Aging Brain Initiative

NEWS 2022

Inside

Massachusetts Institute of Technology

From the Director

Dear Friends,

As 2022 begins to draw to a close, I am proud—but even more grateful—to bring you this update on the progress of research at MIT related to the aging brain.

In these pages, for instance, you can read about advances in fundamental understanding of neurodegenerative conditions including Alzheimer's, Parkinson's, and Huntington's diseases. You'll also see updates on emerging potential therapies and new technologies that will advance research still further. Beyond the lab bench, we are also thinking about how to improve the economic climate for treatment and technology innovations (see p. 5).

And you'll also see stories (including on this page) about how the involvement of people like you are contributing directly to our progress in the lab. We are all deeply thankful for support provided by philanthropic gifts. They make our work possible and they are especially crucial in helping us to launch new ideas before they can be funded with traditional grants.

We wish you a happy and healthy Holiday Season and we look forward to continuing our work in the new year.

All the best,

Li-Huei Tsai
Director, The Aging Brain Initiative

ABI Seed Grants Amplify New Ideas

In 2022, the Aging Brain Initiative's donor-supported seed grants launched promising, novel projects to understand, prevent and treat the aging brain. Awarded their yearlong grants in April, the five recipients are well underway in their investigations.

MIT engineers selected for seed funding are developing new tools to assess cognitive decline and uncover cellular processes. **Thomas Heldt**, associate professor of electrical and biomedical engineering, in partnership with Vivienne Sze, associate professor in MIT's Department of Electrical Engineering and Computer Science, is designing a device that helps diagnose neurodegenerative disorders by monitoring people's eye movements. Heldt's invention is powered by artificial intelligence and designed for at-home use on everyday consumer electronics.

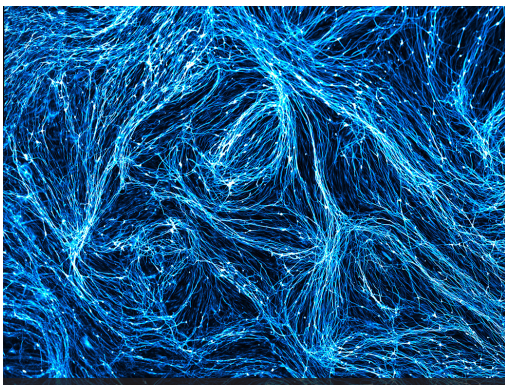
Ritu Raman, the d'Arbeloff Career Development Assistant Professor of Mechanical Engineering at MIT will create a tool to better understand the neuroscience behind amyotrophic lateral sclerosis. Equipped with the tool to finely sample interstitial fluid within tissues, Raman's team will monitor and compare cell-cell signaling in models of the junction between nerve and muscle. With deeper insight into these cellular processes, Raman seeks to identify new therapeutic targets.

Other fund recipients are exploring the genetic and molecular underpinnings of brain diseases. Institute Professor **Ann Graybiel's** lab in the Department of Brain and Cognitive Sciences will test the hypothesis that mutations on a specific gene may lead to the early emergence of Alzheimer's disease in the striatum. This line of inquiry could provide new insight into the progression of the disease and introduce a new biomarker that virtually all other studies have overlooked. Picower Institute Associate Professor **Gloria Choi** will use her grant to examine whether the brain's meninges release signaling molecules that create an inflammatory state. Recent research suggests that immune inflammation may play a significant role in the development of Alzheimer's disease. Also, an international collaboration led by **Peter Dedon**, Singapore Professor in MIT's Department of Biological Engineering, will assess if Alzheimer's pathology is driven by dysregulation of transfer RNAs and the dozens of natural tRNA modifications in the epitranscriptome.

Major support for the seed grants, which provide each lab with $100,000, came from generous gifts by David Emmes SM '76; Kathleen SM '77, PhD '86 and Miguel Octavio; the Estate of Margaret A. Ridge-Pappis, wife of the late James Pappis ScD '59; the Marc Haas Foundation; and the family of former MIT President Paul Gray '54, SM '55, ScD '60, with additional funding from many annual fund donors to the Aging Brain Initiative Fund.

ABI seed grant winners (clockwise from top): Ann Graybiel, Thomas Heldt, Peter Dedon, Ritu Raman, and Gloria Choi. ***Images by Julie Pryor, Lillie Paquette.***

Unlocking APOE4's Role in the Development of Alzheimer's



MIT researchers generated neurons that express the gene APOE3 from induced pluripotent stem cells. Dendrites of the neurons are stained cyan.

Half of the people living with Alzheimer's disease carry the APOE4 risk gene variant yet it is unclear why it is such a major genetic risk factor. By illuminating APOE4's cellular processes, postdoc **Matheus Victor**, working in the lab of **Li-Huei Tsai**, director of ABI and The Picower Institute, offers new insight into the decline of neural activity, and consequent cognitive decline in patients.

For several years, Tsai's lab has been studying the effects of APOE4 on a variety of cell types in the brain. Victor's new study shows that when microglia, the brain's immune cells, express APOE4, they are unable to metabolize and remove lipids from their environment. Eventually, the buildup of fatty molecules interferes with the activity of nearby neurons and their ability to communicate with each other.

Victor discovered that communication resumed when microglia were exposed to Triacsin C, a drug that hinders the formation of lipid droplets. Triacsin C is too toxic for use in humans, but the findings suggest that restoring normal lipid metabolism in microglia might help treat Alzheimer's symptoms. The Tsai lab separately showed that the diet supplement choline might do just that.

"The question is, how do you restore lipid homeostasis across multiple cell types?" Victor said. "It's not an easy task, but we're tackling that through choline, for example, which might be a really interesting angle."

Illuminating Cellular Structures in the Brain

An enhancement of "expansion microscopy" is illuminating the architecture of cells and tissues in entirely new ways. For Alzheimer's patients, this method provides a new understanding of amyloid beta, a peptide that forms plaques in the brain that are the best known hallmarks of Alzheimer's pathology.

ABI core member **Edward Boyden**, MIT's Y. Eva Tan Professor in Neurotechnology, pioneered expansion microscopy in 2015 and also developed this latest advancement. The technique uses swellable gels to expand tissues that are naturally packed tightly inside a cell. With this approach, molecules and cellular structures that were once hidden can now be imaged. Collaboration with the lab of **Li-Huei Tsai** revealed that amyloid beta form unusual periodic clusters and create helical structures along axons.

This advance has wide-ranging applications for other brain diseases and disorders. Investigations are underway to study protein aggregates that are linked to Parkinson's and other diseases as well as pathogens that are linked to the aging brain. Preliminary results from these studies have also revealed novel structures. You can see the helical amyloid structure on the cover of this newsletter.

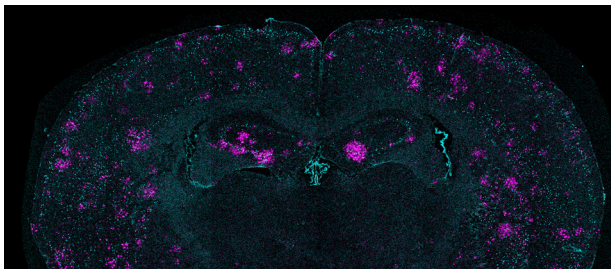
Using a new microscopy technique researchers captured the helical structure of amyloid-beta, which was not revealed using previous techniques. *Image by Zhuyu Peng.*

A More Precise Way to Quiet Inflammation in the Brain

Research from postdoc **Gwyneth Welch** has revealed for the first time that neurons initiate an inflammatory response when their DNA is damaged. This new knowledge deepens understanding of how neurons influence inflammation and may provide a new method to stop these inflammatory pathways from contributing to cell death and the onset of Alzheimer's.

Welch, who worked as a graduate student in the laboratory of **Li-Huei Tsai**, director of the ABI and The Picower Institute, found that when the brain accumulates double-stranded breaks of DNA, neurons first try to repair the genetic material. When that proves unsuccessful, neurons send molecular signals to microglia, the brain's immune cells. In response, microglia take on a more inflammatory state. Further experiments with NFkappaB, a protein that controls transcription of DNA into RNA during inflammation, showed that once immune signaling was interrupted, microglia remained in their normal state and did not try to mute neural circuit connections.

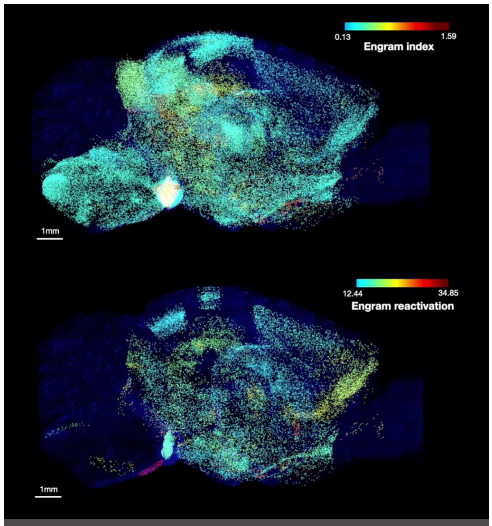
"It's more a proof of principle that if you turn off a major switch for inflammation, that will change how microglia and neurons interact," Welch said. "If your goal is to target inflammatory pathways, focusing on specific signaling molecules might be the more precise way to intervene."



A mouse-brain cross section shows a marker of double-stranded breaks in teal and the immune system cytokine Cxcl10 in magenta.

Memory Mapping

An ambitious study has revealed that a single memory is stored across many connected brain regions. Although whole-brain storage of memory has been theorized for more than a century, discussions on memory storage have typically focused on the hippocampus and the cortex.



Many brain regions found likely to be involved in encoding a memory (top) were also found to be involved in recall upon reactivation (bottom).

Research co-led by ABI core member **Susumu Tonegawa** and former grad student **Dheeraj Roy**, now McGovern Fellow in the Broad Institute of MIT, leveraged technology developed by Picower Institute Associate Professor **Kwanghun Chung**, to reveal that memory-encoding cells known as engrams can be found at many other locations in the brain.

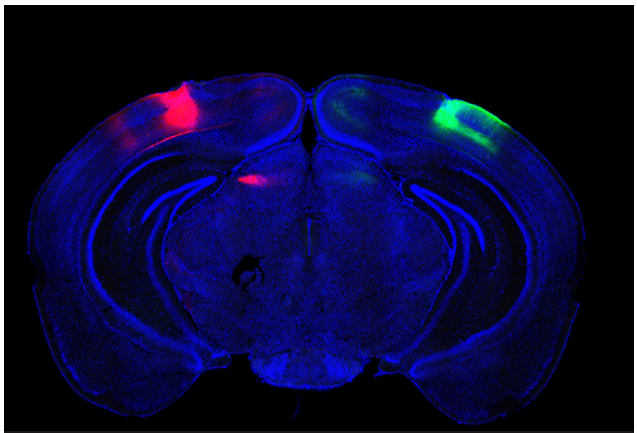
In the study, mice were taken from their home cage to another cage and experienced a small but memorable electrical zap. In one group, neurons were engineered to become fluorescent when they expressed a gene required for memory encoding. In another group, fluorescent labeling was applied to cells that were activated when mice naturally recalled the zap memory. Using a computer to count fluorescing cells in each sample, the team produced brain-wide maps of regions with significant memory encoding or recall activity.

For people living with neurodegenerative diseases, this finding could offer a pathway to addressing memory impairment. "If some memory impairments are because of hippocampal or cortical dysfunction, could we target understudied engram cells in other regions and could such a manipulation restore some memory functions?" posited Roy.

How Alzheimer's Degrades Visual Memory

The ability to identify images seen in the past is essential to everyday life, such as knowing where you placed your keys or remembering a familiar face. For people living with Alzheimer's disease, changes in their environment may go unnoticed. New research from **Chinnakkaruppan Adaikkan**, a former Picower Institute postdoc, has illuminated how Alzheimer's disease degrades the structures that are critical for visual memory.

The work, done in the lab of **Li-Huei Tsai**, director of ABI and The Picower Institute, identified neurons that connect the primary visual cortex of each brain hemisphere. The scientists then observed that cross-hemispheric neurons forged connections with target cells and provided them with "excitatory" stimulation that boosted activity. When Alzheimer's is present, however, these connections are disrupted. In mice test subjects, this phenomenon reduced their brain rhythm synchrony and, by extension, lessened their ability to notice when a new pattern appeared on a wall in their enclosure. Additional research may peer into other cross-hemispheric connections and look for ways they might be affected by Alzheimer's disease.



Neuroscientists traced and studied neurons that connect the visual cortices in each hemisphere of the brain.

Alzheimer's Startup Co-founded by MIT Faculty Begins Phase 3 Trials

Cognito Therapeutics, a startup co-founded by **Li-Huei Tsai**, director of the ABI and The Picower Institute, and ABI core member **Ed Boyden**, has launched Phase 3 trials for its non-invasive approach to treating Mild Cognitive Impairment and mild-to-moderate Alzheimer's disease. The company has designed a headset that delivers light and sound to stimulate patients' 40Hz gamma waves. With increased stimulation of these rhythms, Cognito seeks to stimulate a protective response, seen in Tsai's lab mice, that can remove pathological proteins from the brain, and preserve cognitive and functional abilities.

During the Phase 3 study, the headset's efficacy and its potential adverse effects will be examined. Results from previous clinical studies have shown promise and earned Cognito a "Breakthrough Device" designation from the Food and Drug Administration and a "Fierce 15" recognition from news website Fierce Medtech.

Framework for New Approaches to Alzheimer's Disease

Aging Brain Initiative members at MIT are tackling not only scientific research but also the bigger picture problems of how progress toward a cure for disease is advanced. ABI and Picower Institute Director **Li-Huei Tsai** published an op-ed in *The Boston Globe* titled "How science, technology, and industry and work together to cure Alzheimer's." This piece was part of "The Longevity Hub" series, a collaboration between Globe Opinion and MIT's **Joe Coughlin**, ABI member and Director of the MIT AGELAB.

Tsai laid out a series of gaps in the current approach to Alzheimer's research, including the need for broader research outside traditional pharmaceutical drug discovery, as well as the need for more collaborative research across science, engineering, medicine and the general public. She also outlined the need for a "de-risking' consortium that would help reduce the financial risk of supporting novel findings to encourage companies or investors to move forward with early stage discoveries. She also highlighted the need for technological advancement, both in terms of patient care, as well as the computational firepower needed to analyze the new, enormous datasets being generated from genomic, epigenomic, proteomic and metabolomic research.

To help bridge such gaps the ABI is working to launch an "Alzheimer's Innovation Hub.". The Hub will be propelled by the recent hiring of Dr. **Miyoung Chun**, former Executive Vice President of Science Programs at the Kavli Foundation and Co-Founder and CEO of the non-profit Alzheimer's X. Chun will work at The Picower Institute for Learning and Memory to get the initiative off the ground.

The Boston Globe

OPINION

How science, technology, and industry can work together to cure Alzheimer's

The Alzheimer's research community must acknowledge the gaps in the current approach to curing the disease and make significant changes.

By Li-Huei Tsai Updated November 29, 2021, 3:00am

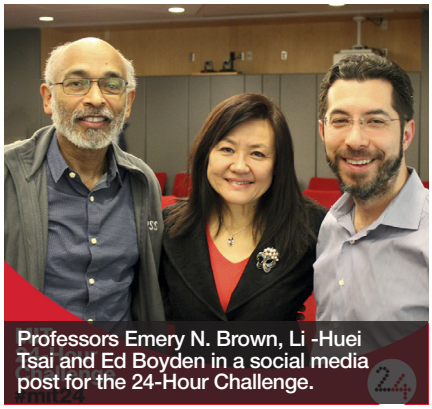
The headline of Li-Huei Tsai's op-ed in *The Boston Globe.*

MIT Giving Challenge Raises Funds for Aging Brain Research

MIT alumni, parents, and friends raised $85,946 in just 24 hours to support scientists and engineers across campus as they seek to unlock the mysteries of the aging brain and find new ways to treat and stop neurodegenerative disorders. The fundraising effort on March 10 was part of MIT's annual 24-hour Challenge. This year, Priscilla King Gray, wife of former MIT president Paul Gray and supporter of the Institute, pledged $5,000 if 100 people made gifts of any size and $10,000 if 200 MIT community members made a donation. With 324 donors, the Institute exceeded Gray's ambitious goal.

Enabling people with Alzheimer's, Parkinson's, and other diseases to live longer, more meaningful lives requires a robust, multidisciplinary effort from neuroscientists, engineers, and computer scientists. Gifts to the Institute support promising ideas that are not yet eligible for grant support but have the potential to transform understanding of the brain.

Priscilla King Gray and former MIT president Paul Gray '54, SM '55, ScD '60



Professors Emery N. Brown, Li -Huei Tsai and Ed Boyden in a social media post for the 24-Hour Challenge.

New Ways to Pay for Alzheimer's Drug Development

Charles E. and Susan T. Harris Professor Andrew Lo. Image courtesy MIT Sloan.

Given the unusually high risk of failure in developing Alzheimer's treatments, society needs to rethink how such efforts are financed and how drug approvals are made, argue ABI member and Sloan School of Management Professor **Andrew Lo** and co-authors in a chapter of the new Cambridge University Press book *Alzheimer's Disease Drug Development: Research and Development Ecosystem*.

Alzheimer's remains so poorly understood that candidate drugs are much more expensive to develop and much more likely to fail in clinical trials, writes a quartet led by Lo, the Charles E. and Susan T. Harris Professor at MIT. A result has been a stark pullback by major pharmaceutical companies and venture capitalists that traditionally sustain biomedical commercialization: "The risk and uncertainty of AD drug discovery and development require new business models and financing structures to successfully traverse the 'valley of death,' the wide funding gap between early-stage research and clinical development."

New options, the authors write, could include a portfolio that bundles many projects and investors together to spread risk, public-private partnerships, venture philanthropy or investments based on royalties and "adaptive financing."

A new mechanism for temporary drug approvals could also help, they add.

"We propose creating a new category of regulatory approval that consists of a temporary license to market 'speculative' therapies for treating high-impact diseases for which there are no existing effective therapeutics," they write. "Such a "spec-license" would not allow off-label use and would expire after a period of 2 or 3 years, during which the licensee is required to collect and share data on the performance of its therapeutic."

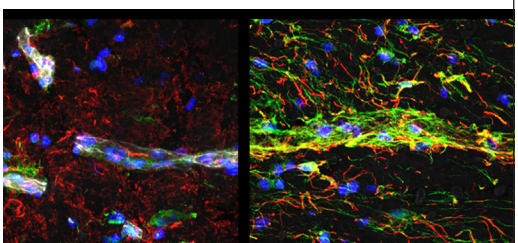
Motor Disorders

Mapping Cerebrovascular Cells and their Role in Huntington's Disease

The brain has relatively few blood vessel, or "cerebrovascular," cells, but they play a critical role in delivering oxygen and nutrients to the brain. After performing RNA-sequencing of more than 16,000 of these difficult-to-find cells and classifying them into 11 different subtypes based on their gene expression patterns, ABI affiliate and Picower Institute member Associate Professor **Myriam Heiman** and ABI core member **Manolis Kellis**, MIT professor of computer science, have created a comprehensive atlas. Demonstrating the disease relevance of this new knowledge, their research revealed differences between cerebrovascular cells from healthy people and those living with Huntington's disease.

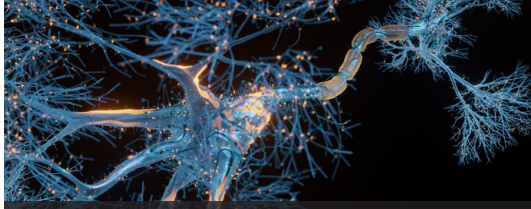
For example, Heiman and Kellis noted a decrease in the membrane-transporter MFSD2A gene expression, increased cellular activity of the Wnt signaling pathway, and a strong immune activation response of endothelial cells. These behaviors could contribute to dysregulation of the blood-brain barrier, a defining trait of Huntington's and other neurodegenerative diseases. Next, Heiman and Kellis will investigate how to design drugs or gene therapy for cerebrovascular cells. Because they can be accessed through the bloodstream, cerebrovascular cells make an enticing target for treating neurodegenerative diseases.

"Our goal is to build a systematic single-cell map to navigate brain function in health, disease, and aging across thousands of human brain samples," Kellis says. "This study is one of the first bite-sized pieces of this atlas, looking at 0.3 percent of cells. We are actively analyzing the other 99 percent in multiple exciting collaborations, and many insights continue to lie ahead."



In vessels of people with Huntington's disease (right) researchers saw higher signs of innate immune signaling (green) and lower levels of a blood-brain barrier integrity protein (white), than in healthy people (left).

Neurodegenerative Disease Can Progress in Newly Identified Patterns



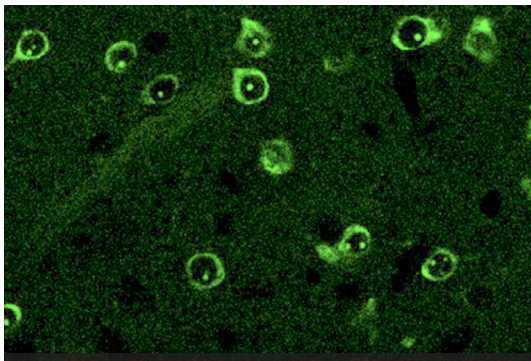
Neurodegenerative diseases, like ALS, affect motor neurons, inhibiting mobility

Understanding the progression of diseases like ALS is critical to enrollment in clinical trials, analysis of potential interventions, and discovery of root causes. However, assessing disease evolution is far from straightforward. Health data can be sparse and subjective, and the heterogeneous nature of disease progression complicates analyses.

Now, a new machine-learning method developed by **Ernest Fraenkel**, ABI member and professor in Biological Engineering, along with other researchers from MIT-IBM Watson AI lab, published in *Nature Computational Science*, aims to better characterize ALS disease progression patterns to inform clinical trial design. The team used machine learning to identify these consistent patterns across patients, and found many robust patterns in ALS progression, many of which are non-linear. Further, these disease progression subtypes were consistent across patient populations and disease metrics. The team additionally found that their method can be applied to Alzheimer's and Parkinson's diseases as well.

NIH Grant Advances Research on Huntington's Disease

A major award from the National Institutes of Health will provide eight years of funding to advance ABI affiliate member Associate Professor **Myriam Heiman**'s groundbreaking work on Huntington's disease. In 2020, Heiman's research led to two discoveries: 1) certain genes can protect against the toxic effects of a mutant protein known to cause Huntington's and 2) stray RNAs can trigger an immune reaction that leads to cell death. With NIH's new support, Heiman will build on her initial findings and study when immune activation and gene expression dysregulation begin and what sets them off. This knowledge can provide new opportunities for designing more effective therapeutics.



Spiny projection neurons labeled for analysis in the Heiman Lab.

Changing Brain Rhythm Frequencies in Parkinson's Disease

Deep brain stimulation (DBS) is an effective but little-understood treatment that helps relieve some of the motor symptoms associated with Parkinson's disease. A computational model developed by postdoc **Elie Adam** in the lab of ABI core member **Emery N. Brown** and in collaboration with Boston University offers new insight into the brain electrical waves involved and may pave the way for more customizable DBS treatments.

Adam's model reveals that cells called fast-spiking interneurons (FSIs) produce gamma-frequency rhythms that regulate medium spiny neurons' (MSNs) beta-frequency rhythms. When the brain does not have dopamine, a defining trait of Parkinson's, FSI's gamma waves do not perform their critical job. Instead, MSN's betas become overly excitable and dominate a loop that connects the subthalamic nucleus (STN) to other neurons and regions of the brain. Electrically stimulating the STN quieted beta activity and prevented it from dominating brain wave activity. Next-generation DBS could identify the optimal gamma rhythms of each patient to produce more tailored therapies.

Events and Awards

Event Examines Biology of Neurodegeneration, Down Syndrome

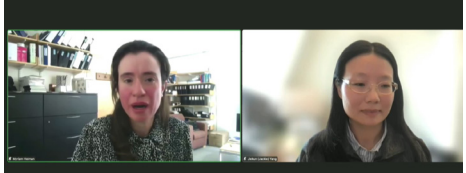
Neuroscientists still have a tremendous amount to learn about the causes and courses of neurodegenerative diseases and Down syndrome, but as speakers at the Oct. 5-6 MIT symposium "Glial and Neuronal Biology of the Aging Brain" pointed out, often when they make a new discovery in the context of one such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

"Our belief is that the study of the aging brain can learn a great deal from the study of Down syndrome and vice versa," said Picower Professor **Li-Huei Tsai** who directs the two MIT entities that jointly hosted the conference: The ABI and the Alana Down Syndrome Center.

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

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

Elizabeth Head, professor of pathology and laboratory medicine at the University of California at Irvine, and Adam Brickman, professor of neuropsychology at Columbia University each related dysfunction of brain vasculature to the connection between Down syndrome and Alzheimer's.



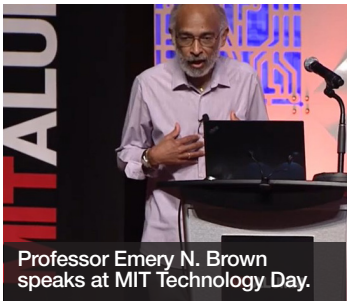
MIT Associate Professor Myriam Heiman answers a question posed by session moderator Jackie Yang, a postdoc in the lab of MIT Computer Science Professor Manolis Kellis.

Several other speakers focused on the brain's immune cells, called microglia, which have a very complex role in neurodegenerative diseases including Alzheimer's.

Complementing the talks' exposition of the variety of cell types and molecular mechanisms at issue across neurodegenerative diseases and Down syndrome were the posters of MIT postdocs and graduate students that followed the talks. A dozen presenters from seven labs affiliated with the ABI, the Alana Center, or both highlighted whole systems approaches to understanding and treating disease. For a deeper recap see: https://bit.ly/ABI-ADSC-2022.

Alumni Event Takes a Deep Dive into Longevity & Innovation

This year's MIT Technology Day, an alumni event for Tech Reunions, dedicated its morning session to longevity and innovation. Peering into the economic, physical, and social implications of aging, MIT faculty from diverse fields shared their ideas on how to advance health and enrich lives during aging.



Professor Emery N. Brown speaks at MIT Technology Day.

ABI core member **Emery N. Brown** discussed how the brain responds differently to anesthesia as we age and why customized administration of the treatment can lessen side effects in the elderly after surgery. Using a combination of drugs and deploying them strategically based on continuous measurement of consciousness from an electroencephalogram can significantly refine the dosage of medication. Brown continues to advance the field of anesthesiology by developing machine learning algorithms that can assist anesthesiologists in helping to monitor and dose anesthesia.

"We have targeted chemotherapies, we should have targeted anesthesia," Brown said. "It's totally feasible. If we lay the scientific background, the engineering background to make this happen, I think we'll get the world to adopt it."

Li-Huei Tsai, director of ABI and The Picower Institute, lamented that people living with dementia have no available treatments that significantly prevent or slow the progression of their disease. As a result, Alzheimer's and other dementias are a leading cause of deaths each year. Tsai's research indicates that boosting the brain's gamma waves might slow or stop cognitive decline. In addition to her ongoing research program at MIT, she cofounded Cognito Therapeutics to further develop and test a non-invasive and effective treatment leveraging the power of light and sound stimulation at a key frequency of 40Hz.

ABI Faculty Earn Honors

In 2022, Institute faculty received some of their profession's highest honors. ABI core member **Emery N. Brown** received the Pierre M. Galletti Award from the American Institute for Medical and Biological Engineering and the Gruber Neuroscience Prize from the Gruber Foundation. Brown's multidisciplinary research in neuroscience, statistics, and anesthesiology has deepened understanding of the brain's neural activity and has created a new paradigm for brain monitoring during general anesthesia.

Also, the Vallee Foundation appointed **Li-Huei Tsai**, director of ABI and The Picower Institute, a Vallee Visiting Professor. The professorship gives faculty a month-long sabbatical and pairs them with other research institutions to encourage intellectual exchanges and new partnerships. Tsai will study at Karolinska Institute in Sweden to broaden her knowledge of the immune system and brain-immune interaction.

Aging Brain Initiative

Massachusetts Institute of Technology

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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.

Participate in research! If you are interested in volunteering for a study, visit https://picower.mit.edu/support/volunteer

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

Collaborative MIT Members:

Alan Jasanoff, McGovern/Bio Engineering/BCS/Nuclear Science; **Andrew Lo**, Sloan/Finance; **Ankur Jain**, Whitehead/Biology; **Ann Graybiel**, McGovern/BCS; **Earl Miller**, Picower/BCS; **Elly Nedivi**, Picower/BCS/Biology; **Ernest Fraenkel**, Bio Engineering/CSAIL; **Gloria Choi**, Picower/BCS; **Jean-Jacque Slotine**, Mech Eng/BCS; **Joel Voldman**, EECS; **John Gabrieli**, McGovern/BCS/IMES; **Joseph Coughlin**, Urban Planning, Engineering Systems; **Kwanghun Chung**, Picower/ChemE/IMES; **Mark Bear**, Picower/BCS; **Matthew Wilson**, Picower/BCS/Biology; **Mriganka Sur**, Picower/BCS; **Myriam Heiman**, Picower/BCS; **Peter Dedon**, Bio Engineering; **Randall Davis**, EECS/CSAIL; **Ritu Raman**, Mech Engineering; **Rudolf Jaenisch**, Whitehead/Biology; **Steven Flavell**, Picower/BCS; **Steven Tannenbaum**, Bio Engineering/Chemistry; **Thomas Heldt**, Bio Engineering/EECS/IMES; **Tod Machover**, Media Lab; **Troy Littleton**, Picower/Biology

Thank you for investing in MIT talent — The Aging Brain Initiative Fund #3895642

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 thank you for your support and hope you will consider renewing your support for the next year. A gift to our Aging Brain Initiative Fund can be made online by entering the fund number 3895642 on MIT's giving site: https://giving.mit.edu/. Unrestricted gifts to the ABI Fund supports priority needs across campus including seed and collaborative grants for launching new ideas into experiments, early human clinical studies, and a bi-annual symposium. To make a named or transformational gift, please contact Director of Development, Dr. Asha Bhakar at abhakar@mit.edu or 617-959-4385.