The Picower Institute for Learning and Memory

The primary mission of the Picower Institute for Learning and Memory 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 research extends to other higher-order cognitive phenomena intimately associated with learning and memory, such as attention, decision-making, and consciousness.

New Building and Inauguration

The Picower Institute moved into its new 125,000-square-foot research space in fall 2005. The Picower Institute shares an additional 83,000 square feet of facilities in the brain and cognitive sciences complex with the Department of Brain and Cognitive Sciences and the McGovern Institute for Brain Research. An historic inaugural scientific symposium, entitled "The Future of the Brain," was held December 1, 2005, to commemorate the occasion. More than 600 people attended the symposium, which brought together a stellar roster of Nobel laureates and other esteemed colleagues and guests 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.

Awards

Mark Bear was awarded the William & Enid Rosen Research Award for outstanding contributions to our understanding of fragile X by The National Fragile X Foundation.

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

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

Earl Miller was elected a fellow of the American Association for the Advancement of Science and was elected to the International Neuropsychological Symposium.

Morgan Sheng was awarded the Fondation Ipsen 2006 Neuronal Plasticity Prize.

Mriganka Sur 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 Massachusetts Lowell.

Promotions and Personnel

Elly Nedivi was promoted to associate professor with tenure.

New faculty member Li-Huei Tsai joined the Picower Institute in May 2006. She has achieved national and international recognition in her field of research on the mammalian nervous system.

Two additional faculty member searches will be conducted starting in fall 2006.

A new human resources administrator, Suzette Clinton, was hired in March 2006.

A new administrative assistant I position in the Picower Institute's administrative headquarters was filled by Nayiri Arzoumanian in May 2006.

The search is under way for a Picower Institute development officer, and we expect the position to be filled during fall 2006.

Programs and Activities

The Picower Institute was founded on the premise that collaboration among disciplines is an integral component of its neuroscience research philosophy. To facilitate these collaborative interactions, the Picower Institute follows a rigorous calendar throughout the year of formal lectures, conferences and workshops, and 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 fourth 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 Miller, Matthew 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 the Picower Institute and RIKEN BSI. We have increased the number of scientists from RIKEN BSI invited to the Annual Picower Retreat (see below). In addition, the second 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. 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 will be hosting their second workshop this fall in Japan. Furthermore, 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 years.

Sponsored jointly by the Picower Institute 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 fifth annual Picower-RIKEN Neuroscience Symposium, New Frontiers in Brain Science: From Molecules to Mind, took place from March 26–28, 2006. More than 15 neuroscientists from around the world presented cutting-edge research discoveries in technology, learning and memory, plasticity, and systems neuroscience. More than 250 attendees participated in the research exchange.

Held annually, the Picower Lecture was named to honor and recognize the generous support of the Picower Foundation for 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 Professor Josh Sanes of Harvard University, was entitled "Analyzing Synapse Formation in Mutant and Fluorescent Mice." This year's lecturer is Professor Roger Nicoll of the University of California, San Francisco. His talk, "Glutamate Receptor Trafficking and Synaptic Plasticity," is scheduled for November 9, 2006.

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 Daniel Madison of Stanford University; Professor James Knierim of the University of Texas Medical School at Houston; Dr. Christopher Fiorillo of Stanford University; Professor Vivian Budnik of the University of Massachusetts Medical School; Professor Bernardo Sabatini of Harvard Medical School; Professor Elizabeth Quinlan of the University of Maryland; Professor Eric Gouaux of Columbia University; Professor Pamela England of the University of California, San Francisco; and Professor Kelsey Martin of the University of California Los Angeles.

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 with colleagues. The Plastic Lunch series provides an opportunity for postdocs and graduate students to improve their presentation skills and also fosters collaborations and builds new relationships across disciplines and between laboratories.

On Addiction, the second conference in the Open Mind Series, was held on May 8, 2006. The series is hosted by the Picower Institute and sponsored by CIGNA, and its goal 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 societal importance. The On Addiction program brought together representatives from different communities—clinicians and employers as well as scientists and their sponsors in the government, private, and nonprofit sectors—to facilitate an exchange of ideas that might lead to better diagnosis, prevention, and treatment of addiction.

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 G. [Chip] Quinn and Sebastian Seung of the Department of Brain and Cognitive Sciences), and collaborators from RIKEN BSI are invited to attend. During the retreat, Picower Institute faculty, postdocs, graduate students, staff, and collaborators present and discuss their research findings. This year, 155 researchers attended the two-day retreat held on Cape Cod, including 15 RIKEN scientists. The retreat included 16 research presentations, two highly interactive poster sessions, and a keynote address by Professor Cornelia Bargmann of Rockefeller University, who is also a member of the Picower Institute's external advisory committee.

The first meeting of the Picower Advisory Council took 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, Barbara Picower, Jeffry Picower, Dr. Stephen Hochschuler, Professor Torsten Wiesel of Rockefeller University, and Professor Huda Zoghbi of the Baylor College of Medicine. The second council meeting took place on May 1, 2006. At the end of each meeting, council recommendations are presented in person to President Susan Hockfield.

The Picower Institute Dean's Scientific Advisory Committee last met on October 14 and 15, 2004. The next meeting is scheduled to take place early in 2006. Committee members are Professor Richard Axel of Columbia University; Professor Cornelia Bargmann of Rockefeller University; 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.

Faculty Research Summaries

Mark 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. 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 the 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 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 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 site. CaMKII has been considered as a signal transduction molecule. However, the Hayashi laboratory presents evidence that it also serves as a structural element necessary for maintaining the synaptic structure. This process is mediated by its ability to cross bundle the cellular structural element actin.

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 neuromuscular junctions. Similar to the role of Synaptotagmin 1 as a presynaptic calcium sensor, the laboratory has identified an isoform of the family, Synaptotagmin 4, that functions as a postsynaptic calcium sensor to release retrograde signals that enhance presynaptic release and synaptic growth. The laboratory has also identified an important synaptic growth pathway present at synapses that is required for modulation of actin-dependent transduction of growth-promoting retrograde signals. Characterization of this presynaptic growth-promoting pathway will provide a clearer picture of how activity changes in neurons alter synaptic wiring in the brain, providing a mechanistic link between short-term synaptic plasticity and activity-dependent rewiring of neuronal connections.

Carlos 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 recently discovered that the time of birth of a class of neurons determines the kinds of contacts they establish in the brain. The laboratory now plans to focus on 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 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 the activity of groups of neurons. 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. The laboratory found that frontal cortex neurons "find" a target first during top-down (volitional) shifts of attention, and parietal cortex neurons find it first during bottom-up (automatic, stimulus-driven) shifts of attention. This finding suggests two different directions of flow for two fundamental types of neural signals. Further, the laboratory discovered evidence that communication between these areas may involve neural coherence that emphasizes different frequency bands, which suggests different "channels" for top-down and bottom-up signals. These findings provide insights into the neural circuitry of a fundamental cognitive function.

Elly Nedivi's laboratory studies the cellular mechanisms that underlie 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-regulated 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, the laboratory has collaborated with Peter 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. The laboratory investigated dendritic arbor stability of pyramidal and nonpyramidal neurons in the supragranular layers of the adult cortex over several months. For the first time, laboratory results showed unambiguous evidence of dendrite growth and remodeling in adult neurons. Neurons could be seen extending and retracting existing branches

and, in rare cases, adding new branch tips. Surprisingly, the neurons exhibiting dynamic arbor rearrangements were exclusively layer 2/3 nonpyramidal interneurons. Dendritic branches of layer 2/3 pyramidal cells and layer 1 nonpyramidal cells remained stable. These results are consistent with the idea that dendritic structural remodeling may be a substrate for adult plasticity and suggest that circuit rearrangement in the adult cortex is restricted by cell-type-specific rules.

Morgan Sheng's laboratory is interested in the molecular mechanisms by which synapses in the brain change their strength and connectivity in response to experience. Dendritic spines are specialized structures that house excitatory synapses; the growth and structural modification of dendritic spines are believed to mediate information storage in the brain. During the past year, the Sheng laboratory discovered that the phosphoinositide-3-kinase-mTOR signaling pathway and the molecular motor myosin II regulate spine morphogenesis and spine shape in neurons.

Mriganka Sur's laboratory studies mechanisms of development and plasticity in the cerebral cortex. In the past year, the laboratory used gene discovery methods and genomics analyses to discover the role of a novel molecular pathway in activity-dependent plasticity in the visual cortex. The laboratory used high-resolution imaging methods in vivo to discover subtle structural changes in synapses alongside functional rewiring of connections that accompany manipulations of activity. The group described novel dynamic changes in neuronal responses in the early visual cortex influenced by the internal state in alert, behaving animals. In a set of studies with tremendous potential for understanding and treating developmental disorders such as autism, the laboratory discovered the function of specific genes that have been linked to autism and mental retardation.

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 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 1 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 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"). Tonegawa's laboratory has recently invented a 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. The group focuses on a kinase (an enzyme that changes proteins) called Cdk5. Cdk5, paired with the protein p35, helps new neurons form and migrate to their correct positions during brain development, but Cdk5, paired with an aberrant form of p35 called p25, also is implicated in age-related neurodegenerative diseases. Tsai's laboratory has developed an innovative mouse model that exhibits the onset of Alzheimer's symptoms in a fraction of the time previously possible. She uses this and other techniques to zero in on the trigger of the cascade of events that leads to Alzheimer's disease.

Work in Matt Wilson's laboratory has continued to focus 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. Recent experiments have 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 diagnosis and treatment for 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. The laboratory has also extended its earlier work, which found that memories for sequences of past events were replayed during slow-wave sleep by demonstrating that rats that stop for food reward during wakefulness also replay recent event memory, but in reverse time order. This ability to evaluate memory sequences in forward and reverse time order, during both sleep and wakeful states, has extended our understanding of the role of sleep in the process of learning and the establishment of long-term memories of experience.

Susumu Tonegawa
Director
Picower Professor of Biology and Neuroscience

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