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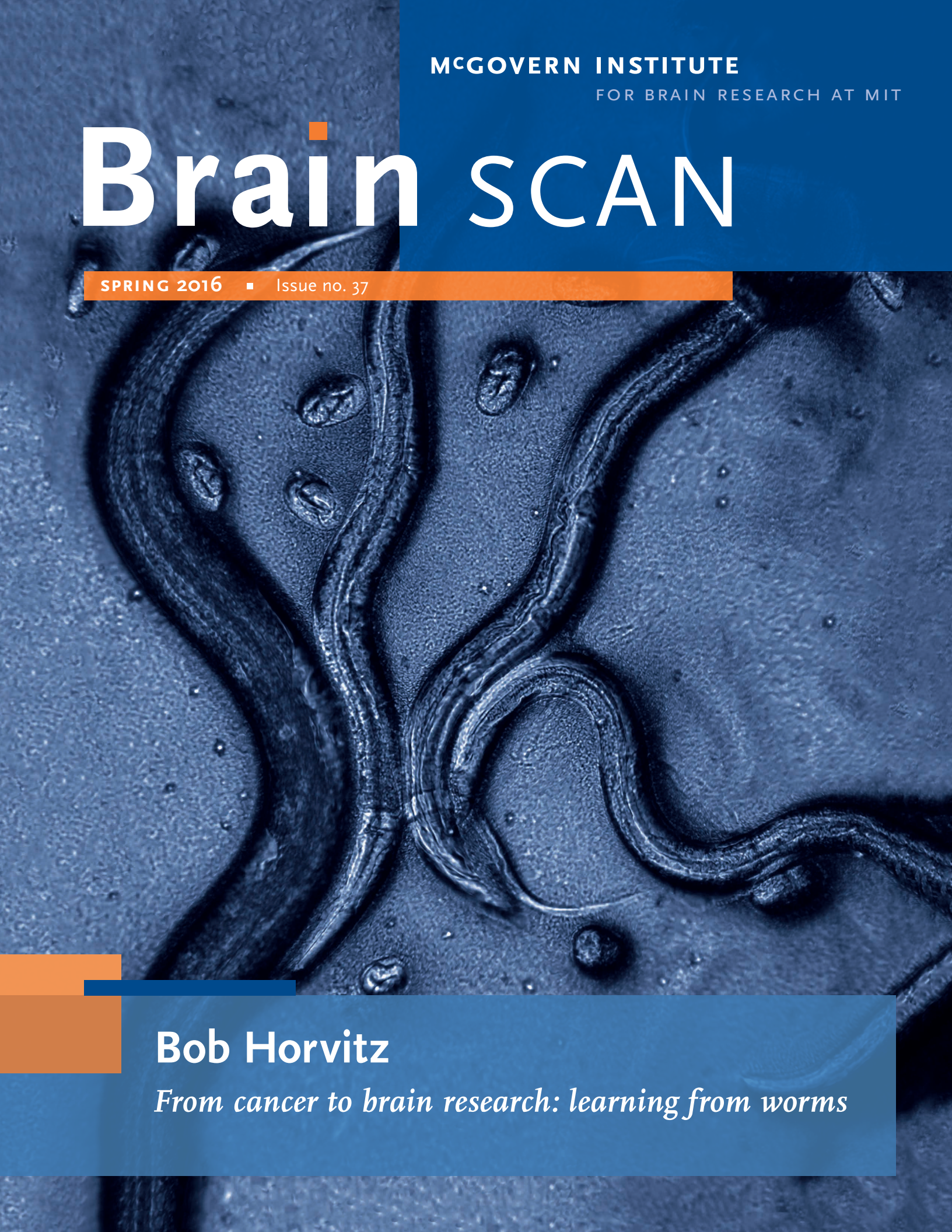


Bob Horvitz

From cancer to brain research: learning from worms

FROM THE **DIRECTOR**

I have often written in this column about the central importance of basic research, the engine of discovery that drives all of science. There is no better example than the work of my colleague Bob Horvitz, who has devoted his career to studying the microscopic worm known as *C. elegans*. As you can read in this issue, this tiny creature has revealed profound insights into many aspects of biology, from embryonic development to cancer to aging and neurodegeneration. Bob is perhaps best known for his work on cell death and its relationship to cancer, for which he shared the 2002 Nobel Prize for Medicine, but he has also made major contributions to neuroscience, including studies of brain development, synaptic function, and the control of behavioral states. Most recently, along with his collaborator and spouse Martha Constantine-Paton, he has uncovered a new gene with profound effects on synaptic signaling and a potential link to autism. All of this has emerged from genetic studies on an organism with less than a thousand cells, including a nervous system of just 302 neurons.

Bob has also been an influential mentor, and last month we were delighted to host one of his most prominent former trainees, Cori Bargmann, winner of this year's Scolnick Prize. Cori's lecture provided a remarkable illustration of how fundamental mechanisms of brain function can be studied in simple organisms, at a level of precision that would be impossible in other more complex species.

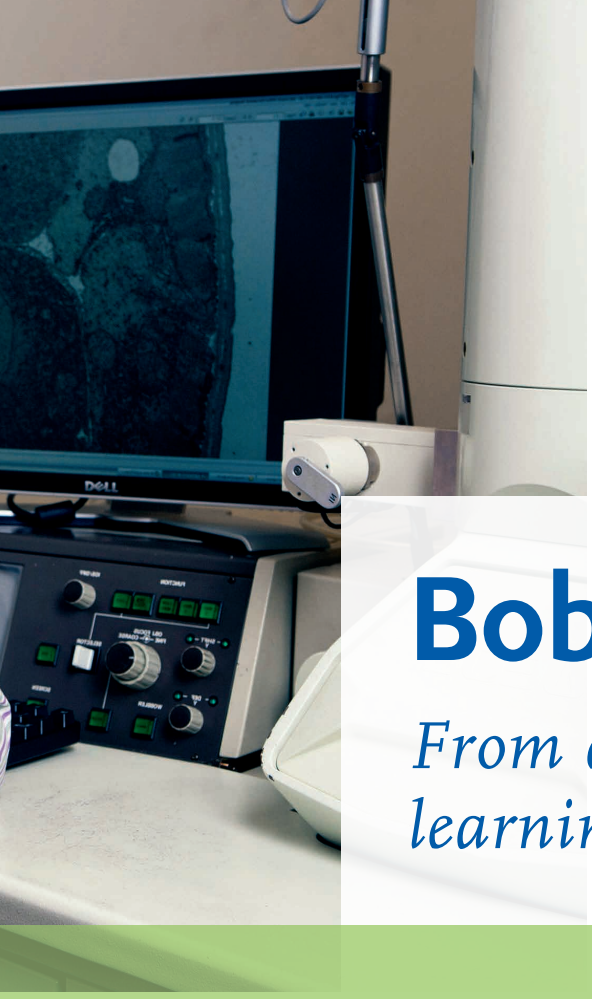
Bob Desimone, Director
Doris and Don Berkey Professor
of Neuroscience

On the cover:
The nematode worm Caenorhabditis elegans *has provided answers to many fundamental questions in biology.*
Image: Bob Horvitz

Bob Horvitz approaches science with patience and the confidence that he will find answers to big questions if he explores important problems in tractable ways.

In Bob Horvitz's lab, students watch tiny worms as they wriggle under the microscope. Their tracks twist and turn in every direction, and to a casual observer the movements appear random. There is a pattern, however, and the animals' movements change depending on their environment and recent experiences.

"A hungry worm is different from a well-fed worm," says Horvitz, David H. Koch Professor of Biology and a McGovern Investigator. "If you consider worm psychology, it seems that the thing in life worms care most about is food."



Bob Horvitz

From cancer to brain research: learning from worms

Horvitz's work with the nematode worm *Caenorhabditis elegans* extends back to the mid-1970s. He was among the first to recognize the value of this microscopic organism as a model species for asking fundamental questions about biology and human disease.

The leap from worm to human might seem great and perilous, but in fact they share many fundamental biological mechanisms, one of which is programmed cell death, also known as apoptosis. Horvitz shared the Nobel Prize in Physiology or Medicine in 2002 for his studies of cell death, which is central to a wide variety of human diseases, including cancer and neurodegenerative disorders. He has continued to study the worm ever since, contributing to many areas of biology but with a particular emphasis on the nervous system and the control of behavior.

In a recently published study, the Horvitz lab has found another fundamental mechanism that likely is shared with mice and humans. The discovery began with an observation by former graduate student Beth Sawin as she watched worms searching for food. When a hungry worm detects a food source, it slows almost to a standstill, allowing it to remain close to the food. Postdoctoral scientist Nick Paquin analyzed how a mutation in a gene called *vps-50*, causes worms to slow similarly even when they are well fed. It seemed that these mutant worms were failing to transition normally between the hungry and the well-fed state.

Paquin decided to study the gene further, in worms and also in mouse neurons, the latter in collaboration with Yasunobu Murata, a former research scientist in Martha Constantine-Paton's lab at the McGovern Institute. The team, later joined by postdoctoral fellow Fernando Bustos in the Constantine-Paton lab, found that the VPS-50 protein controls the activity of synapses, the junctions between nerve cells. VPS-50 is involved in a process that acidifies synaptic vesicles, microscopic bubbles filled with neurotransmitters that are released from nerve terminals, sending signals to other nearby neurons. If VPS-50 is missing, the vesicles do not mature properly and the signaling from neurons is abnormal. VPS-50 has

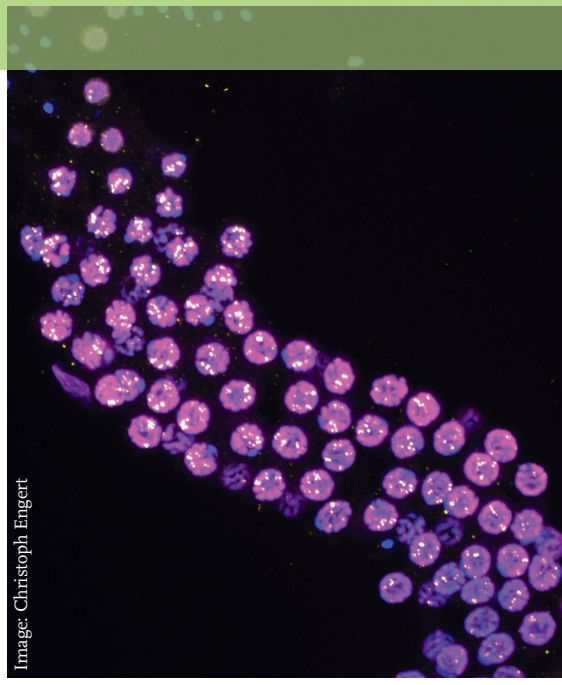


Image: Christoph Engert

Individual cell nuclei in a developing worm. Horvitz helped chart the entire sequence of cell divisions by which a fertilized egg gives rise to an adult animal.

remained relatively unchanged during evolution, and the mouse version can substitute for the missing worm gene, indicating the worm and mouse proteins are similar not only in sequence but also in function. This might seem surprising given the wide gap between the tiny nervous system of the worm and the complex brains of mammals. But it is not surprising to Horvitz, who has committed about half of his lab resources to studying the worm's nervous system and behavior.

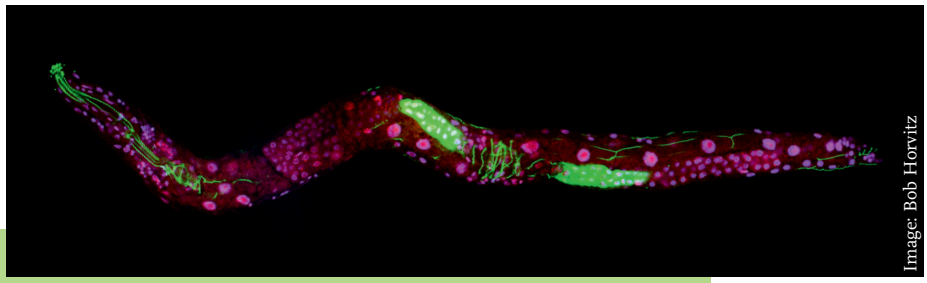


Image: Bob Horvitz

The nematode worm C. elegans *measures about 1mm in length, and has 959 somatic cells.*

"Our finding underscores something that I think is crucially important," he says. "A lot of biology is conserved among organisms that appear superficially very different, which means that the understanding and treatment of human diseases can be advanced by studies of simple organisms like worms."

Human Connections

In addition to its significance for normal synaptic function, the vps-50 gene might be important in autism spectrum disorder. Several autism patients have been described with deletions that include vps-50, and other lines of evidence also suggest a link to autism. "We think this is going to be a very important molecule in mammals," says Constantine-Paton. "We're now in a position to look into the function of vps-50 more deeply."

Horvitz and Constantine-Paton are married, and they had chatted about vps-50 long before her lab began to study it. When it became clear that the mutation was affecting worm neurons in a novel way, it was a natural decision to collaborate and study the gene in mice. They are currently working to understand the role of VPS-50 in mammalian brain function, and to explore further the possible link to autism.

The Day the Worm Turned

A latecomer to biology, Horvitz studied mathematics and economics as an undergraduate at MIT in the mid-1960s. During his last year, he took a few biology classes and then went on to earn a doctoral degree in the field at Harvard University, working in the lab of James Watson (of double helix fame) and Walter Gilbert. In 1974, Horvitz moved to Cambridge, England, where he worked with Sydney Brenner and began his studies of the worm. "Remarkably, all of my advisors, even my undergraduate advisor in economics here at MIT, Bob Solow, now have Nobel Prizes," he notes.


Photo: Justin Knight

Horvitz and members of his lab listen as graduate student Kaitlin Driscoll presents her findings at their weekly group meeting.

The comment is matter-of-fact, and Horvitz is anything but pretentious. He thinks about both big questions and small experimental details and is always on the lookout for links between the worm and human health.

"When someone in the lab finds something new, Bob is quick to ask if it relates to human disease," says former graduate student Nikhil Bhatla. "We're not thinking about that. We're deep in the nitty-gritty, but he's directing us to potential collaborators who might help us make that link."

This kind of mentoring, says Horvitz, has been his primary role since he joined the MIT faculty in 1978. He has trained many of the current leaders in the worm field, including Gary Ruvkun and Victor Ambros, who shared the 2008 Lasker Award, Michael Hengartner, now President of the University of Zurich, and Cori Bargmann, who recently won the McGovern's 2016 Scolnick Prize in Neuroscience. "If the science we've done has been successful, it's because I've been lucky to have outstanding young researchers as colleagues," Horvitz says.

Before becoming a mentor, Horvitz had to become a scientist himself. At Harvard, he studied bacterial viruses and learned that even the simplest organisms could provide valuable insights about fundamental biological processes.

The move to Brenner's lab in Cambridge was a natural step. A pioneer in the field of molecular biology, Brenner was also the driving force behind the adoption of *C. elegans* as a genetic model organism, which he advocated for its simplicity (adults have fewer than 1000 cells, and only 302 neurons) and short generation time (only three days).

Working in Brenner's lab, Horvitz and his collaborator John Sulston traced the lineage of every body cell from fertilization to adulthood, showing that the sequence of cell divisions was the same in each individual animal. Their landmark study provided a foundation for the entire field. "They know all the cells in the worm. Every single one," says Constantine-Paton. "So when they make a mutation and something is weird, they can determine precisely which cell or set of cells are affected. We can only dream of having such an understanding of a mammal."

It is now known that the worm has about 20,000 genes, many of which are conserved in mammals including humans. In fact, in many cases, a cloned human gene can stand in for a missing worm gene, as is the case for vps-50. As a result, the worm has been a powerful discovery machine for human biology.

In the early years, though, many doubted whether worms would be relevant. Horvitz persisted undeterred, and in 1992 his conviction paid off, with the discovery of ced-9, a worm gene that regulates programmed cell death. A graduate student in Horvitz' lab cloned ced-9 and saw that it resembled a human cancer gene called Bcl-2. They also showed that human Bcl-2 could substitute for a mutant ced-9 gene in the worm and concluded that the two genes have similar functions: ced-9 in worms protects healthy cells from death, and Bcl-2 in cancer patients protects cancerous cells from death, allowing them to multiply. "This was the moment we knew that the studies we'd been doing with *C. elegans* were going to be relevant to understanding human biology and disease," says Horvitz.

Ten years later, in 2002, he was in the French Alps with Constantine-Paton and their daughter Alex attending a wedding, when they heard the news on the radio: He'd won a Nobel Prize, along with Brenner and Sulston. On the return trip, Alex, then 9 years old but never shy, asked for first-class upgrades at the airport; the agent compromised and gave them all upgrades to business class instead.

Discovery Machine at Work

Since the Nobel Prize, Horvitz has studied the nervous system using the same strategy that had been so successful in deciphering the mechanism of programmed cell death. His approach, he says, begins with traditional genetics. Researchers expose worms to mutagens and observe their behavior. When they see an interesting change, they identify the mutation and try to link the gene to the nervous system to understand how it affects behavior. "We make no assumptions," he says. "We let the animal tell us the answer."

While Horvitz continues to demonstrate that basic research using simple organisms produces invaluable insights about human biology and health, there are other forces at work in his lab. Horvitz maintains a sense of wonder about life and is undaunted by big questions.

For instance, when Bhatla came to him wanting to look for evidence of consciousness in worms, Horvitz blinked but didn't say no. The science Bhatla proposed was novel, and the question was intriguing. Bhatla pursued it. But, he says, "It didn't work."

So Bhatla went back to the drawing board. During his earlier experiments, he had observed that worms would avoid light, a previously known behavior. But he also noticed that they immediately stopped feeding. The animals had provided a clue. Bhatla went on to discover that worms respond to light by producing hydrogen peroxide, which activates a taste receptor. In a sense, worms taste light, a wonder of biology no one could have predicted.

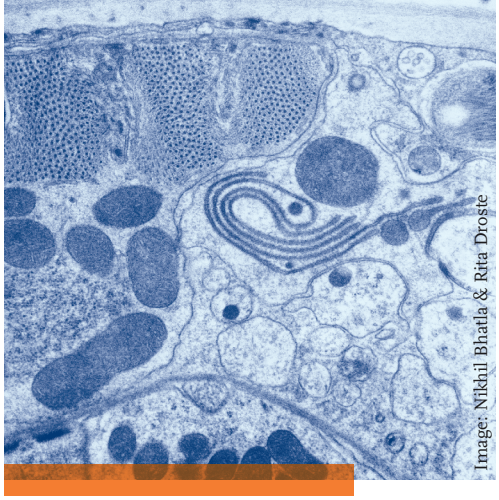


Image: Nikhil Bhatla & Rita Droste

Electron micrograph of C. elegans *head, showing muscle fibers and nerve cells. By reconstructing thousands of such images, researchers were able to discover the complete wiring diagram of the worm nervous system.*

Some years ago, the Horvitz lab made t-shirts displaying a quote from the philosopher Friedrich Nietzsche: "You have made your way from worm to man, and much within you is still worm." The words have become an informal lab motto, "truer than Nietzsche could ever have imagined," says Horvitz. "There's still so much mystery, particularly about the brain, and we are still learning from the worm." ■

Photo: Horvitz Lab, MIT

Horvitz and lab members, with the Boston skyline beyond.

INSTITUTE NEWS

Shenzhen Bay Bridge, China.

China Symposium on Primate Research

In March, the McGovern Institute co-organized an international symposium at the Shenzhen Institute for Advanced Technology (SIAT), to discuss new opportunities in primate neuroscience. The meeting drew many leading neuroscientists from the US, China, Europe and Japan, for two days of discussion on how the field can take advantage of recent technical advances in areas such as genome editing.

Although ethical considerations point to the use of rodents or other simpler organisms wherever possible, certain questions about brain function can only be studied in primates. In particular, many psychiatric diseases involve disruption of higher cognitive functions or social behaviors that are very difficult to model in rodents. Recent advances such as CRISPR are now making it possible to apply genetic approaches in primates, allowing the development of new disease models. China has emerged as a leader in this area, and the McGovern Institute is collaborating with SIAT to establish a new primate facility in Shenzhen and to develop methods for applying new genetic methods in primate models. To fully realize the benefits from this and other similar projects, a large collaborative effort will be needed, involving labs in many countries, and the main goal of this meeting was to launch a discussion on how this can best be achieved.

The meeting was organized by Bob Desimone, Guoping Feng and Feng Zhang at the McGovern Institute, along with Liping Wang and Huihui Zhou at SIAT. We are grateful to SIAT for hosting the meeting, and to the Ministry of Science and Technology of China and the Chinese Academy of Sciences for their support. ■

McGovern Welcomes First Lundbeck Fellow

Thorvald Andreassen joined Guoping Feng's lab in April 2016 as the McGovern Institute's first Lundbeck Postdoctoral Fellow. Thorvald received his PhD from the University of Copenhagen in 2016 where he studied the pre- and post-synaptic processes involved in dopamine signaling.

The Lundbeck Fellows Program has been created by the Lundbeck Foundation and Lundbeck Pharmaceuticals to provide young Danish neuroscientists with training fellowships at the world's top neuroscience institutions. The McGovern Institute is most grateful to Lundbeck for the creation of this program. ■

Lundbeck Fellow Thorvald Andreassen.

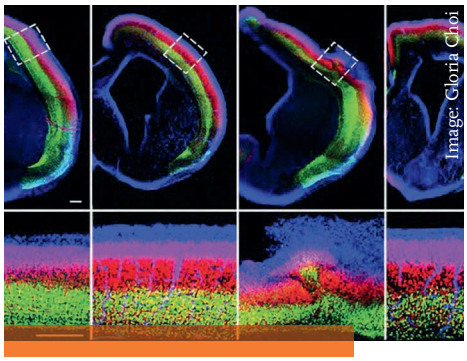
AWARDS & HONORS

Feng Zhang, an investigator at the McGovern Institute, a core institute member of the Broad Institute, and W. M. Keck Career Development Associate Professor in MIT's Department of Brain and Cognitive Sciences, has been named a recipient of the 2016 Canada Gairdner International Award — Canada's most prestigious scientific prize — for his role in developing the CRISPR-Cas9 gene-editing system. Zhang, who was recently promoted to tenure at MIT, will share the Gairdner Award with Jennifer Doudna, Emmanuelle Charpentier, Phillipe Horvath and Rodolphe Barrangou.

John Gabrieli has been elected to the American Academy of Arts and Sciences, one of the country's oldest learned societies. Gabrieli and the other members of the class of 2016 will be inducted at a ceremony on October 8th in Cambridge, MA. ■

McGovern Investigator Feng Zhang.

Children at heightened risk for depression show hyperconnectivity of subgenual anterior cingulate cortex (shown in orange).



Inflammation during pregnancy can affect the developing mouse brain.

A new brain imaging study from the McGovern Institute and Harvard Medical School may lead to a screen that could identify children at high risk of developing depression later in life. In the study, the researchers found distinctive brain differences in children known to be at high risk because of family history of depression. The finding suggests that this type of scan could be used to identify children whose risk was previously unknown, allowing intervention before they develop depression, says **John Gabrieli**, one of the study's authors.

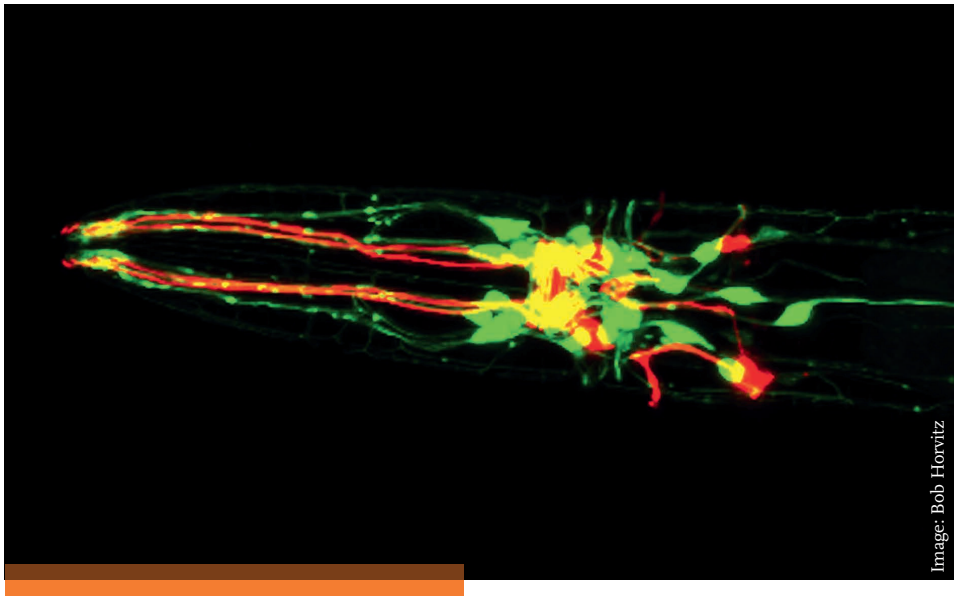
Guoping Feng has previously developed a mouse model of autism based on a mutation in the *Shank3* gene, which is linked to autism in humans. His team has now shown that many of the mutation's effects on brain and behavior can be reversed by restoring *Shank3* gene activity in adult mice. The findings offer hope that it will eventually be possible to reverse some of the effects of autism in human patients.

In a separate study, **Guoping Feng** and collaborators at New York University have linked ADHD and other attention difficulties to the brain's thalamic reticular nucleus (TRN), which is responsible for blocking out distracting sensory input. In a study of mice, the researchers discovered that a gene mutation found in some patients with ADHD produces a defect in the TRN that leads to attention impairments. The findings suggest that drugs boosting TRN activity could improve ADHD symptoms and possibly help treat other disorders that affect attention.

MIT neuroscientists led by **Bob Horvitz** and **Martha Constantine-Paton** have discovered a gene that plays a critical role in controlling nerve cell communication and the switch between alternative behavioral states (see pg 2). Their study was conducted using both nematode worms and mice. In humans, transitions between behavioral states include hunger-satiety and sleep-wakefulness, for example. The worm gene, which the researchers dubbed *vps-50*, affects the processing and release of neuropeptides — chemical signals used by neurons to communicate with other cells. Neuropeptides are also important in controlling human physiology and behavior. Several lines of evidence led the researchers to propose that the human counterpart of *vps-50* might be linked to autism.

In 2010, a large study in Denmark found that pregnant women who suffered an infection severe enough to require hospitalization were much more likely to have a child with autism. Now research from **Gloria Choi's** lab reveals a possible mechanism for how this may occur. In a study of mice, the researchers found that immune cells activated in the mother during severe inflammation produce a molecule called IL-17 that appears to interfere with brain development. The researchers also found that blocking this signal could restore normal behavior and brain structure in the offspring.

We can easily recognize objects independent of their size or viewing angle, but we also perceive these variables and use them to interpret complex visual scenes. **Jim DiCarlo** and colleagues have developed a computational model that mimics the brain'svisual recognition capabilities and explains how the visual system can achieve both of these tasks in parallel. ■



EVENTS

Photo: Lance Hayashida/Caltech

Sharp Lecturer Markus Meister.

On March 8, Dr. Markus Meister of Caltech delivered the 2016 Sharp Lecture in Neural Circuits. The lecture is sponsored by Biogen in honor of Dr. Phillip Sharp, who served as founding director of the McGovern Institute from 2000-2004. Meister's talk, "Neural computations in the retina: from photons to behavior" may be viewed on our website.

Photo: Justin Knight

Cornelia Bargmann, winner of the 2016 Scolnick Prize for Neuroscience.

Dr. Cornelia Bargmann of The Rockefeller University was awarded the 2016 Scolnick Prize in Neuroscience at a ceremony on March 20. Bargmann studies how genes, experience and neural circuits influence behavior in the nematode worm *C. elegans*. Her prize lecture, "Genes, neurons, circuits and behavior: an integrated approach in a compact brain" may be viewed on our website.

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, with the goal of improving human welfare, communication and understanding through their support for neuroscience research. The director is Robert Desimone, who is the Doris and Don Berkey Professor of Neuroscience at MIT and former head of intramural research at the National Institute of Mental Health.

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

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