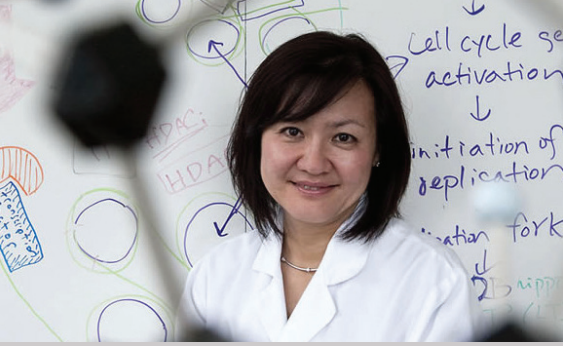
'Risky' research

How bold new neuroscience research projects get off the ground ***Pg. 8***

Neuroscience News

WINTER 2021

THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY



DIRECTOR'S **MESSAGE**

Dear Friends,

Before our ideas can become innovations and our postulates can become published papers, we scientists must find a way to cross the expensive gap between intention and action. If a hypothesis is truly novel then at the very beginning all we can offer is the prediction that we are right and an acknowledgement of the risk that we won't be. After all, we won't be able to claim a discovery unless we manage to find out what no one else has before. To get started, we need support from people who not only share our vision but are willing to share in that risk.

In this edition we focus on that earliest stage, when potentially game-changing new hypotheses are ready to launch. How do we get our best, newest ideas off the ground?

Very often the initial boost comes from philanthropic foundations and individuals who are willing to seed-fund ideas while they are still too risky to earn traditional government grants. Our cover story (see p. 8) illustrates several historical and current examples of how private sources of gifts and grants have helped us invent new research approaches to address Alzheimer's disease, autism spectrum disorders, Parkinson's disease and schizophrenia. In a companion story (see p. 10) we focus on how the sustained support of the JPB Foundation led by Barbara Picower has provided us not only with the freedom to try bold new ideas, but also enabled us to pursue much more funding from additional sources by covering a portion of the "indirect" costs that those sources do not.

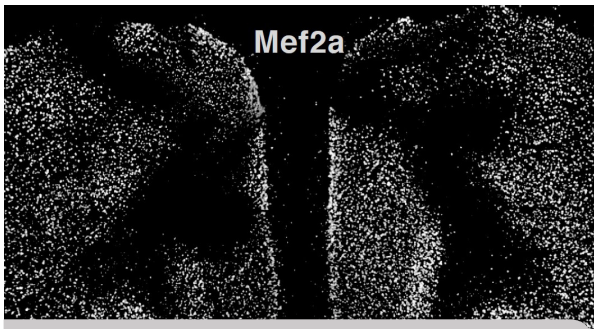
Without the philanthropy of the Picowers and many others, so much less science could be done. All next year we will celebrate the 20th Anniversary of the gift that made us "The Picower Institute for Learning and Memory." As we mark "Two Decades of Discovery & Impact," (see p. 11) we will do so with gratitude and excitement about the next new ideas we will strive to launch.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

Gene family linked to cognitive resilience

Many people remain sharp well into old age, even if their brains show underlying signs of neurodegeneration.



When scientists knocked down expression of a MEF2 family gene in the prefrontal cortex (blank areas), mice weren't able to cognitively benefit from enrichment.

Among these cognitively resilient people, researchers have identified education level and amount of time spent on intellectually stimulating activities as factors that help prevent Alzheimer's and other dementias. A new study by MIT researchers shows that this kind of enrichment appears to activate a gene family called MEF2, which controls a genetic program in the brain that promotes resistance to cognitive decline.

The researchers observed this link between MEF2 and cognitive resilience in both humans and mice. The findings suggest that enhancing the activity of MEF2 or its targets might protect against age-related dementia.

"It's increasingly understood that there are resilience factors that can protect the function of the brain," says Li-Huei Tsai, director of The Picower Institute and MIT's Aging Brain Initiative. "Understanding this resilience mechanism could be helpful when we think about therapeutic interventions or prevention of cognitive decline and neurodegeneration-associated dementia."

Tsai is the senior author of the study in *Science Translational Medicine*. The lead authors are recent MIT PhD recipient Scarlett Barker and MIT postdoctoral fellow and Boston Children's Hospital physician Ravikiran (Ravi) Raju.

Studies have linked education level, type of job, number of languages spoken, and amount of time spent on activities such as reading and doing crossword puzzles to higher degrees of cognitive resilience. The MIT team set out to try to figure how these environmental factors affect the brain at the neuronal level. They looked at human datasets and mouse models in parallel, and both tracks converged on MEF2 as a critical player.

In two human datasets comprising slightly more than 1,000 people, the team found that cognitive resilience was highly correlated with expression of MEF2, a transcription factor, and many of the genes that it regulates. Many of those genes encode ion channels, which control a neuron's excitability, or how easily it fires an electrical impulse.

To study cognitive resilience in mice, the researchers compared mice who were raised in cages with no toys, and mice placed in a more stimulating environment with a running wheel and toys that were swapped out every few days. As they found in the human study, MEF2 was more active in the brains of the mice exposed to the enriched environment. These mice also performed better in learning and memory tasks.

When the researchers knocked down the gene for MEF2 in the frontal cortex, this blocked the mice's ability to benefit from being raised in the enriched environment, and their neurons became abnormally excitable.

The researchers then explored whether MEF2 could reverse some of the symptoms of cognitive impairment in a mouse model that expresses a version of the tau protein that can form tangles in the brain and is linked with dementia. If these mice were engineered to overexpress MEF2 at a young age, they did not show the usual cognitive impairments produced by the tau protein later in life. In these mice, neurons overexpressing MEF2 were less excitable.

The findings suggest that enhancing MEF2 activity could help to protect against dementia; however, because MEF2 also affects other types of cells and cellular processes, more study is needed to make sure that activating it wouldn't have adverse side effects.

Fragile X treatment can incur resistance, but study suggests new strategies

A new study in mice provides substantial evidence that a promising treatment for fragile X syndrome, the most common inherited form of autism, missed the mark because the brain builds up resistance, or "tolerance" to it. Importantly, the research also points to several new therapeutic opportunities that could still turn the tide.

Mark Bear

Picower Professor Mark Bear and his team led by postdoc David Stoppel showed that giving just a few doses early in life while the brain is still developing and then not giving further doses as they got older, could produce lasting benefits in cognitive ability. That finding suggests that the timing and duration of drugs that inhibit the neurotransmitter receptor mGluR5 are more important than previously recognized.

"The development of acquired treatment resistance to a medication is nothing new," said Bear, senior author of the new paper in *Frontiers in Psychiatry*. "The fact that it happens doesn't mean that, therefore, you give up all hope. It means that you have to be aware of it."

In addition to the strategy of administering mGluR5 inhibitors at a young age and then stopping, the study also implies that patients could benefit if dosing were structured with breaks to prevent a buildup of resistance, Bear said. Moreover, the study also suggests that amid treatment resistance Fragile X mice resumed synthesis of an unknown protein that leads to symptoms. Identifying and targeting that protein, Bear added, could also be a fertile new avenue for drug development.

These new findings follow on a 2020 study in *Science Translational Medicine* (STM) by Bear's lab and scientists at The Broad Institute of MIT and Harvard in which they developed a compound, BRD0705, that acts downstream in the molecular pathway between mGluR5 and protein synthesis. BRD0705 did not incur treatment resistance in mature fragile X mice.

Fragile X syndrome is caused by a mutation in which repeats of the nucleotides CGG disable a gene's ability to make the protein FMRP. In the absence of FMRP, neurons exhibit excessive protein synthesis, degraded circuit connections called synapses, and hyperexcitability leading to symptoms such as cognitive disability. In the early 2000s, Bear's lab recognized that inhibiting the mGluR5 receptor in brain cells could prevent the problems with protein synthesis and treat many Fragile X symptoms. After successful animal tests, the treatment was tried in clinical trials.

One participant in the trial of the drug mavoglurant was Andy Tranfaglia of Massachusetts. At the time of treatment eight years ago, he was 24, said his father Dr. Michael Tranfaglia, medical director of FRAXA Research Foundation, an organization working to find a cure for the disorder.

"Andy had an almost miraculous response to the drug and showed dramatic improvement in virtually all areas of function, behaviorally and cognitively, but he also had significant improvements in motor function and a complete resolution of lifelong, severe gastroesophageal reflux (GERD)," Tranfaglia said. "Unfortunately, after 3-4 months, the benefits of the treatment began to wane and continued to decrease over time."

Indeed a 2005 study in the journal *Neuropharmacology* by Dr. Tranfaglia and researchers at Columbia University showed that in a common test of an mGluR5 inhibitor, whether audio tones lead to seizures, found a treatment resistance effect in mature Fragile X mice. Until recently, though, the evidence that patients were acquiring treatment resistance wasn't abundant, Bear said.

In the new study, Bear's lab replicated the 2005 findings and showed that treatment resistance emerges in two other assays as well. Given the evidence that treatment resistance can build, the researchers said, a more effective approach to sustaining benefits from the drugs may be to give patients breaks between doses to allow resistance to subside.

The experiments showing treatment resistance also yielded another important result. In each case researchers were able to restore the benefits of the medication by adding a drug called CHX, which broadly suppresses protein synthesis. That finding suggests that amid resistance the Fragile X mice resumed producing a protein that restored disease symptoms. Bear said a key next step for his lab will be to try to identify that protein.

Based on a clue from a 2019 University of Edinborough study that Bear co-authored, the MIT team also treated some Fragile X mice with CTEP only a few times around 28 days after their birth—roughly equivalent to about 10 years old for humans. Then, after no further treatment, at 60 days of age, the team administered a memory test. Fragile X mice left untreated as a control group showed difficulty, but the Fragile X mice who were treated with CTEP while young were much more successful, indicating that timely treatment during a critical period had a lasting benefit.

3 Questions for: Emery N. Brown

Improving anesthesia with neuroscience

Long before Emery N. Brown chaired Massachusetts General Hospital's recent 175th anniversary celebration of the first public demonstration of ether anesthesia, he was thinking deeply about how far anesthesiology has come and could still go.

Anesthetic drugs act on the brain, but the field has barely explored the innovations that could come from integrating neuroscience into anesthesiology practice, said Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience. A neuroscientific approach could reduce side effects, make drug delivery more precise, manage post-operative pain better, and usher in new treatments for sleep or methods for coma recovery.

Brown performs neuroscience and statistical research in The Picower Institute and the Institute for Medical Engineering & Science and puts it into practice as an anesthesiologist at MGH. Now he is launching a new research center. The Picower Institute asked him to discuss these ideas more.

After 175 years of history, what are the frontiers for anesthesiology now?

The first public demonstration of ether anesthesia at MGH was really the start of a new era in medicine. It changed surgery overnight from being a trauma to being a reasonable and life-saving therapy. The focus of research at the time had been on coming up with better contraptions to hold you down so they could conduct a surgical procedure without anything to effectively mitigate the pain. In this regard, the field has come quite a long distance.

On the other hand, the neuroscience of anesthesia has been slow to be developed. That's what we've been working on over the last several years and I think that's where I see the future being. The frontier in anesthesiology lies in neuroscience.

What has your recent research shown about the neuroscience of anesthesia?

We now have a lot of detailed, hard data showing that anesthetic drugs create oscillations in brain circuits that impede the ability of various parts of the brain to communicate.

In recent work with my colleague Earl Miller, we came to appreciate how far away the dynamics of brain oscillations under anesthesia are from the dynamics the animals showed when conscious. You dramatically alter how much the neurons spike. What propofol is doing is slowing down brain oscillations to create an alternate dynamic, one which doesn't allow you to be conscious. The same thing is true with ketamine, but instead of the brain being slowed down, slow activity oscillates with faster activity at a very regular pace. This is also a dynamic that is quite far from the dynamic we see when an animal is conscious.

So becoming unconscious with anesthetics is not so much about turning the brain "off" as changing the dynamics. We see this in humans, too, and that's extremely helpful to us, because now I can interpret the oscillations I see when a patient is anesthetized in the operating room. I have very good neurophysiological evidence as to why I should feel comfortable the person is unconscious in those conditions. We can measure these oscillations in real time via EEG. I do it with all my patients. I'm encouraging colleagues to do it as well.

What advances do you hope to develop in the new center?

I couldn't be more excited about setting up the center because neuroscientific ideas can be turned into new approaches to taking care of patients.

For example, those oscillations that are part of the mechanism through which anesthetics induce unconsciousness are also part of the mechanism through which the drugs contribute to brain dysfunction after surgery, which we know is highly prevalent in older patients. What we have to do is develop alternate ways to inactivate circuits, so that we can create the states and do away with the side effects.

We need to take on anesthesia as a neuroscience question to address how we can develop very precise ways to control the delivery of anesthesia so the person gets just enough – not too much or not too little. How can we develop procedures to accurately read and interpret the EEG during surgery, so the anesthesiologist can reliably know when a patient is unconscious? How can we develop accurate ways of measuring the level of nociception, meaning pain that a patient is perceiving during surgery, so we can more accurately titrate analgesics during surgery? How do we work out ways to turn brain communication back on so that we can restore functionality once someone's anesthesia is completed?

A long-range goal will be to have very site-specific methods to activate or inactivate only the brain regions and circuits that are necessary and leave the other areas untouched.

To do this we need deep neuroscience and engineering expertise. What better place than MIT in collaboration with our clinical colleagues at MGH. It's the perfect marriage, if you will.

There's even greater potential as we learn fundamental things about the brain from studying how anesthesia affects inter-regional communication and inhibitory networks. We can develop better ways to control the "on" and "off" of brain communication. Maybe that's a new approach for helping someone sleep better or if we're able to reboot the brain from a very fundamental level, maybe that's a way to help foster coma recovery.

Heiman earns NIH award for collaborative study of **neurodegenerative** motor diseases

Though accumulation of a protein called TDP-43 appears to be a signature of almost all cases of amyotrophic lateral sclerosis (ALS), scientists don't yet know exactly how that may contribute to the devastating damage to neurons that characterizes both ALS and the related condition, frontotemporal lobar degeneration with motor neuron disease (FTLD/MND). With a Transformative Research Award from the National Institutes of Health, a new research team will launch a groundbreaking, five-year investigation to pinpoint what may be going wrong in specific brain cells and to help identify new treatment approaches.

Myriam Heiman

The five-year project will fund a collaboration among four labs, including the Picower Institute team of Associate Professor Myriam Heiman, to uncover detailed biological differences between the brains of affected and unaffected individuals and then test which differences play a causal role in the response to and effects of TDP-43 accumulation. By uncovering underlying molecular mechanisms of how cell viability fails amid TDP-43, they'll gain insights into what to do about it.

"A strength of this study is that we are bringing together a team that has the expertise for wonderful sample selection, computational expertise and analysis and also the ability to dissect phenotypes and test causality of our predictions in multiple ways," Heiman said. "We can't just take one approach to study these complex diseases."

Her lab will join forces with those of Manolis Kellis, MIT professor of computer science, and colleagues Chris Donnelly at the University of Pittsburgh and Veronique Belzil at the Mayo Clinic.

The collaboration will compare and analyze differences in gene expression and various factors that can cause gene transcription to vary, by sequencing genetic material in millions of individual cells from key brain regions and spinal tissue of 50 people diagnosed with ALS, 50 people diagnosed with FTLD/MND and 50 people who did not have either condition. By integrating this massive amount of data with data from genome-wide association studies, the team will be able to make precise predictions about which genes and which regulators of their expression may be impacting TDP-43 pathology in scores of different brain cell types. It will also allow them to predict how those effects might occur.

Once they identify their top genetic suspects, they will use a new technique called "perturb-seq" to screen the effects of those suspects across many different brain cell types in a high throughput manner. Using induced pluripotent stem cells derived from patients, they will culture many different types of brain cells. Then they will genetically engineer their suspected genetic culprits into these cultured cells. That will allow them to screen for and observe the effects of each of their manipulations in each of the cell types.

They will also engineer the suspect genes into mice to validate whether they modulate disease phenotypes in whole, complex living mammalian nervous systems modeling TDP-43 pathology. In cases where they see ill-effects like those observed in ALS and FTLD/MND, their precise knowledge of the underlying genetic differences that have caused them will help advance new ideas about interventions that then might help.

Pitching accurate Covid-19 science

Izabella Pena on the field at Fenway Park.

In recognition of her work promoting vaccination and disseminating sound scientific information about the Covid-19 pandemic for LatinX/Hispanic communities, Picower Institute postdoc Izabella Pena joined top Moderna researchers to throw a ceremonial First Pitch at Fenway Park Sept. 5. "It all started when I recorded short WhatsApp audio messages to explain about the SARS-Cov-2 virus to my family and friends in Brazil," Pena said. Her messages spread far and wide from there. "There was a need for communication of what was going on with Covid-19 using scientifically accurate information and in lay terms. I realized how much voice scientists like me can have on social media and then I moved into creating a YouTube channel in Portuguese and focused on sharing informative threads on Twitter to explain and promote vaccines."

Alzheimer's research awards

Congratulations to Picower Clinical Fellow Diane Chan of the Tsai lab on winning a Clinical Scientist Development Award from the Doris Duke Charitable Foundation. Also, at the Alzheimer's Association International Conference earlier this year her research poster, "Gamma Frequency Sensory Stimulation Prevents Brain Atrophy, Improves Sleep and Memory in Probable Mild Alzheimer's Patients" earned the honor of best virtual postdoc poster in the theme of Drug Development (see p. 8 for more about the research).

Picower scientists present projects at 'SfN'

Even though this year's Society for Neuroscience Annual Meeting was entirely online, it remained an important opportunity for young scientists to share their work with the world. Picower postdocs and graduate students presented numerous research projects at the conference.

"I always encourage my students and postdocs to present their work at SfN and other meetings. Their careers will depend on not just doing science but also communicating science," said Picower Professor Earl Miller. "I think everyone wishes it was an in-person meeting but nonetheless, it is an opportunity for the students and postdocs to present their work. Besides, there is a lot of cool work going on in the lab. Why should we keep that to ourselves?"

Networks & Circuits

Several Miller lab presentations described how higher-level cognition emerges from brain waves coordinating networks of neurons. Postdoc Sayak Bhattacharya's presentation tracked how waves "travel" around the prefrontal cortex (PFC) during working memory tasks. Others led by former postdoc Andre Bastos showed that brain waves consistently show distinct layer by layer patterns across the cortex's six-layer structure. Postdoc Alex Major demonstrated that suppression of specific PFC cortical layers can differentially affect visual cortical activity.

Meanwhile, graduate student Leo Kozachov presented two projects. In one he combined neural activity measurements and computational models to assess how the brain remains dynamic enough on one hand to account for new sensory input but stable enough to still produce reliable computations. In the other he and fellow Miller Lab graduate student Adam Eisen show how anesthetic drugs might shut down sensory input by making the brain so stable as to be impervious to new sensory input.

That project was a collaboration with Professor Emery N. Brown who also collaborated with postdoc Elie Adam on a presentation explaining how deep brain stimulation treats Parkinson's disease by restoring waves of several frequencies in the stimulated area.

Neurons are coordinated not only by brain waves but, of course, by circuits. Tudor Dragoi, former research associate in the lab of Professor Mriganka Sur, presented research showing how marmoset primates use several brain regions to formulate predictions (also see p. 8).

Learning & Memory

Naturally, a function of particular Picower Institute interest is learning and memory.

Graduate student Nhat Le presented his study of how rodents appeared to switch their approach to learning, exploring less and relying more on their accumulated knowledge of the environment, as they gained experience in a foraging task.

In the lab of Professor Matt Wilson, postdoc Honi Sanders showed that individual animals vary in the degree to which their brain "remaps" representation of a spatial context when it changes. Wilson lab postdoc Wei Guo, meanwhile, showed that over the course of training, with periods of sleep, more neurons become involved in representing spatial contexts, fine tuning mental maps of places.

Development & Plasticity

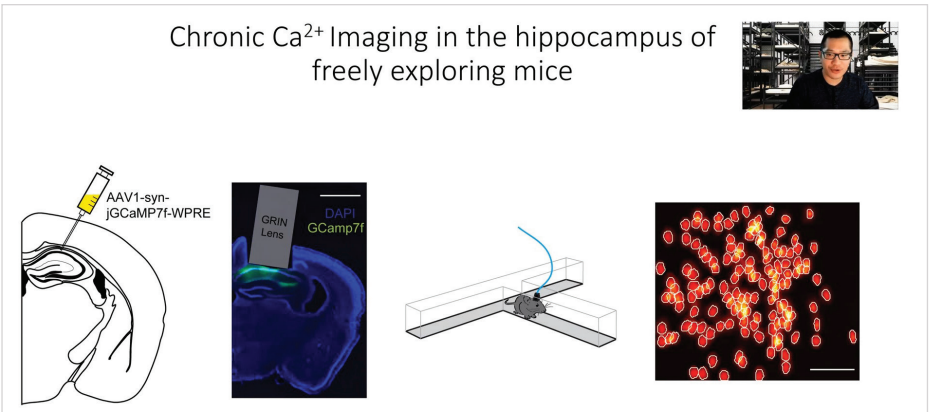
Circuits arise when neurons connect via synapses. Several presentations from Professor Troy Littleton's lab revealed how synapses develop. Research scientist Suresh Jetti tracked structural and molecular differences explaining the fundamentally different activity of two common synapse types. Graduate student Ellen Guss screened for proteins which control assembly and maturation of the synaptic active zone. And graduate student Elizabeth Brija showed how synapses are affected by RNA editing of a key synaptic protein called complexin.

Synapses can come and go, strengthen or weaken, a property called "plasticity." Members of Professor Mark Bear's lab study related developmental diseases. In fragile X autism excessive protein synthesis weakens synapses. Graduate student Max Heinrich's presentation detailed the search for proteins whose overproduction have particularly deleterious effects. David Stoppel discussed his new paper on treatment resistance to a method of reducing protein overproduction (see p. 3). Postdoc Ming-fai Fong detailed her recent work showing how exploiting plasticity by temporarily anesthetizing a retina resets synapses to treat the vision disorder amblyopia. Postdoc Héctor De Jesús-Cortés, meanwhile, described a vision test the lab can use to assess recovery in lab mice after amblyopia treatment.

Innovations & Inventions

New methods and tools are integral to enabling new discoveries. Brown lab graduate student Indie Garwood, working with MIT Professor Polina Anikeeva, described a fiber-based technology that can deliver chemicals to individual cells to affect their activity. And Wilson Lab postdoc Jie Zhang debuted a new camera that enables vivid imaging of electrical activity in neurons.

Even if remotely, young Picower scientists had a variety of advances to share.



Wilson lab postdoc Wei Guo employed calcium imaging of neural activity to show that over the course of training, with periods of sleep, more neurons become involved in representing spatial contexts, fine tuning mental maps of places.

Oct. 12 symposium spotlights crucial roles of dendrites

At the Picower Institute's online fall symposium, "Dendrites: Molecules, Structure and Function," neuroscientists presented many of the latest findings about how dendrites not only provide the infrastructure for incoming neural circuit connections, or synapses, but also help to process information for brain functions including perception, learning and memory.

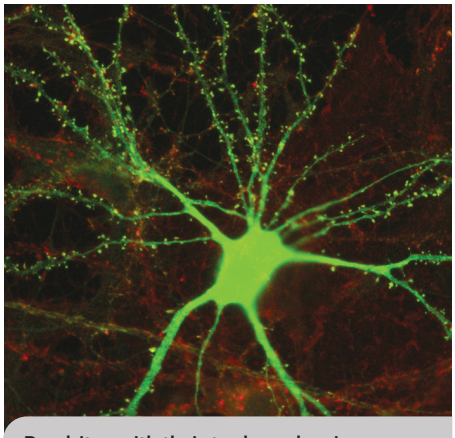
"One of the things that people in the dendrites field have thought about for a while but is now getting broader recognition is that while neurons are computational devices, a lot of that information processing and integration happens almost immediately at the level of the dendrites," said Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience in The Picower Institute and lead organizer of the meeting. "Dendrite architecture is therefore really critical to these functions, both the anatomy and the molecular composition."

Mindful of the ongoing need for social distancing and the Picower Institute's intention to reduce air travel that contributes to climate change, Nedivi arranged an experimental program for the all-online symposium. One of her key goals was to ensure that even with five keynotes by senior researchers, the agenda showcased the work of junior researchers and provided fulfilling networking opportunities. Young neuroscientists delivered 10 public talks and presented in two poster sessions. At multiple private networking opportunities built into the day, senior and junior attendees also had the chance to virtually mingle. In all, more than 640 people from 32 countries registered to attend presentations by about 60 scientists from a dozen nations.

Talks elucidated how dendrites and the synapses they house grow and change. Others showed how dendrites aid brain function. Among the highlights:

Samantha Ing-Esteves, a graduate student at the University of Toronto, discussed how dendritic branches "self-avoid" as they grow, preventing unwanted overlaps by employing molecular mechanisms that trigger retraction when they come into contact with each other.

Associate Professor Corette Wierenga of the University of Utrecht in the Netherlands showed that when there is a lot of activity among excitatory connections on a dendrite, that triggers a specific molecular signaling pathway to call out to nearby axons (the wiring that carries incoming signals from other neurons) of inhibitory neurons. They then begin building new inhibitory synapses to bring in a balancing input.



Dendrites with their trademark spiny structures extend from a neuron body.

Graduate student Dimitra Vardalaki of the lab of MIT professor and meeting co-organizer Mark Harnett discussed her findings that new synapses can emerge, even in adults, from an abundance of "filopodia." With stimulation, she said, these wispy structures, which she found by using a tissue expansion technology called MAP, developed by Picower Institute Associate Professor Kwanghun Chung, can grow to become synapses.

Nedivi lab postdoctoral fellow Josiah Boivin described an innovative microscopy method he uses to track how individual types of inhibitory synapses develop and mature on dendrites in young mice.

Masanori Murayama, a team leader at the RIKEN Center for Brain Science in Japan, described how neurons in the brain's thalamus forge synapses with neurons in the cortex to regulate the response to regularly repeated, and therefore expected, touch stimulation. He used advanced imaging methods to see it in action across dendrites in a wide area of the cortex.

Professor Fritjof Helmchen of the University of Zurich in Switzerland showed that as animals learned a texture discrimination task, different dendritic branches represented different parts of the process, such as the sensory stimulation or representation of the provided reward.

To examine how circuit connections between specific cell types in the cerebellum are architected to help the brain distinguish patterns (a key ability for learning), Harvard Medical School Assistant Professor Wei-Chung Lee, a former Nedivi lab graduate student, developed an innovative 3D, high-resolution imaging system. He found that connections between granule cells and mossy fiber cells in the cerebellum appear architected with some redundancy to ensure a balance of computational robustness and processing capacity.

Megha Seghal, a postdoctoral scholar at UCLA, described patterns of how related contextual memories not only become represented by overlapping groups of neurons in the retrosplenial cortex, but even become linked at the level of dendrites. She has found evidence that spine structures responsive to two contexts that are closely associated in time appear along the same dendritic branches.

Tomoe Ishikawa, a member of Picower Institute investigator Gloria Choi's lab, noted that a key mechanism of memory reactivation in the hippocampus, exposure to sharp wave ripple brain waves, tends to activate spines serially along dendrites.

Dendrites may not be the root of everything, but as the symposium speakers showed, these root-like conduits of information into neurons play substantial roles in shaping much of what the central nervous system does. For a fuller recap visit https://bit.ly/PILM-dendrites.

'Risky' research

How do bold, untested research projects get off the ground? Philanthropy provides scientists the freedom to try completely new ideas

Li-Huei Tsai

Graduate student Hunter Iaccarino came to the lab of Institute Director and Picower Professor Li-Huei Tsai eager to try an idea that circa 2014 seemed somewhere between provocative and preposterous. Aware that 40Hz frequency brain waves were reduced in Alzheimer's disease patients and mouse models, and knowing that the Alzheimer's-focused Tsai lab had shown how to increase the power of exactly those 40Hz "gamma" rhythms, Iaccarino figured Tsai would take a chance on testing whether boosting the rhythms would affect the course of the disease.

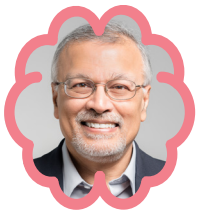
Never mind that the conventional wisdom assumed that rhythms were nothing more than indications of brain activity, not anything worth attempting to manipulate in hopes of profoundly affecting an incurable and devastating brain disease. From that viewpoint, altering rhythms to treat disease should be no more consequential than trying to fix a car's motor by fiddling with the "check engine" light.

So what could Tsai and Iaccarino do to get this unprecedented and untested idea off the ground? They couldn't just apply for a traditional government grant. Those require solid preliminary data. Trying this untried idea would instead require private, philanthropic support. In fact, many of the boldest, riskiest ideas in the Picower Institute, and in science at large, get their start because of private gifts and awards, either from foundations or individual donors who know that true innovation requires investment, sometimes in people more than projects, and that investment carries risk.

And so Tsai and Iaccarino started up the very first experiments by drawing on funds provided to the Picower Institute by its naming benefactor, the JPB Foundation of Barbara Picower (see p. 10). Once they began to see, and confirm, the earliest results—that boosting 40Hz rhythm power substantially reduced protein plaques that are hallmarks of Alzheimer's pathology—with the help of former MIT Chairman Robert Millard and his wife Bethany, they showed them to donors including Jeff and Nancy Halis who helped propel the early research forward, culminating in a landmark paper in 2016 and more papers since. More seed funding from many donors including the Eleanor Schwartz Charitable Foundation, the Degroof-VM Foundation, and the Halis, DiSabato and Siegelman families, launched human clinical studies that have now shown significant therapeutic benefits. Moreover, it has proved that manipulating rhythms can have direct effects on cellular and molecular processes of Alzheimer's disease.

"Our research on gamma rhythms was completely launched with philanthropic giving," Tsai said. "Long before new research typically can get grants from the standard programs at the government agencies, private support is essential."

Maybe Marmosets



Mriganka Sur

What's true for studying neurodegenerative disease is also true for studies of autism spectrum disorders. A few years ago Newton Professor Mriganka Sur and colleagues in MIT's Brain and Cognitive Sciences department realized that to better understand the fundamental neuroscience of autism, they needed an animal model more cognitively and socially sophisticated than mice, but less logistically challenging than rhesus macaque monkeys. The answer, they realized, might be marmosets. About the size of large squirrels, marmosets are highly social primates that are more easily housed than macaques, reproduce much more frequently, and produce larger litters (an important need when breeding genetic research lines).

"When it comes to primates, they are probably the best possible testbed for understanding autism," Sur said.

Maybe, but no one had shown that marmosets exhibit behaviors and underlying cellular and circuit mechanisms with meaningful relevance to autism. To become the first, Sur teamed up with fellow MIT Professors Ann Graybiel, Bob Desimone, and Alan Jasanoff. How could they get started attempting to develop a brand new animal model for autism? They brought together private support from the Simons Center for the Social Brain (an MIT program Sur directs with funding from the Simons Foundation

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Autism Research Initiative), the Stanley Center at the Broad Institute, and the Hock E. Tan and Lisa Yang Center for Autism Research at MIT's McGovern Institute for Brain Research.

Each lab is now testing different aspects of marmoset neurophysiology and behavior. Sur's lab, for instance, is finding that marmosets are very good at playing a game that tests their ability to form expectations and make predictions. After seeing a picture of a fellow marmoset on a screen, the animal can get a reward if it taps the screen as soon as possible after the image disappears. Success stems from learning to predict when the image will disappear (a probability set by the researcher). All the while the scientists measure brain activity via electrodes on the marmoset's head to see which brain regions are involved in its mental calculations. The next step will be to test what happens when marmosets engineered with autism-associated mutations try the game. Will they show a similar difference as people with autism? Will it be because of similar activity changes in the same brain regions?

In parallel, Graybiel is looking at how activity in a region called the striatum may contribute to abnormally repetitive behaviors, Desimone is looking at how marmosets perceive faces, and Jasanoff is tracking brain activity evoked by social cues.

All these experiments are unprecedented in marmosets but if they are successful, then the team will have introduced a powerful new autism animal model. Sur envisions MIT becoming a global resource for marmoset-based studies of autism.

"If this takes off it will lead to a new model for neuroscience. But it could all fall flat," Sur said. "Private foundations or internal sources of funds are essential for carrying this work forward."

Making a Mark on Fragile X

Mark Bear

Today Picower Professor Mark Bear is a leading authority on the neurobiology of fragile X syndrome, the most common inherited form of autism, but back when he made a seminal discovery about the disorder, he had no familiarity with it at all.

Bear's lab had been working to understand the molecular means by which circuit connections between neurons would weaken, a process called "long-term depression," or LTD. He and postdoc Kim Huber had found that activating a receptor called mGluR5 triggered LTD, and that it could be constrained by a protein called FMRP. Aware that silencing of the FMRP gene causes Fragile X, it dawned on them that excessive mGluR activation in Fragile X could potentially give rise to multiple symptoms of the disease. In Fragile X patients where FMRP was gone, they reasoned, inhibiting mGluR5 might treat the condition.

With no reputation in the Fragile X field, Bear nevertheless dared to present the idea at a meeting of experts.

"I come up with this outlandish idea and I just absolutely remember there was a stunned silence at the end of the talk," Bear said. "You could just see everybody rubbing their chin, as if thinking 'this idea is so out there it's got to be wrong and yet we can't immediately think of a reason why it's wrong'."

That kind of doubt and silence was all he would encounter in those days trying to fund his nascent hypothesis through traditional means. Instead he was able to persist because of open-ended funding he had earned from the Howard Hughes Medical Institute and because FRAXA, a private foundation that funds Fragile X research, had agreed to fund a fellowship for Huber. FRAXA continues to fund Bear's research, which has now yielded several drugs worthy of testing in stage III clinical trials (see p. 3).

Trying ideas in new ways

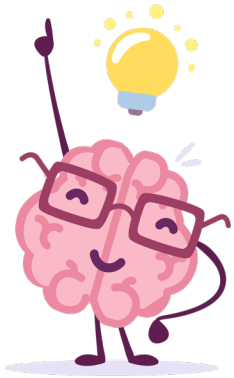
Myriam Heiman

Much as Bear was not known in Fragile X circles, Myriam Heiman has not yet published much about Parkinson's disease or schizophrenia. She has, however, helped to develop TRAP, an innovative method for studying the unique patterns of gene expression among different cells in the brain. She has also achieved the first ever genome-wide screen in a mammalian brain to discover which genes help cells fight back against the toxic protein that causes Huntington's disease. That involves disabling each gene in the entire mouse genome, one gene per neuron, in an area of the brain highly affected in disease to see which genes' absences make neurons more vulnerable. Recognizing that these methods might help in the study of schizophrenia and Parkinson's disease respectively, she has embarked on studies to try.

The schizophrenia research is supported by Eduardo Elejalde-Arena, founder of the Natalia Mental Health Foundation named for his daughter who had schizophrenia. With Elejalde-Arena's support and further funding from JPB, Heiman has been using TRAP to determine which cells antipsychotic drugs such as clozapine affect to help patients, and exactly how those neurons respond to it. Learning this precise mechanism could help in designing new drugs that are more effective and have fewer side effects.

And after discovering which genes are necessary to endow vulnerable cells with defenses against Huntington's disease, Heiman is embarking on a new study to determine whether her technique could do the same for the study of Parkinson's disease. That untried idea is proceeding with funding from the Mathers Foundation.

It's much too soon to say whether Heiman will find anything that ends up showing promise in clinical trials, like Bear and Tsai's discoveries have done, but that's exactly the point. These are new ideas. There is a risk they won't work. But with funders willing to take that risk alongside Picower Institute researchers, innovative science has launched and soared many times before.



JPB Foundation helps Picower researchers bridge traditional funding gaps

Targeted philanthropy nurtures new ideas and innovations, helps cover essential overhead costs other grants don't

If your mental image of scientific research funding is a professor applying for and receiving a government or foundation grant, you have a valid, but incomplete picture in mind. If that traditional model were all there was, a lot less research would happen than you might think.

That's because the traditional model leaves important gaps. Government grants typically only fund ideas that already have substantial amounts of preliminary data. Funding to get those first results, however, must come from somewhere else. Meanwhile, many foundation grants may support earlier-stage ideas but they often don't cover the very real but "indirect" costs of research projects, such as building and laboratory facilities, researcher salaries, animal care and other support staff, shared instruments, and many other costs that labs must contribute toward to sustain the research enterprise. Some grants that don't provide funding for these necessary "indirect" charges can perversely become too expensive to win.

To bridge these gaps, thereby enabling the Picower faculty to develop and test their most promising new ideas, the JPB Foundation led by Barbara Picower has funded two programs at The Picower Institute. Major new gifts this year renewed support for the Picower Institute Innovation Fund (PIIF), which seed funds new ideas before traditional grants can be pursued, and the Catalyst Fund, which covers a portion of indirect costs, enabling Picower scientists to apply for foundation grants they otherwise couldn't receive.

"For us to make progress, in science or any other field, we must be able to launch, develop and test promising new ideas," said Barbara Picower, president of the JPB Foundation, who together with late husband Jeffry Picower first endowed the Institute in 2002. "By creating targeted funds to encourage innovative thinking by overcoming the gaps that would block their path we've enabled a lot of exciting research to move forward."

By helping Picower faculty overcome traditional research funding gaps, the programs have been key contributions to making the Picower Institute an exceptional place to do exceptional neuroscience, said Institute Director and Picower Professor Li-Huei Tsai. They not only spur new research, they also advance the training and careers of scores of postdocs and graduate students.

"Some of our most productive and impactful discoveries and inventions have started as projects supported by the PIIF," Tsai said. "More recently the Catalyst program has opened many new doors for us, vastly expanding our access to funding by making grants that don't sufficiently cover indirects more attainable."

By enabling his lab to pursue private and foundation giving, for example, Catalyst Program funding has helped Picower Professor Mark Bear secure grants to advance a promising new treatment approach for amblyopia, a common vision disorder in which partial occlusion of one eye during childhood leads to permanent vision impairment as the brain rewires during development to favor the "good" eye. His research has shown how to "reboot" the brain's visual system to restore lost vision for the unfavored eye after the occlusion is resolved.

Catalyst support has also helped Tsai secure private funding for her work to develop a non-invasive potential treatment for Alzheimer's disease in which sound and light stimulation increases the power of a key brain rhythm, leading to a healthier response to disease pathology.

The program also helped Associate Professor Myriam Heiman use the CRISPR gene editing technology to screen brain cells for a potential new drug target for Huntington's disease, a fatal neurodegenerative disorder.

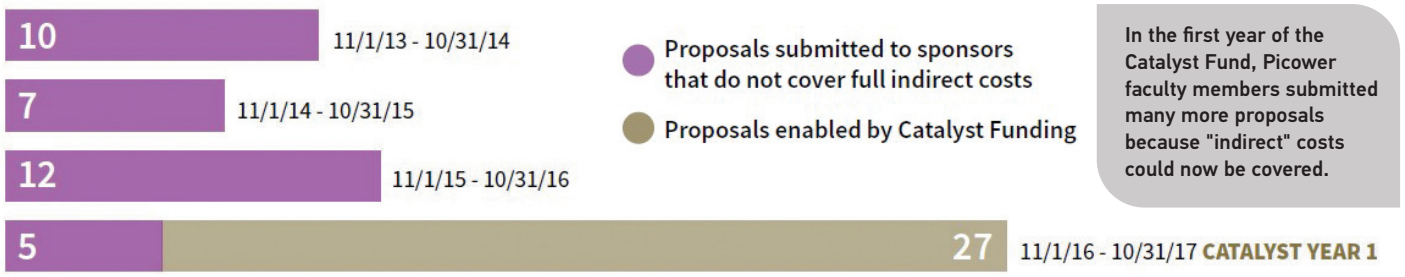
After the Catalyst program began in 2016, faculty applications for foundation grants soared because indirect costs had more coverage (see chart below).

PIIF funding, meanwhile, has spawned other key research. Associate Professor Steven Flavell has used PIIF support to invent innovative microscope systems that give him a nearly complete simultaneous view of every behavior an animal carries out and all the neural activity underlying those behaviors. Picower Professor Susumu Tonegawa credits PIIF support for helping him show that memory deficits in amnesia occur because successfully stored memories become inaccessible, rather than because they couldn't be stored in the first place.

And Picower Professor Earl Miller has employed PIIF funding for his efforts to formulate and test a new theory of how the brain dynamically employs rhythms of various frequencies to coordinate the neural activity necessary for cognitive functions such as working memory, paying attention to what's new, and recognizing what things have in common.

"In doing right now what I believe to be the most innovative work of my career, my lab is asking how brain waves weave the diverse processes of perception and thought together into our unified experience of consciousness," he said. "Because of the PIIF, we are breaking new ground in both theory and experiment."

These examples, and many more, show how crucial philanthropy is for enabling research.



In the first year of the Catalyst Fund, Picower faculty members submitted many more proposals because "indirect" costs could now be covered.

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20 years

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Neuroscience News Winter 2021

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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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BOTTOM ROW: **Earl Miller**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Elly Nedivi**, William R. (1964) & Linda R. Young Professor of Neuroscience, The Picower Institute for Learning and Memory, 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, Investigator, Howard Hughes Medical Institute, Investigator and Director of the RIKEN-MIT Center for Neural Circuit Genetics; **Li-Huei Tsai**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director, The Picower Institute for Learning and Memory; **Matthew Wilson**, Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology, Associate Director, The Picower Institute for Learning and Memory.