Picower Institute for Learning and Memory

The Picower Institute for Learning and Memory (PILM) is a world-class focal point for research and education in the field of neuroscience, learning, and memory. Learning and memory are central to human behavior and the Picower Institute's research aims to understand the mechanisms underlying these cognitive functions at the molecular, cellular, brain circuit, and brain systems levels. The Picower Institute's research also extends to other higher-order cognitive phenomena intimately associated with learning and memory, such as attention, decision-making, and consciousness.

Awards and Honors

Assistant professor Kay Tye was awarded the Whitehead Career Development professorship.

Professor Earl Miller has been invited to give the keynote address at the Eastern Psychological Association.

Research Breakthroughs

Major research advances in the Picower Institute faculty laboratories during the report period are summarized below.

Through studies conducted in professor Li-Huei Tsai's laboratory, researchers have discovered the role of enzymes (and reduced caloric intake) in regards to anti-aging benefits and the preservation of cognitive function in mice. Researchers hope to use this information to delay the progress of age-associated impairments in the brain

Research conducted by Earl Miller's laboratory has helped identify and understand the neuronal activity of flexible neurons known as "mixed selectivity neurons." These studies have shown the relation between such neurons and expanded brain capacity. Professor Miller also conducted a study that helps explain how groups of neurons form thoughts and aid the ability to change one's mind. The results show that the nature of thought may be rhythmic.

Through an experiment performed on fruit flies, professor Troy Littleton's laboratory recognized that mutations in glial cells can produce epileptic seizures. Littleton claims that reacting to the effects of glial mutations may be a promising strategy for developing epilepsy treatment. Two other studies run by the Littleton laboratory reveal how neurons alter the cell's standard fusion machinery in order to control the release of neurotransmitters at the neuron's chemical connectors (synapses).

Kay Tye's laboratory discovered that states of depression in rodents can be altered through use of optogenetic (the injection of light-reactive proteins by genetically modified viruses). Her laboratory also discovered a possible alternative for more effective antidepressants. By identifying brain cells involved in depression, and stimulating these cells to deliver dopamine to other parts of the brain, researchers were able to eliminate symptoms of depression in mice.

Research conducted by scientists in professor Mriganka Sur's laboratory found evidence suggesting that astrocytes are critically important for processing sensory information in the brain. These brain cells relay messages telling neurons of the visual cortex to respond strongly to the visual information they are receiving. Sur and his colleagues have shown how some neurons and circuits of the brain inhibit neural activity. Through activation of neurons and simple mathematical computations, they were able to understand more about neurological disorders such as autism, schizophrenia, and bipolar disorder.

Professor Matthew Wilson's laboratory found that they could influence the dreams of rodents through use of audio cues that were previously used while the rodents navigated through mazes. Wilson hopes these manipulations will lead to new methods of learning and behavioral therapy in brain systems while sleeping.

Personnel

In addition to 11 faculty members, the Picower Institute includes other researchers, students, and technical and administrative support personnel. More than 270 MIT community members participated in Picower Institute activities during AY2013: 11 faculty members, three visiting scientists/scholars, 61 postdocs, 66 undergraduates, 28 graduate students, 81 research and technical staff, and 17 administrative and service staff.

Items of note during the academic year included the following:

Kwanghun Chung was hired as a junior faculty member (assistant professor) with a joint appointment in Chemical Engineering at the Institute for Medical Engineering and Science and the Department of Brain and Cognitive Sciences. Chung will start in summer 2013.

Cindy Stafford was hired as administrative support staff for Dr. Tsai in June 2013.

Fan Gao was hired as a bioinformatician to support the Picower faculty. Gao will start with the Picower Institute in September.

Bioinformatician Jia Meng departed from the Picower Institute in spring 2013 to pursue other endeavors in China.

Resource Development

Finding the resources to enable the faculty and students in the Picower Institute to carry on their work continues to be a high priority. In fiscal year 2013, many Picower faculty members gave freely of their time for meetings with donors and potential donors. Additionally, there were smaller gifts from alumni and friends.

This year, PILM received a $2.7 million gift from the JPB Foundation to continue their support of the Picower Institute Innovation Fund. Thanks to the generous support of the JPB Foundation and the Jeffry Picower Bequest, researchers at PILM have been able to expand their research horizons and venture into high-risk, high-reward areas of science that are not typically funded by the National Institutes of Health and that may have otherwise been left unexplored. The programs that have stemmed from these funding sources afford us a truly unique research environment and provide support for which our faculty, lab members, and administrative team are immensely grateful.

With this funding four new programs were created and developed.

The MIT-MGH Clinical Fellowship Program

In keeping with the shared intentions of the JPB Foundation and the Picower Institute, the clinical fellowship program was established to create opportunities for advanced study and research in neuroscience, and to serve as a bridge between clinical training and the development of a research career. As such, a full-time stipend is awarded to up to two researchers from Harvard affiliated institutions annually for a period of one to two years based on interest in the program and availability of candidates whose research interests mesh well with those of the institute.

The Picower Neurological Disorder Research Fund

The Picower Neurological Disorder Research Fund supports faculty research on neurological disorders, emphasizing collaborative effort. Each grant is awarded with the advice of our internal advisory committee, following the submission of a proposal to be reviewed by experts in the disorder of interest, not affiliated with MIT. Applications that emphasize collaborations between Picower faculty members receive the highest priority.

The Junior Faculty Support Fund

The Junior Faculty Support Fund is used at the discretion of the Picower Institute director with advice from the Picower Institute internal advisory committee. This fund will be used to supplement start-up funds, or to sustain the research of early or mid-career faculty members based on need. Given the difficulty of securing research funding, we foresee situations in which junior faculty members will need additional research support beyond that provided when they are hired.

The Symposium Fund

A portion of the funds received from the Jeffry Picower Estate were allotted to our Symposium Fund. These monies were used to fund the Picower Institute's 10 year anniversary gala and symposium and also supported the annual Picower Institute Symposium, both of which aim to bring together neuroscience researchers from MIT and the global neuroscience community to foster collaborations and new research initiatives.

Media Recognition

The Picower Institute has attained a distinguished international reputation as a leader in neuroscience research. The scholarly excellence of our faculty is reflected in their distinguished publication records. During AY2013, Picower Institute faculty published 21 articles in hallmark science journals (*Science*, *Neuron*, *Cell*, *Nature*, *Nature Neuroscience* or the *Journal of Neuroscience*) and in 50 peer-reviewed publications overall.

The Picower Institute issued 11 MIT press releases in the same time period. Articles appeared in the following major media outlets: *The Boston Globe*, *The New York Times*, *F1000Research*, Science Daily, and FOX News. Picower Institute research breakthroughs were also broadcast via the web on CNN.com, Boston.com, and Dailymail.co.uk, Picower.mit.edu, as well as on WBUR, Boston's national public radio station.

Programs and Activities

The Picower Institute was founded on the premise that collaboration among disciplines is an integral component of its research philosophy. To facilitate these collaborative interactions, the Picower Institute follows a rigorous calendar of formal lectures, conferences, and workshops as well as other informal events. Activities are designed to bring Picower researchers and the MIT neuroscience community together with other neuroscientists and practitioners from the public and private sectors.

The annual Picower Lecture, named in honor of the generous support of The Picower Foundation, features the work of a current leader in the area of brain research. This year's lecture, "Searching for the Molecular Basis of Major Depressive Disorder," took place on May 16 and was given by Dr. Paul Greengard of The Rockefeller University in New York City.

The Picower Institute Colloquia brings learning and memory researchers of the highest caliber from universities throughout the world to share their findings and experiences with the MIT community, as well as to create working relationships with members of the Picower Institute. During the past year, colloquia speakers included Eric Klann of New York University, Mark Hübener of the Max-Planck-Institute of Neurobiology, and Pascal Fries of the Ernst Strüngmann Institute.

In the language of neuroscience, "plasticity" refers to the minute but crucial physical changes that take place in our synapses every time we learn, experience, or remember something new. "Plastic Lunch" refers to a biweekly series of informal talks during the academic year that give post doctorates and graduate students from across the Picower Institute a chance to share their latest research with colleagues. The Plastic Lunch series provides an opportunity for participants to improve their presentation skills; it also fosters collaborations and builds new relationships across disciplines and between laboratories.

The Postdoc Association is an endeavor targeted at the Picower Institute's postdoctoral community which aims to provide resources to support activities that build community and enrich interactions between postdoctoral colleagues and future associates. Over the past year, the Postdoc Association expanded from a Picower-only association to a Building 46 sponsored group. A new board was elected and the association has convened a series of informal talks, educational seminars, and social events for the entire Building 46 postdoctoral community.

A monthly Picower Institute faculty lunch, known as the Picower Power Lunch, allows faculty and guest speakers to informally relate recent research findings or present new ideas. After the close of the academic year, the Picower Institute hosts an annual retreat for its community members. The sixth annual Dana and Betty Fisher Retreat took place on May 30 and 31, 2013. More than 130 researchers attended the event held in South Yarmouth, MA. The retreat included 11 laboratory research presentations, a highly interactive poster session (24 submissions), and a keynote address by Sebastian Seung of the Department of Brain and Cognitive Sciences.

Research Initiatives

The Induced Pluripotent Stem Cell (iPS) Core Facility that was launched in November of 2010 integrates the various research goals of members of the Picower and McGovern Institutes and the Department of Brain and Cognitive Sciences (BCS). Each of the BCS, McGovern, and Picower laboratories have their own expertise and experience with different experimental protocols which, when combined in a collaborative manner to the study of human cells, can result in accelerated research progress. Beginning in FY2014, the iPS facility will become a fee-for-service facility and will open its doors to other MIT and non-MIT users.

The fate of human fibroblast cells can be changed by introducing some genes of interest, such as Octamer-4 (OCT4), Nanog homeobox (NANOG), SRY-related HMG-box gene 2 (SOX2), cMYC proto-oncogene myc (cMYC), and Kruppel-like factor 4 (KLF4) into pluripotent stem cells, which can be called induced pluripotent stem (iPS) cells. These iPS cells resemble embryonic stem cells. Various patient-derived skin primary fibroblast cells are being used to make iPS cells. These patient-specific iPS cells allow researchers to examine a variety of fundamental questions of human disease, which cannot easily be done with embryonic stem (ES) cell technology because ES cells generally don't "know" the health status of an unborn embryo. Therefore, this iPS cell technology creates a powerful research tool that will enable researchers to study disease processes for which they have had only limited access. The iPS cells allow the creation of cell lines that are genetically customized to a patient; thus the issue of immune rejection can be potentially overcome. The iPS cells can be used to screen patient-specific novel therapeutic drug screening and to study the mechanism of multiple neuropsychiatric and neurodegenerative disorders.

Faculty Research Summaries

Mark Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences. Efforts to understand the causes and consequences of experience-dependent synaptic plasticity are focused on mechanisms and regulation of naturally occurring synaptic plasticity in primary visual cortex (V1), and on synaptic pathophysiology of fragile X (FX) and related developmental brain disorders.

Work on the effect of deprivation on visual cortex has led to an understanding of the molecular basis for amblyopia, a common form of visual impairment affecting over 2% of the world's population. Our discoveries that visual experience can dramatically modify responses in adult visual cortex has led to new insight into how stimulus familiarity is learned through synaptic plasticity and manifested behaviorally as habituation, and into the neural basis for spatiotemporal sequence learning. These discoveries are potentially relevant to the pathophysiology of schizophrenia and dyslexia. The finding that protein synthesis is increased at synapses downstream of metabotropic glutamate receptor activation in fragile X syndrome has led to several new treatment approaches for this disease, the most common inherited cause of intellectual disability and autism. Clinical trials based on the lab's research are currently in progress and have advanced to phase III. Our ongoing studies of other single-gene causes of autism have suggested an axis of pathophysiology that can be targeted with drugs to improve the course of these diseases.

Myriam Heiman, Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Core Member at the Broad Institute.
During the past year, Dr. Heiman's laboratory has focused on three areas: the study of a novel G-protein coupled receptor intracellular signaling molecule that may contribute to cellular aging phenotypes; how normally non-pathogenic polyglutamine proteins enhance the toxicity of mutant Huntingtin protein; and the development of a methodology that allows for synthetic lethal genetic screening in a mouse brain. These studies aim to understand the molecular basis of the selective cellular vulnerability that is observed for many neurodegenerative diseases, as well as to understand the contribution of normal cellular aging to neurodegenerative disease.

Troy Littleton, Picower Professor of Neuroscience, Departments of Biology and Brain and Cognitive Sciences.
The focus of the Littleton laboratory's work is to understand the mechanisms by which neurons form synaptic connections, how synapses transmit information, and how synapses functionally and structurally change during plasticity. To complement this basic research in neuroscience, the lab also studies how alterations in neuronal signaling contribute to several brain diseases, including epilepsy, autism and Huntington's Disease. We combine molecular biology, protein biochemistry, electrophysiology, and imaging approaches with *Drosophila* genetics to address these questions. Despite the dramatic differences in complexity between *Drosophila* and humans, genomic and functional analysis has confirmed that key neuronal proteins and the mechanisms they govern are remarkably similar. We are attempting to elucidate the pathways mediating synapse formation, function, and plasticity using *Drosophila* as a model system. Recent progress in the lab has allowed the generation of transgenic tools to image single synaptic vesicle fusion events at individual active zones in *Drosophila*, allowing us to characterize the spatial and temporal dynamics of exocytotic events that occur spontaneously or in response to an action potential. Our findings indicate neuronal connections contain two channels of information transfer that can be spatially segregated and independently regulated. Additional work in the lab has characterized a new glial-neuronal signaling pathway that regulates neuronal excitability, and contributes to epilepsy when disinhibited. By characterizing how neurons integrate synaptic signals and modulate synaptic growth and strength, we hope to bridge the gap between molecular components of the synapse and the physiological responses they mediate.

Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences.
The overarching goal of Earl Miller's laboratory is to understand cognitive functions in a broader context, as a product of interactions between networks and circuits of neurons, brain areas and systems. In the past year, the Miller Laboratory has made discoveries that suggest that the brain regulates the flow of neural "traffic" via rhythmic synchrony between neurons. Neurons form ensembles, and ensembles become part of larger functional networks when they "hum" together. Conversely, they don't form ensembles, and don't interact, when they don't hum together. In other words, rhythmic synchrony can reinforce or prevent communication between neurons. Thus, by changing the rhythmic synchronization between neurons, their communication can be altered, changing the flow of information through the brain. Synchronized brain rhythms may also explain the most obvious and objective fact about consciousness: it is very hard, often impossible, to think about more than one or a few things at the same time.

Elly Nedivi, Picower Professor, Departments of Brain and Cognitive Sciences and Biology
The Nedivi lab studies the cellular mechanisms that underlie activity-dependent plasticity in the developing and adult brain through studies of neuronal structural dynamics, identification of the participating genes, and characterization of the proteins they encode. After identifying a large number of activity-regulated genes, researchers focused in on several specific ones and characterized their different activities.

Consistent with structure prediction algorithms, researchers recently found that the activity regulated gene CPG2 physically interacts with components of the synaptic endocytic machinery and the spine cytoskeleton in the postsynaptic compartment (Loebrich et al. submitted). The role of the actin cytoskeleton in Clathrin Mediated Endocytosis (CME) is recognized as fundamental, yet, it remains poorly understood and we lack a mechanistic understanding of the cytoskeletal/CME association, its functional consequences, and its regulation. CPG2 reversibly associates with F-actin, and this association is positively regulated by protein kinase A (PKA), and is an important regulator of both glutamate receptor internalization and postsynaptic strength. These findings enable several conceptual advances. The unequivocal demonstration that CPG2 binding to actin is required for synaptic AMPAR CME provides the first clear evidence of functional coupling between actin and the synaptic endocytic process. CPG2 mediates the functional association between CME and actin by physically connecting actin with parts of the CME apparatus and acting as a physical linker between the two. The fact that this association is reversibly regulated by PKA adds another dimension, namely that second messenger pathways can regulate CME through CPG2 by reversibly removing or enabling the interaction with actin. Thus, our results identify CPG2 as essential for functional coupling of synaptic AMPAR CME with the spine cytoskeleton and as a key integration point for PKA signaling in the synaptic endocytic process.

Mriganka Sur, Paul E. Newton Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director of The Simon's Center for the Social Brain.
Mriganka Sur's laboratory has continued to use cutting-edge technologies for probing the function of specific cell classes in the cerebral cortex. Researchers showed that two distinct classes of inhibitory neurons have unique functions: soma-targeting parvalbumin-expressing inhibitory neurons carry out the arithmetic operation of division, whereas dendrite-targeting somatostatin-expressing inhibitory neurons carry out subtraction. Astrocytes, which complement neurons in cortical circuits, are acutely sensitive to acetylcholine and mediate plastic changes underlying attention and memory. Because inhibitory neurons and astrocytes are implicated in many developmental brain disorders, these findings provide a conceptual framework for understanding mechanisms underlying such disorders and developing strategies for their treatment.

Susumu Tonegawa, Picower Professor of Neuroscience, Departments of Brain and Cognitive Sciences and Biology.
Susumu Tonegawa's laboratory continues to seek to decipher the brain mechanisms underlying memory and its disorders. During the past year, The Tonegawa laboratory made the following major discoveries.

Distinct preplay of multiple novel spatial experiences in the rat. The activity of ensembles of hippocampal place cells represents a hallmark of an animal's spatial experience. The neuronal mechanisms that enable the rapid expression of novel place cell sequences are not entirely understood. The lab found that during sleep or rest, distinct sets of hippocampal temporal sequences in the rat preplay multiple corresponding novel spatial experiences with high specificity. These findings suggest that the place cell sequence of a novel spatial experience is determined, in part, by an online selection of a subset of cellular firing sequences from a larger repertoire of preexisting temporal firing sequences in the hippocampal cellular assembly network that become rapidly bound to the novel experience. We estimate that for the given context, the recorded hippocampal network activity has the capacity to preplay an extended repertoire of at least 15 future spatial experiences of similar distinctiveness and complexity.

Rescue of fragile X syndrome phenotypes in Fmr1 KO mice by the small-molecule PAK inhibitor FRAX486. Fragile X syndrome (FXS) is the most common inherited form of autism and intellectual disability and is caused by the silencing of a single gene, fragile X mental retardation 1 (Fmr1). The Fmr1 KO mouse displays phenotypes similar to symptoms in the human condition-including hyperactivity, repetitive behaviors, and seizures-as well as analogous abnormalities in the density of dendritic spines. Researchers took a hypothesis-driven, mechanism-based approach to the search for an effective therapy for FXS. Hypothesizing that a treatment that rescues the dendritic spine defect in Fmr1 KO mice may also ameliorate autism-like behavioral symptoms, we targeted a protein that regulates spines through modulation of actin cytoskeleton dynamics: p21-activated kinase (PAK). Results demonstrated that a potent small molecule inhibitor of group I PAKs reverses dendritic spine phenotypes in Fmr1 KO mice. This PAK inhibitor— called FRAX486—also rescues seizures and behavioral abnormalities such as hyperactivity and repetitive movements, thereby supporting the hypothesis that a drug treatment that reverses the spine abnormalities can also treat neurological and behavioral symptoms. Finally, a single administration of FRAX486 is sufficient to rescue all of these phenotypes in adult Fmr1 KO mice, demonstrating the potential for rapid, postdiagnostic therapy in adults with FXS.

Optogenetic stimulation of a hippocampal engram activates fear memory recall. A specific memory is thought to be encoded by a sparse population of neurons. These neurons can be tagged during learning for subsequent identification and manipulation. Their ablation or inactivation results in reduced memory expression, suggesting their necessity in mnemonic processes. However, it is unclear whether it is possible to elicit the behavioral output of a specific memory by directly activating a population of neurons that was active during learning. Researchers showed that optogenetic reactivation of hippocampal neurons in mice activated during fear conditioning is sufficient to induce freezing behavior. We labeled a population of hippocampal dentate gyrus neurons activated during fear learning with channelrhodopsin-2 (ChR2) and later optically reactivated these neurons in a different context. The mice showed increased freezing only upon light stimulation, indicating light-induced fear memory recall. This freezing was not detected in non-fear-conditioned mice expressing ChR2 in a similar proportion of cells, nor in fear-conditioned mice with cells labeled by enhanced yellow fluorescent protein instead of ChR2. Activation of cells labeled in a

context not associated with fear did not evoke freezing in mice that were previously fear conditioned in a different context, suggesting that light-induced fear memory recall is context specific. Together, these findings indicate that activating a sparse but specific ensemble of hippocampal neurons that contribute to a memory engram is sufficient for the recall of that memory.

Li-Huei Tsai, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences.
Li-Huei Tsai's laboratory uses a combination of molecular/cellular, genetic, and behavioral approaches to study neuropathologies that affect cognitive function. The Tsai lab focuses on neurodegenerative disorders such as Alzheimer's disease as well as on neurodevelopmental disorders such as autism and schizophrenia. In particular, Tsai is interested in the epigenetic control of gene expression as it impacts cognitive function in the brain. Epigenetic modifications include those that impact gene expression without altering DNA sequence. These mechanisms include the modification of histone proteins in the chromatin, via enzymes such as the histone deacetylases (HDACs), as well as DNA methylation and post-transcriptional control of gene expression by micro RNAs. Recently published work from the Tsai lab shows that the Tet1 protein regulates neuronal gene expression via control of DNA methylation, and that mice lacking this protein have specific memory and synaptic plasticity impairments. Also, new work shows that the interaction of the deacetylase SIRT1 with HDAC1 is crucial to the maintenance of genome integrity in neurons, and that this relationship is impaired both in neurodegenerative disease as well as during normal aging. Tsai researchers have found that the familial amyotrophic lateral sclerosis gene, FUS, also interacts with HDAC1 to maintain healthy DNA in the neuron. The lab has shown that activation of the SIRT1 enzymes appears to underlie the amelioration of Alzheimer's disease-like phenotypes by calorie restriction in mouse models of severe neurodegeneration, and that this effect can be recapitulated by small-molecule activations of the SIRT1 protein.

Tsai has also made major advancements in understanding the biology of neurodevelopment, and how perturbations early in this process may underlie neuropsychiatric disorders such as schizophrenia and autism. Ongoing work in the lab elucidates the importance of the Wnt signaling pathway in early brain development, and how gene mutations associated with schizophrenia and autism may disrupt normal Wnt signaling in the embryonic brain. One particular area of interest is how genetic polymorphisms in the microRNA 137 gene—which have been linked to a risk of schizophrenia and autism—alter brain development and adult synaptic plasticity via the epigenetic regulation of neuronal genes. Two recent publications showcase the synaptic regulator Cdk5 protein, which has previously been associated with neurodegeneration, but which Tsai researchers have found also plays important roles in the homeostasis of synaptic plasticity. One paper describes the role of Cdk5-mediated phosphorylation of calcium channels in the synapse, and the importance of this function for synaptic plasticity. An upcoming work finds that deletion of Cdk5 in forebrain excitatory neurons leads to disruptions in emotional and cognitive behavior in mice.

Matthew Wilson, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology.
Work in Matthew Wilson's laboratory continues to focus on the role of the hippocampus in the formation, maintenance, and use of memory in the mammalian nervous system during awake and sleep states. Previous experiments have shown that the hippocampus reactivates memories of recent experience during sleep in what may be described as the animal correlate of dreaming. Recent findings have demonstrated that reactivation of specific memories can be triggered through the use of auditory cues, effectively "engineering" dream content, providing the means to establish the causal relationship between memory processing during sleep and subsequent awake behavior. They have also found that hippocampal memory reactivation that occurs while animals stop briefly on a maze to "think," is paired with information about anticipated rewards, providing insights into potential mechanisms of goal-directed planning and decision-making.

Weifeng Xu, Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.
Weifeng Xu's laboratory studies the molecular events underlying the changes of neuronal properties responding to neural activity and behavioral stimulation. This activity-dependent neural plasticity is essential for information processing and storage in the brain (learning and memory). Many genes involved in this process are associated with neurological and psychiatric disorders, and the dysregulation of this process is thought to underlie some of the cognitive impairment in these diseases. To understand the molecular mechanism of neural plasticity, the lab uses a combination of cutting-edge molecular biology, biochemistry, electrophysiology and behavioral techniques to test how manipulating specific genes or neuronal processes will impact protein interaction, neuronal properties, network activity, and animal behavior. Two lines of research are conducted in the laboratory, the regulation of synaptic function by scaffold proteins, and the regulation of synaptic plasticity by activity-dependent expression of neurogranin.

Neurons communicate with each other through a specialized apparatus called a synapse. Neurotransmitter receptors reside in the postsynaptic scaffold complex. Previous work has shown that PSD-MAGUK scaffold proteins have overlapping yet distinct effects on regulating properties of synaptic transmission, including synapse numbers, synaptic current kinetics, and activity dependence. These results suggest a specific coordinated and compensatory mechanism at work to maintain the synaptic function via PSD-MAGUK scaffold proteins. Researchers also found that manipulation of different members of the Shank family proteins show different impacts on synaptic strength, suggesting differential contributions of family members in maintaining synaptic strength. The lab is now directing its efforts to identify candidate targets in synaptic scaffolds critical for mediating synaptic plasticity.

Calcium handling is a critical issue for neurons in response to external stimuli. Neurogranin, a small neuronal protein, binds to Ca-binding protein calmodulin (CaM) and is hypothesized to regulate calmodulin availability and dynamics in neurons. Researchers have found that the levels of neurogranin in the hippocampus can be rapidly regulated by novel context exposure and adrenergic stimulation, providing

an additional layer of regulation of signaling cascade for plasticity. The lab found that bidirectional change in neurogranin levels lead to bidirectional changes in neuronal excitability, synaptic efficacy, and spike-timing dependent plasticity. Overexpression of neurogranin in the hippocampus facilitates context memory formation. Given the fast and widespread change of neurogranin levels in the hippocampus in response to relevant behavioral stimulation, this pathway may contribute to moment-to-moment, activity-dependent modulation of neuronal network activity important for information coding in the central nervous system. The aim of the lab's research is to examine how rapid experience-dependent translation of neurogranin is involved in context memory formation and its potential impact on network plasticity, as well as to identify other candidate genes that share a similar activity-dependent translation profile within the same temporal domain.

Kay Tye, Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences.

Dr. Tye's work uses "reverse translational" approaches to identify the circuit and synaptic mechanisms underlying emotional processing and motivated behaviors in both health and disease in rodent models. The long-term objective of the lab is to identify common circuit perturbations that may underlie comorbidity between psychiatric disease states such as addiction, anxiety and depression. To do this, the Tye Lab employs an interdisciplinary approach integrating electrophysiological, optogenetic, pharmacological, and imaging techniques to study the neural bases of behavior. The lab has submitted a manuscript describing the identification of a novel pathway from the amygdala to the ventral hippocampus that can bidirectionally control anxiety-related behaviors. Furthermore, the lab is working on a new story looking at the functional encoding dynamics of optogenetically identified midbrain-projecting lateral hypothalamic neurons during a reward-seeking task. The hope is to connect the mesolimbic dopamine system with the amygdalar glutamatergic network and identify common pathways that may underlie multiple behavioral phenotypes relevant to anxiety, addiction, and depression.

Li-Huei Tsai
Director
Picower Professor of Neuroscience