the spatial distribution of these receptors influence various aspects of commissural axon pathfinding within the spinal cord. In addition, we are identifying synaptic targets for genetically distinct commissural axons and elucidating the molecular logic that guides specific subsets of commissural/projection axons from the spinal cord to the brain. A parallel effort is aimed at identifying the molecular logic that regulates the development of spinal accessory motor neurons, a unique class of spinal motor neurons that projects axons to and through discrete and readily identifiable lateral exit points. These studies make use of cell surface markers and reporter mice that selectively label spinal accessory motor neurons and their axons, as well as our previous observation that a particular transcription factor is required for the exit of spinal accessory motor axons from the CNS. In ongoing studies, we have identified axon guidance systems that may directly facilitate the exit of these axons. In our *C. elegans* studies, we have carried large scale RNAi screens to identify molecules that regulate the branching of dendrites associated with the PVD neuron. Thus far, our results implicate key roles for dynein microtubule motors and associated proteins, components of several axon guidance systems, as well as proteins that interact with the Fragile-X Mental Retardation protein in regulating the proper formation of dendritic arbors within the *C. elegans* nervous system.


Kamran Khodakhah
Neuroscience
Professor

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.


Adam Kohn
Neuroscience
Assistant 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.


**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 (between 60-80%). 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 iPS cells, which essentially allows investigators to reprogram somatic cells into pluripotent stem cells capable of differentiating into neurons and other cell types, provides an opportunity to create patient-specific neurons in vitro. The Lachman lab has begun to develop iPS cells from controls and patients with SZ, including a subset that carries a well characterized 22q11.2 del found in ~1% of patients. These cells are being induced to differentiate into glutamatergic neurons and are being subjected to gene expression profiling and epigenetic analysis to identify patient vs control differences. We are using next generation sequencing available through the Einstein Epigenetics Core facility. Gene expression profiling using next generation
sequencing (RNA-Seq) carried out on a subset of our samples is providing us with a wealth of molecular data relevant to disease pathogenesis as well as human neurogenesis. Noteworthy so far is discovery of several novel long non-coding RNAs (IncRNAs) that appear to be involved in regulating \textit{HOX} gene expression and early neurogenesis. In addition, based on disease mapping studies using genome wide association and our preliminary RNA-Seq data, we identified two IncRNAs that we suggest are involved in the development of SZ in a small subgroup of patients.

Epigenetic analysis and knockdown of SZ candidate genes coding for transcription factors and chromatin modifying enzymes followed by gene expression profiling are in the process of being carried out in differentiating human neurons derived from iPS cells.

Erika Pedrosa, Vladislav Sandler, Abhishek Shah, Reed Carroll, Chanjung Chang, Shira Rockowitz, Xingyi Guo, Deyou Zheng, Herbert M. Lachman Development of patient-specific neurons in schizophrenia using induced pluripotent stem cells. (in press, Journal of Neurogenetics)


\textbf{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.


Alan D. Legatt
Neurology/Neuroscience
Assistant Professor

- Topographic analysis of evoked potentials and identification of evoked potential generators.
- Intraoperative neurophysiologic monitoring.
- Studies of seizures and EEG spikes recorded during longterm monitoring in patients with epilepsy.
- Studies of sensory evoked potentials and cognitive event-related potentials in patients with epilepsy and other neurologic disorders.
- Studies of the effects of epileptic EEG discharges on evoked potentials.


Xiaobo Li
Radiology/Neuroscience/Psychiatry & Behavioral Sciences
Assistant Professor

§ Functional MRI analysis – developing and translating refined quantitative mathematical and statistical methodologies for functional organization analyses to elucidate the pathophysiological mechanisms underlying normal brain development, and disorders such as Schizophrenia, ADHD, Depression, etc..
§ Computational Neuroanatomy – developing refined quantitative mathematical measures of cortical shape development and geometric shape modeling of brain structures using structural MRI and DTI
§ Integrated analyses of brain structure and function applying structural MRI, fMRI, DTI, PET, EEG/MEG measures and psychological and psychopharmacological factors.
Clinical Applications:
§ Functional and anatomical developments of language processing circuit and default-mode network system during normal brain maturation and onset of Schizophrenia.
§ Functional and anatomical impairments in visual- and auditory-language processing circuit in patients with Schizophrenia, ADHD, Depression, other inheritable mental disorders, and the genetic high-risk children and adolescents
§ Pharmacological stimulant effects to the efficiency of default-mode network system and cognition in ADHD and Depression


Wanlin Zhu, Tianzi Jiang, Xiaobo Li (2005) Local Region Based Medical Image Segmentation Using J-
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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Mark Mehler
Neurology/Neuroscience/Psychiatry
Professor and Chairman 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 the knowledge gained from these multidisciplinary studies to design innovative epigenetic- and stem cell-based regenerative therapies.
We are in the process of defining the dynamic roles of environmental factors, cell-cell signaling pathways and cell autonomous cues in promoting stem cell activation, expansion, lineage restriction, lineage commitment, cell cycle exit and terminal differentiation. We have identified specific transcription factor and epigenetic codes that endow the progeny of specific stem cell subpopulations with their unique cellular properties. These insights have already allowed us to “reprogram” different regional stem and progenitor cells both in vitro and in vivo to acquire the cellular properties of specific neuronal and glial subtypes that are lost in different classes of neurological diseases. We have also utilized embryonic stem cells, both to define initial stages of neural induction and patterning of the neural tube that have previously been difficult to examine experimentally, and as therapeutic reagents for those diseases of the nervous system in which multiple regional neuronal and glial subtypes are targeted.

A better understanding of the pathogenesis of individual neurological disorders will allow us to more effectively employ our emerging neural regenerative strategies. For example, we are investing 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.


**Sophie Molholm**  
Pediatrics/Neuroscience  
Associate Professor

I am a basic and translational researcher. My work is focused on sensory processing in the auditory, visual, and somatosensory domains, and the integration of multisensory inputs to form coherent objects. 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. The primary tools that I use are high-density electrophysiology and psychophysics. 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 and intracranial recordings, part of the toolset that we use in the lab, precise anatomical localizations of function can be achieved. To complement the translational side of our work, the lab includes a team of senior and junior clinicians that are involved in the phenotyping of participants. Genetic samples are collected from participants with the goal of linking phenotype to genotype, identifying mediating endophenotypic markers. Additional interests of mine include investigations into speech processing and comprehension, and attentional influences on information processing.


**Solomon L. Moshé**  
Professor of Neurology & Neuroscience  
Vice Chairman of Neurology  
Charles Frost Chair of Neurosurgery & Neurology

Clinical and research data suggest that the immature brain is more susceptible to seizures than the mature brain. The focus of the laboratory is to study, in animals, the epileptic process, its modifiers and consequences as a function of age and gender, translating novel findings to clinical applications. Projects include: 1) Identification of specialized subcortical circuits that modify seizures and are involved in the expression of increased seizure susceptibility of the immature brain. Ongoing studies indicate age and sex related differences in GABA function in the substantia nigra, a site critical involved in seizure control. These changes should be taken into account when drugs are developed to treat age-specific and sex-specific disorders in humans. 2) Identifications of factors responsible for the decreased vulnerability of the immature brain to seizure induced brain injury. 3) Identification of surrogate markers that may predict whether seizures may beget seizures or predict the development of an epileptic encephalopathy. 4) Determination of the relation of disorders of carbohydrate homeostasis to epilepsy and its consequences. Students interested in normal brain function or brain function during disease (epilepsy) can choose thesis projects utilizing a variety of in vivo and in vitro techniques available in the lab. The lab has received consistent funding since 1979.


**Scott Nawy**

Ophthalmology and Visual Sciences/Neuroscience Professor

The primary interest of the lab is an understanding of information processing in the retina at the level of individual synapses. Emphasis is on the molecular mechanisms by which synaptic information is modified by short and long-term changes in the visual scene.

The synapse between photoreceptors and an interneuron called the On bipolar cell is a critically important synapse in vision because all visual information flows through it. It has long been appreciated that this is a
very different kind of synapse because it is inhibitory despite the fact that glutamate is the transmitter. The On bipolar cell expresses a metabotropic glutamate receptor (mGluR6) that negatively couples to the synaptic channel, recently identified by our group as the novel channel Trpm1 (Shen et al, 2009). In the dark, binding of glutamate to mGluR6 activates a G protein, and one or more G protein subunits then closes the synaptic channel. In the light, glutamate is not released by photoreceptors, and so the synaptic channel (Trpm1) now opens and the cell depolarizes. Thus glutamate mimic an inhibitory transmitter by closing an excitatory synaptic channel. Currently it is not known how the G protein closes Trpm1. A possibility that we are testing, using both molecular and physiological techniques, is that the Gbg subunit of the G protein can act as an inhibitor of the channel. This would be a novel and exciting finding because G proteins have never been shown to interact directly with Trp channels before now. Our work may also shed light on the underlying cause of congenital stationary night blindness, a disease which has been traced to a mutation in trpm1.

A second project in the lab (a collaboration with Dr. Reed Carroll) is to study synaptic plasticity in On ganglion cells (Xia et al, 2007). We have recently made an exciting new discovery regarding the ability of ganglion cells to “learn” and adapt. Specifically we have found that the visual experience of ganglion cells changes the composition of AMPA receptors from those that contain a GluR2 subunit and are impermeable to Ca2+ to a type of receptor that lacks the GluR2 subunit and is Ca2+ permeable. This form of plasticity has never been reported before in the retina, and is similar to the kind of plasticity that is the basis for memory and learning in other brain regions. An important question to be addressed is the contribution of AMPA receptor plasticity to vision. To address this question, we use a combination of physiological, molecular and behavioral approaches. One hypothesis to be tested is that synaptic expression of the Ca2+-permeable AMPA receptor makes On ganglion cells moresensitive to small changes in transmitter release (i.e, increases synaptic gain), allowing for better vision under dim light conditions.


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 D₃ is hypothesized to be important for fertility and reproductive success. The mechanism by which vitamin D₃ deficiency affects the hypothalamic-pituitary-gonadal axis is unknown. Our lab is interested in the role of vitamin D₃ in female reproductive physiology and how vitamin D3 deficiency disrupts fertility. We are investigating the impact of vitamin D₃ 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.


Saleem Nicola
Neuroscience/Psychiatry
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.


José L. Peña

Neuroscience
Associate Professor

The owl’s brain is a showcase in Systems Neuroscience for allowing the analytical approach to information flow using variables that are relevant for sound localization behavior. 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 on the space-specific neurons. We have focused on two regions of the brain that are crucial for this synthetic process: the nucleus laminaris, where the difference between the arrival times of the sound to each ear is initially derived, and the external nucleus of the inferior colliculus, where space-specific neurons 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 avian brain provides a system to test models of psychoacoustics at levels from single cells to networks of neurons. In the future, we plan to study how information flows in the sound localization pathway using in vitro electrophysiological approaches as well as the recording of neural activity in anesthetized and behaving animals.


**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.


Diana L. Pettit
Neuroscience
Associate Professor

I am investigating neuron-neuron communication in the mammalian brain. Neuronal communication involves a complicated sequence of events from the release of transmitter by the presynaptic cell to the integration of synaptic signals by the postsynaptic cell. We use a number of techniques to examine the processes underlying each event including whole-cell voltage clamp recordings, optical and imaging techniques. Previous work, which focused on postsynaptic aspects of transmission, investigated the distribution and modulation of glutamate, GABA, and brain nicotinic neurotransmitter receptors in rat brain slices. This was accomplished by local photolysis of caged compounds and real-time confocal imaging to measure the density, subtype and regulation of these receptors. This method allows for the activation of a few microns of dendritic membrane with temporal resolution in the ms range. Future work will include experiments designed
to examine changes in receptor distribution and subtype following plastic events such as learning and memory. In an effort to isolate a single synapse, we will also be using two-photon excitation to perform these experiments. This method allows for superior spatial resolution and excitation of single neuronal spines. These experiments will provide vital information about the basic processes underlying brain function and are a critical step in understanding how to treat the errors of transmission that occur in neurological disorders such as Alzheimer’s and Parkinson’s Disease.


Cedric S. Raine
Pathology/Neurology/Neuroscience
Professor

This investigator is a neuropathologist engaged in studies pertaining to the pathogenesis and neuroimmunology of multiple sclerosis and its animal models. Trained in the U.K., Dr. Raine 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 runs a team of faculty and fellows in a 2500 sq. ft. laboratory located in the Forchheimer Building (1st floor). His research is funded by grants from the NIH, the NMSS and industry. The majority of his work is 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).

Ongoing projects on multiple sclerosis nervous tissue involves the analysis of cytokine and adhesion molecule profiles, the involvement of tumor necrosis factor ligand and receptor families in MS lesions, cell death pathways, oligodendrocyte responses, remyelination, T cell receptor analysis, heat shock proteins and the re-expression of immature myelin genes during repair of the MS lesion. Animal experimentation includes the treatment of chronic relapsing EAE in mice with reagents that block pro-inflammatory cytokines, with neurotrophic growth factors, and with strategies that promote a cytokine switch from a pro-inflammatory to a regulatory-type (Th1 (Th2). In the furtherance of these studies, immunologic approaches, immunocytochemistry, morphology, in situ hybridization, FACS analysis, ELISA, RT-PCR, Western blotting and light and electron microscopy are applied. In recent years, numerous Neurology and Pathology residents from the USA and abroad have spent research electives and/or postdoctoral fellowships in this lab and have then moved on to careers both in clinical and research disease-related Neuroscience.


**Eliana Scemes**  
Neuroscience  
Professor

Gap junctions and ATP purinergic receptors are two components mediating calcium signaling in glial cells. These intracellular calcium transients modulate several cellular functions, including progenitor cell migration, release of transmitters from glial cells, and cell-to-cell signaling. Projects of the laboratory include the (1) evaluation of the contribution of these two groups of proteins to neural progenitor cell migration and differentiation, (2) determination of the mechanisms of ATP release from progenitor and mature astrocytes, and (3) characterization of mechanisms involved in the cross-talk between gap junctions and purinergic receptors.


**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.


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.


Roy Sillitoe
Neuroscience
Assistant Professor

The cerebellum controls are number of neural functions including motor learning, motor control and balance. Accordingly, genetic insults that affect the cerebellum result in diseases such as ataxia, a severe form of uncoordinated movement. The major goal of my lab is to determine the cellular and molecular mechanisms that shape the architecture and function of cerebellar circuits. Our experimental approach consists of systematically manipulating these mechanisms and asking whether modifying the normal wiring patterns of cerebellar circuitry causes defects that model specific neurological diseases.

My laboratory uses a combination of techniques including sophisticated mouse molecular genetics, biochemistry, neuroanatomy, in vivo electroporation of engineered DNA, stereotaxic surgery, classic embryology, and imaging. Since our lab has expertise in designing and generating transgenic mice, we are excited to further develop animal models of human diseases in order to determine the embryonic origins of developmental brain diseases.


Robert H. Singer
Anatomy and Structural Biology/Cell Biology/Neuroscience
Professor and Co-Chair

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.


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. We are studying the plasticity of expression and function of electrotonic synapses between neurons in culture and between astrocytes, and a major effort of the laboratory is to examine functional roles of gap junctions within sensory ganglia in mouse models of chronic pain. In the heart and vasculature, gap junctions allow impulse propagation and second messenger diffusion throughout the tissues; current research interests on heart include mechanisms of arrhythmias resulting from chronic parasitic infection (Chagas' disease) and use of stem cell therapy in treatment in a mouse mode of this disease. Studies on endothelium focus on mechanotransduction through the glycocalyx. In embryonic tissues and in liver and lens, gap junctions presumably play a role in metabolite exchange; of interest are the conductance and permeability of individual channels, conditions that determine expression of these channels and the extent to which the channels are open or closed, and whether certain pathological states are ascribable to alteration in gap junction function. 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.


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.


**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.


Connexins (Cxs) comprise a family of membrane proteins that form gap junction (GJ) channels, which provide an important pathway for intercellular signaling in many tissues. Each GJ channel is a multimer of Cx subunits that is formed by the docking two pre-assembled hemichannels, one from each of two apposed cells. Mutations in the GJB2 gene that encodes the Cx26 GJ protein are one of the most common causes of inherited deafness in the human population. A subset of these mutations leads to syndromic forms of deafness in which sensorineural hearing loss is accompanied by severe, inflammatory skin disorders, such as keratitis-ichthiosis-deafness (KID) syndrome. The underlying basis of syndromic deafness appears to be aberrantly behaving hemichannels, a relatively new mechanism identified among Cx-related disorders. These hemichannels do not participate in the formation of intercellular GJ channels, but rather remain undocked and function as large, ion channels in the plasma membrane. The mutant hemichannels behave in a "leaky" manner leading to compromised cell function and cell death. We use a combination of molecular, biophysical and imaging approaches to investigate the mechanisms by which Cx hemichannels are dysfunctional in KID syndrome. The mutations notably cluster in two domains, the N-terminus (NT) and the first extracellular loop (E1), which we identified to be principal components of the Cx channel pore and to play essential roles in Cx hemichannel gating by voltage and regulation by extracellular Ca\(^{2+}\). Using a recently published crystal structure of Cx26, we are examining specific models of inter-subunit interactions involving E1 and NT residues that mediate hemichannel regulation by extracellular Ca\(^{2+}\), the most prevalent regulatory mechanism that is dysfunctional in KID syndrome mutants. We also identified a mechanistic link between Ca\(^{2+}\), pH and a distinct form of voltage gating, we term loop gating, which robustly regulates opening and closing of Cx hemichannels. Using cysteine-substitution accessibility, we established that two KID syndrome mutants are pore-lining and are investigating whether permeabilities to key signaling molecules, such as ATP and Ca\(^{2+}\), are significantly altered. One of these pore-lining mutants, G45E, leads to a particularly severe, often fatal form of KID syndrome and our initial studies suggest increased permeability to Ca\(^{2+}\), rather than Ca\(^{2+}\) dysregulation, may be the key contributing factor. We extend our studies to keratinocytes isolated from transgenic animals carrying the G45E mutation driven under an inducible keratinocyte-specific promoter. Finally, some KID mutants fail to function as GJ channels despite functioning as hemichannels and we are investigating whether these mutant hemichannels exhibit an impaired ability to dock. Together, these studies explore the mechanistic bases of hemichannel dysfunction in Cx26 that lead to severe disorders in humans. These studies should also shed light on a growing list of disorders ascribed to hemichannel dysfunction that includes atherosclerosis, stroke, neuropathy and congenital cataractogenesis.


**Steve Walkley**

**Neuroscience/Pathology/Neurology**

**Professor**

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 storage diseases include not only lysosomal hydrolases but also soluble and membrane-associated proteins often of unknown function. Animal models of storage diseases 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 (see figure at left, arrows), formation of axonal defects, compromise 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 subsequent induced changes in trafficking and signaling events within affected neurons. Therapeutic strategies are primarily focused on small molecule therapy directed at reducing substrate storage, so-called substrate reduction therapy.


Deyou Zheng  
Neurology/Neuroscience and Genetics  
Assistant 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. Please see our website for more details:  
http://dain.aecom.yu.edu/zhenglab  


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R. Suzanne Zukin
Neuroscience
Professor

There are four major lines of ongoing research in the Zukin lab. First, we are studying the mechanisms that regulate trafficking and targeting of NMDA-type glutamate receptors to and from synaptic sites. We have found that protein kinase C regulates NMDA receptor trafficking and gating. We identified SNAP-25 as the molecular target of PKC phosphorylation critical to insertion of new NMDA channels. We found that calcium influx through NMDA receptors in dendritic spines is under the control of cAMP/PKA signaling and that PKA is critical to NMDA receptor-dependent long term potentiation at hippocampal synapses. Recently, we discovered that the gene silencing transcription factor REST acts via epigenetic mechanisms to regulate the switch in NMDA receptor phenotype during brain development. New questions are: What is the molecular target of PKA? Can fear-inducing stimuli activate PKA and regulate calcium signaling through NMDA receptors? How do maternal deprivation and schizophrenia dysregulate the switch in NMDA receptor subtype during brain development? Our interest stems from the fact that NMDA receptors play a central role in cognitive functions such as learning and memory and formation of neural circuitry. NMDAR 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 such as ischemia and seizures activate the gene silencing transcription factor REST, critical to renewal of pluripotent stem cells, in adult hippocampal neurons and that REST is critical to death of hippocampal neurons. The AMPA receptor GluR2 subunit is a target of REST. Silencing of GluR2 leads to expression of calcium permeable AMPA receptors and neuronal death. We have found that REST promotes epigenetic remodeling of AMPA receptors in response to neuronal insults. We have initiated studies to examine epigenome-wide dysregulation in animal models of stroke, Huntington’s disease and Alzheimer’s disease. Our goal is to identify novel strategies to protect the brain from injury 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 together with the Etgen lab found that a single, acute injection of estradiol administered after an ischemic event ameliorates hippocampal injury and cognitive deficits. We also found that estrogens act via estrogen receptors ERα and GPR30 and JAK/STAT signaling to protect cells. Objectives are to identify mechanisms by which estrogen rescues neurons. Studies address STAT3 and CREB-induced epigenetic remodeling and transcription of target genes. Our interest stems from data that estrogen reduces the risk of cardiac arrest and stroke in humans.

A fourth area of interest is that of RNA trafficking and local protein synthesis in Fragile X. Fragile X syndrome is a leading genetic cause of intellectual disabilities and autism. We found that mTOR signaling is overactivated in Fragile X mice. We showed that dysregulation of mTOR signaling is linked to impaired synaptic plasticity in these mice. We also found that targeting of AMPAR mRNAs to synapses is dysregulated in Fragile X neurons. We are using the lentivirus expression system to genetically manipulate key proteins in the mTOR pathway and examine the impact on spine morphology, synaptic plasticity and cognition in the Fragile X mouse. It is hoped that these studies will accelerate the development of novel therapeutic strategies to ameliorate cognitive deficits in humans with Fragile X Syndrome.
Positions for graduate students and postdoctoral fellows are available in all four areas of research. Independent researchers and ideas are welcome, while well-defined and achievable projects are waiting for motivated, young investigators.


