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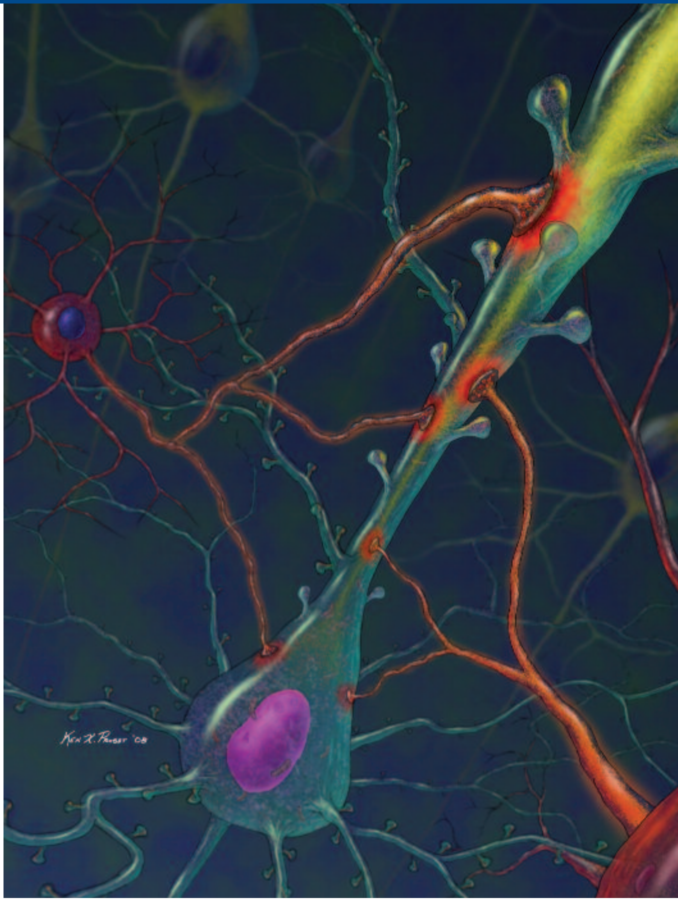


From the director

Through the McGovern Institute Neurotechnology (MINT) program, we are supporting innovative new projects that can drive the future development of our field.

Like many neuroscientists, I fervently believe that we are standing on the cusp of a new age of understanding the brain in both sickness and health. But to usher in that age with all its promise, we need to foster the technical innovation that, now more than ever, is required to advance both basic discovery research and the development of new therapies. Indeed, one of my own motives for moving to MIT from the National Institutes of Health was the opportunity to take advantage of the extraordinary collaborative environment here to develop the next generation of neurotechnologies.

Shortly after arriving at the McGovern Institute, I began to develop this vision by establishing the McGovern Institute Neurotechnology (MINT) program and recruiting my colleague Charles Jennings to direct it. Our aim is to encourage our faculty to think about the technical challenges that have impeded research progress and to connect them with technical experts in and around MIT with whom they could collaborate to find solutions. Such collaborative projects are often considered too risky to fund from traditional sources. Through the MINT program, however, we can provide seed funding to allow researchers to test new ideas for one or two years, and see where they lead. We've been encouraged by the enthusiasm among the faculty here and in other departments for these collaborative efforts. Some of our seedling projects are already sprouting figurative leaves and roots, producing publications and attracting follow-on funding from other sources. We have just made a new round of grant awards, which you can read about in the feature article on page 2.

I am also delighted to introduce our newest faculty member, Yingxi Lin, who joins us from Harvard Medical School, where she was a postdoctoral researcher in the lab of Michael Greenberg, the recipient of our 2006 Scolnick Prize. A profile of Yingxi appears on page 5. I hope you will enjoy reading about these developments and our other news in this issue of *Brain Scan*.

Bob Desimone, Director

Cover image: Yingxi Lin studies the development of inhibitory synapses, depicted here in red, whose function is to prevent brain cells from becoming over- active.

Artwork by Kenneth X. Probst, Xavier Studio.

Charles Jennings, Director, McGovern Institute Neurotechnology (MINT) Program

MINT: MINING MIT FOR TECHNICAL KNOW-HOW

Where do innovative ideas come from and how can we accelerate them? That's the challenge and mandate of the McGovern Institute Neurotechnology (MINT) program.

The technologies that drive neuroscience research sometimes come from unexpected sources. Consider for example the 2008 Nobel prize for chemistry, awarded for the invention of fluorescent genetic 'tags' for visualizing proteins in living cells. The original breakthrough happened 20 years ago when one of the prizewinners had the idea of putting a gene from a fluorescent jellyfish into a worm in order to make it glow in the dark. The idea may have seemed a little crazy at the time, yet it has led to over 20,000 papers, and has become a key technology for neuroscience and many other areas of biology.

There will always be an element of serendipity in new innovations. But are there ways to make innovation more likely to occur? That's the challenge for the McGovern Institute Neurotechnology (MINT) program, established in 2006 to support interdisciplinary collaborations to develop new technologies for brain research. "Progress in the field is heavily dependent on new technologies, both for basic research and for translational research on brain disorders and new therapeutic approaches," says MINT program director Charles Jennings. "We think the Institute is in an exceptionally good position to generate these ideas, given the extraordinary range of expertise that exists on and around the MIT campus."

The right stuff

The MINT program aims to promote collaborations between neuroscientists and researchers from other disciplines by providing seed funds for new projects, typically for one or two years. "We don't expect every project to get to the finish line in that time," says Jennings. "But it's a way to test a new idea quickly, to do a 'proof-of-concept' experiment that, if successful, can make it possible to attract additional funds elsewhere."

In addition to MIT's talent pool, the MINT program also benefits from the McGovern Institute's financial support. "This type of work is often high risk, and so it's difficult to support from traditional sources," says Jennings. "We're incredibly fortunate to have the funds from our donors that allow us to have this program. Instead of forcing researchers to write long applications and wait months for a decision, we can keep the paperwork to a minimum and give our applicants quick answers."

A natural attraction

Money is just one ingredient to success; it takes the right chemistry, too. Jennings sees himself as a matchmaker, making connections between neuroscientists with technical problems and experts from other disciplines with potential solutions. At MIT, with almost 1000 faculty members, he usually need not look too far for willing collaborators.

For example, a few months ago he was considering whether carbon nanotubes, a material used for many applications including advanced electronics, could be used as electrodes for brain recording and stimulation. A few clicks on the MIT website revealed that Jing Kong, a professor of electrical engineering just across the street from McGovern Institute, works with this material. "We asked her if she was interested in a MINT project and she answered 'Yes' with little hesitation." Kong is now collaborating with McGovern investigator Emilio Bizzi, who studies the brain control of movement. Bizzi hopes to use these materials for long-term recordings of neural activity, initially for basic research but ultimately as prosthetic devices for human therapy. Such devices might, for example, allow a paralyzed patient to control a robotic arm or a computer directly from the brain.

Kinder, gentler, smarter recordings

The carbon nanotube collaboration is one of several interrelated projects on brain-machine interfaces that are supported by the MINT program. "The idea of an implantable device that could record and stimulate brain activity over long periods of time is very exciting," Jennings says, "but it's also very challenging, and many of the most promising ideas are still at an early stage. We need a lot more academic research before the clinical or commercial potential can be fully realized,"

To overcome one of the hurdles, Bizzi is collaborating with Robert Langer, a renowned MIT chemical and biological engineer, to devise a way to get thin flexible polymer electrodes into brain tissue without bending them. Their proposed solution is a biodegradable coating that can provide temporary stiffness but disappears after insertion. In another MINT collaboration, Michale Fee of the McGovern Institute is working with Rahul Sarpeshkar, an expert on electrical engineering, to develop the miniature low-powered electronics needed to decode the signals from intracranial recording devices.

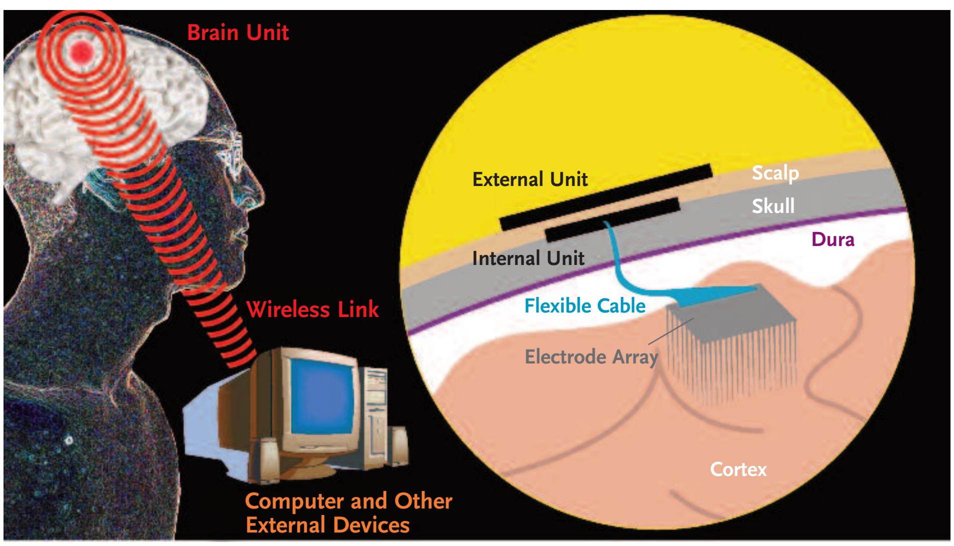
"Ideally, we'd like a tiny implant that can sit inside the brain without damaging it, maintain electrical contact with neurons for long periods of time, signal wirelessly through the skull, and never need a battery change," Jennings muses. "We're still a long way from being able to do that in a clinical setting, but any progress that we make toward that goal will also be tremendously useful for basic research."

Sharper imaging

The MINT program is also exploring new approaches to human brain imaging, taking advantage of MIT's expertise in computer science. In two parallel projects, McGovern's Nancy Kanwisher, who uses functional MRI to understand how the human brain recognizes visual objects, will collaborate with computer scientists to test different approaches to the problem of analyzing the very large datasets produced by functional brain imaging studies.

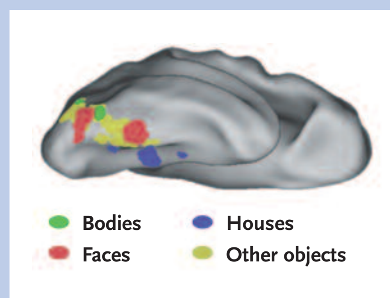
In one project, Kanwisher will collaborate with Polina Golland in the MIT Computer Science and Artificial Intelligence Laboratory (CSAIL) to search for brain

continued, page 4



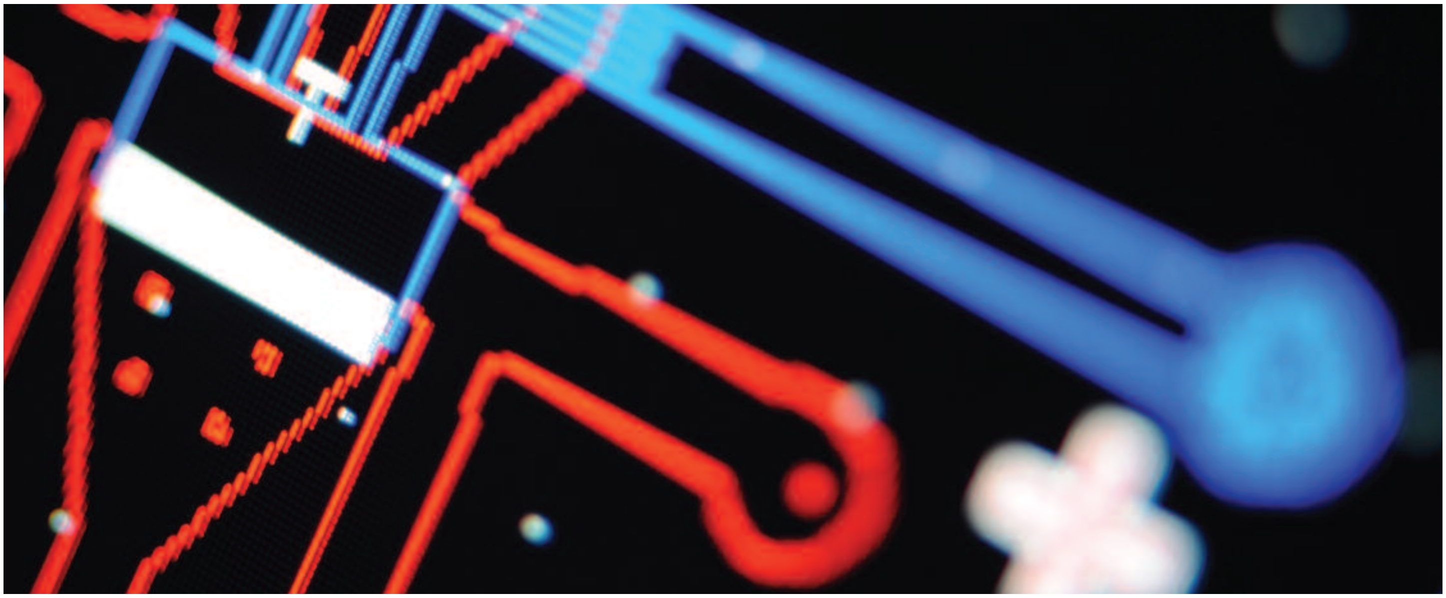
Schematic design for a wireless brain-machine interface. Future applications include therapies for paralysis, stroke, Parkinson's disease, epilepsy and blindness, as well as experimental neuroscience in animal models.

Courtesy Rahul Sarpeshkar, MIT



Nancy Kanwisher studies how the human brain represents different object categories. In two new MINT projects, she is collaborating with computer scientists to test novel analytical methods that she hopes will reveal new insights into the brain's functional organization.

Courtesy Nancy Kanwisher, MIT



Computerized design of a microfluidic chip, used to analyze the tiny quantities of material extracted from single cells.

Courtesy M. Fatih Yanik, MIT.

areas that respond to specific categories of visual objects. Golland has developed a computational model for identifying brain areas without the assumptions that may bias most current methods.

Kanwisher is also collaborating with a startup company called Navia Systems that was recently spun off from MIT research. Navia's founders have developed data-mining methods that can be used to identify clusters in large datasets, and they plan to test their approach on Kanwisher's imaging data. If successful, the method could also help to identify relationships between brain activity, genetics and clinical symptoms.

"I'm excited that we're starting to work with companies." Jennings says. "It's a chance for us to try something that could be really powerful and that might be hard to do in a purely academic setting. And for the company, it's a chance to validate their technology with some enthusiastic collaborators. It's a win/win collaboration."

Many points of light

Several MINT projects will use powerful new optical methods to manipulate brain tissue. For example, Ed Boyden, an associate member of McGovern Institute, has begun a collaboration with Shuguang Zhang, a protein engineer at the MIT Center for Biomedical Engineering. With MINT funding they plan to extend Boyden's technology for optical control of electrical activity (described in the Fall 2008 *Brain Scan*) to manipulate the intracellular signaling pathways by which brain cells respond to chemical signals such as neurotransmitters and hormones. By using light to mimic the effect of these signals, they hope to gain new insights into the function of these pathways, many of which are important targets for drug development.

In another project, Ann Graybiel at McGovern will work with M. Fatih Yanik in the MIT department of Electrical Engineering and Computer Science, to develop what might be termed an 'optical scalpel'. Yanik, an expert on laser optics, is building a precision laser system that he hopes will make it possible to dissect individual neurons from brain tissue in three dimensions. "A fundamental problem with molecular analysis of the brain is that it's such a complex mixture of cells, and the details are often lost when you look at the average," explains Jennings. "We need better ways to isolate individual neurons cleanly in order to analyze them chemically."

Yanik is also building microfluidic devices that can be used to analyze the tiny quantities of material extracted from single cells. Graybiel hopes that Yanik's approach will lead to new precision tools that will accelerate her research on the basal ganglia, including their involvement in conditions such as Parkinson's disease and drug addiction.

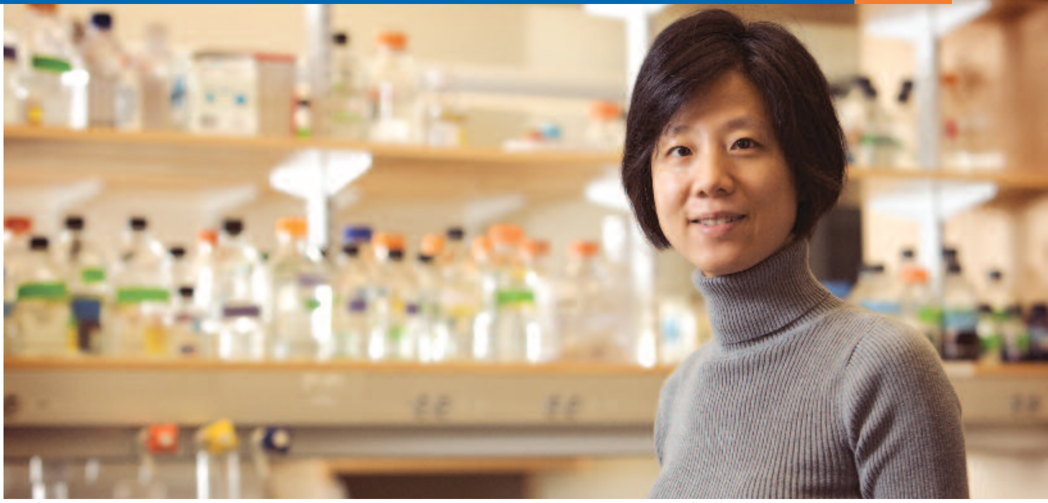
Bright horizons

When Jennings thinks about the potential for neurotechnology, he is inspired by the dramatic progress in human genomics over the last few years. "When they finished the first human genome sequence in 2003, the total cost was over $100 million. Now, five years later it's down to about $100,000, and there's already a company promising to sequence your genome for $5,000 starting next year. That's what technological innovation can do. If we could come remotely close to that in neuroscience, the impact would be enormous."

The MINT program is currently funded through contributions from the institute's founding donors Patrick and Lore McGovern, but Jennings hopes to expand the program through additional philanthropic support. "We're looking for people who 'get' the importance of technology," he says. "It's not about any one disease in particular—instead it's an opportunity to have an impact across the board."

He also hopes that some of the ideas emerging from the program will eventually be commercialized. Given MIT's extensive connections to industry and its long track record of launching new companies, the prospects for the future seem bright. "The therapeutic market for brain disorders is enormous," he says. "If we can develop technologies that can accelerate progress toward new therapies, I'm confident the commercial interest will be there." ■

New Faculty Member Yingxi Lin



Yingxi Lin joined the McGovern Institute in September 2008.

Yingxi Lin joined the McGovern Institute faculty in September 2008 from Harvard Medical School, where she has been studying the development of inhibitory circuits within the brain. Originally from China, she received her bachelor's and master's degrees from Tsinghua University in Beijing, and her Ph.D. in biophysics from Harvard University. Most recently she was a postdoctoral fellow in the laboratory of Michael Greenberg, the 2006 recipient of the McGovern Institute's Scolnick Prize in Neuroscience.

"I am happy to be joining the McGovern Institute because it has everything from high level cognitive and disease research to very basic molecular research," comments Lin. "Having all this expertise at one institute is the best way to integrate these two ends of spectrum, which is very important to me."

Lin's overall research goal is to understand how inhibitory circuits form within the brain, and how they are shaped by activity and experience. Like a conventional electrical circuit, the brain uses both positive and negative components to amplify desirable signals while maintaining the overall stability of the system. Lin hopes to understand how the brain achieves the right balance between excitation and inhibition.

In work that was recently published in the prestigious journal *Nature*, Lin, Greenberg and their colleagues identified a gene called Npas4 that appears to be a master regulator of inhibitory synapse formation. Npas4 is a transcription factor, a class of molecules that work by controlling the activity of other genes. Lin hopes to identify additional genes that are regulated by Npas4 and may also be important for inhibitory synapses, and to understand how inhibitory circuits are shaped by electrical activity and experience.

Her work may have important clinical implications, because many brain disorders have been linked to deficits in inhibitory circuits. For example, Lin has found that mice that lack Npas4 are prone to seizures, and may therefore be useful for studying human epilepsy. In another study, conducted in collaboration with a team of human geneticists at Harvard Medical School, she also helped to show that one of the genes controlled by Npas4 is a genetic risk factor for autism.

In her new laboratory at the McGovern Institute, she will use a combination of molecular genetic and electrophysiological approaches to pursue these discoveries further. She is also looking forward to working with other McGovern faculty members and taking advantage of MIT's rich collaborative environment. ■

Labs of Their Own

One way that McGovern Institute is shaping the future is by training young scientists for independent research careers. Finding the first independent position is among the most important and most competitive steps of a researcher's career. Among the McGovern researchers who have landed independent research appointments since 2007 are the following:

- David Cox, Ph.D., (DiCarlo lab) became a principle investigator at the Rowland Institute at Harvard University.
- Nadine Gaab, Ph.D., (Gabrieli lab) became an assistant professor of pediatrics at Children's Hospital Boston and Harvard Medical School.
- Tim Gardner, Ph.D., (Fee lab) will move to a faculty position at Boston University.
- Georgia Gregoriou, Ph.D., (Desimone lab), has accepted a faculty position at University of Crete, Greece.
- Nicole Rust, Ph.D., (DiCarlo lab) will join the faculty at University of Pennsylvania.
- Davide Zoccolan, Ph.D., (DiCarlo lab) will take up a tenure-track research appointment at the International School for Advanced Studies (SISSA), Italy.

Jane Pauley Speaks at New York City Event

Jane Pauley, a member of the McGovern Leadership Board

On October 6th, Leadership Board member Robert Buxton hosted over 30 guests at an evening event entitled "The Future of Brain Disorders Research." The event was held at the Knickerbocker Club in New York, and the guest speaker was TV journalist Jane Pauley, a member of the McGovern Leadership Board. Other speakers included director Bob Desimone, along with faculty members Ann Graybiel and John Gabrieli.

The speakers discussed recent research findings in autism, schizophrenia and Parkinson's disease, and emphasized the importance of support for basic research into the brain functions that are disrupted in these conditions. They also described the enormous opportunities arising from recent advances in genetics, brain imaging and neural stimulation devices, and the many ways in which McGovern researchers are exploiting these new technologies. ■

McGovern Research Presented at Neuroscience Meeting

The annual Society for Neuroscience meeting attracts thousands of participants.

Courtesy Society for Neuroscience

The McGovern Institute was strongly represented at the annual meeting of the Society for Neuroscience, held this year in Washington DC from November 12-19, 2008. McGovern researchers from 12 different labs presented a total of 48 talks or posters at the meeting, one of the largest scientific gatherings in the world. In addition to the formal agenda, the McGovern Institute co-hosted a well-attended party along with the Picower Institute and the MIT Department of Brain and Cognitive Sciences. ■

Brain Research Symposium in Beijing

The famous lotus pond at Tsinghua University in Beijing

The McGovern Institute is organizing a symposium at Tsinghua University in Beijing on February 24-25, 2009. This meeting, which is titled 'New Frontiers in Brain Research', is supported by a gift from Hugo Shong, an executive with International Data Group (IDG) whose recent gift to McGovern Institute is helping to promote scientific collaboration between McGovern researchers and colleagues in China (see *Brain Scan*, Summer 2007). ■

New Chair, Members of Leadership Board

Bob Metcalfe, the founding chairman of the McGovern Institute Leadership Board, is stepping down after three years. Metcalfe plans to remain on the board that he has helped to build, but he will hand the reins to fellow board member Jim Poitras. Poitras, along with his wife Patricia, who is also a board member, established the Poitras Center for Affective Disorders Research at the McGovern Institute to support translational research on depression and other mental illnesses.

We are also pleased to welcome five new members to the Leadership Board: Robert Buxton, executive vice president of Peter Kimmelman Asset Management; Regina Pyle, chair of the Friends of the McGovern Insitute; Robert L. Richmond, president of the Robert L. Richmond Foundation; Roberta S. Sydney, president of Sydney Associates; and Chris Varma, Ph.D., a partner at Flagship Ventures. ■

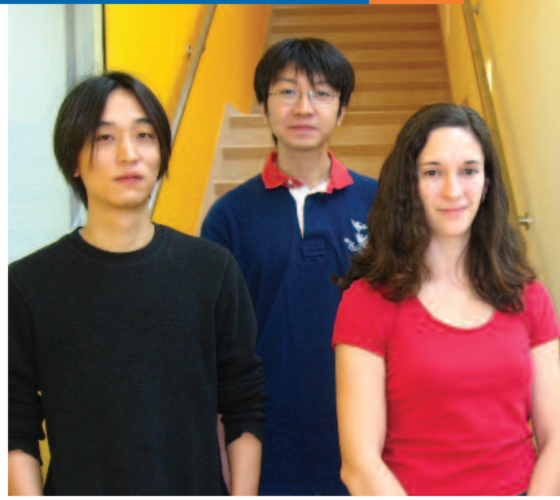
Graduate Fellowship Recipients

Graduate students are integral to the work of the McGovern Institute, and we are fortunate to be able to offer three fellowships to support graduate research: the Schoemaker Fellowship, which was established by the late Dr. Hubert JP Schoemaker, Ph.D. '76 and his wife Anne; the Razin Fellowship, established by Sheldon Razin '59 and his wife Janet; and the Friends of the McGovern Institute Fellowship, which is made possible through the annual contributions of the Friends of the Institute. Here are the 2008-2009 recipients:

Schoemaker Fellowship: Shunji Nakano in H. Robert Horvitz's lab. Nakano studies the formation of left-right asymmetry, a fundamental problem in developmental biology. For, example, the heart is on the left and the human brain's left hemisphere normally governs language. "I'm studying how this asymmetry develops in a model organism, the worm *Caenorhabditis elegans*," Nakano explains. "We know the complete wiring diagram of the worm's nervous system, and we also know that its asymmetries result in part from the generation of left-right asymmetric neurons." Nakano discovered that four genes cause a precursor cell on the right to become a neuron, while the corresponding cell on the left becomes an epithelial cell. Interestingly, two of these genes are similar to mammalian genes involved in nervous system development. The other two are similar to genes involved in human cancer.

Razin Fellowship: Nuo Li in James DiCarlo's lab. Li is studying how the brain learns to recognize a given object regardless of its location within the visual field. "The ease at which we recognize objects belies the computational difficulty of the task, because every object in the world can produce infinite number of different images on our retina due to changes in its position, size, pose, etc.," he explains. Li's work suggests that eye movements may be the key to learning to recognize different objects. Eye movements happen very frequently (about three times per second) whereas physical objects tend to change much less frequently. Thus, when images appear at different places on the retina in rapid succession, the most likely reason is that the eyes have moved. Li has shown that the brain uses this rule of thumb to learn object invariance, and that the brain can be confused by images that change suddenly as the eyes move. He is currently examining whether this form of learning can be incorporated into artificial vision systems.

Friends of the McGovern Institute Fellowship: Theresa Desrochers in Ann Graybiel's lab. Desrochers studies how the brain acquires new habits. "We're interested in understanding habitual behavior partly because it's so central to our daily lives," she explains. "But we also study habit formation because addiction, obsessive compulsive disorder and Parkinson's disease can be seen as habits gone wrong." Most animal studies involve explicit training, but Desrochers is studying more natural behaviors in naïve monkeys as they freely explore visual patterns on a computer screen. As the animals look at the same patterns repeatedly, certain sequences of eye movements become habitual. Desrochers hopes that understanding the neural origins of such habits could provide new insights into a variety of mental disorders.



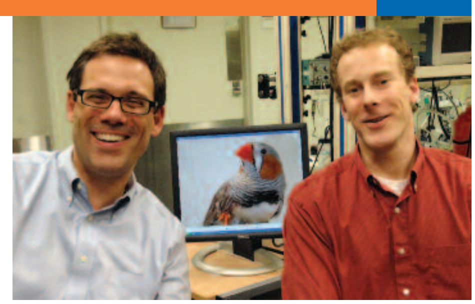
Shunji Nakano, Nuo Li and Theresa Desrochers

Desrochers speaks for all the recipients when she says, "Funding for science is very difficult to get these days, so I'm very grateful for the opportunity to continue my research through this fellowship." ■

IN THE NEWS

Discover Magazine named Associate Member **Ed Boyden** among its top 20 scientists under 40. The article, which appears in the December issue of the magazine, cites Boyden for his work on optical technologies for brain stimulation.

Michale Fee's new study on bird song in the November 13, 2008 issue of *Nature* received coverage in the *New Scientist* magazine, *The Boston Globe*, the Canadian Broadcasting Corporation, and other national and international news outlets and science blogs. The study, coauthored with postdoctoral fellow Michael Long, helps explain how timing is represented within the brain. ■



Michale Fee (left) and Michael Long

Ann Graybiel Named Institute Professor, Receives Vanderbilt Prize

Ann Graybiel, a McGovern Investigator, has been named an Institute Professor, the highest honor MIT can bestow on a member of the faculty. She joins just 13 other Institute Professors, including the McGovern Institute's Emilio Bizzi and founding director Phillip A. Sharp. In announcing the award, MIT President Susan Hockfield said: "Even by the very high standards for appointment as an Institute Professor, Ann Graybiel stands out. Her work has been profoundly important, both in terms of fundamental science and consequences for human health."

In her lab at the McGovern Institute, Graybiel studies the basal ganglia, brain regions involved in the control of movement and which are also implicated in Parkinson's disease, addiction, learning disorders and schizophrenia. Graybiel's work has shown that the basal ganglia do not just control movement and gesture, as previously thought, but also play a broader role in learning, memory and habits formation. Her insights have helped further our understanding of disorders such as Tourette Syndrome, obsessive compulsive disorder and attention deficit disorder—and why, for example, good habits are so hard to make and bad habits so hard to break.

Ann Graybiel, Institute Professor

Photo: Donna Coveney, MIT

Graybiel has also received the 2008 Vanderbilt Prize in Biomedical Science, which is awarded once a year to a woman scientist of national reputation for her stellar record of research accomplishments and her mentorship of other women in science. Graybiel's award lecture was entitled "Our Habitual Lives: How the Brain Makes and Breaks Habits." ■

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://web.mit.edu/mcgovern/

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