INNOVATIONS +INVENTIONS

Picower faculty have helped to create many treatments, technologies, methods and models pg.6

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Neuroscience News

MIT FALL 2018

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

DIRECTOR'S **MESSAGE**

Dear Friend,

Like all academic scientists, our core mission is to discover and disseminate knowledge through research, teaching and publication. On pages 2-4 we feature several of the Institute's latest papers from the Littleton, Miller, Nedivi and Sur Labs.

But especially because neuroscience is no ordinary science, there are ways to make an impact beyond discovery. The central nervous system is uniquely intricate and dynamic across several orders of magnitude of space and time. Moreover, the consequences of this system are at least as challenging and consequential to study in that they span our consciousness, memories, behaviors, thoughts and feelings, as well as innumerable disorders.

These distinguishing frontiers in neuroscience provide us with additional opportunities to make lasting and meaningful contributions. Because we often ask new questions of this complex subject matter, we sometimes must invent tools, technologies and methods that did not exist before.

Meanwhile, when we observe and validate novel research results, we can recognize the new hope they may offer for mental health. Eager to make that difference in society, we work to translate our discoveries to the public via the clinic and the marketplace. Sometimes we even form new companies. On page 9, a panel of us discusses the experiences we've had with entrepreneurship.

In this issue we highlight a rich sampling of the "Innovations and Inventions" that Picower faculty members have helped to develop (see p. 6). We'll also celebrate innovation in the broader field with our Fall Symposium, "Frontiers in Neurotechnology," Oct. 23 (see p. 10).

Indeed science rarely advances in isolation. These Innovations and Inventions are collaborative by nature, for instance with mentors, colleagues, postdocs, or students.

I hope you enjoy learning about the many ways we've strived to advance science and society. Thank you for reading and being part of our community.

LI-HUEI TSAI, DIRECTOR
Picower Institute for Learning and Memory

Antidepressant Restores Plasticity in Aging Mice

A NEW STUDY PROVIDES EVIDENCE THAT the decline in the capacity of brain cells to change, called "plasticity," rather than in total cell number may underlie some of the sensory and cognitive declines associated with normal brain aging. Picower Institute scientists show that inhibitory interneurons in the visual cortex of mice remain just as abundant during aging, but their arbors become simplified and they become much less structurally dynamic and flexible.

In the *Journal of Neuroscience* study they also restored a significant degree of lost plasticity to the cells by treating mice with the commonly used antidepressant medication fluoxetine, also known as Prozac.

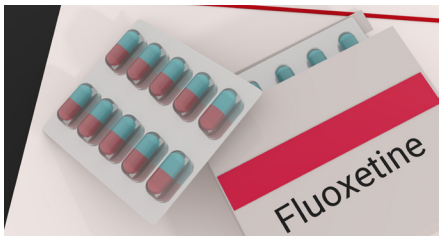
"Despite common belief, loss of neurons due to cell death is quite limited during normal aging and unlikely to account for age-related functional impairments," wrote the scientists, including lead author Ronen Eavri and corresponding author Elly Nedivi, professor of biology and brain and cognitive sciences. "Rather it seems that structural alterations in neuronal morphology and synaptic connections are features most consistently correlated with brain age, and may be considered as the potential physical basis for the age-related decline."

Nedivi and co-author Mark Bear, Picower Professor, are affiliated with MIT's Aging Brain Initiative, a multidisciplinary effort to understand how aging affects the brain and sometimes makes the brain vulnerable to disease.

In the study the researchers focused on the aging of inhibitory interneurons which is less well understood than that of excitatory neurons, but potentially more crucial to plasticity. Plasticity, in turn, is key to enabling learning and memory and in maintaining sensory acuity. In this study, while they focused on the visual cortex, the plasticity they measured is believed to be important elsewhere in the brain, as well.

■ In **J. Neurosci:**

Interneuron simplification and loss of structural plasticity as markers of aging-related functional decline, Aug. 14, 2018, http://bit.ly/nedivineuron



Where The Brain Transforms Seeing Into Acting

IN A NEW STUDY IN *NATURE COMMUNICATIONS*, a Picower Institute team reports that the posterior parietal cortex (PPC) plays an important role in converting vision into action.

"Vision in the service of action begins with the eyes, but then that information has to be transformed into motor commands," said senior author Mriganka Sur, Paul E. and Lilah Newton Professor of Neuroscience in the Department of Brain and Cognitive Sciences. "This is the place where that planning begins."

Sur said the study may help to explain a problem some people have after brain injury or stroke, called "hemispatial neglect." In such cases, people are not able to act upon objects on one side of their visual field. Some studies have implicated the PPC.

Former graduate student Gerald Pho and former postdoc Michael Goard led the research. The team trained mice that if they saw a striped pattern on the screen drift upward, they could lick a nozzle for a reward but if the stripes moved sideways, they should not lick, lest they get a bitter liquid. In some cases the nozzle wouldn't emerge, leaving them no reason to move in response.

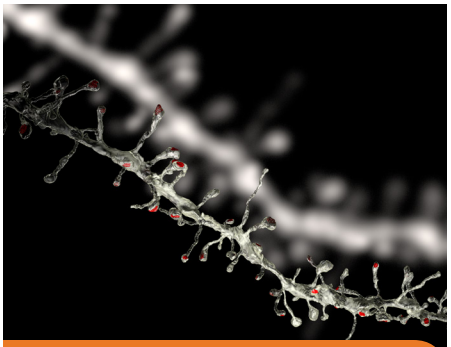
The researchers recorded the activity of hundreds of neurons in the visual cortex, and the PPC. Some PPC neurons responded simply to the visual input but most were active based on whether the pattern was moving the right way to prompt a lick and only if the nozzle emerged.

To gain further proof, the researchers switched the rules of the task. Now, the reward came with the sideways stripe pattern and the bitter liquid came when stripes moved up. The PPC response changed along with the rules. Neurons that had been activated selectively for licking upon the upward cue now responded instead to the sideways pattern.

■ In **Nature Comms.:**

Task-dependent representations of stimulus and choice in mouse parietal cortex, July 3, 2018, http://bit.ly/mrigankaPPC

Sur Lab Discovers Fundamental Rule of Brain Plasticity



A section of dendrite rendered with electron microscopy (foreground) and two-photon microscopy (background).

OUR BRAINS ARE "PLASTIC" BECAUSE NEURONS can do new things by forging new or stronger connections. But as these synapses strengthen, neurons must somehow compensate lest they become overwhelmed. In a study in *Science*, researchers at the Picower Institute showed how this balance is struck: when one synapse strengthens, immediately neighboring synapses weaken thanks to a protein called Arc.

"When one synapse goes up, within 50 micrometers there is a decrease in the strength of other synapses using a well-defined molecular mechanism," said senior author Mriganka Sur, Paul E. and Lilah Newton Professor of Neuroscience and the Department of Brain and Cognitive Sciences.

Sur said the rule helps explain how learning and memory might work at the individual neuron level because it shows how a neuron adjusts to the repeated simulation of another.

Postdocs Sami El-Boustani and Jacque Pak Kan Ip, invoked plasticity by changing a neuron's "receptive field," or the patch of the visual field it responds to. To do that, the scientists pinpointed the exact spine on the relevant dendrite of the neuron, and then monitored its synapses as they showed a mouse a target in a particular place on a screen that differed from the neuron's original receptive field. Whenever the target was in the new receptive field position they wanted to induce, they reinforced the neuron's response by stimulating it.

As the synapse for the new receptive field grew, the researchers could see under a two-photon microscope that nearby synapses also shrank. They did not observe these changes in experimental control neurons.

To see how neurons implement the rule, they used a chemical tag to watch how key "AMPA" receptors changed in the synapse. Synaptic enlargement and strengthening correlated with more AMPA receptor expression while shrinking and weakening correlated with less.

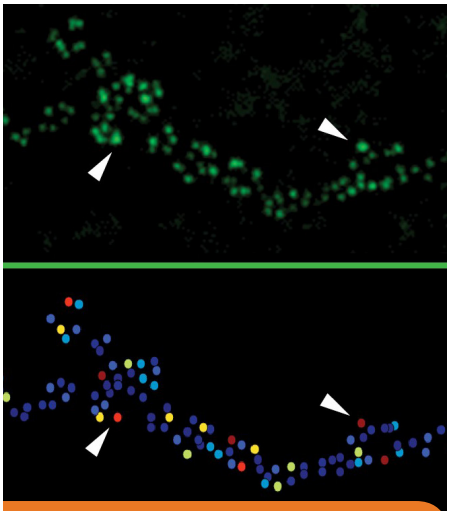
Arc regulates AMPA receptor expression, so the team sought to track Arc. To make that possible, co-authors at Kyoto University and the University of Tokyo invented a novel chemical tag.

The team saw that the strengthening synapses were surrounded with weakened synapses that had enriched Arc expression. Synapses with reduced amount of Arc were able to express more AMPA receptors whereas increased Arc in neighboring spines caused those synapses to express less AMPA receptors.

■ In **Science:**

Locally coordinated synaptic plasticity of visual cortex neurons in vivo, June 22, 2018, http://bit.ly/SurArc

Distinguishing Strong Synapses From Weak Ones



Calcium channels (labeled green at top) denote active zones along a fly neuron. Their brightness correlates well, for instance at white arrows, with higher synaptic strength (denoted by warmer colors at bottom).

FOR THE BRAIN TO BE ABLE TO LEARN AND adapt, it needs the connections, called synapses, to be able to strengthen or weaken. A new study by Picower Institute neuroscientists helps to explain why strong synapses are stronger, and how they get that way.

By pinpointing the properties of synaptic strength and how they develop, the study could help scientists make synapses weaker or stronger. Deficiencies in "synaptic plasticity" have a role in many brain diseases such as autism or intellectual disability, said senior author Troy Littleton, Menicon Professor of Neuroscience in MIT's Department of Biology.

In the study, published in *eLife*, Littleton's team used innovative imaging techniques in the model organism of the fruitfly *Drosophila* to focus on "active zones" in synapses.

Postdoctoral researcher Yulia Akbergenova and graduate student Karen Cunningham directly visualized the activity of 300 individual active zones with unprecedented resolution using "optical quantal imaging." Across many flies, the team consistently found that only about 10 percent of the active zones at the junction were strong, as indicated by the high probability they would release the neurotransmitter glutamate when the presynaptic neuron was stimulated. About 70 percent of the active zones were much weaker. Another 20 percent were inactive. The strongest active zones had release probabilities as much as 50 times greater than weak ones.

At strong synapses, active zones had a significantly greater influx of calcium ions through a notably higher abundance of calcium ion channels than weak synapse active zones did. Meanwhile, on the postsynaptic side, when the scientists measured glutamate receptor subtypes they found a dramatic difference at strong synapses. In the typical weak synapse, GluRIIA and GluRIIB containing receptors were mixed together. In strong synapses, the A subtype, which is more sensitive, crowded into the center while B was pushed out to the periphery.

The team also used "intravital imaging" to track how synaptic strength developed. By anesthetizing larvae each day they could check for changes. They saw synapses mature and found that strength was related to active zone age. They also found that active zones matured faster with more activity.

■ In **eLife:**

Characterization of developmental and molecular factors underlying release heterogeneity at Drosophila synapses, July 10, 2018, http://bit.ly/TroySynapse

As Brain Extracts Meaning From Vision, Study Tracks Process

CONSIDER A BANANA. A NEW STUDY THAT tracked how the brain turns sensory inputs, such as "green," into meaningful categories, such as "unripe," shows that the information follows a progression through many regions of the cortex, and not exactly in the way many neuroscientists would predict.

The Picower Institute-led study undermines the classic belief that separate cortical regions play distinct roles. Instead, as animals in the lab transformed sensation into cognition, brain cells in each of six cortical regions operated along a continuum between perception and categorization.

"The cortex is not modular," said Earl Miller, Picower Professor of Neuroscience in the Department of Brain and Cognitive Sciences at MIT. "Different parts of the cortex emphasize different things and do different types of processing, but it is more of a matter of emphasis. It's a blend and a transition from one to the other. This extends up to higher cognition."

The study in the *Proceedings of the National Academy of Sciences* could inform psychiatrists' understanding of disorders in which categorization judgements are atypical, such as schizophrenia and autism spectrum disorders.

Scott Brincat, a research scientist in Miller's lab, and Markus Siegel, principal investigator at the University of Tübingen in Germany, are the study's co-lead authors.

In the research, animals played games where they had to make categorical judgements after seeing visual cues. While they did, the researchers eavesdropped on the activity of hundreds of neurons in six regions across the cortex: prefrontal (PFC), posterior inferotemporal (PIT), lateral intraparietal (LIP), frontal eye fields (FEF), and visual areas MT and V4. The team analyzed the data, tracking each neuron's activity to determine how much it participated in sensory vs. categorical work, accounting for the possibility that many neurons might well do at least a little of both. First they refined their analysis in a computer simulation, and then applied it to the actual neural data.

Among their findings was that while sensory processing was largely occurring where classic neuroscience would predict, most heavily in the MT and V4, categorization was surprisingly distributed. As expected, the PFC led the way, but FEF, LIP and PIT often showed substantial categorization activity, too.

■ In **PNAS:**

Gradual progression from sensory to task-related processing in cerebral cortex, July 10, 2018, http://bit.ly/cortexblend

This Debate About Working Memory Must be Resolved

IN A DEBATE WHERE THE STAKES ARE NOTHING short of understanding how the brain maintains its "sketchpad of conscious thought," researchers argued over exactly what makes working memory work in dueling papers in the *Journal of Neuroscience*.

Working memory is how you hold things in mind like the list of specials at a restaurant. Working memory capacity is a strong correlate of intelligence and dysfunction is a major symptom in common psychiatric disorders such as schizophrenia and autism, so it's important to understand how it works, said Mikael Lundqvist, a Picower Institute postdoc and lead author of one of the papers.

"Working memory deficits are associated with virtually every major psychiatric disorder, but if we can figure out how working memory works, we can figure out how to fix it," added corresponding author and Picower Professor Earl Miller.

The opposing "Dual Perspectives" paper in the journal was led by Christos Constantinidis of the Wake Forest School of Medicine.

The central issue of the debate is what happens after you hear or see what you need to remember and must then hold or control it in mind to apply it later. During that interim, or "delay period," do neurons in your brain's prefrontal cortex maintain it by persistently firing away, like an idling car engine, or do they spike in brief but coordinated bursts to store and retrieve information via the patterns of their connections, akin to how longer-term memory works?

In their essay, Lundqvist, Miller and Pawel Herman of the KTH Royal Institute of Technology in Stockholm take the latter position. They argue that brief, coordinated bursts are clearly evident in the observations from the most recent experiments and that such activity can more satisfactorily produce key attributes of working memory, including efficient, independent control of multiple items with precise timing.

Earl Miller gives a recent talk on working memory. *Photo: Adrianne Mathiowetz*

"Storing information with a mixture of spiking and synapses gives the brain more flexibility," Lundqvist said. "It can juggle the activation of different memories, allowing the brain to hold multiple memories without them interfering with each other. This could explain how our working memory is not erased by things that temporarily distract us."

■ In **J. Neurosci:**

Working Memory: Delay Activity, Yes! Persistent Activity? Maybe Not, Aug. 8, 2018, http://bit.ly/nopersist

Building 46 Shares Science at Retreat

In Newport, RI, June 4-5, members of the Picower Institute joined colleagues from the McGovern Institute and the Department of Brain and Cognitive Sciences for an annual retreat. Three Picower researchers gave talks, and 13 others presented posters as part of the scientific program. Above, attendees from across the MIT neuroscience community gathered for a photo in the official event tee shirt. We extend many thanks to Wendy Fisher and siblings, whose 2008 gift in honor of their parents Dana and Betty Fisher helps to make Picower retreats possible.

PICOWER PEOPLE

To further advance his research harnessing synaptic plasticity to promote recovery from amblyopia, commonly known as "lazy eye," **Mark Bear** has earned the 2018 Beckman-Argyros Vision Research Award. Presented annually, the award recognizes an individual who has made and is continuing to make significant, transformative breakthroughs in vision research; particularly through the development of an innovative technology or fundamental scientific breakthrough that has been applied to, aided and/or improved the vision sciences. Bear and MIT will receive $100,000 and $400,000, respectively from the Arnold and Mabel Beckman Foundation. In work spanning several decades, Bear's laboratory discovered many of the fundamental principles and mechanisms of synaptic plasticity in the cerebral cortex, which is the way the brain adjusts to sensory experience or deprivation. Through this research, they uncovered the synaptic basis of amblyopia, a severe visual impairment caused by poor quality vision during infancy and early childhood. "It's an honor to be able to recognize Dr. Bear for his exceptional work in understanding the neural effects of sensory deprivation," explained Anne Hultgren, the Beckman Foundation's Executive Director. "Dr. Bear's work is an excellent example of how fundamental discoveries can directly lead to novel treatment possibilities for patients with conditions once thought incurable."

On Sept. 7, The Florida Inventors Hall of Fame honored **Emery Brown**, formally inducting him into its membership. A practicing anesthesiologist at Massachusetts General Hospital, Brown is also a noted statistician and a member of the faculty of both the Picower Institute and Harvard Medical School. Born and raised in Ocala, FL, he holds three U.S. patents and has made major contributions to the neuroscience of anesthesiology and to methods of statistical analysis. The Hall of Fame is located at the University of South Florida in Tampa.

In July the MIT School of Science recognized **Steven Flavell** by naming him the Lister Brothers Career Development Professor, making him one of eight professors across the school to be so honored. The Flavell lab's long-term goal is to understand how neural circuits generate sustained behavioral states, and how physiological and environmental information is integrated into these circuits. They study the model of C. elegans worms to examine how neuromodulators coordinate activity in an entire nervous system.

Recognizing his potential both as a scientist and a role model, the Howard Hughes Medical Institute has awarded Tsai Lab postdoc **Matheus Victor** a Hanna H. Gray fellowship, which will support his career for the next eight years, including when he launches his own lab someday. The award is designed to sutain accomplished life scientists from underrepresented backgrounds who can become leaders in academic research and inspire future generations to see that science could be for them, too. Victor emigrated to the U.S. from Brazil when he was 15 and performed extensive outreach to Latino students as a graduate student at Washington University in St. Louis. Now at MIT, Victor will study the role of specific cell types in brain aging and cognitive decline.

PICOWER FACULTY

INNOVATIONS +INVENTIONS

Aim to Enhance Life, Advance Science

"The nervous system is vast, diverse and dynamic, and so to make progress in our research we are determined to create capabilities that didn't exist before."

LI-HUEI TSAI

During their careers Picower faculty members haven't just applied the latest technologies to make discoveries, they have helped to create them. Groundbreaking and entrepreneurial, as well as analytical and rigorous, they often see new ways of approaching problems, such as mental illness, and bringing these novel ideas to the clinic, the community and the marketplace.

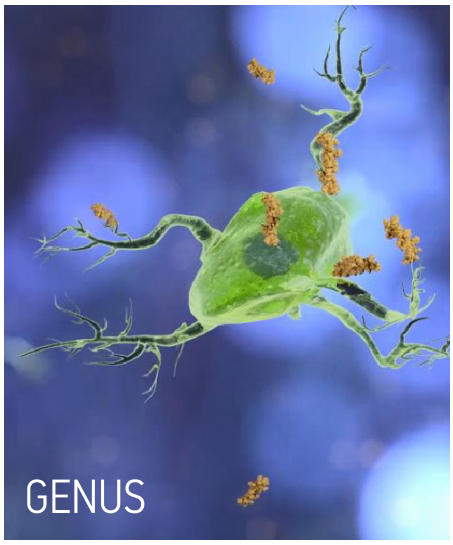
"The nervous system is vast, diverse and dynamic, and so to make progress in our research we are determined to create capabilities that didn't exist before," said Institute director Li-Huei Tsai, Picower Professor of Neuroscience. "Moreover, we know that our work has the potential to make a difference outside the lab. When we find a new way to help people, we strive to see that through."

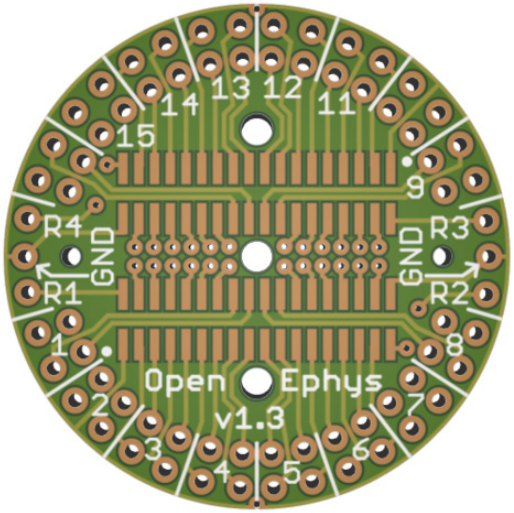
On October 23 the Institute will mark the importance of pioneering new tools for brain science research by convening the daylong symposium "Frontiers in Neurotechnology," organized by Kwanghun Chung, assistant professor of chemical engineering and neuroscience (See page 10).

Read on for many (though by no means all) examples of the potential treatments, new technologies, unique research models, startup companies and organizations, and other innovations that Picower faculty have helped to introduce over the years, working with collaborators ranging from their mentors early on to the postdocs and students they mentor today. To learn more, visit our new web gallery (http://picower.mit.edu/research/innovations-inventions).

TO ENHANCE LIFE

Gamma brain rhythms around 40Hz are notably reduced in Alzheimer's patients. The labs of Li-Huei Tsai, Emery Brown and Ed Boyden teamed up to create **GENUS**, or Gamma ENtrainment Using Sensory stimuli. Using blinking light or sound pulses, it non-invasively instills gamma waves to restore the rhythm. Human trials are underway to determine if several beneficial effects seen in mice carry through.





Tsai's lab was the first to show that memory deficits in mice could be rescued using deacetylase **HDAC2 inhibitors**, which affect chromatin structure to regulate the expression of neuronal genes supporting synaptic plasticity, learning, and memory. The protein Sp3 works with HDAC2 and she's shown that deactivating Sp3 in Alzheimer's-model mice also helped restore memory.

Years of basic research on genes involved in synaptic plasticity led Mriganka Sur's lab to discover that mutations in the gene MECP2 lead to immature synapses in Rett Syndrome, an autism-like condition that typically affects girls. The team showed that the molecule **IGF1** has strong therapeutic potential to remedy the deficit. An IGF1 therapy is in a phase III trial, and might also treat Fragile X syndrome.

Anesthesiologists monitor blood pressure, heart rate, and movement, but general anesthesia principally affects the brain. Emery Brown studies those mechanisms and the hallmark EEG (brainwave) patterns the anesthetized brain exhibits. His lab has developed technology for anesthesiologists to monitor the EEGs to keep patients anesthetized with much lower doses. He founded **http://www.anesthesiaeeg.com** to help colleagues learn how neuroscience can improve anesthesiology.

General anesthesia takes a while to wear off, resulting in prolonged grogginess for recovering patients, and the need for recovery room staff and beds to remain occupied. In 2011 Brown and colleagues published in *Anesthesiology* that mammals could be quickly and lucidly revived with the stimulant Ritalin, a process he calls **"reanimation."** The finding has opened the door to actively bringing patients out of general anesthesia.

Amblyopia is a visual impairment caused by an imbalance in the inputs to the brain from the two eyes during infancy and early childhood. Mark Bear's lab has shown how altered visual experience weakens synapses in the visual cortex, and more recently has shown that vision can be restored in animal models if the **visual system is "re-booted"** by temporarily anesthetizing the retinas using a blowfish toxin called TTX.

Fragile X syndrome is caused by the silencing of the *FMR1* gene. After Bear's lab (at Brown University at the time) discovered that the gene's protein FMRP regulates glutamate receptors and constrains protein synthesis at synapses, he realized that drugs inhibiting excess glutamate signaling, including **Arbaclofen**, could help patients. The approach reached stage III clinical trials. New studies continue to show promise.

In 2009 Earl Miller's lab discovered that cognitive capacity – your ability to consciously perceive – varies around the visual field and is different for each person. Since then he's co-founded the company **SplitSage**, which has patented a process to assess that for applications such as heads up vehicle displays, sports and military training and medical diagnostics.

Distinct, competing clusters of neurons in the amygdala associate episodic memories with rewarding or aversive feelings. In studies between 2014 and 2017 led by former graduate student Joshua Kim, Susumu Tonegawa's lab identified the neurons' unique genetic markers and boosted mouse mood by **suppressing negative circuits or activating positive circuits** with optogenetics, an innovative proof of concept for future anxiety and depression therapies.

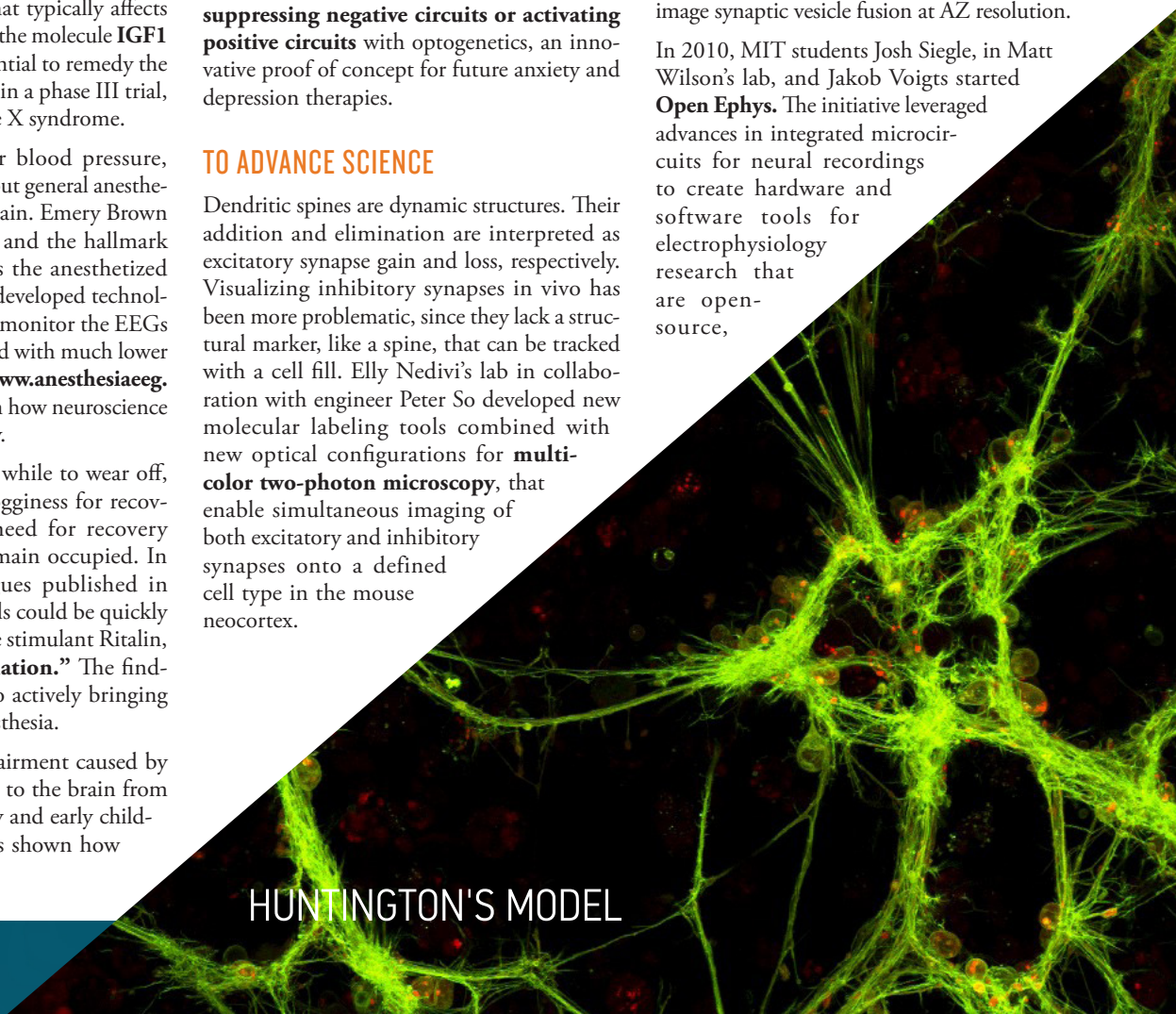
TO ADVANCE SCIENCE

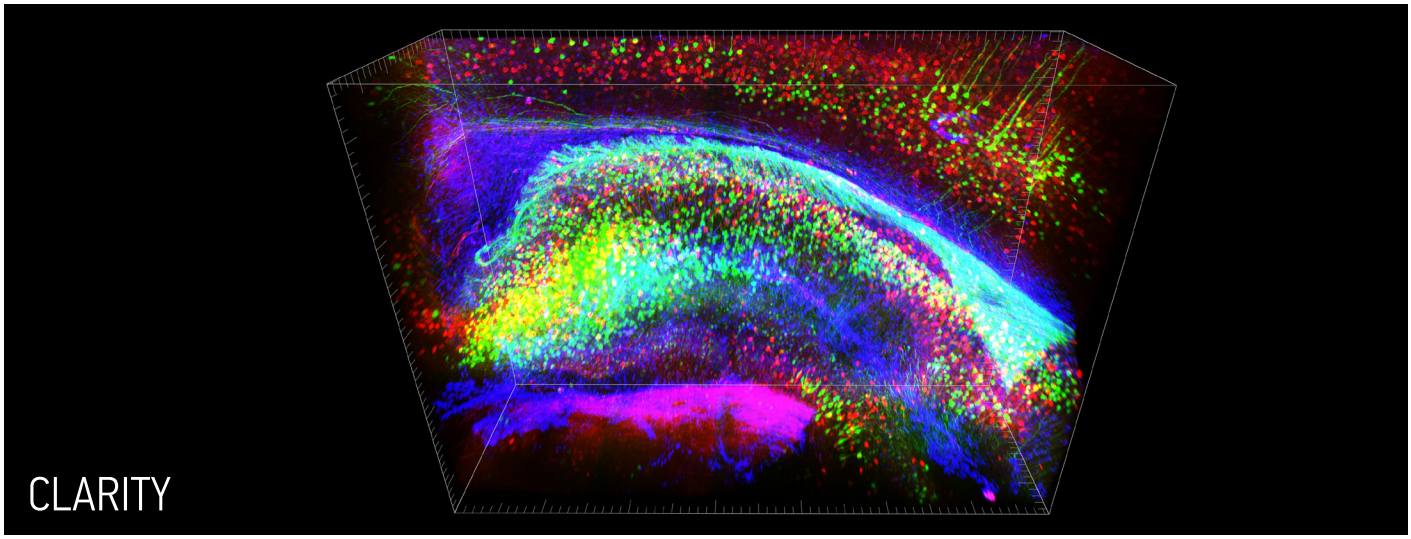
Dendritic spines are dynamic structures. Their addition and elimination are interpreted as excitatory synapse gain and loss, respectively. Visualizing inhibitory synapses in vivo has been more problematic, since they lack a structural marker, like a spine, that can be tracked with a cell fill. Elly Nedivi's lab in collaboration with engineer Peter So developed new molecular labeling tools combined with new optical configurations for **multicolor two-photon microscopy**, that enable simultaneous imaging of both excitatory and inhibitory synapses onto a defined cell type in the mouse neocortex.

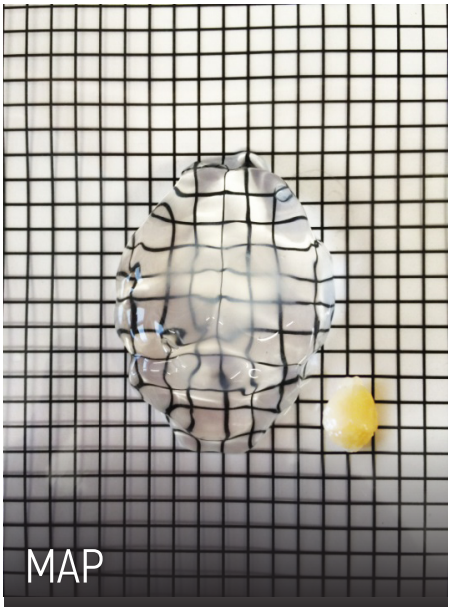
In Huntington's disease, mutation of the *huntingtin* gene leads to a runaway aggregation of the protein. Troy Littleton's lab's engineered a fruit fly that produces the mutant protein attached to a genetically encoded fluorescent protein so that aggregation can be visually tracked in live animals. Former postdocs Katharine Sepp and Joost Shulte formed startup **Oxalys** based on drug discovery using the innovation.

Synapses release neurotransmitters at active zones (AZs). Littleton's lab has generated new genetically encoded sensors to monitor the activity of hundreds of AZs at a time in fruit flies using **Optical Quantal Imaging** (see p. 3). By tethering a fluorescing calcium sensor to a postsynaptic membrane across from AZs, the team led by former graduate student Jan Melom and current research scientist Yulia Akbergenova can image synaptic vesicle fusion at AZ resolution.

In 2010, MIT students Josh Siegle, in Matt Wilson's lab, and Jakob Voigts started **Open Ephys.** The initiative leveraged advances in integrated microcircuits for neural recordings to create hardware and software tools for electrophysiology research that are open-source,







thoroughly documented, field-tested, and affordable. Siegle and Wilson published the first paper using an Open Ephys system in *eLife* in 2014. Since then the system has been used in hundreds of labs around the world.

Kwanghun Chung amazed much of the neuroscience world and even the press in 2013 when he and Stanford colleagues unveiled **CLARITY**, a tissue processing technique that makes tissue transparent, but preserves the structures and molecules within, which can then be labeled. This allows for 3D imaging and phenotyping of the brain like never before.

Chung' lab at Picower soon followed with **SWITCH,** a technique that controls the chemistry needed for multiple rounds of labeling and imaging of the same tissue. Using the technique, researchers don't have to pick one or a few different cells or molecules to label. Over several rounds, they can tag and image them all.

To help fellow scientists complete their labeling and imaging work faster, Chung also invented a process called **stochastic electrotransport**, which can shuttle molecules through tissue without damaging surrounding structures. The technique can cut the time required to label a mouse brain from around a month to a couple of days.

MAP, or Magnified Analysis of Proteome, is the Chung lab's chemical process to make a whole brain not only clear but also "size adjustable" while preserving everything a neuroscientist might want to see at different scales. Though many microscopes are limited to 250 nanometers of resolution, MAP allows for a resolution down to an original size of 60 nanometers, by allowing small structures to become physically larger.

Sur's lab has helped to pioneer **three-photon microscopy,** and built one of the earliest scopes. The technology improves on two-photon scopes by penetrating more than a millimeter deep, exposing more of the mammalian brain, *in vivo*, for exploration than ever before. Sur Lab postdoc Murat Yildirim also developed a variant, "third harmonic generation microscopy," that doesn't require a fluorescent label.

Together with Alice Ting, who later moved to Stanford, Kay Tye invented **FLARE**, a quick way to turn on an inserted gene in a neuron when the cell becomes active in a circuit, either to identify newly activated neurons or to manipulate them. FLARE works more quickly than other labeling tools, giving scientists much more temporal resolution.

By isolating messenger RNA, **TRAP**, or Translating Ribosomal Affinity Purification, allows scientists to identify different neurons based on the genes and proteins they express. Myriam Heiman invented it in 2008 at Rockefeller University as a postdoctoral fellow with Paul Greengard and Nathaniel Heintz. She now applies it at the Picower Institute to study the specific cell types most afflicted in Huntington's and Parkinson's diseases.

While a Stanford postdoc in 2006 Weifeng Xu and colleague Oliver Schlüter developed the technique of **Molecular Replacement,** which employed a virus to simultaneously knock down expression of an innate protein and express an inserted version in precisely targeted cells. This allowed for side-by-side comparisons with unaltered controls. Xu has continually evolved it to deliver complex alterations within cells or brain regions, essential for attacking mechanistically driven problems.

Tsai led the creation of one of the most powerful mouse models for Alzheimer's disease, the **p25 mouse**, as a result of doing cancer research early in her career. Her study of the enzyme CDK5 at Harvard led her to discover that it's regulated by the protein p35. When p35 breaks down to p25, it causes very similar pathology as seen in AD.

IN GOOD COMPANY:

Picower Faculty Discuss Entrepreneurship

Many Institute faculty members hold patents, have inventions and innovations listed with MIT's Technology Licensing Office, or have started companies to translate their discoveries to the marketplace.

Though both are part of the same continuum of translation, research and commerce are different worlds. Below, three professors with startups talk about why they've engaged in entrepreneurship and what it has meant to them.

Mark Bear (MB) co-founded Sention and Seaside Therapeutics, which developed a potential Fragile X and autism therapy in collaboration with Roche. He is considering another startup for a new way to treat amblyopia. Earl Miller (EM) co-founded SplitSage, which has developed a process for measuring the unique spatial patterns of visual cognitive capacity. Li-Huei Tsai (L-HT) co-founded Cognito Therapeutics to help advance GENUS, a potential sensory-based, non-invasive, non-pharmaceutical treatment for Alzheimer's disease.

Why did you decide to start a company?

MB: How do you go from an exciting preclinical finding in an animal to delivering a treatment to patients? You either attract the interest of a commercial entity that's going to foot the bill and carry it forward or you take the initiative yourself. I don't necessarily have my heart set on starting a company over the amblyopia treatment but I do have my heart set on translating our discoveries. It would be very gratifying at this stage of my career to see some of the work that we have done be translated to help patients. That's why we invested so much time and effort, blood, sweat, tears and money in Fragile X. It's not enough to cure Fragile X in a mouse. It's not enough to cure amblyopia in a mouse.

EM: It just occurred to me one day walking to work that there was a practical application. My first motivation was reducing car accidents. It felt like there was a chance to benefit society and it felt like if I could stay involved with it, I could guarantee it would go in that direction. We have multiple markets, but that's one market I'm going to make sure we keep a hand in.

Another application is cognitive testing, which is important for developing therapies for neurological disease, among other things. The problem is that current batteries of cognitive tests are really poor. They are not reliable. Our test is superior because it directly tests the most fundamental aspect of cognition, your mental bandwidth.

L-HT: To further validate the work from my basic research. The additional resources of a company can help us move further and faster toward developing a therapy for Alzheimer's disease.

What have you found remarkable about the experience?

L-HT: After learning the translational aspect of science, I feel that I am more motivated to do rigorous basic research to understand normal physiology of the brain and the mechanisms underlying brain dysfunction. The thought that any of our work may have impact in society is exciting and humbling.

MB: It opens your eyes to the challenges of translational work and financing it. It's also exhilarating to create a team where everybody is rowing in the same direction to achieve a common goal. It's a little bit different than academic science.

It's fun because it's different. I also find it to be intellectually stimulating because I'm learning so much about the challenges of drug development, patient recruitment and clinical trial design. It broadens your horizons.

EM: It's been key to get a good CEO who knows what they are doing. In the past four years since we incorporated I've had a crash course in business. I know a lot more than I did. There are potholes out there you wouldn't see coming and there are strategies that would never occur to you unless you were a businessperson.

The other thing is to listen to the market. Don't think you have all the ideas about what to do with your product.

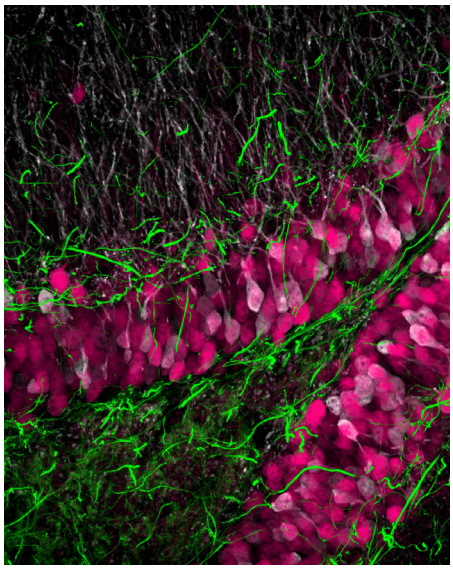
How does early stage investment help you get your research out of the lab?

EM: We had some angel investors at first. We needed to do things like hire software developers to develop that part of our process. We also needed an office. Once we start selling, people will need some training to learn how to use our process. So as funding grows we'll be able to hire more full-time employees, like a trainer.

MB: There is a big energy barrier to get something out of the lab and into the world. One of those energy barriers is lack of expertise in elements of development that are beyond what we do in the lab. It takes somebody who would say, Mark, I'll give you the financing and opportunity—and help you build a team—to take the amblyopia research from where it is now to the point where it could be partnered with an established pharmaceutical company, or attract a Series A investment and grow into a stand-alone company.

Upcoming EVENTS

For the *latest* information on all our lectures, symposia and other events, please visit: **picower.mit.edu/events**



SYMPOSIUM

10.23.2018 *Frontiers in Neurotechnology*

The Picower Institute's Fall Symposium, organized by Assistant Professor Kwanghun Chung, will bring together experts who are working at the leading edge of the development of neurotechnology.

Paola Arlotta, PhD, is a professor at Harvard University. Her work includes generating next-generation, long-term cultures of 3D cerebral organoids, starting from human induced pluripotent stem cells, as part of an overall research agenda of studying programming, reprogramming and modeling of the mammalian cerebral cortex.

Emery Brown, PhD, MD, the Edward Hood Taplin Professor at MIT and a member of the Picower Institute, is an anesthesiologist-statistician whose research has made important contributions to understanding how anesthetics act in the brain and has developed signal processing algorithms to solve important data analysis challenges in neuroscience.

Kwanghun Chung, PhD, is a member of the Picower Institute, assistant professor in MIT's Department of Chemical Engineering and Institute for Medical Engineering and Science. He has invented several tissue transformation and processing techniques that vastly improve the data available through neuroimaging including CLARITY, SWITCH, stochastic electrotransport, MAP, and SHIELD.

Elizabeth Hillman, PhD, is a professor of biomedical engineering at Columbia University. A major theme of her lab is *in vivo* neuroimaging, for instance to study blood flow and neuronal activity, leading to the development of advanced technologies including laminar optical tomography and hyperspectral two-photon microscopy.

Na Ji, PhD, associate professor of molecular and cell biology and of physics at UC Berkeley, develops and applies novel imaging methods to understand the brain. Ji also aims to extend the applications of her lab's technologies to other living (and nonliving) systems.

David Kleinfeld, PhD, holds the Dr. George Feher Experimental Biophysics Endowed Chair at UC San Diego. His lab employs a wide variety of techniques for studies of phenomena including sensory behaviors, microcirculation in the brain, neuromodulation, and learning.

Ed Lein, PhD, is an investigator at the Allen Institute for Brain Science providing scientific guidance and oversight for the creation of large-scale gene expression atlases of the mammalian brain, including the human brain, as online resources for the scientific community.

Sergiu Pasca, MD, is an assistant professor of psychiatry and behavioral sciences at Stanford University. His lab studies brain development and dysfunction. Techniques include 3D "brain in a dish" tissue cultures and other state-of-the-art stem cell biology, genome engineering, live imaging and neurobiology approaches.

Orly Reiner, PhD, is a professor in the Department of Molecular Genetics at the Weizmann Institute of Science where she studies embryonic brain development and disease using approaches combining molecular, biochemical, *in vivo*, *ex vivo*, and *in vitro* studies with mouse and human brain organoid models.

EXHIBIT

The Beautiful Brain: Now – Dec. 31

Spanish neuroscience pioneer Santiago Ramón y Cajal made transformative discoveries of neural anatomy. "The Beautiful Brain: The Drawings of Santiago Ramón y Cajal," which opened this spring at the MIT Museum, includes approximately 80 of his drawings.

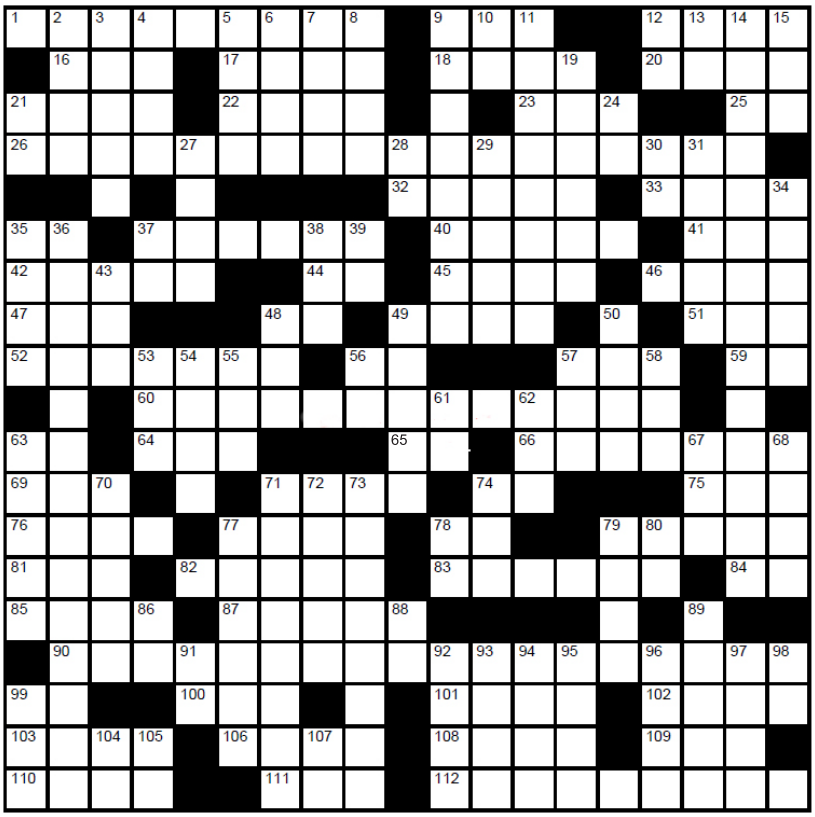
Cajal's historical works are complemented with contemporary neuroscience images by scientists from MIT (including Picower faculty members Susumu Tonegawa and Kay Tye) and around the world. Many of them were created using technologies pioneered here at MIT as well. This traveling exhibition, supported by the Picower Institute, is organized by the Frederick R. Weisman Art Museum and the Cajal Institute in Madrid. It runs through December 31, 2018, so stop by if you can.

UPCOMING TALKS

Photo: Adrianne Mathiowetz

11.26.18 | *Aging Brain Initiative Seminar*
Magdalena Götz, PhD
Ludwig Maximilian
University of Munich

12.06.18 | *MIT Colloquium on Brain & Cognition*
Scott Waddell, PhD
University of Oxford



Neuroscience in the News

(To solve major clues, look to the stories on pages 2-4)

ANSWERS AT bit.ly/PILMXWORD

ACROSS

1. Where Miller study's progression ends
9. Command for dog
12. Duplicate
16. Compensation
17. Tomato type
18. Not quite gallop
20. Busch of NASCAR
21. Teen expression for dissatisfaction
22. Wee sip of scotch
23. Solution for a tired toddler
25. To the same degree
26. Components in Littleton's study
32. Japanese eel
33. Syndrome Sur lab fights
35. Sur study's co-lead author
37. Memory trace
40. Bump on a tree
41. Architects org.
42. Callow
44. Subjective "us"
45. Pulls along
46. Fantasy monsters
47. Old-school screen
48. Poet ___ Cummings
49. Bird like an emu
51. Best univ. in Cambridge
52. DNA packaging protein
56. Jazz Musician Sun _____
57. What you do with 58 down
59. Baseball great ___ Cobb
60. Miller's "sketchpad of consciousness"
63. Inhuman pronoun
64. Greek exclamation
65. Begley, Asner or Boyden
66. In which one solves for x
69. Tic's partner
71. Univ. in Providence
74. News org.
75. Picower's Mriganka ___
76. Alda or Greenspan
77. Refuse blame
78. Dr. for special deliveries
79. Internet jerk
81. Successor of 47 across
82. Popular nut
83. A kind of enzyme
84. Famed biologist ___ Wilson
85. Nostalgic times
87. Relating to kidneys
90. Key measure for Littleton
99. Kind of med. scan
100. Belonging to a dude
101. Attractive
102. Legalese for "pertaining to"
103. Building toy
106. Denim king _____ Strauss
108. Orchestra instrument
109. Reagan's solution to USSR nukes
110. Coding part of a gene
111. Familiar name for a physician
112. Where Miller study's progression begins.

DOWN

2. Precious stone
3. The whole range
4. Andrei Gromyko's famous utterance
5. Theme park transit
6. New York City area college
7. Leave out
8. Neck part
9. See 73 down
10. Part of the EM spectrum of light
11. Picower's Susumu _____
12. Disgraced comedian Louis ___
13. Yiddish exclamation ___ vey
14. What Sur's study discovered
15. "Say ___ to the Dress"
19. Pig-like animals
21. Electronics brand
24. Helps you recover after 30 down
27. Teenage affliction
28. Putin's internet domain
29. What a paddler portages
30. Surgery venue, for short
31. Supply anew with weapons
34. Delectable
35. Not much length
36. Region of interest in Sur study
37. Tesla or Nissan Leaf for short
38. Amazement
39. What you call you
43. Belonging to 63 across
48. Adorable expression of fear
49. Carried on in anger
50. A whole lotta ice
53. The smallest prime number
54. Often precedes "sorry"
55. Org. of Firearm enthusiasts
56. Med. provider
57. Spanish sun
58. Optical organ
61. Often works with 56 down
62. One of Chung's inventions
63. When in Rome you're also here
67. MA musical institution
68. Folk singer _____ Guthrie
70. A group trained for a purpose
71. Took a break in court
72. Idiotic
73. With 9 down, what 90 across indicates
74. MIT approach to neuro-degeneration in the elderly
77. Push off track
78. Easiest way to agree when texting
79. Picower's Li-Huei _____
80. Memo-ese for "with regard to"
86. Train to the Cubs
88. Atomic no. 103
89. Language in India
91. What did you say?
92. Spanish bears
93. Actress _____ Neuwirth
94. Neural projection
95. "Say your good_____"
96. To put a house up for sale
97. Between duo and quartet
98. "You," way back when
99. City of NBA's Cavaliers
104. Where Monopoly games begin
105. Atop
107. Video narration, for short

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OUR VISION

The Picower Institute is a community of scientists dedicated to understanding the mechanisms that drive learning and memory and related functions such as cognition, emotion, perception, and consciousness. Institute researchers explore the brain at multiple scales, from genes and molecules, to cells and synapses, to circuits and systems, producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

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