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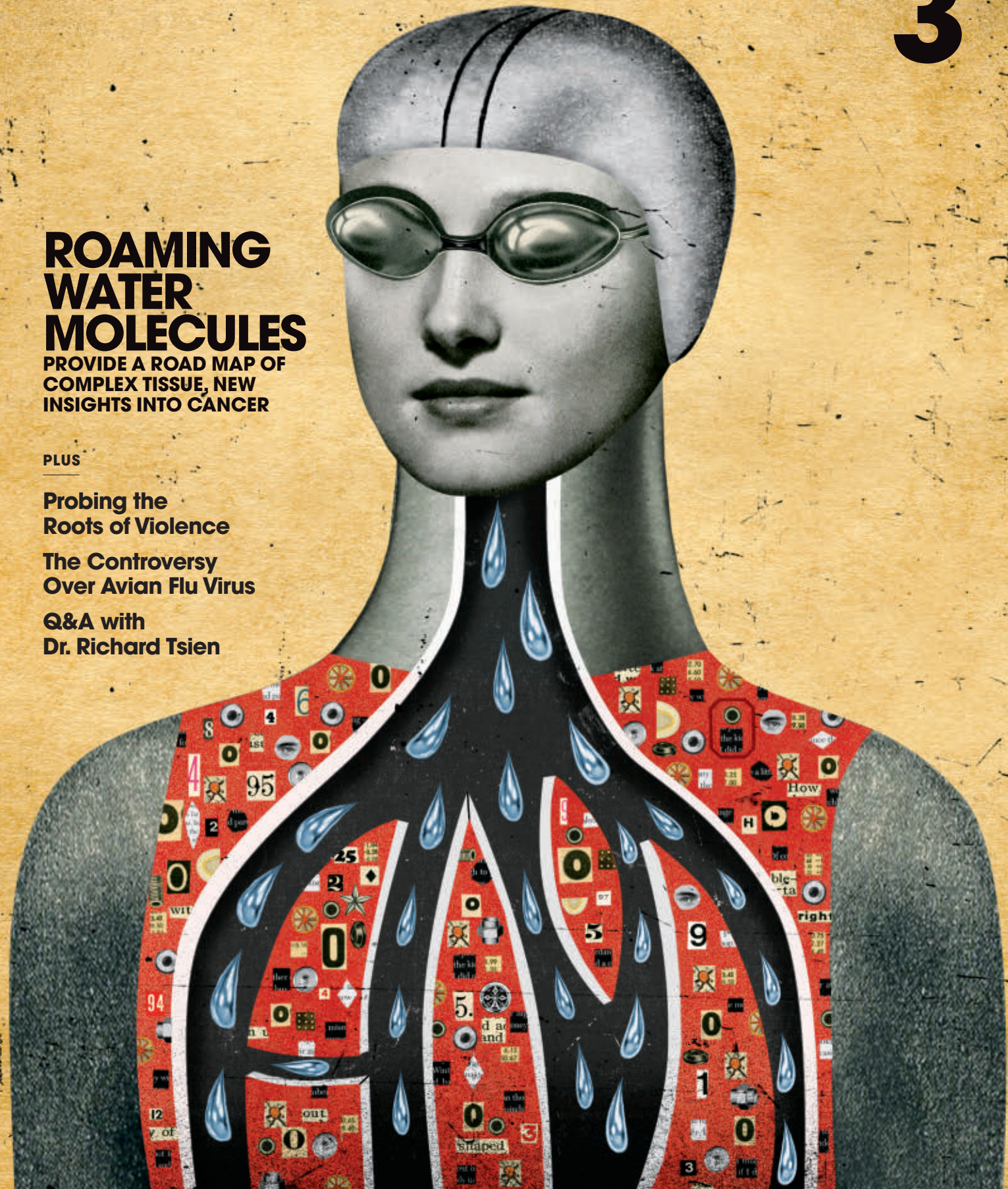

ROAMING WATER MOLECULES

PROVIDE A ROAD MAP OF COMPLEX TISSUE, NEW INSIGHTS INTO CANCER

PLUS

Probing the Roots of Violence

The Controversy Over Avian Flu Virus

Q&A with Dr. Richard Tsien

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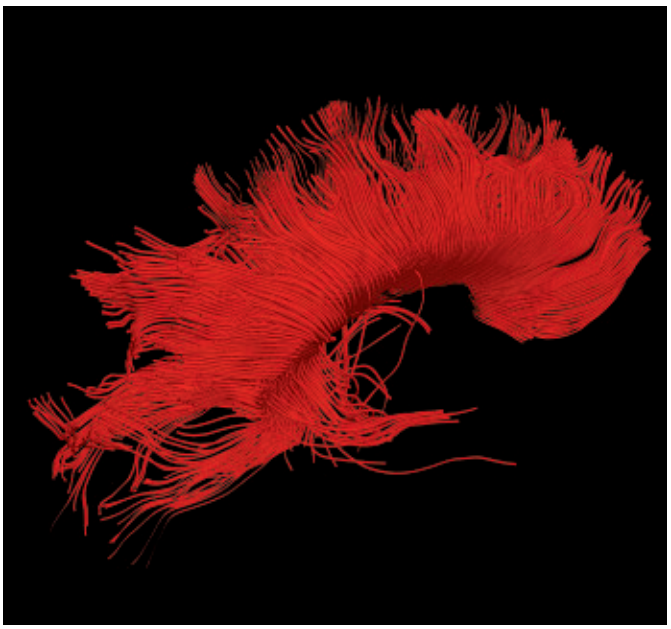


The corpus callosum connects the brain's hemispheres and comprises more than 100 million myelinated axons. Diffusion-tension imaging, which tracks moving water molecules, reveals the structure's thick band of insulated nerve fibers.

COVER STORIES

DEPARTMENTS

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

IMAGE: MARIANA LAZAR, PHD, DEPARTMENT OF RADIOLOGY

A Cornucopia of Discoveries

THIS ISSUE OF ***NYU PHYSICIAN*** *MAGAZINE* features a virtual cornucopia of discoveries by our researchers who are using advanced techniques in radiologic imaging and microscopy to explore the body's tissues in unprecedented detail.

The development over the last decade of advanced diffusion-based imaging techniques, in particular, has yielded tremendous insights into the microarchitecture of our tissues. In the cover story about this work you will meet some of the researchers who are at the forefront of pioneering efforts to transfer these insights to the clinic, mainly as biomarkers for cancer progression. This is the very heart of translational research. • You will also find in these pages extraordinary micrographic images of a variety of cells and tissues, many produced by members of The Helen L. and Martin S. Kimmel Center for Stem Cell Biology at the NYU School of Medicine. On a related note, the issue features a profile of one of our illustrious alumni, Dr. Arnold Kriegstein, who heads the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of California, San Francisco. I also urge you to read about behavioral neuroscientist Dr. Dayu Lin, who joined our faculty in 2010. Her work to identify nerve cells associated with violent behavior in mice is a model of creative research. • Finally, I am especially pleased that readers will have the opportunity to meet Dr. Richard Tsien, the first Druckenmiller Professor of Neuroscience, chair of the Department of Physiology and Neuroscience, and director of the Neuroscience Institute at NYU Langone Medical Center. His seminal research in signaling within the brain and the heart is a voyage of wondrous discovery. • Louis Pasteur once said that "to be astonished at anything is the first movement of the mind towards discovery." Indeed, research is about discovery, and the work featured in these pages astonishes. •

DEAN & CEO ROBERT I. GROSSMAN, MD

PHOTOGRAPH BY
JOHN ABBOTT

The Gift of Education

Q&A with Larry Silverstein

REAL ESTATE DEVELOPER LARRY SILVERSTEIN AND HIS WIFE, KLARA, recently donated $5.25 million to create the Silverstein Scholarship Fund endowment at NYU School of Medicine, which will provide tuition costs for up to five scholars annually. This gift is the latest example of their extraordinary generosity and of Mr. Silverstein's long-standing leadership of both New York University and the School of Medicine. You might say that NYU is in Mr. Silverstein's DNA. He graduated from New York University in 1952 and became a trustee of the university in 1976. In the late '90s, he became a trustee of NYU Langone Medical Center and the School of Medicine. The Silversteins have been married for more than 54 years, and two of their children graduated from NYU.

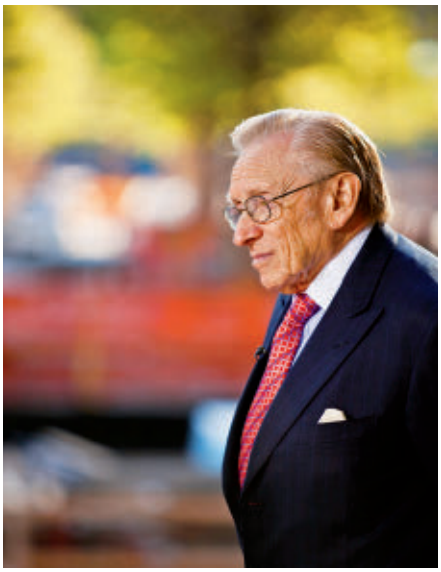
Mr. Silverstein is president and CEO of Silverstein Properties, Inc., a well-known Manhattan-based real estate development and investment firm that manages 35 million square feet of office, residential, and retail space. Many of the firm's properties are renowned, and he is the driving force behind the redevelopment of the World Trade Center. *NYU Physician* recently spoke to Mr. Silverstein.

NYU PHYSICIAN: *Why did you make a commitment to establish a scholarship fund for medical students?*
MR. SILVERSTEIN: It is a sure way to attract the best and brightest talent. For many years we have had a scholarship program at Washington Square for undergraduates, and we have seen how it has affected the lives of young people. The pleasure it has given us has been tremendous. We have established many fulfilling relationships with the recipients of these scholarships, and we wanted to continue that at the School of Medicine, which is very close to our hearts. Of course, we hope the scholarships will alleviate the stress that comes from building up some $200,000 worth of tuition loans over the educational term. Students have to spend many years of their lives paying it back, and it is extremely difficult.

NYU PHYSICIAN: *As a developer, are you slightly in awe of the building projects under way at the medical center?*
MR. SILVERSTEIN: I've been watching the work that has been going into this process for a number of years, and it is really quite remarkable. You won't feel the impact until the new buildings go up. We will maximize the developmental capability of the site and tie the buildings together in a much more efficient fashion. Everything will be superior to what exists today. You can't help but feel excited. It has truly been a labor of love to watch the institution grow not just in size but in quality and performance.

NYU PHYSICIAN: *Why does NYU hold a special place in your heart?*
MR. SILVERSTEIN: I remember my father asked me when I graduated if I had benefited from my college education. Yes, I answered. He then told me that at the appropriate time I had to give back. The conversation didn't particularly hit me with any force at the time, except that when I was asked to become an active alumnus, I thought about my father and said sure. Then one thing led to another, and that involvement deepened and broadened.

NYU PHYSICIAN: *You are a dyed-in-the-wool New Yorker, a lifelong New York City resident. What do you love most about the city?*
MR. SILVERSTEIN: Its vitality and diversity. You can accomplish anything here. ●



"It has truly been a labor of love to watch the institution grow not just in size but in quality and performance."

PHOTOGRAPHY: ERIKA L. KOOP

Learning Is Forgetting

A window on the living brain reveals unexpected circuit changes as memories are made and unmade.

We tend to think of learning as a gain of new neural connections and forgetting as a loss of old ones. But NYU Langone Medical Center researchers have found that some neural circuitry works the other way: In an area of the mouse cortex, learning to fear something eliminates pre-existing connections, while unlearning the fear restores the connections.

"It's the opposite of what we expected, and it's also unexpectedly simple," says Wen-Biao Gan, PhD, associate professor of physiology and neuroscience and senior author of the study, published March 1, 2012, in *Nature*.

Cora Sau Wan Lai, PhD, a postdoctoral researcher, shaved the skulls of young mice to transparency, creating an ultrathin window on the brain so that their neurons could be imaged directly with a sophisticated optical technique called two-photon fluorescence microscopy. This view onto the brain allowed her and Dr. Gan to observe that certain neuronal structures were eliminated when fear memories were created. Specifically, dendritic spines—tiny knoblike protrusions from the branching ends of nerve cells—disappeared.

Extinguishing the fear memory, using a standard behavioral technique, caused a regrowth of spines in the same locations, while reestablishing the fear memory eliminated the spines again. The spine changes persisted over many days and correlated strongly with behavior changes.

"We may have found an important circuit that is prewired to inhibit the fear response during an animal's development and then is weakened or strengthened by experience," Dr. Gan says. Previous work in his laboratory has shown that dendritic spines were gained when mice learned a new motor task. These spines create numerous synapses or junctions where nerve cells communicate.

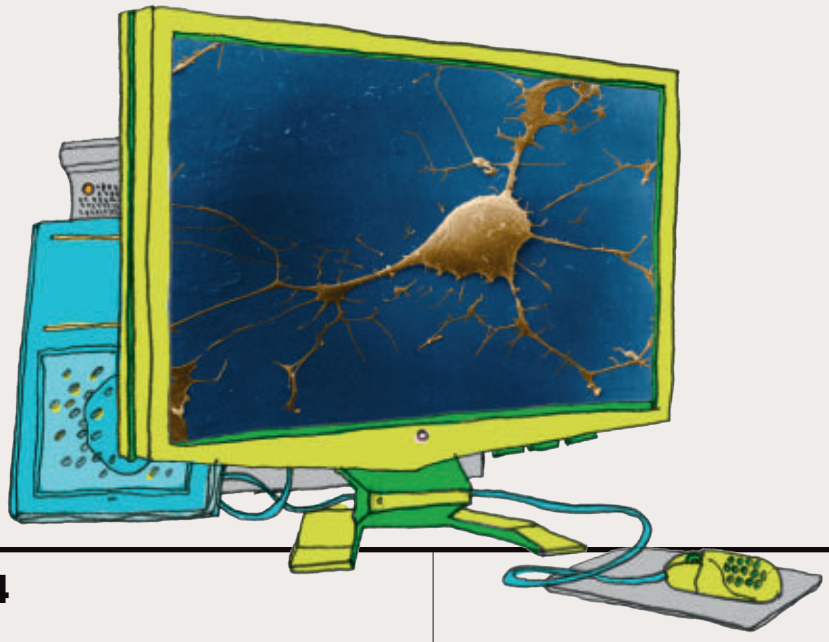
The making and unmaking of a fear memory is a basic paradigm in the neuroscience of learning. A lab mouse that hears an auditory tone at the same time it experiences a mild electric shock to the feet will learn to go rigid at the mere sound of the tone. Repeated presentations of the tone without the foot shock will extinguish the memory. Different models explain what goes on in the brain during these behavior changes. But the dominant view is that fear learning and extinction are mediated by separate brain circuits, which respectively strengthen or weaken activity in the amygdala, a deep and evolutionarily primitive brain structure associated with fear.

In contrast, Dr. Gan's results show that both an initial fear memory and its extinction correspond to opposing changes in the same circuit, in a frontal cortex area whose role in fear learning had never been investigated. "We looked at this area because it was one of the areas with projections to the amygdala that we could image with our transcranial microscopy technique," Dr. Gan says. "So we were pretty lucky." Co-author Thomas F. Franke, associate professor of psychiatry and pharmacology, helped design the behavioral experiments with the mice.

Dr. Gan now plans to look for fear-learning-related circuit changes in other neuronal types and brain areas. "It would be very exciting to investigate how different cell types work together and generate reversible and precise changes at the level of individual synapses within vastly complicated neural networks," he says. ●

—JIM SCHNABEL

The branch-like extensions of a human nerve cell are seen here in a color-enhanced scanning electron micrograph.



DAVID M. PHILLIPS / PHOTO RESEARCHERS, INC

ILLUSTRATIONS BY
PETER OUMANSKI

Another Way That TB Subverts the Immune System

New findings could open the way to better vaccines.

Sometimes it really does pay to kill the messenger—especially when it comes bearing tuberculosis. That is the message of a study published in the January 2012 issue of *Cell Host and Microbe* by Joel Ernst, MD, the Jeffrey Bergstein Professor of Medicine and professor of pathology and microbiology.

An electron microscope captures clusters of the rod-shaped tuberculosis bacterium.

In a series of experiments, Dr. Ernst and his colleagues demonstrated that *Mycobacterium tuberculosis* subverts the immune system by prolonging the lives of cellular couriers called neutrophils.

One-third of the world's population is infected with the bacterium that causes tuberculosis, and an estimated 1.7 million people die from the disease each year. Current tuberculosis vaccines are only partially effective, and Dr. Ernst's discovery of a novel mechanism by which the bacterium thwarts the immune system could lead to better vaccines.

Dr. Ernst and his collaborators had previously discovered that neutrophils, white blood cells known as the immune system's first responders, contribute to activating T cells, specialized white blood cells that play a leading role in combating tuberculosis. Their most recent work reveals precisely how neutrophils act as cellular messengers to trigger the body's adaptive immune response to tuberculosis and how *M. tuberculosis* works to stop them.

Usually, neutrophils in the lungs engulf foreign bacteria and then self-destruct through a precisely orchestrated process called apoptosis, or programmed cell death. Once they have expired, other immune cells called dendritic cells convey the dead neutrophils and their bacterial cargo to lymph nodes. There, the T cells recognize unique proteins in the bacteria and target them for destruction.

This process works properly, however, only if the neutrophils actually die on schedule. And that is where *M. tuberculosis* gums up the works.

Researchers already knew that the bacterium uses a gene called *nuoG* to inhibit the suicide of macrophages, larger immune cells that also swallow pathogens. Now Dr. Ernst, Ludovic Desvignes, PhD, assistant professor of medicine, and postdoctoral fellow Robert Blomgran, PhD, now at Linköping University, Sweden, and their collaborator Volker Briken, PhD, at the University of Maryland, discovered that *M. tuberculosis* uses the same gene to inhibit the death of neutrophils as well. By postponing the suicide of these cellular messengers, the bacteria stop the neutrophils from delivering their cargo to dendritic cells and short-circuit the body's immune response.

"Evolutionarily, that's probably the reason that mycobacteria adapted this capability," Dr. Ernst says. He and his colleagues show that mice infected with a mutant strain of *M. tuberculosis* that lacks the *nuoG* gene have higher rates of T cell activation because their neutrophils die more promptly, get handed off to dendritic cells more rapidly, and activate T cells earlier.

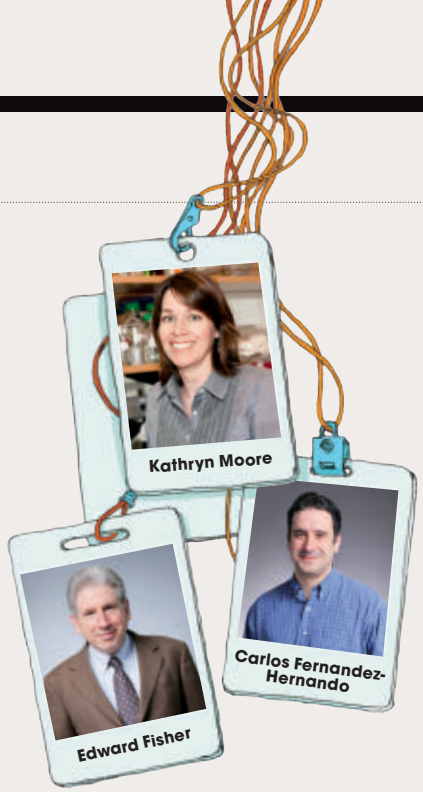
Dr. Ernst's work could promote development of more effective tuberculosis vaccines that counteract the ability of the bacterium to keep immune cells alive longer than nature intended. "Discovering how this mycobacterium perturbs the immune system helps the whole field as we work together to try to beat back tuberculosis," Dr. Ernst says. ●

—ALEXANDER GELFAND

NYU MICROSCOPY CORE FACILITY

From the Bench to the Bedside

A drug that inhibits microRNA and lowers cholesterol and triglycerides is ready for human testing.



Kathryn Moore, PhD, associate professor of medicine and cell biology, may have greatly raised the bar as to what can be accomplished in the lab in just two years. That's how long she has been on the faculty of NYU School of Medicine. Yet already tucked under her belt are publications in *Science* and *Nature*, among others, and the development of a drug that is being readied for human clinical testing.

If successful, the agent would increase the amount of high-density lipoprotein (HDL) in the bloodstream. HDL picks up the fat that low-density lipoprotein (LDL) dumps into heart arteries, clogging them with plaque. The drug would also decrease triglycerides in the arteries, a kind of fat that increases both heart disease and the risk of diabetes.

Katey Rayner, PhD, who has worked alongside Dr. Moore as a research fellow in the Department of Medicine, couldn't agree more. "It has been amazing to watch this project—it reminds me why I love what I do."

Their first breakthrough occurred when Dr. Moore collaborated with Carlos Fernandez-Hernando, PhD, assistant professor of medicine and cell biology. Both researchers are members of the Marc and Ruti Bell Vascular Biology Program. They identified a microRNA molecule in mice that, when inhibited, significantly raised HDL. They were joined by two other faculty members in the Bell Program, Edward Fisher, MD, PhD, MPH, the Leon H. Charney Professor of Cardiovascular Medicine and professor of pediatrics and cell biology, and Yajaira Suarez, PhD, assistant professor of medicine.

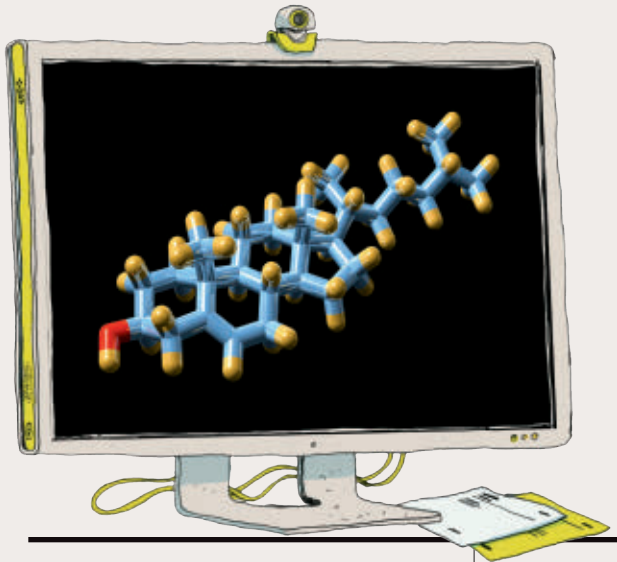
MicroRNAs are small RNA molecules that do not encode protein but instead regulate gene expression. MicroRNAs are believed to regulate more than one-third of all human genes, and a single microRNA can regulate entire networks of genes.

In 2010 the researchers showed that a microRNA called miR-33 was controlling three genes involved in transporting cholesterol and in synthesizing HDL in mice. They later demonstrated that inhibiting miR-33 with a novel agent (developed by Regulus Therapeutics in collaboration with Dr. Moore) increased HDL in mice by about 40 percent and reduced plaque size by some 35 percent.

Although everything looked "really, really promising" in mice, as Dr. Moore says, she knew that large mammals, including humans, have two copies of miR-33—miR-33a, identical to the gene found in mice, and miR-33b, which may greatly increase during metabolic syndrome and insulin resistance—hallmarks of diabetes. Both genes have the same structure and repress the same genes but are regulated in different ways, so the hope was that the Regulus agent could tackle both risk factors.

In a study published in *Nature* last fall, Dr. Moore and her colleagues showed that the miR-33 inhibitor, tested over 12 weeks in African green monkeys, caused a 50 percent increase in HDL, as well as a marked reduction of triglycerides, which was not observed in mice. "Metabolic syndrome is an emerging global problem, caused by low levels of HDL and high levels of triglycerides. An effective treatment could have an enormous public health impact," Dr. Moore says. "I can't wait to see what happens next when miR-33 inhibitors move into clinical trials." ●

—RENEE TWOMBLY



A molecular model of cholesterol—carbon (blue), hydrogen (yellow), and oxygen (red).

DR. MARK J. WINTER / PHOTO RESEARCHERS, INC

ILLUSTRATIONS BY **PETER OUMANSKI**

Smelling the Roses Once Again

A study raises hope that a sense of smell can be regained.

Losing a sense of smell may not be life threatening but it can certainly drain the joy out of life. Smell and taste are inextricably bound, and without the nose there is no pleasure in eating a juicy apple, drinking a glass of robust wine, or inhaling the scent of freshly brewed coffee.

Why smell weakens remains a mystery, although both aging and illness have been offered as explanations, and a loss of smell occurs early in the course of Alzheimer's disease. Recent laboratory research by NYU Langone Medical Center scientists shows how smell may be lost and then regained.

"Our findings suggest that while olfactory impairment may reflect real damage to the sensory system, in some cases it may be a 'use it or lose it' phenomenon amenable to retraining," says Donald A. Wilson, PhD, professor of child and adolescent psychiatry at NYU School of Medicine and senior research scientist at the Emotional Brain Institute at Nathan S. Kline Institute for Psychiatric Research.

Dr. Wilson and Julie Chapuis, PhD, a postdoctoral fellow, report in a recent study in *Nature Neuroscience* that rats can be trained to improve their sense of smell. They made this observation based on a series of experiments in which thirsty rats recognized various smells composed of a mix of 10 chemicals. The researchers trained the rats to look for water in one of three holes based on a particular scent and rewarded them with water when the rats selected the correct odor. However when one component of the odor had simply been removed the rats could not differentiate the smells.

The scientists then anesthetized the rats and inserted electrodes into their brains to capture and record electrical activity during the experiments. The data showed that, within the olfactory bulb, a structure beneath the frontal cortex that receives nerve impulses directly from the nose, each smell produced a different pattern of electrical activity. But in the piriform (olfactory) cortex, an inch-size area of the cerebral cortex, the odors that rats could tell apart produced distinct patterns of activity—a sort of odor signature—while those the rats could not distinguish produced identical patterns.

Some smell disorders extinguish the sweet aroma of roses and honeysuckle.

Drs. Wilson and Chapuis then trained a new group of rats to discriminate between the odors the first animals couldn't tell apart by rewarding them over and over with sips of water for choosing the appropriate hole. "We made them connoisseurs," Dr. Wilson says. In the rats' piriform cortex, activity patterns elicited by these similar odors were now different as well. They subsequently trained a third group of animals to ignore the difference between odors the first rats could readily distinguish, which effectively dulled their sense of smell: the rats couldn't tell one smell from the other, even for a reward. Their loss of discrimination was reflected in the piriform cortex, which then produced similar electrical patterns in response to both odors.

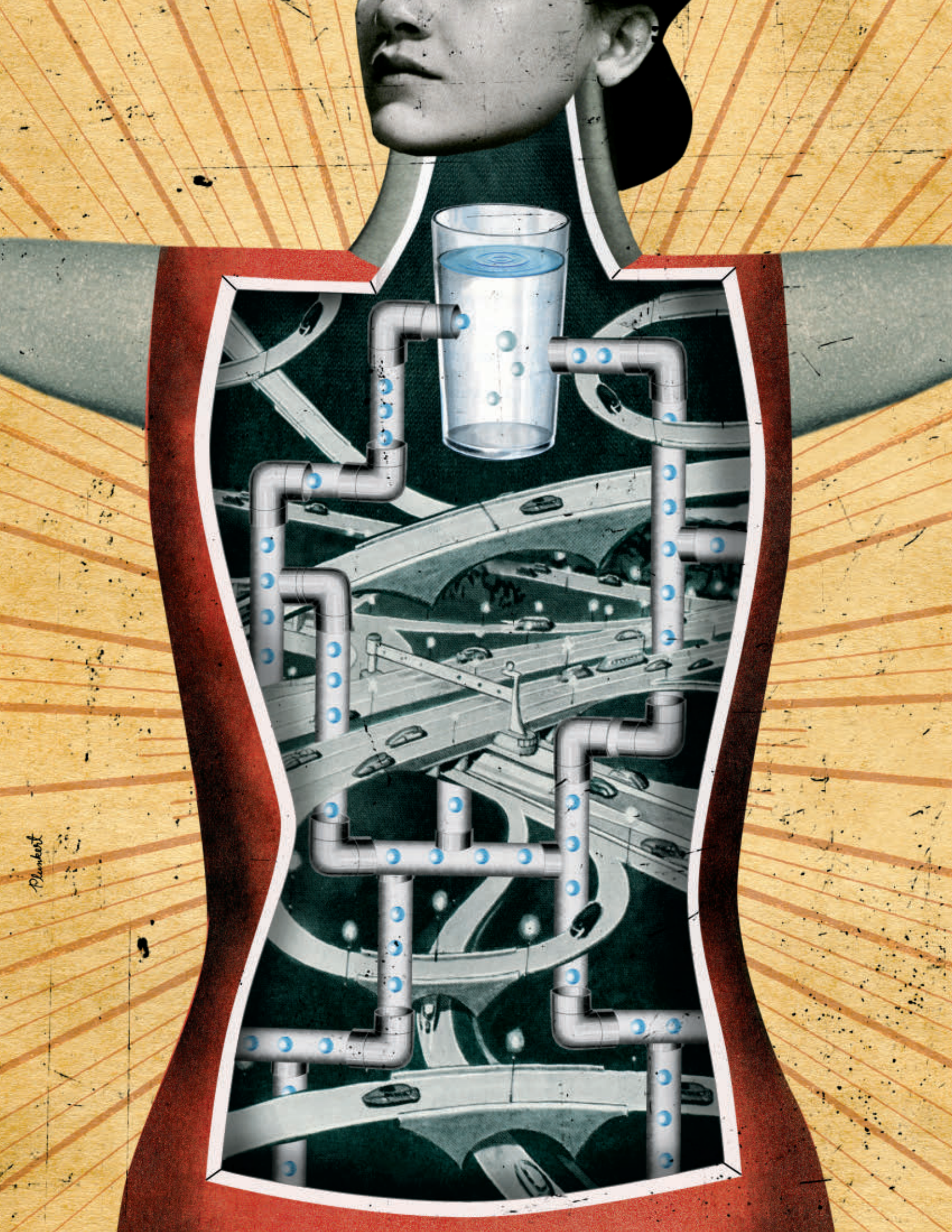
The findings, says Dr. Wilson, suggest that ignoring differences between smells can rewire the brain to lose its ability to make those discriminations. Fortunately, training that highlights differences between smells can reverse that rewiring, raising hope for recovery from some smell disorders. ● *—CARL SHERMAN*

ROSES: ERIKA CRADDOCK / PHOTO RESEARCHERS, INC

A NEW KIND OF CANCER PROBE

ADVANCED IMAGING TECHNIQUES RELY ON ROAMING WATER MOLECULES TO VISUALIZE COMPLEX TISSUE.

BY BRYN NELSON
ILLUSTRATIONS BY DAVID PLUNKERT



TRACKING A WATER MOLECULE

THROUGH THE HUMAN BODY IS LIKE FOLLOWING A TRAVELER THROUGH A VAST CITY. OBSTACLES, AVENUES, AND OPEN SPACES ALL DETERMINE WHERE A WAYFARER MIGHT LINGER, MEANDER, OR MOVE BRISKLY. OVER TIME, MAPPING OUT THE PRECISE MOVEMENTS OF MANY TRAVELERS CAN REVEAL RICH INSIGHTS ABOUT THE CITY'S PATTERNS AND STRUCTURAL FEATURES.

Since the 1980s, imaging techniques have relied on the diffusion of water through living tissue as a lens to view the inner workings of the brain and map out its elaborate architecture. The more recent evolution of this technology, based on magnetic resonance imaging (MRI), now allows scientists to trace the displacement of water in unprecedented detail as it flows through the body's other regions. This kind of in vivo microscope, some studies suggest, can track molecules moving as little as 1 micron, or one-fifth of the way across a red blood cell. Some of these slight alterations, in turn, may help signal disease.

"If you think about it, a water molecule is a wonderful probe of tissue, because what does it do? If it's inside the axon of a nerve, it bounces around until it hits the edge, and then it bounces right back," says Daniel K. Sodickson, MD, PhD, director of the Bernard and Irene Schwartz Center for Biomedical Imaging and associate professor of radiology and physiology and neuroscience. "If you can capture something about that behavior, you've just learned that there's an edge there."

At NYU Langone Medical Center, the development of this potent biomarker of subtle shifts has advanced rapidly over the past few years, offering opportunities for collaborative research aimed at tracking early stages of disease. Last year an interdisciplinary group of basic scientists and clinicians published three studies demonstrating how a type of diffusion-based imaging might reveal the warning signs of a malignant breast tumor. "We have now joined forces to make a multifaceted attack on breast cancer using new imaging tools," Dr. Sodickson says.

Team member Linda Moy, MD, assistant professor of radiology, says imaging techniques have traditionally revealed little more than the shape and size of abnormal tissue. "I'm enthusiastic because now we're starting to understand tumor biology a little bit more," Dr. Moy says. "The long-term goal is that this will give us more understanding about the physiology of breast tumors and, I hope, more tools to treat the cancer."

Eric Sigmund, PhD, assistant professor of radiology and another team member, says cancer researchers began to realize the potential of a method known as diffusion-weighted imaging after discovering that it can help visualize how aggressive cell proliferation restricts the movement of water. A refinement called intravoxel incoherent motion, or IVIM, is more adept at characterizing how networks of tiny blood vessels and tubules within tumors direct the flow of water, and the group is using both techniques in tandem.

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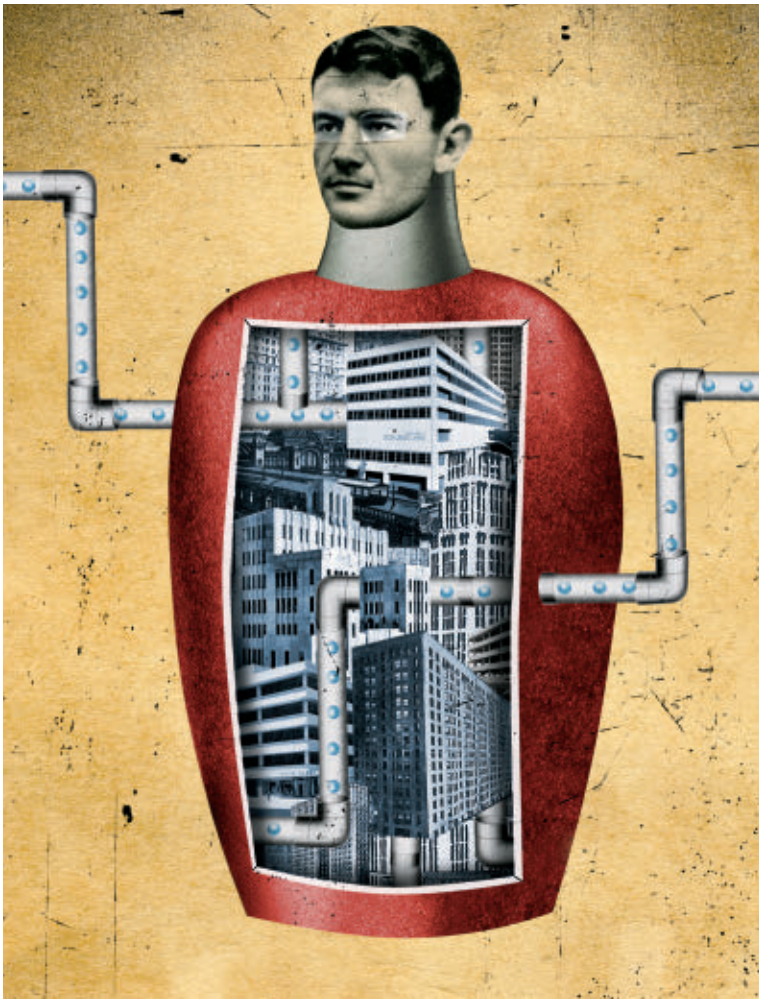
CONVOLUTED BLOOD VESSELS

Like other malignant tumors, aggressive breast cancer feeds itself by ordering the rapid buildup of blood vessels to deliver oxygen and nutrients. The new recruits are often bulky and misshapen, however, resulting in a sluggish flow through a tangle of leaky vessels that spill fluid within the mass. As the cells proliferate and viscous fluid fills the confined space, the compression among those cells, called the interstitial fluid pressure, begins to soar. Eventually, the tumor bulges like a water balloon, the soaring pressure making it increasingly difficult for any drugs to make their way through the malformed blood vessels.

Silvia Formenti, MD, the Sandra and Edward H. Meyer Professor and chair of the Department of Radiation Oncology, says the pressure can grow so intense that tissues once spongy become rocklike, with cores nearly



impenetrable by anticancer drugs. In a proof-of-principle study published last year, the team demonstrated this phenomenon with a synthetic system that mimicked the microenvironment of a tumor. They used a sponge as a stand-in for tumor tissue and three different configurations of valves, tubes, and pumps that simulated how different tumor behaviors might control the flow of water. In configurations that led to a pressure increase, essentially imitating the behavior of an aggressive cancer, IVIM imaging of the sponge revealed a corresponding drop in flow. The results suggested that the method might be sensitive even to minuscule changes in how water diffuses through a real tumor.

In a follow-up study, funded in part by the Breast Cancer Research Foundation (BCRF), the team demonstrated similar results in a mouse model of breast cancer. It linked higher interstitial fluid pressure within a developing tumor to slower movement of water through that cancerous tissue, as measured by the IVIM technique. A third study, also funded in part by BCRF, of patients with diagnosed or suspected locally advanced breast cancer found the imaging pointed out significant differences between normal tissue and malignant lesions. The researchers are now testing whether these imaging-derived pressure measurements may be linked to lower blood flow, indicating more aggressive tumors.

Decreased circulation might pose a serious problem for typical body tissue due to lack of oxygen, but cancer's structure is anything but normal. "It's believed that when you have a tumor that has this high interstitial fluid pressure, you also have some of the nastiest cells, the ones that are the most robust, lurking in the center," Dr. Sodickson says. "Even though they have less oxygen, you're selecting for the cells that can survive under the most hostile conditions, which then end up being the most invasive cells."

THE MORE RECENT EVOLUTION OF THIS TECHNOLOGY, BASED ON MAGNETIC RESONANCE IMAGING (MRI), NOW ALLOWS SCIENTISTS TO TRACE THE DISPLACEMENT OF WATER IN UNPRECEDENTED DETAIL AS IT FLOWS THROUGH THE BODY'S OTHER REGIONS.

For patients, says Dr. Sodickson, the phenomenon is a double whammy: The massing of abnormal, leaky blood

"IT'S A PERFECT LITTLE MICROSCOPIC PROBE OF WHAT'S REALLY HAPPENING IN THE TISSUE, AND YET WE CAN SEE IT MACROSCOPICALLY IN OUR IMAGES."

vessels signals a dangerous tumor, and the accompanying buildup in interstitial fluid pressure blocks the entry of many conventional drug therapies. If clinicians can accurately measure the pressure, as well as the signatures of expanding tumor cell and blood vessel formation, they might have a better handle on the aggression. "This is a marker that this tumor isn't going to quit," Dr. Sodickson says. "This is one that we need to throw everything we can at, because it's going to invade as opposed to something else that might just sit there, and then the treatment might be worse than the disease."

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GUIDING THERAPY

The collaborators are now recruiting breast cancer patients and using the IVIM technique to create maps of each tumor's cell and vessel expansion, as well as interstitial fluid pressure. By comparing the imaging-derived information to what can be gleaned from a more invasive needle-based pressure reading and standard biopsy, they hope to demonstrate IVIM's potential not only for diagnosis but also for treatment guidance and monitoring efforts. "Recognizing when the pressure is high can in principle determine the right therapy," Dr. Sigmund says.

Ultimately, the team envisions a three-part clinical strategy. First, doctors would image a patient's tumor by IVIM to measure the interstitial fluid pressure and microarchitectural markers. For the subset of patients with abnormally high pressure, clinicians could prescribe a drug that renormalizes blood flow by blocking tumors from recruiting new blood vessels. "Instead of giving it to all patients and getting maybe 10 percent to respond, you can figure out in advance, what are the 10 percent who will respond—who have an increased interstitial pressure—and just focus on them," Dr. Formenti says. That potential for a significantly higher response rate, she says, fits with personalized medicine's goal of more individually tailored treatments.

With a renormalized blood flow, the tumor might prove more susceptible to subsequent chemotherapy, a potential vulnerability that Dr. Formenti says is supported by recent studies focused on colorectal cancer and other tumors.

One top candidate for renormalizing blood flow, the drug Avastin, recently lost its Food and Drug Administration approval as a breast cancer therapy because of concerns about dangerous side effects. The NYU Langone collaborators, with the aid of Robert Schneider, PhD, the Albert B. Sabin Professor of Microbiology and Molecular Pathogenesis, can test other options in mice and use diffusion-based imaging as one of the indicators of the candidate drugs' abilities.

"It's a perfect little microscopic probe of what's really happening in the tissue, and yet we can see it macroscopically in our images," Dr. Sodickson says. With that extraordinary view as a guide, the team is continuing to chart the intricate patterns of health and disease that may strongly influence how cancer is diagnosed and treated.

ADVANCE WARNING OF EARLY DISEASE

Throughout NYU Langone Medical Center, imaging techniques based on the diffusion of water molecules are providing advance warning of early disease. "We're trying to see early enough and finely enough that we can tell the difference between a condition that is reversible or irreversible, a tumor that's invasive or noninvasive," Dr. Sodickson says.

Many MRI scanners have been outfitted with new software packages needed to extract the additional details, and several methods are spreading widely throughout the medical center. One well-known type of diffusion-based imaging process known as diffusion tensor imaging, or DTI, is particularly good at characterizing the flow of water through tissue in three dimensions. This multidirectional probe is now routinely used for presurgical planning and along with standard diffusion-weighted imaging has become a clinical biomarker for assessing damage due to strokes.

A project led by José Raya, PhD, a research scientist in the Department of Radiology, is also using DTI to ask whether the progressive destruction of cartilage that characterizes the joint disorder osteoarthritis might be reversible in its initial stages. By measuring how water diffuses through the tissue in multiple directions, DTI can provide details about the two major structural components that make up the cartilage matrix. In a recent study, Dr. Raya and colleagues showed that this imaging method can accurately differentiate between healthy people and patients with early osteoarthritis of the knee.

If diffusion-weighted imaging is akin to measuring the average movement of everyone in a city, another variant known as diffusion kurtosis imaging, or DKI, lets researchers pick out patterns in individual neighborhoods. One section of town may be full of obstacles while another is far more open, and the pace of traffic in both places can diverge greatly from the overall flow. Identifying that added complexity and how it differs from the average movement in a body tissue, Dr. Sigmund says, "allows you to pick up on subtle degeneration before it becomes a macroscopic problem."

NYU Langone scientists devised the DKI method in 2005. Since then, medical center researchers have studied the technique's potential use as a biomarker for a range of conditions, from attention deficit-hyperactivity disorder and traumatic brain injuries to Alzheimer's disease.

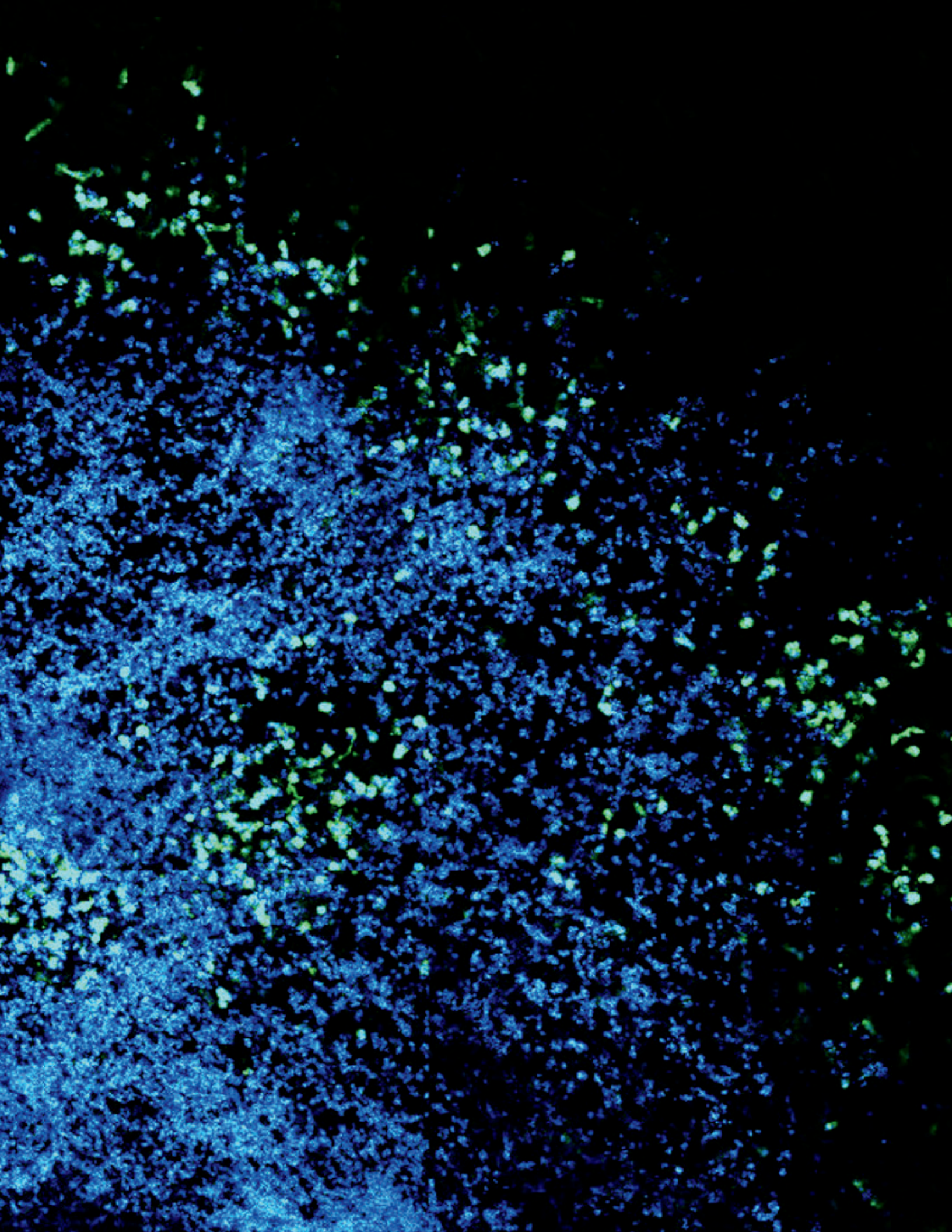
DKI is also aiding an ambitious collaborative effort to better understand prostate cancer. Andrew Rosenkrantz, MD, assistant professor of radiology, says a biopsy does not always correctly characterize prostate tumor features. The mathematically advanced DKI technique, he says, might provide a more reliable assessment of a tumor's complex architecture and therefore a more accurate prediction of its Gleason score, the standard indicator of tumor aggression.

Hersh Chandarana, MD, assistant professor of radiology, is using IVIM to examine flow patterns through the fine network of vessels and tubules in renal tissue and blood flow in renal tumors. In collaboration with Dr. Sigmund, Dr. Chandarana is testing whether IVIM-aided measures of a tumor's blood vessels and architectural features might improve assessments of its aggressiveness. "There's a growing effort to preserve as much kidney function as possible, and to do that, you have to understand the biology of the lesion that exists," Dr. Sigmund explains. "The more properties that can be teased out of the tumor from imaging, the better sense you have of its biology in a noninvasive way."

The imaging method could help clinicians further subdivide renal tumors based on their behavior, Dr. Chandarana says. "But I think the most important clinical application would be as a marker for early treatment response to drug therapy in metastatic disease." A sensitive early measure of effectiveness, he says, could signal when to continue the same therapy and when to change course. ●

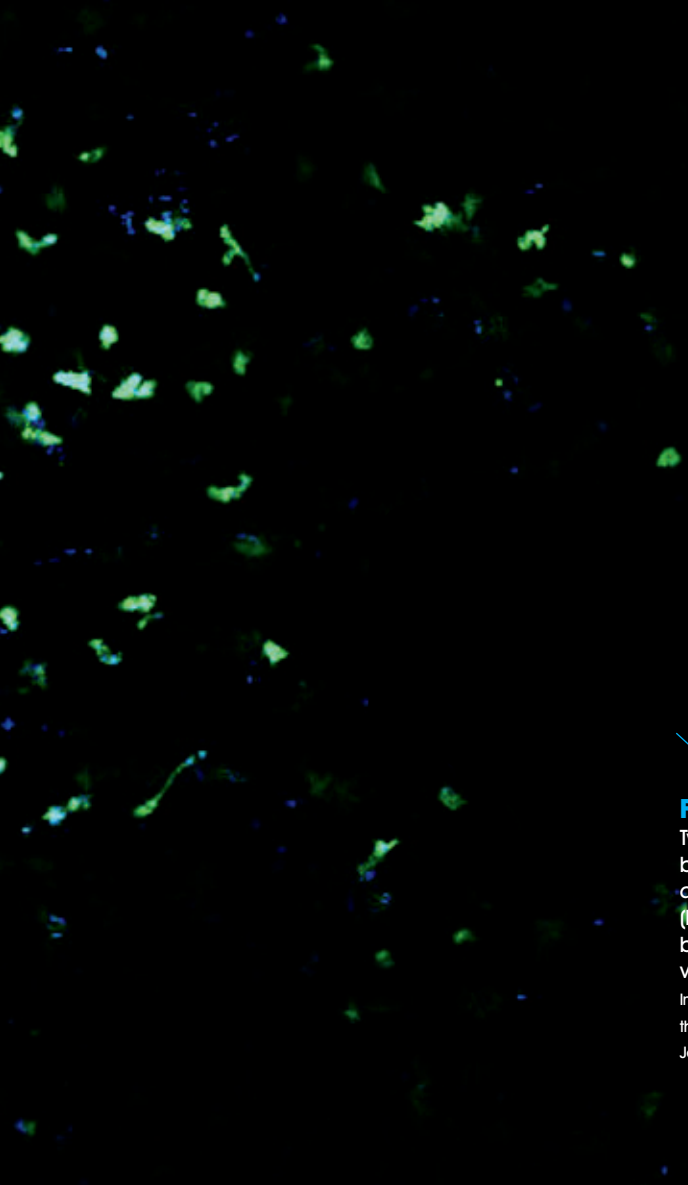
From left: Eric Sigmund, PhD, Linda Moy, MD, and Daniel K. Sodickson, MD, PhD.

PHOTOGRAPHY: BUD GLICK



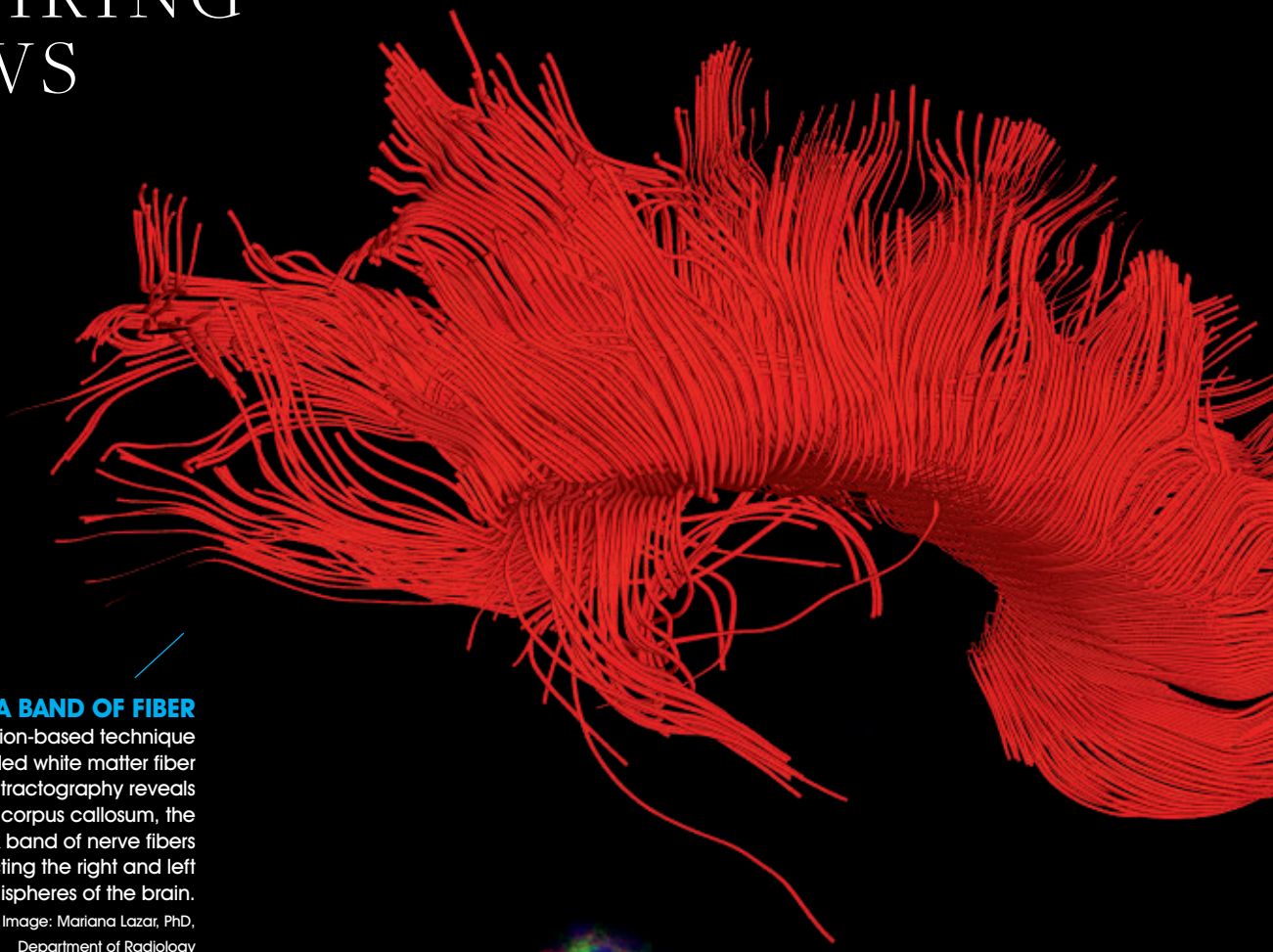
Seeing IS BELIEVING

Extraordinary ADVANCES IN RADIOLOGIC IMAGING and FLUORESCENCE MICROSCOPY have allowed scientists to track the movement of water along nerve cells, locate stem cells that give rise to cancer, and capture the IMMUNE SYSTEM'S SOLDIERS in the act of defending the body against foreign invaders.

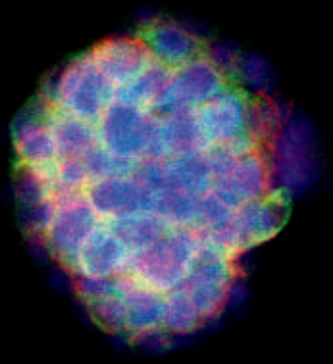


FIGHTING SOLDIERS
Two-photon microscopy captures white blood cells converging on a *Staph aureus* skin infection. The bacteria (blue) and immune cells (green) have been genetically engineered to express variants of a fluorescent protein.
Image: Michael Dustin, PhD, and Richard Novick, MD, the Skirball Institute of Biomolecular Medicine, and Jan Liese, PhD, University of Tübingen

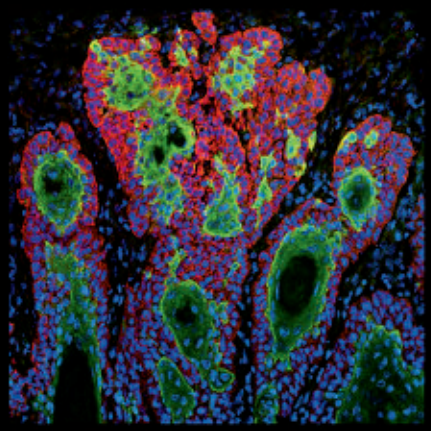
INSPIRING VIEWS



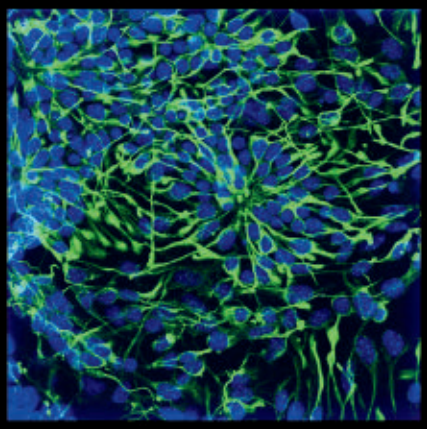
A BAND OF FIBER
A diffusion-based technique called white matter fiber tractography reveals the corpus callosum, the thick band of nerve fibers connecting the right and left hemispheres of the brain.
Image: Mariana Lazar, PhD, Department of Radiology



DEADLY GLUE
Clusters of inflammatory breast cancer cells are revealed by special fluorescent stains that identify proteins that enable tumor cells to adhere tightly to each other.
Image: Deborah Silvera, PhD, and Robert Schneider, PhD, Department of Microbiology



HARD TO FIND
Stem cells lurk among immature cancer cells, in red, in this image of cutaneous squamous cell carcinoma. Cells at the edge of the tumor and at the center of mature cells are green. Genetic material in the nucleus is blue.
Image: Markus Schober, PhD*

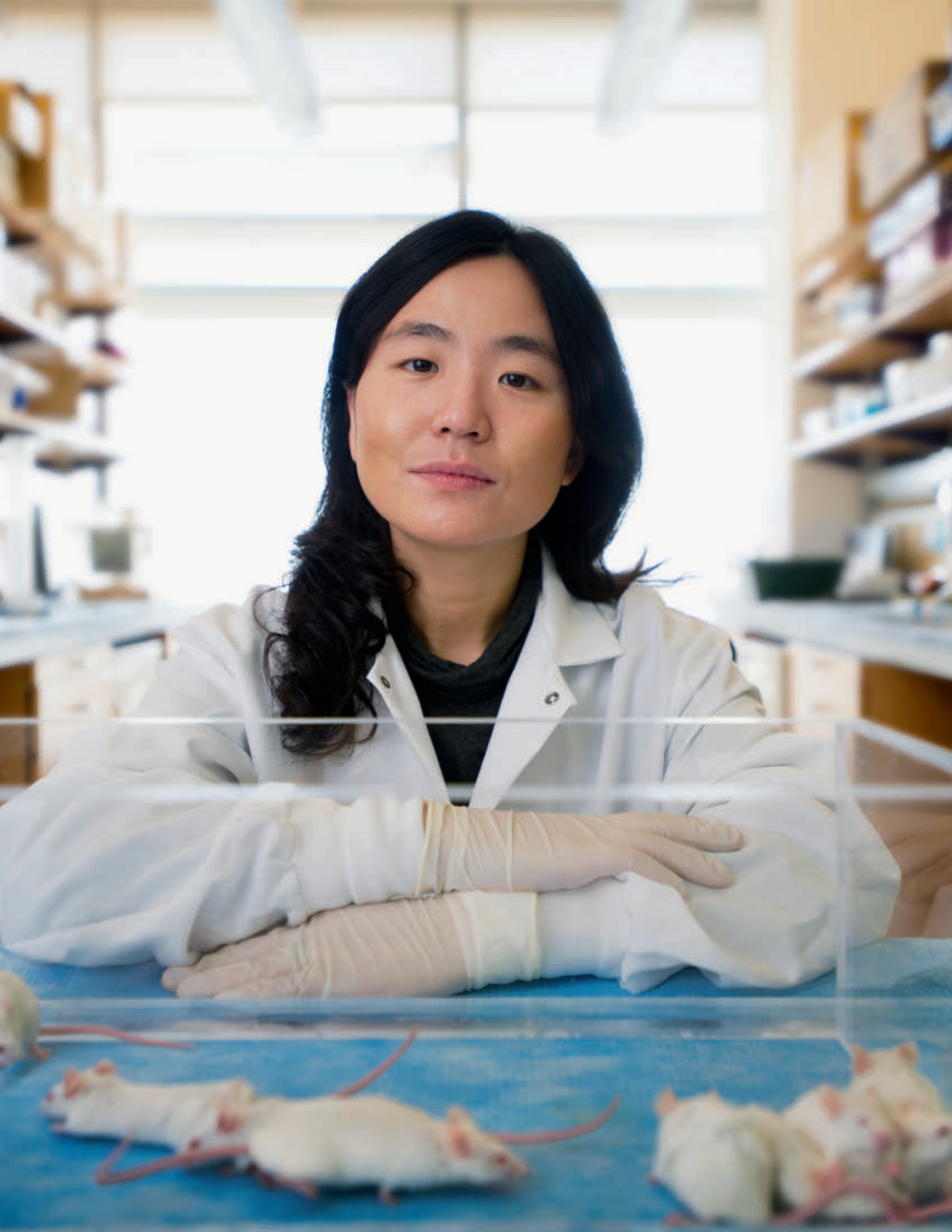


MULTIPOTENT
Neural stem cells (green), cultured from mouse embryonic stem cells, have been engineered to produce a mutant gene that causes neurodegeneration. DNA in each cell is stained blue.
Image: Naoko Tanese, PhD*

MOTOR HIGHWAY
Motor nerve cells send their outgoing messages along axons, which innervate muscle. This micrograph shows motor axons in the forelimb of a 13-day-old mouse embryo.
Image: Jeremy Dasen, PhD*

UMBRELLAS
Toxins in the urine cannot penetrate flattened umbrella cells in the bladder's lining. A scanning electron micrograph shows the specialized cells. A red blood cell (lower right) is small by comparison.
Image: Tung-Tien Sun, PhD*, and Bechara Kachar, MD, NIH

*Members of The Helen L. and Martin S. Kimmel Center for Stem Cell Biology at the NYU School of Medicine.



Illuminating

THE ROOTS OF VIOLENCE

RESEARCHER **DAYU LIN** IDENTIFIES SPECIFIC BRAIN CELLS TIED TO AGGRESSION IN MICE

BY KAREN HOPKIN
PHOTOGRAPHS BY JOSHUA BRIGHT

A LONE BLACK MOUSE MEANDERS around his home cage, sniffing at this, poking at that. Jutting from his head is a tether through which researchers can control the activity of select cells in his brain. Suddenly a white mouse drops down from above, like a soldier parachuting into enemy turf. The resident responds, pouncing on the intruder, biting at his flanks. The ferocious attack continues—until Dayu Lin, PhD, assistant professor of psychiatry and physiology and neuroscience, pushes a button, shutting down the behavior as if she were switching off a light.

That a mouse would defend his territory with tenacity and teeth is not surprising: aggression is a natural behavior, universal among animals and essential for survival. What's remarkable is that Dr. Lin and her colleagues have devised a method for manipulating that behavior by modulating the activity of the animal's brain, culminating years of work exploring the neural circuits that regulate fighting in mice. Their findings are leading to a deeper understanding of the roots of animal aggression and possibly to novel medicines to quell violence in humans. >>

Research on aggression began in the 1920s, when scientists found they could elicit rage in cats by electrically stimulating certain areas in their brains. The dramatic research, producing iconic images of snarling cats with arched backs and bared claws, earned Swiss physiologist Walter Hess a Nobel Prize in 1949.

By the 1980s studies in rats had confirmed that the hypothalamus, an evolutionarily ancient structure that sits at the base of the brain, was linked to such fury. But the hypothalamus is a complex command center that regulates a range of bodily functions. Determining which regions within that structure are specifically involved in aggression proved technically daunting. "The whole line of research became quiescent for 20 years," Dr. Lin says.

THE FINDING SUGGESTED THAT CELLS THAT ARE EXCITED BY MATING COULD SHUT DOWN THE CELLS THAT ELICIT AGGRESSION.

LONG ROAD

Dr. Lin was educated in China, where she attended the best high school in Shanghai. After completing an undergraduate degree in biology, she came to the United States to pursue her interest in the brain. At Duke University she studied olfaction, a sense that's actually tied to aggression. "Rodents rely on smell to recognize their opponents—or their mates," she explains. Her thesis on how olfactory neurons encode information earned the budding researcher her first *Nature* paper. As a postdoctoral fellow, she wanted to study something "more behavioral." Aggression and mating seemed a natural choice.

At the California Institute of Technology, Dr. Lin and her mentor, David Anderson, homed in on the hypothalamus. They wanted to identify the specific cells that perk up during an aggressive encounter in mice. They tracked the activity of a gene that turns on when a neuron is excited, showing that these cells are located in a discrete area of the ventromedial hypothalamus called VMHvl. Interestingly, cells in that region of the hypothalamus are also active when the animals mate. "If I showed you two pictures of a mouse brain and asked you to tell me which one was taken after fighting and which after mating, it would be very difficult," Dr. Lin says.

To explore this relationship between love and rage at the cellular level, the researchers inserted electrodes into individual aggression cells in a mouse's ventromedial hypothalamus (VMH) and monitored their activity. When the animal faced a foe, these cells chattered excitedly. But when the researchers removed the adversary and introduced an attractive female, the fighting cells fell silent. Dr. Lin, who joined NYU School of Medicine in November 2010, says, "I was surprised that the result was so dramatic." The finding suggested that cells that are excited by mating could shut down the cells that elicit aggression.

A light sensitive protein called channelrhodopsin in photosynthetic green algae responds to blue light by moving ions through channels in the eyespot membrane of the algae. Dr. Lin inserted a piece of DNA that encodes for the protein into cells in the ventromedial hypothalamus (VMHvl) of mice. Activating the cells with blue light opened sodium and calcium channels in their membranes, allowing ions to rush in and triggering aggressive behavior in the mice.

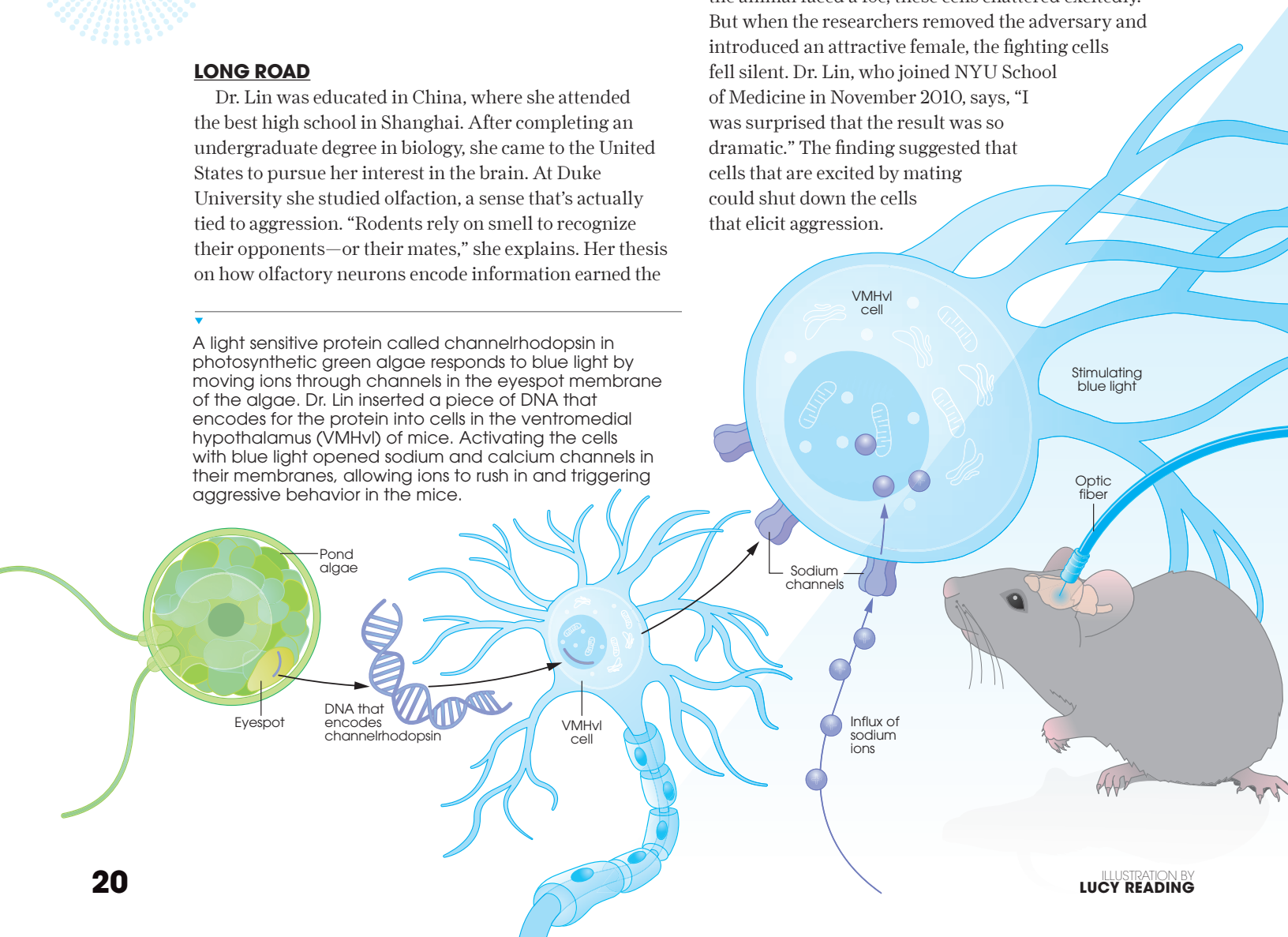


ILLUSTRATION BY **LUCY READING**

OFF AND ON

Although the aggression cells in the VMH were active during a fight, Drs. Lin and Anderson did not know whether they could actually instigate behavior. To find out, they reached into the toolkit of molecular biology.

All cells have in their membrane proteins that act as private passageways through which small molecules can move into and out of the cell. In neurons these channels are responsible for promoting—or inhibiting—cell activation. Channels that allow negatively charged chloride ions to flow into the neuron tend to turn it off; those that allow positively charged sodium to rush in, turn it on.

The researchers used a virus to ferry a specially formulated chloride channel into cells in the VMH. When they shut down the fighting cells (by activating these channels), they produced substantially subdued mice. "It took the animals much longer to initiate a fight, and many did not fight at all," Dr. Lin says.

So, if quieting the cells in the VMH reduces aggression, would simply turning them on be enough to precipitate an attack? To address that question, the researchers turned to optogenetics, a powerful new technique that allows scientists to control the activity of select cells in living animals with exquisite precision, simply by exposing the cells to a beam of blue light. The method involves introducing a light-sensitive sodium channel, purified from photosynthetic green algae, into the cells of interest—in this instance, the neurons controlling aggression. A fiber-optic cable implanted into the VMH then serves as a remote control that allows the team to activate these doctored cells with the flip of a switch.

By flashing the fighting cells with a pulse of blue light, Dr. Lin discovered she could launch an assault even when the other animal in the cage was a mate. "The mouse would go from mounting the female to immediately attacking her," she says. The target of the attack did not even have to be an animal. When Dr. Lin threw the switch, the mouse even mauled an inflated rubber glove, which was "better than my hand," she says, laughing.

Using this revolutionary technique to provoke an attack in a living animal "is something no one has ever done before," says neuroscientist Klaus Miczek, who studies mouse aggression at Tufts University. "It's really quite a remarkable accomplishment," he notes. Dr. Lin published her findings last year in *Nature*.

UNDER CONTROL

In her lab at NYU School of Medicine, Dr. Lin is now applying this illuminating method to map out the rest of the brain's aggression circuitry—tracing, for example, where the signal to fight goes once it leaves the middle of the VMH. More important, she hopes to determine how aggressive behavior can be brought under control. A primary area of focus is the prefrontal cortex. In humans this brain region, which sits just behind the eyes, plays a major role in both generating and controlling emotions.

Dr. Lin has found that flashing the prefrontal cortex with a bit of light can prompt a mouse to abandon an attack and keep him from initiating any further aggression. "We see this very reproducibly," she says, "and we're really trying to figure out how this is being achieved." By determining exactly which cells can suppress aggression and what makes these cells unique, it might be possible to target them with a drug to control violence in people.

"As a clinician, it gives me a different perspective when I can look at a patient and think that there's a specific part of his brain where there's a problem," says Stephen Trevick, MD, a resident in neurology and psychiatry who volunteers in Dr. Lin's lab. Approaching psychiatric illness from multiple directions—the cells as well as the psyche—"makes you a better doctor," he says.

Dr. Lin acknowledges that translating her findings to the bedside is a daunting task. "So I think my research will keep me busy for quite a while."●

MAMA BEAR

For the most part, it's male mice that show aggression, particularly when defending their territory. But there are times when female mice, too, can be fierce. "When they're protecting their young, females will attack an intruder," Dr. Lin observes. She wants to know why.

One interesting observation is that the region of the brain harboring the cells that drive aggression is sexually dimorphic. "It's bigger in males than it is in females," Dr. Lin says. And the appearance of the cells themselves changes during pregnancy. "So it's conceivable that something happens to that region during pregnancy that causes females to behave dramatically different toward intruders."

A likely agent is hormones, and indeed Dr. Lin is finding that it is not possible to induce an attack in a female mouse by stimulating the VMH—unless the animal is lactating. "That's a very preliminary result, and we're trying to test more animals to see if we find it consistently." In the meantime, exploring the affect of hormones on these cells is a first step toward showing how an adaptable aggression circuit can turn a mother mouse into a mama bear.

The Wizard

The director of the recently established Neuroscience Institute at NYU Langone Medical Center aims to help bridge the gap between basic and clinical research.

Dr. Richard Tsien

RICHARD W. TSIEN, DPHIL, was born in China and grew up in New York City, where his parents settled in 1947. Raised during the Sputnik era, he developed an interest in science early in life. After receiving bachelor's and master's degrees in electrical engineering from the Massachusetts Institute of Technology, he won a Rhodes scholarship to attend Oxford University. He had intended to study physics and political science, but a friend persuaded him to consider the brain and other excitable tissues, and he earned a doctorate in biophysics.

One of the world's leading neuroscientists, Dr. Tsien has devoted his career to understanding signaling within the brain and the heart; he is best known for his studies of calcium channels, which drive a multitude of critical processes in the body. He has most recently turned his attention to using mice to study a human mutation that generates a rare form of autism called Timothy syndrome. An admirer once characterized one of his published studies as "yet another fine brew from the wizard's cauldron in the Tsien lab."

Dr. Tsien returned to his childhood home after illustrious careers at Stanford University and Yale University, and today is the Druckenmiller Professor of Neuroscience, chair of the Department of Physiology and Neuroscience, and director of the Neuroscience Institute at NYU Langone Medical Center, launched with an extraordinary $100 million gift from Fiona and Stanley Druckenmiller. During a conversation with *NYU Physician*, Dr. Tsien spoke about his scientific journey and the future of the Neuroscience Institute.

PHOTOGRAPH BY **SASHA NIALLA**

How did you get started in your career as a neuroscientist?

The brain always amazed me but I took the scenic route to becoming a brain scientist. At Oxford I started out by studying the cardiac impulse, and in Denis Noble's lab worked on the heart rhythm and how it was regulated by neurotransmitters like epinephrine. We discovered new classes of ion channels—proteins that allow ions, or charged particles, to flow into and out of cells—that regulate the heartbeat and that go awry in arrhythmias. Later, at Yale, my group went on to study ion channels selective for calcium ions. These are vital for triggering many critical processes in the body—muscle contraction, neurotransmitter release, hormonal secretion, and signaling to the nucleus for control of gene expression. We became experts on these types of calcium channels in the heart, and that led to studying novel calcium channels in the nervous system. This, in turn, led to studying neurotransmitter communication in the brain that was regulated by the calcium channels and then to focusing on learning and memory.

What attracted you to NYU Langone?

I was ready for a challenge, and when weighing my options, it was clear to me that NYU Langone had the greatest ambition and potential. I found the challenge of taking on a job that involved interactions with hundreds of people across multiple disciplines to be extremely enticing. Science in general, and neuroscience in particular, offers an absolutely wondrous chance for discovery and the potential for greater understanding of the human condition. So I'm happy to be working in the lab to explore the brain at the network and system level, while also working with the NYU community to make the Neuroscience Institute world-class.

We aim to create an institute where scientists are performing innovative science and working to overcome roadblocks that delay or prevent the translation of basic science into clinical applications. We strive to make the breakthroughs that will push the field forward.

"NYU Langone had the greatest ambition and potential. I found the challenge of taking on a job that involved interactions with hundreds of people across multiple disciplines to be extremely enticing."

What were the most important breakthroughs in neuroscience in the last five years?

One big recent breakthrough was the development of technology that gives us new tools to do cutting-edge experiments. For example, optogenetics, an invention of two of my former graduate students, Karl Deisseroth and Ed Boyden, uses light to activate brain pathways. Another former student, Alex Aravanis, was the first to use fiber-optic bundles to deliver the activating light in living animals. Their successes exemplify the joys of mentoring young scientists. Today scientists, including leading practitioners at NYU, are using optogenetics to unravel neural circuits in unprecedented ways.

Another breakthrough was the realization that many diseases aren't actually as distinct as we had originally thought. They depend on a combination of nature and nurture—in other words, genes and environment—and oftentimes the genes that support them are involved in more than one disease. In describing the genetic basis of schizophrenia, depression, and autism, for example, there is an area of common intersection, containing genes implicated in all three disorders. So a lot of diseases are distinct enough to be categorized differently based on symptoms, but some of them may share similar underlying pathology at the network level.

Other diseases, such as Alzheimer's and Parkinson's, likely involve malfunction at the level of individual neurons or even their components—so the fundamental lesion is at the level of the cell or bits of the cell. In the long run this means that the logical categorization of diseases may not be between what neurologists and psychiatrists currently see as distinct states, but between what constitutes a network disease or a cell biological disease. The challenge is to orchestrate a coordinated effort at multiple levels, cutting across the traditional boundaries of medical school departments.

What are brain networks?

A network could be an ensemble of neurons with a specific task. Consider a sports analogy: The network is the whole team, but it may be broken down into groups of players. In the nervous system, various functional groupings may include the division between excitatory neurons or inhibitory neurons, and their sometimes opposing and sometimes synergistic effects. There are persuasive theories that an imbalance of excitatory and inhibitory transmission may contribute to schizophrenia, autism, epilepsy, and other diseases.

Would treatments differ based on whether the disease is considered network or cellular?

The hope is that appropriate disease classification will lead to more rational use of potential treatments. But we should keep in mind that the agents we use often don't go specifically to the brain region or neuron that generates the disease. The disease may cause *(Continued on page 25)*

Dr. Gourevitch Named Chair of New Department of Population Health

MARC GOUREVITCH, MD, MPH, the Adolph and Margaret Berger Professor of Medicine, has been appointed to lead a pioneering new department at NYU Langone Medical Center, the Department of Population Health. As founding and current chair of the Division of General Internal Medicine in the Department of Medicine, Dr. Gourevitch is widely recognized for integrating public health research with investigations into how most effectively to meet the complex medical needs of diverse population groups.

Population health is an emerging science focused on promoting health, preventing disease, and more effectively

managing illness across entire populations, whether ethnic groups, residents of a specific area, patients within a particular hospital or health system, or those with a specific disease that afflicts millions. The Department of Population Health will integrate research and training, bringing together investigators in epidemiology, biostatistics, health policy, prevention, and related disciplines to advance the science of improving human health at the population level. "If you want ... to solve the challenge of advancing the health of populations in this century and in this environment," Dr. Gourevitch says, "you need to bring to bear solutions and perspectives that bridge disciplines." A graduate of Harvard Medical School, Dr. Gourevitch completed his residency at NYU School of Medicine in primary care/internal medicine, followed by a fellowship at Montefiore Medical Center/ Albert Einstein College of Medicine, and earned a master's degree in public health with a concentration in epidemiology from Columbia University.

As director of the Division of General Internal Medicine, Dr. Gourevitch helped cultivate a talented corps of investigators. Now, leading a multidisciplinary group recruited from NYU Langone and other institutions, Dr. Gourevitch says the department "will allow us to merge our strengths across many disciplines and serve as a leader in optimizing the impact of healthcare and policy at the population level." ●

DR. CAPLAN TO HEAD NEW DIVISION OF MEDICAL ETHICS

ARTHUR CAPLAN, PHD, HAS been appointed director of the new Division of Medical Ethics in the Department of Population Health, and he will officially join the faculty on July 1, 2012. A renowned bioethicist, Dr. Caplan built the University of Pennsylvania's Center for Bioethics into one of the premier programs of its kind in the world, and he chaired the Department of Medical Ethics from 2002 through 2009. He is the Sidney D. Caplan Professor of Bioethics at the University of Pennsylvania Perelman School of Medicine, professor of medicine, philosophy, and psychiatry at the University of Pennsylvania, and a senior fellow of its Leonard Davis Institute of Health Economics.

Prior to joining the University of Pennsylvania in 1994, Dr. Caplan taught at the University of Minnesota, the University of Pittsburgh, and Columbia University. He was the associate director of the Hastings Center from 1984 through 1987.

A prolific author and editor, Dr. Caplan is a fellow of the Hastings Center, the New York Academy of Medicine, the College of Physicians of Philadelphia, the American College of Legal Medicine, and the American Association for the Advancement of Science. He has also served as a member of many special committees and panels, including the Presidential Advisory Committee on Gulf War Illnesses.

In his new position, Dr. Caplan will play a fundamental role incorporating a strong bioethical framework into global health initiatives at NYU Langone Medical Center and New York University, says Robert I. Grossman, MD, Dean and CEO of NYU Langone Medical Center. "Dr. Caplan's extensive experience in and passion for medical ethics will be invaluable," says Dr. Grossman. ●

PHOTOGRAPH OF DR. GOUREVITCH AND DR. NIXON BY BEN SCOTT

Dr. Nixon and Colleagues Awarded $10 Million Grant

A TEAM OF SCIENTISTS LED BY Ralph Nixon, MD, PhD, professor of psychiatry and cell biology, has received a $10 million NIH grant to explore a new theory of how Alzheimer's disease starts in the brain. The theory puts defects in a protein-disposal system at the top of the cascade of problems that leads to Alzheimer's dementia. The new grant is the third and largest in a series that began in 2002 and will fund the early development of drugs that can boost this system.

"Our view represents a paradigm shift from what has been the prevailing view of the origin of Alzheimer's," says Dr. Nixon, who directs the Comprehensive Center on Brain Aging and the Silberstein Alzheimer's Institute at NYU Langone Medical Center, as well as the Center for Dementia Research at the Nathan S. Kline Institute for Psychiatric Research in Orangeburg, New York. He was recently named chair of the Alzheimer's Association Medical and Scientific Advisory Council and was appointed to the association's national board of directors.

The prevailing view focuses on amyloid beta, a small protein that aggregates in the brain, starting in the early stages of the disease. Dr. Nixon and his colleagues have found evidence that the protein clumps typically appear only after damage to a waste disposal system in brain cells involving endosomes and lysosomes. Endosomes are bubble-like structures within a cell that draw in proteins or other material from the cell's outer membrane. If the material is useful, endosomes deliver it back to the cell surface or to internal transport networks. If the material is unwanted, endosomes take it for disposal within acid- and enzyme-filled sacs in the cell called lysosomes.

This waste-removal system is especially important for the health of neurons, most of which are meant to function for a lifetime. Amyloid beta and other protein aggregates can clog and damage this system, but Dr. Nixon's work suggests

that this damage often originates from other factors, and only then leads to protein aggregation.

"There are multiple risk factors for Alzheimer's, and it now appears that most of them cause defects to the endosomal-lysosomal system in one way or another," Dr. Nixon says. "A key point is that these defects can harm neurons independently of any toxicity from amyloid beta aggregates."

Among his collaborators are Efrat Levy, associate professor of psychiatry and pharmacology, Paul Mathews, PhD, assistant professor of psychiatry, and Stephen Ginsberg, PhD, associate professor of psychiatry and physiology and neuroscience. ●

Continued from page 23
(Faculty Conversation with Dr. Tsien)

a series of downstream effects, and one could intervene at any number of steps. It isn't about repairing the specific genetic alteration but changing the biochemical or physiological pathway that the disease modifies. Thus, it is conceivable that some therapies may act at a network level to ameliorate a disease of cell biological origin.

How much of the brain do we understand?

Our understanding now is pretty crude, so the opportunities for exploration and discovery are endless. We certainly know what some of the regions of the brain do in broad strokes. But we don't understand nearly well enough how these functions originate from the network behavior of individual neurons or classes of neurons. Lack of clarity about the organization of brain networks is one reason why it has been so hard to find treatments.

What are your plans for the Neuroscience Institute at NYU Langone?

It will take roughly three years for our ultimate home, the new Science Building, to be built, right near the heart of the Medical Center and hospital. Meanwhile we will be moving to the ninth floor of the Alexandria Center for Life Science. I'm looking forward to having my colleague from Rutgers, György Buzsáki, join me there. Dr. Buzsáki is an internationally renowned neuroscientist and the author of the book, *Rhythms of the Brain*. We will join forces with Gordon Fishell, currently director of the Smilow Neuroscience Program and an expert on inhibitory neurons, who will become the associate director of the new Institute. Ultimately, we hope to have 30 faculty members in the new Science Building, and many more in the Institute, which will function both as physical entity and as an organization without walls.

We aren't here to compete with drug companies or tell our talented clinical brethren how to practice their hard-earned skills. But I know that basic scientists can help clinicians understand the disorders we treat here at NYU Langone and that we can work together toward an amelioration of the brain diseases that so profoundly affect the human condition. Ultimately we need to understand how the brain works at a fundamental level in order to achieve this. ●

An Enduring Passion

A neuroscientist ponders how our powerful brains evolved.

BY JIM SCHNABEL

Dr. Arnold Kriegstein

ARNOLD KRIEGSTEIN (MD, PHD '77) has had a brilliant career, but it began in frustration and near failure. The year was 1973, and he was enrolled in a joint MD/PhD program at NYU School of Medicine and NYU Graduate School of Arts and Science. He had planned to become a neuroscientist, and his thesis adviser was Eric Kandel, MD ('56), the future Nobel Prize winner.

For his PhD project, he wanted to detail the neural development of *Aplysia californica*, a two-foot-long, burgundy-ink-spewing sea slug prized for its supersize, easily studied neurons. Yet for nearly a year he had been working in a laboratory in Woods Hole, Massachusetts, trying to grow *Aplysia* in saltwater aquariums.

"The problem," recalls Dr. Kriegstein, "was that I couldn't study *Aplysia* development until I figured out how to grow them in captivity." One central mystery was the metamorphosis of *Aplysia* from a free-swimming larva to a plump adult that crawls on seaweeds and sea bottoms. Some factor triggered this transformation in the wild, but no one knew what it was, and therefore the animal had never been grown in the laboratory.

At last, one day the budding researcher had a eureka moment. He recalled that the shipments of adult *Aplysia* from the supplier in California sometimes inadvertently included larvae, which were always colored bright red but then turned greenish brown after feeding on the green-brown seaweed used in Dr. Kandel's lab. Perhaps *Aplysia* naturally fed on red seaweed and needed it to metamorphose? He called the supplier and asked him to send out every species of red seaweed he could find. "Sure enough," Dr. Kriegstein says, "one of the dozen or so red seaweeds he sent, *Laurencia pacifica*,

PHOTOGRAPH BY KIM STEELE

did the trick: the larvae settled on the branches and metamorphosed over three days." Dr. Kandel would later write in his autobiography of "Kriegstein's extraordinary in-house seminar in December, 1973, when he first described his discovery ... [that] opened up the study of development and cell culture in *Aplysia*." (The sea slug was the model for Dr. Kandel's pioneering work on learning and memory.)

AFTER HIS TRIUMPH IN APLYSIA biology, Dr. Kriegstein went on to become one of the world's best-known developmental neuroscientists. Over the past decade, especially in his current post as director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of California, San Francisco, he has also become a prominent expert on the biology of neural stem cells and a developer of future stem cell–based treatments. (Last year Dr. Kriegstein received the Solomon A. Berson Alumni Achievement Award in basic science from NYU School of Medicine.) He and his collaborators recently developed methods to turn stem cells into potentially therapeutic adult brain cells called inhibitory interneurons and are now testing them in animal models of epilepsy.

"He is one of those rare scientists who have succeeded in breaking new ground in whatever field he has entered," says Gordon Fishell, PhD, a developmental neurobiologist and professor of cell biology at the NYU School of Medicine.

DR. KRIEGSTEIN IS THE CHILD OF concentration camp survivors. Born in 1949, he spent his early years in a small German town near the border of the former Czechoslovakia. His family eventually obtained United States visas, and they settled among relatives in New York City. Dr. Kriegstein's father, who had founded a profitable bus line during his few years in Germany, set up a jewelry factory.

Growing up in Manhattan, Arnold and his identical twin brother, Henry, found that they had an affinity for science and technology. "We built models together, we did science projects together, and we constantly reinforced each other's interests," Dr. Kriegstein says. They were remarkably studious and serious. While still only in junior high school, in Teaneck, New Jersey, where the family had moved in the late 1950s, the two boys decided that they would become biologists or doctors, or both. By their early college years—Arnold at Yale, Henry at Harvard—they had resolved to pursue MD/PhD degrees.

As a student at NYU School of Medicine, Arnold determined that he wanted to research neural development, an especially challenging area of neuroscience, and he has continued working in that area up to the present.

"He is one of those rare scientists who have succeeded in breaking new ground in whatever field he has entered."

Henry went to Stanford for his MD/PhD, opting in the end for a career in ophthalmological microsurgery. He made his own mark on science however as an amateur fossil hunter and collector. *Raptorex kriegsteini*, a small tyrannosaurus-like species, bears the family name.

The brothers also share a rare passion for naval history and since their student days have collected antique model ships from the 1600s and early 1700s, many of them crafted by the same shipbuilders who put together the full-size vessels. In a foreword to their book showcasing the collection, Simon Stephens, curator of ship models at the National Maritime Museum in Greenwich, England, praises their "meticulous research," which has "clearly added to a rather scarce surviving knowledge about ships models from the 17th and 18th centuries."

It seems that enduring love of knowledge is stamped on the Kriegstein character. "The two of us," Henry says, "have always been curious about how things work, how things happen, where things come from."

INDEED THE BIGGEST QUESTIONS THAT motivate Dr. Kriegstein concern the origins of the human brain. How does it grow in all its complexity from an initial clump of embryonic cells? How did it evolve to its present size and sophistication from the more ancient nervous systems seen in small mammals and reptiles?

These questions have informed his research throughout his career. At Stanford University in the 1980s, Dr. Kriegstein studied the ancient archicortex of turtles, which shares features with the human seahorse-shaped hippocampus. By the time he was at Yale University in the 1990s, he had switched to the more modern mammalian cortex of rodents. In 2001, while at Columbia University, he and his colleagues published in *Nature* a much-cited finding concerning radial glial (RG) cells in the embryonic mammalian brain. RG cells had been known to guide the migration of baby neurons in a radial direction from the ventricles of the brain, so that they line up in layered columns. Dr. Kriegstein's group showed that RG cells are in fact stem cells and don't merely guide baby neurons, they give birth to them. "This was a seminal paper that after more than

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Publish vs. Perish

An unprecedented request by the U.S. government stirs controversy.

BY BRYN NELSON

Dr. Linda Miller

IN DECEMBER THE NATIONAL SCIENCE ADVISORY Board for Biosecurity (NSABB), overseen by the National Institutes of Health, recommended that new research on a potentially pandemic strain of avian influenza not be published in full, for fear that such information could potentially aid bioterrorists.* The research identified mutations that might allow the bird flu virus to spread more easily from person to person through coughing or sneezing. The eventual goal is to provide early warning of an impending outbreak and to identify targets for better medical interventions, but some critics have questioned whether the research should have been conducted at all. In February the World Health Organization (WHO) weighed in on the debate and advocated full disclosure of the research upon publication. Linda Miller, PhD, formerly executive editor of *Nature* and now NYU Langone Medical Center's associate dean for basic science and associate professor of pathology, brings a unique perspective to this discussion. Dr. Miller recently spoke with *NYU Physician* about the struggle to balance the free flow of scientific information with the risks such freedom entails.

What's the importance of this bird flu research? Should it have been done at all?

Nature has provided us with a very clever organism that has always found ways, it seems, to infect whatever it wants to infect. Flu has been around for a while. To say that we should not have been looking into what accounts for its most virulent strains or what makes them more transmissible, is to say that we shouldn't learn everything about it or that we shouldn't develop all of the most effective tools to fight it.

What do you think about the recommendation not to publish all of the research details?

I disagree with it, actually. The NSABB's job is to weigh risks versus benefits. But my problem with a decision that says, "You can publish this, but you can't publish all of the details" is, who are we keeping the details from? It's been presented at a public meeting. The advisory board is trying to make sure that the information, if it's not published, would be disseminated to the "right" people. But flu is a big field. Who would the right people be? A free flow of information has the highest chance of yielding a vaccine or something else that might prevent a virus with these particular mutations from gaining a foothold, even if it came about naturally. My other problem with the decision is that it flies in the face of the agreement made with the journals in 2003 to self-police, on condition that they continue to publish papers that have enough information so they can be verified.

So by restricting access to the information, you could be denying scientists the data needed to make a real advance in combating one of these very deadly viruses?

Right. And biology is so complex that you never know all the ramifications of the information you have. Putting this information with another piece of information may give you a totally surprising result about the life of the virus or its transmissibility or the body's reaction to it.

*Editor's note: In April the NSABB reversed itself and recommended publishing the research in full. The advisory board said the new manuscripts showed the research wasn't as dangerous as it originally appeared.

PHOTOGRAPH BY **JOHN ABBOTT**

Do you see this as a dangerous precedent?

This is the first time the NSABB has weighed in on a biological question and recommended not to publish the results. Setting the precedent makes it easier to do something similar in the future, and that concerns me. Scientific information has a way of wriggling free. But even more worrying is the chilling effect this could have on the quality of infectious disease researchers in the future. Why not work in other, freer areas?

How does the WHO's conclusion affect the current debate?

The WHO committee examined the two papers and decided that publication of a redacted version is unlikely to prevent dissemination of the information–so basically they agreed with my instinctual response. But it's not over till it's over! The papers will not be immediately published. Instead, the journals are likely to wait for some international agreement on the extent of the safety precautions needed when working with such agents, for the safety of both the public and those performing the experiments.

Now that it is more likely that the full papers will be published, how concerned are you about "garage biologists"?

Frankly, synthetic biology that takes place in settings that lack accountability concerns me. Proponents of synthetic biology envision a warehouse of synthetic, biologically active genetic components that can be mixed and matched as easily as the switches and resistors in RadioShack. But all the safety regulations and precautions in the world don't help if one can eventually alter infectious agents in your backyard lab, with your armpits as your 37-degree incubator and some spinning tire-swing as your centrifuge. Still, creating a new virus isn't easy, and most viruses can grow in only a few cell types, making

the process dependent on old-fashioned cell culture, which can be as much art as science. But I am all for a good national and international dialogue about the merits of synthetic biology, which has already begun. This was an interesting topic of discussion last year at an NSABB-sponsored biosecurity webcast, which I participated in as a panelist.

As gatekeepers of information, what role should scientific journals play in guarding against the potential misuse of scientific research?

Editors really do feel that they're helping scientists by using peer review and editorial judgment to help select the best research for their pages. They guard the process, so this is a kind of responsibility that comes with the territory. But why wait until the very last step in a process to do something as serious as assess security? If there were a strong possibility that some research could produce results that pose a security risk, decisions should be made way upstream, by funders, and at institutional biosafety committee reviews, rather than after the results are already in and someone has submitted a paper. That's way too late. Once you fund it, you should be able to publish it.

Is there a global solution?

Complete transparency, perhaps, because you can't control the international flow of information for long anymore. But along with that we need a globally consistent, fact-based understanding on the appropriate and safe way to conduct hazardous infectious agent research. ●

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a century of controversy unequivocally identified the RG cell as the stem cell population that makes the mammalian brain," Dr. Fishell says.

Dr. Kriegstein later turned to the study of the human cortex, in part to tackle the perennial question: how did it get so big, compared to those of mice or monkeys? His team soon zeroed in on a class of RG-derived cells, which they dubbed oRG

> "The science of development is the foundation of stem cell medicine."

cells, that flourish in a region relatively far from the ventricles and seem to be particularly active in producing cortical neurons while the brain is expanding most rapidly. Last year they reported that oRG-like cells are also found in mice but are much less prolific there. Thus, the human cortex, he speculated, may owe much of its bulk and power to relatively simple mutations that boosted the fecundity of oRG cells. "We think that this key element of the human cortex was already evolved 300 million years ago and then became amplified in the lineages that led to primates and humans," Dr. Kriegstein says.

The intricate details of highly evolved developmental programs in stem cells are precisely what scientists need to discover, if they are to turn such cells into useful therapies. "The science of development is the foundation of stem cell medicine," says Dr. Kriegstein. ●

What Pregnant Women Should Know About Their Thyroid

Low thyroid levels can affect the mother's health and her child's development.

BY AUBIN TYLER

Dr. Loren Greene and Kristen Mulvihill

IN THE FALL OF 2008, fashion and photography editor Kristen Mulvihill hadn't even unpacked from her honeymoon when her new husband, David Rohde, a *New York Times* reporter, was kidnapped by the Taliban in Afghanistan and held for more than half a year.

Within weeks of his dramatic escape and their emotional reunion in Dubai, the couple learned she was pregnant. "We'd missed 8 months or so—we wanted kids," Kristen says.

But now there were new hurdles. At 40, with an underactive thyroid, which ran in her family, Kristen knew her pregnancy needed to be closely monitored. "I'd heard of women miscarrying due to thyroid problems, and I had been worried about my ability to get pregnant." Before the 1970s, when newborns began to be routinely tested for thyroid function, a cousin of hers had been born without a thyroid gland and had developed mental delays as a result.

The first symptoms of Kristen's hypothyroidism—fatigue that went beyond being merely sleepy or tired, hoarseness, weight gain, constipation, dry hair and skin—had started a decade earlier. "I knew some of the symptoms from my mom, who was treated for hypothyroidism in her 40s," says Kristen.

On the advice of her gynecologist, Kristen sought out endocrinologist Loren Wissner Greene, MD, clinical associate professor in the Department of Medicine at NYU Langone Medical Center, who monitored her thyroid level every two weeks throughout her pregnancy, raising her dose as the pregnancy progressed.

The thyroid, a butterfly-shaped gland in the front of the neck "is a major pacemaker of many, many body functions—brain, heart

PHOTOGRAPH BY BUD GLICK

rate, blood vessel tone, bowel functions, reproduction, appetite, and weight," Dr. Greene says. Pregnancy itself increases the body's need for thyroid hormone, making hypothyroidism the most common thyroid problem in pregnancy. For women already taking thyroid hormone, as in Kristen's case, half may need a dosage increase right away, often as much as 30 percent or more.

For Kristen, the constant monitoring and dose adjustments were worth it. She experienced a normal pregnancy and delivered a healthy baby girl, Ella, now almost 2. During the pregnancy, the couple wrote a book about the Taliban kidnapping, *A Rope and a Prayer*, published in 2011. "Ella was due April 10, and the book was due April 1," she says, with a laugh.

At least 5 percent of Americans, mostly women, are hypothyroid, and that number rises with age, according to the National Institute of Diabetes and Digestive and Kidney Diseases. Of the 4 million births in this country each year, some 2 to 2.5 percent of moms—or 100,000 women—are hypothyroid, says Susan Mandel, MD, an endocrinologist at the Perelman School of Medicine, University of Pennsylvania.

"Early on, the baby relies on mom's thyroid hormone," because the fetal thyroid doesn't kick in until the 12th week of pregnancy, says Dr. Mandel. "Increased dosage needs can start at the six or seventh week of pregnancy, often before the first obstetrician visit."

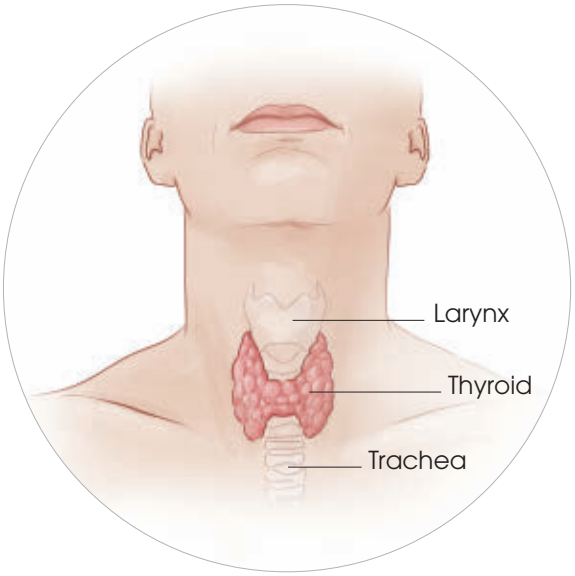
Inadequate levels of thyroid hormone in the fetus can result in poor neural and cognitive development, even mental retardation, if not treated in the first month of life. For the mother, the two most serious consequences are preterm delivery and pregnancy-induced hypertension.

Even after the fetal thyroid begins to function, the fetus still depends on the mother's intake of iodine to make the thyroid hormones thyroxine, or T4, an amino acid core surrounded by four iodine atoms, and triiodothyronine, or T3, with three iodine atoms.

In the United States, as of 2009, only half of prenatal vitamins contained iodine, and their measured content was only 75 percent of their labeled content. The World Health Organization recommends 250 mcg daily, some of which is obtained through diet. For pregnant women, supplementing the diet with 150 mcg of potassium iodide daily is important. "Any woman who's pregnant needs that," Dr. Mandel says.

Postpartum thyroiditis is another common thyroid condition in pregnancy, affecting 4 to 10 percent of pregnant women. It has been linked to postpartum depression. The cause is unknown.

Margaret Gould, 36, a school guidance counselor, had no history of thyroid disease when, after her second child was born in the spring of 2011, she rapidly lost 25 pounds. "I lost the weight so fast—in just a few weeks—I was below my prepregnancy weight," she says. Already anxious and exhausted after the birth, she noticed that her hair started falling out as soon as she stopped breastfeeding. "In the first phase of the illness, the thyroid gland just pours out thyroid hormone, which explains the rapid weight loss," says Dr. Greene. "The second phase—hypothyroidism—



starts a month or so after delivery." Most women regain normal thyroid function within a year after giving birth, though the condition tends to recur with subsequent pregnancies.

Today, Margaret takes thyroid hormone and has her thyroid function tested regularly. "I feel better. I'm still tired, and I've been have trouble sleeping, but it's hard to tease out whether it's the thyroid or having two kids under 4," she says. Her new baby, now 9 months, is "amazingly" healthy, she says. "He's crawling and getting up on his knees. He looks like the Gerber baby."

Ilona Shpayzman, 30, a Brooklyn speech pathologist, became hypothyroid after her thyroid was surgically removed because of a cancerous tumor. Doctors told her it was most likely caused by exposure to nuclear radiation in her native Belarus after the Chernobyl disaster in 1986, when she was 4.

A year ago, with the help of thyroid hormone replacement and careful monitoring by Dr. Greene, Ilona and her husband had a healthy baby boy, their first child. "I live checkup to checkup," she says. "I stay positive and take care of myself."

Ilona's family moved to New York when she was 10. By her mid-20s, she was in graduate school, working and engaged. "I was tired all the time, but I had a lot on my plate," she says. "I just thought it was normal." One day, sitting at the kitchen table over coffee, her mother noticed a swelling at the base of her neck and insisted she get it checked.

In early 2009 surgeons removed her entire thyroid gland and then treated her with radioactive iodine, which detects and destroys residual thyroid cancer cells. Scans after the treatment showed cancer cells in her lungs. "That was probably the lowest point in my life," she says. "It knocked the wind out of me."

Six months later, Ilona had a second round of treatment. This time, the news was good. The cancer was gone. Six months after that, following her honeymoon, she learned she was pregnant. "It was a shock, but it was nice shock." ●

ILLUSTRATION: TAMI TOLPA

GOODWIN BREININ, MD

Goodwin "Dud" Breinin, MD, professor emeritus of ophthalmology and the longest serving chair in the history of that department, died peacefully at home on December 14, 2011, at the age of 93.

Wry and engaging, Dr. Breinin was an erudite philosophy buff who peppered his speech with Greek and Latin. In a eulogy delivered at his funeral, Norman Charles, MD, clinical professor of pathology and ophthalmology, who married Dr. Breinin's niece, Barbara, referred to his mentor as "The Iron Man" for his strength and courage in the face of his 10-year battle with malignant melanoma. As Dr. Breinin put it, "I have started chemo—which is an interesting experience. I am exchanging heated words with the Demiurge. Actually it's one-way—he doesn't choose to debate." After losing his hearing, he read all the novels of Trollope, Eliot, Dickens, and Hardy.

Dr. Breinin earned his medical degree at Emory University and served in the Army for two years during World War II. In 1947 he entered the ophthalmology residency program at NYU School of Medicine, choosing to focus on ocular motility because he felt it to be the most difficult and challenging of the subspecialties. He joined the faculty in 1951 as an instructor and in 1956 became the Daniel B. Kirby Professor of Ophthalmology, a position he held for 50 years.

Dr. Goodwin Breinin

Early in his career, Dr. Breinin became a leading researcher in the field of ocular physiology, pioneering the use of electromyography to study the neurophysiology of strabismus (muscle imbalance) in children and adults. For his work, he was awarded the American Medical Association Knapp Medal for Contributions to Ophthalmology in 1957.

Dr. Breinin served for 41 years, from 1959 to 2000, as chair of the Department of Ophthalmology. He sought to integrate clinical and basic sciences, leading a prominent group of investigators to produce landmark discoveries in muscle research, retinal physiology, and ophthalmic pathology. As part of his administrative duties, Dr. Breinin was director of the Eye Service at University Hospital (now Tisch Hospital) and Bellevue Medical Center, as well as the chief ophthalmologic consultant to the Manhattan VA Hospital.

During his career, Dr. Breinin served on the board of directors of the American Board of Ophthalmology and chaired the ophthalmology sections of the American Medical Association and the New York Academy of Medicine. He authored or co-authored several books and over 100 articles, including *The Electrophysiology of Extraocular Muscle* (1962), a monograph published by the American Ophthalmological Society, which remains a primer on ocular electromyography today. In 1993 he was awarded the Emory Medal, the highest distinction conferred by Emory University, for his lifetime achievements in medicine and contributions to the university.

Upon his retirement in 2006, Dr. Breinin's patients, friends, and faculty colleagues endowed a visiting professorship at NYU School of Medicine in his honor. As professor emeritus, Dr. Breinin continued teaching and maintained his research lab.

Dr. Breinin's wife of 58 years, art historian Rose Helen Breinin, died in 2005. He is survived by a son, Bartley Breinin, and daughter-in-law Rachel Breinin; a daughter, Constance Paton, and son-in-law Nigel Paton; and four grandchildren. ●

—AUBIN TYLER

JOHN M. STEWART

Longtime NYU Langone Medical Center trustee John Stewart passed away peacefully at his home in New York on May 19, 2011, at the age of 79.

For more than 10 years, Mr. Stewart served on the Medical Center's Patient Care and Quality Assurance Operations Committee, contributing his astute knowledge of the broader context of organization-wide performance improvement, gleaned from a nearly 40-year career with McKinsey & Company.

"Helping with institutional change and solving complex organizational problems was one of John's great interests, so working with NYU Langone was a very good fit for him," recalls his wife, Eliot Stewart. "The more complex it was, the better John liked it. He found it extraordinarily rewarding to take on the challenge of trying to solve some of the major problems confronting health care and hospitals today."

Prior to joining McKinsey in 1961, Mr. Stewart served in the U.S. Navy from 1953–1955 and worked as a program manager for TRW's Saturn missile project. He also served on the Defense Science Board, Yale University Council, National Council on Economic Education, and as executive director of the U.S. National Commission on Productivity. In recent years, he also served on the board of trustees of the Woods Hole Oceanographic Institute and consulted with a Gates Foundation initiative to reduce HIV/AIDS in India.

John Stewart

In addition to his wife, Eliot, Mr. Stewart is survived by their four children: Diane Stewart, Sandi Stewart, Ian Highet, and Eliot Patty; and nine grandchildren. ●

—GINA SHAW

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