

The Picower Institute for Learning and Memory

The [Picower Institute for Learning and Memory](#) is a community of scientists dedicated to understanding the mechanisms that drive learning, 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 and synapses, and circuits and systems—producing novel insights into how disruptions in these mechanisms can lead to developmental, psychiatric, or neurodegenerative disease.

Awards and Honors

- Professor Emery N. Brown: 2022 Gruber Neuroscience Prize and the 2022 Pierre M. Galletti Award from the American Institute for Medical and Biological Engineering (AIMBE)
- Associate Professor Gloria Choi: Carol and Gene Ludwig Award for Early Career Research, Kenneth Rainin Foundation Innovator Award, promoted to associate professor with tenure
- Associate Professor Myriam Heiman: National Institutes of Health (NIH) Director’s Transformative Research Award, and National Institute of Neurological Disorders and Stroke Research Program Award
- Professor Troy Littleton: AY2022 head of house at the Warehouse graduate dormitory
- Professor Elly Nedivi: Member of the American Association for the Advancement of Science Neuroscience Section Steering Group
- Professor Mriganka Sur: AIMBE College of Fellows Class of 2022
- Professor Li-Huei Tsai: 2021 Institute of Biomedicine of Seville Distinguished Investigator Award and 2022 Vallee Visiting Professorship
- Maxwell Heinrich (Bear Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching
- Madison Leet (Bear Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching and Ruth L. Kirschstein Predoctoral Individual National Research Service Award (NRSA)
- Mark Olchanyi (Brown Lab graduate student): AY2023 MIT-Takeda PhD Fellowship
- Indie Garwood (Brown Lab graduate student): AY2023 School of Science MathWorks Fellowship
- Christian Guay (Brown Lab research affiliate): Margaret Wood Resident Research Award, Association of University Anesthesiologists and Kosaka Best-of-Meeting Abstract Award Finalist, International Anesthesia Research Society
- Francisco Garcia (Heiman Lab graduate student): Distinguished Trainee Award, “Barriers of the CNS” Gordon Research Conference, and Brain and Cognitive Sciences (BCS) Diversity, Equity, Inclusion and Justice Impact Award

- Preston Ge (Heiman Lab graduate student): Kirschstein-NRSA Individual Predoctoral Fellowship
- Elizabeth Brija (Littleton Lab graduate student): 2022 Yale-Princeton-Columbia Graduate Consulting Club Case Competition Prize
- Ellen Guss (Littleton Lab graduate student): Kirschstein-NRSA Individual Predoctoral Fellowship, and Society for Neuroscience Trainee Professional Development Award
- Gabrielle Drummond (Sur Lab graduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching, and NIH-National Institute of Mental Health (NIMH) Individual Predoctoral Fellowship
- Kyle Jenks (Sur Lab postdoctoral researcher): Kirschstein-NRSA Individual Postdoctoral Fellowship
- Sofie Ährlund-Richter (Sur Lab postdoctoral researcher): 2022 Foundation Blanceflor Scholarship
- Yizhi Wang (Sur Lab undergraduate student): Angus MacDonald Award for Excellence in Undergraduate Teaching, and BCS Undergraduate Research Award
- Rezaul Islam (Tsai Lab postdoctoral researcher): 2022 European Molecular Biology Organization Postdoctoral Fellowship
- Mitchell Murdock (Tsai Lab graduate student): 2021 Barbara J. Weedon Fellowship, and BCS Teach Off! Finalist (third place)
- Rebecca Pinals (Tsai Lab postdoctoral researcher): 2022 Victor K. LaMer Award from the American Chemical Society Division of Colloid and Surface Chemistry, 2022 MIT Multi-cellular Engineered Living Systems Symposium Poster Award (first place), 2021 MIT Keystone Symposium Travel Award

Research Advances

Mark Bear's lab discovered in two species that amblyopia can be completely and rapidly reversed by temporarily silencing activity in one retina. This occurs at ages when traditional therapeutic approaches fail. Additionally, they discovered a potential reason clinical trials using mGluR5 inhibitors in humans have failed: profound drug resistance develops. Given this they suggested new therapeutic approaches.

Emery Brown's lab collaborated with Iahn Cajigas at the University of Miami to develop a neuroprosthetic for volitional hand grasp. [This manuscript was published in *Brain Communications*](#). The lab developed a detailed characterization of the neurophysiology of ketamine's electroencephalogram (EEG) signatures in humans and local field potentials in non-human primates. [This characterization was published in *PLoS Computational Biology*](#).

Gloria Choi's lab found a potential mechanism linking autism to intestinal inflammation. In mice, they discovered that maternal infection during pregnancy elevates levels of the molecule Interleukin-17a (IL-17a), altering her microbiome [such that after birth, the newborn's immune system is poised for future inflammatory attacks](#).

Kwanghun Chung's lab developed a next-generation tissue expansion method that improves neural imaging by enabling the labeling of more proteins and deeper studies of circuit junctions in brain tissue. The upgrade is implemented in eMAP, a new and improved version of the Chung lab's 2016 magnified analysis of proteome" (MAP) technology. Using eMAP, Chung and researchers from the Nedivi and Feng laboratories [successfully labeled multiple proteins in the same synapse](#), which was unattainable in the past.

Steven Flavell's lab discovered the architecture of a fundamental decision-making brain circuit that allows a *C. elegans* worm to either forage for food or stop to feast when it finds a source. Capable of integrating multiple streams of sensory information, [the circuit employs just a few key neurons to sustain long-lasting behaviors while flexibly switching between them as environmental conditions warrant](#). The lab also revealed new insight on how a single neuron, AWA, in *C. elegans* integrates multiple states and stimuli into its expression of olfactory receptors, which guides food seeking. [Their findings suggest a model for how sensation helps guide behavior](#).

Myriam Heiman's lab produced the first single-cell atlas of human cerebrovasculature cell types and how they change in Huntington's disease. They also produced the first high-resolution single-cell molecular atlas of genomic changes in the human motor cortex and prefrontal cortex in Amyotrophic lateral sclerosis (ALS) and Frontotemporal lobar degeneration (FTLD).

Troy Littleton's lab determined how neurons build and maintain their capacity to communicate. They demonstrated for the first time, using a model system of fruit fly motor neurons, [the step-by-step process that accounts for the distribution and upkeep of calcium channels at active zones](#). Nerve cells regulate and routinely refresh the collection of calcium channels that enable them to send messages across circuit connections. Moreover, the lab discovered how glial cells regulate neuronal excitability and how their dysfunction contributes to epilepsy. They identified a role for the endoplasmic reticulum store-operated Ca^{2+} entry (SOCE) pathway in perineurial glia (PG). PG cells display diverse calcium waves that spread through SOCE and gap junction activity. Disrupting these components triggers seizure-like episodes.

Earl Miller's lab made several noteworthy research breakthroughs.

- [Traveling waves in the brain's prefrontal cortex help working memory work](#). The lab's study found that the act of holding information in mind involves the coordination of rotating brain waves around central points in the cortex. These waves help organize activity across networks, which is the first discovery of traveling waves in the higher cortex.
- [The electrical fields generated by the brain reliably convey information](#). The researchers found that as the brain strives to hold information in mind, the most consistent and reliable representation of that information is not the electrical activity of the individual neurons involved but an overall electric field they collectively produce.
- [Anesthesia drastically alters the travels of brain waves](#). No one knows why anesthesia causes amnesia. Together with Emery Brown's lab, scientists in

the Miller Lab found that propofol “unrotates” the rotating waves that form memories. Under propofol general anesthesia, slow frequency traveling waves transform and dominate, redirecting and disrupting the higher frequency traveling waves associated with conscious function.

Elly Nedivi’s lab gained new insight into the thalamocortical circuit. They used whole-cell synaptic mapping that combined genetic tools and scalable tissue expansion microscopy to reveal the number, density, and size of thalamic versus cortical excitatory synapses onto individual Layer 2/3 pyramidal cells (PCs) of primary visual cortex (V1). They discovered that thalamic inputs to L2/3 PCs are sparse, originating from the lateral geniculate nucleus and varying in number and density across individual dendrites and neurons. Surprisingly, despite their sparseness, thalamic synapses onto L2/3 PCs are smaller than cortical counterparts and rarely inhabit large spines innervated by both excitatory and inhibitory input. Incorporating these findings into fine-scale biophysical models of L2/3 PC response to visual input illuminates the role of thalamic innervation to supragranular V1. Their anatomically faithful modeling uncovers how individual L2/3 neurons with sparse and weak thalamocortical synapses, embedded in small heterogenous neuronal ensembles, may reliably “read-out” visually driven thalamic input.

Mriganka Sur’s lab demonstrated the remarkable role of the neurotransmitter noradrenaline (NA) in learning. Using novel techniques, they showed that NA dynamically facilitates two functions during learned behavior: task execution and encoding reinforcement to improve performance accuracy. Thus, NA is a critical determinant of reinforcement learning. Furthermore, the two components of NA function indicate modular targeting of cortical structures by the locus coeruleus.

Researchers in the Sur Lab found that somatostatin (SST) and parvalbumin (PV) interneurons facilitate reliable sensory processing in the mouse visual cortex. Their results, supported by computational models, show that SST-interneurons increase output pyramidal neuron reliability by suppressing PV interneurons. These findings reveal a novel role of the SST-PV circuit in modulating the fidelity of neural coding critical for visual perception. They also analyzed lateral posterior (LP) thalamus inputs and outputs using sophisticated anatomical methods. LP neurons that project to the anterior cingulate cortex (ACC), which mediates higher brain functions, receive inputs from widespread cortical regions and extensive subcortical inputs. Their brain-wide anatomical mapping of inputs to the reciprocal LP-ACC pathway provides a [roadmap for how LP and ACC communicate to induce selective attention](#).

Susumu Tonegawa’s lab demonstrated that a single memory is stored in engrams widely distributed in multiple brain regions that are functionally connected.

In Li-Huei Tsai’s lab recent breakthroughs include the following:

- Lipid accumulation in microglia affects neuronal network activity in a human model of Alzheimer’s disease (AD). Findings show how [the expression of the \$\epsilon 4\$ allele of apolipoprotein E \(APOE\) alters how microglia normally process lipids](#). Studies of human-derived pluripotent stem cells differentiated into microglia and neurons showed that APOE4 expressing microglia had a reduced capacity to uptake lipids, resulting in an accumulation of lipids in the extracellular

space. When incorporated into the plasma membrane of neighboring neurons, these lipids changed the electrical properties of the cells, primarily by altering conductance through K channels, making the neurons less excitable and capable of transmitting signals to other neurons in the network. This exciting result could explain how the APOE4 risk gene reduces neuronal activity in AD patients. Treatment of cultures with Triacsin C, which inhibits the formation of lipid droplets, could restore normal neuronal functioning.

- Down Syndrome’s (DS) cellular pathology mirrors senescence changes seen in brains of healthy older adults. They studied how the extra T21 chromosome affected the maturation of neural progenitor cells (NPCs), the precursor cells of several adult brain cells, including neurons and glia. For a normal brain to develop, NPCs must migrate through the tissue and activate a cellular differentiation program—functions requiring gene transcription and transient changes in 3D chromatin structure. New lab results show that in vitro cultured human NPCs with the trisomy 21 defect fail to migrate properly and activate the differentiation program compared to human-derived pluripotent stem cells. These defects partly depend on the extra T21 chromosome physically crowding the other chromosomes, preventing 3D chromatin remodeling and subsequent gene expression. Surprisingly, these changes are similar to those reported in senescent brain cells of geriatric individuals. Remarkably, a senolytic drug (dasatinib and quercetin) that reverses this process in aged brain cells can also restore NPCs’ ability for normal gene transcription, differentiation, migration, and proliferation. These results suggest that drugs that delay “normal” brain aging may also benefit persons suffering from DS, AD, and other neurological diseases.

Personnel

More than 250 community members participated in Picower Institute activities during the reporting period, including 13 faculty members, two visiting scientists, 49 postdoctoral affiliates, 29 research scientists, 35 undergraduate students, 37 graduate students, 50 research and technical staff, 20 administrative and service staff, and 22 staff or research affiliates.

- Mary Mazzanti joined the Tsai Lab as a scientific project manager in October 2021.
- Ute Geigenmuller joined the Tsai Lab as a scientific project manager in April 2022.
- Brittany Greenough was promoted to events administrator in April 2022 to support the department’s expanding event portfolio.
- In January 2022 Mackenzie Abbott was hired through the Howard Hughes Medical Institute to provide administrative assistant support to Professor Tonegawa.
- Antonina Palisano returned to The Picower Institute in June 2022, replacing Athene Wilson-Glover, as Professor Bear’s administrative assistant.

Resource Development

The Picower Institute’s success over recent years continued in FY2022 despite continuous disruptions to in-person visits with prospective and current donors due to

the Covid-19 pandemic. Picower resource development efforts identified and publicized more than 181 formal foundation and government funding requests. The resource development team extended Picower Institute print newsletter outreach to 4,881 individuals worldwide and Institute e-newsletter outreach to 10,688 individuals, hosted more than 82 personalized virtual and in-person visits with prospective and current donors, and helped host 10 major virtual development events to extend Picower's visibility and relationships with a larger audience while sustaining relationships with top donors. The Picower Institute's communications director worked with Picower faculty to draft 15 prize nominations. The development team drafted 26 new formal philanthropic proposals. In FY2022, the Picower Institute received over \$18.62 million in outright gifts and more than \$11.62 million in new gifts and pledges.

Picower researchers continued their ambitious efforts thanks to generous and ongoing gift payments from the JPB Foundation and Barbara Picower. These include support for the Picower Institute's flagship program—the Picower Institute Innovation Fund—which supports bold, high-risk research for each Picower faculty member. The foundation also supports the Picower Catalyst Program to cover indirect costs on new awards, the Picower Fellows Program for young trainees, and the research of Professor Tonegawa's laboratory. As the Picower Fellows Program nears completion, Barbara Picower welcomed a \$5.02 million proposal to renew her support for graduate and postdoctoral fellowships and extend her interest in supporting a new diversity and equity training program for post-baccalaureate scholars.

The Picower Institute continued to receive \$5.9 million in gift payments from the Alana Foundation, a nonprofit organization started by Ana Lucia Villela of São Paulo, Brazil, to host the Alana Down Syndrome Center—an innovative research, technology, and fellowship endeavor to support individuals of all abilities, including Down syndrome. Significant efforts and development resources remain directed toward our major cross-institutional health research initiative on brain aging and related cognitive decline: the Aging Brain Initiative (ABI) at MIT, led by Professor Tsai. New efforts in FY2022 included further developing an Alzheimer's Innovation HUB concept and partnering with Professors Andrew Lo and Bob Langer and the AlzX organization to identify key gaps in the Alzheimer's field and build new technologies, IP commons structures, and financial strategies for the field.

Several virtual meetings raised awareness and increased the visibility of the Picower Institute and the Aging Brain Initiative in FY2022. In November and again in April, approximately 50 ABI leadership circle members met to hear updates on new potential therapeutic directions, new mechanisms of disease pathology, and technologies to better understand brain aging, including human models of disease. In October, we helped host the Champions of the Brain Fellows event to steward top donors of graduate fellowships. In December, we partnered with the MIT Alumni Association by leading a discussion on the science of making and saving memories with Professor Tsai and Picower alumnus Steve Ramirez. In April, Tsai presented an ABI progress update to the MIT Engineering and Science Councils, including new initiatives such as the Alzheimer's Innovation HUB and its potential role in MIT's VITAL concept to revitalize life sciences. In May, the Picower Institute and many faculty and graduate students participated in

the Brains-on-Brains symposium—a day-long event to steward our closest supporters and alumni through lay-friendly talks and interactions. Approximately 100 people attended in person and many more online. On May 14, Li-Huei Tsai presented at MIT's Campaign Closing Weekend to donors and alumni on her role in brain research. Tsai and Emery Brown also gave presentations on May 28 at the MIT Tech Day as part of Reunion Weekend (focused on longevity and innovation) to an approximately 100 in-person and live-streamed audience.

In March, 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 24-Hour Challenge Day. Impressively, 324 individuals rose to the challenge, raising \$85,946. This year, we offered five \$100,000 seed-funding awards to five laboratories with new aging brain ideas. The ABI also completed its third *Aging Brain Update*, a newsletter sent to 4,881 donors and interested friends highlighting the year's accomplishments. In December, the director emailed an annual update letter to all Picower donors thanking individuals for their generous contributions.

A new major initiative to launch a Brain Arousal State Control Innovation Center (BASCIC) is under way. Support from MIT and Massachusetts General Hospital (MGH) senior leaders jump-started Emery Brown's efforts to fundraise and build a cohesive, cross-institutional commitment to anesthesia-related research. In the fall, Dean Nergis Mavalavala hosted her advisory council meeting with a presentation by Brown. After the event, Chair Diane Greene and MIT alumnus George Elbaum made significant commitments to help launch new collaborative projects to spur the effort. On January 20, Brown presented his concept to the MIT resource development community's "Focus on Fundraising" program. Picower development marketing materials and prospective donor tours further highlighted BASCIC.

Notable FY2022 commitments for the Aging Brain Initiative included a generous \$5 million five-year gift pledge from Laurence Belfer and his parents, Robert and Renee Belfer, to support new therapeutic projects and drug screening efforts for individuals harboring the APOE4 risk gene for Alzheimer's. Eduardo Eurnekian committed \$1 million to ABI to support memory and risk gene research. The Carol and Gene Ludwig Family Foundation continued supporting Alzheimer's research with a new \$945,000 pledge and an early career award from Gloria Choi. A \$750,000 gift from the Halis Family helped secure and renovate a new 8,000 square foot space to accommodate the expansion and increased research volume of the Picower Institute. Kathy Octavio, Miguel Octavio, and Glenda Mattes helped support new aging brain projects across MIT through generous six-figure gifts applied as seed funding for science and engineering faculty. The Eleanor Schwartz Charitable Foundation pledged a \$500,000 gift. MIT alumnus Lester Gimpelson '57, Joe and Nancy DiSabato, David Emmes, The Degroof-VM Foundation, and David and Dagmar Dolby gave six-figure commitments to Alzheimer's research. The Belfer family also continued support for Alzheimer's research through the Neurodegeneration Consortium, a collaboration among MIT and other institutions. Additionally, this year the Picower Institute received generous five-figure gifts from many individuals and an increase in smaller annual fund gifts from MIT alumni as well as unaffiliated donors, all of which were vital to Picower's mission of advancing brain research.

Media Recognition

The Picower Institute has attained a distinguished international reputation as a leader in neuroscience research. Publication records reflect faculty scholarly excellence. During the reporting year, Picower Institute faculty published 47 articles in journals such as *Nature*, *Cell*, *Cell Reports*, *Nature Methods*, and *Nature Communications*.

Often working with the MIT News Office, the Picower Institute in FY2022 posted 24 press releases and 12 feature stories on its website and growing social media feeds. Independent media outlets reported Picower research, expertise, and other newsworthy activities more than 60 times, including NPR, *New York Post*, *The Washington Post*, CNN, *The Boston Globe*, *The Scientist*, *Nature*, *Discover Magazine*, *STAT*, *USA Today*, *Quanta*, *Psychology Today*, and many others.

Programs and Activities

The Picower Institute plans a rigorous calendar of formal lectures, conferences, collaborative grant programs, workshops, and other informal events to facilitate cross-disciplinary collaboration. Such activities integrate Picower researchers and the MIT neuroscience community with neuroscientists and practitioners from the public and private sectors to exchange research findings and explore the potential that research advances regarding learning and memory mechanisms offer to science and society.

The Picower Institute Colloquia invites 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, colloquia speakers included Michelle Monje of Stanford University, Hey-Kyoung Lee of Johns Hopkins University, Brenda Bloodgood of the University of California-San Diego, and Gloria Choi of the Picower Institute. These talks occurred online.

At the Picower Institute, “Plastic Lunch” refers to a monthly series of informal talks during the academic year that gives postdoctoral associates and graduate students from across the Picower Institute a chance to share their latest (often pre-published) research with colleagues within the Building 46 community. Throughout AY2022, these talks continued in a virtual format and were well attended with strong engagement.

On October 17, 2021, the Picower Institute hosted its annual fall symposium: “Dendrites: Molecules, Structure, and Function.” Experts from around the globe gathered virtually to share their latest research on how dendrites’ molecular and electrophysiological properties enable them to perform complex computations essential for sensory-motor processing and higher cognitive function and how these can go awry. While the Picower fall symposium has been a long-standing tradition, the format in 2021 was noticeably different. Taking advantage of the virtual format and allowing full participation from attendees all over the globe, this symposium took place over 16 hours from 6 am to 10 pm Eastern Standard Time. The event featured five keynote talks, ten short talks by trainees selected from a large pool of submitted abstracts, two virtual poster sessions with more than 45 presenters, and three virtual networking sessions with tables hosted by more than 25 dendrites experts. The format was a great success, with attendees

remarking that this year’s symposium was the most engaging virtual event they had attended since the pandemic began. The private poster and networking sessions drew 207 people, which required an application and selection by the organization committee, while the public keynote and short talks drew 644 people.

This year’s speakers for ABI’s Aging Brain Seminar Series included Sandra Siegert of IST Austria and Hideyuki Okano of Keio University School of Medicine.

On June 16, 2021, the Alana Down Syndrome Center hosted a seminar entitled “Technology to Improve Ability.” The online event generated interest from a broad group of individuals and was well attended.

Throughout the year, several special seminars were held. Speakers included Johannes Graff of the Swiss Federal Institute of Technology, Evan Feinberg of the University of California-San Francisco, and Emily Osterweil of the University of Edinburgh.

The Post-Doc Association—an endeavor of the Picower Institute’s postdoctoral community to support activities, foster community, and enrich interactions between postdoctoral colleagues and future associates (and now a Building 46-wide association)—continues to expand and improve in partnership with the administration. The Post-Doc Association convened a series of informal talks, educational seminars, and social events throughout the year.

The JPB Foundation’s philanthropic support for research programs allows Picower to provide a truly unique research environment for faculty, laboratory members, and the administrative team. These programs include:

- The Catalyst Program
- The Clinical Collaborative Fellowship
- The Picower Neurological Disorder Research Fund
- Picower Fellows Program
- The Symposium Fund
- The Picower Institute Innovation Fund
- Junior Faculty Awards

Research Initiatives

RIKEN-MIT Laboratory for Neural Circuit Genetics

The RIKEN-MIT Laboratory for Neural Circuit Genetics was founded in April 2008 by Professor Susumu Tonegawa and jointly sponsored by the RIKEN Center for Brain Science in Japan, the Howard Hughes Medical Institute, and MIT. The laboratory’s objective is to deepen our understanding of molecular, cellular, circuit, and brain system mechanisms underlying learning and memory by combining new research tools, technologies, and computational approaches. The laboratory focuses on deciphering

the underlying cellular and neural circuit mechanisms of episodic, semantic, emotional, and social memory in mice, as well as high-level cognitive functions. Our research aims to uncover the fundamental mechanisms operating in the healthy brain, which will aid in understanding how these mechanisms underperform in disease. The RIKEN-MIT agreement funds the laboratory's activities and will primarily support the Tonegawa research group for the next year (as of April 2022). The Tonegawa lab published two *Nature Communications* papers this year. This collaboration helped fund both publications: Roy, DS. et al., 2022; and Takeuchi, D. et al., 2022.

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 disease models. The various laboratories have expertise and experience with different experimental protocols, which, when combined with studying human cells, results in accelerated progress. Patient-derived skin fibroblast cells are reprogrammed into induced pluripotent stem cells (iPSCs) and differentiated into various brain cell types, allowing researchers to examine diseases and gene variants in patient populations directly. This core facility has rapidly become essential to studies of autism, psychiatric disease, Alzheimer's, and other neurodegenerative diseases. Users can access the ICF at any time. A reservation system is available for shared equipment.

Supervisor Tak Ko established an orientation program and training for faculty and potential users. In FY2022, nine researchers and postdocs received iPS training, and more than 100 researchers have been trained in the facility since its inception. Also, collaboration with researchers outside of MIT has continued. "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" are two examples of significant interactions with the Broad Institute. Biotech industries also inquired about iPSC culture service, and Cambridge biotech company Solid Biosciences sent a researcher to learn basic iPSC maintenance techniques and cardiomyocyte differentiation procedures. Data leveraged from the ICF has resulted in many prominent articles published in journals including *Cell Systems*, *Neuron*, *Nature*, *Nat Neuroscience*, *PLoS One*, and *Molecular Psychiatry*. In addition, there are many instances where MIT researchers have been able to leverage ICF capabilities to receive external funding, predominantly from the National Institutes of Health.

3D Imaging Core Facility

In 2020, with funding from the Picower Institute Innovation Fund's VII Equipment Fund, the Picower Institute established a shared 3D imaging core facility after purchasing a lightsheet Lifecanvas microscope. One of Picower's most powerful applications is the Lifecanvas system's ability to image entire mouse brains. We also purchased a Dragonfly Leica imaging system from Andor Technology Ltd., which has a tenfold faster imaging speed than competing systems. Many researchers value this high-speed imaging capability for high-resolution molecular mapping of brain tissues. Furthermore, we purchased a Cambridge Computer Data Storage Server, which connects to the core Picower microscopes (light-sheet and dragonfly) via high-speed

100G internal networking, enabling faster access and storage of microscopic generated data. The facility is open 24 hours a day, seven days a week, to all Picower laboratories.

The Aging Brain Initiative

The Aging Brain Initiative's goals include establishing a long-term investment platform to address this global health imperative through collaborative study, discovery, and rapid integration of brain-aging research into real-world applications. The program brings together MIT's leading memory and neurobiology researchers with engineers, computer scientists, economists, urban planners, social policy experts, clinicians, and industry partners to think creatively about brain aging and tackle ambitious unexplored ideas. High-risk flagship projects include a whole-systems perspective extending beyond today's traditional clinical pathology and genetic approaches to include vital aspects of the challenge, such as understanding memory loss and developing technologies for improved study and care. Frequent multidisciplinary discussion forums and seminars enable open data sharing and accelerated development of new growth ideas.

The ABI's new seed grant program debuted this year. The program awarded \$100,000 to MIT laboratories for risky, ground-breaking, aging-brain research. The program received 17 proposals, selected five projects, and funded yearlong investigations of novel hypotheses concerning Alzheimer's and ALS (amyotrophic lateral sclerosis) causation, biomarkers, and therapies. Awardees included Professors Thomas Heldt, Ann Graybiel, Gloria Choi, Peter Dedon, and Ritu Raman.

ABI members continued to be important contributors to research progress. ABI founding member Emery Brown won the 2022 Gruber Neuroscience Prize and the Pierre Galletti Award from the American Institute for Medical and Biological Engineering. Cognito Therapeutics—founded by Professors Li-Huei Tsai and Ed Boyden (from their ABI collaboration studying light and sound flicker for neurodegenerative disease)—announced a Food and Drug Administration Breakthrough Device designation and the first results of a Phase II study for the devices in clinical trials. Based on precepts developed by the ABI, Tsai also penned a piece in the *Boston Globe* proposing how science, technology, and industry can collaborate to tackle Alzheimer's disease.

The ABI continues to emphasize project- and team-based immediately implementable research to help us 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 focuses on MIT's strengths:

- Big Data-omics approaches
- Circuit and systems therapeutic approaches, including non-invasive stimulation regimens and ways to restore memories
- Personalized approaches to treatment through human and new disease models
- Uncovering mechanisms supporting healthy aging and resilience

As pandemic restrictions receded, ABI laboratories increased their productivity as research resumed full strength. The NIH-funded collaborative grants for cross-

disciplinary projects in the laboratories of ABI members including Tsai, Boyden, Kellis, Heiman, and Ernest Fraenkel. In FY2022, ABI researchers made significant advances. Tsai published several high-profile papers on Alzheimer's, including work in *Cell Stem Cell* and collaborative work with Professor Kellis in *Science Translational Medicine*. Professors Kellis and Heiman published an atlas of cerebrovascular cells in the human brain and Huntington's disease in *Nature*. Both also earned NIH High-Risk, High-Reward research grants.

In *PNAS*, Emery Brown contributed to a team effort to discover the role of brain rhythms in the functionality of deep brain stimulation for Parkinson's disease. Ed Boyden published in *Nature Nanotechnology* and *Science* on new uses for expansion microscopy, including in situ transcriptome sequencing. The group, led by Tsai, Brown, and Boyden, tested a novel light and sound (GENUS, for Gamma ENtrainment Using Sensory stimuli) device for the treatment of Alzheimer's disease, completing their Phase II trial in Alzheimer Disease patients at MIT, and began Phase II trials for the prevention of Alzheimer's and Parkinson's disease at MGH to assess the device's efficacy in these populations.

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 improve the health, autonomy, and inclusion of people with DS.

The ADSC spans laboratories and programs across MIT, engaging the expertise of scientists and engineers to increase understanding of DS biology and neuroscience. The mission is to produce research and technology to help people with disabilities develop greater social and practical skills to enhance their participation in the educational system, workforce, and community.

In FY2022, the ADSC fellowship program supported six fellows (two graduate students and four postdoctoral fellow) and is actively recruiting for another two postdoctoral fellows. Fellows are trained in the center's labs using advanced innovative techniques. Undergraduate students who join these projects have the potential to amplify the center's discoveries throughout their careers.

The results of ADSC research are starting to emerge. Director Li-Huei Tsai and senior ADSC fellow Hiruy Meharena identified a senescence-like state in neurons and neural stem cells with trisomy 21, which resulted in altered nuclear architecture that small molecule drugs could reverse. Furthermore, researchers from the Tsai and Boyden laboratories have begun a Phase I trial of the GENUS device in adults with Down syndrome, intending to test the device's efficacy in preventing both AD, which affects 90% of people with DS over the age of 45, and general cognitive disabilities that accompany DS.

Faculty

Mark Bear, Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences (BCS)

Emery Brown, Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, Institute for Medical Engineering and Sciences (IMES), BCS

Gloria Choi, Mark Hyman, Jr. Career Development Associate Professor, BCS

Kwanghun Chung, Picower Associate Professor of Neuroscience, BCS, Department of Chemical Engineering, IMES

Steven Flavell, Lister Brothers Career Development Associate Professor, BCS

Myriam Heiman, Latham Family Career Development Associate Professor of Neuroscience, BCS

Troy Littleton, Menicon Picower Professor of Neuroscience, Departments of Biology and BCS

Earl Miller, Picower Professor of Neuroscience, BCS

Elly Nedivi, William R. (1964) & Linda R. Young Professor of Neuroscience, Departments of Biology and BCS

Mriganka Sur, Newton Professor of Neuroscience, BCS, Director of the Simon Center for the Social Brain

Susumu Tonegawa, Picower Professor of Neuroscience, Departments of Biology and BCS

Li-Huei Tsai, Picower Professor of Neuroscience, BCS

Matthew Wilson, Sherman Fairchild Professor in Neurobiology, Departments of Biology and BCS

Li-Huei Tsai
Director, Picower Institute for Learning and Memory
Picower Professor of Neuroscience