# Picower Institute for Learning and Memory

The Picower Institute for Learning and Memory's primary function is as a world-class focal point for research and education in the neuroscience of 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'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

J. Troy Littleton received the Fred and Carole Middleton career development professorship from the School of Science (2005–2008).

Carlos E. Lois received the Ellison Foundation Young Investigator Award (2004–2008) and a fellowship from the David and Lucille Packard Foundation (2004–2009).

Earl K. Miller received the Mathilde Solowey Award in the Neurosciences and delivered the Jeffrey Lecture in Cognitive Neuroscience at the University of California, Los Angeles.

Elly Nedivi received the Julie Martin Mid-Career Award in Aging Research from AFAR and the Ellison Foundation.

Morgan H. Sheng was elected a fellow of the Royal Society, the United Kingdom's national academy of science.

Susumu Tonegawa received an honorary degree from the University of Alcalá in Madrid, Spain.

## Personnel

In addition to 11 faculty members, the Picower Institute consists of other researchers, students, and technical and administrative support personnel. More than 200 community members participated in Institute activities during the report period: 11 faculty members, 13 senior researchers, 80 postdoctorates, 33 graduate students, 14 undergraduates, 39 technical staff, and 19 administrative and service staff.

Items of note during the academic year included:

Susumu Tonegawa stepped down as director of the Picower Institute, effective December 31, 2006.

Mark F. Bear assumed directorship of the Picower Institute on January 1, 2007.

J. Troy Littleton, Fred and Carole Middleton associate professor, received tenure.

Two faculty searches were opened: one for a molecular and systems neuroscientist (senior or junior) and a second for a molecular and cellular neuroscientist (junior).

## 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 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.

This is the fifth and final year of the second five-year agreement with the RIKEN Brain Science Institute (BSI). Six laboratories are involved in the international collaboration—those of Susumu Tonegawa, Earl K. Miller, Matthew A. Wilson, Yasunori Hayashi, Morgan Sheng, and Li-Huei Tsai. Over the last two years the RIKEN-MIT Neuroscience Research Center has focused on expanding the relationship between Picower and RIKEN BSI. We have increased the number of scientists from RIKEN BSI invited to the annual Picower retreat. In addition, the third annual Picower-RIKEN Workshop at MIT was hosted by Picower and consisted of two concurrent sessions, one presented by RIKEN BSI personnel and the other by Picower Institute scientists. The workshop topics were relevant to current research, and the meeting was a great success, with each session drawing roughly 100 participants. In response to our continued success, RIKEN hosted their second workshop in fall 2006 in Japan. Furthermore, 10 scientists from Picower have signed up to participate in this fall's third RIKEN BSI retreat, held in Japan in late November 2007. Through cultivation and expansion of these programs, we will continue to improve Picower-RIKEN scientific research collaborations in the coming years.

Sponsored jointly by Picower and RIKEN BSI, the Picower-RIKEN Symposium brings many of the most distinguished and creative neuroscientists from around the world to MIT to present their research results and perspectives. This periodic symposium draws hundreds of participants interested in exploring the brain at every level of its complexity. The sixth annual Picower-RIKEN Neuroscience Symposium, New Frontiers in Brain Science: From Molecules to Mind, took place November 8–9, 2007. Sixteen neuroscientists from around the world presented cutting-edge research discoveries in technology, learning and memory, plasticity, and systems neuroscience. The symposium also celebrated RIKEN BSI's tenth anniversary.

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. The past year's lecture, given by Professor Roger Nicoll of the University of California, San Francisco, was "Glutamate Receptor Trafficking and Synaptic Plasticity." This year's lecturer is Professor Alcino Silva of the University of California, Los Angeles. His talk, "Unraveling Memory: Molecules, Cells and Circuits and the Havoc They Can Cause," was given December 13, 2007.

The biweekly Picower Institute Seminar Series 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, seminar speakers have included Professor Arnold Kriegstein of the University of California, San Francisco; Professor Venki Murthy of Harvard University; Professor Raymond Kesner of the University of Utah; Professor Larry Squire of the Veterans Affairs Medical Center; Professor Pico Caroni of the Friedrich Miescher Institute; Professor Ryohei Yasuda and Professor David Fitzpatrick of Duke University; Professor Hitoshi Sakano of the University of Tokyo; Professor Eve Marder of Brandeis University; Professor Scott Brady of the University of Illinois, Chicago; Dr. Thomas Klausberger of Oxford University; Professor David van Vactor of Harvard Medical School; Professor Alice Ting of MIT; Professor Michela Gallagher and Professor David Yue of Johns Hopkins University; and Dr. Chris McBain of the National Institutes of Health.

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 that give postdoctorates and graduate students from across the Picower Institute a chance to share their latest, often prepublished, research with colleagues. 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.

Each June, after the close of the academic year, the Picower Institute hosts the annual Picower retreat. All members of the Institute, members of some Picower Institute affiliate laboratories (this year, those of professors William Quinn of the Department of Brain and Cognitive Sciences and Alice Ting of the Chemistry Department), and collaborators from RIKEN BSI are invited to attend. During the retreat, Picower Institute faculty, postdoctorates, graduate students, staff, and collaborators present and discuss their research findings. This year, more than 150 researchers attended the two-day retreat held on Cape Cod, including 10 RIKEN scientists. The retreat included 16 research presentations, two highly interactive poster sessions (36 submissions), and a keynote address by Professor Peter So of MIT's Mechanical Engineering Department.

The Picower Advisory Council met on October 19, 2006. The council was created to advise the leadership of the Picower Institute and MIT on issues key to its mission as a world-leading center of neuroscience research and education. The council is cochaired by the Picower Institute director and the dean of the School of Science. Other members are provost Rafael Reif, Mrs. Barbara Picower, Mr. Jeffry Picower, Dr. Stephen Hochschuler, Professor Torsten Wiesel of Rockefeller University, and Professor Huda Zoghbi of the Baylor College of Medicine. At the end of each meeting, council recommendations are presented in person to MIT president Susan Hockfield.

The Picower Institute Dean's Scientific Advisory Committee met January 17–18, 2007. Committee members are Professor Cornelia Bargmann of Rockefeller University (chair); Professor Sydney Brenner of the Salk Institute; Professor Hollis Cline of Cold Spring Harbor Laboratory; Professor Allison Doupe of the University of California, San Francisco; Provost Steven Hyman of Harvard University; Professor Robert Malenka of the Stanford University School of Medicine; Professor Richard Morris of the University

of Edinburgh; and Professor Charles Stevens of the Salk Institute. The committee submitted its report to the dean of the School of Science.

## New Research Endeavor

To fully understand the brain mechanisms underlying a specific cognitive phenomenon such as memory or emotion, it is essential to investigate not only the properties of individual cells, cellular clusters, and brain systems, but also the functions generated by their communications. This is important for uncovering the fundamental mechanisms operating in the healthy brain and for understanding how these mechanisms go astray under disease conditions. Officially launching in April 2008, The RIKEN-MIT Center for Brain Circuit Genetics will be directed by Professor Susumu Tonegawa. The Center will carry out truly interdisciplinary research by combining the cutting-edge transgenic and viral vector techniques, in vivo multielectrode recording technology, optical and magnetic imaging techniques, and behavioral studies. The goal of this research is to understand the brain mechanisms underlying a variety of cognitions and behaviors at the molecular, cellular, neural circuit, and brain systems levels.

## Faculty Research Summaries

The scholarly excellence of the Picower Institute faculty is reflected in distinguished publication records. In AY2006, Picower Institute faculty published 12 articles in hallmark science journals (*Science*, *Neuron*, *Cell*, and *Nature*) and 44 peer-reviewed publications overall. Picower Institute faculty research areas are summarized below.

Mark F. Bear's laboratory seeks to understand how experience modifies the brain. It has long been assumed that experience-dependent synaptic plasticity in the visual cortex is confined to a critical early postnatal period. Research by Bear's laboratory has forced a revision of this view. Using behavioral and electrophysiological approaches, his laboratory found remarkable plasticity in the visual cortex of adult rodents. For example, repeated presentations of visual stimuli greatly increased the cortical response to those stimuli, a phenomenon that closely resembles perceptual learning. Bear's laboratory went on to show that this increase was specifically due to the delivery of new neurotransmitter (glutamate) receptors to the stimulated synapses—providing the first significant insight into the molecular basis for perceptual learning. In a related study, the laboratory provided the first demonstration that learning induces long-term synaptic potentiation in the hippocampus. Additional experiments confirmed that the learning-induced enhancements partially occluded subsequent long-term potentiation (LTP) induction in vivo, indicating that the learning-related enhancements and LTP utilize a common expression mechanism. These data provide direct evidence that LTP-like synaptic strengthening occurs naturally in the hippocampus when new information is learned. This research was published in 2006 and selected as one of the ten breakthroughs of the year by the journal *Science*. Studies now under way are aimed at understanding the duration of these synaptic changes, whether their reversal erases memory, and the traces that accompany nonaversive memory formation. The laboratory continues to aggressively study fragile X, the most common form of mental retardation and a known genetic cause of autism, and has discovered that many aspects of fragile X can be corrected by reducing signaling through metabotropic glutamate receptors, a finding with significant therapeutic implications.

Yasunori Hayashi's laboratory builds understanding of how memory is formed at the molecular level by exploring connections among brain cells in the hippocampus, the memory-forming part of the brain. Using electrophysiology, optical imaging, and molecular biology techniques, the laboratory observes dynamics of individual proteins in single neuron-to-neuron connections. In ongoing efforts to elucidate the molecular mechanisms underlying synaptic function, they recently made several important advances. First, they found a mechanism whereby presynaptic release probability is subject to retrograde control. This mechanism is mediated by the complex formed between postsynaptic PSD-95-neuroligin and presynaptic neurexin. Second, the Hayashi laboratory discovered a mechanism by which the kinase CaMKII affects actin dynamics at the postsynaptic proteins. CaMKII has been considered a signal transduction molecule. However, the Hayashi laboratory presents evidence that it also serves as a structural element necessary to maintain the synaptic structure. This process is mediated by its ability to cross-bundle the cellular structural element actin. Third, they elucidated the atomic resolution structure of an important postsynaptic protein Homer. They found an atypical hybrid coiled-coil partly dimer and partly tetramer at the end of the protein.

Using the fruit fly as a model system, the laboratory of J. Troy Littleton studies the mechanisms by which neurons form synaptic connections, how synapses transmit information, and how synapses change during learning and memory. To complement this basic research in neuroscience, the laboratory also studies how alterations in neuronal signaling underlie several neurological diseases, including epilepsy and Huntington's disease. The Littleton laboratory combines molecular biology, protein biochemistry, electrophysiology, and imaging approaches with *Drosophila* genetics to address these questions. New synapse formation and synaptic rewiring are key elements of neuronal plasticity in the developing and adult brain. Similar to many species, modulation of synapse formation in *Drosophila* has been implicated in learning and memory. Synapse formation requires coordinated signaling to orchestrate pre- and postsynaptic maturation of synaptic connections. New research in the laboratory has characterized a novel synaptic signaling system that mediates short-term synaptic plasticity and long-term synaptic growth. This novel pathway requires postsynaptic targets to transmit retrograde signals through calcium-activated fusion of postsynaptic vesicles by synaptotagmin 4, a key calcium sensor for plasticity. After receiving postsynaptic signals, the synaptic connection undergoes several changes, including a short-term enhancement of spontaneous neurotransmitter release and a long-term proliferation of new synaptic connections. The laboratory has recently demonstrated that spontaneous release at synapses is regulated by complexin, a SNARE complex-binding protein. Analysis of complexin null mutants reveals a dramatic increase in spontaneous fusion and a profound overgrowth of synapses, suggesting that complexin functions as the fusion clamp in vivo and modulates structural remodeling of neuronal connections by controlling the rate of spontaneous release. Together, these studies are beginning to define the molecular mechanisms that the brain uses to mediate synaptic plasticity.

Carlos E. Lois's laboratory is interested in the assembly of neuronal circuits and the genetic control of brain development and function. The laboratory focuses on the process of neuron replacement in the brains of adult vertebrates and seeks to understand how new neurons are incorporated into the circuits of the adult brain and their possible

role in memory storage. The laboratory discovered recently that there are separate classes of stem cells committed to establish specific synaptic contacts in the brain, and is now studying the mechanisms by which these neurons connect with each other in the brain. In addition, the Lois laboratory is actively involved in developing technologies to genetically manipulate the development and function of neurons. Recently, the laboratory developed a transgenic technology based on enhancer trapping in which a viral vector integrates into the cell's genome and recapitulates the expression pattern of the endogenous gene that is near its integration site. Using this method, they have generated transgenic lines of mice that display gene expression in selective cell types in the brain. This method provides an immediate readout of the spatial pattern of gene expression with single cell resolution, and the transgenic mice carrying a particular enhancer probe can be used to regulate the expression of other genes of choice in a highly specific manner.

Earl K. Miller's laboratory is one of a few in the world studying the prefrontal cortex, home of the brain's high-level executive functions such as paying attention, recalling memories, categorizing objects, and piecing together the information it takes to achieve a complex goal and manage daily life. The laboratory links sophisticated behavioral studies with cutting-edge multiple electrode techniques for analyzing activity of neuron groups. The goal is to understand autism, schizophrenia, attention deficit disorder, obsessive-compulsive disorder, and other mental disorders. The Miller laboratory's studies have provided an understanding of how the prefrontal cortex and related brain areas, such as the basal ganglia, premotor, and association cortex, acquire knowledge about the high-level abstract categories, concepts, and rules needed to guide intelligent, goal-directed behavior. These findings have provided a foundation upon which to construct more detailed, mechanistic accounts of how executive control is implemented in the brain. In the past year, the Miller laboratory has made a number of discoveries, including some of the first direct evidence for differential sources of top-down and bottom-up signals in the cortex. They have also recently discovered that precise timing relations between single neuron activity and periodic oscillations of field potentials may encode information in the brain; specifically, the order of remembered sequences. These findings provide insights into the neural bases of a fundamental cognitive function and provide new insight into how information may be encoded in the brain.

Elly Nedivi's laboratory studies the cellular mechanisms underlying activity-dependent plasticity in the developing and adult brain through identification and characterization of the participating genes and the proteins they encode. This work began with the cloning of a large number of activity-regulate genes termed candidate plasticity genes (CPGs). The CPG pool is highly enriched for genes that are relevant to neuronal and synaptic function, and many CPGs are capable of modifying neuronal structure. To test whether CPGs play a role in structural plasticity of the mammalian brain we have collaborated with Dr. So's group in the Department of Mechanical Engineering at MIT to develop a multiphoton microscope for chronic in vivo imaging of neuronal morphology in the intact rodent cerebral cortex. We investigated dendritic arbor stability of neurons in the supragranular layers of the adult cortex over a period of several months, and found clear evidence of dendrite growth and remodeling in adult interneurons. However, the molecular mechanisms underlying such structural dynamics are

unknown. Cpg15 (neuritin) is an activity-regulated gene that is expressed in response to visual input and encodes a membrane-bound ligand that coordinately regulates growth of apposing dendritic and axonal arbors and the maturation of their synapses. Mice lacking cpg15 show decreased synaptogenic events and attenuated synaptic plasticity in adults. These synaptic changes result in reduced performance in learning tasks. To address whether cpg15 is a molecule involved in interneuron arbor dynamics and adult plasticity, we investigated the dendritic arbor stability of cortical interneurons in control and cpg15 knockout mice. We found that dendritic arbor remodeling is decreased in interneurons of cpg15 knockout mice compared to controls. This deficiency in structural dynamics is consistent with a lack of circuit remodeling in cpg15 knockouts, which results in poor learning efficiency. Our data is consistent with cpg15 acting as a regulator of dendritic arbor dynamics and suggests that the adaptive remodeling of interneuron circuitry is critical for efficient circuit function in the adult brain.

Morgan H. Sheng's laboratory is interested in the molecular mechanisms by which synapses in the brain change their strength and connectivity in response to experience. PSD-95 is a major postsynaptic scaffold protein that determines synaptic strength. The Sheng laboratory discovered that PSD-95 phosphorylation by JNK kinase determines synaptic localization and activity of PSD-95. Moreover, dephosphorylation of PSD-95 at this site is induced by NMDA receptor activation and required for long-term depression. This represents the first example of functional regulation of PSD-95 by phosphorylation during synaptic plasticity.

Mriganka Sur's laboratory studies mechanisms of development and plasticity in the cerebral cortex. This year, the laboratory made three key discoveries. Using high-resolution cellular imaging in an intact brain, the laboratory discovered the function of astrocytes in cortex. Astrocytes comprise the majority of brain cells; they receive neuronal inputs and are now found to regulate synaptic strength and hemodynamic responses enabling functional brain imaging. In a finding with enormous potential to treat brain disorders, the laboratory discovered a molecule offsetting a range of dysfunctions in a mouse model for Rett syndrome, an autism-related disorder. A third far-ranging discovery was demonstration that ten_m3, a molecule previously discovered by the laboratory through a gene-finding screen, has a crucial role in structural and functional alignment of projections from the two eyes to the brain. The same molecule is implicated in neurodevelopmental disorders with associated sensory deficits.

Susumu Tonegawa's laboratory seeks to understand the brain mechanism underlying memory and its disorders. Among the laboratory's major discoveries is identifying a protein and neuronal circuits in the hippocampus that prevent a memory from remaining at the "tip of the tongue," a common memory recall deficit pronounced by normal aging and by Alzheimer's disease. Tonegawa's laboratory combines the cutting-edge technologies of genetic engineering, electrophysiology, and behavioral methods. Using a genetic technology it developed, Tonegawa's research team created mouse strains in which one of about 30,000 mouse genes and the protein it creates is knocked out only in a particular type of neuron of a highly restricted part of the brain. By observing the physiological and behavioral deficits of these mice, the Tonegawa laboratory, in collaboration with Matthew A. Wilson's laboratory, discovered that a

single gene encoding a neurotransmitter receptor—the NMDA receptor in the tiny hippocampal area CA3—is critical for two major memory functions: the ability to rapidly form memories of episodes or events in day-to-day life and the ability to recall the details of the memory previously formed with scant information as recalling cues (a phenomenon called "pattern completion"). Most recently, using an analogous approach, Tonegawa's laboratory discovered that the NMDA receptor in another part of the hippocampus, called the dentate gyrus, plays a crucial role in the animal's ability to acquire similar events as distinct memories (a phenomenon called "pattern separation"). This discovery also provides an intriguing explanation for the phenomenon of deja vu and has been widely publicized in both professional journals and the popular press (for example, *Time* magazine). Also widely publicized is another recent discovery made in Tonegawa's laboratory that described a novel method to cure fragile X mental retardation and some forms of autism in a mouse model. In addition, Tonegawa's laboratory has recently invented a novel mouse genetic engineering technology that permits a blockade of neurotransmitter release from a specific population of brain cells. This technique allows scientists to investigate the function of a specific pathway of the brain network in behavior and cognition.

Li-Huei Tsai's laboratory uses a combination of molecular, cellular, and biochemical approaches to study Alzheimer's disease and psychiatric and developmental disorders. Tsai's laboratory developed an innovative mouse model exhibiting onset of Alzheimer's symptoms in a fraction of the time previously possible. Using this model, she explored novel therapeutic approaches to combat cognitive impairment as the consequence of neurodegeneration. Tsai and colleagues reported a remarkable recovery of long-term memories by housing the mice in an enriched environment or treating them with HDAC inhibitors that induce chromatin remodeling. In addition, Sirt1, a gene implicated in longevity, also proved protective against age-dependent neurodegeneration. She is also exploring the mechanism that leads to neurodegeneration in these mice.

Work in Matthew A. Wilson's laboratory continued to focus on the hippocampus's role and interactions with the neocortex during sleep and waking states in formation and maintenance of memory in mammalian nervous systems. Recent experiments found that memories of sequences of past events were replayed during slow-wave sleep in both the hippocampus and visual cortex, demonstrating that memory processing occurs in the neocortex during sleep and that dream states in animals are accompanied by visual imagery. These findings extended our understanding of the role of sleep in the process of learning and the establishment of long-term memories of experience. In a separate study, carried out in collaboration with Susumu Tonegawa's laboratory, ability to rapidly form distinct memories of similar events was found to be localized to a particular region of the hippocampus, providing insight into the precise mechanisms and brain circuits involved in forming unique memories of experience.

**Mark F. Bear**
**Director**
**Picower Professor of Neuroscience**

*More information about the Picower Institute for Learning and Memory can be found at http://web.mit.edu/picower/.*