Aging Brain Initiative

## NEWS 2020

**Massachusetts
Institute of
Technology**

Grants fund collaborative efforts to prevent, treat Alzheimer's disease

With two new grants, the lab of Li-Huei Tsai, Picower Professor of Neuroscience and Director of The Picower Institute for Learning and Memory, is leading two efforts to address Alzheimer's disease via novel means.

With a grant from the Part the Cloud Gates Partnership Grant Program of the Alzheimer's Association, Tsai will launch a new clinical trial with Massachusetts General Hospital to test whether stimulating 40 Hz gamma frequency brain waves with light and sound at that frequency can prevent the advance of Alzheimer's disease pathology even before volunteers experience symptoms such as memory impairment. The technique, called Gamma ENtrainment Using Sensory stimuli (GENUS), has been shown to improve memory, protect neurons and lower protein plaques in extensive mouse testing.

Microglia cells

Meanwhile, key studies over the last five years suggest that misregulation of gene expression in the brain's innate immune cells, called microglia, may play a key role in the progression of Alzheimer's disease. With a grant from the National Institute on Aging, three member labs of The Neuroedgeneration Consortium (NDC), at MIT, MD Anderson Cancer Center, and Icahn School of Medicine, will collaborate to develop a new drug that can inhibit a likely source of the misregulation, the protein PU.1, potentially delaying the onset of Alzheimer's symptoms. The team has already identified a compound with strong and specific effects in reducing PU.1 activity and modulating the expression of the same genes that PU.1 is responsible for regulating.
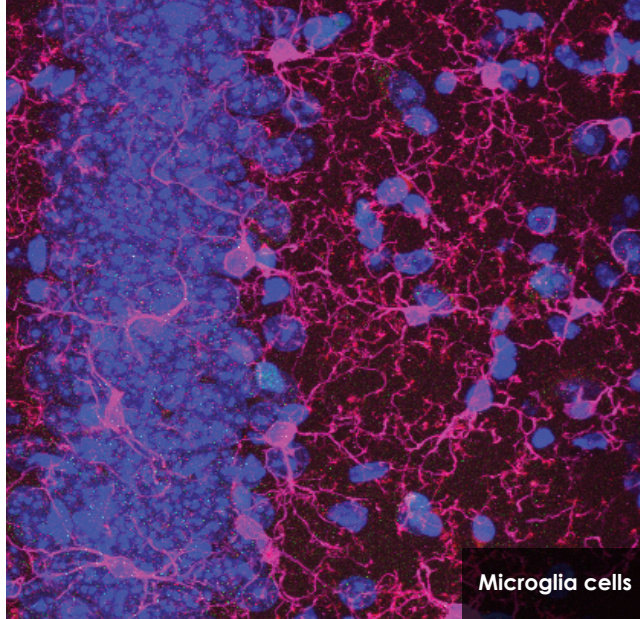
From the Director

Li-Huei Tsai, Ph.D.
Founding director,
MIT Aging Brain Initative

Dear Friends,

At the end of a strange and difficult year, I am glad to have this opportunity to reflect on the hope I have for progress in addressing neurodegenerative disease and brain aging, and the gratitude I feel for the support you have provided to make this progress possible.

Within these pages, you can learn of many of my reasons for hope. In labs all around MIT, members of the Aging Brain Initiative reported numerous important findings in 2020 about disorders such as Alzheimer's and Huntington's diseases, about fundamental mechanisms of memory and regarding how aging affects the cells in our body. These discoveries advance the field's ability to understand how our brains become more vulnerable to disease, especially with age, and what we can do about it. We are pleased, for instance, to have found new prospective drug targets and advanced clinical testing of potential therapies.

Each new insight is the outcome of years of effort by teams of professors, postdocs, students and research staff. It is also the product of philanthropic support that is more important than ever as a bedrock of science and biomedicine.

As we look forward to a new year, we are excited and dedicated to continuing this important work. We are encouraged, as well, to know you are with us in our work.

Thank you and Happy New Year.

Researchers engineered lab models of the human blood brain barrier
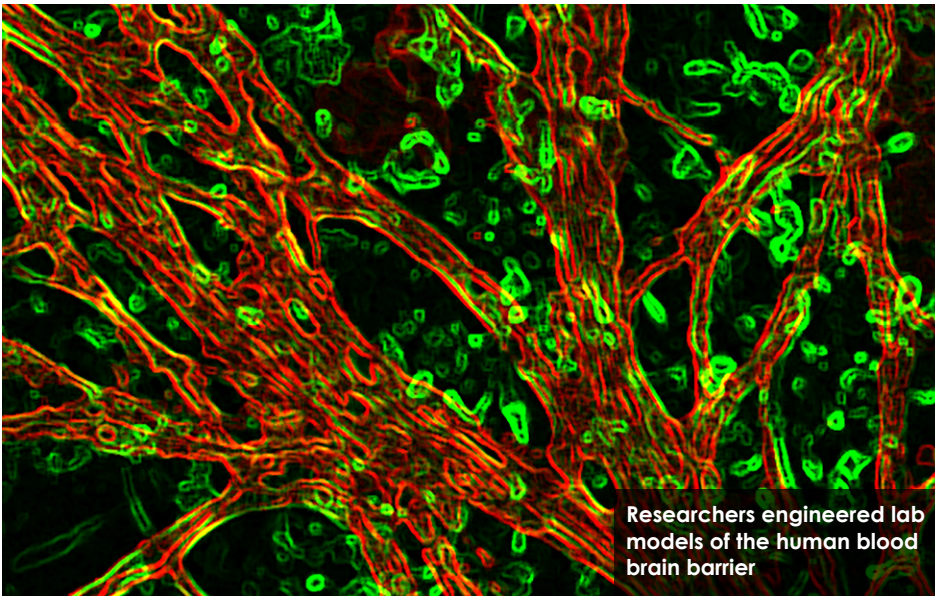
Study finds path for addressing Alzheimer's blood-brain barrier impairment

By developing a lab-engineered model of the human blood-brain barrier (BBB), Aging Brain Initiative neuroscientists have discovered how the most common Alzheimer's disease risk gene causes amyloid protein plaques to disrupt the brain's vasculature and showed they could prevent the damage with medications already approved for human use.

About 25 percent of people have the APOE4 variant of the APOE gene, which puts them at substantially greater risk for Alzheimer's disease. Almost everyone with Alzheimer's, and even some elderly people without, suffer from cerebral amyloid angiopathy (CAA), a condition in which amyloid protein deposits on blood vessel walls impair the ability of the BBB to properly transport nutrients, clear out waste and prevent the invasion of pathogens and unwanted substances.

In the study in *Nature Medicine*, the researchers pinpointed the specific vascular cell type (pericytes) and molecular pathway (calcineurin/NFAT) through which the APOE4 variant promotes CAA pathology.

The research indicates that in people with the APOE4 variant, pericytes in their vessels churn out too much APOE protein, explained senior author Li-Huei Tsai, Picower Professor of Neuroscience and director of The Picower Institute for Learning and Memory. APOE causes amyloid proteins, which are more abundant in Alzheimer's disease, to clump together. Meanwhile, the diseased pericytes' increased activation of the calcineurin/NFAT molecular pathway appears to encourage the elevated APOE expression.

There are already drugs that suppress the pathway. Currently they are used to subdue the immune system after a transplant. When the researchers administered some of those drugs, including cyclosporine A and FK506, to the lab-grown BBBs with the APOE4 variant, they accumulated much less amyloid than untreated ones did.

ABI Founding member Manolis Kellis is a co-author of the study.

Alzheimer's risk gene disrupts endocytosis, but another disease-linked gene could help

MIT scientists report that the most prominent Alzheimer's disease (AD) risk gene may disrupt a fundamental process in a key type of brain cell. Moreover, they found that increasing the expression of another AD-associated gene in those cells could help alleviate the problem.

Scientists have been working for decades to understand why the APOE4 gene variant increases AD risk. The new study in *Cell Reports* finds that in astrocytes, which are the most common non-neuron cell in the brain, the variant hampers the process of endocytosis, which is a major way that cells bring materials in from outside. That deficit could undermine several of the vital roles that astrocytes play in the brain, including how they facilitate communication among neurons or maintain the blood-brain barrier.

As part of their work, which began in the biology lab of the late Susan Lundquist and continued in the Picower Institute for Learning and Memory lab of Picower Professor Li-Huei Tsai, the team also found that in APOE4-carrying astrocytes increasing expression of an AD-associated gene called PICALM reversed the endocytosis defects.

"Both APOE and PICALM are Alzheimer's risk genes," Tsai said. "It is really interesting that the two genes converge on endocytosis. This indicates that faulty endocytosis plays a key role in the etiology of Alzheimer's."

Extinguishing fear is its own reward

When you expect a bad experience to happen and then it doesn't, it's a distinctly positive feeling. A new study explains why: Fear-extinguishing memories and feelings of reward alike are stored by the same neural ensembles, or "engrams." The study in *Neuron* specifically identified these neurons as ones that express the gene Ppp1r1b in the posterior of the basolateral amygdala (pBLA), a region known to assign associations of aversive or rewarding feelings, or "valence," with memories. The research was performed in the lab of Picower Professor Susumu Tonegawa at RIKEN-MIT Laboratory of Neural Circuit Genetics at the Picower Institute and Howard Hughes Medical Institute.

Like a treasure map, brain region emphasizes reward location

MIT neuroscientists have found that as we pursue life's prizes, a region of the brain tracks our location with an especially strong predilection for the location of the reward. This pragmatic bias of the lateral septum (LS) suggests it's a linchpin in formulating goal-directed behavior. The LS dedicates a much smaller proportion of its neurons to encoding location than does the hippocampus, but a much larger proportion of those cells respond when the rat is proximate to where the reward lies in a maze. Also, the pace of LS neural activity peaks closest to reward locations. The lab of Matthew Wilson, Sherman Fairchild Professor of Neurobiology, conducted the study published in *eLife*.

In this mouse brain, yellow shows the location of engram neurons.

Neuroscientists discover a molecular mechanism that allows memories to form

New memories are encoded in neurons called engram cells. Engrams are reactivated during memory recall. A new study in *Nature Neuroscience* by the lab of Picower Institute director Li-Huei Tsai reveals that this process is controlled by large-scale remodeling of neurons' chromatin over several days.

Changes to the density and arrangement of chromatin, a highly compressed structure consisting of DNA and proteins called histones, can control how active specific genes are within a given cell.

Right after a memory is formed, in many regions of DNA chromatin becomes looser, allowing the DNA to become more accessible. Nearly all of these regions contain noncoding sequences called enhancers, which interact with genes to help turn them on.

Five days after memory formation, as memories were strengthened, the 3D chromatin structure around the enhancers brought the enhancers closer to their target genes. Then, upon memory recall, the primed enhancers interacted frequently with their target genes, leading to a surge in the expression of those genes. Many of the genes promote protein synthesis at synapses, helping neurons strengthen their connections with other neurons.

Researchers find memory cells that help us interpret new situations

Say you are at a new restaurant, trying dishes you haven't had before amid the novel decor. As the meal proceeds, your brain recognizes the similar segments of this experience, such as perusing a menu, ordering appetizers, and splurging on dessert. In *Nature Neuroscience*, MIT neuroscientists identified cell populations that encode such segments. These memory chunks, stored in the hippocampus, are activated whenever a similar experience takes place, and are distinct from storage of detailed memories of specific locations or flavors.

The researchers believe that this "event code," which they discovered in mice, may help the brain interpret novel situations and learn new information by using the same cells to represent similar experiences.

"When you encounter something new, there are some really new and notable stimuli, but you already know quite a bit about that particular experience, because it's similar to what you have already had," says Susumu Tonegawa, professor of biology and neuroscience at the RIKEN-MIT Laboratory of Neural Circuit Genetics at The Picower Institute.

Genetic screen offers new drug targets for Huntington's disease

Using a genetic screen that had previously been impossible in the mammalian brain, MIT neuroscientists identified hundreds of genes that are necessary for neuron survival. They also found genes that protect against the toxic effects of a mutant protein that causes Huntington's disease.

These efforts yielded at least one promising drug target for Huntington's: a family of genes called "Nme" that may normally help cells to break down the mutated huntingtin protein before it can aggregate and form the clumps seen in the brains of Huntington's patients

"These genes had never been linked to Huntington's disease processes before. When we saw them, that was very exciting because we found not only one gene, but actually several of the same family, and also we saw them have an effect across two models of Huntington's disease," says Myriam Heiman, associate professor of neuroscience and senior author of the paper in *Neuron*.

Knocking down Nme1 allowed more huntingtin to accumulate (red specks, right panel)
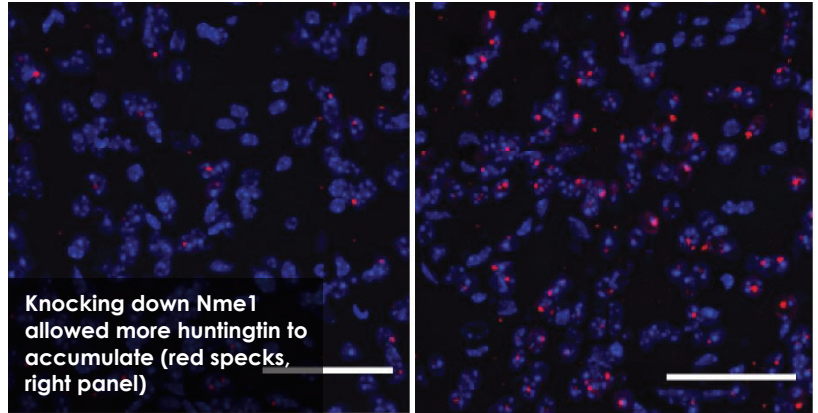
The researchers' new screening technique, which allowed them to assess all of the roughly 22,000 genes found in the mouse brain, could also be applied to other neurological disorders, including Alzheimer's and Parkinson's diseases, says Heiman, who is also a member of MIT's Picower Institute for Learning and Memory and the Broad Institute of MIT and Harvard. ABI Founding member Manolis Kellis, Professor of Computer Science, is a co-author.

Neural vulnerability in Huntington's disease tied to release of mitochondrial RNA

In the first study to comprehensively track how different types of brain cells respond to the mutation that causes Huntington's disease (HD), MIT neuroscientists found that a significant cause of death for an especially afflicted kind of neuron may be an immune response to genetic material errantly released by mitochondria, the cellular components that provide cells with energy.

In different cell types at different stages of disease progression, the researchers measured how levels of RNA differed from normal in brain samples from people who died with Huntington's disease and in mice engineered with various degrees of the genetic mutation. Among several novel observations in both species, one that particularly stood out is that RNA from mitochondria were misplaced within the brain cells, called spiny projection neurons (SPNs), that are ravaged in the disease, contributing to its fatal neurological symptoms. The scientists observed that these stray RNAs, which look different to cells than RNA derived from the cell nucleus, triggered a problematic immune reaction.

"When these RNAs are released from the mitochondria, to the cell they can look just like viral RNAs and this triggers innate immunity and can lead to cell death," said study senior author Myriam Heiman, Associate Professor in MIT's Department of Brain and Cognitive Sciences, The Picower Institute for Learning and Memory, and the Broad Institute of MIT and Harvard. "We believe this to be part of the pathway that triggers inflammatory signaling which has been seen in HD before."

The findings appeared in *Neuron*. ABI Founding member Manolis Kellis, Professor of Computer Science, is a co-author.

Research highlights immune molecule's complex role in Huntington's disease

Many people with Huntington's disease (HD) exhibit high levels of an immune-system molecule called interleukin-6 (IL-6), so researchers suspect IL-6 of promoting the condition's neurological devastation. A new study by the lab of MIT Associate Professor Myriam Heiman shows the story isn't so simple. Instead, they found that HD model mice bred to lack IL-6 showed worse symptoms than HD mice that still had it.

Heiman' team studied why this surprising finding occurred by sequencing RNA in thousands of individual cells to measure gene expression in all the major cell types in the striatum, the brain region most affected in HD. Huntington's mice without IL-6 showed significantly less expression of genes important for synapses, the connections that link neurons into circuits.

"Perhaps this worsening of the phenotype is due to perturbation of those synaptic signaling pathways," Heiman said.

New data affirms anti-aging supplement safety

Decades of research in the MIT lab of Leonard Guarente, Novartis Professor of Biology, has shown that sirtuin proteins can help prevent aging-associated declines in cellular health and promote longevity. Newly published data add to the evidence base that a supplement promoting sirtuin activity in cells is safe.

The supplement, nicotinamide riboside (NR), is a naturally occurring form of vitamin B3. It elevates synthesis of NAD+, which sirtuins require for their activity. NAD+ levels can decline with age.

In the *International Journal of Toxicology,* Guarente and colleagues at a company he co-founded, Elysium Heatlh, published findings showing that a high-purity, nature-identical, synthetic NR (NR-E), manufactured under the guidelines of good manufacturing practices for dietary supplements showed no adverse effects in rats at any dose. Male rats at the highest dose did see a small loss of weight.

NR is the key ingredient in Elysium's supplement Basis, which in a 2017 clinical trial was shown to elevate NAD+ levels by an average of 40 percent in human adults. The company also recently debuted a brain-health supplement called Matter.

Neurons in the bottom row, missing the HDAC1 gene, show higher levels of DNA damage (green).
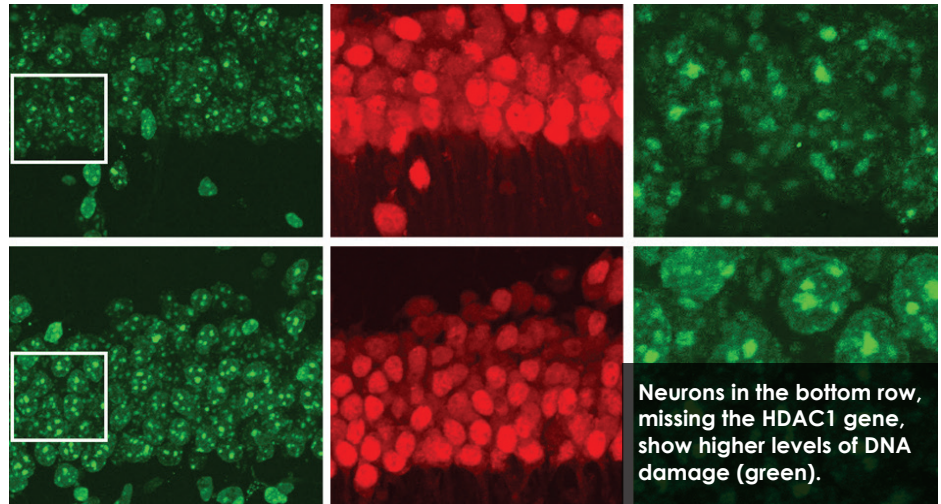
Study finds critical enzyme for repairing DNA in aging neurons

MIT neuroscientists have discovered that an enzyme called HDAC1 is critical for repairing age-related damage to genes involved in memory and other cognitive functions.

Prior studies of Alzheimer's patients have shown high levels of a type of oxidative DNA damage. In a new study in *Nature Communications*, researchers showed that as mice age and HDAC1 is lost, this oxidative DNA damage built up.

An enzyme called OGG1 is responsible for repairing this oxidative DNA damage. The researchers found that HDAC1 is needed to activate OGG1. They also showed that they could reverse this damage and improve cognitive function in the mice with a drug that activates HDAC1. The study suggests that restoring HDAC1 could have positive benefits for both Alzheimer's patients and people who suffer from age-related cognitive decline.

"It seems that HDAC1 is really an anti-aging molecule," says Li-Huei Tsai, the director of MIT's Picower Institute for Learning and Memory and the senior author of the study. "I think this is a very broadly applicable basic biology finding, because nearly all of the human neurodegenerative diseases only happen during aging. I would speculate that activating HDAC1 is beneficial in many conditions."

'ACTIONet' improves analysis of RNA data

To understand how gene expression differs in each type of cell in the brain amid health or disease, scientists are increasingly using a technique called single cell RNA sequencing. "scRNAseq" produces a flood of data that scientists are still learning to analyze optimally.

A new study in *Nature Communications* led by computer science Professor Manolis Kellis presents a new method, called ACTIONet.

"ACTIONet provides a robust, reproducible, and highly interpretable single-cell analysis platform," wrote Kellis' team, which last year partnered with Li-Huei Tsai's lab to produce a groundbreaking study of scRNAseq data in Alzheimer's brains.

In the new study, Kellis' team used ACTIONet to produce a unified analysis of data sets from three different studies of the human cortex.

"ActionNET is our main workhorse for Alzheimers, Schizophrenia, ALS, Huntington's disease and more: a multi-scale network-based archetype approach for learning cell types and cellular states in health and disease," Kellis said.

Sipser steps down as dean; MIT welcomes Mavalvala as successor

Michael Sipser, Donner Professor of Mathematics and Aging Brain Initiative co-founder, stepped down as dean of MIT's School of Science in September after six years of service. Succeeding him is the Curtis and Kathleen Marble Professor of Astrophysics, Nergis Mavalvala.
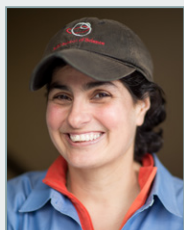
An MIT News announcement of Sipser's decision to return to research and teaching listed the founding of the ABI in 2015 as one of the key accomplishments of his tenure as dean.

"We are immensely grateful to Mike for his deep engagement and tireless support in helping to launch and sustain the Aging Brain Initiative over the last several years," said Li-Huei Tsai. "We are excited to continue this work now with Nergis, who is also a brilliant scholar and a wonderful colleague."

Mavalvala is renowned for her pioneering work in gravitational-wave detection, which she conducted as a leading member of LIGO, the Laser Interferometer Gravitational-Wave Observatory.

ABI faculty earn notable honors

In 2020, several members of the ABI Faculty earned significant honors and awards.

Edward Boyden, Y. Eva Tan Professor in Neurotechnology, won the 2020 Wilhelm Exner Medal awarded by the Austrian Association of Entrepreneurs.

Emery N. Brown, Edward Hood Taplin Professor of Computational Neuroscience and Health Sciences & Technology, earned the Society for Neuroscience's Swartz Prize for Theoretical and Computational Neuroscience.

Li-Huei Tsai, Picower Professor of Neuroscience, was elected a senior fellow of the National Academy of Inventors.

UCSF researcher Lennart Mucke speaks during a panel discussion.

Symposium highlights leads for combating neurodegeneration

In essence, the 10 neuroscientists who spoke at the MIT's Aging Brain Initiative symposium, "Molecular and Cellular Mechanisms of Neurodegeneration" Sept. 22 addressed a simple, two-part question: What goes wrong in the aging brain and how can finding that out help us do something about it? Their answers provided many tangible signs of progress and reasons for hope.

Their words reached what may be the biggest audience ever for an ABI event. More than 1,300 people from 48 countries tuned in online over the course of the day.

"Neurodegeneration is a very multifaceted and difficult problem that affects tens of millions of people around the world," said Li-Huei Tsai, Picower Professor of Neuroscience, director of The Picower Institute for Learning and Memory, and founding director of the ABI. "The good news is that many very talented and dedicated researchers are working on it."

Indeed, speaker after speaker throughout the day not only shared new insights into the nature of diseases that cause brain cells to die, but also described promising new treatment strategies. Many are advancing through clinical trials.

For instance, Diane Chan, a neurologist and postdoctoral researcher in Tsai's lab, is leading human clinical studies of a potential Alzheimer's therapy. After observing that the power of neural rhythms at the "gamma" frequency of 40 Hz are lessened in Alzheimer's, Tsai's lab led the discovery that exposing mice to light or sound at that frequency can increase gamma power and restore synchrony of neural activity across brain regions. In mouse models the technique improves memory and cognition, prevents neural death and reduces the accumulation of proteins known as key biomarkers of disease progression.

In a small sample of human volunteers tested so far, the method has proven safe and well tolerated, increases 40 Hz gamma rhythm power and network connectivity and may be contributing to improved sleep, Chan reported. Testing for improvements in memory and cognition have not been completed yet, however.

To keep up with future Aging Brain events, visit the Aging Brain Initiative website: https://picower.mit.edu/about/aging-brain-initiative

La Caixa Foundation creates three ABI fellowships

To acccelerate the Aging Brain Initiative's research and advance the development of treatment of disease, the "la Caixa" Foundation in Spain has established three postdoctoral fellowships for postdocs to work on brain aging, memory and/or neurodegenerative-related research at MIT. Fellows will be supported for up to three years.

The first fellow named under the program is Martin Kahn, who began working in the lab of Li-Huei Tsai this summer. Kahn studies brainstem circuits in Alzheimer's Disease because they are very early targets in the disease and have strong links to cognition, sleep, and autonomous brain functions.

By "la Caixa" request, preference will be given to top candidates who have graduated from a Spanish or Portuguese institution, or secondarily to graduates of institutions in Europe.

For more information, contact:
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picower.mit.edu/about/aging-brain-initiative

About the Aging Brain Initiative

This interdisciplinary research effort pulls together faculty expertise, knowledge, and technical resources from across MIT to solve the mysteries of the aging brain. It spans neuroscience; fundamental biology and genetics; investigative medicine; engineering and computer science; economics; chemistry; urban planning; and artificial intelligence to enable a comprehensive systems approach.

What's the ultimate mission? To deliver the foundational research that makes possible new tools to address the challenges of brain aging and create a better future for millions.

Faculty of the Aging Brain Initiative at MIT

Core MIT Members:

Ed Boyden, McGovern Institute for Brain Research, Media Lab, Departments of Biological Engineering and Brain & Cognitive Sciences; **Emery Brown**, Picower Institute for Learning and Memory, Department of Brain & Cognitive Sciences, and Anesthesia, Critical Care & Pain Medicine at Massachusetts General Hospital; **Leonard P. Guarente**, Department of Biology; **Robert Horvitz**, McGovern Institute for Brain Research and Koch Institute for Integrative Cancer Research, Department of Biology; **Manolis Kellis**, Computer Science and Artificial Intelligence Lab, Broad Institute, Department of Electrical Engineering & Computer Science; **Michael Sipser**, Past Dean of School of Science, Department of Mathematics; **Susumu Tonegawa**, Picower Institute for Learning & Memory, Departments of Brain & Cognitive Sciences and Biology; **Li-Huei Tsai**, Director, Aging Brain Initiative and Picower Institute for Learning & Memory

Angelika Amon, ABI Core faculty member and Professor of Biology in the Koch Institute, passed away Oct. 29, 2020.

Collaborative MIT Members:

Mark Bear, BCS, Picower; **Gloria Choi**, BCS, Picower; **Kwanghun Chung**, Chem Eng, IMES, BCS, Picower; **Joseph Coughlin**, Urban Planning, Engineering Systems; **Randall Davis**, CSAIL; **Steven Flavell**, BCS, Picower; **Ernest Fraenkel**, BioEngineering/CSAIL; **John Gabrieli**, BCS, McGovern; **Ann Graybiel**, BCS, McGovern; **Myriam Heiman**, Picower, BCS, Broad; **Rudolph Jaenisch**, Whitehead, Biology; **Alan Jasanoff**, BCS, McGovern; **J. Troy Littleton**, BCS, Picower; **Andrew Lo**, Sloan, Finance; **Tod Machover**, MIT Media Lab; **Earl Miller**, BCS, Picower; **Elly Nedivi**, BCS, Picower: **Jean-Jacques Slotine**, Mech Eng; BCS **Mriganka Sur**, BCS, Picower; **Steven R. Tannenbaum**, Bio-engineering, Chemistry and Toxicology; **Matthew Wilson**, BCS, Biology, Picower

Thank you for investing in MIT talent — The Aging Brain Initiative Fund

The only way to decode the mysteries of the brain and to find a cure or better treatments for the dementias of aging—and to build on the momentum already created by the Aging Brain Initiative—is to support the innovation pipeline: the faculty, students, and other scientists engaged in fundamental brain aging research, and the tools and facilities that enable their work.

As we continue with this work and push forward to complete our next goals, we are proud to recognize the generosity of those friends and alumni who supported this pipeline and made our progress possible. Thank you. We deeply appreciate your trust and generous contributions. With your help, we have been able to turn curiosity into discovery, changing what we know about the world.