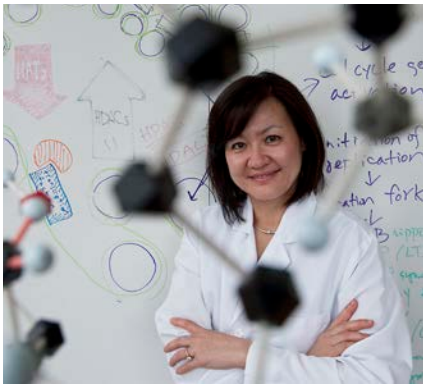
Neuroscience News

Summer 2013

THE P COWER INST TUTE
FOR LEARN NG AND MEMORY



Li-Huei Tsai

Director, Picower Institute for Learning and Memory

Photo / Len Rubenstein

FROM THE DIRECTOR
LI-HUEI TSAI

We wrapped up a busy academic year on a high note with the sixth annual Dana and Betty Fisher Retreat on May 30 and 31, 2013.

The retreat fosters opportunities to learn from each other and interact in ways not possible in our daily work lives in individual laboratories, thanks to a $1.2 million endowment from the Dana and Betty Fisher Foundation. Besides providing valuable practice for scientific meetings, these presentations introduce young researchers to those in other labs, and also stimulate ideas for cooperative projects.

I am grateful to the Fisher family for endowing the retreat and providing an opportunity for us to form new collaborations, because that is how we will find solutions to problems that are too complex for one-dimensional approaches. The idea of this retreat was born under the leadership of my predecessor, Mark Bear. Together, the institute and foundation envisioned a retreat where faculty, post-docs, graduate students, and staff present their research findings from the past year and build connections across the Institute's labs.

In fact, connections emerged as an informal theme at many levels. The two days were filled with stimulating conversations and fresh insights, as well with meeting new colleagues and renewing friendships. Keynote speaker Sebastian Seung, MIT professor of computational neuroscience, spoke about the telling structural connections in the retina that give neurons their directional selectivity.

In other talks, one student or postdoctoral fellow from each Picower Institute laboratory presented their latest findings and works in progress. The poster session displayed more thought-provoking projects from additional lab members, with a reception that allowed everyone to browse and chat. For the first time this year, we added a friendly competitive spirit with an award for best oral and poster presentations. The high quality of the polished reports made the decision difficult in both categories. An anonymous judging committee singled out Keigo Kohara (Susumu Tonegawa lab) for the top poster, which was announced after the clambake dinner and before the dancing in the beachside tent. The next day, at the lunch before people returned to their labs, Emily Osterweil (Mark Bear lab) learned she earned top honors for her talk that morning, as selected by a panel of faculty judges. You can read about all of the talks and the winning poster on the next three pages.

We were pleased to greet our newest junior faculty member at the retreat more than a month before his official start date. As a postdoctoral fellow at Stanford University, Kwanghun Chung invented a novel technology called CLARITY, which rapidly transforms intact brain tissue into an optically transparent structure while retaining molecular information.

I'm gratified to see the fresh discoveries and groundbreaking progress in understanding the brain and opening new avenues in neuroscience. The combination of science, sun and sea helps build a vibrant research community and inspires collaborations and ideas that we take back to our labs.

COVER:
Researchers attending presentation at the retreat
Credit: Azeddine Tahiri

DAY 1 PRESENTATIONS

Creating a False Memory

Xu Liu & Steve Ramirez - Tonegawa Lab

Eyewitness accounts are notoriously unreliable, because recent events can mingle in the hippocampus to form false but convincing memories. To investigate how memories are formed and recalled in mice, graduate student Steve Ramirez and postdoctoral fellow Xu Liu trained mice to respond to certain cues and surroundings. The researchers isolated one memory with optogenetics, using light-activated proteins to identify and turn on individual cells in the dentate gyrus of the hippocampus with millisecond precision and recreate the same memory. They followed up by linking the artificially activated memory with other cues. Mice appeared to experience the false memories as real, as measured by other brain activity and behavior. ●

Steps in Synapse Formation

Jai Subramanian - Nedivi Lab

Experience is the best teacher for brains to make and keep the right connections. In the mouse visual cortex, experience guides remodeling of synapses into adulthood. Using dynamic imaging of all the synaptic inputs of individual neurons, postdoctoral fellow Jai Subramanian is probing the role of a membrane protein called CPG15. Synapses form atop the tiny spiky protrusions called spines. Mice missing the protein grew about double the number of new spines as normal, but they faded away before recruiting a mature synapse molecule. The preliminary findings suggest a new step in the sequence: Nascent spines must be stabilized before synapses are established. The talk ended with a cliffhanger: Does CPG15 act as an experience detector? ●

Large-Scale Imaging of Working Memory

Michael Goard - Sur Lab

Working memory allows brains to temporarily store and manipulate information, which is essential to learn, reason, and even follow this thought to the end of the sentence. Unlike long-term memory, which relies on permanent modification of synapses, working memory is thought to involve sustained neural activity in distributed regions of the brain. To investigate the underlying mechanism, postdoctoral fellow Michael Goard has developed a technique to record thousands of single neurons at once, using two-photon calcium imaging in behaving mice. In animals meticulously trained to respond to a visual cue, Goard found that neurons in the parietal cortex, but not the visual cortex, show sustained activity during working memory delays of up to 6 seconds. He plans to use optogenetics to further explore working memory function. ●

Sleep-Like Activity Accompanies Awake Memory Replay

Hector Penagos & Gregory Hale - Wilson Lab

Slow brain waves are a defining feature of deep sleep. So postdoctoral fellow Hector Penagos and graduate student Gregory Hale were surprised to find the same sleeplike state transiently emanating from the retrosplenial cortex (RSC) in awake rats when the animals paused, as trained, in a navigation task for a unexpectedly large reward or new task. The cortex signals correlate with brief electrical "ripples" in the hippocampus that uncannily mirror the specific neural activity of past travels when the rats pause. The hippocampus also produces ripples during sleep. The distinctive sleeplike firing pattern in RSC cells may help it communicate with the hippocampus to process memory information, the researchers speculate. ●

KEYNOTE ADDRESS

Structural Clues: Direction Selectivity in the Retina

Keynote: Dr. Sebastian Seung,
MIT Professor of Computational Neuroscience

Sebastian Seung studies what the shape and location of neurons in the brain say about their connections and how the connection patterns reveal the function of neurons. His book, Connectome: How the Brain's Wiring Makes Us Who We Are, was just released in paperback and last year made the Wall Street Journal's Top Ten Nonfiction of 2012. Seung's group spent six years developing computer software to reproduce three-dimensional images of electron microscope scans of a mouse retina in order to accurately show the shapes and arrangement of the neurons. But computers cannot yet outperform humans in the crucial step of tracing the fine detail of dendritic branches. So he and his team recruited more than 70,000 research assistants around the world to help identify individual neuron projections by packaging the task in a competitive online game at Eyewire.org. Preliminary data about a newly discovered type of retinal ganglion cell, called the J cell, shows how interconnected starburst amacrine and bipolar cells influence its unique motion selectivity by the timing of excitatory and inhibitory signals. ●

DAY 2 PRESENTATIONS

Mending Fragile X

Emily Osterweil - Bear Lab, CONTEST WINNER

Stimulated synapses make proteins crucial for sustaining long-term connections in the brain, but in Fragile X syndrome, the leading single-gene cause of autism, synapses make too much protein. Postdoctoral fellow Emily Osterweil traced the protein synthesis

process and found a key signaling molecule in a pathway too important and widespread to target directly. She came up with an unconventional solution: A common cholesterol lowering drug, lovastatin, approved for use in children, acted upstream of the molecule to reduce protein synthesis and ease seizure symptoms in mice. The findings suggest a promising treatment strategy to test in children with Fragile X. ●

Enhanced Functional Connectivity with Category Learning

Evan Antzoulatos - Miller Lab

Two connected areas of the brain, the prefrontal cortex (PFC) and striatum form a network involved in learning, including how to group different experiences into useful categories, such as "food" and "mate." To better understand this network, postdoctoral fellow Evan Antzoulatos designed a task to compare electrical activity in monkeys during two kinds of learning, first memorizing individual stimulus-response associations and gradually advancing to abstract categories. Category learning seemed to strengthen specific one-way connections from the PFC to the striatum, but not within each area. Graduate student Roman Loonis is following up the surprising results by looking at more global coordination of local processing. ●

Neurogranin Modulates Long-Term Memory

Hongik Hwang - Xu Lab

In the hippocampus, the expression level of a brain-specific protein called neurogranin rapidly increases after some experiences, such as an enriched environment. In response to other stimuli, such as fear conditioning, neurogranin levels drop. Graduate student Hongik Hwang followed up on experiments reported at last year's retreat by postdoctoral fellow Kendrick Jones, who correlated neurogranin levels with changes in neuronal excitability. The overexpression of neurogranin enhances long-term potentiation (LTP), a lasting increase in synapse strength thought to underlie learning and memory, while knocking down neurogranin abolishes LTP in certain conditions, according to preliminary data. Next, Hwang will investigate how neurogranin levels affect the amount and kinetics of calcium influx through the synaptic spines. ●

Neural Encoding Dynamics in a Reward-Related Task

Edward H. Nieh - Tye Lab

The pleasure of eating ice cream comes from a reward circuit in the brain that is essential for survival and may be malfunctioning in cases of addiction or depression. One brain circuit implicated in the process of anticipating or predicting, consuming, and enjoying the reward involves lateral hypothalamic (LH) neurons that project to the dopamine-producing ventral tegmental area (VTA). In experiments that first cued and then sometimes rewarded mice, graduate student Edward Nieh, postdoctoral fellow Gillian Matthews, and their colleagues tracked the reward signaling through the circuit and discovered a feedback loop between the LH and VTA. The LH lets the VTA know about the possible reward, and the VTA sends positive reinforcement back to the LH upon consumption. ●

The Role Of DNA Methylation in Regulating Immediate Early Gene Expression and Behavior

Andrii Rudenko - Tsai Lab

In contextual memory, certain sights, sounds and smells may trigger a positive or negative reaction. A way that genes are switched on or off without altering the underlying DNA sequence may play a key role helping people re-learn associations, known as memory extinction. Postdoctoral fellow Andrii Rudenko looked at the role of a ten-eleven translocation protein (Tet1) in mice for its potential to reverse an epigenetic annotation known as called DNA methylation, which usually suppresses genes, sometimes in a lasting way known as hypermethylation. Rudenko and his collaborator, postdoctoral associate Meelad Dawlaty from the Rudolf Jaenisch lab at MIT's Whitehead Institute, discovered that Tet1 prevents hypermethylation of certain neuronal genes, keeping them poised to respond to extinction stimuli. ●

Imaging Individual Active Zones

Yulia Akbergenova - Littleton Lab

Many of the same molecules help make, strengthen and change the neuronal connections known as synapses in mammals and active zones in fruit flies. To investigate the details, postdoctoral fellow Yulia Akbergenova and graduate student Jan Melom modified an imaging tool so that it could detect neurotransmitter signals at the high resolution of individual post-synaptic active zones. The neurotransmitters are emitted in vesicles that were believed to release only when the nerves were stimulated, but the team found a significant population of active zones that discharged signals only when they were not stimulated, suggesting a new kind of information flow at synapses. ●

A Novel Memory Circuit In The Hippocampus

Keigo Kohara - Tonegawa Lab,
POSTER CONTEST WINNER

Can you recall something nice that happened yesterday? That memory may have been formed by newly discovered major neural circuits in the hippocampus. In the winning retreat poster, postdoctoral fellows Keigo Kohara and Michele Pignateli, with collaborators from RIKEN Brain Science Institute in Japan, combined Cre transgenics, optogenetics, patch-clamp recordings and immunohistology in mice to target specific cells and trace connections with higher precision than previously reported. ●

Day two of the retreat opened with Keigo Kohara (above right) accepting congratulation from Li-Huei Tsai for winning the poster contest and closed with Emily Osterweil (below right) receiving the presentation award from Matthew Wilson.

Li-Huei hands over prize to poster contest winner Keigo Kohara

Matt Wilson hands over prize to presentation contest winner Emily Osterweil

In The News

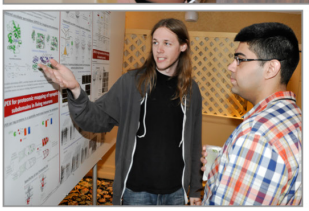
Picower Institute staff members were recently featured and recognized for their achievements in national and international media outlets and in social media:

- Dr. Kay Tye, was awarded a 2012-15 Whitehall Foundation Award Career Development award. She was also selected for a 2013 Klingenstein Fellowship Award in the Neurosciences for "Dissecting the Neural Circuits Underlying Anxiety."
- In July, Dr. Kwanghun Chung joined MIT as assistant professor of Chemical Engineering at the Institute for Medical Engineering and Science with a joint appointment within the Department of Brain and Cognitive Sciences at the Picower Institute for Learning and Memory.
- Nobel laureate Dr. Paul Greengard of The Rockefeller University delivered the Spring 2013 Picower Lecture, " Understanding the Molecular Basis of Major Depressive Disorder: A Work in Progress."
- Dr. Alik Widge, the second recipient of the Picower Clinical Fellowships in Neuroscience Program, will begin year one this summer. Dr. Michael Halassa will be going into year two. Funded by the JPB Foundation, the program was established in 2011 to enable clinical researchers and physician scientists to conduct research at the Picower Institute and help translate scientific findings into medical treatments and therapies for neurological disease.
- In its second year of funding from the JPB Foundation, the Picower Neurological Disorder Research Fund (PNDRF) enabled several labs to make progress in applied neuroscience, as witnessed by retreat talks from the labs of Dr. Li-Huei Tsai, Dr. Mark Bear and Dr. Kay Tye.

Researchers Attending the 6th Annual Dana & Betty Fisher Retreat of The Picower Institute



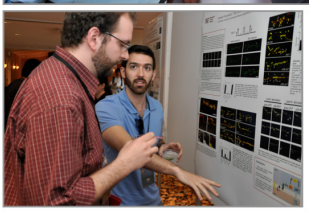


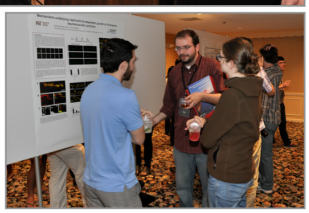










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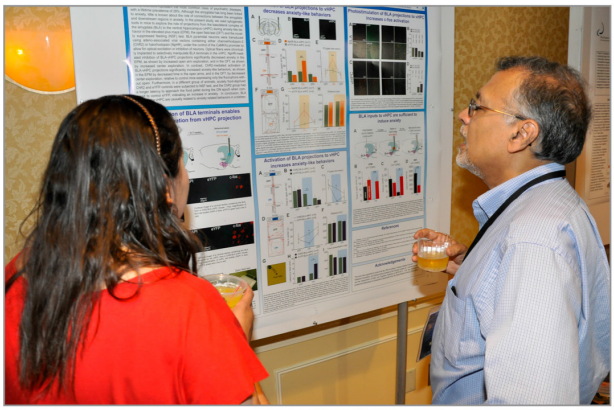















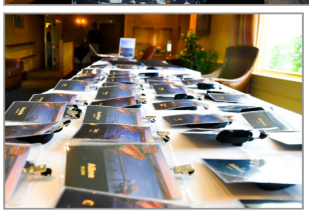

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TOP ROW: Mark F. Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); Kwanghun Chung, Assistant Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences. Myriam Heiman, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Broad Institute core member; Troy Littleton, Picower Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences.
MIDDLE ROW: Earl Miller, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; Elly Nedivi, Professor, Departments of Brain and Cognitive Sciences and Biology; Mriganka Sur, Paul E. Newton Professor of Neuroscience; Director of The Simons Center for the Social Brain; Susumu Tonegawa, Picower Professor of Biology and Neuroscience, Departments of Brain and Cognitive Sciences and Biology, Alumni Investigator, Howard Hughes Medical Institute, Alumni Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics.
BOTTOM ROW: Li-Huei Tsai, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory, Investigator, Howard Hughes Medical Institute. Kay Tye, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences, Matthew Wilson, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory; Weifeng Xu, Assistant Professor of Neuroscience, Department of Brain and Cognitive Sciences

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