Picower Institute for Learning and Memory

The primary mission of the Picower Institute for Learning and Memory (PILM) is to create a world-class focus for research and education in neuroscience. 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

Mark Bear was elected a fellow of the American College of Neuropsychopharmacology in 2005.

Troy Littleton received the Fred and Carole Middleton career development professorship from the School of Science.

Carlos Lois received the Ellison Foundation Young Investigator Award (2004–2008).

Morgan Sheng was elected a fellow of the American Association for the Advancement of Science in September 2004, as well as a fellow of the American Association for Arts and Sciences in 2005.

Susumu Tonegawa received an honorary degree from his alma mater, Kyoto University.

Ongoing Programs and Activities

The Picower Institute was founded on the premise that research collaboration among disciplines is an integral component of its neuroscience research philosophy. To facilitate these collaborative interactions, the institute plans a rigorous calendar throughout the year 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. Described below are ongoing programs and activities.

This year is year three of the second five-year agreement with the RIKEN Brain Science Institute. Currently there are five laboratories involved in the international collaboration—those of Susumu Tonegawa, Earl Miller, Matt Wilson, Yasunori Hayashi, and Morgan Sheng. Incoming faculty member Wolfram Schultz will join the program in the winter. Over the last 12 months, the RIKEN-MIT Neuroscience Research Center has focused on expanding the relationship between the Picower Institute and the RIKEN Brain Science Institute (BSI). We have increased the number of scientists from RIKEN BSI invited to the Annual Picower Retreat (please see below). In addition, the first annual Picower-RIKEN Workshop at MIT was hosted by the Picower Institute and consisted

of two concurrent sessions—one presented by RIKEN BSI personnel and the other by Picower Institute scientists. Organized by a committee consisting of Picower Institute postdocs and graduate students, the workshop topics were extremely relevant to current research, and the meeting was a great success, with each session drawing roughly a hundred participants. In response to our success, RIKEN is following our precedent and will be hosting a similar workshop this fall. In addition, more than 20 scientists from the Picower Institute have signed up to participate in this fall's RIKEN BSI Retreat, to be held in Japan in late October. Through cultivation and expansion of these programs, we will continue to improve Picower-RIKEN scientific research collaborations in the coming year.

Sponsored jointly by the Picower Institute and the RIKEN Brain Science Institute of Japan, the Picower-RIKEN Symposium brings together many of the most distinguished and creative neuroscientists from around the world to MIT to present their perspectives. This periodic symposium draws hundreds of participants interested in exploring the brain at every level of its complexity. The next symposium is scheduled for March 2006.

Held annually, the Picower Lecture was aptly named to honor and recognize the generous support of the Picower Foundation to the neurosciences at MIT. Each lecture features the work of a current leader in the area of brain research. The past year's lecture, given by David Anderson of the California Institute of Technology, was entitled "Neural Circuits for Innate Behaviors in Flies and Mice." This year's lecturer is Josh Sanes of Harvard University.

The bimonthly 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 Lamberto Maffei of Scuola Normale Superiore, Pisa, Italy; Dmitri Chklovskii of Cold Spring Harbor Laboratory; Istvan Mody of the University of California–Los Angeles; Rick Huganir of Johns Hopkins University School of Medicine; Ed Vogel of the University of Oregon; Randy O'Reilly of the University of Colorado–Boulder; Bai Lu of the National Institutes of Health; Nick Spitzer of the University of California–San Diego; Florian Engert of Harvard University; and Leslie Griffith of Brandeis 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 that give postdocs and graduate students from across the Picower Institute a chance to share their latest—often prepublished—research work with colleagues. The Plastic Lunch series 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 as well as collaborators from the RIKEN Brain Science Institute in Japan are invited to attend. During the retreat, Picower Institute faculty, postdocs, graduate students, staff, and collaborators present their

research findings. This year 155 researchers attended the two-day retreat held on Cape Cod, including 18 RIKEN scientists. The retreat included 19 research presentations and two highly interactive poster sessions, as well as a keynote address given by Dr. Richard Morris of the University of Edinburgh.

The Picower Institute Scientific Advisory Committee met October 14–15, 2004. This past year, Professor Robert Desimone stepped down from his post on the committee due to his taking over the directorship of the McGovern Institute. Since its inception, the rest of the membership has stayed the same and consists of Professor Richard Axel of Columbia University; Professor Cornelia Bargmann of Rockefeller University; Professor Hollis Cline of Cold Spring Harbor Laboratory; Professor Allison Doupe of the University of California–San Diego; 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.

New Programs and Activities

The following new initiatives were designed to complement successful ongoing activities and explore new opportunities.

On Depression is the inaugural conference in a new series entitled The Open Mind Series. Hosted by the Picower Institute and sponsored by CIGNA, the goal of the series is to explore the possibility that insights gained by Picower Institute neuroscientists studying learning and memory mechanisms in the brain might be usefully applied to problems of great societal importance. The program for September 19, 2005, brings together representatives from different communities—patients, clinicians, employers, as well as scientists and their sponsors in the government and the private and nonprofit sectors—to facilitate an exchange of ideas that might lead to better diagnosis, prevention, and treatment of depression. A second conference planned for the spring of 2006 will focus on drug addiction.

The first meeting of the Picower Advisory Council will take place on October 24, 2005. 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 faculty-led neuroscience research and education. The council is cochaired by Professor Susumu Tonegawa and the dean of the School of Science, Professor Robert Silbey. Other members are Provost Rafael Reif, Mrs. Barbara Picower, Mr. Jeffry Picower, Dr. Stephen Hochschuler, Professor Torsten Wiesel, and Professor Huda Zoghi. The council's recommendations will be presented in person to President Susan Hockfield at the close of the meeting.

New Building

Designed collaboratively by Charles Correa and Associates of Bombay, India, and Boston-based Goody, Clancy and Associates, the Picower Institute's new 125,000 sq ft research building will for the first time unite all the institute's laboratories under one roof. An additional 83,000 sq ft of facilities will be shared with other MIT brain science initiatives. An inaugural scientific symposium entitled The Future of the Brain will be held on December 1, 2005, to commemorate the occasion. The symposium will bring a roster of Nobel laureates and other esteemed colleagues and guests together to discuss

the future of neuroscience, the potential impact of learning and memory research on human health, and the relationship between the human brain and the mind.

Personnel

Two successful faculty searches were conducted this year and two new faculty members will join the Picower Institute in the coming academic year as full professors. Dr. Li-Huei Tsai has achieved national and international recognition in her field of research on the mammalian nervous system. Her work on Cdk5 has provided important insights into the critical roles played in the neuronal migration and development by protein phosphorylation. She also has uncovered molecular mechanisms that are likely to be important in offering therapeutic targets for devastating neurogenerative diseases—particularly Alzheimer's. Dr. Wolfram Schultz is a world leader on the neural mechanism for predictive reward, a subject highly relevant for learning. A search for an additional faculty member will be conducted in 2006.

Andrea Hatch, assistant director for administration, retired from MIT after 24 years of service at the end of January 2005. The position was filled in April by Judith Korch.

In February 2005, Edward Harvie was promoted to a financial assistant II.

There will soon be a search under way for a new Picower Institute development officer position.

Faculty Research Summaries

Mark Bear's laboratory seeks to understand how connections among brain cells in the hippocampus—the brain region critical for memory formation—and in the visual cortex are modified by signals from the outside world. The laboratory's recent discovery on how synapses are weakened promises to shed light on disorders such as mental retardation, autism, and Alzheimer's disease. By blocking a single brain chemical—a metabotropic glutamate receptor—many of the psychiatric and neurological disabilities associated with a leading cause of mental retardation could be treated. The Bear laboratory also discovered a key molecular mechanism underlying plasticity in the visual cortex, showing that the striking loss of vision in an eye temporarily deprived of normal vision during a critical postnatal period is a consequence of residual retinal afferent activity that fails to correlate with evoked postsynaptic responses in the visual cortex. The deprivation induces a series of events that cause the unused synapses to be eliminated. In addition, the laboratory discovered that when adult rats learn the association of a simple stimulus with a reward, the responses of a substantial fraction of visual cortical neurons evolve from those that relate solely to the physical attributes of the visual stimulus to those that accurately predict the timing of reward. In addition to revealing a remarkable type of response plasticity in adult V1, the data demonstrate that reward timing activity—a "higher" brain function—can occur very early in sensory processing paths (only two synapses from the retina).

Yasunori Hayashi's laboratory builds understanding of how memory is formed at the molecular level by exploring the connections among brain cells in the memory-forming part of the brain, the hippocampus. Using electrophysiology, optical imaging,

and molecular biology techniques, the laboratory observes the dynamics of individual proteins in single neuron-to-neuron connections. In their ongoing efforts to elucidate the molecular mechanisms underlying synaptic function, they have recently made several important advances. First, they have made progress in their understanding of the postsynaptic scaffolding protein Homer. Prior to their recent study, consensus held that Homer was a dimer; however, Hayashi laboratory structural analysis indicates that it is actually a parallel tetramer. Further structural analysis of Homer is ongoing. Second, the laboratory found a mechanism whereby presynaptic release probability is subject to retrograde control. This mechanism is mediated by the postsynaptic PSD-95-neuroligin complex. Third, the Hayashi laboratory discovered a mechanism by which the kinase CaMKII affects actin dynamics at the postsynaptic site.

Using the fruit fly *Drosophila* as a model, the Troy Littleton laboratory studies the alterations in neuron-to-neuron signaling and connections that underlie epilepsy, Huntington's disease, and other genetically complex disorders. The laboratory also studies how the connections among neurons change during learning and memory. The Littleton laboratory seeks to elucidate the molecular mechanisms underlying synapse formation, function, and plasticity by combining molecular biology, protein biochemistry, electrophysiology, and imaging approaches with genetics. New research in the laboratory has identified a novel mechanism by which synaptic connections communicate. Although communication from the presynaptic neuron via calcium-dependent synaptic vesicle fusion has been well characterized, the molecular mechanisms that allow postsynaptic targets to transmit retrograde signals are relatively unknown. The laboratory has recently discovered a novel retrograde signaling pathway that is required for synapse-specific potentiation and growth at *Drosophila* glutamatergic NMJs. Similar to the role of Synaptotagmin 1 as a presynaptic calcium sensor, the laboratory has identified an isoform of the family Synaptotagmin 4 that is present on postsynaptic vesicles. Mutational analysis of Synaptotagmin 4 indicates that it functions as a postsynaptic calcium sensor to release retrograde signals that enhance presynaptic release following high-frequency synaptic stimulation, as well as stimulating synaptic differentiation and growth. These findings indicate that retrograde signals released via calcium-stimulated postsynaptic vesicular fusion initiate an acute change in synaptic function that is converted to synapse-specific growth, providing a link between short-term synaptic plasticity and activity-dependent rewiring of neuronal connections.

Carlos Lois's laboratory investigates the process of neurogenesis—the surprising ability of certain animal species to grow new brain cells in adulthood and integrate them into existing brain circuits. The Lois laboratory uses genetic technologies to manipulate the migration of newly generated neurons through the brain and their incorporation into brain circuits. Research concentrates on two main aims: first, understanding the mechanisms that regulate the migration of new neurons into selective parts of the brain, and second, investigating the role of synaptic activity on the incorporation of newly generated neurons into functioning brain circuits. A long-term goal is to harness this regenerative ability to correct neurological defects from injury or disease. The laboratory has recently succeeded in redirecting the migration of newly generated cells into two areas of the mouse brain (striatum and neocortex) that never receive new neurons in physiological circumstances. In the next year they will focus their efforts on studying

the mechanisms utilized by these cells in their ectopic migrations and characterizing the neuronal types to which they give rise.

Earl 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 techniques for analyzing the activity of groups of neurons with the goal of understanding autism, schizophrenia, attention deficit disorder, obsessive-compulsive disorder, and others. The Miller laboratory's studies have provided insight into how the prefrontal cortex and related brain areas—such as the basal ganglia—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 key discoveries, including that more primitive brain regions may play a leading role in learning new behavioral-guiding rules than more advanced brain regions. They found that the more primitive basal ganglia show learning-related changes in neural activity faster and earlier than the more advanced prefrontal cortex but that improvements in behavior follow the slower changes in the prefrontal cortex. This suggests that learning may first occur in the basal ganglia, which in turn "train" the prefrontal cortex. Slower learning in the latter may allow it to gather a more judicious "big picture" of what is going on by taking into account more information.

Using molecular biology techniques, Elly Nedivi's laboratory pinpoints which of the brain's genes are involved in making memories and details how they work. This fundamental understanding may eventually help scientists design highly targeted drugs for disorders such as Alzheimer's disease. Nedivi's laboratory is working on characterizing *cpg15*, a gene isolated in a genetic screen that may play a role in synaptic plasticity. The gene encodes a small protein, CPG15, present in vertebrate species. The laboratory has shown that the soluble, secreted form of CPG15 is expressed in regions that are undergoing rapid proliferation and apoptosis in the embryonic brain. CPG15 is the first identified survival factor expressed by undifferentiated neurons, and it may provide a selective force for the protection of specific neuronal subpopulations during morphogenesis of the mammalian forebrain. In 2005, Elly Nedivi's laboratory identified a gene expressed only in brain areas responsible for high-level thinking and feeling. This gene may be key to the brain's ability to respond rapidly to new input and may one day allow researchers to manipulate the level or speed at which people learn new information. The Nedivi laboratory also found that CPG15 could potentially be used to develop therapies for renewing damaged or diseased tissue by manipulating stem cells in the adult brain.

Morgen Sheng's laboratory is interested in the molecular mechanisms by which synapses in the brain change their strength and connectivity in response to experience. The growth of neuronal dendrites and the formation of synapses is critical for development of brain circuits. During the past year, the Sheng laboratory uncovered the involvement of several proteins—the LAR receptor tyrosine phosphatase, the scaffold protein GRIP,

and the EphB receptor tyrosine kinases—in the growth and maturation of dendrites and synapses. Moreover, the subcellular distribution of mitochondria in dendrites was shown to be critical for synapse development and plasticity.

Mriganka Sur's laboratory studies mechanisms of development and plasticity in the cerebral cortex. In particular, the laboratory seeks to understand how patterns of electrical activity lead to functional changes in synapses and structural changes in neurons in the developing and adult visual cortex. Mechanisms of brain development lead naturally to the study of developmental disorders of the brain. The laboratory has started to examine the causes of autism by focusing on the genes and molecules responsible for the regional parcellation of the cerebral cortex into discrete processing areas and for synaptic plasticity in these areas; both of these features are implicated in autism and related disorders. Finally, in the past year, the laboratory has discovered key rules by which the brain is wired and functions. These include experimental demonstration of mathematical principles by which different kinds of maps coexist in visual cortex and principles of balance and homeostasis by which excitation and inhibition create novel response properties in cortical networks.

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 circuitry 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 Alzheimer's. Tonegawa's laboratory combines the cutting-edge technologies of genetic engineering, electrophysiology, and behavioral methods. Using a new genetic technology they developed, Tonegawa's research team created mouse strains in which only 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 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 a day-to-day life and 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 dentate cyrus—plays a crucial role in the animal's ability to acquire similar events as distinct memories (a phenomenon called "pattern separation"). Tonegawa's laboratory also knocked out a gene for the enzyme calcineurin only in the front part of the brain. This mouse strain displayed a number of behavioral deficits shared by human schizophrenia patients. Tonegawa and collaborators showed for the first time that variation in a human calcineurin gene is associated with schizophrenia. This is the first study that uses animals demonstrating an array of symptoms observed in schizophrenia patients to identify specific genes that predispose people to the disease. The work provides novel molecular targets for the development of new therapeutic and diagnostic methods for schizophrenia and possibly for related psychiatric diseases such as bipolar disease and autism.

Using techniques that make it possible to measure the responses and interactions of large groups of neurons, Matthew Wilson's laboratory is studying how memories of personal experience are formed and used. This effort has led to the study of sleep and the dreaming life of rats, yielding surprising insights into the relationship between dreams and memory. Wilson's laboratory, in collaboration with the Tonegawa laboratory, demonstrated for the first time the role of circuits within the hippocampal area CA3 in mice in the formation of memories of novel events. These findings have implications for the formation of human memories. The Wilson laboratory focuses on the role of the hippocampus and its interactions with the neocortex during sleep and waking states in the formation and maintenance of memory in the mammalian nervous system. In a study that increases understanding of the role of sleep in establishing long-term memories, the laboratory has demonstrated the replay of memories for sequences of events during slow-wave sleep. Recent experiments have also found that certain brain rhythms may serve to coordinate the functions of widely separated brain areas during memory-guided planning and decision making. This finding may lead to new methods of the diagnosis and treatment of a variety of neurological disorders, such as schizophrenia and autism, which may involve the disruption of communication between brain structures such as the hippocampus and prefrontal cortices.

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