INSIDE

20th Anniversary Exhibition

The Picower Institute community celebrates two decades on the forefront of neuroscience research and beyond.

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Neuroscience News

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THE PICOWER INSTITUTE
FOR LEARNING AND MEMORY

20 years
OF DISCOVERY & IMPACT

DIRECTOR'S **MESSAGE**

Dear Friends,

Science builds on and scrupulously references what came before, but it does not live in the past. In academic research our business is training the next generation of scientists and making discoveries that advance knowledge.

This inherently forward-looking mindset is why our 20th Anniversary Exhibition on Sept. 22 did not focus on reminiscence. Instead, via quick, lay-friendly talks, our 13 speakers provided a representation from each of our labs of the leading edge of different areas of research. Quite intentionally these speakers were a mix of faculty, current trainees and "alumni." Our impact, after all, is not only reflected in what's discovered here, but also in what our training has helped people go on to accomplish in the next chapters of their careers.

In all it was a wonderful celebration. After the talks concluded we held a bustling poster session featuring dozens more projects and we unveiled a new painting by artist Mila Sheng, "Learnings and Memories," in our lobby. You can read our summary coverage on page 8 and by following the embedded QR code, you can see a YouTube playlist of our 20th Anniversary Video and many of the day's talks.

Even as we looked to the future, we acknowledged the extraordinary vision and generosity that not only launched this endeavor but also has sustained it ever since. Susumu Tonegawa, who is pictured on the cover delivering his exhibition talk, had the vision in 1994 to launch a center at MIT dedicated to learning and memory research. And in 2002 a transformative gift from The Picower Foundation of Barbara and Jeffry Picower elevated our research capacity and excellence to the level of a leading neuroscience institute.

Read on for more news and features about our research, people and events. We wish you a happy Holiday Season and, in the spirit of looking forward, a new year full of discovery, health and joy.

LI-HUEI TSAI, DIRECTOR

The Picower Institute for Learning and Memory

Bear elected member of National Academy of Medicine

The National Academy of Medicine announced in October that its members have elected Mark Bear, Picower Professor of Neuroscience in The Picower Institute for Learning and Memory, to join their esteemed ranks.

Election to the Academy is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service, the Academy noted in announcing the election of 100 new members including Bear.

Bear's citation from the Academy reads: "For his discovery of fundamental mechanisms by which sensory experience and deprivation modify synapses by increasing or decreasing their strength during the development of the brain, and how these mechanisms contribute to, and can be marshalled to treat, developmental brain disorders."

Synapses are the connections neurons make to form the circuits that enable brain functions including perception and cognition. During several decades of research, including the last 20 years at MIT, Bear's lab has made key discoveries about the molecular means by which synapses dynamically change in response to experience, a capability known as "plasticity." In 2006, for example, Bear and co-authors provided the first direct demonstration that a key strengthening mechanism, long-term potentiation, occurs during memory formation in the hippocampus region of the brain. In the 1990s, Bear's lab led the discovery that reduced sensory input weakens synaptic connections by a mechanism called long-term depression, or LTD.

Subsequent studies in Bear's lab have led to potential therapies for disorders related to LTD. One is the common vision disorder amblyopia, in which occlusion of an eye during childhood, for instance from a cataract, weakens connections in the brain serving that eye. Bear's lab has shown in multiple animal models of amblyopia that temporarily anesthetizing the normal or "fellow" eye resets the threshold for synaptic plasticity, allowing incoming sensory input to strengthen rather than weaken synapses, even in adulthood when other treatments fail. The result is a recovery of vision in the weakened eye without any cost to the fellow eye.

Picower Professor Mark Bear. Photo: Endeavor Films

Bear's lab has also advanced potential therapies for autism spectrum disorders including Fragile X syndrome, in which the genetic loss of a protein called FMRP leads to too much LTD. His lab has discovered that intervening in the molecular mechanisms of LTD can have substantial therapeutic effects in mouse models and has shown promise in clinical trials. Bear has continued to work to develop therapies based on the discovery.

Bear said that the Academy's recognition of these discoveries and achievements honors the many young scientists with whom he has worked in his lab over the years.

"I am delighted and grateful to have received this honor, which I accept on behalf of the many students and postdocs who have contributed to the science my laboratory is recognized for."

Bear joins Picower Institute colleagues Emery N. Brown, Mriganka Sur, and Li-Huei Tsai as National Academy of Medicine members. In addition to Bear, MIT Chemistry Professor Laura L. Kiessling earned election to the Academy this year.

With DNA breaks, **Alzheimer's** neurons seek help

Picower Institute researchers have found evidence in both mouse models and postmortem human brains of a direct link between two problems that emerge in Alzheimer's disease: a buildup of double-stranded breaks (DSBs) in the DNA of neurons, and the inflammatory behavior of microglia, the brain's immune cells.

The connection is that the ailing neurons instigate the inflammatory response. "This is a novel concept in neuroscience: the idea that neurons can be activating inflammatory activity in response to DNA damage," said study lead author Gwyneth Welch, a former graduate student in the lab of senior author Li-Huei Tsai.

"The general idea was that neurons have a more passive relationship with microglia regarding age-associated neuroinflammation."

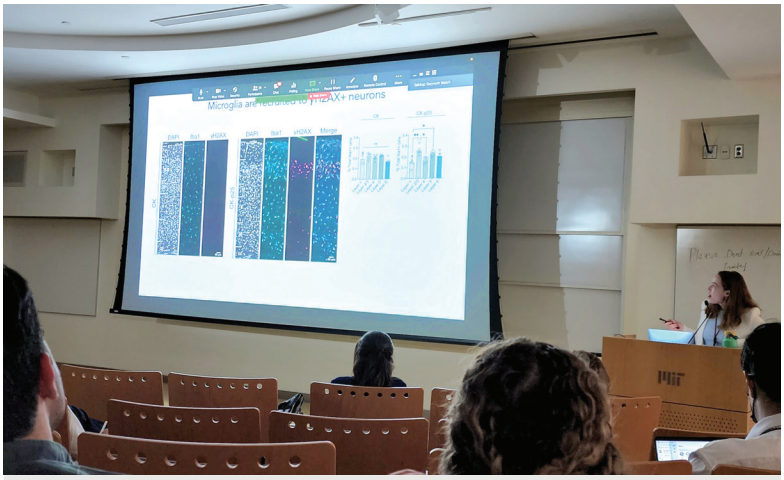
Instead, what Welch, Tsai and co-authors report in *Science Advances* is that neurons coping with mounting DSBs go through stages of first trying to fix their DNA and then, when that fails, signaling microglia, which respond by taking on a more inflammatory state. In experiments where the scientists interrupted the signaling, they prevented microglia from entering that state and degrading neural circuit connections, or synapses."We have a longstanding interest in understanding DNA breaks in neurons," said Tsai, Picower Professor of Neuroscience and a founder of MIT's Aging Brain Initiative.

"We previously showed that DNA double stranded breaks are necessary for the induction of activity-regulated gene expression in neurons but we also observed profound DNA damage in neurons in the early stages of neurodegeneration.

"We now know that DNA-damaged neurons exhibit senescent phenotypes and play an active role in eliciting an immune response from microglia and perhaps astrocytes," Tsai said.

Welch used the lab's "CK-p25" mouse model of Alzheimer's, in which disease pathology can be induced. She observed that DSBs appeared within a week, peaked in number after two weeks and then tapered off by six weeks. Meanwhile, neurons progressively lost their ability to express a molecular marker of neuronal identity. This suggested that coping with DSBs occurs in stages. First neurons have few DSBs and strong identity (baseline), then high DSBs with no loss of identity (stage 1), then high DSBs and a loss of neuronal identity (stage 2).

To understand what cells were doing differently in each stage, Welch and the team used multiple "transcriptomics" technologies to track differences in gene expression. Neuronal identity genes were most strongly expressed at baseline, DNA repair genes were strong during stage 1, and immune signaling genes became prominent during stage 2.



Gwyneth Welch presents her research at her PhD thesis defense.

Among the immune signaling genes were ones governed by the master transcription regulator NFkappaB. These included the cytokines Ccl2 and Cxcl10.

When Welch also looked at gene expression in the brains of people with DSBs and with Alzheimer's she also found many significant overlaps.

"We found that stage 1 and stage 2 gene signatures were active in human DSB-bearing neurons," the researchers wrote. "This neuronal immune signature was further amplified in the context of AD pathology, suggesting that it may serve a functional role in disease-associated neuroinflammation."

Having established that DSB-afflicted neurons employ NFkappaB to send out immune signals such as Ccl2 and Cxcl10, Welch and the team then asked what the effect was. For this analysis Welch used spatial transcriptomics. She divided up both uninduced and induced mouse brains into many areas, and rated each area based on the strength of their DSB signal. Then she analyzed gene transcription in each area and found that locations with high DSBs also had many more microglia in an inflammatory state than locations with low DSBs. They were also able to directly image this relationship, yielding the observation that inflammatory microglia (evidenced by abnormally large cell bodies) were co-located with high-DSB neurons.

Then the team disrupted NFkappaB regulated transcription in neurons by interfering with a key molecular cog in that machinery called p65. That step resulted in reduced proliferation of microglia and reduced microglia cell body size. It also induced beneficial changes in microglia gene expression, making them more consistent with their normal "homeostatic" state.

In other experiments they found that depleting Cxcl10 and Ccl2 from the brain prevented microglia from becoming reactive.

And looking back at the neurons, they saw that while knocking down NFkappaB activity didn't prevent them from dying, it did preserve circuit connections, or synapses, on the neurons that remained alive. That's important because those circuit connections underlie brain function and microglia are known to prune those.

"We show that inhibition of NFkappaB rescued synaptic loss in neurodegeneration, further elucidating of impact of the neuroimmune response on synaptic integrity and cognitive function," Tsai said.

How environment and state are integrated to control **behavior**

Say you live across from a bakery. Sometimes you are hungry and therefore tempted when odors waft through your window, but other times satiety makes you indifferent. Sometimes popping over for a popover seems trouble-free but sometimes your spiteful ex is there. Your brain balances many influences in determining what you'll do. A new study examines this in a much simpler animal, highlighting a potentially fundamental principle of how nervous systems integrate multiple factors to guide food-seeking behavior.

All animals share the challenge of weighing diverse sensory cues and internal states when formulating behaviors. To learn how, Picower Institute researchers turned to the *C. elegans* worm, whose well-defined behavioral states and 302-cell nervous system made the complex problem tractable. They emerged with a case study of how in a crucial olfactory neuron called AWA, many sources of state and sensory information converge to independently throttle the expression of a key smell receptor. The integration of their influence on that receptor's abundance then determines how AWA guides roaming around for food.

"We dissected the mechanisms that control the levels of a single olfactory receptor in a single olfactory neuron, based on the ongoing state and stimuli the animal experiences," said senior author and Associate Professor Steven Flavell. "Understanding how the integration happens in one cell will point the way for how it may happen in general, in other worm neurons and in other animals."

Postdoc Ian McLachlan led the study in *eLife*.

"We were surprised to find that the animal's internal states could have such an impact on gene expression at the level of sensory neurons—essentially, hunger and stress caused changes in how the animal senses the outside world by changing what sensory neurons respond to," he said. "We were also excited to see that chemoreceptor expression didn't just depend on one input, but on the sum total of external environment, nutritional status, and levels of stress. This is a new way to think about how animals encode competing states and stimuli."

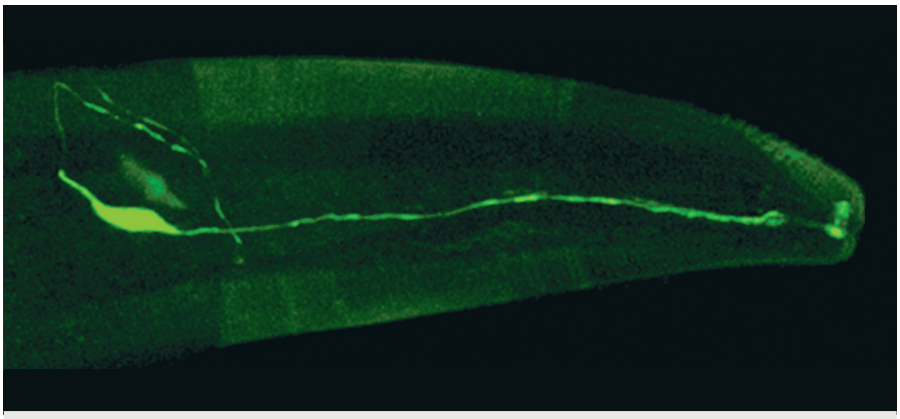
The team started by looking at what genes changed in expression the most when worms were kept from food for three hours compared to when they were well fed. As a category, genes for many chemosensory receptors showed huge differences. AWA proved to be a neuron with a large number of these upregulated genes and two receptors, STR-44 and SRD-28, appeared especially prominent among those.

This result alone showed that an internal state (hunger) influenced the degree of receptor expression in a sensory neuron. McLachlan and his co-authors then showed that STR-44 expression also independently changed based on the presence of a stressful chemical, based on a variety of food smells, and on whether the worm had received the metabolic benefits of eating food. Further tests by graduate student and co-second author Talya Kramer revealed which smells trigger STR-44, allowing the researchers to then demonstrate how changes in STR-44 expression within AWA directly affected food-seeking behavior.

For example, the team showed that while both fed and hungry worms would wriggle toward the receptors' favorite smells if they were strong enough, only fasted worms (which express more of the receptor) could detect fainter concentrations. They also found that while hungry worms will slow down to eat upon reaching a food source even as well-fed worms cruise on by, they could make well-fed worms act like fasted ones by artificially overexpressing STR-44.

Multiple factors push and pull on STR-44. When the researchers added a chemical that stresses the worms, that ratcheted down STR-44 expression even in fasted worms and suppressed the worms' urge to wriggle toward the odor that STR-44 responds to.

Technical assistant Malvika Dua helped to reveal how other food-sensing neurons affect STR-44 expression in AWA via insulin signaling and synaptic connections. Cues about whether the worm is actively eating come to AWA from neurons in the intestine that use a molecular nutrient sensor called TORC2. These, and the stress-detecting pathway, all acted on FOXO, which is a regulator of gene expression. In other words, all the inputs that affect STR-44 expression in AWA were doing so by independently pushing and pulling on the same molecular lever.



The neuron AWA stretches from a worm's brain to its nose. A new study shows that the brain routes many internal states and sensory cues to this neuron, affecting expression of a smell receptor.

Flavell and McLachlan noted that pathways such as insulin and TORC2 are present in not only other worm sensory neurons but also many other animals including humans.

Basic insights from this study could help inform research on how gut-brain signaling via TORC2 works in people.

"This is emerging as a major pathway for gut-to-brain signaling in *C. elegans* and I hope it will ultimately have translational importance for human health," McLachlan said.

Student earns ‘Open Data’ prize

Djuna von Maydell, a graduate student in the lab of Picower Professor Li-Huei Tsai earned one of MIT’s Inaugural “Open Data” prizes for making freely available the first database of gene expression in multiple types of brain cells in people who have the Alzheimer’s risk gene variant APOE4. Maydell received the award at the Hayden Library October 28.

“We asked the question of how this APOE4 variant might be affecting individual cells,” said von Maydell who worked with colleagues Leyla Akay, Joel Blanchard and Jose Davila-Velderrain. “But there are many other questions that could be asked.” That was just one of the reasons she cited for making the data freely available. Doing so also honors the brain tissue donors who made their gifts to advance science, and making the data free empowers labs that can’t afford to build analogous datasets.

Djuna von Maydell delivers a talk about her dataset. Photo: Bryce Vickmark

Providing new pathways for neuroscience research and education

Payton Dupuis’s interest in biology research began where it does for many — witnessing a relative struggling with an incurable medical condition. Her uncle suffered from complications from diabetes. Dupuis, a senior at Montana State University, says diabetes is prominent on the Flathead Reservation in Montana where she grew up, and witnessing the impacts of the disease inspired her to pursue a career in research. Since then, that passion has taken Dupuis around the country to participate in various summer research programs in the biomedical sciences.

Most recently, she participated in the Bernard S. and Sophie G. Gould MIT Summer Research Program in Biology. The program, offered by the departments of Biology and Brain and Cognitive Sciences, encourages students from underrepresented groups to attend graduate school and pursue careers in science research. More than 85 percent of participants have enrolled in highly ranked graduate programs, many of them returning to MIT, just as Dupuis is considering.

Dupuis worked in the lab of Troy Littleton, Menicon Professor of Neuroscience in The Picower Institute.

“I definitely fell in love with the lab,” she says. With Littleton, Dupuis completed a project looking at complexin, a protein that can both inhibit and facilitate the release of neurotransmitters like serotonin. It’s also essential for the fusion of synaptic vesicles, the parts of neurons that store and release neurotransmitters.

Human neurological diseases have been linked to complexin deficiency. To learn more about how the protein affects neurons, Dupuis used gene editing to vary the amounts of different subtypes of the protein in fruit flies, which normally have two subtypes. Using fluorescent staining, Dupuis compared how neurons lit up in flies that had no complexins, both, or just one or the other. Her work illuminated how altering the amount of complexin changed how the flies released neurotransmitters and formed new synaptic connections.

Researching neuronal activity in fruit flies in the lab of Professor Troy Littleton. Photo: Steph Stevens

Dupuis says that the study was the perfect fit intellectually, and a formative experience as a researcher.

As for what’s next, Dupuis says her experience at MIT has sold her on pursuing graduate work in brain science. “Boston is really where I want to be and eventually work, with all the biotech and biopharma companies around,” she says. The program includes professional development opportunities. Though Dupuis had always been interested in industry, she says she appreciated attending career panels this summer that demystified what that career path really looks like and what it takes to get there.

A "golden era" to study the brain

As an undergraduate, Mitch Murdock was a rare science-humanities double major, specializing in both English and molecular, cellular, and developmental biology at Yale University. Today, as a Brain and Cognitive Sciences doctoral student in The Picower Institute, he sees how his English education expanded his horizons as a neuroscientist.

"One of my favorite parts of English was trying to explore interiority, and how people have really complicated experiences inside their heads," Murdock explains. "I was excited about trying to bridge that gap between internal experiences of the world and that actual biological substrate of the brain."

At Yale Murdock was in a traditional molecular biology lab. He planned to stay after graduation as a research technician but advisor Ron Breaker encouraged him to explore. He ended up in the lab of Conor Liston, an associate professor at Weill Cornell Medicine who studies how factors such as stress and sleep regulate the modeling of brain circuits. There Murdock was first exposed to neuroscience and began to see the brain as the biological basis of the philosophical questions about experience and emotion that interested him.

"It was really in his lab where I thought, 'Wow, this is so cool. I have to do a PhD studying neuroscience,'" Murdock laughs.

He examined the impact of chronic stress on brain activity in mice. Specifically, he was interested in ketamine, a fast-acting antidepressant prone to being abused, with the hope that better understanding how ketamine works will help scientists find safer alternatives. He focused on the spines along the vine-like dendrites of neurons that help transmit electrical signals and provide a physical substrate for memory storage. The research suggested that ketamine works by recovering dendritic spines that can be lost after periods of chronic stress.

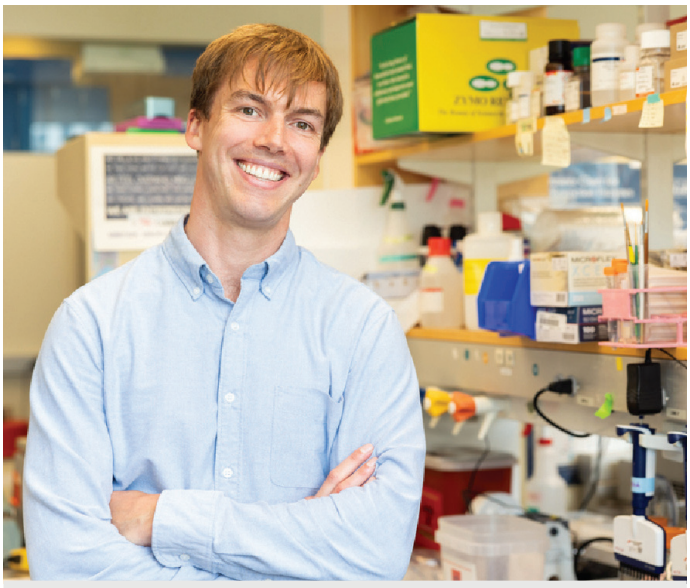
After three years at Weill Cornell, Murdock decided to pursue a PhD, hoping to continue some of the work he started with Liston. He chose MIT because of the dendritic spines research in the lab of Elly Nedivi, the William R. (1964) and Linda R. Young Professor of Neuroscience in The Picower Institute.

During lab rotations, Murdock spent time shadowing a physician at Massachusetts General Hospital who was working with Alzheimer's disease patients.

"If you have Alzheimer's disease, there's very little that can be done," he says. "That was a big wake-up call for me."

Murdock planned his remaining lab rotations and eventually settled into the lab of Li-Huei Tsai, Picower Professor and director of The Picower Institute. For the past five years, Murdock has worked with Tsai on Alzheimer's research.

Members of the Tsai lab have shown how non-invasive 40Hz light and sound stimulation induce brain activity that can improve memory loss in mouse models of Alzheimer's. Scientists think that during sleep small movements in blood vessels drive spinal fluid into the brain, which, in turn, flushes out toxic metabolic waste. Murdock's research suggests that the sensory stimulation might drive a similar process, flushing out waste that can exacerbate memory loss.



Doctoral student Mitch Murdock uses new technology and fundamental biological techniques to study the impacts of Alzheimer's disease on the brain. Photo: Steph Stevens

Much of his work to understand Alzheimer's (and to contribute to the development of new treatments) is focused on the activity of single cells in the brain. Are certain neurons or types of neurons genetically predisposed to degenerate, or do they break down randomly? Why do certain subtypes of cells appear to be dysfunctional earlier on in the course of Alzheimer's disease? How do changes in blood flow in vascular cells affect degeneration?

To answer these questions, Murdock relies on new single-cell sequencing techniques that he says have changed the way we think about the brain.

"There are a lot of different cell types in the brain, and we think that they might contribute differentially to Alzheimer's disease risk," says Murdock. "We can't think of the brain as only about neurons."

Murdock says that that kind of "big-picture" approach — thinking about the brain as a compilation of many different cell types that are all interacting — is the central tenet of his research. To look at the brain in the kind of detail that approach requires, Murdock also works with Ed Boyden, the Y. Eva Tan Professor in Neurotechnology. This collaboraton has allowed Murdock to use new technologies such as expansion microscopy and genetically encoded sensors to aid his research.

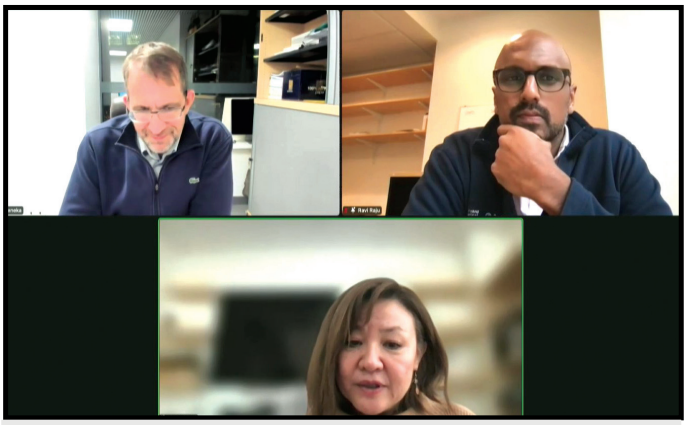
Such technology has helped blow the field wide open, he says: "This is such a cool time to be a neuroscientist because the tools available now make this a golden era to study the brain."

That rapid intellectual expansion applies to the study of Alzheimer's as well, including newly understood connections between the immune system and Alzheimer's — an area in which Murdock says he hopes to continue after graduation.

Event examines links between neurodegeneration and **Down syndrome**

Neuroscientists still have a tremendous amount to learn about the causes and courses of neurodegenerative diseases and Down syndrome, but as speakers at the Oct. 5-6 MIT symposium "Glial and Neuronal Biology of the Aging Brain" pointed out, often when they make a new discovery in the context of one such condition, it teaches them something relevant to others.

"Our belief is that the study of the aging brain can learn a great deal from the study of Down syndrome and vice versa," said Picower Professor Li-Huei Tsai who directs the two MIT entities that jointly hosted the conference: The Aging Brain Initiative and the Alana Down Syndrome Center. "It would be a wonderful outcome of this symposium if we can play even a small role in bringing these two communities of scientists, physicians, and engineers, and even caregivers closer together."



Li-Huei Tsai, bottom, asks a question of speaker Michael Heneka (top left) while moderator Ravi Raju listens.

Tracy Young Pearse of Harvard Medical School (HMS) and Brigham and Women's Hospital discussed her lab's finding that the three copies of the genes APP and DYRK1A found in DS neurons (because they have three copies of chromosome 21), increase phosphorylated tau (a pathological hallmark of Alzheimer's) and promote excessive transport and release of neurotransmitters across connections with other neurons, a potential source of circuit dysfunction.

MIT Associate Professor Myriam Heiman said breakdown of the blood-brain barrier, which strictly filters what the body and brain exchange, may be a key contributor to many neurodegenerative diseases. In new research that produced a novel "atlas" of cell types in the brain's blood vessels, her lab showed clear evidence that vascular integrity is weakened in Huntington's disease and that the degradation is associated with a problematic innate immune response.

Elizabeth Head of UC Irvine related vasculature dysfunction to DS and Alzheimer's. In DS patients an excess of amyloid protein in brain blood vessels leads to cerebral amyloid angiopathy (CAA), a condition closely associated with Alzheimer's. Head's lab has shown that people with DS and CAA exhibit microbleeds along their brain blood vessels.

Head collaborates with Adam Brickman of Columbia University. He presented research showing that MRI of "white matter hyperintensities" and other vascular problems can be a biomarker of Alzheimer's pathology in people with DS. The hyperintensities correlate with microbleeds.

Other speakers focused on the brain's immune cells, called microglia, which take on many different states in Alzheimer's ranging from beneficial to harmful.

Beth Stevens of HMS & Boston Children's Hospital described methods her lab has developed for culturing microglia from stem cells and then coaxing them into these many states by tailoring either their genetic background, their environmental context, or both.

Molecular manipulations of microglial state can sustain the brain's resilience to Alzheimer's pathology, said Li Gan of Weill Cornell Medicine. By reducing expression of the gene transcription factor NFkappaB in microglia, her lab reduced tau spreading. Gan also showed how intervening in a runaway immune pathway in microglia by knocking down a key molecule improved learning and memory in mice. The method increased activity of a resilience-promoting transcription factor called MEF2 that Tsai's lab has also identified as beneficial.

Nancy Yuk-Yu Ip's lab at Hong Kong University of Science and Technology found that in Alzheimer's a form of the molecule ST2 intercepts the immune molecule interleukin 33 (IL-33) that would otherwise prompt a transition of microglia into a beneficial state. She showed how injecting IL-33 improves Alzheimer's pathology in mice and has described a protective genetic variant found in people.

Michael Heneka of the Luxembourg Centre for Systems Biomedicine showed how microglia extend "tunneling nanotubes" to neurons beset with tau or alpha-synuclein (a toxic aggregate most prevalent in Parkinson's disease) to remove the proteins and to supply neurons with fresh mitochondria to rescue them from oxidative stress.

Rather than microglia or vasculature, Shane Liddelow of NYU focused on astrocytes, another key brain cell type. He shared research indicating that subtypes of astrocytes have inflammatory responses in disease and in the case of Alzheimer's, associate with pathology in particular parts of the brain.

And Gilbert Di Paolo of Denali Therapeutics presented his company's potential therapy for a subset of frontotemporal dementia cases. In those cases, mutations reduce levels of progranulin, which undermines the function of lysosomes in several cell types. By restoring levels of progranulin in cells the company restores lysosomal function and indicators of cell health.

Complementing the talks were posters of a dozen MIT postdocs and graduate students from seven labs affiliated with the Aging Brain Initiative, the Alana Center, or both. Many highlighted systemic approaches to understanding and treating disease including imaging innovations and potential interventions at the level of brain circuits and networks.

Celebrating 20 years of discovery, Picower Institute looks ahead to continuing impact

At an exhibition marking two decades since a transformative gift from The Picower Foundation, current and alumni members described research at the forefront of neuroscience and beyond

If there ever was an event that would seem designed for dwelling on the past, it would be the anniversary celebration of an Institute centered on the study of memory, but the first of many insights offered by the 20th Anniversary Exhibition of The Picower Institute for Learning and Memory at MIT Sept. 22 was that memory is all about the future.

Ever since UC Berkeley psychology Professor David Foster was a postdoc in the Picower Institute lab of Fairchild Professor Matthew Wilson, his research has employed sophisticated neural recordings and behavioral experiments showing that animals don't just store memories of the spaces and objects around them. In the first talk of the day, Foster demonstrated that during periods of rest animals often think about where they might want to go and rehearse possible future routes in their mind. In other words, much like people do, they use past memory of their experiences to consider how to move forward in the future.

Picower Professor Susumu Tonegawa, who founded MIT's Center for Learning and Memory in 1994 and worked with the Picower family to create the Picower Institute in 2002, spoke right after Foster. He described new research led by postdoc Afif Aqrabawi showing how the brain physically turns individual memories of experience into generalizable knowledge for use in the future. Tonegawa offered the example of restaurant dining. After a few delicious dinners, you learn the general idea of what to expect the next time. A decade ago Tonegawa's lab showed how individual event memories are represented by connected ensembles of neurons called engrams. Aqrabawi's new findings essentially show how the brain produces generalized knowledge by extracting and integrating the similarities among the individual experiences stored in those engrans.

Picower Professor Earl K. Miller discussed how flexible high-level cognition emerges from brain networks.

Just as the meaning of memory is to inform the future, a clear message of the symposium was that the last two decades of The Picower Institute's research, discoveries and innovations, as well as the training it has provided to hundreds of scientists who have carried on independent careers, are helping to shape the present and future of neuroscience, medicine and industry.

Postdocs and graduate students treated audience members to their latest research at a poster session following the speaking program. Photos: Faith Ninivaggi

Each of The Picower Institute's 13 labs were represented through talks delivered by the primary investigator, a current trainee or a member of Picower's growing "alumni" community. As Picower Professor and Institute Director Li-Huei Tsai framed it for the hybrid audience of about 1,700 people, "Each of today's talks will illustrate in different ways the impact of our research and training on current questions across many areas of neuroscience."

MIT President L. Rafael Reif, in a pre-recorded message, presaged the broad and urgent significance of the research those talks would cover when he praised the Picower Institute as "a brilliant collective of scientists who work together…to help us better understand ourselves and to advance solutions that offer people with brain disorders real, practical hope."

Reif and Tsai also led many speakers in thanking Barbara Picower, President of the JPB Foundation, not only for the gift she and her late husband Jeffry gave back in 2002, but for continued support, vision and insight ever since.

In her remarks Picower reflected those expressions of gratitude back on the researchers.

"I am only an enabler," she said. "It wouldn't matter how much money anybody put into the Institute if we didn't have great scientists doing great work. So I would like to turn this around a little bit and say thank you to our scientists, many of them who have also been at the Institute for 20 years or more."

Graduate student Indie Garwood speaks about her research on ketamine anesthesia.

Impacts at Picower

One of those long-tenured scientists is Picower Professor Earl K. Miller whose talk took on a past-and-future theme explicitly. He described his lab's 27-year journey from a time when neuroscientists thought the brain worked like clockwork—individual parts all playing single, distinct roles—to the modern era where advances in technology and understanding have revealed that amazing cognitive abilities such as working memory, prediction, categorization and attention emerge from the brain's ability to process information through dynamically assembled networks. His work, for instance, has shown that neurons can take on multiple roles and that brain waves of particular frequencies can assemble and coordinate ensembles of neurons as needed to sculpt the flow of information across the brain's cortex. Hardwired connections, therefore, represent possible routes for information flow but don't determine it.

In fact, Lister Brothers Associate Professor Steve Flavell noted that while his lab's model organism, the *C. elegans* worm, is the only animal on the planet whose whole neural wiring diagram has been mapped out, it is still capable of producing a rich and flexible repertoire of behaviors. He described how his lab has developed advanced microscopy and computational techniques to enable unprecedentedly comprehensive correlations of the little animal's neural activity and behavior. That in turn has allowed him to demonstrate fundamental principles of how nervous systems can account for many variables, such as internal states and environmental conditions, to generate situationally appropriate behaviors even from "hardwired" circuits.

Jeongtae Kwon, a postdoc in the lab of Mark Hyman Jr. Associate Professor Gloria Choi, described a vivid new example of behavioral flexibility in mice. He recently led a study showing that while male mice have a powerful mating instinct, a circuit connecting olfactory regions with a brain region called the amygdala will override that instinct if a potential mating partner smells like she is sick. Essential to this "social distancing" circuit's function is the presence of the neuromodulatory chemical TRH. Kwon said he planned to continue his work when he started his own lab in Korea in October.

Picower researchers are not only illuminating how the brain produces knowledge, cognition and behavior, but also consciousness. Representing the lab of Emery N. Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, graduate student Indie Garwood described how the lab has shown how ketamine general anesthesia works. They've found that it promotes an unusual signature of gamma wave activity that disrupts consciousness and that the waves arise from how the drug promotes elevated production of the neuromodulatory chemical acetylecholine. Such findings point to new ideas for the future, she said, including improving monitoring anesthesia in the operating room, improving understanding of how ketamine affects the brain at a systemic level, and understanding more about how drugs like ketamine affect consciousness.

In his talk, Newton Professor Mriganka Sur traced an arc of his lab's 30 years of research from the past to the future, showing how fundamental research can lead to the development of clinical treatments. Beginning with a revolutionary study in which he demonstrated the brain's "plasticity" by showing how a developing ferret's brain would repurpose the auditory cortex to augment the visual cortex if cut off from input from the ears, Sur's lab has gone on to study cortical plasticity intensely. His lab has produced powerful demonstrations of how neural activity changes with learning and how individual neural connections, or synapses, change to enable such adaptive flexibility. He also described how such investigations have revealed a promising treatment for Rett syndrome: In 2009 the lab showed how a protein that is crucial for regulating synaptic plasticity is lacking in the developmental condition and that many symptoms can be improved with doses of the protein called IGF-1. A company that has run with the idea has now successfully completed phase III clinical trials and asked the FDA to approve the treatment.

"We expect that IGF-1 peptide, with two methyl groups added so that it is bioavailable longer, will be approved as the first therapeutic for any neurodevelopmental disorder," Sur said.

Ever since Associate Professor Myriam Heiman joined the institute in 2011, her research has been guided by the principle that fundamental understanding can lead to breakthroughs in addressing disease. She focused her talk on a new, highly emblematic and collaborative study led by grad student Francisco Garcia. Using several innovative techniques the research not only produced the first comprehensive map of the cell types that make up the brain's blood vessels, but also identified specific ways in which the integrity of the blood-brain barrier unravels in Huntington's disease. Because blood-brain barrier deficiencies are noted in many other diseases, she said, the findings could help address many disorders.

Impact beyond

As much as The Picower Institute contributes to the field through research in its labs, it also contributes by training researchers, like Foster and Kwon, who then establish their own. When he was a postdoc in Tsai's lab, for example, Joel Blanchard engineered a cutting-edge model of the human blood-brain barrier using stem cells to investigate the effects of an Alzheimer's risk gene. Now an assistant professor at Mt. Sinai, he continues to use stem cells to study aging and neurodegenerative disease. In his talk, Blanchard described a new study in which his lab used stem cells to model the pathology of a gene mutation that causes a rare juvenile form of Parkinson's disease. The models have revealed that the mutation causes cells called astrocytes to become toxic to neighboring dopamine-producing neurons and have helped the lab identify a drug that can prevent the adverse pathology.

Members of the lab of Associate Professor Kwanghun Chung pose with Tim the Beaver, decked out in his lab coat and goggles.

Much as Blanchard has continued his neurodegeneration work, Ben Auerbach, an alumnus of the lab of Picower Professor Mark Bear, has continued to study autism in his lab as an assistant professor at the University of Illinois. Auerbach described how his team has used rats modeling Fragile X syndrome to understand, at multiple levels of brain physiology, how the genetic mutation underlying the disease produces a symptom common across many autism spectrum disorders: sensory hypersensitivity. He's found that it derives from hyperactivity among neurons in the auditory cortex and shown that chemically intervening to promote inhibition reduces auditory hypersensitivity.

In his talk, Boston University Assistant Professor Jerry Chen discussed how his lab has been developing technologies to allow measurements spanning neural gene expression, connectivity, activity and animal behavior to produce "vertically integrated" insights for every animal subject in the lab. Earlier this year the lab used the approach to identify and characterize the key role a previously unknown type of neuron plays as a hub of cortical circuits enabling sensory processing in mice. As he spoke he traced roots of the success back to both technologies and scientific ideas he learned when he was in the Picower lab of William R. and Linda R. Young Professor Elly Nedivi.

There is, of course, no requirement at all that alumni carry on their research with such clear continuity. Sometimes the training and exposure they gain at the Picower Institute proves just as valuable for launching into distinct career territory.

For example, Sung-Yon Kim, now a professor at Seoul National University, was the first postdoc in the Picower Institute and Chemical Engineering lab of Associate Professor Kwanghun Chung. In Chung's lab, Kim contributed to developing innovative technologies for clearing, labeling, preserving, imaging and analyzing brains and other tissues. But in his own research he's making discoveries about something quite different: identifying the neural and circuit mechanisms that underlie survival behaviors including finding warmth and regulating eating.

And Zacchary Piccioli, an alumnus of the lab of Menicon Professor Troy Littleton didn't speak about neuroscience at all. Instead, as a director of R&D strategy at Moderna, he discussed how the company hopes to use the distinct advantages inherent in mRNA vaccines (like the company's highly successful Covid-19 vaccines) in the fight against other infectious diseases such as influenza.

"I think Zach is a really wonderful example of how Picower alumni have impacts beyond just the field neuroscience including in clinical therapeutics," Littleton said.

Right before she closed the day by inviting viewers and attendees to the unveiling of the new painting "Learnings and Memories" by artist Mila Sheng in the Picower Institute lobby, MIT School of Science Dean Nergis Mavalvala noted that a particular excitement she finds in science is that finding the answers to research questions often yields new questions that evoke further discovery. There will always be more to learn. "We're not only celebrating the past 20 years of Picower Institute history but we are also kicking off the next 20 years of discovery and impact," Mavalvala said. "The quest goes on."

Scan the QR code to view talks and other videos from the event.

Picower Institute staff members David Orenstein and Will Lawson drop the cloth to unveil "Learnings and Memories," a new painting by artist Mila Sheng in the Picower Institute main lobby.

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TOP ROW: **Mark F. Bear**, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences, Investigator, Howard Hughes Medical Institute (HHMI); **Emery Brown**, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Gloria Choi**, Mark Hyman Jr. Career Development Associate Professor, Department of Brain and Cognitive Sciences; **Kwanghun Chung**, Associate Professor, Departments of Chemical Engineering and Brain and Cognitive Sciences, Institute of Medical Engineering and Science core faculty; **Steven Flavell**, Lister Brothers Career Development Associate Professor of Neuroscience, The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; **Myriam Heiman**, Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences; **Troy Littleton**, Menicon Professor of Biology and Neuroscience, Departments of Biology and Brain and Cognitive Sciences.

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.