Brain SCAN

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

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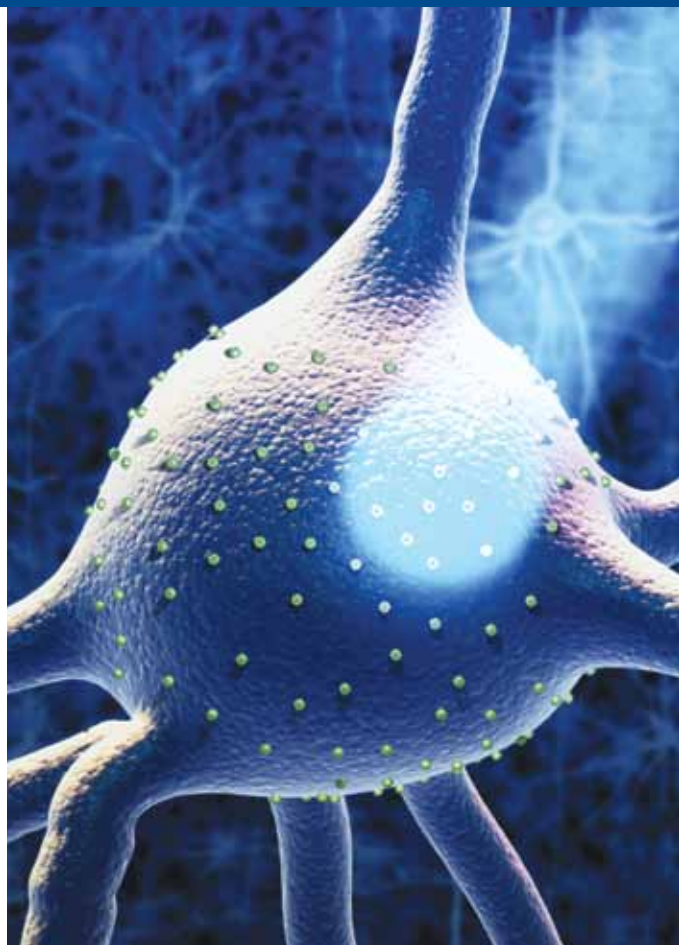
From the director

In this issue we celebrate the emerging field of optogenetics, a method that enables us to control brain activity with extraordinary precision. Many of the pioneers in this new field are now at the McGovern Institute.

Progress in science is often driven by new technologies, and brain research today is being transformed by a radical new technology known as optogenetics, which allows us to control brain activity using light. Several of my colleagues at the McGovern Institute have made seminal contributions to optogenetics, including Ed Boyden, who co-invented the technology as a student at Stanford. I have been using it in my own lab to study the brain circuits that control attention, and I have benefited greatly from collaborating with Ed, who never ceases to push the frontiers of what's technically possible.

Much of this work has been supported by philanthropic funding, which now accounts for more than a third of our total research budget. In the current economic climate, the support of our donors is more important than ever, allowing us to support innovative high-payoff ideas that are often impossible to fund through traditional government grants. As always, my sincerest thanks go to all our donors who are making this work possible.

With this issue, we also welcome Feng Zhang, who joins us as an assistant professor with a joint appointment at the Broad Institute. Feng, who has also made great contributions to optogenetics, is now working to develop new methods for controlling gene expression in the brain. Given his stellar track record, I am confident that this new work will soon bear fruit.



Cover image: A neuron expressing the protein channelrhodopsin is activated by light.

Image: Sputnik Animation

In other news, we are sorry to lose Chris Moore, who is moving to Brown University as a tenured professor in the department of neuroscience. We congratulate Chris on his appointment and look forward to continued collaborations with him in the future.

And finally, I am delighted to announce the establishment of the IDG/McGovern Institute for Brain Research at Tsinghua University in Beijing. I am looking forward to working with Pat McGovern and Hugo Shong on this exciting project, and to developing a close relationship with our new colleagues at Tsinghua University.

Bob Desimone, Director

Optogenetics allows researchers to control complex neural circuits with light.

A LIGHT SWITCH FOR NEURONS

A new technology called optogenetics is sweeping the field of neuroscience, offering unprecedented control of neural circuits and holding promise for treating human brain disorders.

Restoration of sight is a longstanding dream in medicine, and this dream recently came one step closer to reality, thanks to the work of McGovern Investigator Ed Boyden. He has helped to develop a revolutionary new technology, known as optogenetics, which makes it possible to control brain activity with light. In a study that was just published last month, Boyden and his colleagues were able to use the new method to restore vision to blind mice.

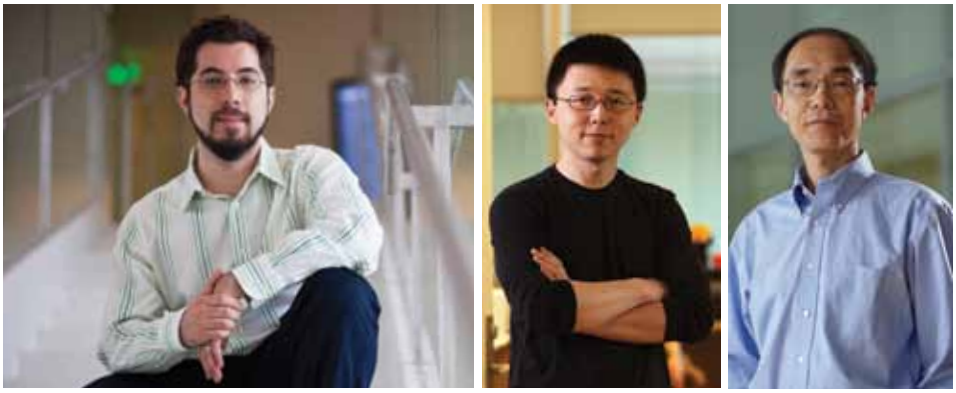
Vision restoration is just one example of how optogenetics could lead to an entire new class of therapies. The new method, in which neurons are genetically modified to respond to light, has opened new avenues of research in many different areas of biology. It is now being used by hundreds of labs worldwide, and was recently recognized by *Nature Methods* as its 2010 "Method of Year."

A moment of illumination

Like many new technologies, optogenetics was born of necessity. "We needed a way to control brain activity with precision," says Boyden, who recently published a short history of the invention. "The brain contains thousands of different cell types that are connected to each other in incredibly precise ways. When you treat the brain with drugs, you are bathing all those cells indiscriminately, with effects that usually last for hours or days. We wanted a new way to target specific types of neurons, and to manipulate them with millisecond precision, because that's the level of precision that the brain cares about."

Boyden hit on the solution about seven years ago, while he was a student at Stanford. The idea emerged through discussions with his then-collaborator Karl Deisseroth. For several years the two had been discussing different ways of controlling brain activity, when in 2004 they got an inspiration from an unexpected source.

A group in Germany, led by Ernst Bamberg and Georg Nagel, had been studying how a species of pond algae called Chlamydomonas responds to light. These microscopic single-cell organisms swim toward light with the help of a light-sensitive structure called an eyespot. The eyespot contains a protein called channelrhodopsin, which responds to light by conducting charged particles, known as ions, across the membrane.



Many of the pioneers in optogenetics are now at the McGovern Institute, including Ed Boyden (left), Feng Zhang (center) and Guoping Feng (right).

Photos: Kent Dayton; Dominick Reuter, MIT News

Boyden and Deisseroth realized that if they could make neurons sensitive to light, then they could manipulate the activity of these light-sensitive neurons with an unprecedented degree of control. So they contacted the German researchers to obtain the channelrhodopsin gene, which they then inserted into neurons in a culture dish. Late one night, they put the dish under a microscope that was equipped with a fast-switching light source, and fired light pulses to see if they could trigger electrical activity in their culture.

"To my amazement, it worked the first time," recalls Boyden. "It was as if we had installed tiny solar panels in the neurons. We could flash light and trigger an electrical pulse in the neurons, not just once but over and over again. We realized at once that we could use this to create artificial brain activity."

The potential of the new method was quickly apparent to other researchers. Among the early adopters was Guoping Feng, now a faculty member at McGovern Institute. While at Duke University, he was the first to express channelrhodopsin in the brains of transgenic mice, thus opening the door to controlling animal behavior with light. Feng Zhang, who joined the McGovern faculty earlier this year, was involved in many of the pioneering studies while he was a student in the Deisseroth lab at Stanford. He developed several additional light-sensitive molecules, along with improved methods for delivering them to neurons, and he was among the first to show that optogenetics could be used to probe the neural circuits underlying behavior.

Illuminating brain circuits

Since the first paper on optogenetics was published in *Nature Neuroscience* in 2005, the technique has already led to dozens of subsequent papers, with hundreds of new projects underway, at the McGovern Institute and other labs throughout the world. The ability to control specific neurons within the brain allows researchers to probe the workings of the brain's intricate circuits in ways that would have been unimaginable a few years earlier.

Boyden's colleagues at the McGovern Institute have been quick to embrace the new technological opportunities. For example, institute director Bob Desimone has collaborated with Boyden to test the optogenetic technology in monkeys, an important step toward eventual human clinical applications. Chris Moore and Ann Graybiel have used a combination of optogenetics and functional brain imaging to trace the brain's long-distance connections. By scanning mice while specific parts of their brains were stimulated by light, the researchers were able to determine which brain structures receive connections from the stimulated area. Boyden is now collaborating with Ki Goosens to test whether optogenetic methods can be used to suppress fearful memories in mice – a model for understanding the origins of post-traumatic stress disorder (PTSD) and other anxiety disorders.

A neuroengineering toolkit

Meanwhile, Boyden is continuing to expand the optogenetic tool kit. One of his first projects after joining MIT was to develop an inhibitory counterpart to channelrhodopsin. By using other light-sensitive molecules, known as halorhodopsins and archaerhodopsins, he showed that light can also be used to temporarily suppress brain activity in specific regions. He has also been searching for new light-sensitive molecules with greater potency or other desirable properties, such as the ability to respond to light of different colors. One key to this strategy is to make use of nature's own "inventions," searching the tree of life for other light-sensitive molecules that could be co-opted for the purpose of neuroengineering.

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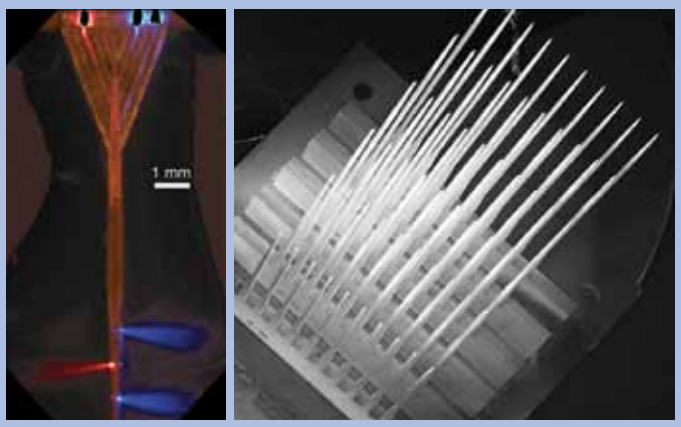
Researchers borrow DNA from photosynthetic algae like Chlamydomonas, shown here, to make neurons sensitive to light.



High-tech fiberoptic devices can guide laser light to specific locations in the brain (left). In collaboration with Clif Fonstad, Boyden is working to build arrays of these light guides that can then be inserted into the brain (right).

Images: Anthony Zorzos, Jorg Scholvin, Clif Fonstad, Ed Boyden

For practical applications of optogenetics, however, finding the ideal light-sensitive molecule is only half the battle. "We also need ways to deliver light itself to the brain," Boyden explains. Much of his lab is devoted to this engineering challenge – building high-tech fiberoptic devices that guide laser light to specific locations within the brain.

His earliest experiments used relatively crude optical fibers, but he is now building much more sophisticated versions, in collaboration with Clif Fonstad, a professor in the MIT Department of Electrical Engineering and Computer Science and an expert in the design of optoelectronic devices. With support from the McGovern Institute Neurotechnology (MINT) program, they have been able to fabricate tiny light guides onto a narrow shaft that can be inserted into the brain with minimal damage, allowing light to emerge from tiny windows to illuminate the surrounding brain tissue (see image).

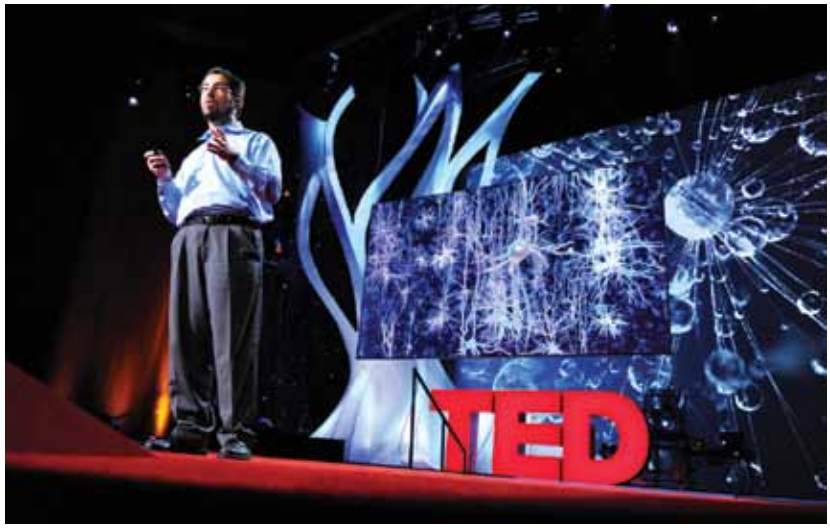
Boyden is keen to see his methods used by other researchers, and he shares his results widely. His optogenetic molecules have been distributed to some 400 labs around the world, and instructions for building and using his optogenetic devices are made freely available on his lab web site, where they are updated monthly as new methods are developed. He also runs a training program, funded by the National Science Foundation, that enables scientists from other institutions to come to his MIT lab to learn new technologies which they can then take back to their own labs.

Promise of new therapies

The value of optogenetics as a research tool has been well established since its invention more than seven years ago. But in the longer term it also holds great promise as a potential therapy for brain disorders. Many diseases involve abnormal patterns of brain activity, and optogenetics could potentially offer a far more specific tool than drugs for correcting these problems. Epileptic seizures, for example, could be silenced before they spread beyond their site of origin; depression might be treated by stimulating specific pathways that regulate mood; or Parkinson's disease could be treated by blocking the circuits that cause tremors or other symptoms. This would require the development of new prosthetic devices, but given that electrical stimulators are already widely used – for example cochlear implants for hearing loss and deep-brain stimulators for Parkinson's disease – the notion of optical prosthetics may not be so far-fetched.

The earliest clinical application of optogenetics may be for retinal blindness. In the recent mouse vision study (see above), Boyden collaborated with Alan Horsager at the University of Southern California to restore vision in mutant mice with retinitis pigmentosa, a disease that destroys the light-sensitive cells of the retina. By inducing light sensitivity in other retinal cells that survive the disease, the researchers were able to rescue enough vision for the mice to navigate a maze. The study was performed in collaboration with researchers at Eos Neuroscience, a startup company that Boyden and Horsager co-founded in 2007. The company hopes to move to human clinical trials within the next few years.

Given the wide range of diseases that involve abnormal brain activity, the therapeutic potential is huge, but much remains to be done. In particular, a lot of engineering is needed to deliver light to the brain. That will be a challenge, Boyden acknowledges. "But we've been encouraged by the progress we've made. Development of any new therapy takes many years, but we take the long view. This could some day be transformative." ■



Boyden delivered a talk on optogenetics at the 2011 TED Conference in March.

Photo: James Duncan Davidson/TED

Dedication of New MEG Scanner

On April 14, the institute held a dedication ceremony for the new MEG lab and Leadership Board members made a toast to donors Thomas F. Peterson, Jr. '57, and Kay and Edward Poitras, whose generous support made the MEG facility possible.

MEG is a safe and non-invasive imaging technology that detects tiny magnetic signals at the surface of the head. The new scanner is expected to be used for many different projects, including studies of basic brain function as well as many different brain disorders.

Kay and Edward Poitras were unable to attend in person but were represented by Edward's brother James Poitras '63 and his wife Patricia Poitras, both members of the Leadership Board. Another board member, Sheldon Razin '59, generously volunteered to be a test subject for the researchers who were assessing the newly installed system. ■

Tom Peterson is toasted by fellow Leadership Board members, Institute co-founder Pat McGovern, director Bob Desimone, and McGovern scientists at the MEG dedication ceremony.

Photo: Justin Knight

Left: Leadership Board member Shelly Razin volunteers to have his brain scanned by Dimitrios Pantazis, who oversees the operation of the MEG lab. Right: MEG supporters Edward and Kay Poitras.

Photo: Justin Knight

Leadership Board and Friends Attend Seminar with Autism Speaks

Following the dedication of the MEG lab (see above), Leadership Board members were joined by Friends of the McGovern Institute and guests from the research and advocacy organization Autism Speaks, for a seminar on the causes of autism.

Michael Rosanoff of Autism Speaks reviewed the evidence for an "autism epidemic." The number of diagnosed cases has risen sharply over the past 20 years, but it is unclear how far this reflects increased awareness, rather than an actual increase in the condition. Rosanoff argued that growing awareness can explain only part of this rise, and that there is also likely to be some real increase. The reasons for this are not known, he said, adding that much more work is needed to understand the genetic and environmental causes of autism.

McGovern Investigators Guoping Feng and John Gabrieli then summarized their current work on the causes of autism. Feng described a new mouse model with a genetic mutation that resembles human autism. These mice show several symptoms reminiscent of human autism, including repetitive behaviors and avoidance of social interactions. He is currently trying to understand which brain circuits are disrupted in these mice and how this could lead to the observed behavioral effects. Gabrieli discussed two recent studies from his own laboratory: a behavioral study on how moral decision making differs between autistic and control subjects, and a neuroimaging study on how the human brain responds to eye contact, an important social cue that many autistic individuals have difficulty in processing. Videos of all three talks are available on our website. ■

Bruce McEwen to Receive 2011 Scolnick Prize

This fall, the McGovern Institute will award the 8th annual Scolnick Prize in Neuroscience to Bruce McEwen of The Rockefeller University. McEwen is a pioneer in understanding how hormones affect the brain.

Over his long and distinguished career, McEwen has published more than 900 papers that span many different areas of neuroscience. He was the first to discover brain receptors for the stress hormones known as corticosteroids, and he has also made major contributions to our knowledge of sex differences in the brain. McEwen is a prominent advocate for "brain health" and a regular advisor to the National Academies of Sciences and other public organizations.

Bruce McEwen, winner of the 2011 Scolnick Prize.

Photo: The Rockefeller University

The prize ceremony and lecture will take place on September 26 at 4pm. ■

Feng Zhang Joins McGovern Faculty

In this issue we welcome our newest faculty member, Feng Zhang, who also has a joint appointment at the Broad Institute. Originally from China, Zhang was a graduate student with Karl Deisseroth at Stanford, where he made important contributions to the development of optogenetic technology (see pg 2).

After his PhD, he was awarded a prestigious Harvard Junior Fellowship to work in the laboratory of genomics pioneer George Church. There he began a project to develop new tools for regulating gene expression in living cells. The first results were recently published in *Nature Biotechnology*, where he described a new class of "designer proteins" that can be customized to bind any DNA sequence. The new method is expected to have many applications in neuroscience and other fields of biology. ■

Feng Zhang is developing new ways to manipulate gene expression in mice and other animals.

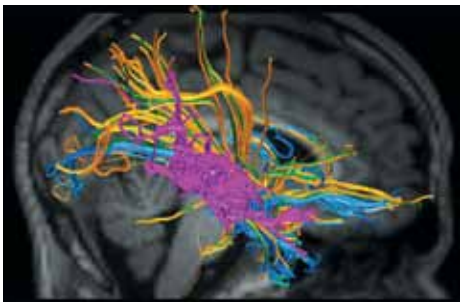
Image: Darryl Leja, NHGRI

Annual Symposium: Inhibition and Neural Circuit Function

The theme of this year's symposium was inhibition – not the psychological version, but rather the study of inhibitory neurons within the brain.

The human brain contains over a trillion synapses but they fall into just two major classes: excitatory synapses, which cause their target neurons to become more active, and inhibitory synapses, which have the opposite effect, serving to dampen brain activity. These inhibitory connections are much less well studied than their excitatory counterparts, but as the speakers at this symposium made clear, they are equally important. The eight talks discussed the development and function of inhibitory synapses as well as their significance for understanding diseases such as epilepsy, anxiety disorders and schizophrenia. Videos of the talks are available on our website. ■

Lunch break at the annual McGovern symposium.



Tractography-based segmentation reveals patterns of connectivity in the brain.

Image: Zeynep Saygin and John Gabrieli

John Gabrieli, in collaboration with colleagues at MGH, reported a new method for mapping fine brain structures of human brain regions such as the amygdala, which is implicated in fear, anxiety and many disorders. Their method, known as tractography-based segmentation, can be performed in a single 10-minute scan, and will be useful for many basic and clinical studies.

By studying brain activity in rats as they learned to navigate a maze, **Ann Graybiel** and colleagues described patterns of activity in basal ganglia that may represent the boundaries between activities, allowing us to separate complex action sequences into more manageable "chunks."

Ed Boyden, in collaboration with colleagues at the University of Southern California, used optogenetic technology to restore visual behavior in blind mice (see pg 2). The work was sponsored by Eos Neuroscience, a company that Boyden helped to found, and which hopes to begin testing this tool in humans within 2-3 years.

Tomaso Poggio and **Robert Desimone** collaborated on a study that examined how visual attention allows us to focus on a single object within a cluttered scene. The paper was published in *Proceedings of the National Academy of Sciences.*

McGovern scientists explain why meditation helps tune out distractions.

Image: Christine Daniloff, MIT News

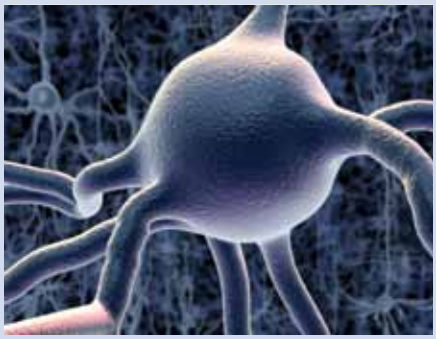
In collaboration with Harvard researchers, **Chris Moore** has used magnetoencephalography (MEG) to show that meditation can modulate brain waves called alpha rhythms, which help tune out distractions from the surrounding environment.

In a study published in *Nature,* **Guoping Feng** described a new mouse genetic model of autism. These mice, which carry a mutation in a gene that is also implicated in human autism, show two of the traits most characteristic of autism – repetitive behavior and avoidance of social interactions. The mice are providing new clues to the brain deficits that underlie human autism, and may help lead to new treatments for the condition.

Nancy Kanwisher's group reported the identification of human brain regions that respond specifically to moving rather than static faces – an ability that is key to human social interaction.

Video Spotlight

Optogenetics, a new technology for controlling brain activity with light, holds promise for treating a wide range of brain disorders (see pg 2). This five-minute animation explains how the technology works: by inserting a light-sensitive protein into neurons, researchers can selectively turn on or turn off specific sets of cells with pulses of light. The animation is now available on our website.



A 3D rendered neuron in the new optogenetics animation.

AWARDS AND HONORS

Alan Jasanoff, an associate member of the McGovern Institute and a professor in the department of biological engineering, has been awarded tenure at MIT. Jasanoff's research is focused on understanding the brain's reward systems, and on developing new technologies for imaging brain activity with MRI (*Brain Scan,* Summer 2010).

Ed Boyden has been awarded the National Institutes of Health EUREKA Award, which funds innovative research projects that could have "an extraordinarily significant impact on many areas of science."

Top left: The agreement to establish the new institute was signed by GU Binglin, President of Tsinghua University, Patrick J. McGovern, co-founder of the McGovern Institute and Chairman of IDG, and SONG Jun, Vice Chairman and Secretary General of the Education Foundation of Tsinghua.

Top right: Tsingua University campus in Beijing.

Bottom right: Pat and Lore McGovern with LIU Zhou of Shenzhen Fortune Venture Capital Co., Ltd.

Images: Karen Ren, IDG

IDG, McGoverns Establish Brain Research Institute in China

The McGovern Institute for Brain Research will soon have a sibling in China. On April 22 an agreement was signed to establish the IDG/McGovern Institute for Brain Research at Tsinghua University (IMIBR-TSU) in Beijing.

The IMIBR-TSU will conduct research in all areas of neuroscience, with an emphasis on cellular, molecular, systems and computational neuroscience. The new institute is expected to open in 2013, and will eventually grow to at least 16 research groups, each headed by a Tsinghua faculty member. ■

The McGovern Institute for Brain Research at MIT is led by a team of world-renowned neuroscientists committed to meeting two great challenges of modern science: understanding how the brain works and discovering new ways to prevent or treat brain disorders. The McGovern Institute was established in 2000 by Patrick J. McGovern and Lore Harp McGovern, who are committed to improving human welfare, communication and understanding through their support for neuroscience research. The director is Robert Desimone, formerly the head of intramural research at the National Institute of Mental Health.

Further information is available at: http://mcgovern.mit.edu

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