

weillcornellmedicine

FALL/WINTER 2006

THE MAGAZINE OF THE JOAN AND SANFORD I. WEILL MEDICAL COLLEGE AND GRADUATE SCHOOL OF MEDICAL SCIENCES OF CORNELL UNIVERSITY

Special Issue

From Bench to Bedside

Breakthroughs by Weill
Cornell researchers
promise to transform
health care

From the Big Apple to the Big Red

Research and collaboration to be the focus of a new \$4 billion capital campaign

In the presence of New York City Mayor Michael Bloomberg, Peter C. Meinig, chairman of the Board of Trustees of Cornell University, and Sanford I. Weill, chairman of the Board of Overseers of Weill Cornell Medical College, Cornell University President David J. Skorton announced on October 26 that the university and its Weill Cornell Medical College are launching a \$4 billion capital campaign—the largest for Cornell, New York’s land grant university, and the second largest goal in the history of higher education—to advance education, discovery, and public service, and to make transformative contributions in areas of critical social importance.

The comprehensive campaign will raise in excess of \$4 billion to support undergraduate and graduate students, with a focus on increasing scholarship support and financial aid; recruiting the next generation of faculty, scientists, and scholars; and by renewing and building state-of-the-art facilities best suited for twenty-first century teaching, learning, and research, across the University’s campuses.

“The impact of this campaign on higher education and research will be felt across the State of New York and across the world,” said Mr. Weill. “It is my belief that one day, the translational research conducted by doctors at Weill Cornell and Cornell scientists in Ithaca will help to eradicate some of the world’s most daunting and debilitating health threats while improving the quality of life for all. Our goal is to speed research discoveries from the bench to the bedside, where they can improve the quality of care and the quality of life for patients here in the city, across the nation, and around the world.”

A hallmark of the new campaign is the expansion of collaboration between Cornell’s Ithaca and New York City campuses, which encompasses areas such as biomedical

engineering; cancer-related cell biology; nano-medicine; chemical biology and experimental therapeutics; and global health and infectious diseases—all in the service of improving health and saving lives. In fact, a shared pool of campaign funding will be earmarked specifically for these upstate/downstate, cross-disciplinary collaborations.

“One of the most important aspects of this campaign is the commitment to expand collaborative research across disciplines and across campuses to produce life-saving advances in science and medicine,” said Dr. Antonio M. Gotto Jr., Stephen and Suzanne Weiss Dean of Weill Cornell Medical College and Provost of Medical Affairs of Cornell University. “By bridging the distance between Ithaca and Manhattan and bringing our best research minds together to develop solutions for the most daunting health issues of our time, I am confident we will unlock scientific and medical discoveries that can improve lives around the globe.”

At Weill Cornell in New York City, the campaign will fund programs such as the construction of a new \$650 million, 350,000-square-foot Biomedical Research Building in the vicinity of the Medical College. This new facility will double Weill Cornell’s existing research space, accommodating more laboratories and scientists to accelerate biomedical discoveries. The building will be designed with laboratories in an open layout to foster communication and collaboration among scientists.

The campaign will also fund new translational and clinical research programs focused on global health and infectious disease, cancer, cardiovascular and neurodegenerative disorders, diabetes and metabolic diseases, reproduction and fertility, aging, and strategic scientific methods such as stem cell and developmental biology. “We have our work cut out for us,” Mr. Weill said. “But we are poised for greatness.”

THE CAMPAIGN FOR CORNELL

DISCOVERIES THAT MAKE A DIFFERENCE
THE CAMPAIGN FOR WEILL CORNELL MEDICAL COLLEGE

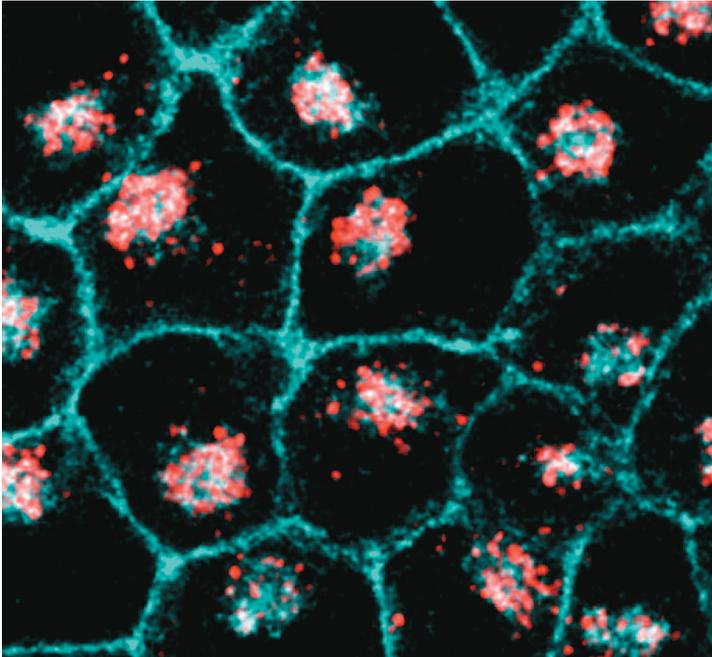


CORNELL UNIVERSITY AND ITS
WEILL CORNELL MEDICAL COLLEGE

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Special Issue



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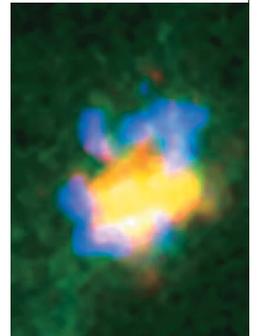
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On the cover: Acute promyelocytic leukemia cells from a patient with excessive annexin 2. (See page 34.)

A Special Message from the President of Cornell University

a N IVY LEAGUE UNIVERSITY AND THE land-grant university for the State of New York, Cornell University is known for its collaborative, interdisciplinary culture, and the breadth and depth of its research enterprise. More than ever before in its history, Cornell is drawing on the combined strength of its Weill Cornell Medical College and its Ithaca campus to improve human health through pathbreaking basic and translational research.

One of the early success stories to come from inter-campus collaboration is the development of biodegradable artificial skin for burn victims as the result of collaboration between a surgeon at Weill Cornell and a professor of textiles and apparel at the Ithaca campus. Spurred by a small grants program funded jointly by the Weill Cornell Medical College and Cornell University in Ithaca, and guided by faculty committees whose membership spans both campuses, Cornell is developing collaborations in several areas that offer exceptional promise: biomedical engineering, nanomedicine, and systems biology; multidisciplinary approaches to cancer biology; chemical biology and experimental therapeutics; and global health and infectious diseases. In addition, graduate student linkage programs are

beginning to provide opportunities for graduate students to travel between Ithaca and New York City for study and research.

Cornell's intercampus collaborations received a significant boost in October, when New York State Governor George Pataki announced a \$10 million grant from the state to benefit both the Ithaca and Weill Cornell campuses, with the intent of enabling Cornell to contribute even more substantially to the state's stature as a leader in biomedicine, biotechnology, and other dynamic high-technology fields.

As someone who has faculty appointments on both campuses, I am convinced that there are tremendous advantages to be gained through intercampus collaborative research and graduate education. I invite you to explore this issue of *Weill Cornell Medicine* to discover some of the groundbreaking research being conducted at the Medical College and the Graduate School of Medical Sciences. The collaborations among researchers on the New York City and Ithaca campuses—which are enabling Cornell to expand knowledge of life processes and to make transformative contributions to advancing health and combating disease—will be featured in an upcoming issue.

—David J. Skorton, MD



From left to right: President Skorton, Dean Gotto, Sanford Weill, and Dean Hajjar

RICHARD LOBEL

The Science of Healing

Improving the human condition through research

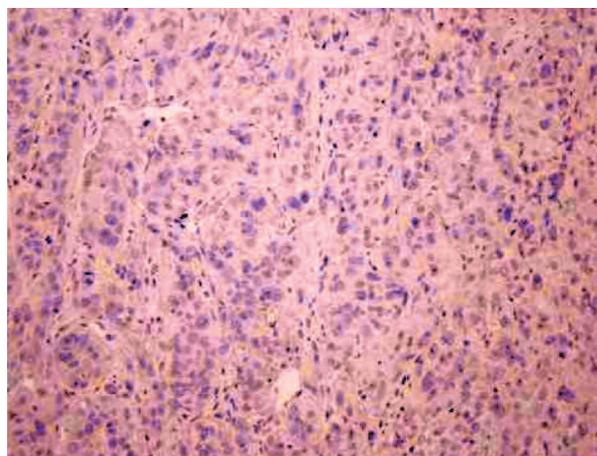
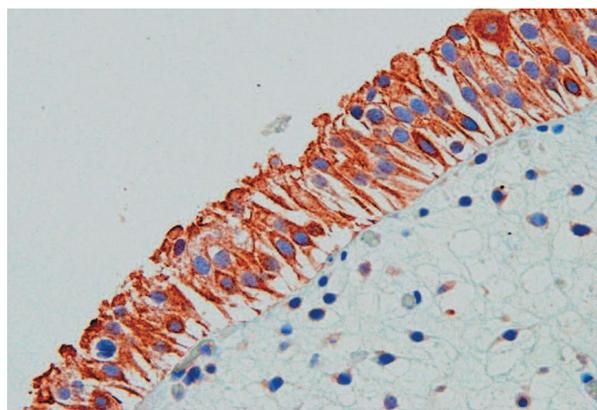
tHIS SPECIAL ISSUE OF *WEILL CORNELL MEDICINE* magazine focuses on the important and extraordinary work being done by the talented researchers and scientists in our Weill Cornell Graduate School of Medical Sciences. Led by Dean David P. Hajjar, the Graduate School now ranks as one of the top research institutions in the country. True to the Cornell spirit, our graduate students, researchers, and faculty are leaders in the advancement of the basic sciences, and thus will help shape the future of medicine and the improvement of the human condition. In the pursuit of this essential goal, we are fortunate to have the Sloan-Kettering Institute and the Rockefeller University as our neighbors and partners.

As noted by President David Skorton, a fellow physician, in his accompanying message, the call for greater intercampus collaboration between Weill Cornell Medical College and Ithaca has created an invigorating sense of new possibilities—and the year ahead promises even more exciting innovations, initiatives, and breakthroughs to deliver on our goals of unexcelled patient care, research, and education.

In order to strengthen the bridge being built between the Ithaca and the New York City campuses, we have launched a massive—and crucial—capital campaign that seeks to raise more than \$4 billion in the next five years to support the students, faculty, and facilities of Cornell University. Just over \$1 billion will go to the Medical College, including funding for a proposed research and basic science building to be built near our Upper East Side campus. Gifts to the campaign will also help us recruit the most talented and creative researchers around the world to bolster our talented faculty.

As we take the first steps in this campaign, our tripartite mission of education, research, and patient care can be seen with more clarity than ever. I am confident that the generosity of all the alumni, friends, and supporters of Weill Cornell Medical College will bear fruit in research that will benefit not only our local population but people around the world, especially those in developing nations.

Some 225 miles may separate Ithaca and New York



Battling bladder cancer: Pharmacologist Dr. Lorraine Gudas is studying the expression of an antibody called LRAT, found in a normal organ (above) but absent in an invasive tumor (below). Story on page 18.

City, but this will not deter us from building a true collaborative environment that will allow us to deliver on our promise of bringing research “from bench to bedside” as quickly as possible.

—Dean Antonio M. Gotto Jr., MD

from the bench



Dr. Claudia Henschke

MICHAEL CHRISTOPHER BROWN / NY TIMES

Leading a Revolution in Lung Cancer Detection

Early detection of tumors can increase survival rates in lung cancer patients so dramatically that it could alter the way we think about the disease, Weill Cornell researchers have reported. The article in the October 26 issue of the *New England Journal of Medicine*, which chronicled the results of a long-term study by radiology professor Dr. Claudia Henschke and colleagues, made headlines around the world, including a front-page piece in the *New York Times* and coverage on network evening newscasts. Although some have taken issue with the findings, the work could spark a revolution in the way the disease is treated—and sharply reduce its mortality rate.

Each year, about 160,000 Americans die of lung cancer, more than the death toll for colon, breast, and prostate cancers combined. Because the disease is often detected late in its progression, it presently has a five-year survival rate of just 14 percent. The study, launched by Weill Cornell researchers in 1993 and eventually comprising nearly 32,000 patients and thirty-eight institutions in seven countries, examined the effectiveness of an annual low-dose CT scan of the lungs—roughly akin to a mammogram for breast cancer prevention—as a way to detect cancers early in people at higher risk for the disease. (Most participants were smokers, former smokers, or people exposed to secondhand smoke or occupational hazards such as asbestos.) It found 484 cases of lung cancer, 412 of which

were at Stage I—the only stage at which patients have a high likelihood of a surgical cure.

The Stage I patients who declined treatment all died within five years. But those treated with surgery had a ten-year survival rate of 92 percent—a vast improvement from the odds without the scans. “We believe this study provides compelling evidence that CT screening for lung cancer offers new hope for millions of people at risk for this disease,” says Henschke, the study’s lead author and chief of NewYork-Presbyterian’s chest imaging division, “and could dramatically reverse lung cancer death rates.” The new diagnostic power is the product of technological innovations that allow the detection of much smaller tumors: although a CT scan once yielded only thirty images, current methods have increased that number to 600, and submillimeter “slicing” can now be applied to the entire chest in a single breath-hold. The scans, which are not yet considered standard and therefore unlikely to be covered by insurance, cost \$200 to \$300.

Henschke is the author of the general-interest book *Lung Cancer: Myths, Facts, Choices—And Hope*, published by W. W. Norton in 2002. In July, she made headlines with another finding: that women are almost twice as likely to develop lung cancer as men, but are also more likely to survive it. Those results, published in the *Journal of the American Medical Association* in July, were based on a study of nearly 17,000 U.S. smokers and former smokers.

Widening the Arsenal Against Bioterror

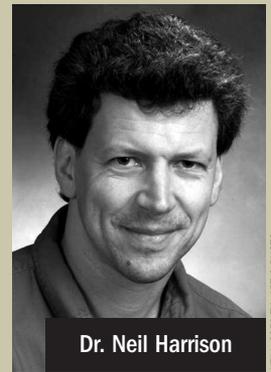
Two potential bioterror agents may become far less deadly, thanks to work by Weill Cornell virologists. Hendra and Nipah are related zoonotic viruses that can spread from their natural reservoir in fruit bats to other species, including humans. The mode of transmission remains unclear, but it's thought to be relatively easy—either via close contact with an infected host or inhalation of microscopic pathogens. Infection often leads to fatal encephalitis.

In October, Weill Cornell researchers reported in the *Journal of Virology* that, by tweaking a peptide related to parainfluenza virus, they may be able to prevent Hendra and Nipah from infecting human cells. “The goal,” says pediatrics, microbiology, and immunology professor Dr. Anne Moscona, “has been to have some kind of drug like this that could be stored at key points around the world, ready for mobilization in case of an outbreak.” Nipah first emerged among pigs, and then humans, in Southeast Asia, while Hendra was found among horses and their handlers in Australia. Both have been included as potential bioweapons on

parainfluenza, the researchers knew that the virus has a molecule known as “G” that binds to the surface of a cell and activates a special fusion protein that changes shape and helps the virus enter. They found that a specific peptide would inhibit this shape change and halt the fusion process in other viruses—similar to the function of the early HIV-suppressing drug Fuseon. “Today, HIV-positive patients typically receive a combination of drugs to keep the virus at bay,” Moscona says. “We envisage that a similar strategy might work someday against Hendra and Nipah, where doctors would use a handful of different drugs to stop infection by targeting various points in the viral life cycle.”

A Better Night's Sleep?

A drug now in Phase III clinical trials shows promise as the next generation of sleep aid, and a team of researchers thinks they've pinpointed how it works. Neuroscientists at Weill Cornell, the University of Pittsburgh, and UCLA published their findings about the drug, called gaboxadol, in the *Proceedings of the National*



Dr. Neil Harrison

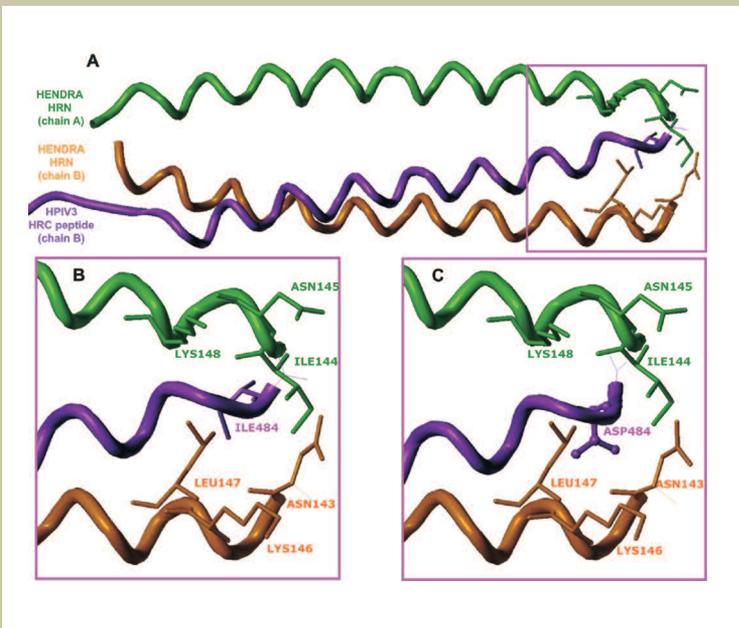
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Academy of Sciences last fall. The drug, they found, works in an entirely different way from currently popular sleep aids like Ambien or older benzodiazepine drugs such as Valium, and may be less likely to interfere with the natural ratio of REM to non-REM sleep. “Drugs like Ambien work on the alpha-1 subtype of receptors for the neurotransmitter GABA—that's akin to an ‘on/off switch’ for the central nervous system,” says Dr. Neil Harrison, professor of pharmacology in anesthesiology. “On the other hand, gaboxadol works on another subtype, called alpha-4—it's more of a ‘dimmer switch’ that might help regulate sleep in a less disruptive way.”

In studying the drug's mechanism, researchers engineered a “knockout” mouse that lacked the alpha-4 receptor; when administered gaboxadol, the mice remained awake, while their normal counterparts were sedated. In contrast to the “on/off” quality of alpha-1, the alpha-4 receptors are thought to cause specific neurons in the thalamus to fire at a slow, regular rhythm; that pattern, known as tonic inhibition, sends the brain into restful, slow-wave sleep. If the

findings are correct, it would make gaboxadol the first hypnotic to work via this mechanism, therefore mimicking natural sleep.

According to the National Sleep Foundation, nearly 60 percent of Americans have insomnia at least a few nights a week, and as many as 25 percent say they have used sleep medica-



A Case of the Flu: Dr. Anne Moscona and colleagues are using a peptide related to parainfluenza virus (purple) to foil the potentially deadly Hendra virus (green and orange) as well as its relative, Nipah.

the National Institute of Allergy and Infectious Diseases' Biodefense Research Agenda.

The breakthrough in infection-prevention draws on work by the study's lead author, assistant professor of microbiology in pediatrics Dr. Matteo Porotto. Based on his past studies of

from the bench

tions at least once in the past year. However, many sleep aids have undesirable side effects, particularly daytime grogginess. Gaboxadol, which may have fewer side effects, was originally developed in Denmark in the Seventies as an anticonvulsant for epileptics, but was rejected as too sedating; it was revived in the mid-Nineties as a possible hypnotic, or sleep aid. Although the drug is being developed and tested by Merck & Company, the study received no private funding.

DNA & Depression

Patients suffering from depression long for immediate relief—but finding the right medication is often a months-long process of trial and error. However, researchers led by psychiatrist Dr. Francis Lee may have found a genetic reason why many patients don't respond to certain drugs, and the discovery could make treating depression a more exact science.

In a paper published in *Science* in October, researchers at Weill Cornell and the Rockefeller University describe the potential basis for a diagnostic test: a variant in the gene that encodes a protein called Brain Derived Neurotropic Factor (BDNF). Patients with the variant gene would be unlikely to respond to selective serotonin reuptake inhibitors—the most commonly used class of antidepressants, which includes Prozac, Celexa, Paxil, and Zoloft.

Their experiments included work with mice engineered to have the BDNF variant. Engineered and normal mice were treated with Prozac and put in stressful settings; those without the variant demonstrated less anxiety, while the engineered mice were much less responsive to the drug.

Tallying the Costs of HIV

Total lifetime medical care for a patient with HIV will cost an average of \$618,900 under current standards, according to a study by researchers at Weill Cornell and several other institutions. In the November issue of the journal *Medical Care*, the researchers reported the results of the study, which was intended to guide future funding allocations. They found that average monthly care costs are \$2,100—70 percent of which goes to medications—with a life expectancy of 24.2 years from the time of diagnosis. “Policymakers need accurate and up-to-date predictions of the future expense of HIV treatment if they seek to ensure broad access to high-quality care,” says Bruce Schackman, chief of the Division of Health Policy and the study's lead author. “If they rely on outdated cost information, treatment programs will be underfunded and the economic value of HIV prevention will be understated.”



Dr. Francis Lee

WEILL CORNELL ART & PHOTO

The lifetime per-person cost of HIV care, the study found, is comparable to the estimated cost of care for a woman under 65 with cardiovascular disease: both have long life expectancies with correct medical management. When costs are discounted to reflect the fact that they will be covered in the future, the projected lifetime figure is actually \$385,200 in today's dollars, and the expense that can be avoided by preventing each HIV infection is \$303,100.

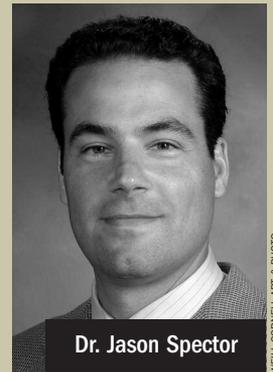
With the advent of new drug therapies, expected outcomes for HIV patients have changed radically over the past decade. In 1993, the study reports, the life expectancy for an infected adult without symptoms was just 6.8 years. The Centers for Disease Control and Prevention estimates that about 40,000 Americans become infected with HIV each year. Of the roughly 1 million HIV-positive people in the U.S., one-fourth are unaware that they are infected.

Shape Shifting

Nearly a third of American adults are obese, and 5 percent are considered morbidly so. Each year, some 170,000 of these severely overweight patients undergo gastric bypass (or bariatric) surgery. Although the operation can offer hope for people who've long struggled with their weight, it's rarely the end of the process. “Massive post-surgical weight loss leaves most patients with unsightly excess folds of skin and fat,” says assistant professor of surgery Dr. Jason Spector, “and in some ways the patient can actually look worse, not better.”

For many people, the next step is to undergo body contouring, where surgeons remove excess tissue and sculpt the physique. An emerging field, body contouring remains unfamiliar to many non-specialists—a fact that prompted Spector and two colleagues at New York University to author a paper on the subject. Their “state of the science” review was published in the November 7 issue of the *World Journal of Gastroenterology*.

In 2005, nearly 56,000 bariatric surgery patients underwent body contouring procedures—including tummy tucks, breast augmentation, and lifts of the thighs, buttocks, and arms. Spector notes that doctors typically recommend such procedures not be performed until a patient's weight has stabilized for at least three to six months. Although complications are rare, they include blood loss, clots, and abdominal hernias. “When it's over, patients generally tell us that every step along the way was more than worth it,” Spector says. “They say they feel healthier, more attractive, happier. And for us, that's the goal.”



Dr. Jason Spector

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Hope for Paralysis Patients

The discovery of a molecular “missing link” that drives nerve cell growth has brought researchers a step closer to repairing injured spinal cords. The work, reported in the October issue of *Nature Neuroscience*, concentrates on an enzyme called soluble adenylyl cyclase (sAC), which has been found to spur the growth of nerve endings in rat embryos. The research, which was funded in part by the Christopher Reeve Paralysis Foundation, could also lead to breakthroughs in the treatment of certain developmental disorders or a way to repair damage to peripheral nerves caused by diabetes.

The enzyme sAC was first identified eight years ago by two Weill Cornell pharmacologists, Dr. Jochen Buck and Dr. Lonny Levin, co-authors on the *Nature Neuroscience* paper; they also discovered that sAC is essential to the activation of a biochemical “growth switch” called cAMP. (High levels of cAMP are present during fetal development, but only in miniscule amounts in adult nerve cells.) In their work on nerve cells from embryonic rats, the researchers found that when sAC was removed, developing axons suddenly failed to grow. “In fact,” says lead author Dr. Samie Jaffrey, associate professor of pharmacology, “without sAC, these embryonic axons began to resemble axons in injured adult spinal cords—axons that were incapable of growth.” Then they reversed the experiment by flooding nerve growth cones with sAC—and axonal growth accelerated.

The team’s next step will be to introduce sAC to adult axons via a harmless virus genetically designed to zero in on growth cones and express sAC in large quantities. “With this new piece of the puzzle, we can begin serious work on introducing sAC directly into damaged spinal cords, where we hope it will encourage axons to seek out vital new connections,” says Jaffrey. “The ultimate goal is a treatment that can prevent paralysis or restore movement to paralyzed individuals.”

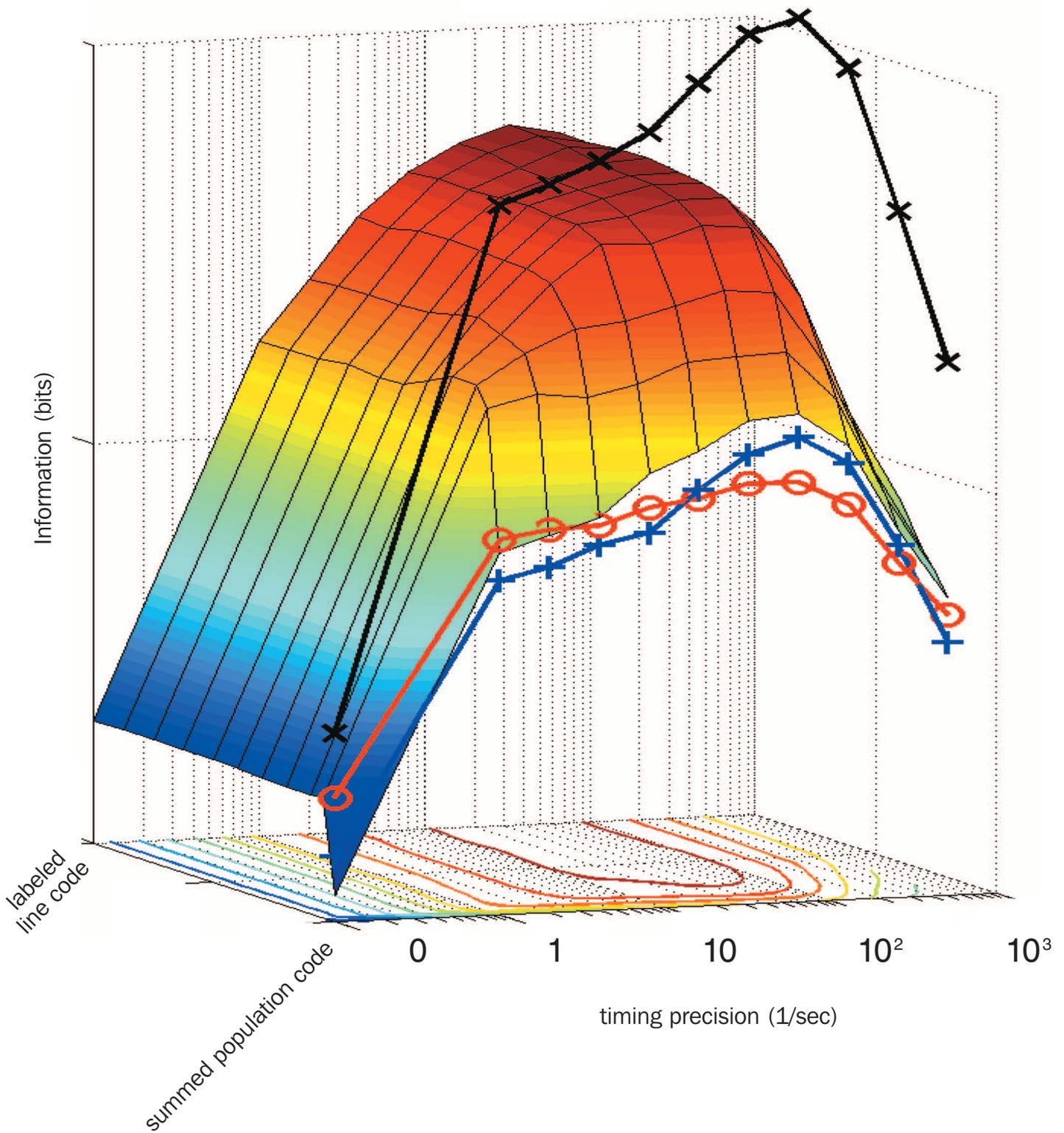
Bathroom Break

A combination of two common medications could become the standard therapy for men suffering from overactive bladder (OAB). A major clinical trial has found that tolterodine (sold as Detrol LA) and tamsulosin (Flomax) work better together than either drug does alone. The latter drug helps regulate bladder contractions while the former eases the symptoms of enlarged prostate, thought to be an underlying cause of male OAB.

It’s estimated that 10 million American men aged forty and up suffer from OAB. The double-blind, randomized clinical trial—by researchers at Weill Cornell, the University of Texas Southwestern Medical Center, and the Medical University of South Carolina—involved more than 850 patients treated at ninety-five urology clinics around the country. For twelve weeks, participants received either one of the drugs, both, or a placebo; they were asked to chart their symptoms in diaries, and their urinary flow rates and volume were checked before and after the experimental period.

“A full 80 percent of men with moderate-to-severe OAB—which is characterized by symptoms such as urgent and frequent urination—who received these drugs together reported a real benefit within three months of treatment,” says urology professor Dr. Steven Kaplan, the study’s lead author. “In contrast, patients receiving either tolterodine or tamsulosin alone reported improvements that were little more than those seen by patients on placebo.” The results were published in the November 15 issue of the *Journal of the American Medical Association*.

Weill Cornell Medicine is now available online. www.med.cornell.edu/publications



Vision quest: A computational analysis of neuronal activity in the visual cortex, carried out in Dr. Jonathan Victor's laboratory. These types of analyses, which model small cell populations at an abstract level, require hours to days of computer time. They reveal how the timing and distribution of activity across neurons contribute to the representation of visual information—and, ultimately, perception.

mind + machine

the label usually begins “SIDE EFFECTS MAY INCLUDE” and then goes on to detail a litany of undesirable—and sometimes downright alarming—side effects that a medication might cause. To computational biologist Harel Weinstein, such lists reveal a fundamental flaw in the way medical research has led to these medications. “Today, research takes on a protein involved in a particular diseased state—depression, Alzheimer’s, diabetes—and then the biomedical community and the pharmaceutical firms try to find therapies that modulate that protein’s function to ameliorate or cure the disease,” says Weinstein, director of Weill Cornell’s HRH Prince Alwaleed Bin Talal Bin Abdulaziz Al-Saud Institute for Computational Biomedicine (ICB). “The problem is that even if this is partially successful—if you block or activate the protein—because of its new state it triggers a whole set of totally unforeseen consequences. Sometimes they’re just side effects and sometimes they make the patient worse.”

To make the best possible use of the new discoveries from biomedical research, says Weinstein, researchers will have to shift their focus away from treating the components of a biological system as though they were static and look more deeply into the dynamic relationships among those components, recognizing that real understanding depends on it and that any unknowing intervention could ricochet throughout an organism. “Unless we think about integration,” says Weinstein, “we won’t understand how the

At the Institute for Computational Biomedicine, researchers explore the body’s infinite complexity.

body functions and will not achieve therapies that don’t mess us up while they try to make us better.”

Integrating the copious volume of data that researchers have already collected far exceeds the analytical capacity—and life-spans—of mere mortals. So Weinstein and his colleagues have turned to mathematical equations, transforming biological data into sophisticated electronic models that reveal the interactions among genes and individual molecules, among molecular assemblies and cellular function, and among cells and their assembly in organs. “The overall vision of our institute is to use what we call multi-scale systems analysis to address physiological systems—the basis of medicine,” says Weinstein. “The aim is to understand how human physiology works in healthy and diseased states, and to use this understanding to design means for disease prevention and therapy.”

ICB researcher Colleen Clancy focuses on the relationship between electrical disorders—such as epilepsy, which affects more than 2 million Americans, and cardiac arrhythmia, the leading killer in the developed world—and specific mutations in genes encoding ion channel proteins in the cell. “The biggest challenge



Silicon allies: Dr. Harel Weinstein (left) and ICB colleagues Dr. Sheila Nirenberg, Dr. Colleen Clancy, and Dr. Jonathan Victor use the power of computers to tackle complex biological problems.

effectively transform individual physiologic data points into meaningful computer models. “When we design a research question, we frame it knowing the limitations of our computers,” says Victor, the Plum Professor of Neurology and a member of the ICB steering committee. “It would be no trouble to formulate an interesting question that would take more than the life of the universe to solve.”

is understanding how a genetic mutation manifests at many levels in a system,” says Clancy, an assistant professor of physiology and biophysics, and of computational biomedicine. “How does a defect affect the protein that the gene encodes, the electrical signals of the cell, the interactions between cells, up to the organ-level behavior that relates to a disease state?”

In vivo studies using transgenic animals have suggested preliminary answers. But to learn how the system operates in humans, Clancy relies on supercomputers. “We’re investigating these emergent properties of disease *in silico*,” she explains. “We try to describe the behavior of sub-cellular processes using mathematics and then bring together all of those processes in what we call a ‘virtual transgenic cell.’ Then we bring the cells together to see how the disease disrupts cellular interactions. We can not only pinpoint how a mutation affects multiple scale processes, we can look for the precise interactions among processes.”

Meanwhile, computational neuroscientist Sheila Nirenberg has tackled the question of how individual neurons collaborate to solve a problem. “Say you’re making a decision to turn left or right,” suggests Nirenberg, an associate professor of physiology and biophysics, and of computational neuroscience. “Sensory input comes into your brain and produces electrical activity that propagates from network to network. Somewhere in that propagation it undergoes a switch, and this triggers the decision that results in behavior. We’re trying to find out how the switch occurs and how the decision is ultimately made.” While Clancy integrates vast data sets collected by other researchers, Nirenberg’s team collects its own—observing how photoreceptors in the retina transmit information to the ganglion cells, then using computer models to test how the neural circuits in the brain carry out computations.

Like Nirenberg, Jonathan Victor, MD ’80, investigates the activity of neurons and how they process information. Through behavioral analysis of human subjects, as well as experimental manipulations of cell populations and individual cells, Victor focuses on developing the theoretical underpinnings that

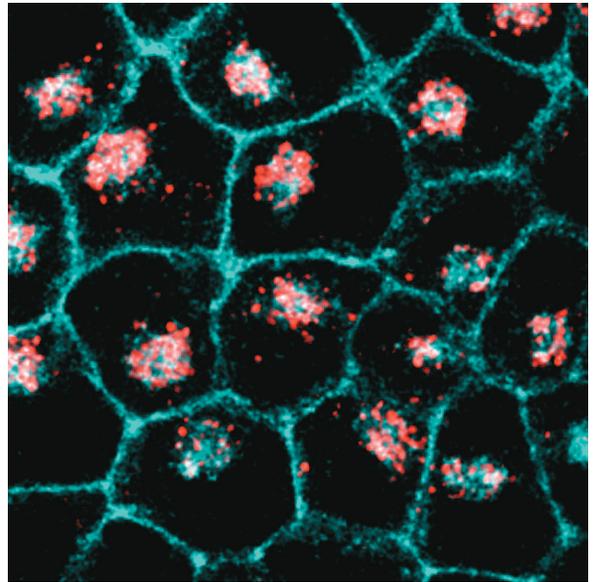
The trick, then, is creating equations that streamline computations, glossing over inconsequential details and focusing time and processing power on the most relevant features of the information being analyzed. “One of the biggest issues in modeling is choosing the appropriate level,” says Victor. “Modeling at the molecular level may require hours of computer time to understand how a process evolves over tiny fractions of a second. Modeling at the level of neurons and networks—billions and billions of molecules—sacrifices some detail, but often will allow an understanding of how a process evolves on time scales relevant to behavior.”

At the ICB, researchers don’t have to restrict themselves to just one level of modeling. “We try to achieve a complete, quantitative representation of these organ systems from the most fundamental genomic level all the way to whole-system behavior, which in the case of the brain means human behavior,” says Weinstein, whose own work investigates the genetic and molecular function of g-protein coupled receptor molecules, the target of 50 percent of all pharmaceutical interventions, and proteins known as transporters, which are targeted by antidepressants such as Prozac. “When you trigger the receptor, you trigger a new state in the cell,” he explains. “We needed to understand the sequence of events produced in the cell’s signaling pathway by that trigger, and represent it quantitatively as a transformation of the components; this necessitates looking at all these components together as an assembly, and following their fate in the cell in the space and time dimensions.”

Ultimately, says Weinstein, the ICB draws its strength both from the multitude of levels at which its researchers conduct their analysis and their diversity of academic backgrounds—from electrical engineering and computer science to physics, biology, chemistry, mathematics, and genetics. “We have a lot in common even though we work at different scales,” says Weinstein. “The conceptual framework of integration and multi-scale analysis—understanding the behavior of the entire system as it emerges from that of its components—is what brings us together.”

— Sharon Tregaskis

Eye for an eye: The lipofuscin component A2E (red) causes abnormal accumulation of cholesterol (blue) in human RPE cells in culture.



PROVIDED BY DR. SILVIA FINNEMANN

in. sight

Dr. Enrique Rodriguez-Boulan and his colleagues are tracking a potential treatment for a common cause of blindness.

Can you read this? Thank your retinal pigment epithelium. The RPE, as it's known, plays a vital support role in the eye: it's the retina's trash compactor. This function and other RPE functions are essential for the survival of the light-sensitive cells in the retina, the photoreceptors. These cells are damaged by light exposure, which is why nature has developed a mechanism to replenish the photoreceptors every ten days. This is done in daily bits.

When we open our eyes in the morning, we shed about one-tenth of each photoreceptor, making room for new growth. It's up

to the RPE to consume this cellular debris—and with each RPE cell in charge of about thirty photoreceptors, it's a full-time job. "It's a big breakfast—imagine eating an amount of material equivalent to your weight every morning," says Dr. Enrique Rodriguez-Boulan. "That's what these cells have to do their entire lives."

But when the RPE falls down on the job, researchers believe, it can lead to big trouble: diseases like age-related macular degeneration (AMD) and retinitis pigmentosa. Rodriguez-Boulan, director of research at Weill Cornell's Dyson Vision Research Institute, focuses on AMD, which affects about a third of Americans over the age of seventy. There is no effective treatment for the condition, which



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More than meets the eye: (Left to right) Dr. Enrique Rodriguez-Boulan with Dr. Silvia Finnemann and postdoc Aparna Lakkaraju.

leads to sharply decreased vision and, ultimately, blindness—and as the nation’s population ages, the number of cases will only increase. “It’s a devastating disease,” Rodriguez-Boulan says, “and it affects a very large segment of our senior population.”

Rodriguez-Boulan and Dr. Silvia Finnemann, a Dyson faculty colleague, hope they’re on the trail of a way to stop AMD. They believe that a lipid mix called lipofuscin—and, more specifically, a compound within it known as A2E—is responsible for compromising RPE’s ability to do its good work. Lipofuscin accumulation is a normal result of human aging; in living eyes, the lipid shows up under fluorescent light as many bright spots, says Finnemann.

There appears to be a correlation between the amount of lipofuscin and the level of visual impairment in AMD patients—up to the point where the retinal cells are completely destroyed, and the lipid along with it—but why the disease strikes some people and not others remains unclear. “There are several new findings in the area of macular degeneration that suggest in the next five to ten years we may have an idea of how the disease is generated,” says Rodriguez-Boulan. “That’s an important step toward getting a treatment.”

One of the reasons the RPE cells are vulnerable to getting clogged with lipofuscin is that—like neurons—they don’t divide. The body’s supply is finite and doesn’t regenerate or refresh itself. “Our cells in the intestine divide in such a way that the entire

mucosa is replaced every three days,” Rodriguez-Boulan notes. “The cells in the skin divide so that every three weeks we replace all of them.” RPE cells, by contrast, get no substitutes in the garbage-munching game: the original cells have to keep up their work day after day. “Essentially, it’s like running a marathon with a backpack full of stones,” he says. “The cells don’t perform their function properly because they are accumulating lipofuscin in their lysosomes that prevents them from digesting the photoreceptor residue.”

Rodriguez-Boulan and Finnemann are still in the process of convincing the vision community that lipofuscin and A2E are directly detrimental to the retina. Over the past five years, Finnemann says, they’ve come a long way—and recent studies carried out by Aparna Lakkaraju, a postdoctoral fellow at the Dyson Institute, suggest that perturbation of the lysosomal function by lipofuscin may lead to accumulation of cholesterol in RPE. This could, in turn, promote the initial development of the disease.

“Ultimately, we hope to actually rejuvenate a patient’s eyes by providing a mechanism for the RPE to expel or digest lipofuscin, and therefore generate a clean environment,” Finnemann says. “If we are able to decrease the lipofuscin accumulation—let’s say, when people reach retirement age—we could significantly prolong normal human vision. That would be a huge step forward.”

— Beth Saulnier

find your niche

Understanding the relationship between a stem cell and its environment is the key to unlocking its power.

One of the wonders of the human body is its continual process of self-renewal, made possible by stem cells. Stem cells get instructions for renewal from their surrounding microenvironment, or niche; located in specific anatomic areas, these niches keep the stem cell alive and self-renewing while preventing unbridled growth. Understanding the exchange of molecular signals between stem cells and their cellular niches, a process called the stem cell-niche interaction, is a critical step toward harnessing stem cells' therapeutic potential. And at the moment, it's at the forefront of nearly every path of stem cell research.

Every organ in the body contains adult stem cells responsible for maintaining tissues and repairing damage. As scientists learn more about stem cells and their niches, however, they are discovering that some stem cells may also play a harmful role: while they are responsible for repairing damaged tissue, they may also contribute to the growth of tumors and tumor metastasis.

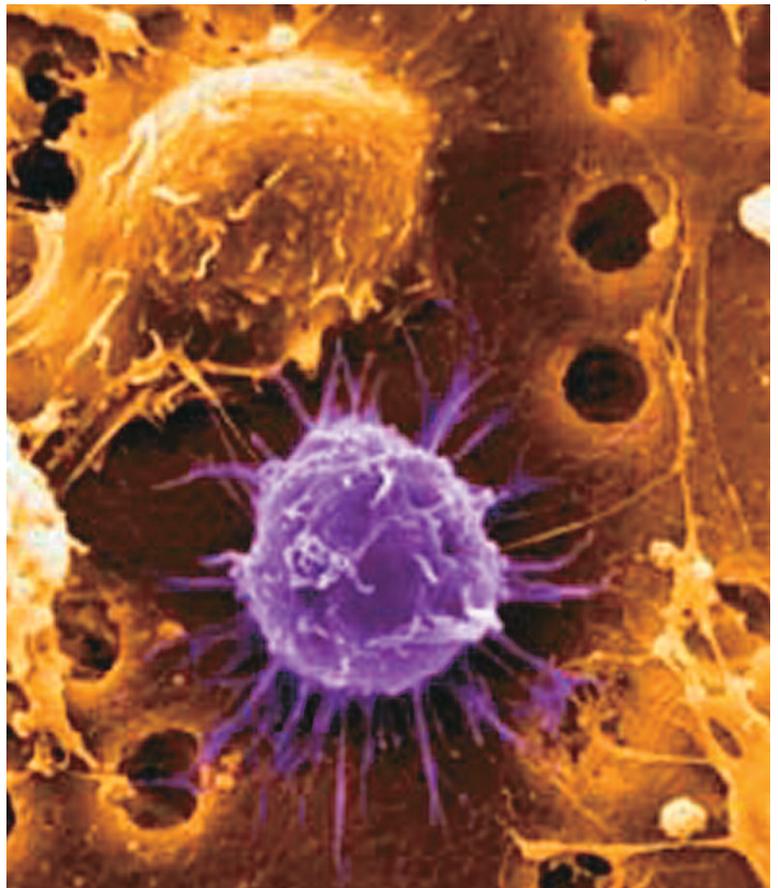
This has become increasingly clear in the case of hematopoietic stem cells—adult blood stem cells found primarily in the bone marrow that are responsible for producing blood cells and, in part, for blood vessel growth. Blood stem cells have been studied more than any other adult stem cell over the last fifty years and are currently the only adult stem cells used in clinical trials. But a recent trio of European studies published in the *New England Journal of Medicine*, in which blood stem cells were injected directly into the heart to repair coronary artery damage, yielded mixed results, illustrating that there is a great deal more work to be done.

Scientists at Weill Cornell have been mapping the stem cell-niche interactions that control blood stem cells in ever-increasing detail, pointing out the ways in which bone marrow-derived blood stem cells can be used to promote the regeneration of blood vessels and to prevent cancer metastasis. Much of the work is done in the lab of Shahin Rafii, director of the Ansary Center for Stem Cell Therapeutics. Although tissue regeneration and cancer metastasis may appear to be disparate research interests, they have an elegant biological overlap. "One might say that a cancer is like a wound that doesn't heal," Rafii says. "Cancer is regeneration gone haywire."

A stem cell's ability to differentiate, or morph into specific cells, is regulated by proteins sent to a dormant

Inside job: Researchers are studying how stem cells interact with the niches where they're found in the human body.

ANDREW LEONARD, SCIENCE PHOTO LIBRARY



stem cell's niche. Within this niche, the stem cell receives instructions about when and where to differentiate into more mature cells. Blood stem cells have two anatomic niches: they are present in both the bone marrow (the osteoblastic niche) and in circulating blood (the vascular niche). Rafii's lab has been describing signal pathways at both locations.

Working with Barbara Hempstead, a professor of medicine specializing in nerve growth factors, and David Lyden, associate professor of pediatrics and cell and developmental biology, among others, Rafii is using mouse models to describe the vascular niche where blood vessel growth takes place. When new vessels grow in an adult, either to heal an injury or nourish a tumor, growth fac-

tors and enzymes are released at the site, unleashing a signaling cascade that wends its way to the bone marrow. These signals recruit blood progenitor cells (more mature, partially differentiated blood stem cells capable of forming all of the different types of blood cells) as well as endothelial progenitors (cells that will ultimately form the lining of the new blood vessels) from the bone marrow and into the bloodstream. These two progenitor cell groups eventually move to the wound or tumor site and work in concert to stimulate new blood vessel growth.

"Angiogenesis is a partnership between the local blood vessels and these bone marrow-derived progenitor cells that allows blood vessels to regenerate," Hempstead says. "Nature has developed a complex and highly orchestrated program utilizing different growth factors and enzymes that it has already figured out as the best way to help blood vessels grow. Our job is to understand nature's program and use it to deliver an optimal cocktail of growth factors to stimulate blood vessel growth in the injured limb or heart."

Although Rafii and Hempstead have successfully regrown blood vessels in muscle tissue of mice, and are currently describing the complex pathways involved, they face many obstacles. "If we isolate any type of stem cell—brain, blood, or embryonic—and we want to cultivate them in tissue culture by adding any known growth factors, it is impossible to keep them self-regenerating for more than a few weeks," Rafii says. In other words, stem cells are not self-sufficient; they need instructions from surrounding tissues within their niche to tell them when to divide, to grow, or to hibernate. Without this regulation, stem cells would multiply indefinitely and uncontrollably, like tumor cells. It is within the context of cancer growth and tumor metastasis that the more harmful role of blood stem cells is played out. The more scientists understand how and when a stem cell receives instruction for growth, the closer they will be to exploiting stem cells' positive potential.

In the late 1880s, the English surgeon Stephan Paget proposed the "seed and soil" theory of cancer metastasis, arguing that metastasis does not occur by chance but requires the appropriate cancerous seed planted properly in distant soil primed for tumor growth. At the time, he urged scientists to study "the nature of the seed," but noted that "observations of the properties of the soil may also be useful." Most attention has

line drive

Grant supports the derivation of new embryonic stem cells for research

Last summer, the New York City-based Starr Foundation announced a gift of \$50 million over three years to support collaborative research on embryonic stem cells among Weill Cornell and its Tri-Institutional partners, the Rockefeller University and Memorial Sloan-Kettering Cancer Center. Formally known as the Tri-Institutional Stem Cell Initiative, the gift will fund specific stem cell-related research projects as well as build core facilities for the derivation, maintenance, and characterization of new embryonic stem cell lines. The new lines will be derived from embryos specifically designated for stem cell research by their donors: people who have sought IVF treatments but no longer need their embryos.

The initial embryo donation and stem cell line derivation will take place at Weill Cornell in the Tri-Institutional core laboratory at the Center for Reproductive Medicine and Fertility, under the direction of Dr. Zev Rosenwaks. Blastocysts formed in the course of infertility treatments are an indispensable resource for establishing stable stem cell lines, which may be induced to produce virtually any human cell.

"The derivation of these lines will allow scientists to use cell lines within their specific research interests, be it in the derivation of new eggs and sperm, of specific lines—nerve cells, skin cells, muscle cells, heart muscle cells, endothelial cells, and so forth—or in the area of looking at specific genetic disease," says Rosenwaks, the Revlon Distinguished Professor of Reproductive Medicine in Obstetrics and Gynecology. "This resource could ultimately give us the opportunity to answer many important pathophysiological questions, potentially leading to the treatment, and even cure, of many devastating diseases."

Although embryonic stem cell research is supported by the states of Connecticut, Massachusetts, and New Jersey, among others, New York provides no such funding—and less than two months after the gift was announced, President Bush vetoed a bill that would have allowed federal funding for research on stem cells left over at fertility clinics. Currently, there are only twenty-one government-approved embryonic stem cell lines capable of infinite renewal, all of them derived prior to Bush's August 2001 ban. In the ensuing five years, many of these lines have become contaminated by "feeder cells" required to keep stem cells alive or have undergone potentially negative genetic mutations during renewal. The new embryonic lines will provide stem cells with the high level of purity needed for any potential clinical applications. Embryos expressing genetic diseases may be used to derive stem cell lines for the study of those diseases on a molecular level.

After the derivation of new embryonic lines, stem cells will be distributed to scientists within the Tri-Institutional partnership for collaborative research in a wide range of fields, including regenerative medicine, neuroscience, and cell cycle studies, among others. In August, the first of the Tri-Institutional Stem Cell Initiative research grants were announced, totaling \$6.7 million over two years. Weill Cornell scientists will lead four of the seventeen projects, including research on cancer stem cells, the derivation of brain and heart cells, and the transformation of eggs into embryos. They will also be co-investigators on seven of the other projects.

been placed on understanding “the seed,” and scientists have only recently begun to understand the “soil” side of the equation. “This is one area in medicine and science where much remains to be learned,” Lyden says. “Once a patient has metastatic disease like pancreatic cancer or metastatic colon cancer, treatments are less effective.”

Several years ago, Rafii and Lyden were publishing collaborative work on blood stem cells with two therapeutic possibilities: promoting blood vessel growth in damaged organs or tissues, and halting blood vessel growth within tumors with the aim of eventually starving metastatic tumors. In describing the growth factors and enzymes involved, Rafii and Lyden noted something startling: stem cell levels in circulating blood spiked in animal cancer models, and some of these stem cells eventually found their way to future sites of metastasis.

In a paper published in *Nature* late last year, Rafii, Lyden, and colleagues including Dr. Rosandra Kaplan, assistant professor of pediatrics, showed that blood progenitor cells were recruited from the bone marrow by growth factors sent from primary tumors; these progenitor cells then traveled to sites of future metastases, where they set up pre-metastatic niches—the “soil”—where incoming tumor cells could thrive. They also found that a monoclonal antibody could block reception of the initiating growth factor, called VEGF, and treatment with this antibody halted the formation of these pre-metastatic niches and stopped metastasis altogether. In short, they found a way of making sure the soil could not nourish the seed. “For the first time,” Lyden says, “we’re identifying the critical factors that allow tumor metastases to thrive.”

The development holds diagnostic promise as well, which Lyden believes may ultimately be even more important. Now that they have identified the specific blood stem cells that function in

pre-metastatic sites, the sharp increase of these cells in the blood prior to and during metastasis can be measured. In the near future, Rafii, Lyden, and their colleagues will begin measuring the amount of these cells in the circulating blood of cancer patients undergoing surgery, radiation, and chemotherapy in an effort to better plan the patient’s ongoing treatment. “We need to find the time when these cells are important—early on, and perhaps even late in the process, when these bone marrow stem cells associate themselves with tumor sites,” Lyden says. “We believe that by targeting these stem cells, we can really change the course of metastasis.”

— Gabriel Miller



AMELIA PANICO

Stem cell pioneers: Medicine professor Barbara Hempstead (above) specializes in nerve growth factors. Dr. Shahin Rafii (far right), director of the Ansary Center for Stem Cell Therapeutics, calls cancer “regeneration gone haywire.”



JOHN ABBOTT



DENNIS MACDONALD / VEER

elder hostile

the elderly man came into the hospital alone one night in October, disheveled and disoriented. The resident on duty presented the case to Dr. Mark Lachs, with a differential diagnosis of Alzheimer's disease, depression, and blood on the brain. "And then he said, 'This could be elder abuse and neglect. The family was nowhere to be found to provide a history—they just dropped him off,'" Lachs recalls. "I was delighted." It wasn't that Lachs was glad about the man's sorry condition, of course; the longtime researcher on aging was simply thrilled that the resident had thought to include abuse as a possibility. "One of my goals in life is to make physicians aware," says Lachs, who is director of Weill Cornell's Center for Aging Research and Clinical Care, co-chief of the Division of Geriatric Medicine, and the Irene F. and I. Roy Psaty Distinguished Professor of Clinical Medicine.

At the Center, Lachs and his colleagues work to improve sen-

Dr. Mark Lachs investigates—and works to prevent—abuse and neglect of senior citizens.

iors' quality of life by integrating research, teaching, and clinical care. The Center holds regular symposia, mentors junior researchers in aging, and encourages Weill Cornell medical students to pursue careers in geriatric medicine. Lachs is also a co-director of the Cornell Institute for Translational Research in Aging (CITRA), a collaborative effort of the Manhattan, Westchester, and Ithaca campuses with close ties to senior service providers in New York City. Current research topics by pilot grantees in that program include non-drug approaches to back pain in older people, the psychology of seniors who hoard possessions at the expense of their well-being, and the effect of the Meals

on Wheels program's switch to frozen foods rather than daily deliveries of fresh meals.

But Lachs's abiding passion is the prevention of elder abuse and neglect. Perhaps the nation's most prominent physician-researcher in the field, he has been studying the subject for nearly twenty years, since seeing his first cases as an intern. In 1998, he and Ithaca-based gerontologist Karl Pillemer and colleagues published a seminal paper in *JAMA* that dramatically demonstrated elder abuse's potentially fatal consequences: at the end of thirteen years of follow-up in a longitudinal study of about 3,000 older people in New Haven, Connecticut, 41 percent of the subjects who had not experienced abuse were still living—compared to just 9 percent of the abuse victims.

Prior to the study, Lachs notes, such deaths were often ascribed to chronic conditions like cancer, heart disease, or emphysema. "All forms of family violence get under-reported," says Lachs, who holds a master's of public health as well as an MD. "We think that elder abuse is particularly under-reported, and here's the reason: if you're a kid who comes to school with a black eye, you're in the system. If someone comes to work wearing dark glasses, a co-worker might ask what's going on. But in older people, because of social isolation, it's often invisible."

One of the few opportunities to recognize abuse, Lachs says, may come during a visit to the doctor—but the abuser is often the patient's primary caretaker and the very person accompanying him or her to the physician's office. Since victims may be reluctant to speak up, Lachs says it's vital that doctors keep the possi-

bility of abuse in the forefront of their minds. "Pediatricians have adopted the issue of child abuse and made it theirs," he says. "They've integrated it into the medical curriculum; in pediatrics textbooks, you'll find 'child abuse' next to 'leukemia.' It's one of the finest examples of physician social advocacy. Internists have just failed with respect to the same problem in older people."

Mistreatment may be verbal as well as physical, or it may constitute neglect in the form of withheld food, medication, or personal care. It could also take the form of financial exploitation, where a caregiver gets control of a senior citizen's bank accounts or credit cards and uses them for personal gain. With the graying of the Baby Boomer generation—and wealth increasingly concentrated among older Americans—that type of abuse is seeing "explosive" growth, Lachs says. "There's a myth we dispelled in our research that an elder abuse victim is typically dependent upon an adult child for housing, when in fact it's quite the opposite: often it's an underachieving adult child living in the home of an older person." Sometimes, he says, siblings are relieved that this "underachiever" is willing to assume the responsibility to care for an older parent, and they may be reluctant to acknowledge the neglect.

Elder abuse and neglect of all types are more common than one might think: studies by Lachs and other researchers have consistently found the rate in Western cultures to be between 3 and 5 percent. "If the prevalence is 5 percent," he says, "that means that one in twenty older people seen by an internist will be a victim."

— Beth Saulnier



Mentor and student: Lachs with Dr. Maria Pavlou, a Hartford Geriatric Center of Excellence Scholar. The Hartford Foundation funds outstanding fellows at the Center for Aging Research and Clinical Care for a year of concentrated study to become national leaders in their field.

social science

Pharmacologist Dr. Lorraine Gudas believes that a successful lab must be catalyzed by personal chemistry.

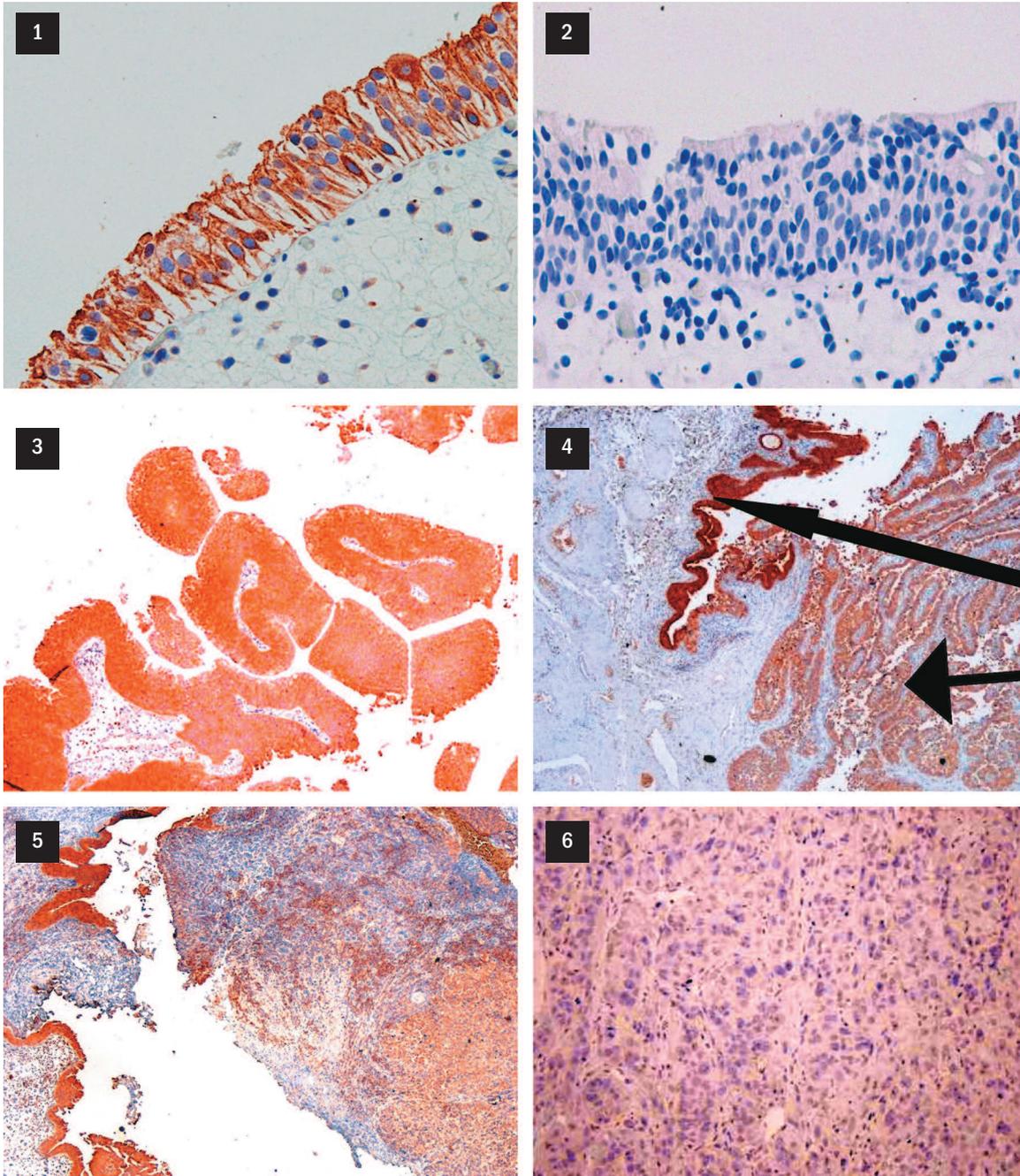
In her lab, Dr. Lorraine Gudas is expanding the role of pharmacology in cancer treatment, with a focus on the therapeutic promise of the vitamin A derivatives known as retinoids. Running a successful lab, however, also involves a more unconventional form of chemistry: finding the right mix of personalities. “People sometimes think of scientists as off in a dark corner working by themselves, but it’s actually a pretty social environment,” says Gudas, a professor of pharmacology and chair of the graduate program in pharmacology since 1992. “So whenever I’m hiring someone new, they may be brilliant, but if they can’t interact with other people, it can really disrupt the lab. I actually think about that a lot.”

The lab was humming on a recent fall afternoon, as the researchers moved smoothly through their tasks, some of them grooving to iPods tucked into the pockets of their white coats. The cell culture incubator was well-stocked with live cell cultures, each one neatly labeled with a researcher’s first name; every few paces through the lab’s close but comfortable quarters, a scientist was engrossed in a different phase of his or her project. Says Gudas: “It’s important that they know how to share and cooperate and help each other.”

The two dozen scientists working under Dr. Gudas are identifying and analyzing the genes that vitamin A regulates, in an effort to understand how it elicits changes in various cells—including

cancer cells. The vitamin’s use as an anti-aging and anti-acne agent (sold as the drug Retin-A) in topical creams is well-known, but in recent years it has been found to be extremely effective in fighting cancer; treating one type of leukemia with retinoic acid (a bio-active form of vitamin A) has increased the survival rate from 20 percent to more than 80 percent. In attempting to expand those results to solid-tumor cancers, Gudas, with her co-workers and collaborators, has been tracking the extraordinary machinations of vitamin A in the body, specifically in stem cells and epithelial cells, in the hopes of unlocking its anti-carcinogenic potential.

Humans don’t produce vitamin A themselves but obtain it primarily from dairy products, vegetables (in the form of beta carotene), and supplements. “There is a correlation between people who are partially vitamin-A deficient and slightly higher incidences of cancer,” Gudas says. “Our hypothesis is that vitamin A causes stem cells to become more differentiated cells, and that without appropriate levels of vitamin A, stem cells may just keep dividing and growing, without maturing properly. That could ultimately lead to cancer.” It is those stem cells—whose potential to become specific cells, like those of the skin or muscle, has not yet been realized—that may hold the answer to how cancer develops. “We knew when I started my lab that vitamin A could influence gene expression,” Gudas says. “We’ve also been working on stem



BOORJIAN ET AL. CLINICAL CANCER RESEARCH (2005)

Targeting tumors: Sections show human bladder tumors of various stages, incubated with the LRAT antibody. (1) A normal bladder stained to show LRAT; (2) an unstained control; (3) expression of LRAT in a superficial tumor; (4) a superficial tumor showing that LRAT levels are higher in the normal cells of the adjacent epithelium (upper arrow) than in the cancer itself (lower arrow); (5) even lower LRAT levels are seen in more invasive tumors; and (6) no LRAT is seen in a specimen from an invasive tumor.



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Teamwork: Dr. Lorraine Gudas chats with PhD students Sue Ellen Touma (left) and Dan Su.

cells for a long time—it's trendy now, but we've been doing it for almost twenty years."

Using mouse embryonic stem cells, Gudas and her colleagues compared the types of genes expressed in cells treated and untreated with retinoic acid, and they were able to determine which genes could be used as good "markers" for normal function in adult stem cells. Struggling to understand how and why specific genes react to vitamin A is part of unraveling the process wherein stem cells begin to behave abnormally, and at which point that abnormality might be corrected.

Two of the lab's "star" genes are a transcription protein known as REX-1, which is found in high levels in stem cells, and LRAT. In healthy cells, the LRAT protein helps the cell store vitamin A, whereas in cancer cells the LRAT gene is "silenced" and unable to perform normally. "That silencing occurs somewhere in a long carcinogenesis process," Gudas says. "Going from a normal cell to a tumor cell takes many steps—years—so we have to figure out new ways to deliver vitamin A to the cells or try to restore it to the tumor."

Patience is key in working to unravel the mysteries of carcinogenesis, but one of the rewards for Gudas's research team is the opportunity to work with other departments to conduct human trials. Gudas has collaborated most recently with Dr. David Nanus, an oncologist and clinical co-chief of hematology, testing a combination of retinoic acid and interferon—as well as retinoic acid and suberoylanilide hydroxamic acid, a drug that influences gene transcription—on kidney and prostate cancer patients. "We expect all of the research we're doing here in the lab to lead to new clinical trials down the road," Gudas says, sitting in her office before a bookcase piled high with science texts, "and to designing better drugs."

There was a knock at the door—one of several interruptions, phone calls, and pleas for advice fielded over the course of an hour. A colleague was mildly alarmed and excited about something she had seen in a cell culture, and requested an extra pair of eyes. Gudas headed for the microscope.

— Michelle Orange

mind full

Dr. David Silbersweig,
Dr. Emily Stern, and their
colleagues capture the brain
in living color.



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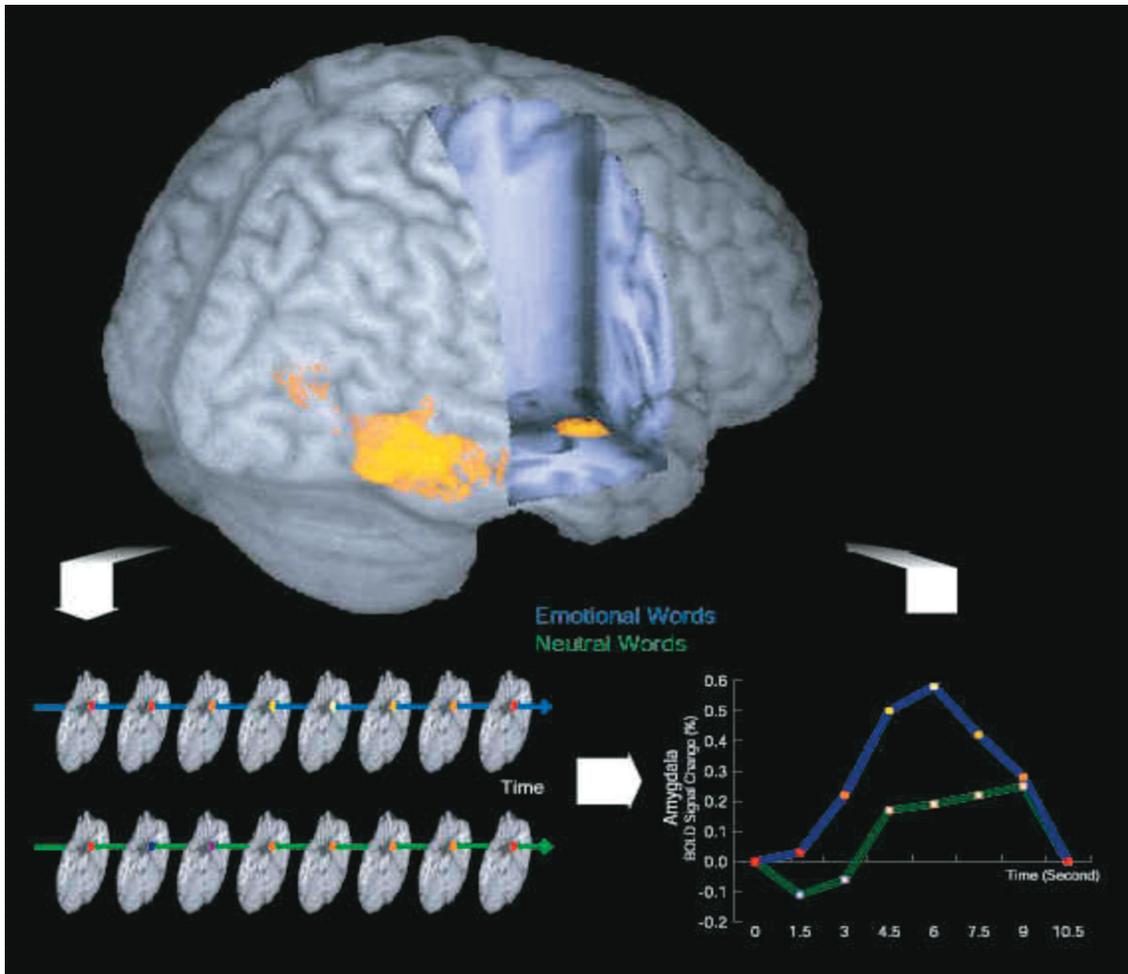
In the Functional Neuroimaging Laboratory at Weill Cornell Medical College, there are brains everywhere. Pictures, that is: cross-sections of brain images, some resembling color-by-numbers paintings, some implanted with electrodes, some sporting bright neon patches that indicate abnormalities. Co-director David Silbersweig, MD '86, points out a colored-pencil sketch of twelve disordered brains that sits on his bookcase. "We live and breathe this stuff," he says.

The seventeen-person lab includes specialists in psychiatry, neurology, radiology, mathematics, behavioral and neural sciences, and computer engineering. It is also part of the Center for Neuroscience of Fear and Anxiety, a multi-institutional research center funded by the National Institute of Mental Health that bridges basic and clinical scientific approaches. "We study the

Form and function: Dr. David Silbersweig and Dr. Emily Stern attend to a research subject in the fMRI.

brain at the systems level, which complements the investigations of our basic science colleagues," says Silbersweig, a neurologist and psychiatrist. Emily Stern, MD '87, a radiologist and co-director of the laboratory, points out that they are also working on "new methods to detect neural activity in key regions of the brain, including regions that we've never had access to before."

One research team is tracking the substrates of emotional function in a patient suffering from severe epilepsy, via electrodes implanted in his brain for clinical reasons. Neurologist-researcher Tracy Butler, who is performing this work, also studies how psychological disorders manifest themselves differently in the brains



PROVIDED BY DAVID SILBERSWEIG

Deep thoughts: Silbersweig and his colleagues at the Center for Neuroscience of Fear and Anxiety are studying the brain's emotional circuitry by evaluating patients' reactions to positive, negative and neutral words.

of men versus women. Related to this work, a recent study (on which Xenia Protopopescu, an MD-PhD student in the lab, is first author) has identified and localized changes in emotional circuit function in women across the menstrual cycle and in association with premenstrual dysphoric disorder.

Whatever the topic, all of the lab's experiments make use of neuroimaging techniques, including a relatively new type of MRI that has changed how the brain is studied. The way in which scanning and analysis is done—"it's the numbers behind the pretty pictures that count," says Stern—is always being improved, and the directors work closely with Dr. Hong Pan, the lab's image analysis scientist, in this ongoing process.

Silbersweig started out as a philosophy major, but the leap to neuroscience and psychiatry seemed perfectly logical. "I was always fascinated by how people think and what affects their thoughts and emotions," he says. "That developed into a desire to know and understand the science behind the human mind, in health and disease, and to use that knowledge to help people suffering from mental illness." He and Stern have been at the forefront of this research for a decade, initially for using positive emission tomography (PET) scans in the mid-1990s to identify brain regions active in schizophrenics as they hallucinated, landmark work that has led to new treatment approaches targeting the

regions of abnormal activity.

The team's work recently hit a turning point with the use of the blood oxygen level-dependent functional MRI (BOLD fMRI), which tracks the oxygenation of blood to various regions of the brain, indicating neural response and activity. "It's the least invasive method we have of seeing the brain in action while people are in various mental and disease states," Stern says. One of the NIH-funded fMRI studies they are currently conducting examines another major psychotic symptom of schizophrenia, paranoid delusions. Silbersweig and Stern are testing a unified pathophysiological model of fronto-limbic circuit dysfunction in psychotic symptom formation. In new experiments, the lab is working collaboratively to link such imaging approaches with new genetic techniques to identify endophenotypes and to understand the effect of variations in specific genes on the circuit dysfunction.

In a study recently published in the *American Journal of Psychiatry*, the lab's researchers, including neuropsychiatrist Dr. Jane Epstein, investigated patients with major depression. Volunteers in the fMRI scanner were shown a series of seventy-two words—positive ("success," "heroic"), negative ("worthless," "bleak"), and neutral—that flashed across an LCD screen. While reading each word, the subjects pressed a button to alert the researchers. After emerging from the fMRI, the volunteers read a

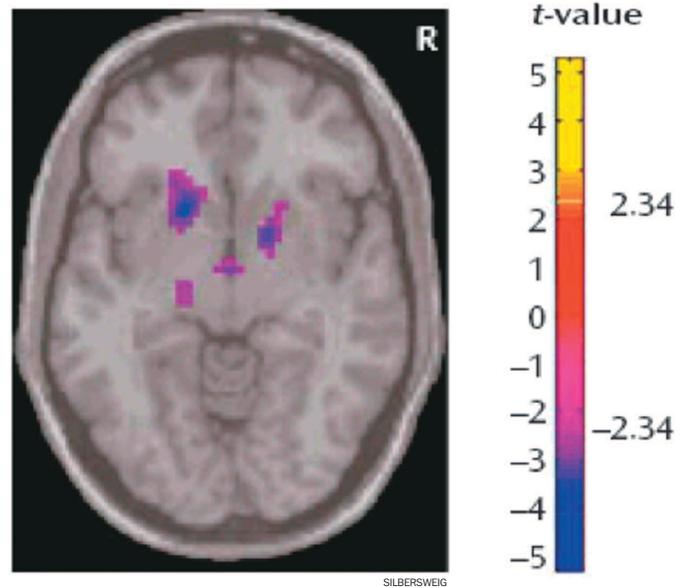
list of words—those they had seen, plus an additional thirty-six—and identified the ones they remembered seeing in the scanner. After conducting the fMRI analyses, the research team confirmed their hypothesis that the ventral striatal (nucleus accumbens) region of the brain—which is associated with reward, motivation, and salience—was less activated in the depressed subjects, compared with control subjects. Among patients, the degree of failure to activate the ventral striatum was correlated with their lack of interest in, and participation in, work and other activities, a measure of anhedonia—a core feature of depression.

Silbersweig believes that fMRI results such as these, with appropriate follow-up studies, could eventually lead to alternative therapeutic strategies that more specifically target such brain regions in individual patients. While volunteers are told that the experiments will have no direct effect on their treatment because the research is still in its early stages, helping patients is the ultimate goal. “We are all physicians first and foremost,” Silbersweig stresses. “We want to make our patients’ lives better.” In working toward this goal, Silbersweig and Stern collaborate closely with other clinical scientists in the Department of Psychiatry, including Dr. James Kocsis (on mood and anxiety disorders), Dr. Adam Savitz (on schizophrenia), and Dr. Otto Kernberg (on borderline personality disorder).

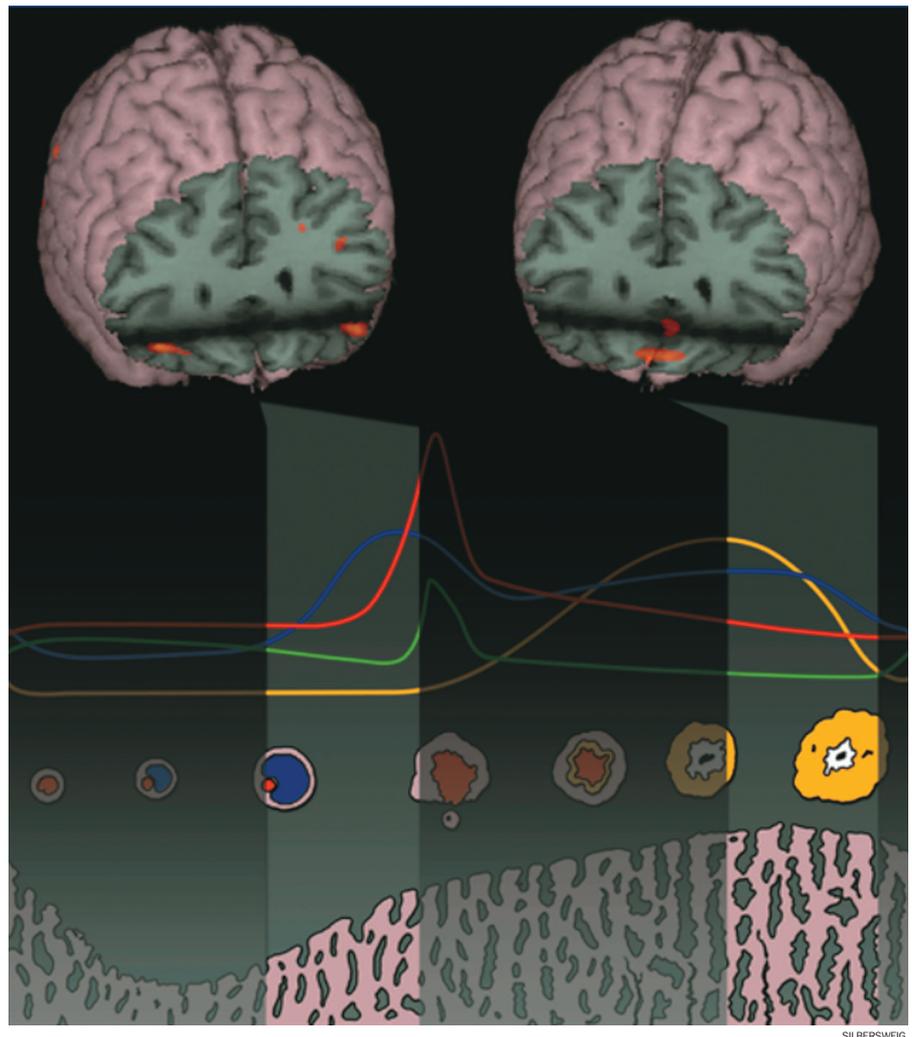
After 9/11, Silbersweig, Stern, and lab colleagues including neuropsychologist Dr. James Root decided to expand their studies of anxiety disorders to include post-traumatic stress disorder (PTSD) studies of Manhattanites who had experienced the attacks firsthand. “The subject population for that experiment includes everyone from New Yorkers who barely escaped the Twin Towers to those who were in the city but less directly affected,” Root notes. Almost every volunteer for the post-9/11 study has exhibited some traumatic emotional response when viewing the images associated with the disaster. “By studying the neural mechanisms associated with varying levels of stress,” Silbersweig says, “we are able to test hypotheses derived from animal work concerning evolutionarily conserved fear circuitry, to see how the brain reacts under such circumstances, to better determine who has more risk or resilience, and to lay a groundwork for improved interventions.”

Silbersweig and Stern say they feel fortunate to be part of an expanding field that is unlocking the mysteries of our most complex organ and transforming psychiatric biomedicine. They and their colleagues believe they have only scratched the surface of the uses for fMRI and complementary methods in studying neural activity. “The brain is still relatively uncharted territory,” Silbersweig says, “and it’s our job to map it and to understand its mechanisms in the service of our patients.”

— Neeraja Viswanathan



Brain power: A scan (above) shows decreased activation of the ventral striatum to positive emotional stimuli in a patient with major depression. Below: Researchers tracked changes in orbitofrontal emotional and inhibitory processing during the menstrual cycle. The follicular phase is at left, the luteal at right.



double duty

David Hajjar brings a researcher's eye to his role as dean of the Weill Cornell Graduate School.

flashback to 1981: Ronald Reagan took over the Oval Office, and *Raiders of the Lost Ark* took over the box office. De Loreans and Rubik's Cubes were hot; the study of inflammation was not. Most medical researchers weren't interested in such a basic process of the human body. But David Hajjar, a twenty-eight-year-old biochemist

fresh from a postdoc at the Rockefeller University, was betting that inflammation—in the form of herpes infections—had much to tell scientists about how arteries hardened into the condition known as atherosclerosis. And Cornell was betting on Hajjar, appointing him to its faculty that same year.

Flash-forward a quarter century: Today, De Loreans and Rubik's Cubes are Trivial Pursuit answers, but inflammation has become one of the most important issues in medical science, with researchers around the world racing to figure out its role in everything from heart disease to Alzheimer's. Hajjar's focus on inflammation and atherosclerosis proved to be a solid bet: he has found important links between herpes viruses and the metabolic disorders that can lead to cholesterol buildup on artery walls. And Cornell's hiring of Hajjar turned out to be a sound wager as well: he is not only one of the most well-funded researchers in the history of the Medical College, bringing in more than \$150 million in grants over the last three decades, he has also helped

to create an institution where scientists at every stage of their careers can thrive.

"The best environment for research is one in which you can walk out into the hall and run into other people doing interesting work and discussing new ideas," says Hajjar, who has been the

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On the job: David Hajjar in his office (opposite) and in his Weill Cornell lab with colleagues (left to right): Hideaki Nakaya, MD, PhD; Rita Upmacis, PhD; Lea Benguigui (technician); Ruba Deeb, PhD; Hajjar; Barbara Summers (technician); and Cynthia Cheung (technician).

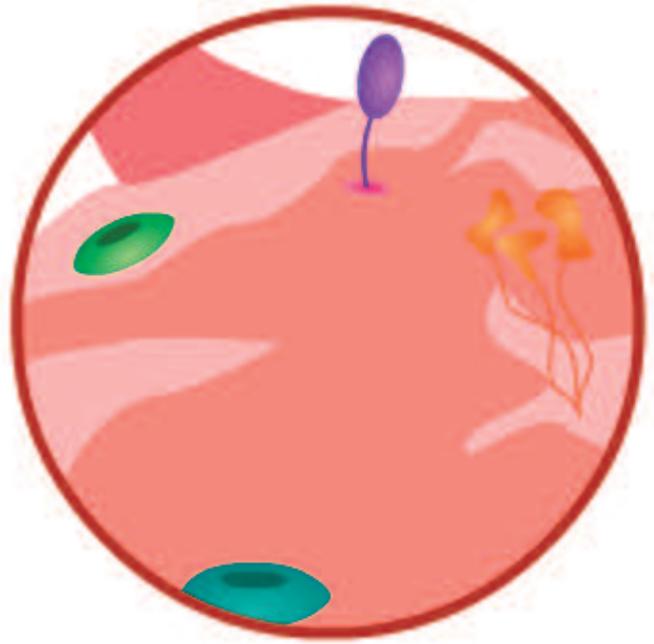
Frank Rhodes Distinguished Professor and dean of the Graduate School of Medical Sciences since 1997, vice provost of the faculty since 2000, and executive vice dean for research since 2003. "That's what I found when I came here to study cardiovascular diseases, and it's what I want to duplicate across the Medical College, in areas like neuroscience and metabolic diseases and genetics. Weill Cornell has been a wonderful place for me, and I want it to be a wonderful place for other researchers, too."

Every medical school strikes a different balance among the education, research, and clinical missions of their institution. As both a scientist and an administrator, Hajjar has found that those goals are complementary. Collaborations between clinicians and researchers are driving new developments across Weill Cornell, he says, and scientists benefit from being educators, too. "The training of new researchers is a constantly evolving process," says Hajjar. "It's more than teaching them 'the scientific method'; it's exposing them to a wide range of issues, from ethics to research compliance to how to train people yourself once you start running your own lab." Hajjar believes that senior scientists have a responsibility to help the junior members of their labs "sift through everything that is happening in modern medicine and figure out how you personally can make a difference"; at the same time, the fresh perspectives of graduate students and postdocs can help an

established researcher remain innovative.

Hajjar's own lab within the Center of Vascular Biology, which he directs, is home to twelve researchers: junior faculty, postdocs, and technicians. Dr. Ruba Deeb, now an assistant professor in pathology at the Medical College, joined his team as a postdoc in 1998. Deeb credits Hajjar with helping her develop the confidence to pursue her own ideas. "David had faith in my scientific ability, and he allowed me to test myself and see what I was capable of," she says. "He believes that when you hire somebody, you have to trust them. You can't micromanage. You will get some people who fail you, but you are going to get more people who are loyal to you and work hard." In this case, "fostering independence" isn't just a euphemism for a busy administrator leaving his team members to fend for themselves, Deeb says. "I have never heard him say, 'I don't have time for you.' Whenever I need to see him, he's there within minutes and his question is always, 'What will it take on my end to help you accomplish your goal?'"

It's a question that Hajjar asks on an institutional level, too, says Dr. Harry Lander. The associate dean for research administration first came to the Medical College in 1987 as a graduate student and stayed on to become a faculty member. He left in 2000 for a position on Wall Street, but returned in 2003 to work with Hajjar. "I came back because he has a vision that I share,"

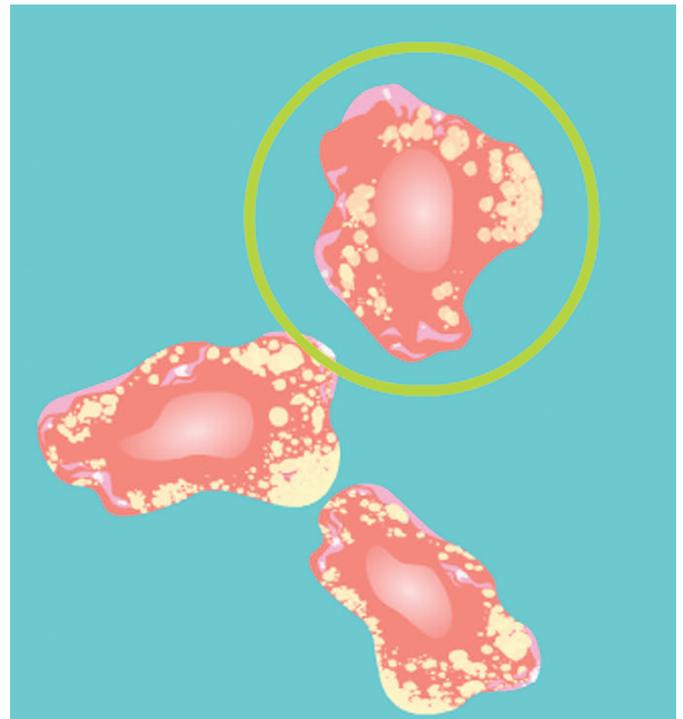


Halting heart disease: Hajjar’s work includes studies of several classes of scavenger receptors (inset, upper right) on the macrophage that have been implicated in the uptake of oxidized low-density lipoprotein (LDL), commonly known as “bad cholesterol.” The binding of LDL to its receptors is key to the accumulation of fat-laden macrophages (lower right), called “foam cells,” which leads to atherosclerosis.

says Lander, who is spearheading the development of new online administrative systems. “Researchers today have huge regulatory burdens to deal with, but we can facilitate those processes and make Weill Cornell a more user-friendly place. David wants to make it easier for them to focus on their work instead of their paperwork.”

Hajjar believes that streamlining administrative procedures will make Weill Cornell more attractive to top talent. In addition to the projects that Lander is initiating, Hajjar wants to improve the physical space for research and increase the resources available to department chairs. “The perfect environment is one in which the institution takes care of your needs so you can do what you were hired to do,” he says. “A scientist has to be thinking about his or her work 24/7. It’s a way of life, not just an occupation.”

Hajjar speaks about the life of a researcher with feeling—after all, he has devoted much of his own life to research. He has been working on the relationship between inflammation and cholesterol metabolism since he was a graduate student at the University of New Hampshire in the late 1970s. His early studies of herpes viruses looked at the way in which the virus latches onto receptors on cells in arterial walls and changes the way that those cells break down cholesterol, leading to atherosclerosis. He went on to study the role of the signaling molecule, nitric oxide, in regulating the dilation of arteries and how it may affect inflammation



in blood vessel walls. Over the past ten years, Hajjar has focused on how inflammation affects the receptors that regulate the way in which cholesterol is trafficked in and out of the blood vessel wall. His lab has used a genetic approach to knock out one of these receptors and found that doing so prevented the wall from becoming atherosclerotic.

Now Hajjar is ready to take what he has learned over the last thirty years and turn it into treatments for atherosclerosis, which

‘I want to move more quickly from bench to bedside. It’s not about how many papers I publish; it’s really about whether or not your work makes a difference.’

can lead to heart attacks, aneurysms, and other life-threatening complications. “I want to move more quickly from bench to bedside,” says Hajjar. “That’s what this is all about. It’s not about how many papers I publish; it’s really about whether or not your work makes a difference. Many of us who have done basic science for years now want to partner with clinicians and get more involved in translational research.”

Hajjar plans to move forward with his research even as he juggles his administrative positions—believing that those jobs make him a better scientist, and vice versa. His leadership post has given him an aerial view of what is happening across medical research today; and, on weekends, he reads a wide variety of scientific journals so he can “talk the talk” (a favorite Hajjar phrase) with faculty in many fields. That broad perspective has informed his own research agenda, keeping him aware of both basic science and clinical advances. And as an administrator, he has credibility with Weill Cornell faculty because he’s a scientist himself. “Researchers know that I feel their pain because I have my own lab and my own projects,” says Hajjar.

Hajjar’s colleagues marvel at his ability to handle his administrative jobs and run a lab. “Sometimes I get tired just thinking about everything he has to do,” says Deeb. “It’s his trust in people that allows him to be so efficient. If he felt that he had to be looking over everyone’s shoulder all the time, he’d never get anything done.”

Lander chalks up Hajjar’s efficiency to “his limitless energy, his incredible organization, and his ability to make tough decisions and move on.” Hajjar tempers his decisiveness with humor, says Lander. “Even when everyone is deadly serious, David is able to make people step outside themselves and get a fresh perspective. He might tell you that you’re behaving like Khrushchev pounding the table with his shoe at the U.N.—and, well, that is going to make you stop and laugh and be willing to see a bigger picture.”

Hajjar has his own theory about how he does it all. “No hobbies,” he laughs. “Really, it’s all about managing time. If you speak to any chairman in the Medical College, they’re dealing with the same issues I am.” With one difference: as dean, Hajjar has to address the concerns of faculty, staff, and students across the entire Graduate School. “David makes the time to listen to everyone, from a graduate student to a departmental chair,” Lander says. “And people know that if they go to him, they’re going to get a fair hearing. In the end, he always asks, ‘What is best for the institution?’ ”

Hajjar got the chance to address that very issue in the broadest possible terms when Medical College Dean Antonio Gotto appointed him to lead the formulation of the institution’s third strategic plan. Over the last year and a half, Hajjar worked with fac-

ulty and administrators to draft a document, approved in September by the Board of Overseers, that maps a path for Weill Cornell’s future. It includes enhancements to the clinical side and the research enterprise, as well as changes to the MD and PhD curricula. “This is a hugely exciting time for us,” Hajjar says. “We are going to be able to secure Weill Cornell’s position in the very top rank of academic medical centers. We can make this one of the best places in the world to learn, to obtain medical care, and to pursue basic and clinical research.” Gotto concurs, noting that “we are constantly looking to the future in order to keep the Medical College at the cutting edge of new and innovative research. The fruit of our labors in this area will translate directly to the bedside, furthering our commitment to excellent patient care.”

One key element: a new building dedicated to research. Hajjar says that a lack of space has been holding back scientific discovery at Weill Cornell. The proposed new facility, one of the hallmarks of Cornell’s \$4 billion capital campaign, will not only give current faculty members room to expand their research, it will create lab space for approximately fifty new faculty members in areas ranging from established strengths like neuroscience and stem cell biology to such emerging fields as genomics, nanomedicine, and developmental biology. And these additions to the Weill Cornell family will not necessarily be housed within the traditional departmental structure common to all medical schools, but may be in newly developed institutes and centers.

“Now that the genome has been deciphered, people are working in crossover areas, and there’s no need to compartmentalize our researchers,” says Hajjar. “We’ve got neuroscientists working in the psychiatry department and biochemists working in the microbiology department. In the new building, each floor is going to be thematic in its organization. We will move all the stem cell biologists to one floor, for example, so they’re always bumping into people who can talk their talk.”

This physical reorganization will be complemented by an intellectual one that reflects Hajjar’s commitment to making Weill Cornell a hub for interdisciplinary research and education. The new strategic plan calls for the creation of centers that will bring together basic and clinical scientists in disparate fields studying diabetes, cardiovascular disease, neurodegenerative and neuropsychiatric disorders, infectious diseases, and cancer biology, among others. “Focusing specifically on disease processes such as cancer and diabetes will help us to encourage collaboration and translational discoveries,” says Hajjar. “We need to build on our current strengths in hard-core basic science by encouraging the recruitment of all types of scientists including those doing translational research, as called for by our new strategic plan. That will keep us at the vanguard of medical research.”

— C. A. Carlson

taming tb

Weill Cornell immunologists fight one of the world's most intractable diseases.

Call tuberculosis a killer. Call it a scourge on the developing world. But don't call it a "reemerging" disease. "I find that offensive and narrow-minded," says immunologist Dr. Carl Nathan, "because it is the single leading cause of death from bacterial infection worldwide—and has been for time out of mind."

Although Americans may occasionally be alarmed by news stories on drug-resistant TB flourishing in prisons and other enclosed populations—and the disease recently made headlines with the Gates and Buffett foundations' multi-billion-dollar commitment to combat it, along with malaria and HIV—for the most part, it has lapsed from the first-world radar. "TB stopped being a major public health problem in the areas of the world that supported pharmacological research, but it never stopped being a problem in other areas," Nathan says. "It's the leading cause of death in HIV-infected people, and the leading cause of death in women in the middle years of life around the world. It's a huge problem."

Nathan, chairman of the Department of Microbiology and

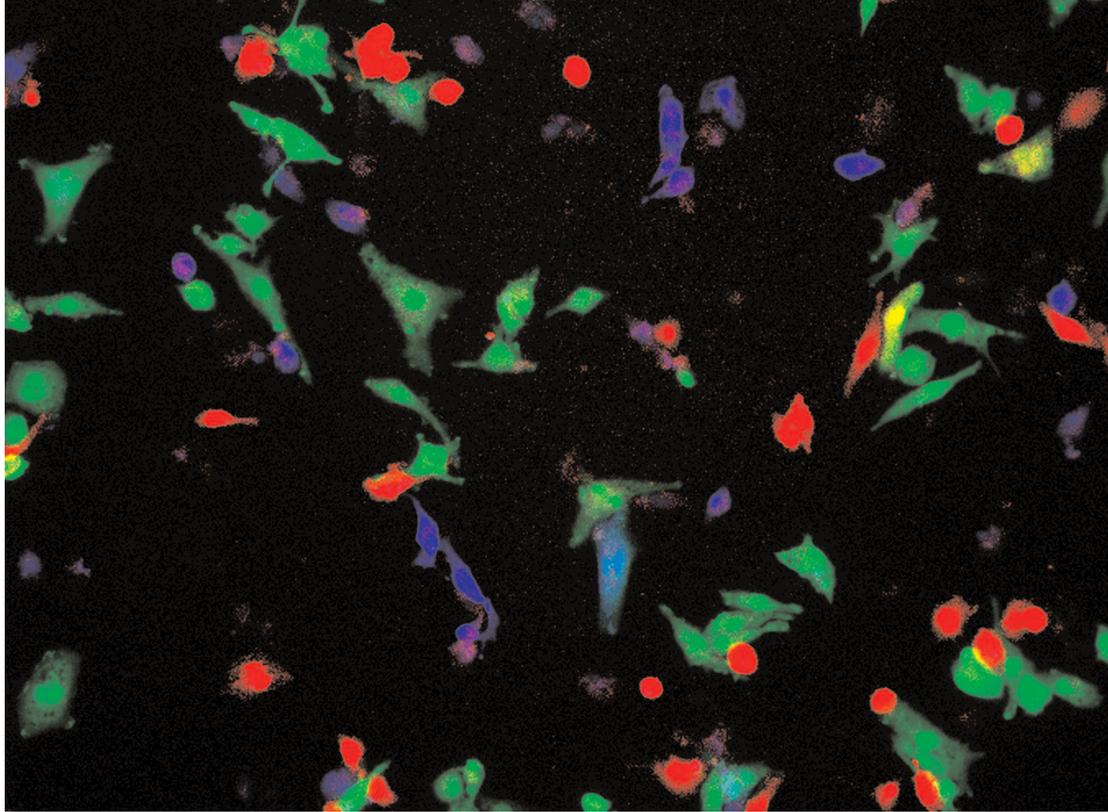
Immunology, has many research interests, including the potential for the toxic gas nitric oxide (produced by inducible nitric oxide synthase, or iNOS) to aggravate Alzheimer's disease, and the possibility of harnessing the power of the immune system to fight cancer. But battling tuberculosis is an abiding passion. "What fascinated me about this particular pathogen is that it's one of a select group that has no natural host other than humans, and it has the capacity to kill," Nathan says. "In fact, the untreated infection has a mortality rate of 50 percent in people with normal immune systems. And it's extremely prevalent: one-third of the people in the world are infected subclinically, meaning they have no active disease but are infected for life."

After medical school, Nathan trained in both internal medicine and oncology, and for years he was active in the field of tumor immunology. The fact that *Mycobacterium tuberculosis* (Mtb)



A good defense: Dr. Carl Nathan and his colleagues are fighting TB on several fronts, including the potential efficacy of the toxic gas nitric oxide as a defense against the pathogen.

Down to the DNA: Nathan, with PhD candidate Aimee Beaulieu and former postdoc Marianne Imhof, has taken a genetic approach to the immunology of tuberculosis. The macrophage cells seen in this micrograph have been engineered to express red, green, or blue fluorescent proteins, corresponding to three different host genes whose expression is stimulated by a mutant form of *Mycobacterium tuberculosis*. Ultimately, Nathan's lab hopes to find a combination of mutations that could lead to a vaccine.



PROVIDED BY DR. CARL NATHAN

often lives for decades as a foreign genome in the human body, he notes, is “reminiscent of the cancer problem, where a genome that once was identical to our own becomes slightly different—and then persists for years, in many cases, before breaking forth and causing disease.” It’s this persistent state—where Mtb lurks in a relatively inaccessible cellular structure called a granuloma—that researchers find both fascinating and vexing: although the immune system temporarily forces the bacterium into a non-replicating state, it doesn’t sterilize it. Nathan’s research focuses on the immune factors that keep TB at bay—and the potential for using them to defeat the disease.

One possible weapon in the fight against TB is iNOS; Nathan’s lab was the first to recognize it as a distinct enzyme, then cloned it and knocked it out in mice. The enzyme appears to play a role in the biology of most living organisms—and its production is a major host defense against TB. Breaking down the products of iNOS, in turn, is a way in which tuberculosis withstands the immune system’s counterattack. “When the body tries to kill Mtb, it basically tries to oxidize it to death—and Mtb regulates a pathway to resist that oxidation,” says Christopher Lima, an associate professor of biochemistry and structural biology at Sloan-Kettering who regularly collaborates with Nathan. “It looks like there are unique enzymes in those pathways, and if we could develop a drug against them we might be able to block the ability of tuberculosis to survive in our immune system.”

In the developing world, conquering TB is a matter of life and death. In 2006, notes Nathan’s colleague Sabine Ehrt, the first strain of Mtb resistant to all current treatments emerged in South Africa. “If you open up Google News, you can read about cases of extremely drug-resistant tuberculosis (XDR-TB) that affected more than a hundred people and killed eighty-one of them within the last few months,” says Ehrt, an associate professor of microbiology and immunology. “And it’s not just multi-drug resistant—it resists all first- and second-line drugs and leaves patients virtually untreatable. It’s really terrible.”

Tuberculosis treatments have long had their limitations. For one thing, even in the best-case scenario, a complete course requires patients to take antibiotics for a minimum of six months. “Very few people comply with that,” Ehrt says. “So if you had a drug that could work in six weeks, it would be fantastic. It would change the whole problem.”

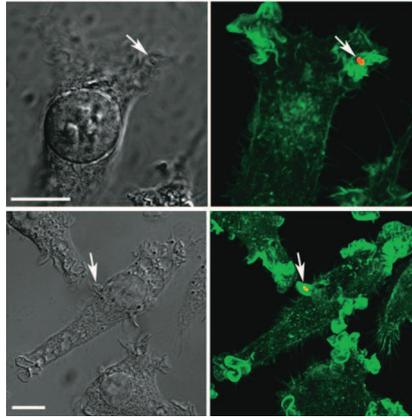
But the search for a short-term, effective treatment requires a switch from conventional pharmaceutical research—and Nathan’s work has found much-needed support with the recent gift of \$7.25 million by Abby and Howard Milstein for the creation of a Chemistry Core Facility and a Program in Chemical Biology at the Medical College. Nathan is convinced that this type of philanthropy, outside of the pharmaceutical industry, is key to developing drugs with the ability to target TB.

Typically, Nathan notes, potential drug compounds are tested under optimal growth conditions, where the bacterium is replicating quickly. That may be the most efficient way of running an experiment, but in the case of diseases like TB it has a serious drawback. “The question you’re asking isn’t, ‘What kills Mtb?’ ” Nathan says. “It’s, ‘What keeps Mtb from growing under conditions where it otherwise can grow at its fastest possible rate?’ ”

Not only are those conditions vastly different from what exists in the body—where Mtb lives inside macrophages whose environment is quite harsh, including a deficiency of oxygen and an abundance of acid—they’re the opposite of what’s going on in the subclinical patient, where Mtb is not actively replicating. And while those people may not be in imminent danger of death, from a public health standpoint their cases are no less urgent. “Five to 10 percent of them will eventually develop active disease—and then before they are successfully treated or die, whichever happens first, it’s estimated that they each will infect fifteen to twenty additional people a year,” Nathan says. “So you never catch up. The current approach to TB drug treatment just can’t work to reduce the proportion of the population that’s infected.”

— Beth Saulnier

be prepared



PROVIDED BY DR. LYNDA PIERINI

On guard against a potential bioterror weapon

tularemia is a rare ailment colloquially known as Hunter’s Disease or Rabbit Fever, since a common method of infection is a cut incurred while skinning an animal that harbors it. In the post-9/11 age, it’s also known as a potential bioweapon: it requires a very low infectious dose and could be easily disseminated via an aerosol spray. “You can inhale as few as ten bacteria,” says Lynda Pierini, an assistant professor of microbiology and immunology, “and get a serious or fatal illness.”

Although the fewer than 200 cases of tularemia that occur in the U.S. each year can be treated with antibiotics, terrorists might be able to engineer a resistant strain. That’s why researchers like Pierini want to know more about the pathogenesis of the bacterium *Francisella tularensis*, both in the entire host and in individual cells.

Tularemia’s deadly potential isn’t a recent discovery; the disease was first identified in the early twentieth century, and both the U.S. and the Soviet Union weaponized it during the Cold War. An outbreak during World War II’s Battle of Stalingrad prompted speculation that the Soviet Army had used tularemia against German troops, accidentally spreading it to Russian civilians.

Pierini, who earned her PhD in chemistry on the Ithaca campus and did a postdoc under Weill Cornell biochemist Frederick Maxfield, has been studying the disease for the past four years. She’s been concentrating on how the bacterium “highjacks” the specialized white blood cells known as macrophages—subverting their normal mission of clearing out invaders, and instead flourishing inside them. In the August 2006 issue of *Cellular Microbiology*, she identified one of the receptors that *F. tularensis* may use when it infects the macrophage. She and her four-person lab have also been screening chemical libraries to find new ways to inhibit the bacterium’s growth when it’s hiding inside the macrophage—and they have two “very promising” leads. (The lab’s other projects include studying how macrophages can malfunction in arteries, consuming cholesterol until they turn into “foam cells,” which form part of the plaque that causes atherosclerosis.) “Obviously, we hope there isn’t ever an intentional release of *tularensis*,” says Pierini. “But *Francisella tularensis* is an excellent model organism, so our research on its lifestyle may lead to insights into the pathogenesis of other bacteria.”

Immune response: In these projection images (above) from a confocal fluorescence microscope, macrophages engulf *Francisella tularensis* bacteria (indicated by the arrows).



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Bio defense: Lynda Pierini (center) in the lab with colleagues Tomokazu Nagao (left) and Inna Grosheva.

—Beth Saulnier

The best way to fight cancer?
When it's still hidden in the genome.



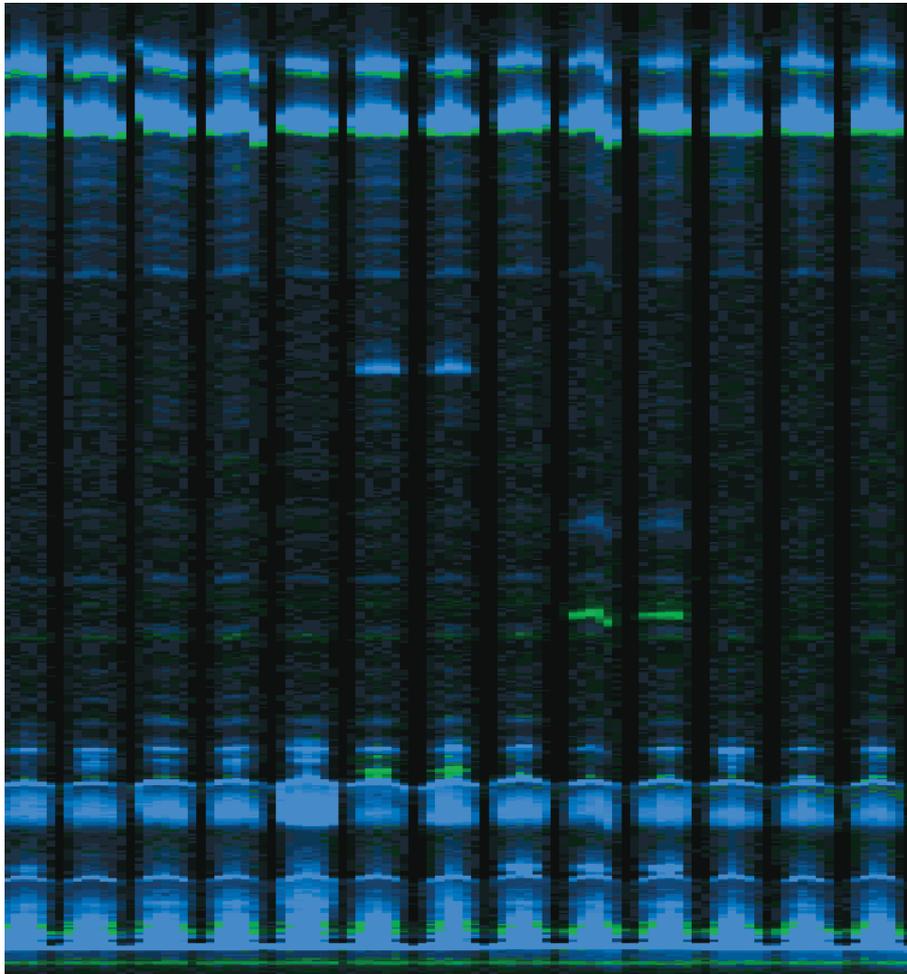
PROVIDED BY FRANCIS BARANY

the enemy within

When a big company—say, Boeing—faces a major challenge like designing the next generation of commercial airplanes, it puts together a team of hundreds of designers, scientists, programmers, and engineers. Professor of microbiology Francis Barany believes that effective cancer research requires a similar approach, where bench researchers from varied disciplines work side by side in a multi-tiered strategy, collaborating with physicians from many specialties. The resulting “bedside-to-bench and bench-to-bedside” approach is the driving force behind Weill Cornell’s Hidden Cancer Identification and Eradication Project, which Barany hopes will be the model for a novel, more powerful way of doing medical research. “It’s not just about what we hope the project will accomplish,” says Barany, “but what we hope to demonstrate: a new way of having clinical and medical researchers collaborate.”

Despite advances in understanding the fundamental biology of cells, cancer is still the second

Field work: During a 1991 trip to Yellowstone National Park, Francis Barany takes samples of organisms at a hot spring, from which he later isolated enzymes used to detect cancer-causing mutations. Microbiologist Carl Batt, a colleague from the Ithaca campus, is in the background.



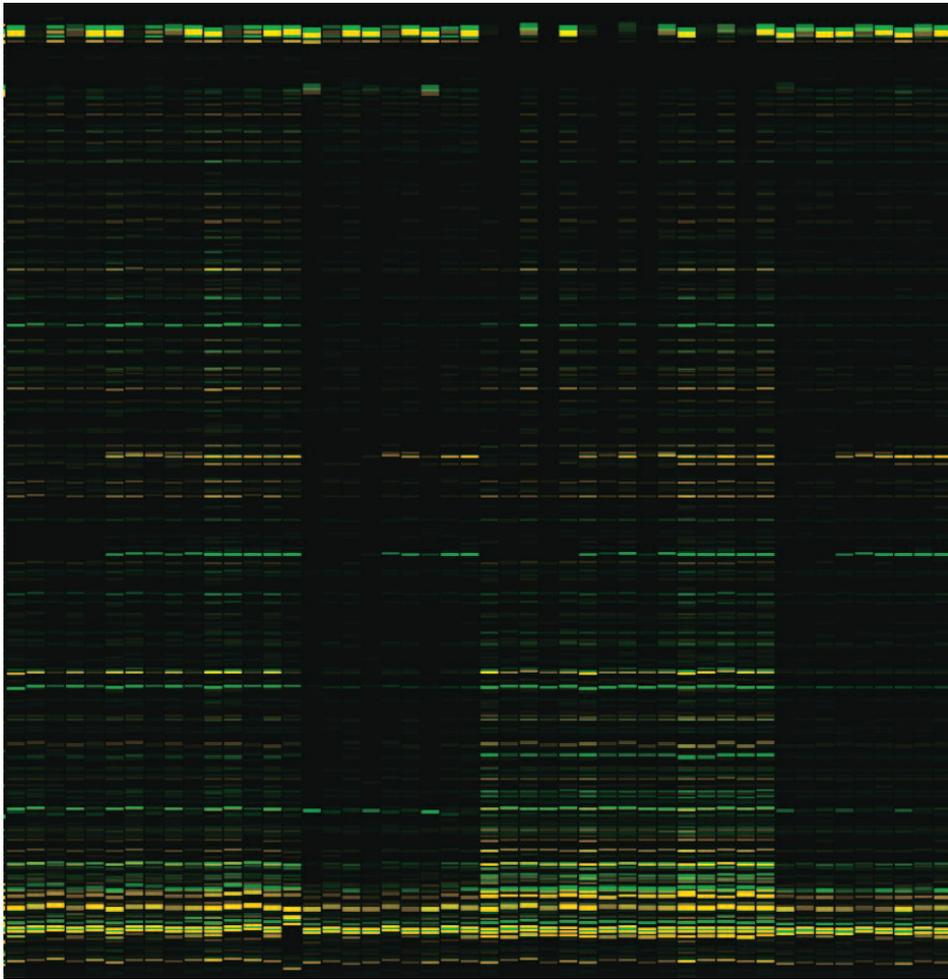
leading cause of death in the U.S., with nearly 1.3 million people diagnosed annually and more than 500,000 dying each year. The Hidden Cancer Project, which Barany has been developing over the last fifteen years, is now ready for its three-year pilot phase, a \$14.5 million endeavor to be funded largely by government, industrial, and private grants. During this phase, Barany hopes to develop tests that not only better identify at-risk patients but also catch the disease earlier, with the long-term goal of providing improved, personalized therapies.

One-quarter of cancer-related mutations are inherited: an abnormal gene is passed from parent to child, posing a greater risk for a particular type of cancer. All other cancers are considered sporadic, meaning they occur spontaneously or due to environmental factors; certain normal genes simply begin to change. With both types of cancer, genes must undergo a number of complex, tumor-specific mutations before the cells develop into a cancerous state. And even then the genes within these cells continue to mutate, making the development of early detection tests and effective drug treatments a formidable task. By developing tests to identify these mutations—and the altered genes and proteins that are responsible for the initiation and progression of the cancer, collectively known as “markers”—the project will identify individuals at risk, as well as those with cancer in its earliest stages, when it is largely hidden but more treatable. A precise genetic diagnosis of cancer type and stage will enable more individualized treatment using

existing medications, and newly discovered molecular markers may facilitate the development of gene-specific drugs.

The project relies on collaborations among physicians and scientists throughout Weill Cornell and the Tri-Institutional community, including researchers at Memorial Sloan-Kettering Cancer Center and the Rockefeller University. (Although there are currently fewer than a hundred researchers and a dozen labs involved, both figures are expected to double in the coming years.) The project’s scientific agenda will be guided by an internal advisory board as well as an outside panel of internationally recognized experts in the genomics of cancer. During the pilot phase, the project will focus on colon, lung, and prostate cancers. As it expands, it will include breast cancer, blood cancers such as leukemia and lymphoma, and others—work that will continue into the foreseeable future. “Science is a long and tedious process,” says Barany. “It’s a marathon, not a sprint.”

Even with an extensive timeline, the project’s goals are ambitious—and would not be possible without the molecular profiling technologies that Barany’s team has developed over the past decade. Their discovery of the DNA and RNA changes that occur in tumors allowed for the identification of previously unrecognized inherited risk factors, cancer-causing mutations that are passed down from parent to child. In 1991, the lab published its work on ligase chain reaction and ligase detection reaction, the technology behind the most commonly used commercial test for cystic fibro-



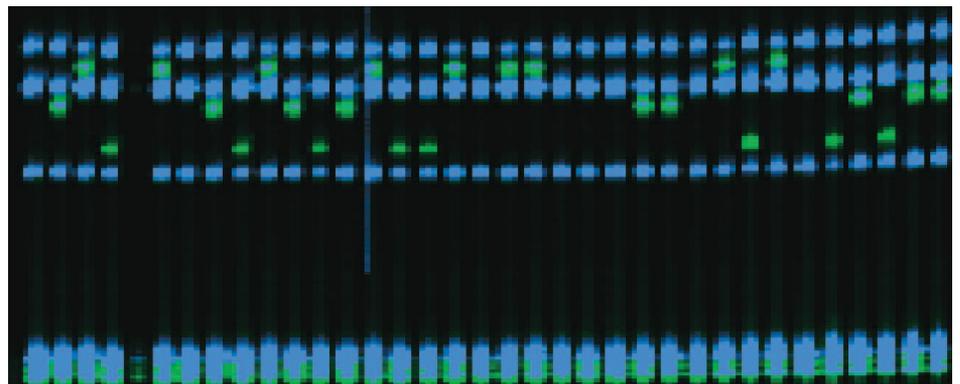
sis. In 1999, it created programmable DNA arrays, or universal DNA chips, which enable the detection of thousands of sequence variations; it's the primary technology used by the International HapMap Project, an effort to catalog genetic similarities and differences. In 2001, the lab published its work on EndoV mutation scanning, the fastest and most accurate way to look for new cancer mutations. And in December 2005, it discovered a shortcut to identifying new genes that cause cancer.

Barany likens his lab's technological approach to ground-penetrating sonar used to detect damage beneath pavement. "A street

is far more complicated than what appears on the surface," he says. "A pothole can be benign, or it can mask serious damage to the network of cables and pipelines below. Just as in cancer, some of the damage may be due to inherited factors, like faulty pipe material, or environmental factors, like heavy trucks damaging the road above." The gene-analysis technology the lab is developing, he says, could offer a view into problems lurking deep underground. "Perhaps," he says, "it could detect the damage early enough so it can be repaired before a main conduit breaks."

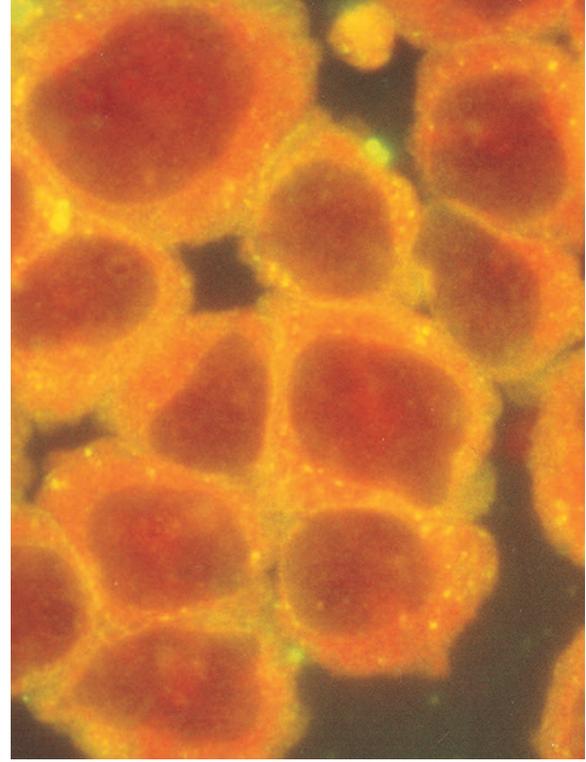
— Tobin Levy

In the genome: Examples (top left and right) of EndoV/ligase scanning to detect mutations of p53, a gene involved in tumor suppression. Right: Polymerase chain reaction/ligase detection reaction tests indicate inherited mutations in the BRCA1 and BRCA2 genes linked to breast cancer.



Dr. Katherine Hajjar links a powerful protein to human disease.

blood work



Proteins called annexins are found in the cells of almost all organisms, from fungi to humans. Although these fifty proteins were discovered in the 1980s, their purpose still puzzles researchers—except for annexin 2. It is the only one whose function is well understood, thanks to Dr. Katherine Amberson Hajjar. Since she discovered the protein's role in 1994, Hajjar has taken her research from the tissue-culture dish to mouse models to tissue samples from

patients. "Right now," she says, "one of the most interesting things about our lab is that we're working at all three levels."

Hajjar's team has uncovered clues about the role of annexin 2 in human disease, from a blood-clot disorder to a type of leukemia (and, perhaps, certain tumors), and has made important discoveries about annexin 2's cellular mechanisms and how they function in mice. In the late 1990s, Hajjar discovered that annexin 2 plays a crucial role in two key processes: angiogenesis, or the formation of blood vessels, and fibrinolysis, or how blood vessels regulate the

removal of clots. It's angiogenesis that is at the heart of her lab's most recent work on human tumor biology. Although their research is preliminary, Qi Ling, assistant research professor of cell and developmental biology, and Jia Ruan, MD '99, PhD '98, assistant professor of medicine, have found several clues suggesting that specific annexin 2 populations seem to enter tumors and are required for their growth.

Hajjar and her colleagues have also linked annexin 2 to thrombosis, or the formation of clots that obstruct blood flow. Earlier this year, she and



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Protein power: Acute promyelocytic leukemia cells from a patient with excessive annexin 2 (top). Left: Katherine Hajjar and assistant research professor Qi Ling measure tumor growth in an annexin 2-deficient mouse.

Team effort: Hajjar and her colleagues in the lab. Back row (left to right): Sarah Church, Arun Deora, Kai-Li He, Bihui Huang, Alison Kuremsky. Front: Angeli Rampersad, Emil Lev, Jia Ruan, Hajjar, Qi Ling, and Menard Gertler.



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Gabriela Cesarman-Maus, a former postdoctoral fellow at Weill Cornell, published research in the journal *Blood* on antiphospholipid syndrome (APS)—a disorder, associated with infertility and pregnancy loss, in which patients develop antibodies to normal blood proteins. Not only were patients with APS more susceptible to thrombosis, the ones with thrombosis were also more likely to have developed antibodies to annexin 2. “That raises the possibility that antibodies to annexin 2 might be pathogenic in some patients with this disorder,” says Hajjar, who is chair of the Department of Cell and Developmental Biology.

Patients with the opposite problem—a tendency toward bleeding and hemorrhage—offered Hajjar the first link between annexin 2 and a human disease. In the 1990s, her lab team discovered that annexin 2 is overactive in patients with acute promyelocytic leukemia. “We think that the overexpression of annexin 2 might prevent them from forming a stable blood clot when they need it,” Hajjar says, “thus leading to the bleeding problem.”

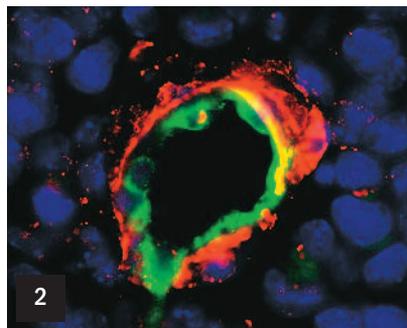
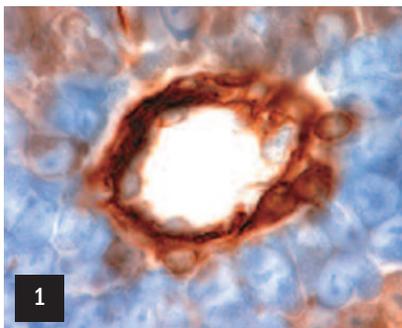
While Hajjar’s researchers work to understand annexin 2’s impact on human disease, they also continue to look at its cellular mechanisms. Arun Deora, assistant research professor of cell and developmental biology, has shown that stimulation of the cells that line blood vessels, known as endothelial cells, prompts annexin 2 to move to the cell surface—where it becomes activated and helps to supply new blood vessels. The stimulation can come from an injury, for example, or a tumor signaling that it wants to grow. Kai-Li He, a research associate in the lab, has discovered that a related protein known as p11, which chaperones

annexin 2 to the cell surface, is also tightly regulated within the cell. These scientists have demonstrated that we’re dealing with a dynamic system, Hajjar says—one that could be manipulated.

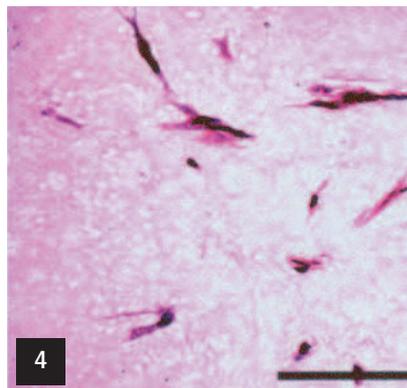
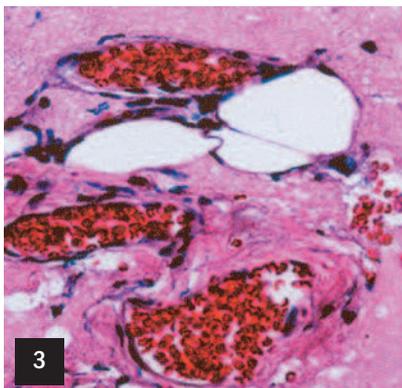
If that’s true, her research could lead to new therapies for patients with a variety of problems. Stimulate the endothelial cell in the right way, and you could increase the activity or amount of annexin 2 and prevent excessive clotting. “That might be useful for the treatment of a person with thrombotic disorder, for example,” Hajjar says. “On the other hand, you might want to inhibit that process in a patient in whom you wanted to block angiogenesis.”

Now that she has unlocked the mysteries of one annexin, there are forty-nine to go. Her lab will likely tackle the others, starting with what could be an important clue: the main portion of each annexin molecule shares up to 61 percent of its amino acid sequences with its cousins. “The annexins might have a common function,” Hajjar says. “That would be exciting to discover.”

— Susan Kelley

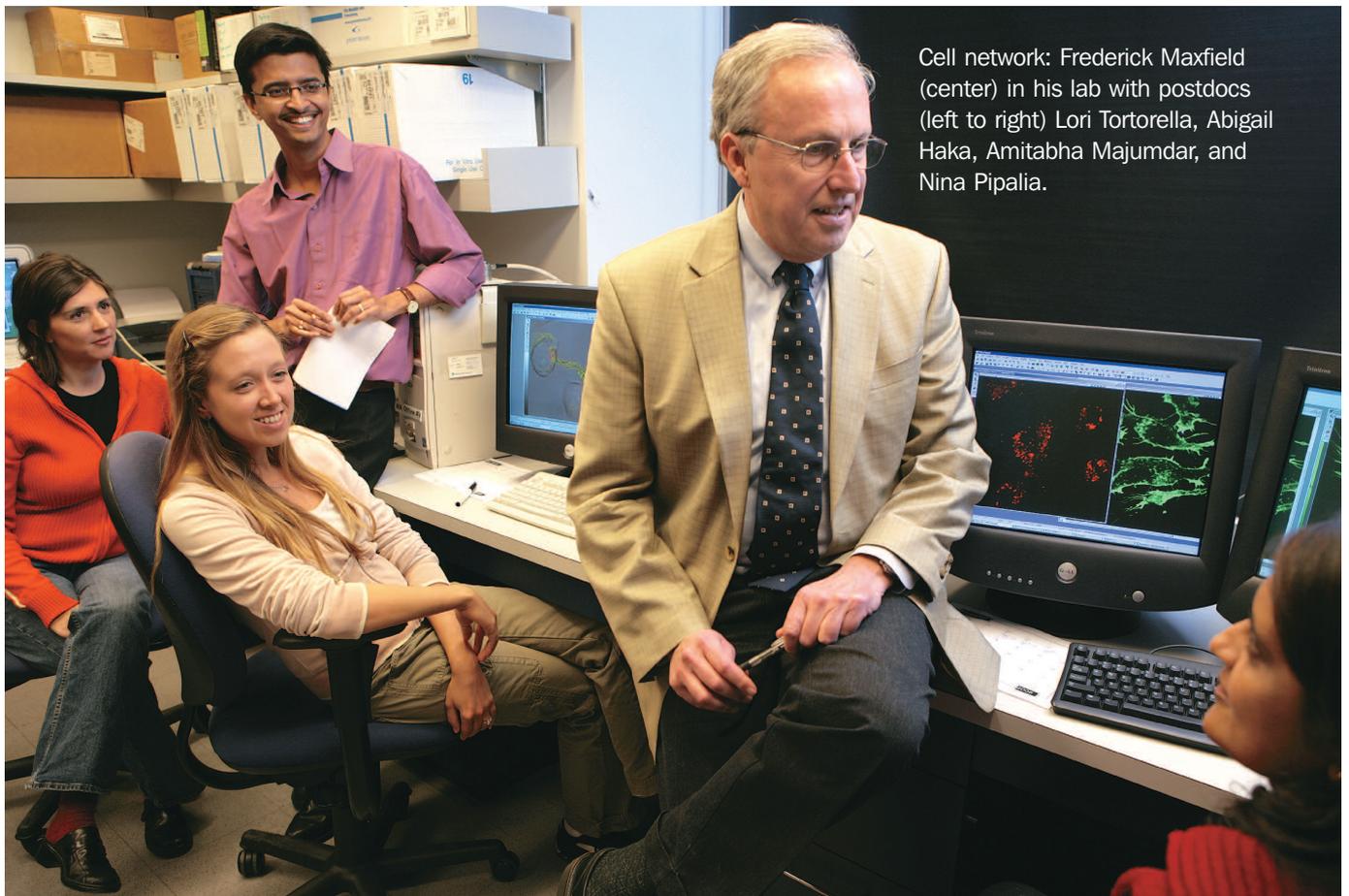


Under the microscope: Expression of annexin 2 in tumor vessels of experimental mouse lymphoma (figure 1); endothelial cells (fluorescing green) and pericytes (red) during tumor angiogenesis (2); robust angiogenic responses are seen in normal mice (3); while weak responses are observed in their annexin 2-deficient counterparts (4). Below: A human blood monocyte showing high-level expression of annexin 2.

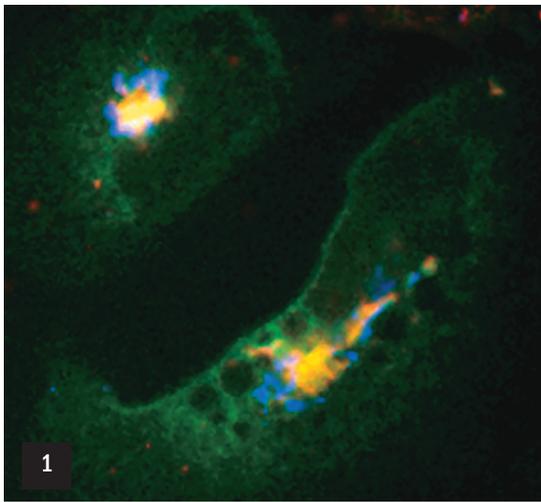


Biochemist Frederick Maxfield battles disease on the cellular level.

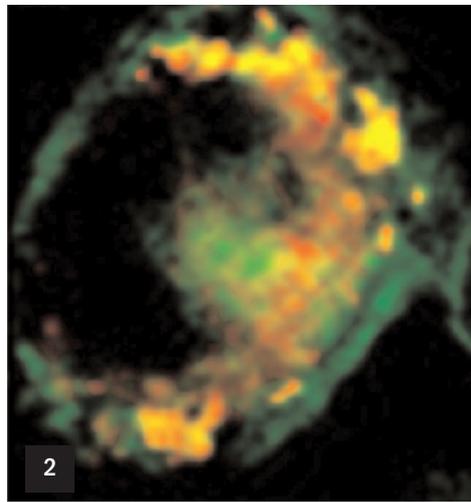
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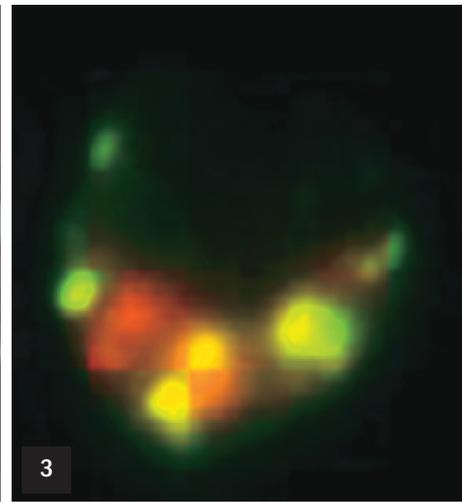
Cell network: Frederick Maxfield (center) in his lab with postdocs (left to right) Lori Tortorella, Abigail Haka, Amitabha Majumdar, and Nina Pipalia.



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Looking at lipids: Two living cells (1) showing fluorescent sterol (green), a fluorescent lipid (blue), and the iron-carrying protein transferrin (red). The yellow area indicates places where cholesterol has entered an organelle into which the transferrin has been delivered. Macrophage cells (2 and 3) showing lipid droplets (red) and fluorescent sterol (green).

Alzheimer's. Hardening of the arteries. Niemann-Pick, type C. At first glance, they seem worlds apart: Alzheimer's involves progressive memory loss, confusion, erratic emotions. Atherosclerosis culminates with explosive force in a heart attack or stroke. The exceedingly rare NPC attacks brain and body, with neurological symptoms and enlargement of the liver and spleen. The first afflicts the elderly, the second usually affects the middle-aged; NPC strikes elementary-school children and often kills them before their twenty-first birthday.

But what you see depends a lot on where you look.

Zoom down to the cellular level and you can see that all three diseases occur because of metabolic failures in the digestive organelles of individual cells. "It seems like a big jump to go from projects that are studying heart disease to studying Alzheimer's disease," says biochemist Frederick Maxfield, who has published papers on a host of basic cellular mechanisms. "But at the cellular level it's almost the same process—or very closely related."

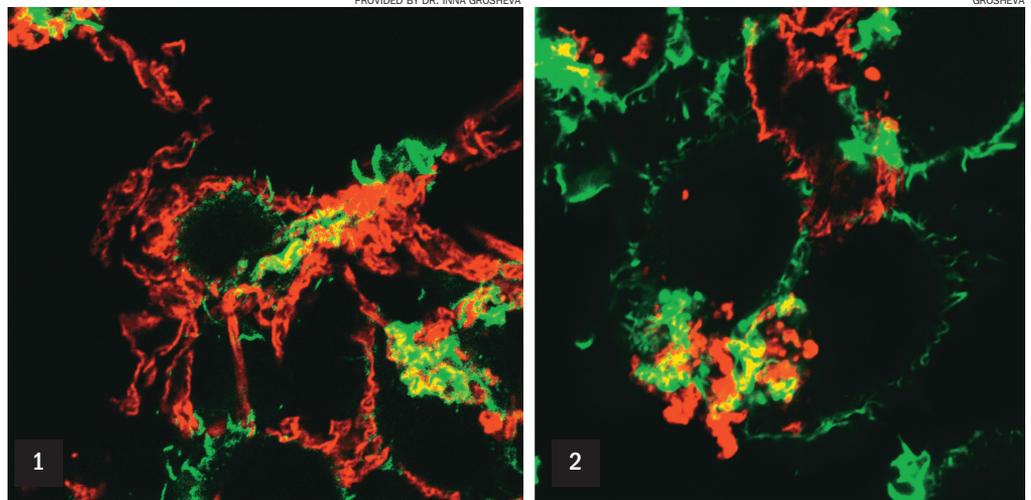
Credit the microscope. Maxfield's research has tackled two intersecting problems: observing the movement of molecules across the cell membrane and among the cell's organelles, and understanding the mechanisms of the process itself, known as endocytosis. "The question I'm interested in, very broadly," says Maxfield, "is: how do cells work?"

To find out, he has deployed a host of techniques including electron microscopy, fluorescence microscopy, confocal microscopy, and, most recently, multi-photon microscopy. "Endocytosis has turned out to be a much more complicated problem than any of us imagined in the 1970s, when I started working on it," says Maxfield, who serves as faculty adviser of Weill Cornell's core facilities for optical microscopy, cell screening, X-ray crystallography, and nuclear magnetic resonance.

Consider atherosclerosis: In a healthy system, cells known as macrophages patrol the extracellular spaces in a blood vessel, continuously digesting dead cells and bacteria. But when a macrophage encounters deposits of a lipoprotein—the bad cholesterol known as LDL—the system stalls. The macrophage consumes the cholesterol molecules, but it is unable to get rid of the ingested cholesterol. And then the macrophage stops moving. Eventually, the bloated cells accumulate along the blood vessel lining in an atherosclerotic lesion that narrows—and ultimately blocks—the blood vessel.

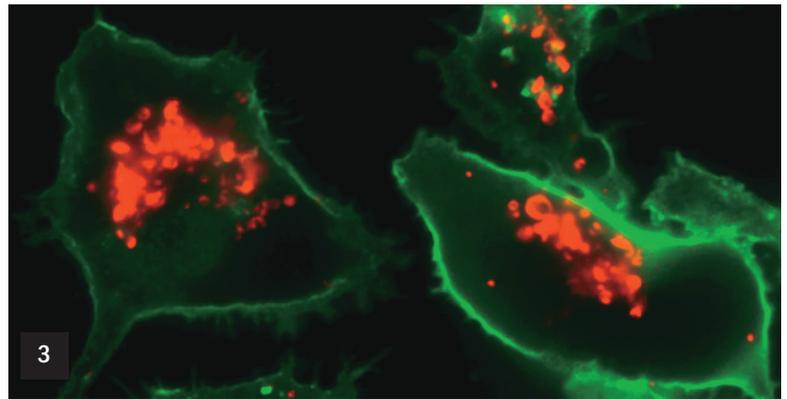
Researchers studied the cholesterol molecule in biochemical assays and with fluorescent staining in fixed tissue, but neither technique directly addressed the molecule's activity in living cells. Maxfield

Living color: Images (1 and 2) of lipoproteins (red) being digested by macrophages (green). 3: A microglial cell (green) has internalized Alzheimer's amyloid protein (red).



and his collaborators used yeast-derived sterols that are naturally fluorescent to label LDL, and then they overhauled the lab's microscope system to detect ultraviolet light, so they could analyze the molecular-level interactions between lipids and macrophages, and, in particular, the movement of cholesterol through the cell membrane.

When Maxfield read a paper linking a certain protein in lipoproteins with the early onset of Alzheimer's, he turned his attention to the neural equivalent of macrophages. These cells, known as microglia, serve as key inflammatory responders in the central nervous system. Like macrophages confronted with LDL, microglia fail to break down amyloid beta, the protein that forms plaque in the brains of Alzheimer's patients. "We realized we could now study a different and important biomedical problem using all the tools that we've been developing for studying macrophages and lipoproteins," Maxfield says. "Now we're finding interesting things about how microglial cells ingest amyloid, and how they can be tickled so they either do or don't digest the amyloid." Relative pH offers a clue. In most cells, lysosomes are acidic. But in microglia, they have a higher pH, perhaps making them less efficient at protein degradation. Altering the pH might kick the microglia into gear. "The challenge," he says, "is to take this research from tissue culture to animals."

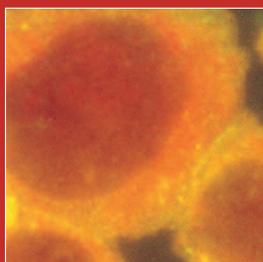
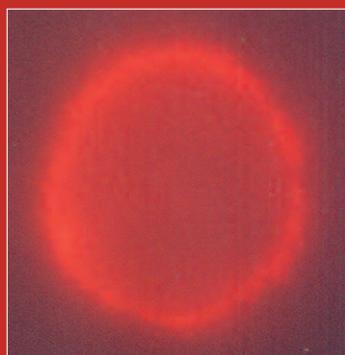


Disrupted cellular digestion also factors prominently in Niemann-Pick, type C: a genetic glitch in the production of certain proteins that hampers the ability of cells to release cholesterol from the lysosomes. The consequent buildup of cholesterol molecules leads to an intracellular traffic jam that engorges the lysosome, kills the cell, and eventually overwhelms the associated organ with lipid deposits. The most severe effects are in the brain, but other organs such as the liver and spleen are also affected. Over the course of the past decade, Maxfield and his group have investigated how the affected protein molecules work within the cell and begun exploring methods for reversing the process. In one project, the group uses robotic microscopes to screen libraries of tens of thousands of chemicals to identify those that could be further tested as novel drugs for NPC. So far, twenty chemicals that reduce cholesterol accumulation have been selected for further study.

Maxfield credits much of his research success to having the right equipment. "We're always on the lookout for new tools that can solve biological problems we haven't been able to solve with the old tools," he says. And if the right tool doesn't exist, he finds someone to make it. This fall, a collaboration with Cornell faculty in Ithaca—physicist Watt Webb and biomedical engineer Warren Zipfel—yielded a multi-photon microscope that Maxfield intends to deploy for observation of cellular processes in living tissue samples. "We'll look at everything from animal models to human tissues," he says. "We're also planning to start using it in collaboration with clinical researchers for diagnostic purposes."

— Sharon Tregaskis

2005–2006



a year in. review

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The Development Office looks back on a successful year, highlighted by the completion of the *Advancing the Clinical Mission* capital campaign and a rewarding reunion with classmates and students.

College Completes Capital Campaign

In January 2006, the Medical College announced the successful completion of its four-year, \$750 million capital campaign, *Advancing the Clinical Mission*—one of the largest campaigns ever undertaken by a medical school. Alumni were responsible for giving and raising more than \$30 million, including \$16 million in scholarship support. “These funds will enable Weill Cornell to recruit the very best faculty and students, and will ensure the College’s global leadership in the prevention and treatment of illness,” said Dean Antonio Gotto Jr.

The centerpiece of the campaign is the new thirteen-story Ambulatory Care and Medical Education Building, the first clinical building in the history of the Medical College. This new facility will consolidate many clinical practices under one roof, offering comfortable, convenient, one-stop shopping to our ambulatory care patients.

By expanding facilities and recruiting new faculty, the campaign’s clinical initiatives will pioneer new health-care paradigms for the heart, the brain, aging, children’s health, women’s health, and specialty care.

The campaign established new biomedical research programs in computational biomedicine, genetic medicine, stem cell research, pediatric research, and chemical biology. These programs will keep Weill Cornell at the forefront of scientific discovery and enable us to translate these findings into superior patient care.

A state-of-the-art Clinical Skills Teaching Unit has been designed, to provide medical students with the key diagnostic, examination, and communication skills necessary to enhance and enrich the doctor-patient relationship and patient outcomes. In addition, endowment funds from *Advancing the Clinical Mission* established a new MBA joint degree program that enables MD and PhD students to combine their Weill Cornell degrees with an MBA from the Johnson Graduate School of Management of Cornell University, giving them the advanced business education they need to succeed in the new health-care landscape.

Through the campaign, donors committed to forty Clinical Scholar Awards, which provide financial support to outstanding junior faculty for their teaching and research interests. The campaign also endowed twenty-four new professorships, acknowledging our intellectual leadership—our most accomplished physicians, scientists, and educators.

Reunion 2006

Reunion 2006, on the weekend of October 13–14, was hosted by Kenneth Swan, MD '60, and Gene Resnick, MD '74, with special dinners for the classes of 1945, 1955, and 1981. Nearly 600 alumni and family attended—the largest reunion total ever. The occasion provided an opportunity for alumni to renew old friendships, take a stroll down memory lane, and hear firsthand about the exciting work in progress at their alma mater. A host of presentations and activities took place both Friday and Saturday, capped by the Reunion Gala with a harbor-side view of Manhattan’s lively parade of river traffic from Pier 60, Chelsea Piers.

The Alumni Association also increased its efforts to reach out to alumni around the country through individual meetings as well as small gatherings, such as the reception held in March in Houston, Texas, to introduce a group of alumni to the affiliation between Weill Cornell and Methodist Hospital.

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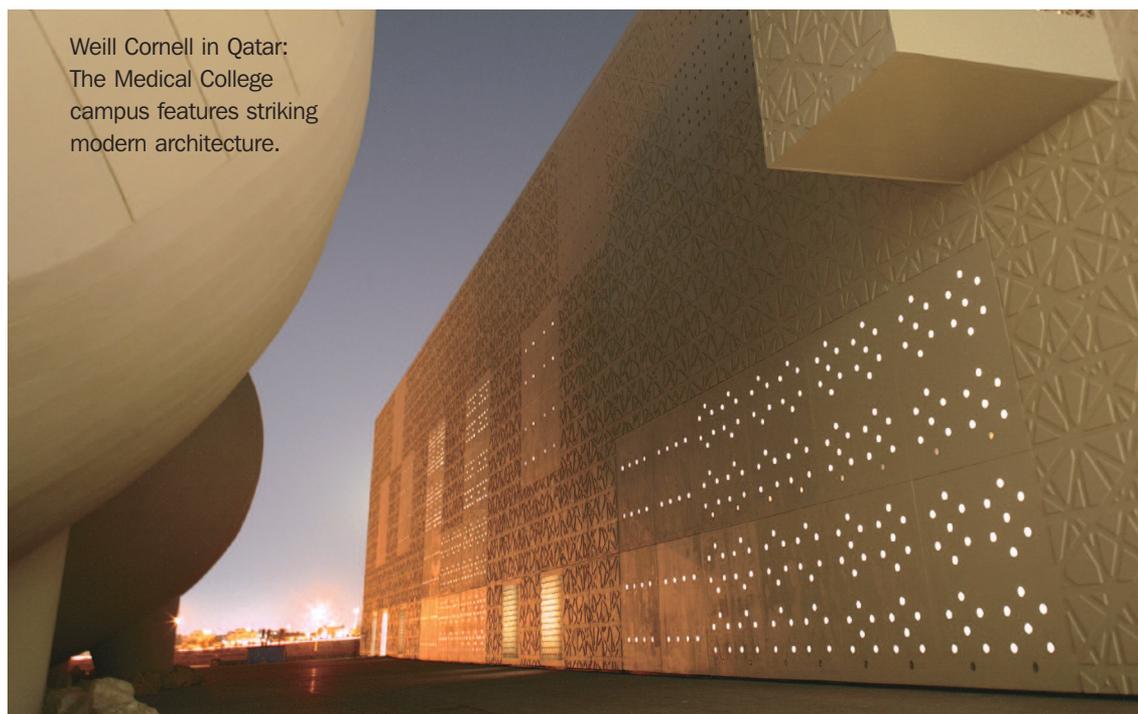
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Weill Cornell Medical College from Past to Present

1898 Cornell University Medical College is established with a gift of \$1.5 million from Colonel Oliver H. Payne

1915 Roscoe Giles is the Medical College's first black graduate, inaugurating the school's pioneering efforts in education for underrepresented minorities

1927 The Medical College joins forces with The New York Hospital

1928 George Papanicolaou reports on his studies of cervical and vaginal cells, leading to the development of the cytological "Pap test" for the early detection of cervical cancers

1952 Partnership between the Medical College and Sloan-Kettering Institute finalized, officially establishing the Graduate School of Medical Sciences of Cornell University

1955 Vincent du Vigneaud wins the Nobel Prize in Chemistry for his discovery of the peptide hormone oxytocin and the synthesis of other protein hormones

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- 1963** First kidney transplant in the metropolitan New York City area
- 1983** First MRI scanner facility in the New York City metropolitan area opens
- 1991** Tri-Institutional MD-PhD Program is established among the Medical College, the Rockefeller University, and Sloan-Kettering Institute
- 1997** The New York Hospital merges with the Presbyterian Hospital to form NewYork-Presbyterian Hospital, linking the Medical College to one of the world's largest health-care institutions

- 1998** Due to their unprecedented generosity and leadership, the Medical College is renamed the Joan and Sanford I. Weill Medical College of Cornell University
- 2002** First medical school in the U.S. to offer its MD degree in a foreign country with the founding of the Weill Cornell Medical College in Qatar
- 2007** New thirteen-story Ambulatory Care and Medical Education Building opens at 70th Street and York Avenue in New York City

Facts and Figures from Weill Cornell Medical College and the Graduate School of Medical Sciences

Student Statistics (Fall, 2006)

Enrolled Students

Medical students	.407
Graduate students	.365
MD-PhD students	.109

Degrees Conferred in 2005-06

MD	.101
PhD	.39
MS	.12

Entering Medical Students

Total enrolled students	.101
Men	.51
Women	.50
New York State Residents	.34
Out-of-State Residents	.66
International Students	.1

Students matriculated in the	
Tri-Institutional MD-PhD program	.11
Average Science GPA	.3.72
Cumulative GPA	.3.72
Average MCAT Score	.11.5
Verbal	.10.8
Physical Science	.11.6
Biological Science	.11.8
Age Range	.21-45
Average Age	.23

Entering PhD Students

Total enrolled students	.56
Men	.17
Women	.39
N.Y. State Residents	.10
Out-of-State Residents	.21
U.S. Citizens	.31
International Students	.25
Underrepresented Minorities	.2

Average Science GPA .3.5

Average GRE Scores (percentiles)

Verbal	.81st
Quantitative	.76th

Faculty Statistics

Total Faculty

Medical College	
Full-Time	.2,031
Part-Time	.191
Voluntary	.1,414

Graduate School of Medical Sciences

Weill Cornell Division	.164
Sloan-Kettering Division	.63

Postdoctoral Associates .215

Fellows .152

House Staff (Residents)* .621

*Figures for NewYork-Presbyterian/Weill Cornell Medical Center only.

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To The Rescue



Local Hero: Sanford Weill, chairman of Weill Cornell's Board of Overseers, with NYC firefighter Steve Halliday, who benefited from intercampus research on artificial skin for burn victims.

In November 2002, FDNY Lieutenant Steve Halliday was searching for survivors at a blazing house fire in Queens when a piece of burning furniture crashed down on him. He was nearly out of air when he was rescued, and his injuries were severe: fingers burned off, third-degree burns over 55 percent of his body.

But after extensive treatment at the NewYork-Presbyterian/Weill Cornell William Randolph Hearst Burn Center—including six surgeries and the application of an artificial skin invented by a team of researchers on the Ithaca and Manhattan campuses—Halliday has made a strong recovery. The firefighter was featured at the launch of Cornell's "Far Above" capital campaign, held at Weill Cornell on October 26. Says Cornell President David Skorton: "If you had any

question about how your gift to this campaign might be used, Steve Halliday is a prime example of how intercampus research is saving and improving lives."

Halliday gave a short speech at the campaign launch, beginning by extending his arms over his head to demonstrate his range of motion. "Some doctors told me I would never walk again," Halliday said. "The docs at Weill Cornell gave me hope, and today I am able to hold my children." And more: Halliday even competes in triathlons. "I'm not the fastest guy there," he told the audience. "But I've completed three races this year, thanks to Weill Cornell."

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Thank you for making Reunion 2006
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