

## The Picower Institute for Learning and Memory

The [Picower Institute for Learning and Memory \(PILM\)](#) 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. Picower Institute researchers explore the brain at multiple scales, from genes and molecules to cells, synapses, circuits, and systems, producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

### Awards and Honors

- Professor Mark F. Bear: RPB Walt and Lilly Disney Award for Amblyopia Research
- Professor Emery N. Brown: 2020 Swartz Prize for Theoretical and Computational Neuroscience
- Associate Professor Gloria Choi: Mark Hyman, Jr. Career Development Professorship
- Associate Professor Kwanghun Chung: promoted to associate professor with tenure
- Associate Professor Steven Flavell: Sloan Research Fellowship
- Associate Professor Myriam Heiman: promoted to associate professor with tenure
- Professor Troy Littleton: Brain and Cognitive Sciences (BCS) Award for Excellence in Graduate Teaching
- Professor Mriganka Sur: 2021 Paul E. and Lilah Newton Brain Science Award
- Professor Li-Huei Tsai: elected member of the American Academy of Arts and Sciences
- Dustin Hayden (Bear Lab graduate student): Walle Nauta Award for Continuing Dedication to Teaching by a Graduate Student
- Daniel Montgomery (Bear Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching
- Gabriel Schamberg (Brown Lab postdoc): 2021 BCS Award for Excellence in Teaching by a Postdoc
- Indie Garwood (Brown Lab graduate student): 2021–2022 School of Science MathWorks Fellowship
- Sirma Orguc (Brown Lab postdoc): 2021 Schmidt Science Fellowship
- Yasmin Yarden (Choi Lab postdoc): Human Frontiers Science Program Postdoctoral Fellowship

- Tomoe Ishikawa (Choi Lab postdoc): Japan Society for the Promotion of Science Overseas Research Fellowship
- Gurrein Madan (Flavell Lab graduate student): 2020–2021 School of Science MathWorks Fellowship
- Preston Ge (Heiman Lab graduate student): Walle Nauta Award for Excellence in Graduate Teaching
- Nhat Le (Sur Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching
- Gabrielle Drummond (Sur Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching
- Cherry Wang (Sur Lab undergraduate student): 2021 BCS Undergraduate Research Award
- Rebecca Pinals (Tsai Lab postdoc): 2021 Schimdt Science Fellowship
- Vishnu Dileep (Tsai Lab postdoc): NIH Pathway to Independence Award (K99)
- Martin Kahn (Tsai Lab postdoc): Swiss Postdoctoral Fellowship
- Brittany Greenough (Picower headquarters): 2021 School of Science Infinite Mile Award

## Research

Below are summaries of major research advances made during the reporting period by Picower Institute faculty members.

Mark Bear's lab published a study in the *Journal of Neuroscience* showing that as novel images become familiar (i.e., because they've been seen repeatedly), that transition is marked by stark changes in the visual cortex. Gamma rhythms give way to lower frequency beta rhythms, and the activity of parvalbumin inhibitory interneurons dies out in favor of a rise in activity by inhibitory somatostatin expressing neurons.

Emery Brown's lab developed a machine-learning algorithm that can accurately predict the state of unconsciousness maintained by GABAergic anesthetics from electroencephalogram (EEG) spectral features. These findings hold promise for designing decision-aids that anesthesiologists can use in real-time to track unconsciousness and for designing closed loop anesthesia delivery systems. This manuscript was published in *PLoS One* (Abel et al. *PLoS One*, 2021).

The Brown lab also established the fundamental property that electrodermal activity can be accurately described by a physiologically based inverse Gaussian statistical model. This research holds promise for characterizing nociception and for developing real-time strategies for tracking nociception (pain) in patients having general anesthesia. (Subramanian et al. *PNAS*, 2020; Subramanian et al., *TBME*, 2021; Subramanian et al., *PLoS One*, 2021; Subramanian et al., *PLoS Comp Bio*, 2021).

Finally, the lab completed detailed studies of the unconscious state maintained by propofol in a non-human primate model. During propofol maintained unconsciousness we recorded from the prefrontal cortex, area 8A, the superior temporal gyrus, posterior parietal cortex, and the central thalamus. We identified two significant features of unconsciousness maintained by propofol: large-scale inhibition of neural spiking across the entire brain, and synchronous activity in the local field potentials across all four areas. We also demonstrated that arousal could be immediately restored by stimulating the central thalamus. This manuscript describing this work was published in *eLife* (Bastos et al. *eLife*, 2021).

Gloria Choi's lab published three groundbreaking papers:

- Park, S., Yu, H., Zhao, R., Yim, Y.S., Woldegebriel, E., Kang, J., Canales, A., Yoel, F., Choi, G.B., Zhao, X., Anikeeva, P., "Adaptive and multifunctional hydrogel hybrid probes for long-term sensing and modulation of neural activity." *Nature Communications* 12, 3435 (2021). <https://doi.org/10.1038/s41467-021-23802-9>
- Kwon, J., Changhyeon, R., Lee, H., Sheffield, A., Jingxuan, F., Cho, D., Bigler, S., Sullivan, H.A., Choe, H.K., Wickersham, I.R., Heiman, M. and Choi, G.B. "An amygdalar circuit that suppresses social engagement." *Nature*. 593(7857):114-118. PMID:33790466.
- Kalish, B., Kim, E., Finander, B., Duffy, E., Kim, H., Gilman C.K., Yim, Y.S., Tong, L., Kaufman, R.J., Griffith, E.C., Choi, G.B., Greenberg, M.E. and Huh, J.R. (2021). "Maternal immune activation in mice disrupts proteostasis in the fetal brain." *Nature Neuroscience*. 24(2):204-213.

Kwanghun Chung's lab developed SCOUT technology that enables high dimensional phenotyping of organoid disease models (Albanese, Scientific Reports, 2020).

Steven Flavell's lab revealed new key insights from examining how the release of neuromodulators like serotonin impacts dynamical activity patterns in the well-defined *C. elegans* nervous system. In a recent study, the lab monitored neuronal activity throughout the circuit that controls roaming and dwelling while animals switched between these locomotor states (Ji et al., *Biorxiv*, 2020). They identified circuit-wide activity patterns corresponding to each state and found that the serotonin and PDF neuromodulators were critical for the emergence of persistent activity in the network and for maintaining mutual exclusivity between the opposing states of circuit activity. They have expanded these studies to the whole-brain scale in new experiments where they now monitor the activity of neurons throughout the entire *C. elegans* brain while eliciting serotonin release. These studies are revealing how the neuromodulatory connections embedded in a network contribute to its overall dynamics.

Myriam Heiman's lab performed the first single-cell atlas of the human blood-brain-barrier as well as the first single-cell atlas of the human primary motor cortex and its changes in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD).

Together with former lab member Moto Yoshihara, Troy Littleton's lab identified and characterized the molecular basis for a *Drosophila* form of Pavlovian conditioning, a

learning paradigm where defined stimuli are associated to induce behavioral switching. They found that conditioning alters signals flowing from the conditioned stimulus into a command neuron, resulting in the strengthening of this connection in a Hebbian-dependent manner.

They also discovered that Synaptotagmin 7, a protein similar to the SV Ca<sup>2+</sup> sensor Syt1, acts as a negative regulator of SV release and refilling of SV pools at the synapse. Moreover, they found increased SV release in animals lacking both Syt1 and Syt7, indicating these two proteins are not the only Ca<sup>2+</sup> sensors that can activate SV release, in contrast to current thinking.

Finally, they discovered that the decoy SNARE Tomosyn is a key presynaptic determinant for tonic versus phasic release properties in *Drosophila*. Tomosyn is highly enriched at tonic synapses and generates tonic release properties with weak synaptic strength and sustained release by interfering with the formation of fusogenic SNARE complexes. These experiments demonstrate Tomosyn is a highly conserved release inhibitor that varies in expression levels between distinct neuronal subtypes to regulate synaptic properties and plasticity, providing a robust mechanism to generate presynaptic diversity across the nervous system.

Earl Miller's lab made several noteworthy research breakthroughs. They discovered mechanisms that allow the brain to make automatic predictions about what will happen next; disruption of this predictive coding is thought to underlie autism spectrum disorder by producing sensory overload. Other research includes the revelation of neural mechanisms whereby anesthesia renders unconsciousness, which can lead to safer anesthetic practice; discovery of mechanisms that transfer and coordinate information between the right and left brain, seamlessness between which is critical for normal cognition; and identification of a mechanism that allows the brain's networks to operate stably and consistently instead of spiraling off into chaos.

Elly Nedivi's lab gained new insights into the cellular mechanisms that underlie myelin plasticity. Myelin plasticity is critical for neurological function, including learning and memory. However, it is unknown whether this plasticity reflects uniform changes across all neuronal subtypes or whether myelin dynamics vary between neuronal classes to enable fine-tuning of adaptive circuit responses. Thus, the lab performed *in vivo* two-photon imaging of myelin sheaths along single axons of excitatory callosal neurons and inhibitory parvalbumin-expressing interneurons in the adult mouse visual cortex. Their results found that both neuron types show homeostatic myelin remodeling under normal vision. However, monocular deprivation results in adaptive myelin remodeling only in parvalbumin-expressing interneurons. Therefore, even when distinct neuronal subpopulations are interconnected within the same circuit surrounded by a shared environment and myelinated by a common set of oligodendrocytes, they display class-specific patterns of myelin changes. The data suggest that adaptive myelination is part of a coordinated suite of circuit reconfiguration processes that are cell type-specific and put forward a conceptual framework in which distinct classes of neocortical neurons individualize adaptive remodeling of their myelination profiles to diversify circuit

tuning in response to sensory experience. The lab published these results in *Science* (Yang, S.M. et al, *Science*, 2020).

Mriganka Sur's lab achieved several significant breakthroughs:

- Refining of label-free, third-harmonic generation multiphoton imaging techniques enabling us to demonstrate the strong relationship between structural substrates of visual cortical areas and their functional representation maps in vivo
- Demonstration of motor and sensory roles of prefrontal/anterior cingulate cortex projections to the superior colliculus and the visual cortex, as well as a circuit motif for prefrontal cortex function wherein anatomically non-overlapping output pathways coordinate visual sensorimotor behavior.
- Finding that a key function of astrocytic glutamate transporter function during development is the experience-dependent refinement of ipsilateral eye inputs relative to contralateral eye inputs in the visual cortex.
- Development of a low-cost, 3D-printed microfluidic bioreactor and chamber to facilitate the long-term growth and imaging of live organoids
- Discovery that a GSK3 $\beta$  inhibitor modulates cerebral organoid development through dose-dependent regulation of apoptosis, proliferation, differentiation and migration
- Application of machine learning techniques to distinguish between six core visual areas in the mouse brain based on their activity patterns, showing that responses from visual cortical areas can be effectively classified with data-driven models

Susumu Tonegawa's Lab achieved two impressive discoveries: differential attentional control mechanisms by two distinct noradrenergic coeruleo-frontal cortical pathways, and the crucial role for CA2 inputs in the sequential organization of CA1 time cells supporting memory.

The attentional control of behavior is a higher-order cognitive function that operates through attention and response inhibition. The locus coeruleus (LC), the main source of norepinephrine (NE) in the brain, is considered to be involved in attentional control by modulating the neuronal activity of the prefrontal cortex (PFC). However, evidence for the causal role of LC activity in attentional control remains elusive. Here, by using behavioral and optogenetic techniques, we investigate the effect of LC neurons activation or inhibition in operant tests measuring attention and response inhibition (i.e., a measure of impulsive behavior). We show that LC neurons stimulation increases goal-directed attention and decreases impulsivity, while its suppression exacerbates distractibility and increases impulsive responding. Remarkably, we found that attention and response inhibition are under the control of two divergent projections emanating from the LC: one to dorso-medial PFC and the other to ventro-lateral orbitofrontal cortex, respectively. These findings are especially relevant for those pathological conditions characterized by attention deficits and elevated impulsivity. These findings were published in *Proceedings of the National Academy of Sciences* in November.

There is considerable evidence for hippocampal time cells that briefly activate in succession to represent the temporal structure of memories. Previous studies have shown that time cells can be disrupted while leaving place cells intact, indicating that spatial and temporal information can be coded in parallel. However, the circuits in which spatial and temporal information are coded have not been clearly identified. Here we investigated temporal and spatial coding by dorsal hippocampal CA1 (dCA1) neurons in mice trained on a classic spatial working memory task. On each trial, the mice approached the same choice point on a maze but were trained to alternate between traversing one of two distinct spatial routes (spatial coding phase). In between trials, there was a 10 s mnemonic delay during which the mouse continuously ran in a fixed location (temporal coding phase). Using cell-type specific optogenetic methods, we found that inhibiting dorsal CA2 (dCA2) inputs into dCA1 degraded time cell coding during the mnemonic delay and impaired the mouse's subsequent memory-guided choice. Conversely, inhibiting dCA2 inputs during the spatial coding phase had a negligible effect on place cell activity in dCA1 and no effect on behavior. Collectively, our work demonstrates that spatial and temporal coding in dCA1 is largely segregated with respect to the dCA2-dCA1 circuit and suggests that CA2 plays a critical role in representing the flow of time in memory within the hippocampal network. These findings were published in *Proceedings of the National Academy of Sciences*.

In Li-Huei Tsai's lab, recent breakthroughs include the reveal of a role for the early endocytic adaptor protein PICALM in the rescue of endocytic defects associated with APOE4. Increasing expression of PICALM or Yap1802p, a yeast homolog of PICALM, can rescue APOE4-mediated defects in human iPSC-derived astrocytes and yeast, respectively. Their study highlights impairment in the conserved endocytic pathway involving functional interactions between two identified risk factors of Alzheimer's disease, APOE4 and PICALM, as potential contributors to AD pathogenesis. The lab published these results in *Cell Reports*.

- The lab also identified the epigenetic state, 3D-genome architecture, and transcriptional landscape of engram cells—neurons responsible for memory—over the lifespan of memory acquisition and recall. Their study found that memory encoding results in an epigenetic priming event characterized by a transcriptionally poised state and increased accessibility of enhancers. Dynamic reorganization of the 3D genome occurs during memory consolidation that, following reactivation of engram cells, enables primed enhancers to engage their target promoters, leading to upregulation of genes involved in local protein translation in synaptic compartments. The lab published these findings in *Nature Neuroscience*.
- Lastly, the Tsai lab discovered that APOE4, one of the strongest risk factors for developing late-onset sporadic Alzheimer's disease, disrupts the intracellular state of lipids in human iPSC-derived astrocytes and in budding yeast expressing the humanized APOE4 allele. Compared to the benign APOE3 allele, APOE4 causes widespread alterations in lipid homeostasis resulting in the accumulation of unsaturated fatty acids and intracellular lipid droplets. They described that APOE4-associated lipid disruption can be nullified by supplementation with choline, a known soluble precursor of phospholipid. Their work opens up a new therapeutic avenue for the treatment of Alzheimer's disease for patients that harbor the APOE4 allele. The lab recently published these critical findings in *Science Translational Medicine*.

## Personnel

More than 261 community members participated in Picower Institute activities during the report period: 13 faculty members, 51 postdoctoral researchers, 26 research scientists, 36 undergraduates, 45 graduate students, 52 research and technical staff, 20 administrative and service staff, and 18 research affiliates.

Items of note during the academic year include the following:

- Nagelore Jean-Caidor joined as financial administrator in February 2021, filling a new position on the financial team.
- Dr. Erin Kitchener joined the Tsai Lab as a clinical neuropsychologist in March 2021—a new position for the lab and department.
- Rhonda Valenti joined as laboratory administrator to Professor Emery Brown in March 2021, replacing Sheri Leone.
- Professor Myriam Heiman gained tenure and transferred her laboratory staff and researchers to PILM from the Broad Institute in July 2021.

## Resource Development

The Picower Institute's impressive success over recent years continued in fiscal year 2021 despite disruptions to in-person visits with prospective and current donors due to the Covid-19 pandemic. These attainments reflect the faith of MIT's most generous alumni and friends, along with numerous corporations and foundations, in the institute's ability to make valuable use of private resources. Picower resource development efforts identified and publicized more than 137 formal foundation and government funding requests, extended institute print newsletter outreach to 4,384 individuals worldwide and e-newsletter outreach to 6,457 individuals, hosted more than 75 personalized virtual visits with prospective and current donors, and helped host nine major virtual development events to extend our visibility and relationships with a larger audience and sustain relationships with top donors. The institute's communications director worked with Picower faculty to draft 16 prize nominations and the development team drafted 49 new formal philanthropic proposals. Outright gift payments to the institute for FY2021 totaled more than \$18.45 million and new philanthropic gifts and pledges totaled more than \$20.3 million.

With the generous support provided from the JPB Foundation, Barbara Picower, and the late Jeffrey Picower, researchers at the institute have continued their ambitious research efforts. Three new JPB gift commitments totaling \$15.4 million renewed the institute's flagship program, the Picower Institute Innovation Fund (PIIF), along with the Picower Catalyst Program and support for Professor Tonegawa's research. The PIIF program empowers institute scientists to take risks as they conduct research into the greatest challenges and fundamental mysteries of neuroscience. To date, the PIIF has enabled more than \$79.3 million in additional funding for the institute, generated more than 243 publications, launched four companies, and has been the basis for global collaboration, firmly establishing the institute as a preeminent neuroscience institute. The Catalyst

program is a gift-matching fund that leverages donations to jumpstart research partnerships with private sponsors by covering a portion of the indirect costs. To date, each dollar donated to the Catalyst program has resulted in an additional \$29 of vital research support.

In FY2021, a total of \$1.89 million in outright gift payments from the JPB Foundation continued to support two other major institute JPB research programs. These include the Picower Fellows Program and Junior Faculty Awards provided through the Junior Faculty Development Program (JFDP). The Picower Fellows program allows the institute to recruit and retain top-level postdoctoral and clinical scientists. To date, the program has supported 47 exceptional young scientists, including 32 international scholars, 19 women scientists, and two from underrepresented groups. The JFDP provides mentoring and career development support to early-career faculty with particular focus on their fifth through seventh years at MIT, a critical time in progression to tenure. JFDP Junior Faculty Awards currently support Professors Gloria Choi and Steven Flavell.

As part of MIT's mission to help build a better world, the institute continued to host the Alana Down Syndrome Center, an innovative research, technology, and fellowship endeavor to support individuals of all abilities, including Down syndrome. A \$28.6 million gift in 2019 from the Alana Foundation, a nonprofit organization started by Ana Lucia Villela of São Paulo, Brazil, created the center. This past year, the center suffered a tremendous loss with the passing of co-director Angelika Amon; a tribute was held in her honor during the center's fall symposium in November, and we are dedicated to continuing her remarkable vision for and impact on science. The center worked to build visibility and outreach with the community through the symposium and a second virtual webinar in June, which focused on technologies and innovations established through the center's Deshpande program. The foundation continued its support with \$5.9 million to the institute, and three annual fund donors joined to help build upon the partnership.

Significant efforts and development resources continue to be directed toward the Aging Brain Initiative (ABI), our major cross-institutional health research initiative on brain aging and related cognitive decline. Led by Picower director Dr. Li-Huei Tsai with seven founding faculty members and the former dean of the School of Science, Michael Sipser, the ABI remains a top health priority as MIT concludes its Campaign for a Better World. New efforts in FY2021 include developing an Alzheimer's Innovation HUB concept, partnering with Professors Andrew Lo and Robert Langer in the AlzX organization to begin to unify the theory of Alzheimer's with other group, and building new technologies and financial strategies for the field.

Several virtual meetings raised awareness and increased the visibility of the ABI this past fiscal year. On November 5 and April 28, ABI leadership circle members met to hear insider updates on brain aging resilience genes, Alzheimer's risk genes, and new potential therapeutic directions. On January 13, Nergis Mavalvala, dean of the School of Science, partnered with the Office of Individual Giving to host Li-Huei Tsai and postdoctoral researcher Maeve Bonner for a webinar discussion about new Alzheimer's research before an audience of approximately 250 alumni and high-level supporters of MIT. On March 11, Priscilla Gray, spouse of past MIT president Paul Gray, generously



offered another challenge gift of \$10,000 if 100 individuals gave to the ABI Fund during MIT's Pi Day 24-Hour Challenge. Impressively, 335 individuals rose to the challenge and raised a total of \$50,012 for the Initiative. The ABI also completed its second *Aging Brain Update*, a newsletter sent to 410 donors and interested friends highlighting accomplishments of the year. The director also emailed an annual update letter thanking individuals for their contributions on December 19.

Notable new FY2021 commitments for the ABI included a generous million dollar gift from Robert and Renee Belfer, a gift of \$630,000 from the Ludwig Family Foundation, and \$500,000 from Jeff and Nancy Halis to support Alzheimer's research through 2021. The Eleanor Schwartz Charitable Foundation pledged a new \$500,000 gift, and six-figure commitments to Alzheimer's research were given by David Emmes, Joe and Nancy DiSabato, David and Dagmar Dolby, Lester Gimpelson, Glenda Mattes, Kathy Octavio, and the Degroof-VM Foundation. The Belfer family also continued support for other breakthrough Alzheimer's research at the institute through the Neurodegeneration Consortium, a collaboration among MIT, the University of Texas MD Anderson Cancer Center, and Mount Sinai School of Medicine scientists.

The Picower Institute successfully hosted our rescheduled daylong biennial symposium Early Life Stress and Mental Health on May 10 to honor Barbara Picower and the JPB Foundation. The event featured talks by neuroscientists, policy experts, physicians, educators and activists who discussed how our experiences and biology work together to affect how our minds develop and what can be accomplished in helping people overcome early disadvantages. More than 300 individuals from around the world were able to attend this virtually hosted event.

On October 10, the institute partnered with the MIT Alumni Association to host a faculty forum online webinar on sleep and memory with Professor Matthew Wilson for more than 200 registrants. On May 4, we helped virtually co-host our department's biennial Brains on Brains symposium for our closest supporters—an event that highlights our research and students.

Another notable gift pledge to the institute includes \$466,000 from the G. Harold and L.Y. Mathers Foundation to support neurodegenerative research in the Heiman lab. Additionally, the Picower Institute continued to receive generous five-figure gifts from many individuals and an increase in smaller annual fund gifts from MIT alumni and new unaffiliated donors, all of which have proved vital to our mission of advancing brain research.

## **Media Recognition**

The Picower Institute has attained a distinguished international reputation as a neuroscience research leader, and faculty scholarly excellence shows in its publication records. During the reporting year, Picower Institute faculty published 78 articles in journals such as *Nature*, *Cell*, *Neuron*, *Cell Reports*, *Nature Neuroscience*, and *Nature Communications*.

Often working with the MIT News Office, the institute posted 38 press releases and five feature stories on its website and growing social media feeds. Institute research,

expertise, and other newsworthy activities were reported on more than 90 times by independent media outlets including NPR, the *New York Times*, the *Washington Post*, CNN, ABC News, the *Boston Globe*, WGBH, *Wired*, *Nature*, *Scientific American*, STAT, *New Scientist*, *Quanta*, *Psychology Today*, and many others.

## Programs and Activities

Collaboration among disciplines is an integral component of the Picower Institute’s research philosophy. To facilitate collaboration, the institute plans a rigorous calendar of formal lectures, conferences, collaborative grant programs, and workshops, along with other informal events. Such activities integrate Picower researchers and the MIT neuroscience community with neuroscientists and practitioners from the public and private sectors to exchange research findings, facilitate cross-disciplinary collaborations, and explore the potential that research advances regarding learning and memory mechanisms offer to science and society.

The Picower Institute Colloquia channel learning and memory researchers of the highest caliber from universities across the world to share their findings and experiences with the MIT community and to create working relationships with members of the Picower Institute. During the past year, all talks occurred online. Colloquia speakers included Dr. Kang Shen of Stanford University, Dr. Mathew Diamond of the International School for Advanced Studies, and Dr. Betty Hong of the California Institute of Technology.

In neuroscience, “plasticity” refers to the minute but crucial physical changes that take place in our synapses when we learn, experience, or remember anything new. “Plastic Lunch” is a monthly series of informal talks held during the academic year that give postdocs and graduate students from across the Picower Institute a chance to share their latest research with colleagues within the Building 46 community. The Plastic Lunch series provides an opportunity for participants to improve their presentation skills, fosters collaborations, and builds new relationships across disciplines and between laboratories. These talks continued this year in a virtual format and were well attended with strong engagement.

On September 22, 2020, the Aging Brain Initiative hosted its second full-day symposium, Cellular and Molecular Mechanisms of Neurodegeneration, where 10 neuroscientists met to share new insights into the nature of diseases that cause brain cells to die, as well as to describe promising new treatment strategies. Attendance was exceptional with 1,929 registrants and 1,310 unique attendees who watched from 48 different countries—the largest audience ever for a Picower Institute symposium.

The Picower Institute hosted its annual fall symposium, Internal States of the Brain, on October 6, 2020. Experts from around the globe gathered virtually to share their latest research findings relating to the governing of the neural mechanisms that influence how sensory information is processed and how behaviors are generated. The event was very well attended, with 1,586 registrants and 989 unique viewers representing 37 countries.

In conjunction with the Massachusetts Down Syndrome Congress and LuMind IDSC Foundation, the Alana Down Syndrome Center (ADSC) hosted the New England Down

Syndrome Symposium on November 10. Clinicians, scientists, and organizations focused on Down syndrome research came together to deliver informative talks discussing the latest basic and clinical research on Down syndrome, advances in technology, and self-advocacy. A moving tribute to Dr. Angelika Amon, the ADSC's late co-director who died shortly before the event, was also held. The full-day virtual event was well attended and livestreamed to a large international audience, notably in Brazil.

After it was postponed in 2020, the Picower Institute hosted its biannual spring symposium, Early Life Stress and Mental Health, on May 10, 2021. Coordinated with Barbara Picower and her team at the JPB Foundation, this symposium featured talks from neuroscientists, activists, physicians, and policy experts examining how experience and biology combine to affect the development of young minds. Additionally, the panel discussion "Outreach and Opportunities in STEM," moderated by Laura Schulz, the associate department head for Diversity, Equity, Inclusion, and Justice Initiatives for BCS, focused on individual and institutional outreach programs at MIT that seek to enhance opportunities for members of groups underrepresented in science, technology, engineering and mathematics (STEM) fields. The virtual event garnered a large and diverse group of attendees from around the world.

There were also several special seminars held throughout the academic year with speakers including Stanford University professor Jin Hyung Lee and Picower faculty members Li-Huei Tsai and Matthew Wilson.

An endeavor targeted to the Picower Institute's postdoctoral community provided resources to support activities that build community and enrich interactions between postdoctoral colleagues and future associates. The Building 46 Postdoctoral Association continues to expand and make improvements in partnership with administration for the postdoc community. Throughout the past year, the postdocs convened a series of informal talks, educational seminars, and social events.

Research programs enabled by philanthropic support from the JPB Foundation afford a truly unique research environment that supports our faculty, lab members, and administrative team. These programs include the Clinical Collaborative Fellowship, the Picower Neurological Disorder Research Fund, the Picower Fellows Program, the Symposium Fund, the Picower Institute Innovation Fund, and the Junior Faculty Awards.

## **Research Initiatives**

### **RIKEN-MIT Laboratory for Neural Circuit Genetics**

Established in April 2008, the RIKEN-MIT Laboratory for Neural Circuit Genetics is directed by Professor Susumu Tonegawa and jointly sponsored by the RIKEN Center for Brain Science in Japan and MIT. The laboratory's objective has been to deepen our understanding of molecular, cellular, circuit, and brain system mechanisms underlying learning and memory. This is achieved by using a combination of new research tools and technologies, such as spatially and temporally restricted transgenic mice, virus vector-based gene introduction, optogenetics, pharmacogenetics, calcium imaging, tetrode recordings and sophisticated rodent behavioral paradigms. The laboratory's focus has

been on deciphering cellular and neural circuit mechanisms underlying the encoding, consolidation, and retrieval of episodic, semantic, emotional, and social memory as well as high-level cognitive functions in mice. Uncovering the fundamental mechanisms operating in the healthy brain aids understanding of how these mechanisms go astray in disease. The RIKEN-MIT agreement funds the activities of the laboratory and will primarily support the Tonegawa research group for the next two years. In the past year, the Tonegawa Lab published two papers in *Proceedings of the National Academy of Sciences*; both publications were partially funded by this collaboration.

### **iPS Core Facility**

Launched in 2010, the iPS Core Facility (ICF) integrates research goals of the Picower and McGovern Institutes and the Department of Brain and Cognitive Sciences to create human and animal cell models of disease. The various laboratories have expertise and experience with different experimental protocols which, when combined collaboratively to the study of human cells, result in accelerated progress in this novel, dynamic, and competitive field. The advent of human induced pluripotent stem cells (iPSCs) heralds a new generation of clinical and basic research into disorders. Patient-derived skin fibroblast cells are reprogrammed into iPSCs and then differentiated into various brain cell types, allowing researchers to directly examine a wide variety of diseases in addition to studying gene variants in patient populations. This core facility has rapidly become essential to studies of autism spectrum disorder, psychiatric disease, Alzheimer's, and other neurodegenerative diseases. The ICF is accessible to users at all hours. Shared equipment is available with a reservation system. The iPS facility became a fee-for-service facility in FY2014 and is open to other MIT users as well as users external to MIT.

The ICF is equipped for the specialized production, maintenance, expansion, preservation, and distribution of human fibroblasts, iPSC lines, iPS- and ES-derived neuronal progenitor cells, iPS- and ES- derived neurons, induced neuronal (iN) cells, and neural organoids. Approximately 1,600 square feet house three tissue culture areas: one room is dedicated for viral work with iPS and ES cells as BL2plus practice for higher safety protocol, and two tissue culture areas are for maintenance, expansion, and general handling of non-viral work with iPS and ES cell culture with BL2 safety practice. There are 15 bio-safety cabinets, 28 CO<sub>2</sub> incubators, including three of the three-gas incubator that allows controlling of hypo- or hyper-O<sub>2</sub> concentration, and bench areas. There are four bio-safety cabinets equipped with microscopes for observation and handling of cells in a clean and protected environment. The ICF has produced more than 100 patient-specific iPSC lines from healthy donors as well as donors with schizophrenia, bipolar disease, depression, Rett syndrome, Alzheimer's, or Down syndrome. Isogenic iPSC lines using CRSPR techniques are also generated/used for various disease model research.

Supervisor Tak Ko has set up an orientation program and trainings to educate faculty and potential users. Since its inception, more than 25 MIT researchers have used the facility. Moreover, collaboration with researchers outside of MIT has continued. Noteworthy interactions with the Broad Institute include applying platforms with pluripotent stem cells for two studies: "A cloud-based pipeline for DIA data analysis enables phosphosignaling studies in genetic risk variants of Alzheimer's Disease" and "Multi-proteomics characterization of diverse brain cell types using low-input

phosphoproteomics and global chromatin profiling.” Biotech industries also inquire about iPSC culture service, and Cambridge biotech company Solid Biosciences sent a researcher to learn basic iPSC maintenance techniques and cardiomyocyte differentiation procedures. Using data from the ICF, many articles have been published in journals such as *Cell Systems*, *Neuron*, *Nature*, *Nat Neuroscience*, *PLoS One*, and *Molecular Psychiatry*.

MIT researchers have often leveraged ICF capabilities to receive external funding. Sources and related projects included the Alana Foundation: Alana USA Fund; National Institute of Health (NIH): The cdk5/p35 kinase; Broad, NIH: There and Back Again—Epigenetic Reinforcement of Cellular Signaling Stages; MD Anderson: The Neurodegeneration Consortium; Cure Alzheimer’s: Circuits Consortium; NIH: Mechanisms Underlying DNA Double Strand Break Response in Alzheimer’s Disease and Frontal Temporal Dementia; NIH: Epigenomic, Transcriptional and Cellular Dissection of Alzheimer’s Variants; NIH: Dissection of Endosomal Trafficking Mechanisms in Alzheimer’s Disease; NIH: Elucidating the Molecular Mechanisms of Neuropsychiatric Symptoms in Alzheimer’s Disease; NIH: Single-Cell Transcriptional and Epigenomic Dissection of Alzheimer’s Disease and Related Dementias; NIH: Construction of an Integrated Immune—Vascular Brain—Chip as a Platform for the Study, Drug Screening, and Treatments of Alzheimer’s Disease; NIH: Development of PU.1 Inhibitory Modulators as Novel Therapeutics for Alzheimer’s Disease; MIT PILM: 2020 PIIF Engineering Grant; Down Syndrome Research Fund.

### **3D Imaging Core Facility**

In 2020, PILM created a shared 3D imaging core facility after the purchase of a Lifecanvas lightsheet microscope. Lightsheet microscopes can image large tissues; one of the most powerful applications in Picower is the ability of the Lifecanvas system to image whole mouse brains. The system additionally provides superior axial resolution with a consistent lightsheet thickness regardless of detection magnification as well as high accuracy Z-stage motion (20nm) and a broad range of motion for larger samples. The facility is available to all Picower labs and accessible for use 24 hours per day, seven days a week.

### **The Aging Brain Initiative**

The bold goals of the Aging Brain Initiative are to begin a transformative process of collaborative study, discovery, and rapid integration of brain-aging research into real-world applications, and to establish a long-term investment platform to address this global health imperative. The program brings MIT’s leading memory and neurobiology researchers together with engineers, computer scientists, economists, urban planners, social policy experts and clinicians, and industry partners to think creatively about brain aging and to collectively tackle ambitious ideas that have not been pursued. High-risk flagship projects include a whole-systems perspective extending beyond the traditional clinical pathology and genetic approaches of today to include vital aspects of the challenge such as understanding memory loss and developing technologies for improved study and care. Frequent multi-disciplinary discussion forums and seminars enable open sharing of data and accelerated development of ideas for growth into new areas.

Although the pandemic changed how labs operated and severely restricted travel, we were still able to make progress on our aging brain research projects, and our members presented virtually in several places. Aging Brain Initiative director Li-Huei Tsai presented research results at the 2023 AD/PD International Conference on Alzheimer's and Parkinson's Diseases and at the Alzheimer's Association International Conference. ABI member Manolis Kellis was part of the 2021 NIH Director's Summit on Alzheimer's Research. ABI member Edward Boyden was awarded the Croonian Medal and Lecture and presented his work on tools to investigate the brain to the Royal Society of the UK. Finally, the Aging Brain Initiative hosted a virtual fall symposium on Cellular and Molecular Mechanisms of Neurodegeneration, which attracted 1,930 registrants from 48 countries—a record for our symposia.

The la Caixa Foundation Aging Brain Initiative fellows program recruited a new postdoctoral fellow from Portugal to join Professor Tsai's lab to study biomarkers of Alzheimer's disease in mice and humans; the lab will continue to recruit two additional postdoctoral fellows for aging brain research at MIT.

The ABI continues to focus on approaches that consist of immediately implementable project- and team-based research to help understand both healthy and unhealthy brain aging, and to develop real-world solutions that reduce cognitive decline, aid home care, and point toward a cure for diseases like dementia. Research centers around MIT strengths such as big data approaches, circuit and systems therapeutic approaches (including non-invasive stimulation regimens and ways to restore memories), personalized approaches to treatment through human and new models of disease, and uncovering mechanisms supporting healthy aging and resilience.

In FY2021, despite the pandemic, ABI researchers published major advances. Manolis Kellis and ABI member Myriam Heiman published work describing mechanisms for immune activation in Huntington's disease in the journal *Neuron*. Kellis and Tsai published collaborative work in the journal *Science Translational Medicine* that describes the role of the Alzheimer's risk gene ApoE in non-neuronal cells of the brain. In *Anesthesia and Analgesia*, Emery Brown found signatures in EEG to identify older people with vulnerable brains who may respond poorly to anesthesia. Ed Boyden published in both *Science* and *Cell* with advances for microscopy imaging and image brain activity as well as performing DNA or RNA sequencing directly in tissue. Finally, the group from the collaboration of Tsai, Brown, and Boyden tested a novel light and sound device for the treatment of Alzheimer's disease, finished their Phase I/II trial in Alzheimer's patients at MIT, and will soon begin a larger-scale Phase II trial at Massachusetts General Hospital to test the efficacy of the device in preventing progression of Alzheimer's markers in people at risk of developing the disease.

### **The Alana Down Syndrome Center**

In March 2019, MIT launched the virtual Alana Down Syndrome Center (ADSC), hosted by the Picower Institute. The ADSC aims to deepen knowledge about Down syndrome (DS) and to improve the health, autonomy, and inclusion of people with this genetic condition. Unfortunately, in the fall of 2020 ADSC co-director Angelika Amon of MIT's Koch Institute for Integrative Cancer Research passed away. The center is working to find additional MIT faculty to follow in her footsteps.

The ADSC is multi disciplinary, spanning labs and programs across MIT. The center engages the expertise of scientists and engineers to increase understanding of the biology and neuroscience of DS. Its mission is to produce research and technology to give people with disabilities the possibility of developing greater social and practical skills in order to enhance their participation in the educational system, the workforce, and community life.

The ADSC pursues progress in three main ways:

- Research investigates mechanisms and potential therapeutic interventions in brain circuits and systems, and in cellular mechanisms and genetic variation. With these approaches, the team strives to improve understanding of why individuals with DS experience functional differences and the best ways to address them.
- Through a joint program with the Deshpande Center called “Technology to Improve Ability,” creative minds across MIT are supported through grants to design and develop technologies that can improve life for people with different intellectual abilities or other challenges. This program has funded two project grants, one developing a device to treat obstructive sleep apnea – which is an incredibly common problem in individuals with Down syndrome – and another developing a device to help augment communication with individuals who are nonverbal.
- Through postdoctoral and graduate fellowship programs, the center builds a pipeline of talent to increase the number of scientists who are enthusiastic about and skilled in Down syndrome research. In FY2021, seven fellows (two graduate students and five postdocs) were supported by the ADSC fellowship program. Trained in the center’s labs with advanced and innovative techniques, this class of fellows, as well as undergraduate students who join these projects, have the potential to amplify the center’s discoveries throughout their careers.

## Faculty Research Summaries

Picower Institute faculty research areas are summarized at their respective websites:

- [Mark Bear](#), Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences
- [Emery Brown](#), Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Institute for Medical Engineering and Sciences (IMES), Department of Brain and Cognitive Sciences
- [Gloria Choi](#), Mark Hyman, Jr. Career Development Associate Professor, Department of Brain and Cognitive Sciences
- [Kwanghun Chung](#), Picower Associate Professor of Neuroscience, Departments of Brain and Cognitive Sciences and Chemical Engineering, IMES
- [Steven Flavell](#), Lister Brothers Career Development Associate Professor, Department of Brain and Cognitive Sciences

- [Myriam Heiman](#), Latham Family Career Development Associate Professor of Neuroscience, Department of Brain and Cognitive Sciences
- [Troy Littleton](#), Menicon Picower Professor of Neuroscience, Departments of Biology and Brain and Cognitive Sciences
- [Earl Miller](#), Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences
- [Elly Nedivi](#), William R. (1964) & Linda R. Young Professor of Neuroscience, Departments of Biology and Brain and Cognitive Sciences
- [Mriganka Sur](#), Paul E. Newton Professor of Neuroscience, Department of Brain and Cognitive Sciences, Director of the Simon's Center for the Social Brain
- [Susumu Tonegawa](#), Picower Professor of Neuroscience, Departments of Biology and Brain and Cognitive Sciences
- [Li-Huei Tsai](#), Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences
- [Matthew Wilson](#), Sherman Fairchild Professor in Neurobiology, Departments of Brain and Cognitive Sciences and Biology

**Li-Huei Tsai**  
**Director**  
**Picower Professor of Neuroscience**