Picower Institute for Learning and Memory

The Picower Institute for Learning and Memory is a world-class focal point for research and education in the field of neuroscience, and 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

Kwanghun Chung: Awarded Cells 40 Under 40, Searle Scholar, and CLARITY was mentioned as a runner-up in Science Breakthrough of the Year 2013

Earl Miller: Distinguished Member, National Society of Collegiate Scholars 2013.

Kay Tye: Received the NIH New Innovator Award, Received the 2014 Sloan Research Fellowship, MIT Committed to Caring Award, and was awarded the Whitehead Career Development Chair

Research Breakthroughs

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

- Researchers out of Li-Huei Tsai's lab found that the overproduction of the protein known as p25 may be the culprit behind the sticky protein-fragment clusters that build up in the brains of Alzheimer's patients. This finding could provide a new drug target for the treatment of the disease.
- A new study from Kay Tye's laboratory found a circuit in the brain that might explain the link between impaired social interaction and anxiety in so many disorders.
- Studies by Mriganka Sur's laboratory have discovered that their trial run in partnership with Children's Hospital Boston, that IGF1 is safe in the cohort tested and that it provides some effectiveness.
- Research conducted by Earl Miller's laboratory has found that as monkeys learn to categorize different patterns of dots, two brain areas involved in learning — the prefrontal cortex and the striatum — synchronize their brain waves to form new communication circuits. Category-learning results in new functional circuits between these two areas, and these functional circuits are rhythm-based, which is key because that's a relatively new concept in systems neuroscience.
- Researchers in the Tonegawa lab, for the first time have linked specific synchronized oscillation patterns with its correlating behavior. This work may lead to new therapies for patients suffering from Alzheimer's and other memory impairments.

- New research out of the Tsai lab suggests that HDACis make the brain more malleable, enabling even deep-rooted traumatic memories to be extinguished.
- Tonegawa lab researchers have now discovered how two neural circuits in the brain work together to control the formation of such time-linked memories. This is a critical ability that helps the brain to determine when it needs to take action to defend against a potential threat.
- Neuroscientists in the Tsai lab have found new evidence that suggests that a failure to repair damaged DNA could underlie not only ALS, but also other neurodegenerative disorders such as Alzheimer's disease.
- In a step toward uncovering better targets, neuroscientists in the Tye lab have discovered a communication pathway between two brain structures — the amygdala and the ventral hippocampus — that appears to control anxiety levels. By turning the volume of this communication up and down in mice, the researchers were able to boost and reduce anxiety levels.

Personnel

In addition to 12 faculty members, the Picower Institute consists of other researchers, students, technical and administrative support personnel. More than 270 community members participated in Picower Institute activities during the report period: 12 faculty members, 2 visiting scientists/scholars, 58 post-doctorates, 80 undergraduates, 29 graduate students, 89 research and technical staff, and 19 administrative and service staff.

Items of note during the academic year included the following:

Asha Bhakar was hired as Senior Scientific Writer and Development Officer in September 2013.

Ngoc Dang Tran was hired as Human Resources Administrator in March 2014.

Eric DiGiovanni was hired as Administrative Support for Headquarters in May 2014.

Liam Brenner was hired as MIT RIKEN- Program Operations Coordinator to support Professor Tonegawa in June 2014.

Resource Development

Raising 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 '14 many Picower Faculty members gave freely of their time for meetings with donors and potential donors. Thanks to the generous support provided from the JPB Foundation and the Jeffry Picower Bequest, the researchers at the Picower Institute for Learning and Memory have continued their research efforts and ventures into high-risk, high-reward areas of science that may have otherwise been left unexplored. Five main programs stem from these funding sources and afford us a truly unique research environment with support for our faculty, lab members, and administrative team. The programs include: 1) The MIT-MGH Clinical Fellowship Program, 2) The Picower Neurological Disorder Research Fund, 3)

The Junior Faculty Support Fund, 4) The Symposium Fund, and 5) The Picower Institute Innovation Fund.

This year the Picower Institute received a $2.7 million dollar pledge payment from the JPB Foundation to continue the support of the Picower Institute Innovation Fund, and an additional outright gift of $200,000 to expand the program to the newest faculty recruit, Professor Kwanghun Chung. Additionally, while we have allocated the majority of funds directly to research, in FY14 the PIIF has allowed us to hire new specific technical expertise in Resource Development, Bio-statistics, and Stem Cell work that will strategically help us to make new advances and delve into unexplored areas of neuroscience research.

In March, a solicited $9M Junior Faculty Development Program gift proposal was submitted to the JPB Foundation to establish a series of activities and funding structures within the Picower Institute with the goal of fostering a positive neuroscience community experience, long-term career success for junior faculty, and work towards the mission of the PILM.

On May 13th, the Spring Symposium provided an opportunity to steward our most generous donor and showcase the work of Picower Faculty and others on a topic very dear to Mrs. Picower. “New Insights on Early Life Stress and Mental Health Symposium” was exceptionally well attended (approximately 500 registrants) and well received. The day concluded with a glorious dinner hosted by President Reif at the Gray House which paid tribute to the vision and commitments of Barbara Picower to MIT and the accomplishments of the Picower Faculty. Subsequently, the JPB Foundation has conveyed intent to fund the Junior Faculty Development proposal and initiated talks around the creation of a collaborative Harvard-MIT consortium on early life stress.

New leadership gifts included additional funds in support of autism work in the Bear and Miller labs. Several smaller annual gifts were also received from alumni and friends particularly for discretionary work on Alzheimer’s, Autism, and Downs Syndrome Research.

This funding allowed for us to create, develop and grow four programs:

The MIT-MGH Clinical Fellowship Program:

In keeping the shared intentions of the JPB Foundation and the Picower Institute for Learning and Memory, 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 (PNDRF) 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 PILM Director with advice from the PILM Internal Advisory Committee. This fund is intended to be used for supplemental start-up funds, or for sustaining 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 are allotted to our symposium fund. These monies were used to fund the Picower Institute's 10 year anniversary Gala and Symposium, while also funding the biennial Picower Institute Symposium, and the biennial Stress Symposium all of which aim to bring together neuroscience researchers from MIT and the global neuroscience community to foster collaborations and new research initiatives.

Raising resources to enable the faculty and students in the Picower Institute to carry on their work continues to be a high priority. This year the Picower Institute received a $2.7 million gift from the JPB Foundation to continue their support of the Picower Institute Innovation Fund, which allows our faculty to perform high-risk, high-reward research, which is not typically funded by the NIH. In fiscal year '14 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.

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. In the reporting year, Picower Institute faculty published 28 articles in hallmark science journals (*Science*, *Neuron*, *Cell, Nature*, *Nature Neuroscience* or the *Journal of Neuroscience*) and 54 peer-reviewed publications overall.

The Picower Institute issued 37 press releases in the reporting period. Articles appeared in the following major print media: National Geographic, The Boston Globe, Forbes Magazine. Picower Institute research breakthroughs were also broadcast via the web on Science20.com, Mirror.co.uk, Independent.ie, Heraldscotland.com, ScientificAmerican.com, Sciencecodex.com, Boston.com, Presstv.ir, Dvice.com, and Wbur.org

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 to exchange research findings, facilitate cross-disciplinary collaborations, and continue to explore the potential that research advances about learning and memory mechanisms in the brain offer to science and society. Ongoing programs and activities are described below.

Held annually, the Picower Lecture was named to honor and recognize the generous support of The Picower Foundation for neurosciences at MIT. Each lecture features work of a current leader in the area of brain research. This year's lecturer was Dr. Carol A. Barnesai from the University of Arizona, in Tucson Arizona. Her talk, entitled "Impact on circuits critical for memory across species," took place on April 3, 2014.

The Picower Institute Colloquia brings the highest caliber of learning and memory researchers 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 were: Dr. Regina M. Carelli of The University of North Carolina at Chapel Hill, Dr. Cristina Alberini of New York University, Dr. Christian Luscher from Geneva University, and Dr. James Surmeier of Northwestern University.

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 anything new. At the Picower Institute, "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, often prepublished, research with colleagues within the Building 46 community. The Plastic Lunch series provides an opportunity for participants to improve their presentation skills and also fosters collaborations and builds new relationships across disciplines and between laboratories.

An endeavor targeted to the Picower Institute's post-doctorate community provided resources to support activities that build community and enrich interactions between postdoctoral colleagues and future associates. The Post-Doc Association, now a building 46 wide association continues to expand and make improvements in partnership with administration for the post-doctoral community. Throughout the past year the post doctorates convened a series of informal talks, educational seminars and social events, which includes all building 46 post-docs.

A monthly Picower Institute faculty lunch, known as Picower Power Lunch, allows faculty and guest speakers to informally relate recent research findings or present a new idea. Each year, after the close of the academic year, the Picower Institute hosts an annual retreat for its community members. The seventh annual Dana and Betty Fisher Retreat of the Picower Institute for Learning and Memory, was held on June 1st and 2nd, 2014. This year the retreat was held in collaboration with the Department of Brain and Cognitive Sciences and The McGovern Institute for Brain Research. More than 300 researchers attended the event held in Falmouth Ma, at the Seacrest Resort. The retreat included 14 laboratory research presentations, and a highly interactive poster session (50 submissions).

Research Initiatives

The iPS Core Facility which was launched in November of 2010 by the Picower Institute, integrates the various research goals of members of the Picower and McGovern Institutes, and the Department of Brain and Cognitive Sciences. The various BCS, McGovern, and Picower laboratories have expertise and experience with different experimental protocols which, when combined in a collaborative manner to the study of human cells, will result in accelerated progress in this novel, dynamic and competitive field. Effective FY14 the iPS facility became a fee for service facility, and opened its doors for the first time to other MIT users and to users external to MIT.

The fate of Human fibroblast cells can be changed by introducing some genes of interest such as OCT4(Octamer-4), NANOG(Nanog homeobox), SOX2 (SRY-related HMG-box gene 2), cMYC(proto-oncogene myc), and KLF4 (Kruppel-like factor 4) 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 previously had limited access. The iPS cells allow for 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 study the mechanism of multiple neuropsychiatric and neurodegenerative disorders.

Currently the iPS Core Facility has produced patient-specific iPS cells from Schizophrenia, Bipolar disease, Depression, Rett syndrome, Alzheimer disease, and a healthy control person's skin fibroblasts. More patient-specific cells are in the process of reprogramming to make iPS cells. Tak Ko, the supervisor of the core facility has also set up workshops to educate faculty and potential users on the types of work that they can do utilizing the core facility. At the moment internal and external labs are using the facility to learn the process of reprogramming to make iPS cells, and to differentiate iPS cells into neurons.

Faculty Research Summaries

Picower Institute faculty research areas are summarized below:

Mark Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences

How is the brain modified by experience, deprivation, and disease? Our overarching interest is in the question of how experience and deprivation modify synaptic connections in the brain. Experience-dependent synaptic plasticity is the physical substrate of memory. This plasticity sculpts connections during postnatal development to determine the capabilities and limitations of brain functions, is responsible for the reorganization of the brain after damage, and is vulnerable in numerous psychiatric and neurological diseases and contributes to their symptoms.

Historically, our major efforts to address this question have been focused on the visual cortex and hippocampus. The visual cortex is a site of robust experience-dependent synaptic plasticity, exemplified by the consequences of temporary monocular deprivation (MD) during childhood. MD sets in motion a stereotyped choreography of synaptic modification whereby the deprived-eye inputs to visual cortex rapidly lose strength and, with a delay, the open-eye inputs undergo a compensatory gain in strength. The behavioral consequence of this plasticity is severe visual impairment in the deprived eye. In humans, this condition is called amblyopia, responsible for loss of vision in over 1% of the world population. Thus, the visual cortex is an excellent preparation to connect the elementary molecular mechanisms of synaptic plasticity to their behavioral consequences. We are currently applying the latest optogenetic and microendoscopic techniques to this problem. Further, insights into how synapses depress or potentiate have possible clinical applications for the treatment of amblyopia, and we are working with clinicians at Children's Hospital Boston to apply this knowledge.

The hippocampus is a cortical structure that is critical to various forms of learning and memory. The simple cellular architecture of the hippocampus also makes it amenable to electrophysiological investigations of synaptic plasticity that are much more difficult in other parts of the brain. In the early 1990's we applied insights gained from a theoretical analysis of synaptic plasticity in the visual cortex to establish a phenomenon called homosynaptic long-term depression (LTD). LTD is the functional inverse of long-term synaptic potentiation (LTP). Although LTD and LTP are expressed at synapses throughout the brain, they are particularly robust at the Schaffer collateral synapses in the CA1 region of hippocampus. The hippocampus is therefore an excellent preparation in which to determine the molecular basis of bidirectional synaptic plasticity. The insights gained here can not only be applied to synaptic modifications elsewhere in the brain, but are also relevant to understanding hippocampus-dependent memory function and diseases of cognition.

In the course of studying LTD we made a discovery that has turned out to have major therapeutic significance for human developmental brain disorders that cause autism. One form of hippocampal LTD is triggered by activation of metabotropic glutamate receptor 5 (mGluR5) and requires immediate translation of mRNAs at synapses. While studying this form of synaptic plasticity, we discovered that protein synthesis (and LTD) downstream of mGluR5 is exaggerated in the mouse model of fragile X (FX). Human FX is caused by the silencing of the FMR1 gene, and is the most common inherited form of intellectual disability and autism. Insight gained by the study of LTD suggested that exaggerated protein synthesis downstream of mGluR5 might be pathogenic, contributing too many symptoms of the disease. Subsequent tests of the "mGluR theory" have shown that inhibition of mGluR5 can correct multiple mutant phenotypes in animal models of fragile X ranging from mouse to fruit fly. Human clinical trials were initiated based on the strength of this science, and results to date indicate that treatments can be developed to substantially benefit this patient population. The mGluR theory has contributed to a major paradigm shift wherein genetic diseases of brain development, historically viewed as untreatable, may be ameliorated, or even corrected, with appropriate therapy.

Kwanghun Chung, Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Department of Chemical Engineering, Institute for Medical Engineering and Sciences (IMES)

Kwanghun Chung started his position in October 2013 in the Department of Chemical Engineering and Institute for Medical Engineering & Science as Hemholtz Career Development Assistant Professor. He is also a PI at the Picower Institute for Learning & Memory. Since Dr. Chung's arrival at the Picower Institute, he has been developing novel technologies for studying function and dysfunction of the brain in a fully integrated manner. One example of such technology is advance CLARITY, a technology Professor Chung developed as a postdoc at Stanford to physically clear tissue and hence unlocks the capacity to study large-scale biological systems comprehensively. His group has also developed a new technique termed eTANGO that enables complete and uniform phenotyping of large-scale intact biological systems within hours. The group has already submitted a manuscript describing the technique and its application for mapping primate brains. Chung was named as a 2014 Searle Scholar and one of Cell's 40 Under 40. CLARITY was a runner up for Science's Breakthroughs of the Year.

Myriam Heiman, Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Core Member at the Broad Institute

The mammalian brain is composed of hundreds of cell types, woven together in an intricate web. While beautiful, this complexity has hampered our ability to conduct molecular studies of individual cell types in situ. In an effort to untangle this complexity, researchers historically have grouped nerve cells (neurons) into classes based on morphology, anatomical location, and a small sampling of the molecules that they express. However, in the post-genome era, there is an opportunity to comprehensively identify all the molecules that distinguish cell classes in the brain. Such an undertaking could have major benefits: for example, in many neurological diseases, certain classes of cells display enhanced vulnerability and are the first to show signs of degeneration, but the basis of this enhanced vulnerability is not known. Factors responsible for cell-type-specific disease vulnerability could thus be exploited as therapeutic targets.
To study the molecular profiles of distinct nerve cell classes in situ, our lab makes use of Translating Ribosome Affinity Purification (TRAP) in transgenic mice. Briefly, TRAP mice express an enhanced green fluorescent protein (EGFP)-tagged ribosomal protein, EGFP-L10a, such that EGFP serves as a ribosomal affinity tag allowing the indirect immunopurification of all translated messenger RNAs (mRNAs). When the EGFP-L10a fusion construct is driven by genetic elements known to target a distinct cell type, the complete translated mRNA profile of that cell type, and only that cell type, can be discerned.

Neuronal profiling in mouse models of Huntington's disease: A fascinating example of enhanced cell-type-specific disease vulnerability is seen in Huntington's disease (HD), a monogenic neurodegenerative disease caused by expansion of CAG (glutamine-encoding) trinucleotide repeats in the huntingtin gene. In HD, medium-sized spiny neurons of the striatum are dramatically affected, and in late stages of this disease, most medium spiny neurons are lost. Eventually, other classes of neurons are also affected in HD, but striatal medium spiny neurons are among the earliest stricken. The enhanced vulnerability of medium spiny neurons cannot be explained merely by the pattern of

huntingtin expression, as the huntingtin gene itself is expressed in many cells. Thus, medium spiny neurons may express other factors that make them especially susceptible to death in HD (or may fail to express factors that would make them more resistant). To identify such susceptibility factors, our lab is using TRAP to compare the molecular profiles of more resistant and more vulnerable cell populations in HD. The levels of factors that correlate with enhanced vulnerability will be genetically manipulated, and the impact of these changes on the phenotype of Huntington's disease model mice will be assessed. The aim of this research is to identify protective factors that may alter the course of Huntington's disease progression and reveal insights into medium spiny neuron physiology.

Neuronal profiling in mouse models of Parkinson's disease: Another focus in our lab is a collaborative project aimed at understanding how long-term adaptations occur in the brain in response to the loss of a key neurotransmitter, dopamine. Specifically, the motor symptoms of Parkinson's disease (PD) – including resting tremor, rigidity, akinesia, and postural instability – are seen upon dopamine depletion in the brain, resultant from the death of dopamine-producing cells in the substantia nigra. A standard treatment for PD is administration of levodopa, which can be converted to dopamine, and which works well in the short term to relieve symptoms. However, interestingly, over the long term, patients receiving levodopa develop debilitating side effects and, over time, this drug loses its efficacy. The lab is currently investigating the levodopa-induced changes that occur in one of the major cell classes that levodopa acts upon – medium spiny neurons in the striatum. The goal of this project is to identify the molecular basis of levodopa-induced side effects which may ultimately lead to therapeutic targets for the long-term treatment of a Parkinsonian state.

The mosaic nature of the brain reveals itself in the course of diseases, including Huntington's and Parkinson's disease, which preferentially strike particular cell types. Our lab is using cell-type specific profiling to identify the molecular basis of this differential vulnerability, in the hope of making progress towards new disease therapeutics, and continuing to unravel the complexity of the mammalian brain.

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 neuronal synapses from, transmit information and undergo plasticity. To complement this basic research in neuroscience, we also study 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. As such, we are attempting to elucidate the pathways mediating neuronal signaling using Drosophila as a model system. Recent progress in the lab has allowed the generation of new imaging tools to visualize single synaptic vesicle fusion events at individual active zones in Drosophila, allowing us to characterize the spatial dynamics of how neurons communicate through synaptic vesicle fusion. We found that individual active zones can vary widely in their strength of

transmission, and that a subset of release sites are specifically dedicated to spontaneous release, suggesting this poorly characterized mode of transmission may transmit unique signals between neurons. Additional studies in the lab have characterized a new glial-neuronal signaling pathway that regulates neuronal excitability, and contributes to epilepsy when disinhibited. We have also made generated important new insights into how the synaptic vesicle fusion machinery is regulated by the SNARE binding proteins Complexin and Synaptotagmin. 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 K. 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. To this end, the Miller Laboratory has developed (and shares) technology and techniques for recording from many separately movable, acutely inserted electrodes, which allows the gap between the global scope of human brain imaging and the spatiotemporal precision of single neuron physiology to be bridged. It also allows examination of precise timing relationships and interactions between neuronal populations. The laboratory couples this with investigating the kind of sophisticated, flexible behaviors at which humans and monkeys are so adept.

In the past year, the Miller Laboratory has made discoveries that suggest that rhythmic synchrony between neurons ("brain waves") plays an important role in learning. They found that when animals learn the categories of objects or when they learn that certain objects "belong together", there are increases in brain wave synchrony between the prefrontal cortex (the brain's "executive") and brain areas involved in learning, the striatum and the hippocampus. This suggests that brain areas that "hum" together, learn together.

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, we focused on several and characterized their very different activities, showing that each provides unique insight into diverse aspects of plasticity mechanisms.
We have previously shown that one such activity-regulated gene, CPG2, localizes specifically to the endocytic zone in dendritic spines where it regulates constitutive and activity induced internalization of synaptic glutamate receptors (Cottrell et al, Neuron, 2004). In neurons, Clathrin Mediated Endocytosis (CME) of glutamate receptors from the postsynaptic membrane is a central mechanism for adjusting excitatory synaptic strength, and is thought to be the substrate for various forms of synaptic plasticity. Loss of CPG2 function disrupts both constitutive and activity-dependent glutamate receptor endocytosis, suggesting a critical role for CPG2 in fine-tuning the number of surface glutamate receptors at synapses.

More recently we found that association of CPG2 with F-actin is obligatory for CME of synaptic glutamate receptors. (Loebrich et al, PNAS, 2013), providing the first clear evidence of functional coupling between actin and the synaptic endocytic process. Yet, the mechanism by which CPG2 F-actin association essentially couples the endocytic process to the spine cytoskeleton remains unclear. In an unbiased approach to identifying CPG2 binding proteins that might be part of, or closely associated with, the endocytic machinery, we immunoprecipitated CPG2 from rat brain and isolated co-precipitating proteins. Mass spectrometry identified Endophilin B2, a member of the endocytic machinery as a potential CPG2 binding partner. We have since validated this interaction and found that the association between CPG2 and Endophilin B2 is critical for activity-induced glutamate receptor internalization. Further, we showed that that CPG2 physically anchors components of the endocytic machinery to the F-actin cytoskeleton, via its direct interaction with Endophilin B2. These results demonstrate that CPG2 acts not just as a functional link, but also as a physical bridge between the endocytic machinery and F-actin, providing a mechanism for cytoskeletal control of synaptic receptor internalization.

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 is developing cutting-edge technologies for massive-scale imaging of single-neuron activity – recording 10,000+ neurons simultaneously – to probe the function of brain areas and circuits involved in visual learning and memory-guided visual decisions. Technologies for targeted recording and manipulation of specific neuron classes have revealed unique inhibitory-excitatory circuits by which neurotransmitters such as acetylcholine influence cortical responses underlying attention and arousal. The lab's work on cortical plasticity and function provides the basis for understanding developmental disorders of the brain. Using a mouse model of Rett Syndrome – a rare neurodevelopmental disorder – the lab has shown that loss of the gene MeCP2 leads to abnormal expression of unique sets of microRNAs that cause deficits in brain growth factors, neuronal function, and behavior. Restoring one growth factor, IGF1, leads to recovery of a wide range of functions in the mice. A clinical trial based on these findings has shown that administering IGF1 to Rett Syndrome patients has substantial therapeutic benefits.

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.

Differential roles of the dopamine 1-class receptors, D1R and D5R, in hippocampal dependent memory

Activation of the hippocampal dopamine 1-class receptors (D1R and D5R) are implicated in contextual fear conditioning (CFC). However, the specific role of the D1R versus D5R in hippocampal dependent CFC has not been investigated. Generation of D1R- and D5R-specific in situ hybridization probes showed that D1R and D5R mRNA expression was greatest in the dentate gyrus (DG) of the hippocampus. To identify the role of each receptor in CFC we generated spatially restricted KO mice that lack either the D1R or D5R in DG granule cells. DG D1R KOs displayed significant fear memory deficits, whereas DG D5R KOs did not. Furthermore, D1R KOs but not D5R KOs, exhibited generalized fear between two similar but different contexts. In the familiar home cage context, c-Fos expression was relatively low in the DG of control mice, and it increased upon exposure to a novel context. This level of c-Fos expression in the DG did not further increase when a footshock was delivered in the novel context. In DG D1R KOs, DG c-Fos levels in the home cage was higher than that of the control mice, but it did not further increase upon exposure to a novel context and remained at the same level upon a shock delivery. In contrast, the levels of DG c-Fos expression was unaffected by the deletion of DG D5R neither in the home cage nor upon a shock delivery. These results suggest that DG D1Rs, but not D5Rs, contribute to the formation of distinct contextual representations of novel environments.

Successful Execution of Working Memory Linked to Synchronized High-Frequency Gamma Oscillations

Neuronal oscillations have been hypothesized to play an important role in cognition and its ensuing behavior, but evidence that links a specific neuronal oscillation to a discrete cognitive event is largely lacking. We measured neuronal activity in the entorhinal-hippocampal circuit while mice performed a reward-based spatial working memory task. During the memory retention period, a transient burst of high gamma synchronization preceded an animal's correct choice in both prospective planning and retrospective mistake correction, but not an animal's incorrect choice. Optogenetic inhibition of the circuit targeted to the choice point area resulted in a coordinated reduction in both high gamma synchrony and correct execution of a working-memory-guided behavior. These findings suggest that transient high gamma synchrony contributes to the successful execution of spatial working memory. Furthermore, our data are consistent with an association between transient high gamma synchrony and explicit awareness of the working memory content.

Island Cells Control Temporal Association Memory

Episodic memory requires associations of temporally discontiguous events. In the entorhinal-hippocampal network, temporal associations are driven by a direct pathway from layer III of the medial entorhinal cortex (MECIII) to the hippocampal CA1 region. However, the identification of neural circuits that regulate this association has remained unknown. In layer II of entorhinal cortex (ECII), we report clusters of excitatory neurons called island cells, which appear in a curvilinear matrix of bulblike structures, directly project to CA1, and activate interneurons that target the distal dendrites of CA1 pyramidal neurons. Island cells suppress the excitatory MECIII input through the

feed-forward inhibition to control the strength and duration of temporal association in trace fear memory. Together, the two EC inputs compose a control circuit for temporal association memory.

Cell type–specific genetic and optogenetic tools reveal hippocampal CA2 circuits

The formation and recall of episodic memory requires precise information processing by the entorhinal-hippocampal network. For several decades, the trisynaptic circuit entorhinal cortex layer II (ECII)→dentate gyrus→CA3→CA1 and the monosynaptic circuit ECIII→CA1 have been considered the primary substrates of the network responsible for learning and memory. Circuits linked to another hippocampal region, CA2, have only recently come to light. Using highly cell type–specific transgenic mouse lines, optogenetics and patch-clamp recordings, we found that dentate gyrus cells, long believed to not project to CA2, send functional monosynaptic inputs to CA2 pyramidal cells through abundant longitudinal projections. CA2 innervated CA1 to complete an alternate trisynaptic circuit, but, unlike CA3, projected preferentially to the deep, rather than to the superficial, sublayer of CA1. Furthermore, contrary to existing knowledge, ECIII did not project to CA2. Our results allow a deeper understanding of the biology of learning and memory.

Impaired Hippocampal Ripple-Associated Replay in a Mouse Model of Schizophrenia

The cognitive symptoms of schizophrenia presumably result from impairments of information processing in neural circuits. We recorded neural activity in the hippocampus of freely behaving mice that had a forebrain-specific knockout of the synaptic plasticity-mediating phosphatase calcineurin and were previously shown to exhibit behavioral and cognitive abnormalities, recapitulating the symptoms of schizophrenia. Calcineurin knockout (KO) mice exhibited a 2.5-fold increase in the abundance of sharp-wave ripple (SWR) events during awake resting periods and single units in KO were overactive during SWR events. Pairwise measures of unit activity, however, revealed that the sequential reactivation of place cells during SWR events was completely abolished in KO. Since this relationship during postexperience awake rest periods has been implicated in learning, working memory, and subsequent memory consolidation, our findings provide mechanism underlying impaired information processing that may contribute to the cognitive impairments in schizophrenia.

Creating a False Memory in the Hippocampus

Memories can be unreliable. We created a false memory in mice by optogenetically manipulating memory engram–bearing cells in the hippocampus. Dentate gyrus (DG) or CA1 neurons activated by exposure to a particular context were labeled with channelrhodopsin-2. These neurons were later optically reactivated during fear conditioning in a different context. The DG experimental group showed increased freezing in the original context, in which a foot shock was never delivered. The recall of this false memory was context-specific, activated similar downstream regions engaged during natural fear memory recall, and was also capable of driving an active fear response. Our data demonstrate that it is possible to generate an internally represented and behaviorally expressed fear memory via artificial means.

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. Her lab focuses on neurodegenerative disorders, such as Alzheimer's disease, with an additional interest in neurodevelopmental disorders such as autism. In particular, she 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.

Previous work in the Tsai lab has shown the HDAC2 enzyme to be a negative regulator of learning and memory genes, which is upregulated following neurotoxicity and in Alzheimer's disease. In a recent work, they further linked the manipulation of HDAC2-mediated gene expression programs to potential treatment of another memory disorder, namely post-traumatic stress disorder (PTSD), which is highly prevalent in military veterans as well as in individuals with aversive childhood experiences. She found that a failure to extinguish aversive memories is a consequence of the neuron's inability to overcome HDAC2-mediated transcriptional repression of synaptic plasticity genes. Using a gene therapy approach or a small molecule inhibitor of HDAC2, her group facilitated the extinction of even remote long-term memories. Increases in HDAC2 expression were also shown by the Tsai group to result from the generation of the p25 peptide, an activator of the Cdk5 kinase. While Li-Huei Tsai's early work showed that Cdk5, in concert with its physiological activator p35, is crucial for brain development, generation of the p25 fragment, via calpain cleavage, has been associated with neurotoxicity and neurodegeneration. Surprisingly, a new study shows that the general of p25 following neuronal activity plays an important role in synaptic homeostasis. In a novel mouse model, in which p35 cleavage to p25 is abolished, the Tsai group shows that activity-dependent p25 plays an important role at the synapse, while chronic elevations in p25 generation underlie amyloid beta (Ab)-associated synaptic dysfunction. Additionally, the blockade of p25 generation in this new mouse model confers a remarkable neuroprotection when crossed to mouse AD models.

The Tsai lab continues its focus upon multiple epigenetic mechanisms that impact cognitive function. For example, they recently showed 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. Other 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 also found that the familial amyotrophic lateral sclerosis gene, FUS, also interacts with HDAC1 to maintain healthy DNA in the neuron. In addition, her 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.

Together, Li-Huei Tsai's groundbreaking work offers insight into the mechanisms underlying memory impairment/loss and pinpoints a novel pathway, namely, chromatin remodeling-mediated neuronal gene expression, as target for the therapeutic intervention into memory loss observed in AD and other brain disorders associated with cognitive impairment.

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

Since Dr. Tye's arrival at the Picower Institute in January 2012, she has been working to use "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 identifying 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. Some of the research from the Tye Lab has already been reported in two publications (Neuron, 2013 and J Neuroscience 2014) describing the identification of a novel pathway from the amygdala to the ventral hippocampus that can bidirectionally control anxiety-related behaviors and social interaction, respectively. 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. Together, we hope 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.

Matthew Wilson
Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology

Work in Matthew A. 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. They have also 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. Using optogenetic approaches to manipulate neural activity, they have identified novel circuits involved in the regulation of attention and sleep, as well as demonstrating the role of brain rhythms in enhancing memory performance.

Weifeng Xu
Picower Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences

Neurons in our brain respond to external stimuli and induce changes in their neuronal properties including the strength and structure of the connections between neurons (synapses) and the ability for the neurons generating propagating signals (neuronal excitability). These long lasting changes (neural plasticity) eventually lead to the encoding of the information in the neural circuit, and are thought to be the cellular substrates for learning and memory. Our overarching goal is to understand the mechanisms of neural plasticity essential for information processing and storage in the brain, and their dysfunction in disease such as autism, schizophrenia, bipolar disorder and mental retardation.

We use a multi-level approach to combine molecular biology, biochemistry, electrophysiology, imaging and behavioral techniques and investigate the functional roles of particular gene targets in regulating neural plasticity at the cellular and circuit levels, and learning and memory at the behavioral level. Two lines of research are conducted in the laboratory.

Project 1: Signaling Scaffold for Synaptic Plasticity.
Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Glutamatergic synaptic connections underlie the feed-forward information processing in the neural circuit. Activity-dependent long-term changes of these connections (synaptic plasticity) are thought to carry the memory trace in response to external stimuli. Glutamate receptors reside in a protein-protein interaction network called post-synaptic density (PSD) composed of many specialized scaffold proteins including PSD-MAGUK family proteins and Shank family proteins etc. These scaffold proteins are not only the structural components in the PSD, but also playing important roles in orchestrating specific signaling events during synaptic plasticity. Many of the genes in this protein complex are associated with neurodevelopmental and neuropsychiatric disorders including autism, schizophrenia, bipolar disorder and mental retardation.

Our previous work found that different family members of PSD-MAGUK proteins have distinct effects on regulating synapse numbers, synaptic current kinetics and activity-dependence. Our current research show that the different PSD-MAGUK proteins interact with different pools of glutamate receptors that have different kinetics and trafficking mechanism, suggesting distinct and potentially coordinated mechanisms of PSD-MAGUK proteins in regulating glutamatergic synaptic function.

We also found that manipulation of the Shank family proteins regulating synapse number and strength similar to the manipulation of the PSD-MAGUK family proteins. However, unlike PSD-MAGUK proteins, elevated excitatory drive cannot compensate the effect caused by loss of Shank family proteins on synaptic transmission, suggesting activity-dependent trafficking and modification of existing PSD cannot compensate the loss of Shank proteins. These results suggest a significant structural role of Shank family protein in terms of regulating glutamatergic synaptic function, whereas PSD-MAGUK proteins are more intimately involved in activity-dependent synaptic trafficking of ionotropic glutamate receptors.

Current research focus on identifying signaling specificity for different PSD-MAGUK proteins, and identifying potential targets in the PSD crucial for the induction and expression of long-term potentiation of synaptic strength.

Project 2: Regulation of Calcium Homeostasis in Learning and Memory.

Calcium (Ca^{2+}) influx via membrane receptors and ion channels is essential in translating extracellular events into intracellular signaling cascades important for activity-dependent neural plasticity. Dysregulation of calcium homeostasis is thought to contribute to neuropsychiatric diseases such as schizophrenia and normal aging. This Ca^{2+}-dependent process is mediated through calmodulin (CaM) that binds to Ca^{2+} and induces Ca^{2+}/CaM-dependent signaling events. CaM is ubiquitously expressed in neurons. There are small neuronal proteins known to interact with CaM, and regulate the affinity of CaM for Ca^{2+} binding. Changes in these CaM-binding proteins will presumably influence the downstream signaling pathways that are important for synaptic plasticity and learning and memory.

We study neurogranin, the only family member of small CaM-binding proteins expressed in the postsynaptic compartment of principal neurons in forebrain and hippocampus. Neurogranin levels fluctuate in response to behavioral, environmental, and hormonal stimulation in rodent models and under pathological conditions in humans. The neurogranin gene has been associated with neurological and neuropsychiatric disorders including schizophrenia and mental retardation. We have evidence showing that the activity-dependent translation of neurogranin in hippocampus serves as a key positive modulator of neural plasticity and learning via shifting the threshold of neural plasticity. Blocking activity-dependent translation of neurogranin in hippocampus interferes with hippocampal synaptic plasticity and hippocampus-dependent learning. Given the fast and widespread change of neurogranin levels in 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.

Our on-going research shows that changes in neurogranin levels have profound impact on neuronal properties, including membrane properties, kinase/phosphatase activities, activity-dependent gene transcription and translation, suggesting neurogranin is a master regulator of calcium signaling in principal neurons in the mammalian brain, crucial for gating synaptic plasticity and signal propagation. Our results will elucidate a critical mechanism for regulation calcium signaling important for learning and memory.

Li-Huei Tsai
Director
Picower Professor of Neuroscience