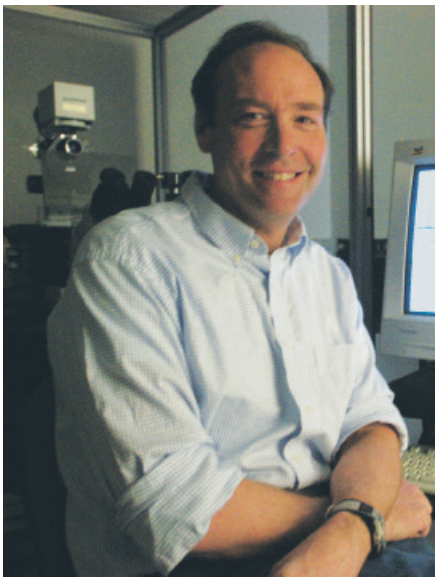
Neuroscience News

Winter 2009
Volume 3, Number 3

The Picower Institute
for learning and memory at MIT



Mark F. Bear, director of the Picower Institute for Learning and Memory, studies how the brain changes in response to experience. Photo/Donna Coveney

in this issue

Cover *Autistic boy spelling out "autism" with alphabet blocks. The latest research findings from the laboratory of Picower Institute researcher Mriganka Sur may lead to new drug targets and treatments for autism and Rett syndrome, the leading cause of mental retardation in girls. (See page 3.) Photo/Kevin Curtis, Science Photo Library*

from the director
mark f. bear

The Picower Institute for Learning and Memory at MIT is a permanent monument to the vision and generosity of Barbara and Jeffry Picower and The Picower Foundation. Thanks to their $50 million gift in 2002, our faculty, postdoctoral researchers, students and staff work in a state-of-the-art facility dedicated to understanding the brain, how it is modified by experience, and how it is disrupted by disease. Our research is at the cutting edge of neuroscience, exploiting the tools of molecular biology and genetics to dissect the precise contributions of brain circuits and molecules to behavior. This knowledge has already suggested novel therapies for psychiatric and neurological diseases—disorders that were thought to be intractable just a few years ago. We are extremely proud that our current and future scientific accomplishments will be a part of the legacy of Picower philanthropy.

It is difficult to find the words to describe my shock and disappointment in learning that The Picower Foundation was forced to close its doors as a consequence of the Bernard Madoff scandal. I have greatly admired the Picower's deep commitment to great societal causes, including the lessening of human suffering from diseases of the brain. We will be eternally grateful for all that the Picowers did to make our Institute the best of its kind in the world.

Looking forward, we clearly face some immediate challenges. As I have written before, we have the key elements in place at the Picower Institute to make scientific contributions of historic proportions: an energetic and collegial faculty, outstanding graduate and postdoctoral students, and wonderful scientific infrastructure. The missing piece was flexible research funding to support "blue sky" projects—projects that were perhaps too risky for traditional funding mechanisms, but that had the potential to have a huge impact. Therefore, I was delighted that The Picower Foundation had agreed to seed a Picower Institute Innovation Fund (PIIF) in 2008. This gift launched 10 new research projects, and led to the establishment of a facility that enables the use of genetically engineered viruses to deliver genes to neurons. Unfortunately, these projects are now at risk due to the loss of funding. A top priority is to raise money from new sources so that this exciting initiative can continue. I hasten to add, however, that I am pleased and proud to report that our faculty continue to compete successfully for grants from the government and private foundations, and that the core mission of the Picower Institute continues unabated. I have no doubts that we will weather this storm and emerge as strong and vibrant as ever.

Mark F. Bear, Ph.D.
Director


Above *Studies by Picower Institute postdoctoral fellows Daniela Tropea, left, and Damon Page led to new insights into Rett Syndrome and autism spectrum disorders. Tropea photo/Michelle Lahey; Page photo/ Travis Emery*

studies point to new treatments, understanding of two autism disorders

Researchers at MIT's Picower Institute for Learning and Memory and the Whitehead Institute for Biomedical Research have found that injecting Rett syndrome mice with a molecule that promotes brain development helped their faulty brain cells develop normally and reversed some of the disorder's symptoms.

In a separate study, by pinpointing two genes that cause autism-like symptoms in mice, Picower researchers showed for the first time that multiple, interacting genetic risk factors may influence the severity of autistic symptoms.

The work on Rett syndrome may lead to new human clinical trials for a derivative of growth factor-1 (IGF-1), currently used to treat growth disorders and control blood glucose. The MIT study indicates that IGF-1 could potentially lessen the severity of symptoms of Rett syndrome, the most common form of autism in girls.

"We demonstrate that a major underlying mechanism behind Rett syndrome in mice is that synapses in the brain remain immature and show persistent, abnormal plasticity into adulthood," said Daniela Tropea, a postdoctoral fellow at the Picower Institute and lead author of the study. "We also propose that a therapeutic based on this mechanism would be directly applicable to humans."

Injecting mice with a peptide fragment of IGF-1, used by the brain for neuronal and synaptic development, reverses a large number of symptoms in mice genetically engineered to display Rett syndrome-like symptoms.

"IGF-1 is critical for brain development. It activates molecules within neurons that make synapses mature," said study co-author Mriganka Sur, the Paul E. Newton Professor of Neuroscience at the Picower Institute and head of the MIT Department of Brain and Cognitive Sciences. "This is a mechanism-based therapeutic for Rett syndrome. It is possible that this or similar therapeutics would apply to other forms of autism, which also have as their basis a persistent immaturity of synapses."

Separately, the autism study led by Damon Page, Picower Institute postdoctoral fellow, lends support to researchers' long-suspected belief that, in individuals whose autism is genetic in origin, more that one gene is implicated.

The work could lead to drugs targeting signaling mechanisms between the two interacting genes responsible for some autism spectrum disorders (ASDs) symptoms. The molecular intersection of the two genes' pathways in the brain may also serve as a diagnostic target or biomarker for a subset of individuals with ASDs.

"We found that two genetic risk factors for ASDs act cooperatively in mice to influence brain size and social behavior, both of which are altered in ASDs," Page said.

Approximately 24 percent of humans with autism have macro-cephaly—head circumference above the 98th percentile—and increased brain size. Studies in ASDs patients have shown that brain size is correlated with the severity of behavioral problems.

"An important implication is that because the majority of instances of autism appear to involve multiple genes, specific gene combinations may worsen effects. New therapeutics may one day be developed that influence particular signaling mechanisms in the disorder," said Sur, co-author on both papers. ■

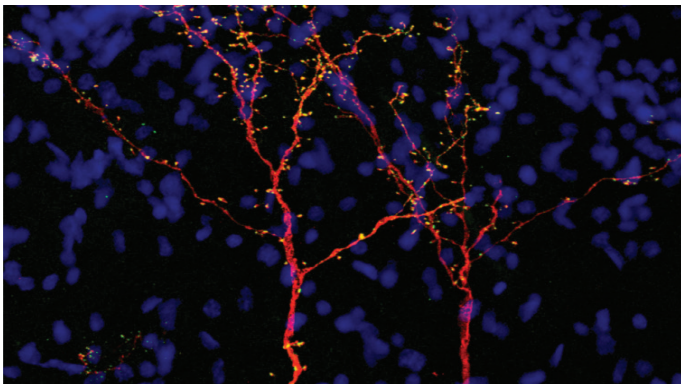
study sees challenges for integrating new neurons into the adult brain

Using adult stem cells to replace neurons lost because of brain damage and disease could be more difficult than previously thought, according to MIT researchers, because newly formed brain cells receive messages before they are capable of sending them.

The work, published in a recent issue of the Proceedings of the National Academy of Sciences, has implications on the treatment of conditions such as Alzheimer's and Parkinson's.

Scientists have long speculated that replacing neurons damaged by neurological disease, brain injury or spinal-cord trauma would be an efficient way to reverse the negative effects of those conditions. But Carlos E. Lois, of the Picower Institute for Learning and Memory, found that adding new neurons to existing circuits would be akin to trying to integrate a new memory card into a running computer.

"Most likely, the computer software will crash because of the sudden addition of a new part to the hardware," said Lois, who is also an assistant professor of neuroscience in the Departments of Brain and Cognitive Sciences and biology. While new parts can be added to an off-line computer, the brain can never be completely shut down. "The addition and elimination of connections of new neurons would be disruptive to the existing brain circuit," he said.



Above *The dendrite of a new neuron in the brain, labeled in red. The small yellow spots are synapses that the new neuron is receiving. Image/Carlos Lois*

In theory, newly created brain cells could be harvested and transplanted where they're needed to replace damaged cells.

New neurons grow from stem cells in only two small regions of the adult human brain: the olfactory bulb, involved in the sense of smell, and the hippocampus, involved in memory.

"Currently, there are two alternative strategies to replace lost neurons. The first one is based on redirecting the progeny of stem cells present in the brain to parts of the brain that have lost neurons," Lois said. "The second one utilizes stem cells grown outside of the body that are coaxed into becoming neurons and then grafted into the diseased areas of the brain."

Both of these strategies face a problem: When new neurons are incorporated into a brain circuit in an adult animal, they have to connect with pre-existing, working neurons.

However, the new neurons are immature and not ready to function, Lois said. They have to be "trained" by removing inappropriate connections and strengthening correct ones.

Further, once the new neuron does begin making output connections to other neurons, "it will be a noisy element," Lois said. "It will be communicating information to other neurons before [it] is appropriately tuned."

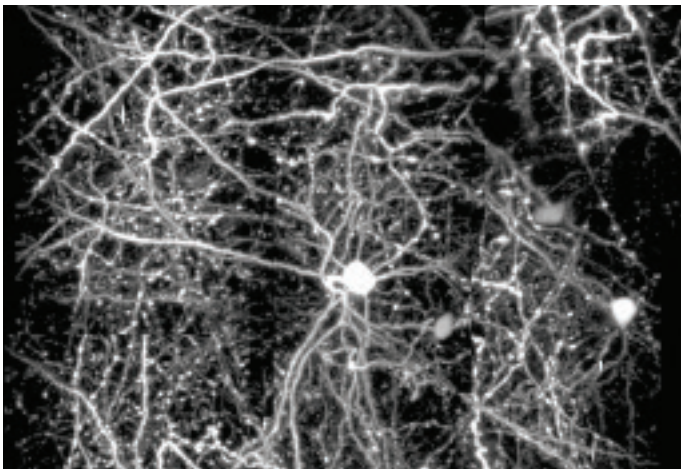
"Our results suggest that any attempts of neuronal replacement employing stem cells would likely need to address the issue of how the connections formed by new neurons will disrupt the function of old neurons during their training period," Lois said. ■

researchers identify cell type that remodels brain circuitry

Overturning a century of prevailing thought, scientists are finding that neurons in the adult brain can remodel their connections. In work reported in the Proceedings of the National Academy of Sciences, Elly Nedivi, associate professor of neurobiology at the Picower Institute for Learning and Memory, and researchers Wei Lee and Jerry Chen found that a type of neuron implicated in autism spectrum disorders remodels itself in a strip of brain tissue only as thick as four sheets of tissue paper at the upper border of cortical layer 2.

In a previous study, Nedivi and Peter So, professor of mechanical engineering and biological engineering at MIT, saw relatively large-scale changes in the length of dendrites—branched projections of nerve cells that conduct electrical stimulation to the cell body. Even more surprising was their finding that this growth was limited to specific type of cell. The majority of cortical neurons were stable, while the small fraction of locally connecting cells called interneurons underwent dynamic rearrangement.

In the current study, they show that the capacity of interneurons to remodel is not predetermined by genetic lineage, but imposed by the circuitry within the layers of the cortex itself. "Our findings suggest that the location of cells within the circuit and not pre-programming by genes determines their ability to remodel in the adult brain," Nedivi said. "If we can identify what aspect of this location allows growth in an otherwise stable brain, we can perhaps use it to coax growth in cells and regions that are normally unable to repair or adjust to a changing environment.



Above *Work by researcher Wei Lee and graduate student Jerry Chen sheds new light on the potential flexibility of cerebral cortex circuitry and architecture that contribute to perception and cognition. Image/Jerry Chen*

"Knowing that neurons are able to grow in the adult brain gives us a chance to enhance the process and explore under what conditions we can make it happen," Nedivi said. "In particular, we need to pay more attention to the unique interneuron population that retains special growth features into adulthood." ■

finding could lead to new alzheimer's treatments

In work that could lead to new drugs to target Alzheimer's disease, MIT researchers and colleagues have shed light on one of the molecular mysteries surrounding this common form of dementia.

The work, reported in Neuron, helps explain the perplexing behavior of some cells in the hippocampus, thought to be the center of learning and memory in the brain. In Alzheimer's disease, stroke and other neurodegenerative conditions, some neurons suddenly start to replicate their DNA as if they were about to divide. This causes them to die.

It is thought that most of the neurons within our brains have formed and exited the cell cycle during gestation and the early postnatal period. No one knows why this sudden reprisal of the cell cycle occurs in adult neurons in Alzheimer's patients. Now, researchers led by Li-Huei Tsai, Picower Professor of Neuroscience, are starting to understand the events that precede the death of the cells.

Tsai and colleagues found that these aberrant events occur when an enzyme called HDAC1, which configures chromatin, the structural component of chromosomes, is blocked.

Conversely, "increasing levels of this enzyme protects neurons from re-entering the cell cycle, losing genomic integrity and dying," said Tsai. "Our findings provide insight into how neurons die in neurodegenerative diseases and offer a new therapeutic strategy for countering neuronal death."

Tsai's finding that HDAC1 is a molecular link between aberrant cell-cycle activity and DNA damage means that the enzyme could be a potential target for therapeutics against diseases and conditions involving neuronal death. ■

2008 holiday party

The Picower Institute community, friends and family came together for food, entertainment and socializing at the 2008 holiday party, held Dec. 10 in the Building 46 atrium. Sponsored by the Picower Institute, the McGovern Institute for Brain Research and the MIT Brain and Cognitive Sciences Department. ■

Top *A clown entertains young guests. In the background are Elly Nedivi, left, associate professor with tenure, departments of Brain and Cognitive Sciences and Biology; and Suzette Clinton, Picower Institute human resources administrator.*

Bottom *From left, MIT President Susan Hockfield; Thomas Byrne of the Harvard-MIT Division of Health Sciences & Technology; Li-Huei Tsai, Picower Professor of Neuroscience; and Ki Ann Goosens, assistant professor, Department of Brain and Cognitive Sciences. Photos / Justin Knight*

tsai, sur named aaas fellows for "outstanding and distinguished" contributions

The American Association for the Advancement of Science (AAAS) has awarded the distinction of fellow to 486 members, including two members of the Picower Institute community.

Mriganka Sur, the Paul E. Newton Professor of Neuroscience and head of the Department of Brain and Cognitive Sciences, and Li-Huei Tsai, Picower Professor of Neuroscience and Howard Hughes Medical Institute investigator, were elevated to this rank because of their efforts toward advancing science applications that are deemed scientifically or socially distinguished.

They were presented with an official certificate and the society's gold and blue (representing science and engineering, respectively) rosette pin on Feb. 14 at the association's annual meeting in Chicago.

Sur was cited for "distinguished contributions to understanding the organization, development and plasticity of the cerebral cortex of the brain, and for leadership in neuroscience at MIT."

Tsai was cited for "outstanding contributions to the understanding of pathogenic mechanisms underlying Alzheimer's disease and the discovery of novel therapeutic approaches that attenuate learning and memory impairments." ■

picower lecture hosts hannah monyer

The 2008 Picower Lecture on Dec. 11 featured Dr. Hannah Monyer of the University of Heidelberg.

Monyer identifies genes involved in the generation of synchronous oscillation in neuronal networks and studies the role of NMDA receptor subtypes in different forms of plasticity. So far, her group has characterized molecular, functional and anatomical receptor expression in cell populations in the GABAergic network. Monyer's lab is also exploring the downstream cascades that occur after NMDA receptor overstimulation.

Monyer has a medical degree from University of Heidelberg, Germany, where she now leads a research group at the Center for Molecular Biology. Since 1999, she has been medical director of the Department of Clinical Neurobiology Heidelberg's University Hospital of Neurology. ■

Top Row: Mark F. Bear Picower Professor of Neuroscience, Howard Hughes Medical Institute (HHMI) Investigator, Department of Brain and Cognitive Sciences, Director of The Picower Institute for Learning and Memory; Yasunori Hayashi Assistant Professor of Neurobiology, RIKEN Investigator, Department of Brain and Cognitive Sciences; J. Troy Littleton Associate Professor, Departments of Biology and Brain and Cognitive Sciences; Carlos E. Lois Assistant Professor of Neuroscience, Departments of Brain and Cognitive Sciences and Biology; **Middle Row:** Earl K. Miller Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Associate Director of The Picower Institute for Learning and Memory; Elly Nedivi Associate Professor, Departments of Brain and Cognitive Sciences and Biology; Morgan H. Sheng Menicon Professor of Neuroscience, HHMI Investigator, Departments of Brain and Cognitive Sciences and Biology; Mriganka Sur Paul E. Newton Professor of Neuroscience, Head of the Department of Brain and Cognitive Sciences; **Bottom Row:** Susumu Tonegawa Picower Professor of Biology and Neuroscience, RIKEN-MIT Investigator, HHMI Investigator, Departments of Biology and Brain and Cognitive Sciences; Li-Huei Tsai Picower Professor of Neuroscience, HHMI Investigator, Department of Brain and Cognitive Sciences; Matthew A. Wilson Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Head, Department of Brain and Cognitive Sciences; Weifeng Xu Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences *Portraits/Betsy Cullen*

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For more information on our research or how to make a gift to the Picower Institute for Learning and Memory, please contact:

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