Picower Institute for Learning and Memory

The Picower Institute for Learning and Memory 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 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

Mark F. Bear was a special lecturer at the 2007 Society for Neuroscience Annual Meetings.

Yasunori Hayashi received the Japan Society for the Promotion of Science Prize for Young Investigators (2008). He also received the Japan Academy Medal for 2008.

J. Troy Littleton received the Distinguished Alumnus Award (2007) from the Baylor College of Medicine and was appointed to the National Institutes of Health study section for "Synapses, Cytoskeleton and Trafficking."

Carlos E. Lois received a fellowship from the David and Lucille Packard Foundation (2004–2009).

Earl K. Miller's paper, "An Integrative Theory of Prefrontal Cortex Function" (Miller and Cohen, 2001), was designated a current classic by Thomson Scientific as among the most cited papers in neuroscience and behavior (April 2008).

Mriganka Sur was a special lecturer at the 2007 Society for Neuroscience Annual Meetings. He also was elected to the Third World Academy of Sciences in 2007.

Li-Huei Tsai was inducted to the Academia Sinica, the national academy of the Republic of China (Taiwan) in the division of life sciences. She also was a special lecturer at the 2007 Society for Neuroscience Annual Meetings.

Research Breakthroughs

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

Mark F. Bear and colleagues corrected key symptoms of mental retardation and autism in mice, suggesting that a certain class of drugs could have the same effect in humans. In separate work that also looks at a key period in early brain development, the Bear laboratory found that anti-obesity drugs that work by blocking brain molecules similar to those in marijuana could interfere with neural development in young children

Studies emerging from the laboratory of J. Troy Littleton found that tiny, spontaneous releases of the brain's primary chemical messengers can be regulated, potentially giving scientists unprecedented control over how the brain is wired. The work could lead to a better understanding of neurological diseases such as schizophrenia.

Carlos E. Lois's laboratory found that stem cell therapies for the brain could be much more complicated than previously thought. The researchers reported that adult stem cells produced in the brain are preprogrammed to generate only certain kinds of connections—making it impossible for a neural stem cell originating in the brain to be transplanted to the spinal cord, for instance, to take over functions for damaged cells.

In his latest trio of studies on the structure and function of synapses, Morgan H. Sheng's laboratory found that the same protein that enables a yeast cell to bud into two daughter cells also helps neurons sprout the branchlike protrusions used to communicate with other neurons. The researchers also zeroed in on enzymes that manipulate a key scaffolding protein for synapses and reported that mice lacking a certain brain protein learn some tasks better but also forget faster. The work may explain the phenomenon of autistic savants in humans and could result in future treatments for autism and other brain development disorders.

Mriganka Sur's laboratory discovered that astrocytes, which compose the majority of cells in the brain, regulate synaptic strength and hemodynamic responses that enable functional brain imaging. The laboratory also identified the gene responsible for melding images from two eyes into one useful picture in the brain.

Susumu Tonegawa's laboratory created a way to see, for the first time, the effect of blocking and unblocking a single neural circuit in a living animal. The revolutionary method allowed researchers to see how bypassing a major memory-forming circuit in the brain affected learning and memory in mice.

Li-Huei Tsai's laboratory found that a group of enzymes known as sirtuins—famed for their reputed ability to slow the aging process—might be a bridge between aging and human neurodegenerative disorders. Tsai also uncovered a molecular mechanism that governs the formation of fears stemming from traumatic events, potentially leading to the first drug to treat the millions of adults who suffer each year from persistent, debilitating fears. In separate work, the Tsai laboratory explored a protein called CASK that helps synapses develop.

Personnel

In addition to 11 faculty members, the Picower Institute consists of other researchers, students, and technical and administrative support personnel. More than 250 community members participated in Picower Institute activities during the report period: 11 faculty members, 14 senior researchers, 7 visiting scientists/scholars, 67 postdoctorates, 45 graduate students, 34 undergraduates, 62 research and technical staff, and 17 administrative and service staff.

Items of note during the academic year included the following:

Mark F. Bear's appointment as director of the Picower Institute was extended until June 2010.

Two faculty searches were reopened: one for a molecular and systems neuroscientist (senior or junior) and one for a molecular and cellular neuroscientist (junior). Weifeng Xu, currently of Stanford University Medical School, accepted a junior faculty position at the Picower Institute (and the Department of Brain and Cognitive Sciences) beginning in January 2009.

Resource Development

The Picower Institute received $4 million from The Picower Foundation to support innovative faculty research. The annual Picower Institute retreat was endowed by a gift from the estate of Dana and Betty Fisher. A search for a senior resource development position was opened, and the position was filled.

Media Recognition

The Picower Institute issued 17 MIT press releases in the reporting period. Articles appeared in the following major print media: *Discover*, *Forbes*, *The New York Times*, *Newsweek*, *Popular Science*, *Pravda* (Russia), *Scientific American*, *Telegraph* (UK), *Time*, and *US News and World Report*. Picower Institute research breakthroughs were also broadcast on BBC News, CBS News, and MSNBC. Matthew A. Wilson was featured on *NOVA scienceNow* in July 2007 in an episode entitled "Why Do We Need Sleep." Li-Huei Tsai was also featured on *NOVA scienceNow* in a June 2008 episode entitled "Of Mice and Memory."

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.

A major symposium, entitled "Genes, Circuits and Behavior" was held May 6, 2008. The symposium brought distinguished neuroscientists from around the world to MIT to present their research and perspectives around the theme of genetic and optical circuit intervention technologies. These technologies are revolutionizing neuroscience by bridging the gap between molecular and cellular neurobiology and systems and behavioral science. Presenters included Professor David Anderson of the California Institute of Technology, Nobel laureate Richard Axel of Columbia University, Professor Cori Bargmann of the Rockefeller University, Professor Karl Deisseroth of Stanford University, Professor Fred Gage of the Salk Institute, Picower Institute faculty member

and Nobel laureate Professor Susumu Tonegawa, Picower Institute faculty member Professor Li-Huei Tsai, and Professor Huda Zoghbi of Baylor College of Medicine.

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 Alcino Silva of the University of California, Los Angeles, was entitled, "Unraveling Memory: Molecules, Cells and Circuits and the Havoc They Can Cause." This year's lecturer is Professor Hannah Monyer of the University of Heidelberg. Her talk is scheduled for December 11, 2008.

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 were Professor Karl Deisseroth of Stanford University; Professor David Sweatt of the University of Alabama, Birmingham; Professor Robert Knight of the University of California, Berkeley; Professor Rachael Wilson of Harvard Medical School; Professor Andreas Lüthi of the Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland; Professor Amy Arnsten of Yale University; Professor Rachael Wong of the University of Washington; Professor Peter Mombaerts of the Rockefeller University; Professor Catherine Woolley of Northwestern University; Professor Pietro De Camilli of the Howard Hughes Medical Institute; Professor Jan Born of the University of Lubeck, Germany; Professor David Fitzpatrick of Duke University; Professor Hey-Kyoeung Lee of the University of Maryland; Professor Frank LaFerla of the University of California, Irvine; and Professor Sacha Nelson 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 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. 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 year, after the close of the academic year, the Picower Institute hosts an annual retreat for its community members. The newly endowed Dana and Betty Fisher Retreat of the Picower Institute for Learning and Memory was held on May 27–28, 2008. More than 150 researchers attended the two-day event held on Cape Cod. The retreat included 6 laboratory research presentations, a highly interactive poster session (19 submissions), and a keynote address by Professor Robert Malenka of the Stanford University School of Medicine.

The Picower Advisory Council met on May 7, 2008. 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

Picower Institute director, Mark Bear, and the dean of the School of Science, Marc Kastner. Other members are Provost Rafael Reif, Mrs. Barbara Picower, Mr. Jeffry Picower, Dr. Stephen Hochschuler, Professor Torsten Wiesel of the Rockefeller University, Professor Huda Zoghbi of the Baylor College of Medicine, and new council members Professor Fred Gage of the Salk Institute, Professor Rick Huganir of the Johns Hopkins University School of Medicine, and Professor Robert Malenka of the Stanford University School of Medicine.

New Research Endeavors

The final year of the original 10-year agreement with the RIKEN Brain Science Institute in Japan was concluded in March 2008. A new agreement, starting in April 2008, created the RIKEN-MIT Center for Neural Circuit Genetics. Directed by Professor Susumu Tonegawa, the center seeks to fully understand the brain mechanisms underlying a specific cognitive phenomenon such as memory or emotion. Investigating not only the properties of individual cells, cellular clusters, and brain systems but also the functions generated by their communications is important for uncovering the fundamental mechanisms operating in the healthy brain and for understanding how these mechanisms go astray under disease conditions. The center will carry out truly interdisciplinary research by combining cutting-edge transgenic and viral vector techniques, in vivo multielectrode recording technology, optical and magnetic imaging techniques, and behavioral studies.

A new initiative this past year was the commitment to create a core facility that will develop genetically modified viruses that can be used to safely deliver genes to neurons. Viral gene delivery is a powerful adjunct to genetically modified mice for sophisticated manipulations of neuronal function. This technology is already in use in some Picower Institute laboratories to answer basic questions of how specific types of neurons contribute to brain function and behavior. The new "viral core facility" will allow all laboratories to take advantage of this approach without having to first become expert virologists—the same way we can now use drugs to manipulate neurons without having to first become medicinal chemists. Viral gene delivery will have as much or more impact on neuroscience research as the introduction of genetically engineered organisms. Using viruses to introduce into specific classes of neurons genes that make them uniquely sensitive to drugs has the potential not only to greatly advance understanding of the brain but also to provide new treatments in humans for neurological and psychiatric disorders. The viral core facility is scheduled to come online in fall 2008. It will be a resource for MIT's neuroscience community and available to others across MIT and beyond in the future.

Faculty Research Summaries

The scholarly excellence of the Picower Institute faculty is reflected in distinguished publication records. In the reporting period, Picower Institute faculty published eight articles in hallmark science journals (*Science*, *Neuron*, *Cell*, and *Nature*) and 39 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 glutamate receptors to the stimulated synapses—providing the first significant insight into the molecular basis for perceptual learning. In related work, the laboratory has provided the first demonstration that learning induces long-term synaptic potentiation in the hippocampus, confirming that learning-induced enhancements partially occluded subsequent long-term potentiation (LTP) in vivo and indicating that learning-induced enhancements and LTP utilize common expression mechanisms. These data provide direct evidence that LTP-like synaptic strengthening occurs naturally in the hippocampus when new information is learned. (This research was selected as one of the 10 breakthroughs of 2006 by the journal *Science*.) Continuing studies are aimed at tracking the duration of these synaptic changes and the effect of their reversal on memory. Other efforts in Bear's laboratory have made extensive use of awake in vivo recordings and two-photon imaging to document the time course of visual cortical plasticity induced by monocular deprivation (an initial deprived-eye depression is followed by potentiation of open-eye responses) and genetic methods to uncover the mechanisms at work in both the temporal and the laminar domain. The laboratory also continues to aggressively study fragile X syndrome (FXS), the most common form of mental retardation and a known genetic cause of autism. Work in Bear's laboratory has established that many aspects of FXS 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 the 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, using a structural biological approach, they found that a postsynaptic protein Homer, along with another protein Shank, forms a polymeric matrix, which is important for synaptic maintenance of various postsynaptic proteins as well as maintenance of synaptic structure. Second, using the state-of-the-art, two-photon photostimulation system, they showed that the delivery of postsynaptic protein after LTP induction happens in a sequential manner, causing a temporal disparity of protein composition in the synapse, which may explain the metaplasticity phenomenon, in which a newly potentiated synapse has a greater sensitivity to depotentiating stimulation than naive synapses.

J. Troy Littleton's laboratory studies the mechanisms by which neurons form synaptic connections, how synapses transmit information, and how synapses change during learning and memory. The laboratory also studies how alterations in neuronal signaling

underlie several neurological diseases, including epilepsy and Huntington's disease. During the past year, the laboratory has discovered an important regulatory pathway for neuronal communication controlled by the complexin protein. Modulation of complexin function can alter the output of presynaptic neurons and regulate the growth of new synaptic connections, potentially allowing targeted growth of specific neuronal pathways in the nervous system. New synapse formation and synaptic rewiring are key elements of 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. The laboratory has also characterized new mechanisms by which postsynaptic targets transmit retrograde signals through calcium-activated fusion of postsynaptic vesicles by synaptotagmin 4, a key calcium sensor for plasticity. Together, these studies are beginning to define the molecular mechanisms by which neuronal activity modifies synaptic connections.

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 vertebrate brain and seeks to understand how new neurons integrate into the circuits of the adult brain and their role in information processing and storage. To address these questions, the laboratory develops new technologies to genetically manipulate the development and biophysical properties of neurons. The laboratory recently developed a method to genetically manipulate the electrical activity of neurons in the brain to increase or decrease their excitability. With this method, it was found that new neurons generated in the brain of postnatal animals have a limited ability to regulate their synaptic activity when rendered hyperexcitable. This finding has important implications for the understanding of the pathological basis of epilepsy in humans. In addition, the Lois laboratory has discovered a new form of migration by which cells navigate through the adult brain. Using in vivo two-photon imaging the laboratory has found that immature neurons migrate long distances in the absence of any scaffold, following tortuous, nonlinear trajectories in a searchlike manner until they cease their migration and start establishing synaptic contacts. Finally, 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. Analysis of one of the transgenic lines generated has demonstrated that astrocytes are generated in columnar structures in the cortex. This finding has implications for the organization of the brain during development, as astrocytes are the most abundant cells in the mammalian brain, and they are involved in key physiological processes such as regulation of brain blood flow and formation of the blood-brain barrier.

The overarching goal of Earl K. Miller's laboratory is to build on what has been learned from classic single-electrode neurophysiology to understand cognitive functions in a broader context: as a product of interactions between different 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 the kind of sophisticated, flexible, rule-based behaviors at which humans and monkeys are so adept. In the past year, the Miller laboratory has made a number of discoveries. They have found that synchronization between the spiking activity of individual neurons and the oscillating activity of the neuron population may help encode the order of two objects held in working memory, as if different phases of the population oscillations provide different memory "slots" for the objects. The Miller laboratory also discovered the first direct neurophysiological evidence for a moving spotlight of attentional focus during searches of the visual environment. Further, the shifts in the attentional spotlight were synchronized with oscillations in population activity, suggesting a "clocking signal" that regulates attentional shifts. 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 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 Nedivi laboratory found the CPG pool highly enriched for genes relevant to neuronal and synaptic function, including many that are capable of modifying neuronal structure. Despite decades of evidence for functional plasticity of the adult brain, the existence and role of structural remodeling in circuit plasticity remains controversial. The Nedivi laboratory collaborated with Dr. 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. They 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. In mapping the location of remodeling interneurons by depth from the pial surface, the laboratory identified a "dynamic zone" where cells exhibit a dynamic index significantly higher than in regions above and below it. They then asked whether the difference had to do with the preponderance of a specific interneuron class in this domain, which would be consistent with remodeling being an intrinsic capacity of certain interneuron subtypes. On the basis of morphological cluster analysis, electrophysiology, and immunohistochemistry, they concluded that dynamic interneurons within the dynamic zone span a range of interneuron classes. The fact that the remodeling is not intrinsic to a specific interneuron class shows that the remodeling is not predetermined by genetic lineage, but rather it is imposed by the local circuit. To gain insight into the molecular mechanisms of adult structural plasticity, they are currently testing the role of CPGs in adult structural dynamics.

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. Proteins that concentrate in synapses and that control synapse structure and function

are emerging as strong candidates for causing human brain disorders ranging from autism to Alzheimer's disease. One family of synaptic proteins originally identified by the Sheng lab (the Shank family of scaffold proteins) has recently been genetically linked to autism. A genetically modified mouse made by the Sheng laboratory lacking one of the Shank family proteins has anatomical and behavioral phenotypes reminiscent of the autism spectrum disorder and may prove to be a useful mouse model of the human illness. In another study, a protein kinase (Plk2) was found to be induced by synaptic stimulation and to cause dismantling of synapses and depression of synaptic strength. This negative feedback mechanism, which was abolished if Plk2 function was disrupted, is probably important for the brain to maintain homeostatic balance. The Sheng laboratory discovered that, without Plk2, brain circuits become overactivated and saturated, potentially leading to epilepsy.

Mriganka Sur's laboratory uses cutting-edge technologies for imaging cells and molecules in the intact brain, combined with novel probes, to reveal mechanisms of cortical plasticity and discover the function of cortical cells and circuits. A major recent finding is that astrocytes—long thought to be support cells of the cortex—actually receive significant neuronal drive, have specific response properties, influence neuronal computations, and regulate blood flow into discrete regions of cortex. Astrocytes thus enable noninvasive brain imaging techniques such as functional magnetic resonance imaging and are strongly implicated in pathologies of brain function that affect local blood flow, such as Alzheimer's disease. Using high-resolution imaging in the intact brain, the laboratory demonstrated that structural changes in synapses are closely related to their function and state of plasticity. In a finding with significant implications for understanding developmental disorders of the brain, the laboratory discovered that a large number of genes expressed in the cerebral cortex switch their expression when activity is altered during a critical period of brain development. These genes thus lie at the intersection of "nurture," or the environment, and "nature," or a genetic scaffold, in wiring the brain and are crucial for explaining normal and abnormal neuronal circuits.

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 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 A. Wilson's laboratory, discovered that a single gene encoding a neurotransmitter receptor—the *N*-methyl-D-aspartate (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 déjà vu and has been widely publicized in both professional journals and the popular press (e.g., *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 type of brain cell. Applying this technique to the major pathway within the hippocampus (CA3 → CA1), Tonegawa's laboratory demonstrated that this hippocampal pathway plays a crucial role in a rapid acquisition of fear-associated memory but is dispensable for slow acquisition of spatial memory by repeated exposures. They also demonstrated that the consolidation of fear memory into a long-lasting form requires repeated activation of relevant CA1 neurons during slow-wave sleep. This genetic technology (dubbed DICE-K) promises to be powerful in the dissection of the functions of neural circuits—neural circuit genetics.

Li-Huei Tsai's laboratory uses a combination of molecular/cellular, genetic, and behavioral approaches to study Alzheimer's disease and psychiatric and developmental disorders. Tsai's laboratory developed an innovative mouse model exhibiting the 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 histone deacetylase (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 continues to focus on the hippocampus's role in the formation, maintenance, and use of memory in the mammalian nervous system during awake and sleep states. Recent experiments found rapid changes in neural firing patterns in the hippocampus during spatial-maze learning that revealed the strategy used by the hippocampus to encode novel events in familiar environments. They found that processing in the hippocampus reflects both memory of the past as well as anticipation of the future. This finding is consistent with recent evidence in humans that suggests that the hippocampus is involved in imagining future events. Current work seeks to characterize the detailed structure of brain activity as rats navigate and contemplate such mazes, and they have successfully demonstrated the ability to reconstruct the content of this activity, providing a potential window into the process of thought itself.

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/.