weillcornellmedicine

THE MAGAZINE OF
WEILL CORNELL MEDICAL
COLLEGE AND
WEILL CORNELL
GRADUATE SCHOOL OF
MEDICAL SCIENCES

FALL 2009

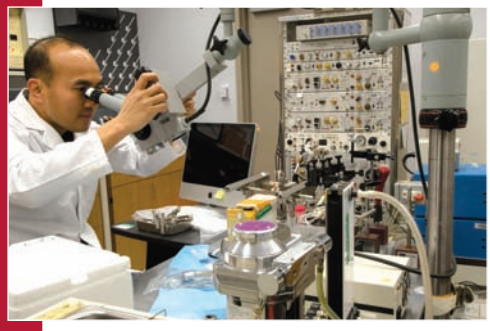
ANNUAL
REPORT ISSUE

The Age of Discovery

How Weill Cornell's Scientific Minds Are Advancing Health Care

Brain Power

This recently converted 70,000-square-foot building on East 61st Street is the nexus of the Medical College's translational initiatives in accelerating discoveries into superior treatments for the Weill Cornell community and beyond. The 61st Street Science Building is now home to the Clinical and Translational Science Center (CTSC), which focuses on bench-to-bedside research and supports the activities surrounding the $49 million grant Weill Cornell received from the National Institutes of Health (NIH). This initiative comprises and coordinates the efforts of eleven institutions in and around New York City and is the largest federal grant ever received by the Medical College.



The 61st Street Science Building also represents the first step in the Strategic Plan to drastically expand laboratory space at Weill Cornell. Notably, this new building has devoted two floors to the Division of Neurobiology Research and will be home to the work of Dr. Costantino Iadocola's investigations into the link between vascular health and the brain. Another floor has been dedicated to the Division of Immunology and the work of the division chief, Dr. Kendall Smith.

We expect that the opportunities created through the 61st Street Science Building and the planned Medical Research Building on East 69th Street will cause a significant acceleration in the discovery and approval of effective new therapies and improved outcomes.

Weill Cornell Medical College

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

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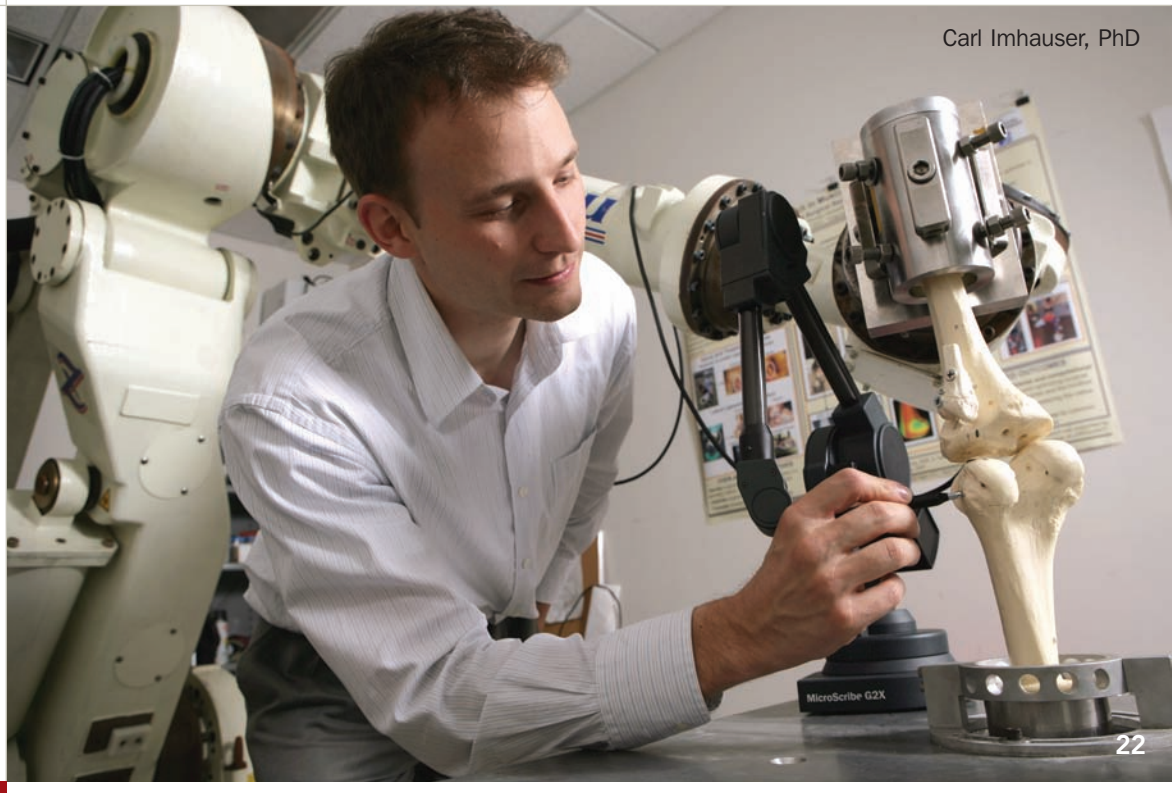

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Katherine Hajjar, MD, with students

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Remembering Weill Cornell alumnus

DAVID A. COFRIN, MD

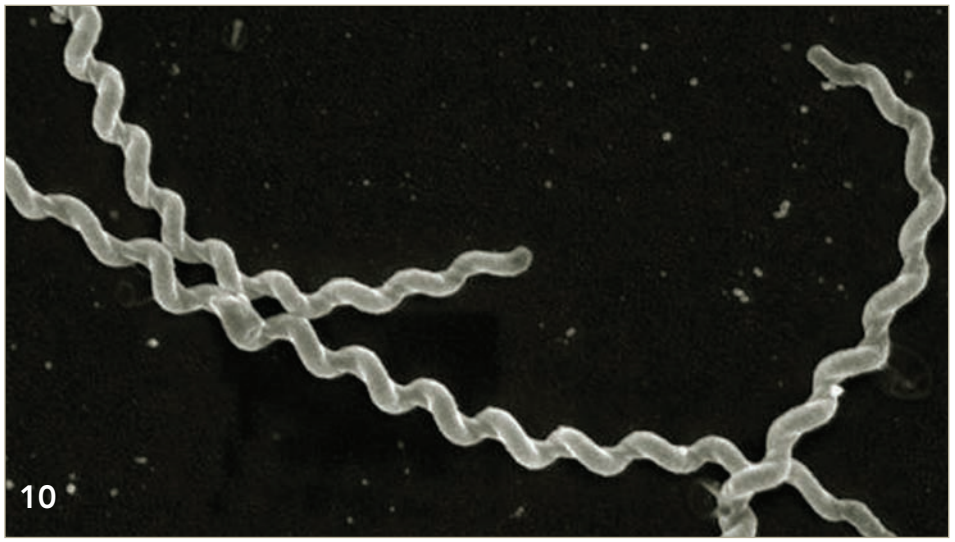
The entire Weill Cornell Medical College community mourns the loss of alumnus David A. Cofrin, who died peacefully on August 11, 2009, in Gainesville, Florida, with his wife, Mary Ann, by his side. He was eighty-five years old.

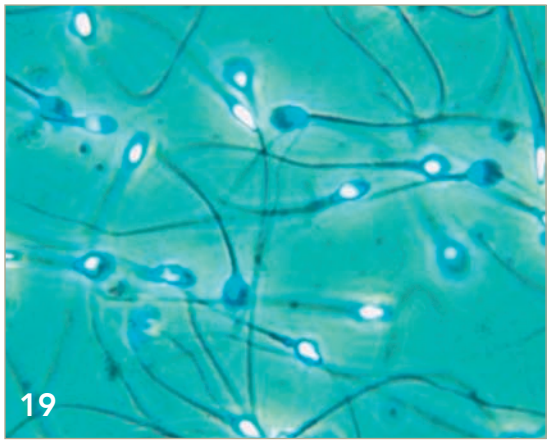
Dr. Cofrin was a "Double Red," having graduated from Cornell University–Ithaca in 1944 and the Medical College in 1947. Throughout his long and accomplished career as a surgeon in Florida, he remained devoted to his alma mater and to scientific inquiry. His desire to share this lifelong love of medicine and exploration fueled Dr. Cofrin's philanthropic support of the Medical College and the growth of its academic programs. He was, in fact, Weill Cornell's most generous alumnus, having given more than $15 million over the course of six decades.

Dr. Cofrin's impact on Weill Cornell is indelible. He generously funded the Structural Biology Institute, provided recruitment support for the chair of the Department of Biochemistry, and contributed to the enhancement of the biochemistry labs. He also supported and facilitated ongoing collaborations between his undergraduate and graduate campuses through funding for the Cornell High Energy Synchrotron Source in Ithaca.

His interest in biomedical informatics led to the establishment of the David A. Cofrin Center for Biomedical Information and included support for a unique resource, the Computer Assisted Visualization Environment. The Center has helped to elevate Weill Cornell's ability to tackle the most challenging questions in systems biology and open the door to major discoveries. For those who recall Dr. Cofrin's tour of the Center during the spring of 2008, it was evident that his energy and genuine love for the Medical College remained guiding passions well into his retirement.

This dear friend of the Medical College is survived by his wife, brother, children, and grandchildren. The Weill Cornell community is honored to pay tribute to Dr. Cofrin.





DEPARTMENTS

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Help Wanted

Antonio M. Gotto Jr., MD, DPhil, Dean of the Medical College

JOHN ABBOTT

The practice of medicine is much more than a career. It is a calling—a lifelong effort to unravel the secrets of the human body. To heed that calling is to invite a life of great sacrifice and endless work. It is not easy, and it is not for everyone.

By that standard, it should come as no surprise that the need for physicians in New York State greatly exceeds the supply—and the gap is growing. According to a recent report released by the State University at Albany's Center for Health Workforce Studies, by 2030 there will be a shortfall of 2,500 to 17,000 physicians.

The report, "New York Physician Supply and Demand Through 2030," finds that the greatest gaps are expected to occur in New York City and the Hudson Valley, where demand is projected to grow most rapidly. While no region will be immune, physician-supply growth should more closely parallel demand growth in the Capital District and Finger Lakes regions, while Western New York is expected to experience a decline.

New York City will have the greatest growth in demand. And while the number of physicians in the city is expected to increase overall, several specialties are projected to show declines, including ophthalmology, pathology, psychiatry, urology, and surgical disciplines. The numbers of practitioners in general internal medicine, family medicine, obstetrics and gynecology, and otolaryngology are expected to grow for a period, but then decline after 2020. Other areas are expected to show growth through 2030, including anesthesiology, cardiovascular disease, emergency medicine, general pediatrics, orthopaedic surgery, and radiology.

Each year, about 5,000 of the brightest and most accomplished undergraduates apply to Weill Cornell. They represent some of the best universities in the United States and abroad, and boast GPAs and MCAT scores that are all but unbeatable. The vast majority of them are seeking medical degrees, while others are prospective PhD students or candidates for our MD-PhD program. Only about 100 of these young men and women will be admitted, and by the time their clinical education, residencies, internships, fellowships, and other activities have concluded, many of them will have left New York City.

But because the city is a unique place to live and work—and also because of the facilities, partnerships, and professional opportunities that Weill Cornell and NewYork-Presbyterian Hospital can offer—many of those students-turned-physicians do stay in the city that never sleeps. They can practice anywhere in the world, but our graduates know only too well how much they are needed here. Many of our longest-serving and most prestigious faculty members began their medical careers on the Upper East Side—a trend that we hope to see continue and grow stronger. More than ever, it appears, we will need them here.

Star Search

David P. Hajjar, PhD,
Dean of the Graduate
School of Medical Sciences

It is no secret that we live in a society obsessed with fame and celebrity. Even in the world of science, the yearning for fame—and maybe worldwide recognition for a major research discovery—is prevalent. But whenever someone mentions the concept of a "superstar" researcher, I can't help but laugh.

The scientists, technicians, and assistants who populate the laboratories of Weill Cornell Graduate School of Medical Sciences are brilliant, accomplished men and women advancing the scope of knowledge in their chosen fields. I don't get the impression that they are daydreaming about stardom. It is the pursuit of knowledge and understanding that drives them, not the pursuit of some individual award or recognition.

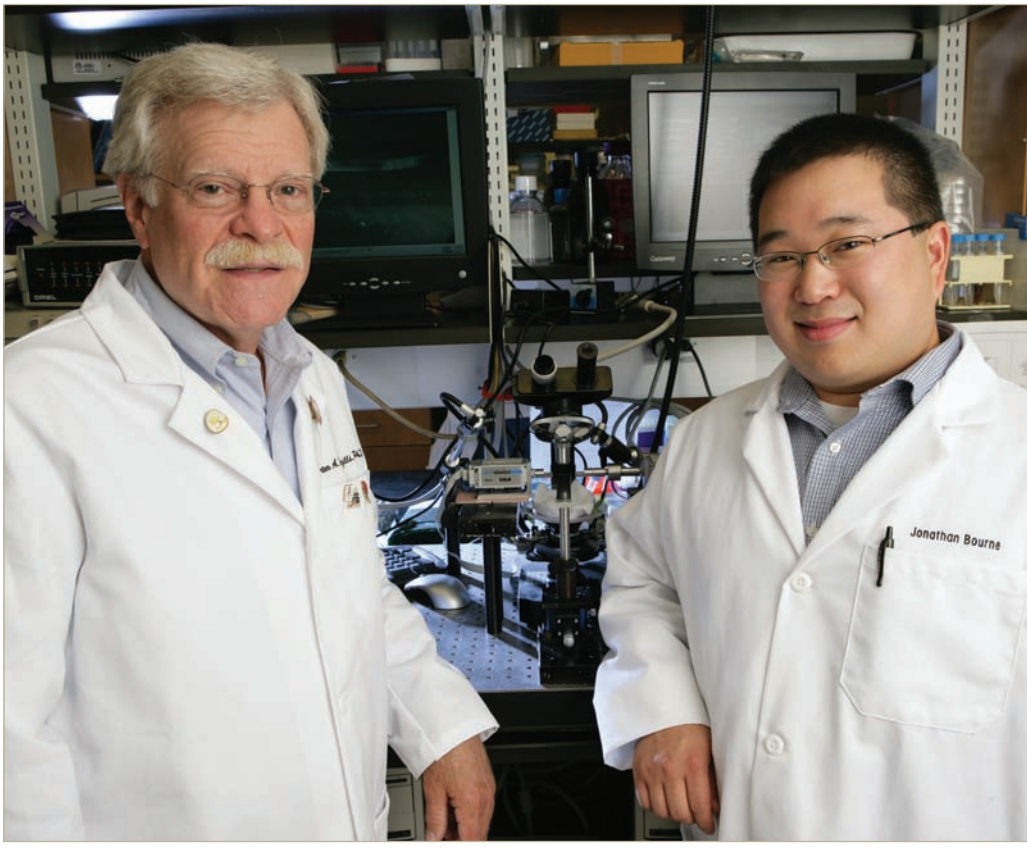
But that's not to say that our faculty and students aren't among national—even world—leaders when it comes to research achievements and funding. For example, Jonathan Bourne—a physiology, biophysics, and systems biology student in Dr. Peter Torzilli's lab—was awarded second place in the PhD student paper competition and poster presentation at the 2009 Summer Bioengineering Conference in Lake Tahoe, California. He placed in the Tissue and Cellular Biomechanics and Imaging category for his presentation, "Collagen Molecular Conformation Exhibits Strain-Rate Dependent Response to Axial Deformation in Silico." Jonathan's research was supported through an NIAMS grant and the NIH-supported Clinical and Translational Education Program of Weill Cornell's Clinical and Translational Science Center, recently established with the help of a $49 million NIH grant.

As you know, grant funding is the lifeblood of research at an academic medical center. Not only does it make our work possible, but support from the NIH and other entities raises the profile of an institution, attracting key personnel and helping to secure needed equipment and infrastructure. It's an open secret that some academic institutions use their funding to promote research "superstars," hoping to bolster their reputations based on a personality rather than the collective intellects of faculty, graduate students, lab assistants, and staff.

Thanks to the American Recovery and Reinvestment Act of 2009 (a.k.a. President Obama's "Stimulus Package"), Weill Cornell Medical College recently secured millions of dollars in new research funding. Much of that money will support scientists in the Graduate School. In fact, as of late September, we have received dozens of stimulus grants to bolster existing programs and launch new ones. We are fortunate to have the full support of our Board of Overseers and the institution's administration, and the mutual respect and confidence of those who provide the funds that support our important work. We have talented people who sincerely believe they can make the world a better place with regard to patient care.

After the Summer Bioengineering Conference, Jonathan Bourne said, "I'm grateful that my work was recognized, but—more important—this award acknowledges the training and mentoring available to us and the relevance of research done at Weill Cornell to the scientific community."

Substance rather than celebrity—I could not have said it better myself.



ABBOTT

Peter Torzilli, PhD, and doctoral candidate Jonathan Bourne

Patient-Focused Heart Institute Opens

Preventing heart disease in women will be a priority of new Ronald O. Perelman Heart Institute

RICHARD LOBELL

Heart felt: On hand to mark the opening of the Perelman Heart Institute were (from left) David Letterman, Mayor Michael Bloomberg, Ronald Perelman, NYPH CEO Herbert Pardes, MD, NYPH trustee David Koch, and Institute head O. Wayne Isom, MD.

In September, NewYork-Presbyterian Hospital/Weill Cornell Medical Center celebrated the opening of the Ronald O. Perelman Heart Institute in a ceremony where dignitaries included New York City Mayor Michael Bloomberg and TV host (and former cardiac patient) David Letterman. The facility—made possible by a $25 million gift from Perelman, a NYPH trustee—will offer comprehensive cardiovascular care and heart-health education. The physical plant includes a new five-story atrium designed to be a "medical town square" featuring a patient welcome center, clinical trials enrollment center, and education resource center. This new facility, said NYPH President and CEO Herbert Pardes, MD, allows the hospital "to build on an already strong foundation, establishing new standards of quality care and a new concept of what is possible for patients and their families."

Among the institute's priorities: bridging the gender gap in cardiovascular medicine. Although women are twice as likely as men to die after a heart attack, heart disease was long considered a man's issue—making women less likely to identify symptoms or seek treatment. "Clearly, we are making a statement to our patients about our commitment to cardiac care, with a special emphasis on heart health and women," said Dean Antonio Gotto. "Mr. Perelman's gift will save many lives."

Stewart Named Senior Associate Dean for Clinical Affairs

Effective January 1, Michael Stewart, MD, will become senior associate dean for clinical affairs. He succeeds retiree E. Darracott Vaughan, MD, now chairman emeritus of the Department of Urology. In his new role, Stewart will oversee matters involving clinical organization and patient care, serving as the chief liaison between clinical faculty, the Physician Organization, and the dean's office. Stewart will remain chairman of otorhinolaryngology at Weill Cornell and otorhinolaryngologist-in-chief at NYPH/WCMC.

WEILL CORNELL ART & PHOTOGRAPHY

Michael Stewart, MD

Medical College Goes Smoke-Free

In August, Weill Cornell joined forces with NYPH and Hospital for Special Surgery to create a completely smoke-free campus. Smoking is now prohibited virtually everywhere on college grounds, including building entrances, courtyards, garages, plazas, and sidewalks. The new "Smoke-Free WCMC" policy has been added to employee and student handbooks, and the Medical College is offering free smoking-cessation workshops and other services for people who want to kick the habit.

Burn Center Sponsors Survivor Event

In August, hundreds of burn survivors and their families attended a conference at the Sheraton Hotel in Midtown, sponsored by Weill Cornell's Hearst Burn Center and the New York Firefighters Burn Center Foundation. The event included workshops on such topics as how to use cosmetics to conceal burns and how burn injuries can impact families. Guest speakers included Roger Yurt, MD, director of the Burn Center, which is the busiest in the nation. Kim Phuc Phan Thai, the subject of a famous photograph taken during the Vietnam War that showed her running down the street crying after suffering burns from a napalm attack, spoke about living with a severe burn injury. The event was hosted by the Phoenix Society, the largest national nonprofit serving burn survivors.

MD-PhD Student Elected to Board of Overseers

Weill Cornell students have elected MD-PhD candidate Jeffrey Russ to a three-year term as student representative on the Board of Overseers. He will attend the board's four annual meetings, serving as the voice of medical and graduate students. Russ, who helped found the Student Green Initiative at the Medical College, ran on a platform of environmental and sustainability issues. "I thought this would be a good way to implement some of the projects that I've been working on with people who can really make changes," he says. A graduate of the University of Pennsylvania, Russ previously served on the Medical Student Executive Committee.

Picture this: A portrait of the Medical College's foremost benefactor, Sanford Weill, and Dean Antonio Gotto was presented at a small ceremony in September. In attendance were (from left) Dean Gotto and his wife, Anita Gotto, and Joan and Sanford Weill. The portrait, by Everett Raymond Kinstler, hangs in the lobby of the Weill Greenberg Building.

RICHARD LOBELL

WCMC-Q Expands Options for Pre-Meds

Starting with the class that matriculates next August, the Qatar branch is adding a third year to its pre-med program. "The three-year pre-medical curriculum will provide greater course breadth, more opportunities for research and independent study, more time to acquire English language skills, and greater opportunity for academic success," says Interim Dean Javaid Sheikh, MD. All students will take the same classes during the first semester; then, based on their grades, some will have the option to finish in two years on an accelerated track.

Grant Establishes Disparities Research Center

Associate professor of medicine and public health Carla Boutin-Foster, MD, MS '99, has been awarded a five-year, $8 million grant from a division of the NIH to support a Comprehensive Center of Excellence in Disparities Research and Community Engagement. The aim of the center—a consortium that includes Weill Cornell, Hunter College, CUNY, and NYU—is to integrate research with community outreach in an effort to improve minority health. Its funding comes from the National Center on Minority Health and Health Disparities; Boutin-Foster will serve as director.

WEILL CORNELL ART & PHOTOGRAPHY

Desiree Pardi, MD, PhD

Remembering Dr. Pardi

Assistant professor of medicine Desiree Pardi, MD, PhD, director of the Palliative Care Consult Service at NYPH/WCMC, died in September after a battle with breast cancer. A 2002 graduate of Mount Sinai School of Medicine, Pardi did her residency in internal medicine at NYPH/WCMC and a fellowship in pain management at Sloan-Kettering. She was board certified in internal medicine and hospice and palliative medicine.

Mark Lachs, MD, co-chief of the Division of Geriatrics and Gerontology, notes that Pardi was one of the founders of the consult service at NYPH/WCMC and a "tireless advocate" for the cause of palliative care. "She was generous of her time and expertise to teach the art and science of palliative care to all levels of learners," Lachs says. "She had a profound impact not only on the thousands of patients whose lives she touched, but played a significant role in transforming the culture of the institution around the issue of palliative care."

The Desiree Pardi, MD, Memorial Fund for Palliative Care has been established; according to Lachs, plans are also in the works to name a family room at the hospital in her honor.

"Dr. Pardi was an inspiration to all of us, enriching our lives and making us all better for having had the privilege and joy of working with her," said three colleagues in a statement announcing her death. "She was beloved by the medical students whose lives she touched in her many teaching activities."

WCMC Garners Federal Stimulus Funds

As of mid-October, Weill Cornell researchers had received more than five dozen NIH grants under the American Recovery and Reinvestment Act of 2009. The stimulus funding includes work in such fields as AIDS, kidney disease, cancer, Parkinson's disease, and more. The single largest grant—$1.9 million from the National Institute on Drug Abuse—went to Ronald Crystal, MD, the Bruce Webster Professor of Internal Medicine, to develop an adenovirus-based anti-cocaine vaccine.

Correction

Due to an editorial oversight, the name of Margaret Bearn, wife of fifty-six years to Dr. Alexander Bearn, was omitted from his obituary in the Summer 2009 issue. In addition to his wife, Dr. Bearn is survived by his two children, five grandchildren, and brother. We sincerely regret the error.

TIP OF THE CAP TO...

J. Emilio Carrillo, MD, associate professor of clinical public health, winner of the National Medical Fellowships Distinguished Alumni Award.

Joseph Fins, MD '86, chief of the Division of Medical Ethics, elected to the American Osler Society, which comprises members of the medical profession and allied fields who follow the example of William Osler, MD, a father of modern medicine.

Heather Taffet Gold, PhD, assistant professor of public health, who won the award for best paper by a young investigator from the Society of Medical Decision Making for "Correlates and Effect of Suboptimal Radiotherapy in Women with Ductal Carcinoma in Situ or Early Invasive Breast Cancer."

Tobias Hohl, PhD '00, MD '01, an assistant professor in the Division of Allergy and Infectious Diseases at the University of Washington, Seattle, winner of the Young Investigator Award from the American Society for Microbiology.

Yoon-Seong Kim, MD, PhD '03, assistant professor of neuroscience, one of ten winners of grants from the Michael J. Fox Foundation to study Parkinson's disease.

David Lyden, MD, PhD, the Stavros S. Niarchos Associate Professor in Pediatric Cardiology, named head of the Champalimaud Metastasis Programme at Weill Cornell.

Michael Posner, PhD, adjunct professor of psychology in psychiatry, awarded the National Medal of Science by President Barack Obama.

Marcus Reidenberg, MD, professor of pharmacology, elected chair of the WHO's Expert Committee on the Selection and Use of Essential Medicines.

Cornell President **David Skorton, MD**, named by U.S. Health and Human Services Secretary Kathleen Sebelius to a four-year term on the advisory council of the National Institute of Biomedical Imaging and Bioengineering.

FROM THE BENCH

Genetic Test Could Aid Colon Cancer Treatment

Some 29,000 people in the U.S. have metastatic colorectal cancer. Of those, one in ten have a variant in their DNA that causes white blood cell counts to drop after they undergo standard chemotherapy, putting them at higher risk for bacterial infections and even death. To prevent this, a new genetic test has been developed to identify high-risk patients, potentially allowing physicians to put susceptible patients on lower doses; researchers have now evaluated its cost effectiveness. In work published in *Cancer*, they determined that testing can be beneficial—but only if reduced doses are as effective as full doses. The work, says lead author Heather Taffet Gold, PhD, assistant professor in the Division of Health Policy, "remains to be verified by clinical research."

Quick Response Is Key in Bioterror Attacks

In the event of an anthrax attack on a major metropolitan area, rapid response and treatment are vital, says associate professor of public health Nathaniel Hupert, MD. In work published in *Medical Decision Making*, Hupert and colleagues report that any delay beyond three days in distributing antibiotics would overwhelm hospitals with critically ill patients. "No matter how well-organized and prolonged a treatment program is, it must be quickly implemented," Hupert says. "In fact, our analysis shows that time-to-treatment is roughly twice as important as the duration of the distribution program."

Targeted Prostate Therapy

Researchers have discovered a new gene fusion that is highly expressed in 5 percent of prostate cancers. The fusion, known as NDRG1-ERG, produces a cancer-specific protein that may serve as a target for drug therapies. According to Mark Rubin, MD, the Homer T. Hirst Professor of Oncology in Pathology, the discovery "may help physicians prescribe tailored therapies for their patients by avoiding the trial and error that is often associated with cancer treatments." The work, which was published in *Neoplasia*, could also make it easier to distinguish between cancer and non-lethal diseases such as benign prostatic hyperplasia.

ECG May Predict Cardiac Death

A measure of the time it takes for an electrical signal to travel through a pumping heart—known as QRS duration, or QRSd—could help physicians identify patients at risk for sudden cardiac death. Using data drawn from the LIFE study (a large, multicenter hypertension study lasting seven years and comprising more than 9,000 patients), cardiologist Peter Okin, MD '80, and colleagues found a clear link between prolonged QRSd and sudden cardiac death. "No one has ever really looked at this," Okin says, adding that further studies on larger patient populations will be needed to ascertain if QRSd is a cause of death or merely an indicator. The research was published in the *European Heart Journal*.

Why Are African Americans Predisposed to Kidney Disease?

African Americans comprise 32 percent of all patients treated for kidney failure and are four times more likely than whites to develop renal disease; a new study may help explain why. Manikkam Suthanthiran, MD, the Stanton Griffis Distinguished Professor of Medicine, and Phyllis August, MD, the Ralph A. Baer Professor of Medical Research, have found that blacks are more likely to have elevated levels of the protein TGF-beta1, which raises the risk of hypertension and kidney disease. Although the mechanisms of TGF-beta1 require further study, the authors say that it may boost retention of sodium in the kidneys and also may affect the activity of renin, an enzyme that constricts blood vessels and raises pressure. The results were published in *Kidney International*.

Preventing Suicide and Depression in Older Adults

"Almost one in ten older adults in the United States has some form of depression," states George Alexopoulos, MD, "and one-fifth among them contemplates suicide." Director of the Institute of Geriatric Psychiatry at the Westchester Division, Alexopoulos is lead author of a two-year study of suicide prevention in older adults that followed some 600 patients. He points out that although most older adults are seen by primary care physicians, depression often goes untreated because of doctors' time constraints and patients' reticence to discuss their symptoms. The results were published in the *American Journal of Psychiatry*.

A New Front in the TB Battle

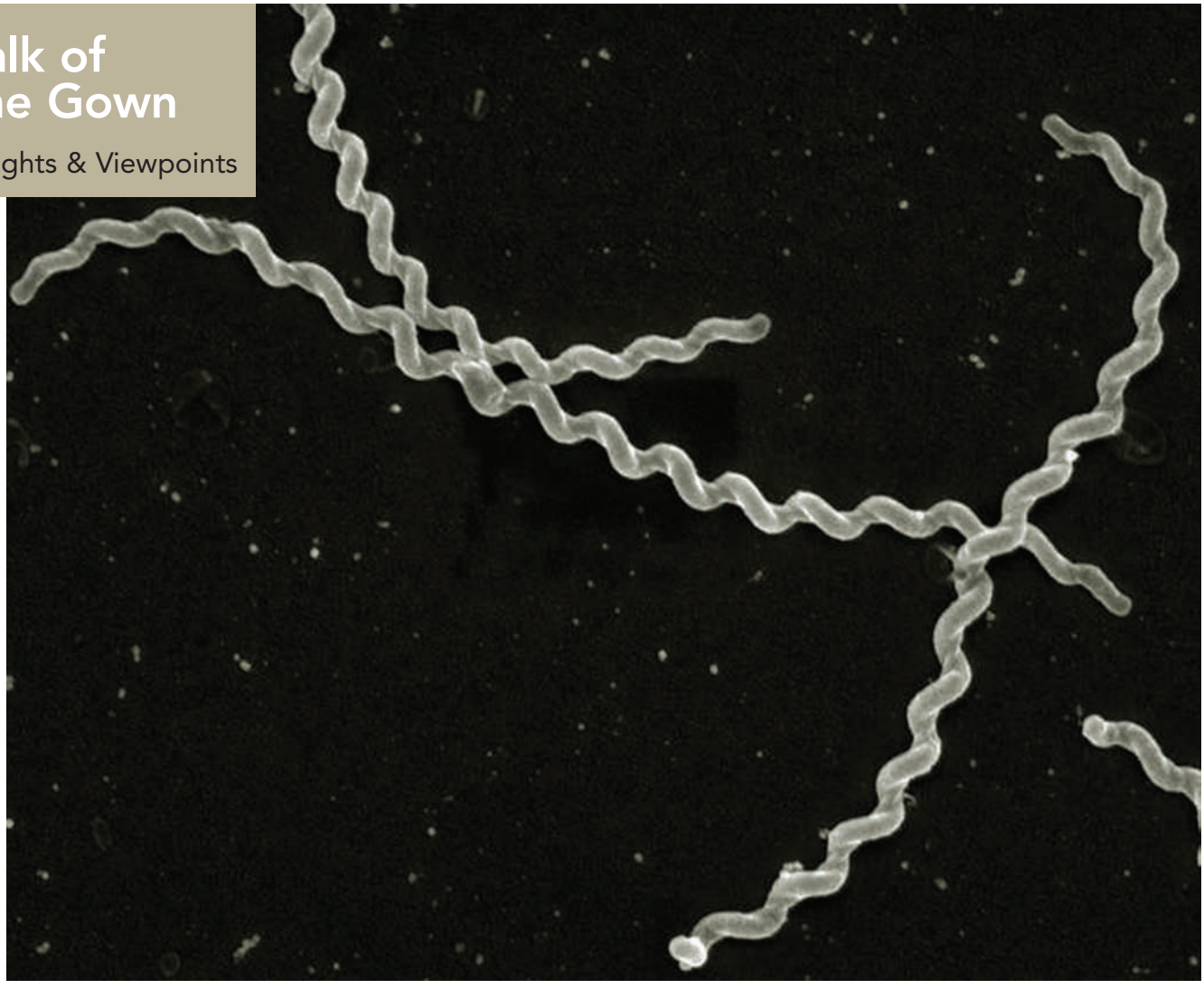
Researchers have identified compounds that inhibit the ability of tuberculosis-causing bacteria to survive dormant in infected cells—a key reason why the disease is so hard to combat. The work, published in *Nature*, could lead to more powerful TB treatments. "There are few drugs that successfully combat TB in its dormant stage, which makes the bacterium so resilient in the body," says senior author Carl Nathan, MD, the R. A. Rees Pritchett Professor of Microbiology, whose team screened 20,000 compounds for TB inhibition activity. "More important, there are many antibiotics that kill bacteria by blocking the synthesis of proteins, but there are none that kill bacteria by interfering with protein breakdown, as we have found here." Worldwide, *Mycobacterium tuberculosis* infects one person in three.

JOHN ABBOTT

Nathaniel Hupert, MD

WEILL CORNELL ART & PHOTOGRAPHY

Peter Okin, MD '80



PROVIDED

Urban Illness

A Brazil-based researcher develops a rapid test for leptospirosis, a scourge of slums in the developing world

Infectious agent: *Leptospira interrogans* bacteria

A disease that causes untold suffering in many desperately poor urban slums is closer to being conquered, thanks to a collaboration among Weill Cornell researchers, Brazilian scientists, and a U.S. biotech company. Little known in the developed world, leptospirosis is endemic in the slums of Rio de Janeiro, Mumbai, Cali, Jakarta, Manila, and other impoverished areas. Infection occurs when people are exposed to urine from rats, cattle, pigs, horses, dogs, and other animals whose kidneys have been colonized by *Leptospira* bacteria; when tropical storms or hurricanes cause open sewers to overflow, people can come into contact with contaminated water or soil.

Because the early symptoms of leptospirosis can resemble illnesses such as flu, malaria, or dengue fever, a definitive initial diagnosis is often difficult. Early treatment is critical, though: illness can quickly progress from the initial stage of fever, chills, and vomiting to the more severe Weil's disease, which can lead to meningitis or failure of the liver or kidneys. Weil's disease has a 10 to 15 percent fatality rate, but an even more dangerous form—severe pulmonary hemorrhage syndrome, in which half of patients die—has emerged in the Brazilian shantytowns, or *favelas*. Each year, there are an estimated 500,000 new cases of leptospirosis worldwide; in Brazil, more than 12,000 people contract the more severe forms of the disease.

Last year, a group of infectious disease scientists led by Albert Ko, MD, an associate professor in Weill Cornell's Division of Infectious Disease who is based in Brazil, developed a successful prototype test for leptospirosis—one that requires only a finger-prick blood test and yields a highly accurate result within fifteen minutes. Because the diagnostic test currently in use is woefully inadequate, a way to establish early infection has been the holy grail. "To make a definitive diagnosis using the current test requires two blood samples, one during the acute illness phase and another three weeks later," says Ko. "But in the *favelas*, where families live on about $2 a day, the patient may not even have the fare to travel back to a clinic for the second test and many die before returning." Even if two samples are obtained, it can take months or even a year to get a diagnosis, because only a few labs in the world do the testing. Without fast and appropriate treatment, the patient may develop profound health problems—particularly devastating because the disease most often strikes adult breadwinners.

PROVIDED

Field work: An urban slum study site. Bottom: Infectious disease professor Albert Ko, MD (in white shirt on far right), with his research team.

PROVIDED

More than forty years ago, under the leadership of Warren Johnson, MD, now director of Weill Cornell's Center for Global Health, the Medical College launched a program to study tropical diseases in Brazil. Since then, urbanization has transformed the country: about 90 percent of Brazilians live in cities and of those, 30 to 40 percent live in *favelas*. Ko came to Brazil as an infectious disease fellow in 1996 and never left; in 1999, the *Lancet* published his early leptospirosis work, which drew attention to the fact that it was changing from a mostly rural phenomenon—striking farmers in China, for example—to one affecting poor city dwellers.

For the 2008 study, Ko collaborated with Konstantin Lyashchenko, PhD, senior R&D director at ChemBio, a New York-based company that specializes in rapid diagnostics, and a team headed by Mitermayer Reis, MD, PhD, at the research branch of the Brazilian Ministry of Health. They discovered how to create biological markers for leptospirosis from antibodies of infected patients; ChemBio created the prototype using a proprietary method that allows heightened sensitivity to protein markers. These Phase I studies showed an 85 percent overall sensitivity rate to the markers and a 78 percent success rate in identifying leptospirosis in the first seven days of illness—the crucial window during which antibiotics provide the greatest benefit.

In Phase II—funded by a $3 million NIH Small Business Innovative Research grant—the team is working to fully develop the rapid test and bring it to market. "Although leptospirosis is a major health problem in many poor countries, it also is an emerging issue in developed countries," says Ko. "As the climate changes and causes more flooding, microbes such as the pathogen that causes leptospirosis will flourish. Coupled with the fact that by 2025 an estimated two billion people will live in cities, infectious diseases like this are going to become better known in many more parts of the world."

— Anna Sobkowski

Soil & Seed

Oncologist David Lyden explores the mechanism of metastasis

In the garden, an abundant harvest relies equally on quality seed and healthy soil. The same principle applies to the metastasis of cancer—without a welcoming niche in distant organs, a primary tumor may grow, but it won't spread. The concept isn't new; in 1889, a young West London physician investigated more than 700 cases of fatal breast cancer, deploying an agricultural metaphor. "When a plant goes to seed, its seeds are carried in all directions," Stephen Paget mused in a paper published in the *Lancet*. "But they can only live and grow if they fall on congenial soil." The metaphor seems intuitive—yet for nearly a century, Paget's hypothesis was largely ignored.

Though prevailing theories of the time credited the circulatory system with distribution of cancerous cells, Paget found that the liver disproportionately hosted secondary lesions—while the spleen, equally exposed to cancer cells in the blood, did not. Metastasis, he concluded, must owe to more than chance. "The best work in the pathology of cancer is now done by those who . . . are studying the nature of the seed," he wrote. "They are like scientific botanists; and he who turns over the records of cases of cancer is only a ploughman, but his observation of the properties of the soil may also be useful."

Since the late Nineties, Weill Cornell pediatric oncologist David Lyden, MD, PhD, has bent his shoulder to the work Paget described, detailing the biochemical mechanisms that prepare the "soil" for metastatic cancer. In the intervening decade, *Nature*, *Science*, and a dozen other journals have published Lyden's step-by-step analysis of the process that transforms healthy cells into tumor emissaries, preparing what he calls the "pre-metastatic niche." "Paget came up with the original theory, but he didn't have the tools to investigate it," says Lyden, the

David Lyden, MD, PhD

JOHN ABBOTT

Stavros S. Niarchos Associate Professor in Pediatric Cardiology. "We were lucky to have the tools—molecular biology, microarrays, characterization of the proteins on the surface of the cells, the known enzymes that participate."

Lyden has high hopes that today's analytic tools and the insights they reveal will transform the prognosis for patients with advanced cancer. Ninety percent of cancer fatalities owe to metastasis, says Lyden—yet oncologists don't know enough about the process in humans to short-circuit it. "Even though standard treatment of surgery and chemotherapy has improved survival, there are too many deaths and too many side effects," says Lyden, who treats children with brain tumors at Memorial Sloan-Kettering Cancer Center. "We need selective therapies and targets." Chemotherapy works by killing any rapidly dividing cell, he notes, from cancer to hair to the lining of the digestive tract. That means there's a lot of collateral damage associated with current treatment options. "The better approach is to understand all of the steps in metastatic disease," he says. "If we understand what's going on in metastatic tissue, and if it's specific to metastatic tissue, then we should target that rather than anything that's a dividing cell."

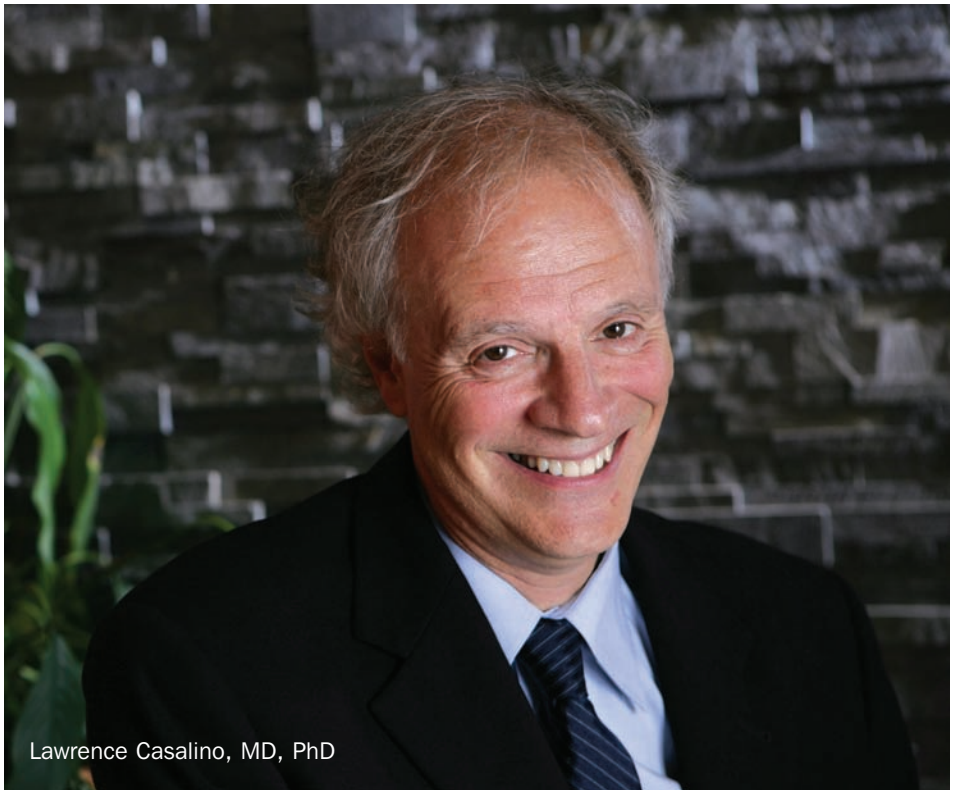
Already, Lyden and his collaborators have documented the role of growth factors secreted by the tumor in preparing the way for metastasis, described how stem cells in bone marrow establish the vascular supply for distant lesions, and detailed the influence of inflammation on the pre-metastatic niche using mouse models. In April 2009, *Nature Reviews Cancer* published "The Metastatic Niche: Adapting the Foreign Soil" by Lyden and Bethan Psaila, a research associate in the Department of Hematology at London's Imperial College School of Medicine, who completed a Fulbright fellowship in his lab. "There's a balance of the cancer and the host," says Psaila. "Targeting the cancer cells alone isn't enough. You also need to target the normal cells, the normal microenvironment, because they play a role. It's obvious that you need to design treatments that attack cancer cells, but it's less obvious that the body is playing a role as well."

Perhaps, the researchers say, the team's most important insight boils down to a matter of timing. "The tumor cells are released early on, circulating even when you have a small, localized tumor," says Rosandra Kaplan, Weill Cornell's Charles, Lillian, and Betty Neuwirth Clinical Scholar in Pediatric Oncology and an assistant professor of pediatrics who did a fellowship in Lyden's lab and continues to collaborate with him. "The circulating cells make a welcoming committee. They're changing the landscape and changing the microenvironment." In their current work using human tissue samples, Lyden and Kaplan have focused on further exploring the biochemical processes under way at prospective metastatic sites at the earliest stages of a primary tumor's development. Says Kaplan: "David challenges people to think differently."

— Sharon Tregaskis

In Practice

Studying physicians on the front lines



Lawrence Casalino, MD, PhD

JOHN ABBOTT

As debate rages over health-care reform, many opponents of the Obama Administration's plan have repeated a common refrain: a system of national health care "will put a bureaucrat between you and your doctor." Regardless of where one stands on the proposals currently battling their way through Congress, a study by Weill Cornell researchers has found that one thing's for sure: there's plenty of red tape already—though not necessarily from government bureaucrats.

In a national survey of physician practices, Lawrence Casalino, MD, PhD, and colleagues reported that, on average, doctors spend the equivalent of nearly three work weeks a year on administrative tasks required by private health insurance companies—and the figure is even higher (more than four weeks) for primary care physicians in small practices. The study, whose results were published in *Health Affairs* in May, also found that nurses spend more than twenty-three weeks per physician per year on such tasks—which include prior authorization, pharmaceutical formularies, claims, billing, and

credentialing—and clerical staff forty-four weeks.

When time is converted to dollars, the annual bill equals $23 billion to $31 billion—and, Casalino adds, when factors such as the costs of computer equipment and office space are included, the figure is more like $41 billion. "It's not just a question of the dollars," he says. "I can tell you, having been in private practice for twenty years, that it's demoralizing to physicians and their staffs to have their days continually interrupted by tasks that seem, at best, irrational."

The response rate for the survey was 58 percent, and the researchers received 895 completed surveys from physicians and medical group administrators. On average, the MDs reported spending the equivalent of about $68,000 worth of their time per year interacting with health plans—nearly a third of the salary, plus benefits, for a typical primary care physician. "Sixty-eight thousand dollars per physician is disturbing," says Casalino, chief of the Division of Outcomes and Effectiveness Research in the Department of Public Health. "For a primary care physician in a small practice, over four weeks a year is spent dealing with health plans. A physician can see a lot of patients in four weeks."

But Casalino stresses that not every interaction with a heath plan should be deemed wasteful. "Some of that $41 billion is probably money well spent," he says. "For instance, if requiring certain physicians to get prior authorization before their patients have an MRI scan means that a lot of inappropriate MRIs are avoided, then you can't say that all the time spent on prior authorizations is wasted." Casalino and his collaborators are currently conducting a similar study on physician practices in Canada.

The surveys on health plan interactions are just one facet of Casalino's studies on physician practices; in other recent work, published in the *Archives of Internal Medicine* in June, he and colleagues examined how often practices fail to inform patients of abnormal test results. They focused on eleven types of blood tests as well as three common screenings: mammography, Pap smear, and fecal occult blood. In analyzing some 5,400 records from twenty-three practices, they found that, on average, patients aren't informed of abnormal results once out of every fourteen cases. At some practices, the rate was zero; at others, it was as high as one in four.

One of the most common reasons for a lapse in reporting results, he says, is the practice of telling patients to assume that "no news is good news." He was motivated to undertake the study after it happened in his own household: his wife had gone for a routine Pap smear, and when the nurse practitioner looked at her record, he says, she "went white." The previous year, Casalino explains, his wife had had a uterine ultrasound, but the troubling results—which might have indicated endometrial cancer—had never been reported to her. "After all the stories she had heard from me over the years, my own wife assumed no news was good news," Casalino says. "These mistakes are widespread." (Luckily, she proved to be cancer-free.)

Having served as a family physician in a nine-doctor group practice in California from 1980 to 2000, Casalino is devoted to improving medicine by focusing on its front lines. Physicians, he says, are the "final common pathway" for health care. "Not to say that nurses and other staff are not important," he says, "but things don't happen unless physicians order them. The cost and quality of health care depend heavily on what physicians do. Understanding more about how physicians practice is fundamental to understanding medical care in the U.S." Alvin Mushlin, MD, ScM, chairman of the Department of Public Health, confirms the importance of Casalino's work and says, "We were delighted to have Larry Casalino join our department to lead this area of research in order to provide insights that can improve the delivery of medical care."

Casalino admits that studying physician practices is logistically challenging. "It's devilishly hard to get data," he says, because unlike hospitals or health plans, there's no national census of medical practices. "When we started doing this in the early Nineties, not many people were studying them, for that reason: no one knows who they are or what physicians are in them." Now, he says, "more people are getting into the field of studying physician practices—but it still isn't studied as much as it ought to be in relation to its importance."

— Beth Saulnier

Blood Ready

Getting closer to a cure for an 'orphan' disease

After sickle-cell anemia, beta-thalassemia major—known as Cooley's anemia—is the world's most common inherited disease. The World Health Organization estimates that between 50,000 and 100,000 children are born with it each year; an estimated 60 million to 80 million people carry the beta-thalassemia trait, which is especially prevalent in Mediterranean countries, North Africa, and Asia. In the U.S., the number of Cooley's patients is estimated to be between 1,000 and 1,500. While it is a small population, they're among the largest consumers of red blood cells in the nation. A 2007 study in the *American Journal of Hematology* estimates that Cooley's anemia can cost as much as $75,000 per patient per year in the U.S. Weill Cornell treats 100 to 200 Cooley's patients annually.

Stefano Rivella, as a PhD student of genetics at Italy's University of Pavia, worked on the Human Genome Project and human genetic disorders. Later, as a postdoc at Memorial Sloan-Kettering Cancer Center, he focused on beta-thalassemia, using mouse models to study the disorder. At Weill Cornell, Rivella and his collaborators have further characterized these mouse models that have mutations in the beta globulin gene responsible for the mutations in red blood cells that cause Cooley's anemia. The finding, published in the journal *Blood* in 2008, is one step toward a cure; preclinical trials show promise for new therapies for patients with splenomegaly (an enlarged spleen), a frequent symptom.

One of the obstacles to research on Cooley's anemia is its status as a so-called "orphan" disease. Although the Centers for

Disease Control and Prevention funds seven Cooley's centers in the U.S., including one at Weill Cornell, the fact that there are relatively few patients in North America means the illness gets little attention here. Studies are rare and under-funded, and current management of the disease is limited to prenatal diagnosis, transfusion therapy, iron chelation, and bone marrow transplants. While this has led to greater life expectancy for Cooley's patients in developed countries—upwards of forty years—the disease is near epidemic levels in such places as the Maldives, Iran, North Africa, and Southeast Asia, where infants born with it face an early death.

The situation may be even graver: worldwide mortality rates are often underestimated, as Cooley's symptoms mimic those of malaria. Even in the U.S., Cooley's is sometimes mistaken for sickle-cell anemia, a disease that disproportionately affects African Americans. Curiously, both sickle cell and thalassemia are believed to be evolutionary adaptations to the presence of malaria in tropical climates, offering some degree of protection from the blood-borne disease.

Thalassemias are genetic disorders marked by the absence of (or defects in) the genes responsible for production of hemoglobin, a protein in red blood cells that carries oxygen. All thalassemias are recessive and inherited from both mother and father, but not all are life-threatening. Severity depends on the mutations and their interplay, with Cooley's being the worst. Patients commonly experience extreme fatigue, shortness of breath, and splenomegaly, caused by a buildup of crippled or dead red blood cells as well as from the frequent transfusions—generally twice a month—needed to sustain life. "The spleen acts like a filter and a sponge, cleansing the blood," says Rivella, associate professor of genetic medicine in pediatrics. "In people with Cooley's anemia, it is overworked and becomes saturated. Because so much blood is sequestered in the spleen, we have to give the patient even more. This comes with a cost."

That cost is a toxic buildup of iron that must be removed by chelation therapy to prevent heart and liver disease, among other problems. The common alternative, surgical removal of the spleen, leaves patients vulnerable to disease and stroke and dependent on a battery of anticoagulants, vaccinations, antibiotics, and auto-immune boosters in addition to transfusions and chelation. Despite the downsides, splenectomy is a common life-saving treatment for thalassemia patients.

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But there may be a way to avoid it. Research on mouse genes and cells has led to a better understanding of the processes of Cooley's anemia, particularly the activity of a gene called JAK2, which plays a major role in the formation of aberrant red blood cells in beta-thalassemia. A new compound developed for clinical trials on patients with myelodysplastic disorders (MDPs), another group of blood diseases, appears to work wonders on mice with beta-thalassemia by blocking expression of JAK2. "We found that this JAK2 inhibitor caused the spleens in the mice to shrink back to normal size," Rivella says. "They also began to produce better red blood cells."

Rivella says the compound could become part of a cure for Cooley's anemia—but so far it has been cleared in the U.S. only for trials on MDPs. He hopes his initial research will not only improve treatment for Cooley's patients but also convince drug companies—and perhaps a sponsor—to support clinical trials. "Based on our observations, it is clear that this JAK2 inhibitor has a positive influence on the disease, and it is a matter of gathering perhaps $200,000 for trials on five or six patients," says Rivella. "That's not a lot when you think about the cost of clinical trials. The drug is available. We don't have to invent it. We just need some help to get started."

— Franklin Crawford


PROVIDED BY STEFANO RIVELLA

Down to size: Mouse spleens illustrate the reducing effects of a promising drug for Cooley's anemia patients.

Sticky Problem

Exploring the mysteries of the malaria parasite

JOHN ABBOTT

Kirk Deitsch, PhD

Each year, 350 million to 500 million people are infected with malaria and more than a million die from it—most of them African children under five. "It's a devastating disease," says Kirk Deitsch, PhD, associate professor of microbiology and immunology, "and to fight it we need a better understanding of the basic molecular and cellular biology of malaria parasites and how they interact with their human and insect hosts."

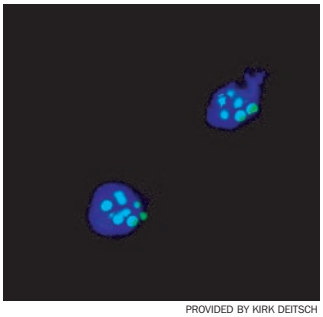
Deitsch has devoted his career to studying how *Plasmodium falciparum*—the protozoan parasite that causes most severe malaria infections—dodges the human immune response. In collaboration with colleagues in pharmacology and microbiology, he also investigates mechanisms of drug resistance and works to develop new antimalarials.

The *P. falciparum* parasites are transmitted to humans via the bite of an infected mosquito. After they first multiply in the liver, the parasites invade and destroy red blood cells, causing symptoms such as anemia and fever. The parasite places a protein called PfEMP1 on the surface of the infected red cells so they become cytoadherent (or "sticky") and cling to the walls of blood vessels; this prevents the bloodstream from carrying the infected cells to the spleen, where they'd be filtered out.

With time, the immune system begins producing antibodies against the protein and destroying the parasites—but a small number of them change the sticky protein they're placing on the surface of infected cells. This process, known as antigenic vari-

ation, lets them avoid the immune response and maintain infection. "Over the length of an infection, you'll see waves in which parasites are getting wiped out and then new populations are arising that express a different protein on the surface," says Deitsch, winner of a 2002 Presidential Early Career Award in Science and Engineering.

The parasite owes its ability to outsmart the immune system to a family of genes called *var*. Within its genome, each parasite contains up to sixty *var* genes. Only one is expressed at a time, determining which protein is displayed on the surface of the infected red blood cell. Deitsch's research focuses on how the parasite coordinates that expression. "It's one of the most fascinating puzzles in all of genetics," he says.



PROVIDED BY KIRK DEITSCH

Gene pool: *Var* genes are highlighted within the nuclei of two malaria parasites.

After completing his doctorate in genetics at Michigan State in 1994, Deitsch spent five years as a postdoc under Thomas Wellems, MD, PhD, in the Laboratory of Parasitic Diseases at the National Institutes of Health. Wellems and his team had recently discovered *var* genes, and his work with Deitsch resulted in the discovery of the two primary DNA elements that control their regulation. In a paper published in *Nature* in 2001, they described how one of the elements sits upstream of each gene along the chromosome and the other sits in the intron (or non-coding section) of each gene; they work together to silence expression of all but one *var* gene at a time. Since joining the Weill Cornell faculty in 2001, Deitsch has continued to explore how those elements interact.

Deitsch and his team have created transgenic parasites that have several *var* genes "on" at one time, as well as parasites with *var* genes that do not encode for the sticky protein. This has allowed them to identify many of the DNA sequences that control how parasites express only a single *var* gene at a time. "By continuing to dissect this regulatory process, we might be able to discover ways to disrupt it," says Deitsch, "and ultimately interfere with the parasite's ability to cause disease." Recently, Deitsch published a paper on a new methodology for controlling the level of expression of a gene that is inserted into the parasite. With colleagues at Weill Cornell and Notre Dame, he is using this technique to find out if over-expression of particular genes plays a role in drug resistance. "Since malaria parasites develop resistance to antimalarial drugs over time and effective vaccines have yet to be developed, we'll always need new drugs in the pipeline," says Deitsch.

Deitsch's research focuses on how the malaria parasite coordinates expression of up to sixty *var* genes. 'It's one of the most fascinating puzzles in all of genetics,' he says.

Pharmacology professors Lonny Levin, PhD, and Jochen Buck, MD, PhD, are working with Deitsch to develop inhibitors of an enzyme that the parasite uses to sense changes in pH and carbon dioxide levels; when the enzyme is inhibited, the parasite fails to replicate and eventually dies. Deitsch is also collaborating with associate professor of pharmacology Anthony Sauve, PhD, to investigate proteins that modify the structure of chromatin (the combination of DNA, RNA, and proteins in the cell's nucleus) and are important for *var* gene regulation. Deitsch cloned the version of the protein found in malaria parasites and gave it to Sauve, who is using it as a target for drug development.

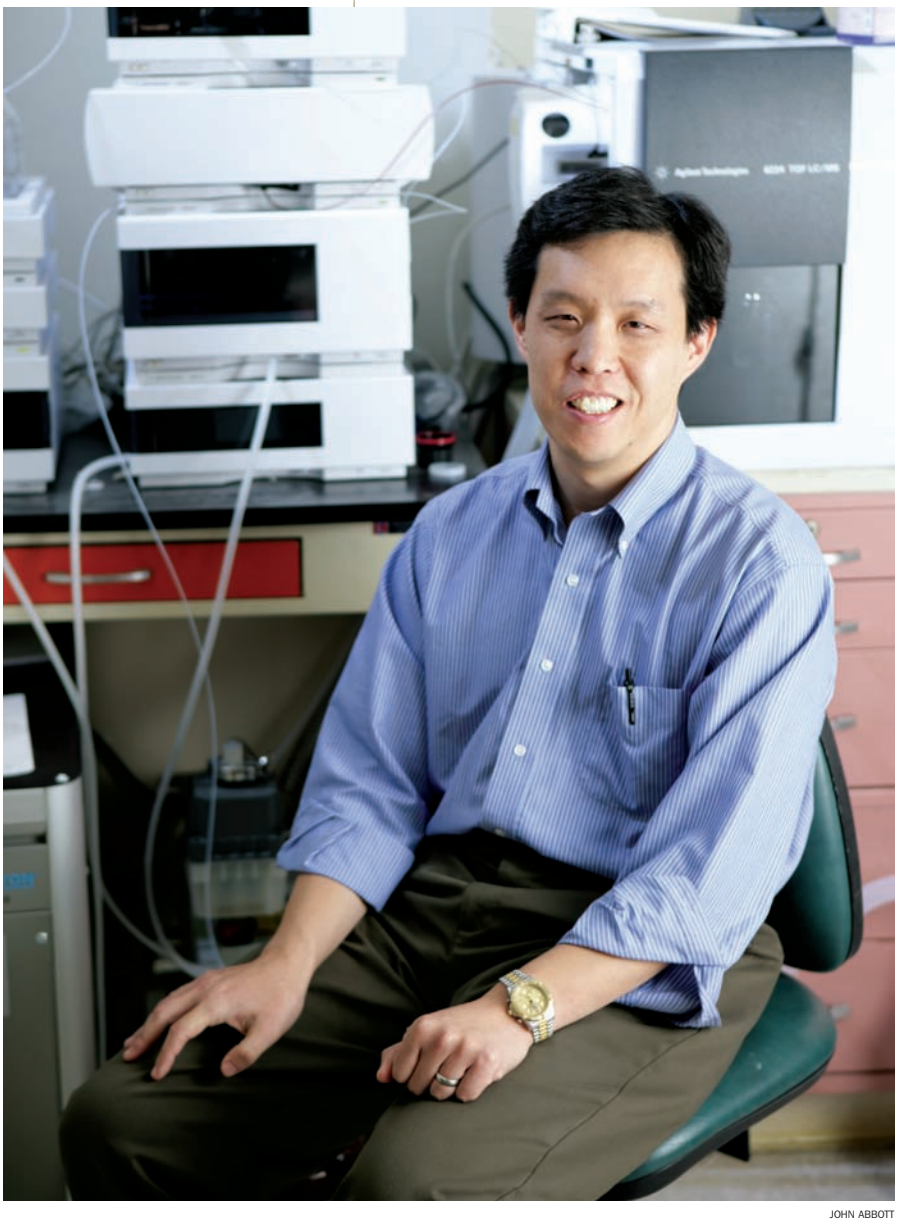
Deitsch is also interested in strategies to prevent malaria during pregnancy. Expectant mothers are particularly vulnerable to the disease, which increases risk of premature delivery, miscarriage, stillbirth, and low birth weight. A gene called *var2csa* is present in all malaria parasites but is expressed only by those infecting pregnant women, adhering to the placenta. Scientists had long wondered why the gene is never expressed in men or in women who are not pregnant. Recently, Borko Amulic, PhD '09, and Deitsch found that *var2csa* has an extra level of regulation; when the parasite is not infecting a pregnant woman, this regulatory element prevents expression of the gene. "If we could work out the mechanism for keeping that gene silent when you're not pregnant," Deitsch says, "perhaps we could switch it 'on,' so women could make natural immunity and would never get placental malaria." He notes that several groups are currently working on developing a vaccine against pregnancy-associated malaria that is targeted to the protein encoded by this gene.

In the future, Deitsch hopes to study gene regulation in other protozoan parasites such as toxoplasma, cryptosporidium, and babesia. "These important pathogens share many basic biological processes," he says, "so discoveries we make while studying malaria parasites are likely to be applicable to them as well."

— Jen Uscher

Think Big

Gates Foundation grant for unorthodox ideas supports a novel way to study tuberculosis



JOHN ABBOTT

Kyu Rhee, MD, PhD

Most grants are awarded on the basis of past performance—a proven track record that makes a research project seem a solid investment. But the Gates Foundation's Grand Challenges Explorations program is different: the application is just two pages long and requires no preliminary data. Twice a year, the foundation gives out dozens of $100,000 awards to researchers with innovative but unproven ideas for improving global health. The program got more than 3,000 proposals for its second round; it funded eighty-one.

Among those winners was infectious diseases professor Kyu Rhee, MD, PhD. His aim: to lay the groundwork for more effective tuberculosis drugs by studying the most basic properties of the causative agent, *Mycobacterium tuberculosis* (MtB), at a molecular level. "This is an idea that wouldn't have been fundable by conventional mechanisms," says Rhee. "It's extremely high-risk, in that it challenges several long-standing assumptions about MtB without clear knowledge of what the answer will be. Nonetheless, the payoff could be enormous."

Rhee is particularly interested in studying MtB during the latent stage of TB, when people are infected but show no sign of disease; this represents about one in every three people on the planet. While he says that only about 10 percent of such patients may go on to become ill during their lifetime, this accounts for 8 million cases and 2 million deaths annually. From an epidemiologic point of view, Rhee says, "detection of every symptomatic case of TB is associated with twenty-five new latent cases, so targeting MtB during this stage of infection is central to establishing control of the TB pandemic."

Worldwide, TB is the leading cause of death from bacterial infection. Although it's relatively rare in the developed world, it poses devilish problems even for patients with adequate health care. The current course of treatment for active TB calls for two to four drugs daily for a minimum of six months—preferably nine or even twelve. Treatment of latent TB is also lengthy, requiring nine months of therapy with a single agent. But with side effects like nausea, G.I. distress, and possible liver and eye damage, many patients don't stay the course. "It's hard to get the average person to take a vitamin every day, so imagine trying to convince someone to take these medications for at least six months," says Rhee, the William Randolph Hearst Foundation Clinical Scholar in Microbiology and Infectious Diseases. "It's incredibly complicated and highlights the inadequacy of our current antibiotics against MtB." He further stresses that's away and apart from the problem of highly drug-resistant strains, which are on the rise—and the very con-

sequence of this inadequacy.

To address this problem, Rhee and his team considered a fundamental question: How do you develop an antibiotic? Current approaches involve one of two plans of attack. "You can take a molecule and hope to find some type of inhibitor that you could convert into an antibiotic," he says. "Or you can take the rainforest approach, where you dig up dirt from all parts of the world, look for something that kills your organism of interest, and then figure out how it works." After debating which of the two methods was more promising, they realized there was a third route. "We came to the decision," he says, "that neither approach would work effectively until we knew more about the basic biology."

Rather than using technology like microarrays that examine organisms at the genetic level, Rhee and his team have adapted a tool from the physical sciences: mass spectrometry. "Think about how drugs work," he says. "Drugs don't work on genes, they work on proteins and cellular physiology. If you want to make a drug, it may be more useful to study proteins and—even better—small molecules, because drugs work at that level. It's biology with a practically oriented angle. So we have decided to tackle TB drug development by studying its biology at this pharmacologically relevant level. To date, we've already uncovered some aspects of MtB metabolism that fundamentally differ from that of other microbes and humans, and may hold major implications for current TB drug-development efforts."

Rhee notes that other bacterial infections—even the most life-threatening ones—typically require drug regimens of far less than six months. Understanding why TB becomes so thoroughly entrenched in the body, and how it can remain dormant for so long before becoming infectious, are among his team's goals. If their work bears fruit, the Gates Foundation could provide additional support of $1 million or more. "TB is a great example of how our existing antibiotics are inadequate," he says. "But without knowing the biology, we don't have much chance of finding better ones."

— Beth Saulnier

'TB is a great example of how our existing antibiotics are inadequate.'

Missed Conception

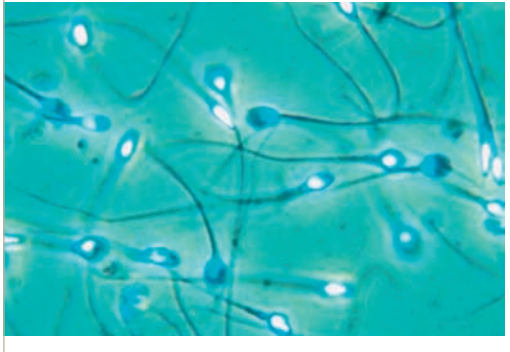
Study finds that SSRIs compromise male fertility

It has long been known that the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) can cause sexual side effects including decreased libido, erectile dysfunction, and inability to achieve climax. But now, Weill Cornell researchers have found that the drugs can also harm fertility. In a study published in *Fertility & Sterility* in June, urology chairman Peter Schlegel, MD, and colleagues revealed that as many as half of men taking paroxetine, sold under the trade names Paxil and Seroxat, suffer from decreased sperm quality. "This drug can have a substantial effect on the chance of pregnancy occurring naturally and even affects the success of advanced reproductive technologies like *in vitro* fertilization," he says, "but these effects are not detected on a standard semen analysis."

The researchers followed thirty-five healthy male volunteers who were given paroxetine for five weeks. They found that the drug did not affect the men's sperm volume, concentration, motility, or morphology—factors evaluated during semen analysis. But in about half of the subjects, significant numbers of sperm had fragmented DNA; the drug, Schlegel says, likely slows the rate at which sperm travels from the testes to the ejaculatory ducts. "The effect typically occurs by causing sperm to 'hang up' in the body at higher temperatures than normal, causing damage—but not so bad that they are completely destroyed." The study also confirmed the effect of SSRIs on sexual function: nearly half of the participants reported ejaculatory difficulties.

While it's known that women as well as men suffer sexual side effects on SSRIs, it's unclear whether the drugs might also affect egg quality—or to what extent the sperm damage might increase the likelihood of birth defects if conception is successful. Schlegel plans to continue his work on SSRIs and fertility, and investigate how other types of antidepressants may compromise sperm quality. He notes that although paroxetine seems to dramatically curtail male fertility and sexual function, the effect appears to be reversible: the men in the study returned to normal a month after stopping the drug. "It appears to wash out within weeks, but more information is needed," he says. "This is a drug that up to 40 million people in the U.S. take, so there's huge potential interest in this."

— Beth Saulnier



Father figures: Healthy human sperm

JOHN ABBOTT

Postdoctoral researcher Yanping Li, PhD, and Chenjian Li, PhD

Mighty Mice

Tiny transgenic creatures may be major players in the battle against Parkinson's

When Weill Cornell researchers began creating transgenic mice to model Parkinson's disease, they weren't sure what to expect. Although they were optimistic about the new technology, the genetic mutation that causes Parkinson's is notoriously problematic to transplant. "We were hoping the mouse model would reflect the human form of Parkinson's, and it does," says senior and corresponding author Chenjian Li, PhD, an assistant professor of neuroscience whose team's findings appeared in the June 7 issue of *Nature Neuroscience*. "After so many failures, there was definitely a feeling of 'Wow, we finally succeeded.'"

Although other researchers have had partial success in creating Parkinson's-affected mice, those engineered in Li's lab are the first definitive animal models of the disease. These new, more accurate mouse models aid researchers on two levels: first, they will enable a mechanistic study of how the disease develops; second, the mice can be used as indicators for drug research.

The mice were modified to express PARK8, a type of Parkinson's disease caused by mutations of a kinase known as LRRK2, which is widely associated with late-onset Parkinson's. "LRRK2 is the most important genetic cause for Parkinson's disease because it accounts for the largest number of cases," says M. Flint Beal, MD, the Anne Parrish Titzell Professor of Neurology and one of the paper's co-authors. "For example, in some special populations it can account for as much as 40 percent; that seems to be the case in North African and Ashkenazi Jewish populations."

Part of the reason a good mouse model of Parkinson's disease has been so elusive, the researchers say, is the complicated structure of LRRK2. The technique that made the difference in their work is called a bacterial artificial chromosome, or BAC. "You take a huge chunk of DNA and inject that into the mouse embryo, which is called a pro-nuclear injection," explains Li, who was part of the Rockefeller University team that originally developed the technology. "And then there is a chance that the DNA is incorporated into the genome." Once a few mice—known as founders—successfully recreate the disease, they are bred naturally.

The animals developed at Weill Cornell express nearly five times the level of the Parkinson's-causing protein. Though the appearance of those phenotypes was encouraging, the team still had to make sure they were accurate models of the disease. Because human Parkinson's is caused by the death of dopaminergic neurons—those involved in transmission of the neurotransmitter dopamine—a common treatment is the replacement of levodopa, a naturally occurring drug lost during cell death. "The mice moved reminiscent of the human condition," Li says, "but to prove the problem is with the dopaminergic system we administered levodopa—and it does alleviate the symptoms."

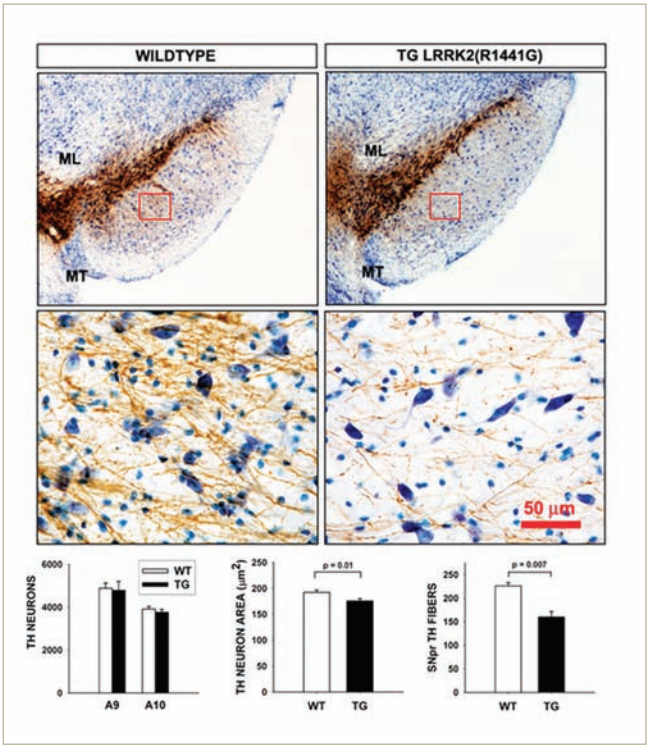
While it is impossible to directly correlate the lifespan of the mouse to that of a human, the progression of Parkinson's appears to be roughly equivalent. With a life expectancy of around two years, the transgenic mice begin to show significantly arched posture and slowness of movement at about ten or eleven months of age, although the researchers say more subtle deficits occur even earlier. The severity of the disease—and the effectiveness of treatments—is measured by the mice's ability to stay on a rotating rod and perform in open-field tests.

The mice developed at Weill Cornell are already available to labs working on the LRRK2 forms of the disease, and the scientists anticipate the animals will generate new Parkinson's studies. "It's as if we're building a stage for many scientists to perform their plays," Li says. "Because the mouse model recapitulates the human condition quite accurately, that creates a strong platform for both mechanistic study and drug testing." Ideally, new research will also benefit patients affected by other forms of Parkinson's disease, not just PARK8.

Work also continues on the genetic structure of the Parkinson's mice. "There are some features of the mice that don't completely replicate idiopathic Parkinson's disease," says Li. "For example, they haven't developed overt large aggregates of Lewy bodies, a pathologic hallmark of Parkinson's disease; instead, they may have micro-aggregates."

In a recent advance, Li's lab successfully developed a new technology that allowed them to create transgenic rat models of the disease. Rats have many biological characteristics that are closer to human and are more sensitive to insults to the brain. "We are still in the basic research stages," Li stresses. "It's a nice step, but it's only the first one on a very long road."

— Liz Sheldon



PROVIDED

On the mind: Mice with the LRRK2 mutation show neurite degeneration in the same dopaminergic system as humans with Parkinson's disease.

Common Cause

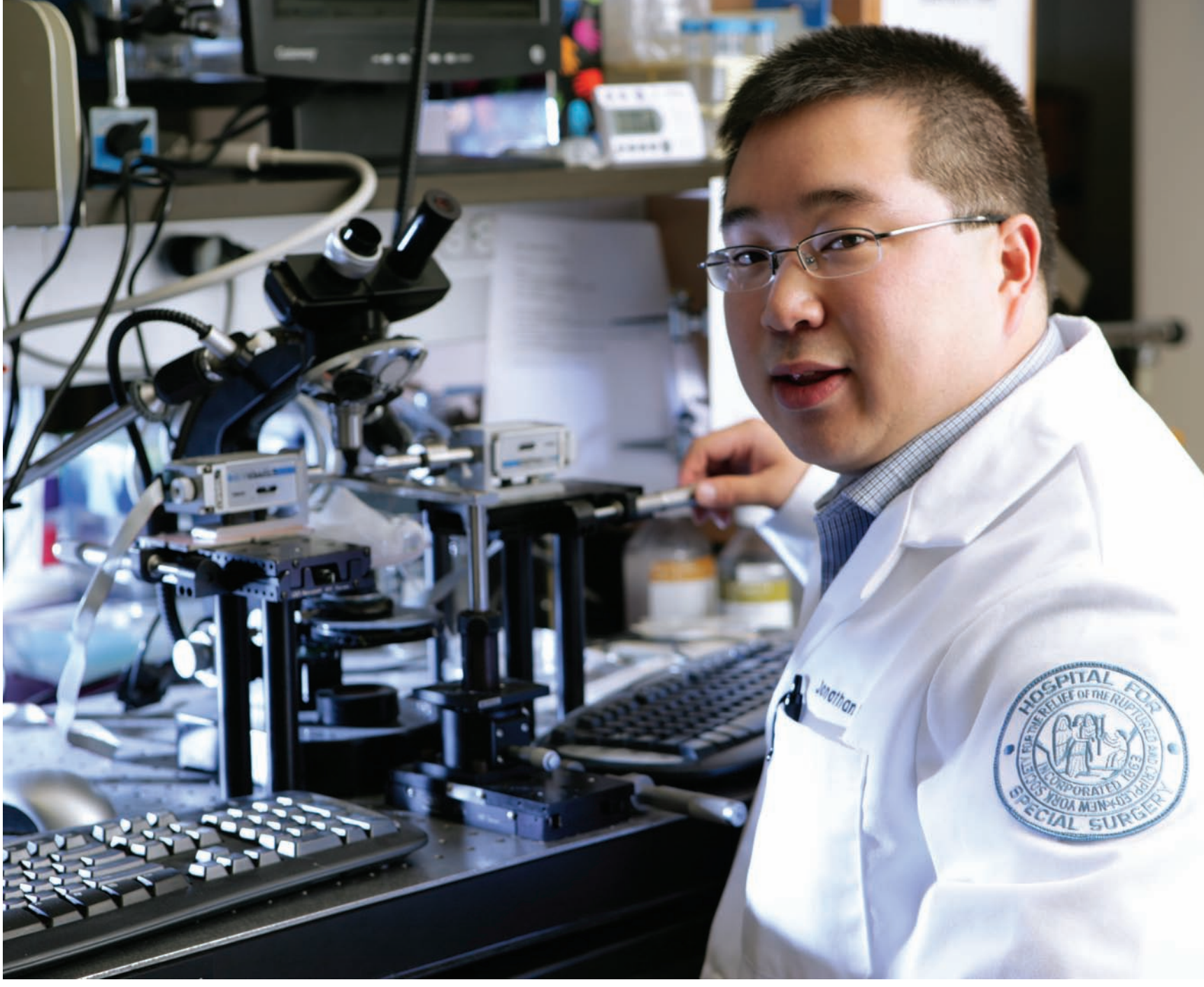
The Clinical and Translational Science Center aims to get researchers out of their 'silos,' promoting collaboration across disciplines—and institutions

By Beth Saulnier

Photographs by John Abbott

When Stefano Rivella, PhD, delved into the genetics of the blood disorder known as Cooley's anemia, his preliminary data was highly promising—opening up what he calls "a positive Pandora's box of scientific discovery." But although the project was going well, he recalls, "I was touching on subjects where I wasn't completely an expert." In the hope of finding the right collaborator, the associate professor of genetic medicine in pediatrics decided to try something unorthodox.

In October 2008, Rivella was among more than eighty basic and clinical scientists who attended the Translational Research Bazaar; the event was modeled on the concept of speed dating, in which singles rotate among prospective partners for brief conversations. But instead of romance, participants had research on their minds. Clinicians, who sat on one side of a long table, had about three minutes to discuss their work with basic scientists before a bell signaled it was time to move on. After thirty-five such rounds, the researchers had the chance to mingle during a reception; 85 percent later



Jonathan Bourne, PhD candidate

reported that they'd found someone they'd like to work with. Among the matches made that day was Rivella's collaboration with Nancy Greenbaum, PhD, a professor of structural biology at Hunter College. Working with her and other collaborators, Rivella is moving closer to a cure for Cooley's anemia, one of the world's most common inherited diseases. (See related story on page 14.)

Facilitating such bench-to-bedside research is the core mission of the consortium that hosted the research bazaar: the Weill Cornell Clinical and Translational Science Center (CTSC). Founded in September 2007 with a $49 million grant from the National Institutes of Health, the CTSC is one of forty-four such centers nationwide—multidisciplinary, trans-institutional entities that bring together researchers and clinicians from disparate disciplines to broaden scientific knowledge, tackle pressing medical issues, and promote community health. Headquartered on East 61st Street, the CTSC unites the health-care institutions in the Upper East Side neighborhood affectionately known as "bedpan alley": Weill Cornell Medical College and Graduate School of Medical Sciences, NewYork-Presbyterian Hospital/Weill Cornell Medical Center, Hospital for Special Surgery, Hunter College School of Nursing, Hunter Center for Study of Gene Structure and Function, and Memorial Sloan-Kettering Cancer Center, in addition to Cornell's Ithaca campus and its New York City Cooperative Extension office. "It's an initiative to bring together researchers from different institutions with different ideas to collaborate and facilitate discoveries," says Julianne Imperato-McGinley, MD, the CTSC's program director and Weill Cornell associate dean for translational research and education, "and then move those

Julianne Imperato-McGinley, MD

discoveries out to the community and the public."

One of the primary ways in which the CTSC aims to accomplish its mission is by offering seed money to investigators, and it has funded dozens of pilot projects since its inception. Rivella was among the early recipients. "Many times, when you apply to granting agencies, you need a lot of preliminary data to convince the reviewers that your work is sound," he says. "The pilot award is a fantastic tool, because you can go to the CTSC with a good idea, but you don't necessarily need to have a lot of the work done that you need to apply for other grants. We're now writing a paper and applying for another grant, which we couldn't have done if the CTSC had not helped us."

Another early pilot award went to Weill Cornell's Ronald Silverman, PhD, and Hunter physicist Ying-Chih Chen, PhD, to support their work on improving the resolution of ultrasound images of the eye via photo-acoustic technology. Echoing Rivella, Silverman says the pilot award opened doors for a bright idea whose promise was unproven. "It's unlikely we'd have ever gotten started without the CTSC," says Silverman, a research professor of computer science in ophthalmology. "Coming to the NIH with an idea and no real preliminary data, you're just not going to get funded; the system doesn't work like that. The CTSC gave us seed money to do pilot experiments and get some infrastructure together."

The grants are only one element of the CTSC. Others include its Clinical and Translational Education Program, which currently comprises more than fifty students. Those attending for one year earn an advanced certificate in clinical investigation; if they continue for a second year, including electives and a mentored research project, they earn a master's degree. The program also offers an MD-PhD, an MD-MS, and modular training in clinical research methodology, holding seminars on such topics as drug and medical device development.

"Part of what's so fascinating about the CTSC is that it spans departments and disciplines," says Jonathan Bourne, a PhD candidate in physiology, biophysics, and systems biology who is also earning a master's in clinical investigation. "You have biomedical engineers and biochemists, and at the other end of the spectrum you have practicing physicians doing clinical research. If I have a question about oncology, I can grab one of the MDs and say, 'Here's what I'm looking at, here's what I was thinking, is this medically correct?' And for the MDs, the PhDs provide a different point of view. I've seen talks where a rheumatologist or an oncologist presents some work, and from a basic science side we can say, 'Have you thought of this mechanism? Have you thought about how fluid flow might be changing drug delivery?' It provides an umbrella to bring together all of these different areas and specialties within a unified and coordinated center."

The CTSC also hosts a variety of events, like the research bazaar, that promote collaboration or facilitate investigation. A pasta dinner at the Griffis Faculty Club drew some sixty-five scientists from CTSC partner institutions for lessons in the role of intellectual property in biomedical research; speakers included Alan Paau, Cornell University's vice provost for technology transfer and economic development. In September 2008, the CTSC emphasized another of its goals—to encourage community organizations to participate in clinical and translational research—with an event devoted to increasing community engagement; more than 100 people attended, including representatives from faith-based groups, health departments, and medical institutions. Partnering with the Hunter Gene Center, the CTSC co-sponsored a symposium—"Translational Cancer Research: Bench, Bedside, and Community"—that drew more than 250 people to the Hunter campus.

For researcher Darshana Dadhania, MD, and her colleagues, the CTSC has been the source of invaluable logistical support as they've searched for urine biomarkers indicating renal transplant rejection. Through the Clinical and Translational Research Unit—which features laboratories, inpatient and outpatient facilities, and nursing and support staff—the researchers have a centralized location for biopsies, blood sampling, and patient monitoring. "The CTSC allows us to standardize our procedures and serves as a central resource for our research studies," says Dadhania, an assistant professor of medicine. "The CTSC support was invaluable in completing the largest translational study in transplantation at New York-Presbyterian Hospital/Weill Cornell Medical Center."

The nationwide collection of clinical and translational centers is the brainchild of former NIH director Elias Zerhouni, MD; as head of the agency, he called on medical researchers to challenge their traditional "silo" approach, in which specialists are isolated in their own disciplines. The NIH Roadmap for Medical Research, announced in 2003 and launched the following year, aims to break down barriers that limit discovery via such initiatives as the agency's Clinical and Translational Science Awards Consortium, of which the CTSC is a member. "In today's world, we realize that disease is a complex entity," says Imperato-McGinley. "For instance, take diabetes. You have genetics, nutrition, economics—many factors that feed into one condition. So it's clear that you need teams of researchers working on all aspects of the disease; you have to look at it in its entirety. That's what Dr. Zerhouni and the Roadmap initiative are trying to do: let everyone get together, talk about it, work on it, develop the ideas. That's the key to modern research."

The following is a sampling of research projects funded or facilitated by the CTSC.

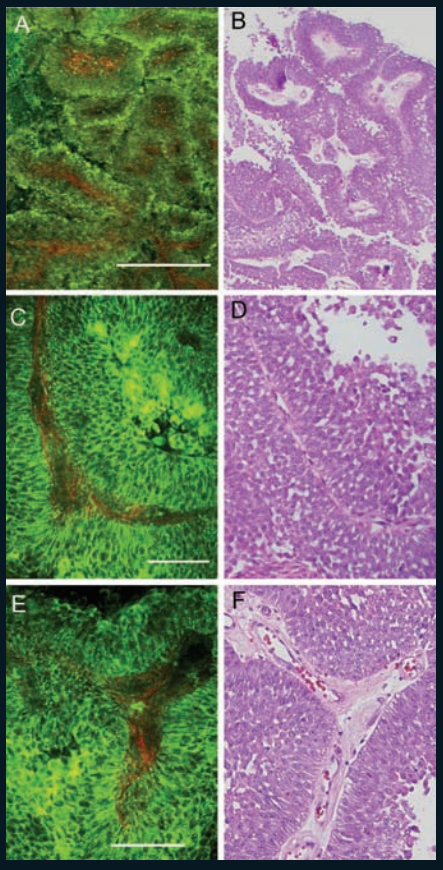
The Endoscope Meets the Multiphoton Microscope


Sushmita Mukherjee, PhD

Two decades ago, Multiphoton microscopy was developed in the lab of Ithaca-based applied physics professor Watt Webb, ScD. Now, researchers there and at Weill Cornell are working together to adapt the technology for human diagnostics—specifically, the detection of cancer in its earliest stages. "You can image live tissue without using contrast or processing it in any way," says Sushmita Mukherjee, PhD, an assistant professor of biochemistry at Weill Cornell and the director of the Multiphoton Microscopy Facility there. "So the idea is eventually to miniaturize this into an endoscopic format and be able to image in real time in a live patient." Among Mukherjee's collaborators: her former postdoctoral mentor, Frederick Maxfield, PhD '77, the Horowitz Distinguished Professor of Neuroscience. "This is innovative—and, from a granting point of view, somewhat risky," he notes. "We're not just doing things a little differently from what people have done before. We're doing things that nobody ever tried, and we don't always know if they're going to work."

In collaboration with surgeons and pathologists, Mukherjee has been focusing on bladder cancer, using fresh human tissue (obtained from biopsied or excised organs), which she views via a Multiphoton microscope that Ithaca-based biomedical engineering professor Warren Zipfel, PhD, custom built for the Medical College several years ago. "We image them, and the same piece is submitted to the pathology department for a standard diagnostic workup; then we compare our data with the pathology analysis, which is the gold standard," Mukherjee says. "Our goal is to build what we're calling a 'Multiphoton human pathology atlas' that has images of different organ systems that have been taken with Multiphoton microscopy and images of the same tissue that have been taken from stained slides prepared for conventional histopathology, so one can compare and contrast and see whether Multiphoton imaging has the same diagnostic potential."

Meanwhile, engineers in Ithaca have been working to miniaturize a Multiphoton microscope for endoscopic use; Mukherjee says a prototype is expected by this fall. "It's a conceptual leap, but if it pans out—and there are many technical hurdles—it is going to revolutionize the patient experience," she says. "Today, during an endoscopic procedure, if something looks suspicious, the only option the surgeon has is to biopsy or resect the area 'to be safe.'" Many of these regions, on later histopathological diagnosis, turn out to be benign or simply inflamed, Mukherjee notes. Since each additional biopsy or resection increases both cost and risk to the patient, a real-time inspection of the suspicious area by Multiphoton imaging is likely to aid surgical decision making. "This, in turn, is likely to reduce the number of unnecessary biopsies, thus reducing procedure cost and improving the patients' experience," she says. "Also, given the real-time nature of this imaging modality, it is possible to visualize a scenario in which the patient can leave the endoscopy suite knowing whether they have cancer, and, if so, what's in store for him or her in the coming weeks and months, depending on the exact stage and grade of the tumor."



Double vision: A bladder tumor seen at various levels of magnification via Multiphoton microscopy (green) and gold-standard histopathology (purple)

After Kidney Transplant, a Safe and Easy Test for Rejection


Darshana Dadhania, MD

For transplant patients, receiving an organ is both a cause for celebration and the beginning of a lifelong relationship with immunosuppressive drugs—and the prospect that their bodies might reject the organ is an ever-present worry. But if work by a team of Weill Cornell researchers fulfills its promise, such patients can look forward to less invasive, more individualized treatment. In studies first published in the *New England Journal of Medicine* in 2001, Manikkam Suthanthiran, MD, and colleagues have been searching for biomarkers that indicate potential allograft rejection in kidney transplant patients. "By measuring certain genes in the urine of transplant patients, we can diagnose rejection with a high degree of accuracy—85 to 90 percent sensitivity and specificity," says Suthanthiran, the Stanton Griffis Distinguished Professor of Medicine. "We anticipate these studies will make a substantive impact in managing transplant recipients."

The results of the initial work at Weill Cornell led to an NIH-sponsored five-center study comprising nearly 500 renal-transplant patients, and the initial results are very promising, the researchers say. The urine biomarker method is already being used at NYPH/WCMC to monitor patients as part of an NIH-sponsored research project, and Suthanthiran hopes it will be developed as an FDA-approved test for clinical care within five years. The new method could offer patients a quick, painless way to check for rejection, currently diagnosed via biopsy. "A major interest for the transplant community is to develop a noninvasive procedure," says Suthanthiran, noting that biopsies are not only costly and time-consuming but run the risk of bleeding and infection. "The transplant immune response is not a one-shot deal, it's day to day. Like blood pressure or blood sugar, you need to monitor it on a continuous basis. A non-invasive test would take the level of care to one that can never be accomplished otherwise. Nobody can biopsy a patient every month for the rest of their lives."

The biomarker test—which could potentially be adapted to other organ-transplant recipients using peripheral blood or urine—would also allow doctors to diagnose problems earlier, getting a head start on treatment and potentially staving off rejection. "Serial studies to look at how early we see the changes in the biomarkers before permanent damage begins to take place in kidney transplants are in progress," says Darshana Dadhania, MD, an assistant professor of medicine, "but I would say we expect to have a lead time of weeks to months, depending on the pathology."

According to Suthanthiran, perhaps the most valuable element of the new monitoring system would be the ability to offer individualized drug therapy. Patients who show no signs of rejection could be put on lower doses of immunosuppressants, reducing the risk of side effects. Twenty years post-transplant, Suthanthiran notes, 25 to 30 percent of patients are diagnosed with cancer, and infection is a constant concern. "Right now immunosuppressive therapy is one-size-fits-all—everybody gets a certain amount," he says. "We believe that this type of test will allow us to personalize immunosuppressive therapy and minimize the threat of complications such as cancer and infections."

Researchers Design 'Dots' That Detect Cancer


Michelle Bradbury, MD, PhD

In a collaboration between two Cornell campuses, researchers have been developing some of the tiniest warriors in the battle against cancer. Working with Ithaca-based engineers, radiologist Michelle Bradbury, MD, PhD, has been developing targeted nanoparticle probes that could be used to diagnose and target tumors. Nicknamed "Cornell dots," the probes were created in the lab of Ulrich Wiesner, PhD, the Spencer T. Olin Professor of Materials Science and Engineering.

Each dot, consisting of dye molecules encased in a silica shell, is on the order of six nanometers in diameter—a nanometer being one-billionth of a meter. The probes are coated with polyethylene glycol, which helps prevent the body from recognizing them as foreign. The shell can be covered in molecules designed to attach to tumors, and the dye fluoresces under near-infrared light emission, identifying areas of malignancy. "Silica is by its very nature something that we ingest in our diets," notes Bradbury, whose primary appointment is at Memorial Sloan-Kettering Cancer Center. "I wanted to pick something that I thought had a good chance of going to the clinic, because I'm a clinician and a scientist—so that whatever we develop could potentially be taken to the clinic in the long term."

In their study of melanoma tumors in a mouse model, the researchers explored the dots' effectiveness using both optical and PET imaging. The results, she says, were highly promising. "We showed that the platform was non-toxic and biocompatible, cleared efficiently through the kidneys, and demonstrated high tissue signal—all characteristics that would permit it to go to the clinic as a next step," Bradbury says. "In imaging, we have some contrast agents that have been around for decades, which are not specific for any particular disease. More recently, relatively small numbers of molecular agents have been developed that can directly target specific tumor types, but we need to develop a larger array of compounds for evaluating a broader range of diseases."

The potential of the Cornell dots is not limited to imaging; they might also be used for drug delivery or advanced diagnostics—for instance, measuring tumor pH levels. Additionally, other diseases, such as infectious/inflammatory states, may be the subject of future investigations. Within a year, Bradbury and her colleagues expect to launch an initial clinical study of the probes' tumor-detection potential. "Everyone talks about personalized medicine, but how do you optimally achieve that?" she asks. "One way to achieve this goal is by developing platforms that allow you to target tumors specifically—and deliver therapies or monitor site-specific biology without concerns of associated toxicity."

Exploring the Biomechanical 'EMK Effect'

Jonathan Bourne is conducting research that could ultimately have implications for a wide variety of patients—from diabetics to the elderly to athletes who've torn an Achilles tendon. Bourne is a PhD candidate in physiology, biophysics, and systems biology working under biomechanics professor Peter Torzilli, PhD, in the Laboratory for Soft Tissue Research at Hospital for Special Surgery. Bourne is studying the protective qualities of mechanical force on collagen tissues, such as tendons and ligaments—what the lab has termed an enzyme mechanokinetic (EMK) effect. "If we understand how the human body is able to slow or change the rate at which these structural tissues are broken down, it provides important information about diseases such as osteoarthritis, Achilles tendon ruptures, ACL repairs," Bourne says. "It helps us understand how and why grafts are resorbed by the body, and how to change those processes. So on the basic science side, we're looking at structural modeling of proteins. And on the translational side, we're looking at how changes that are age related or increased by diabetes—called glycation, which is sugar cross-linking of tissue—to understand how they change the biological process and this protective EMK effect."

Sugar cross-linking is part of aging, causing tissues to stiffen; diabetes, marked by high blood glucose, speeds up the process. But mechanical forces, or "loads"—exerted by tissues against each other—seem to protect against it. Bourne is currently focusing on how such factors affect the tendon grafts commonly used to repair ACL injuries. "We're trying to understand how tendon tissue responds to this sort of abnormal situation and how loading or unloading this tissue might better control the rate at which the body turns the graft into a repaired tissue," he says. "Orthopaedic surgeons had revealed long ago that load is good. They said, 'The graft has to be in tension,' but they never pegged down a specific number. Our work actually describes a certain threshold value for this protective effect to kick in. It's almost an on/off switch."

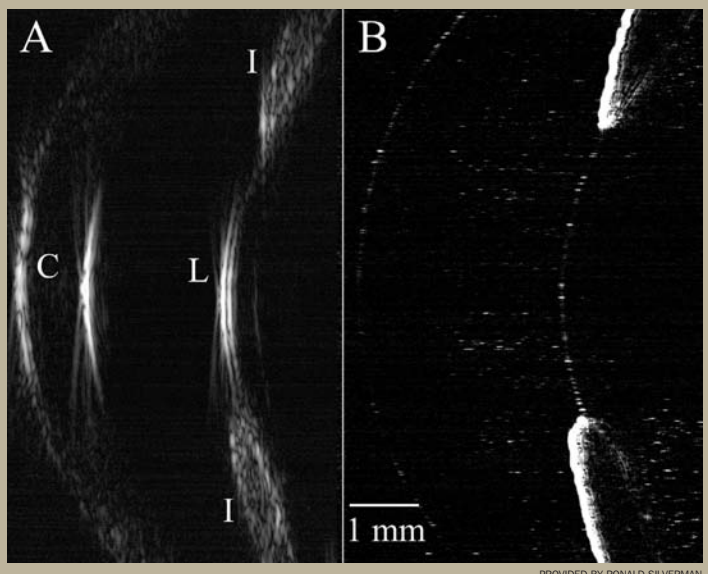
The work of Bourne and his colleagues could lead to a variety of advances, including improved techniques in surgery, physical therapy, and postsurgical care. It could also point the way toward drugs that replicate the protective EMK effect. "There could be chemical or pharmacological agents to reverse the cross-linking," he says. "So it provides an easy target for future applications to change the biology of the process."

Viewing the Eye, at the Speed of Light

"You can't image deeply in tissue with light very well," says Ronald Silverman, PhD, "because when light enters a tissue it starts to get scattered quickly." As an example, the Weill Cornell research professor of computer science in ophthalmology cites the view of a human hand covering a flashlight. "You can see the light coming through, but your hand looks like a blurry pink thing," he observes. "It's not like an X-ray. Just shining light at tissue doesn't get you a nice optical image."

But Silverman and his colleagues are working to harness light—in extremely small slices—to create a better method for viewing the human eye. Through a technique called photo-acoustic imaging (also known as opto-acoustic imaging), a pulsed laser is paired with ultrasound to target specific molecules—say, hemoglobin—that absorb light at known wavelengths. "The photo-acoustic effect was actually discovered by Alexander Graham Bell in the nineteenth century," Silverman says. "So it's been known that if you shine a bright light in a short pulse and it's absorbed by something, you'll generate a sound wave. But it's only in the last decade or less that interest has taken off."

With Hunter College physicist Ying-Chih Chen, PhD, Silverman has been working to design an imaging method that could provide potentially more detailed views than current technologies, such as optical coherence tomography (OCT). "We put together a proposal to develop a system designed specifically for the eye and other superficial tissues, like skin," Silverman says. "The unusual approach we proposed was to use a focused laser. For photo-acoustic imaging you don't have to focus the laser; the only requirement is that the laser have a very short pulse—we're talking nanoseconds, one-billionth of a second. But by focusing the laser, we could create a spot that was smaller than the focus of the ultrasound receiver. This would give us the kind of resolution that people get with OCT, but we'll be able to see deeper, because in OCT once the light is scattered, the signal will blur out."



PROVIDED BY RONALD SILVERMAN

In focus: A pig eye is seen in a conventional ultrasound format (A) and a photo-acoustic image (B). In the ultrasound image, the cornea, lens, and iris are labeled by first letter.

Ronald Silverman, PhD

Silverman hopes the technology could offer better views of such structures as the choroid, which supplies blood to the retina and is suspected to be the point of origin for macular degeneration, the most common cause of blindness in people over sixty-five. "It would also be relevant for glaucoma, if we could image the circulation in the optic nerve area," he says, "because many people believe that the damage that leads to vision loss is caused by ischemia."

But he notes that photo-acoustic imaging has applications far beyond the eye. In fact, most of the work on the technology has been done in relation to breast cancer. Others have explored its use in animal models of cancer, and Silverman himself is interested in using it to study melanoma—which exists not only as a skin cancer but an intraocular one as well. Currently, he and Chen have a proposal out to the NIH, hoping for a four-year grant to continue their work. "The goal is that at the end of the proposed project, we would have a system ready for clinical studies," he says. "We have to make sure that it will be at light levels that are within federal guidelines for laser safety, which we think we can do. And we have a bunch of other problems to solve—but they're all solvable."

Korean Immigrants and Depression

Researchers have long known that immigrants are twice as likely as the general population to suffer from depression. In a recent study, Hunter College nursing professor Kunsook Bernstein, PhD, examined how those rates are reflected in immigrants—particularly those who, like her, came to the U.S. from Korea. "We decided to launch a prevalence study to see how immigrants are adapting to the culture and how it has an impact on their mental health, and depression is one of the common mental health issues," says Bernstein, a board member and research chair of the Korean American Behavioral Health Association. "But most immigrants don't seek help, because they look at it as part of their way of life and just bear it."

With the help of Korean community organizations like churches, senior centers, and college student groups, Bernstein disseminated a questionnaire that explored issues of mental health, cultural assimilation, and discrimination. She got about 300 usable responses—and found that, in fact, the rate of depression (13.2 percent) was more than twice that of the general population. (The study only targeted adults; about 60 percent of respondents were female, and the researchers found no difference in depression rate between the genders.)

Among the most significant factors in immigrants' tendency to depression, Bernstein says, are education, income, and language proficiency; those with higher levels are less likely to be depressed. "It has to do with their adaptation skills," she says. Her study also confirmed that Koreans, like many immigrants, are often reluctant to seek mental health treatment. In collaboration with Heejung Bang, PhD, a Weill Cornell associate professor of biostatistics in public health, Bernstein has since put in another grant application to the CTSC for a study of the barriers preventing people from asking for help. In another project, funded with a small grant from CUNY, she has been exploring the potential of autobiography as a therapeutic outlet for Korean immigrant women. "The Western style of psychotherapy does not work well with them," she says. "But if you ask them to write their life stories, they can find meaning and purpose in their lives."

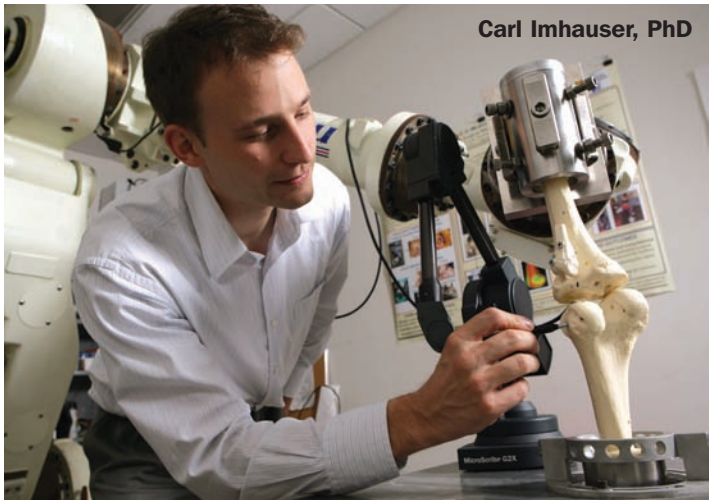
Kunsook Bernstein, PhD

Seeking to Reduce Arthritis After ACL Reconstruction

Each year, some 80,000 surgeries are performed nationwide to reconstruct the anterior cruciate ligament (ACL). The ligament—the vital "rubber band" crossing the knee—is commonly injured by athletes such as skiers or basketball players who stop and turn suddenly. At Hospital for Special Surgery, which performs 700 to 800 of the operations each year, mechanical engineer Carl Imhauser, PhD, is studying the biomechanics of various strategies for ACL reconstruction. His goal: to reduce the incidence of osteoarthritis (OA), which commonly strikes patients a decade or two after surgery. "That's important, in that the people who tear their ACL are usually young," says Imhauser, a postdoc in the department of biomechanics. "Someone who has surgery at thirty and gets OA ten years later still has half his life in front of him or her."

Imhauser notes that the human body is a load-bearing structure, operating under the force of gravity—and that even the most skilled surgical reconstruction involves upsetting the delicate interaction among its cartilage, ligaments, and bones. "OA deals with the breakdown of cartilage, the tissue in your joints that allows the joint to move smoothly," he says. "The health of that tissue is intimately related to the loads that it sees. If those loads are altered, over time you see the onset of OA. But if we can characterize how loads are transferred and target surgeries that best restore normal patterns, then maybe we can help people avoid going down that path."

Imhauser's work includes experiments with cadaver knees, which are mounted on a robot that can move in six degrees of freedom. "It can push or twist the joint in basically any direction and allows us to precisely measure how the joint moves in response to those forces," he says. He's also using the robot to evaluate predictions from a computer model; the model allows him to manipulate a virtual knee joint and see how various surgical approaches would affect the function of the joint. Such work—which could also be applied to other orthopaedic procedures, such as design of knee replacements or meniscus repair—could ultimately allow surgeons to tailor their techniques based on a patient's anatomy. "Each of us has unique bony geometry and ligament structure, which dictates how we move and how loads are transferred across the joint," he says. "For patients with a certain shape of bone and ligament structure, you might be able to say, 'This kind of reconstruction is most appropriate.'" ●



Carl Imhauser, PhD

Female scientists confront the challenges of gender in academic medicine

To Shatter the Ceiling

By Sharon Tregaskis

Photographs by John Abbott

Professor of medicine Babette Barbash Weksler, MD, arrived at Weill Cornell in 1968 as a hematology fellow. In the ensuing forty-one years, the clinician-scientist (and grandmother) has developed an international reputation as an expert in platelet and endothelial cell biology, enjoyed long-term research support from the National Institutes of Health and the American Heart Association, and served at a leadership level in the American Society of Hematology.

On a recent sabbatical in France, Weksler developed a novel endothelial cell line that scientists can use to model the blood-brain barrier, a critical structure for brain health that challenges drug delivery for everything from chemotherapy to treatments for Alzheimer's and depression. Jointly patented by Cornell and the Parisian Institut Cochin, where she spends part of each year, the cell line is now in use by more than 100

research labs around the globe. “After all these years I still find it exciting and stimulating,” says the professor, who splits her time between caring for hematology patients and the lab. While most of her classmates from medical school and college are enjoying more leisurely activities, Weksler admits that she still sits up late into the night reading literature in her field. “To be paid to do what you like is a great privilege.”

Women’s work: Developmental and cell biology chair Katherine Hajjar, MD (center), in the lab with students (from left) MaryAnn Dassah, Caroline Greenberg, and Dena Almeida.


Debra Leonard, MD, PhD

As a child, Weksler had plenty of evidence that women can thrive in medicine and enjoy a rewarding personal life. Her maternal grandmother trained at Cornell when the medical school was still upstate, then transferred to a program in Boston because there weren't enough patients in Ithaca to support the private nursing she did to put herself through school. Weksler's mother, an allergist, worked in private practice. By the time Weksler started her fellowship, she was married to Marc Weksler, MD, now the Irving Sherwood Wright Professor of Geriatrics and professor of medicine at Weill Cornell, and their children—both born before Weksler finished her first year of medical school—were in school in New Jersey, where the family made its home.

It wasn't easy juggling her dual roles, says Weksler, who once aspired to a career as a hand surgeon but abandoned the dream due to the extended training. "It was the usual kind of circus to make sure there was a stable nanny," she says. "Sometimes there was, sometimes there wasn't." These days, at least, patients rarely address Weksler as "nurse," as they often did early in her career. But even though she rose to full professor in 1981 and helped train Barbara Hempstead, MD, PhD, the current co-chief of the Division of Hematology and Medical Oncology, she observes that the overall prospects for women in the upper echelons of academic medicine are still bleak. "The power structure remains biased against women," says Weksler, who created her own antidote to the old boys' network in the form of a nationwide web of female collaborators. "Women in the academic pipeline are as productive as men, but they often aren't given as much laboratory space and they're promoted more slowly."

It's been nearly five years since then-Harvard president Lawrence Summers sparked a public furor when he wondered aloud about women's innate capacities in math and science—and while undergraduate women now match their male peers numerically in most science-based majors, the numbers don't hold up as they proceed through the ranks of academic medicine. In 2006 the National Academy of Sciences issued a 346-page report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, authored by a committee of university presidents, provosts, and government officials. Women constitute a scant 15 percent of the nation's life sciences faculty, the study notes, and the problem goes far beyond the challenge of balancing career with motherhood or a shortage of young women coming through the educational pipeline. "It is not lack of talent, but unintentional biases and outmoded institutional structures that are hindering the access and advancement of women," the NAS committee concluded. "Neither our academic institutions nor our nation can afford such underuse of precious human capital in science and engineering. The time to take action is now."

In June 2008 Dean Antonio Gotto, MD, declared that full professorships for women would be among his top priorities for the next five years. While women are well represented at both instructor and assistant professor levels at Weill Cornell, he noted, they lag far behind men as associate professors and, most notably, as full professors. Currently there are 439 female professors on the faculty compared with 645 male professors—and only two department heads are female. "We will be vigilant in finding ways to increase the promotion of women to associate professor and tenured professor," Gotto said. "This is a top priority."

This year, Weill Cornell launched a program dedicated to addressing the issue: the Office of Faculty Diversity in Medicine and Science, which opened in July. Its mission, Gotto said, is expressed by the acronym IDEAL: "To create a palpable culture of Inclusiveness, Diversity, and Equity in Academic Leadership" at Weill Cornell. "This culture," he said, "will be created through recruitment, mentoring, promotion, retention, and selection for leadership roles to develop and sustain a diverse faculty."

The office will be led by pathologist Debra Leonard, MD, PhD, as Chief Diversity Officer; public health professor Carla Boutin-Foster,

‘Most men don’t know the balancing act often required of women in academic medicine, so as mentors to women they don’t even ask about relevant issues and ways to address them.’

MD, as Director for Diversity in Medicine and Science; and surgeon Rache Simmons, MD, as Director for Women in Medicine and Science. During the 2009–10 academic year, Gotto said, the three will develop plans for the office—among other activities, conducting a faculty survey and holding small group meetings to identify important issues and find the best ways of addressing them. The office’s efforts dovetail with those of the American Association of Medical Colleges, which announced this summer that it would form two new professional development groups—one on women in medicine and science, the other on diversity and inclusion—as well as a new committee on diversity affairs.

As Weill Cornell’s diversity office gears up, women at the Medical College continue to develop the ad hoc strategies that have helped them cope with the challenges facing female scientists. Hempstead, for example, leverages the flexibility of combined research and clinical responsibility to make life easier for the junior scientists in her department. “We try to be accommodating,” says the hematologist, who frequently put her kids to bed and then dashed back to the lab in the evening to get a head-start on the next day’s work during her years as a fellow and young mother. “When you accept graduate students into your lab, you’re not quite adopting them, but almost. The same goes for fellows.” That doesn’t mean compromising on the quality of the work they produce, says Hempstead, but rather insuring that they’ll persevere in the cycle of research, mentorship, and creation and dissemination of new knowledge. “It’s more a question of how can you accommodate their day-to-day family needs so they can get the training and education to be stellar physicians, clinicians, or scientists,” she says. “With some flexibility, everybody ends up winning. You get dedicated individuals coming out of the pipeline who will be better mentors to the next generation.”

Leonard, who serves as vice chair of laboratory medicine, sees mentorship of young faculty as a critical piece of the puzzle. “Recruiting and startup packages cost a lot of money,” she says, noting that a revolving door of young faculty can be an expensive proposition, making retention just as important as recruitment of diverse candidates. “We have the women, we just need to mentor them appropriately so they stay and become associate professors.”

That sounds straightforward, but with a paucity of senior women, most of them already stretched thin, many young female scientists end up with male mentors. In some respects such relationships can yield enormous benefits, but they also pose unique disadvantages, says Leonard, who never had a female mentor herself and has made a point of hosting regular gatherings for female graduate students. “With a male mentor, you can’t go to dinner together, you can’t go for drinks—care must be taken to assure that the reality and the perception are that the relationship is purely professional,” says Leonard, who heads the department’s residency program. Further, she notes that because men haven’t faced the issues women must confront in their careers, they often lack the insight to guide female mentees. “Most men don’t know the balancing act often required of women in academic medicine,” she says, “so as mentors to women they don’t even ask about relevant issues and ways to address them.”

Katherine Hajjar, MD, the Brine Family Professor of Cell and Developmental Biology, has headed her department since 2002, hiring nine junior faculty and boosting the proportion of women to two-thirds of the total. “As chair I’m making sure those six female assistant professors have everything they need to ascend the ladder and get paid at the same rate as the men,” she says. “I’ve tried to protect all of the new assistant professors from major teaching responsibilities until they’re more established, after the first two or three years—these are people who need to get grants to support their research programs, and so far, everyone is funded.” Part of the problem, says Hajjar, boils down to a statistic from the 2006 National Academy of Sciences report: many more male faculty in


Babette Barbash Weksler, MD

Barbara Hempstead, MD, PhD

How to Level the Playing Field

Advice from faculty women

When their children were young, professor of clinical medicine Anne Moore, MD, and her husband, a physician in private practice, rented a house to which they drove on weekends. A senior colleague invited Moore to collaborate on a project, and he suggested she borrow his strategy of doing dictation while his wife drove to their weekend getaway. "I thought, Oh my God, I don't think you know what I do. He had no idea."

It was a different era, says the oncologist, whose children are now in their thirties, but the basic challenge remains: How do you devote the same amount of time and effort to the academic world as a male colleague when you work a second shift at home? "I don't know that there's any way around it," says Moore, a former director of the American Board of Internal Medicine. "Women are given a lot of opportunities, but they've still got the bare-bones facts: if you're having babies and cooking dinner and running the house, there's less time for writing papers in the evening."

Institutions can make it easier for women to find the balance, say Weill Cornell's female scientists. Among their recommendations:

Facilitate childcare. "Having access to high-quality daycare so you can be confident that your baby will be in a good situation is key," says hematologist Barbara Hempstead, MD, PhD, who still recalls the day more than two decades ago that a senior colleague heard her tale of childcare woe and scrawled the sanity-saving phone number for an emergency nanny service on a pad of paper. "There's also a need for after-school programs, programs for kids on school holidays. Any way that can be facilitated ultimately gives you happier, more productive faculty members who are less distracted by day-to-day concerns."

Offer local, affordable housing. During her postdoctoral fellowship, Hempstead and her husband lived close to Weill Cornell. "I could put the kids to bed, run back to the lab and feed some cells, and get a leg up on the next day's work," she recalls. "It afforded tremendous flexibility." Today, she says the Medical College's housing offerings—all within fifteen minutes of 1300 York Avenue—boost recruitment and retention. "It's a perk that helps us attract and retain quality job candidates on almost all fronts."

Stack the deck. Make sure the committees hiring faculty and setting policy reflect the kind of diversity the institution seeks. "We don't recruit enough women in high-power positions," says Randi Silver, PhD, the Graduate School's dean of students. "That's because the search committees are male-dominated. They tend to be senior men and they're looking for guys like themselves. It's a cultural thing. You have to change the culture." Katherine Hajjar, MD, the chair of Developmental and Cell Biology, agrees. "It's critically important that we have

several women on every search committee—and every committee, period. We need to make more of an effort. It's not enough just to put an ad in the *New England Journal of Medicine* and see what comes in. You have to call around the country and say, 'Thanks for sending these names, but are there any women who come to mind?' The more women we get at the upper levels, the more will come."

Improve research support. "One of the wonderful things about being a scientist is that at some level, you're your own boss," says Hempstead. "You're limited only by your creativity and the tools you have to answer interesting questions. Those are rare and wonderful jobs. The part that makes me most wistful is that you bring along graduate students to have those same aspirations, but the current funding environment makes the future much more daunting."

Highlight successful female scientists. "Women sometimes feel that there are no role models," says Hajjar. "If you're at an institution where there are very few women at the senior level and they are working like a dog at work and at home and never coming up for air, those people who are really amazing are invisible."

In the meantime, senior faculty women suggest a few personal tactics for their younger colleagues:

Choose a partner who gets it. As co-chief of hematology and oncology Barbara Hempstead puts it: "When you're a scientist writing a grant, you're working sixty-plus hours a week, almost flat-out, and you need a spouse who will assume—with a nanny or housekeeper—virtually all of the childcare for a couple of weeks and not lose their mind."

Hire helpers. "Women don't always realize the value of paying for more help," says Moore, who had a live-in nanny as backup in case both she and her physician husband were called out of the house simultaneously. "Get a cleaning woman, get the food cooked. There's a lot that women think they need to do themselves, and you just have to give up and hire someone."

Establish a robust local network. "Women have to give some thought to where they end up," says Silver. "Do they have a support system nearby? You can make it work for you with supportive family and a spouse who believes in what you do."

Cristina Fernandez, PhD '08

the biological sciences have partners at home who don't work. Few woman scientists have that luxury. "The men have a wife at home, taking care of the kids," says Hajjar, who credits support from her biochemist husband, graduate school dean David Hajjar, PhD, as a critical element of her own career success. "Institutions need to step up. For example, support for men and women who are in the position where they have to provide childcare or elder care should be a consideration."

But there's another hurdle to women's ascension through the faculty ranks, one over which Weill Cornell has limited control: reduced access to federal research support for all junior faculty. "It's one thing to look at the current funding situation through the eyes of a fifty-some-year-old woman and realize that it's been this bad before and it got better and eventually it will probably get better again," says Hempstead. "But it's awfully daunting if you are a twenty-eight-year-old woman with a baby just getting your thesis done and wondering, How am I ever going to do this? The people who are most vulnerable are the emerging scientific generation. I'm afraid those are the individuals we're going to lose."

For Cristina Fernandez, PhD '08, gender was never an issue in her training as a pharmacologist—her decision not to pursue a career in academic medicine came about in no small part because of the finances of the field. "If there were more funding available, more opportunity, everything would change," says the thirty-year-old. "If you have to be in the lab eighty hours a week, something has to give. If there's more funding, more opportunity, there's less competition, less demand to devote so much time to work."

In her current position as a medical writer at Ogilvy Healthworld, Fernandez works forty to fifty hours a week in an office staffed almost exclusively by female PhDs. "I can't go out for a two-hour cup of coffee or roll in at 10 a.m., but at the same time, very rarely do I have to work weekends or nights." That simple fact has yielded a different kind of flexibility. "I live and work in Manhattan," she says, "but I don't have to be across the street from where I work anymore, because weekends and nights are mine." ●

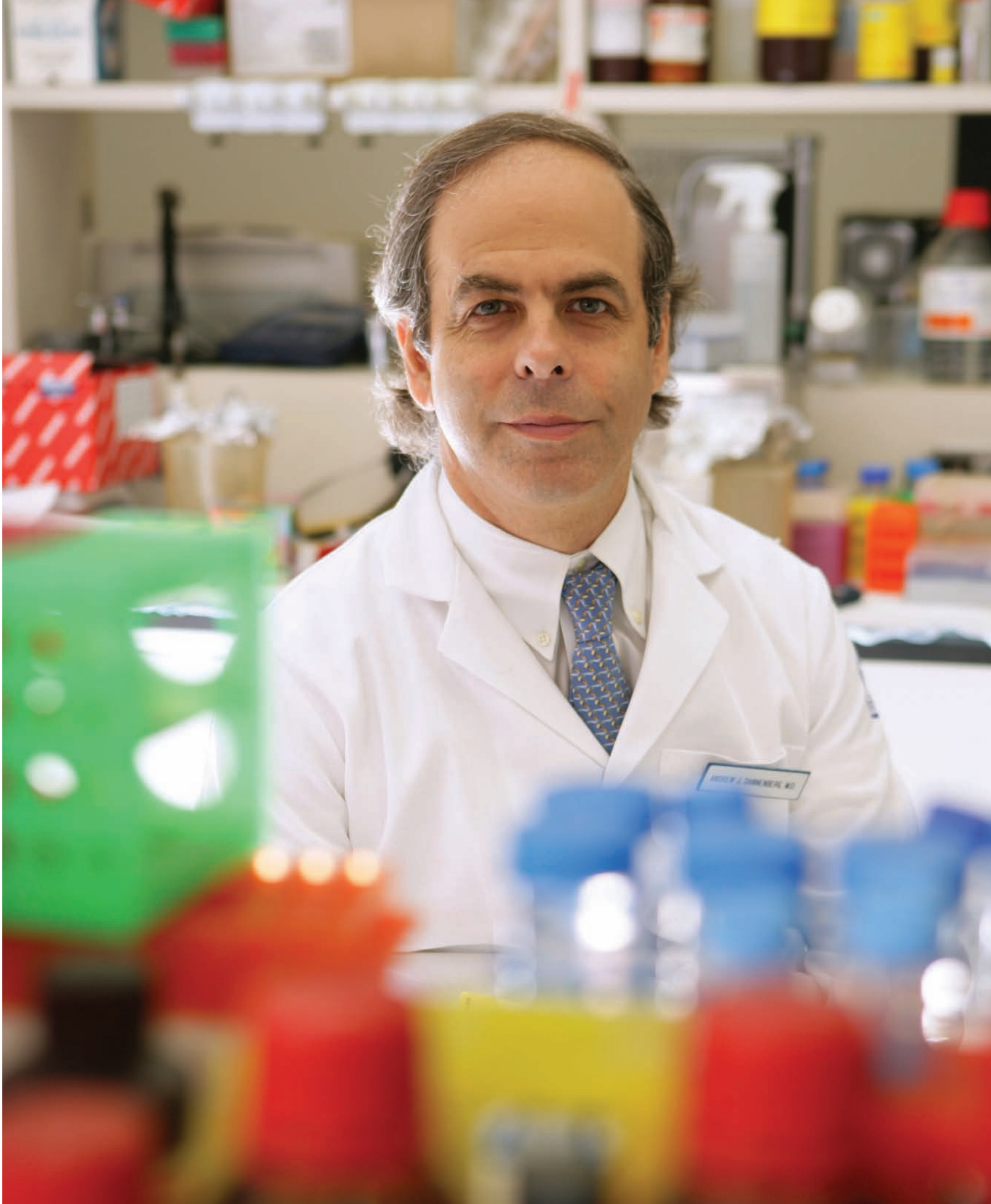
Worth a Pound of Cure

Physician-scientist Andrew Dannenberg, MD, collaborates with scientists around the globe in the quest to prevent cancer

By Beth Saulnier

Photographs by John Abbott

Andrew Dannenberg, MD, has spent the past two decades studying cancer. He has approached the disease from bench to bedside, explored its relationship to everything from smoking to viruses to painkillers, and collaborated with scientists around the world; he has published more than 150 articles, won awards, and served on the editorial boards of prominent journals. But in the end, all of that effort can be distilled down to one word: prevention.



Dannenberg says that more than 20 percent of cancer cases worldwide can be traced to viruses, bacteria, or parasites. 'It's quite a startling number,' he says. 'I don't think the public is sufficiently aware of the link.'

"As a physician-scientist, my goal was always to work on issues that would be of value for the general population," says Dannenberg, the Henry R. Erle, MD–Roberts Family Professor of Medicine at Weill Cornell and director of the Weill Cornell Cancer Center. "I hope that any progress I make translates to clinical benefit—and it's my belief that more emphasis should be placed on efforts to prevent cancer. That doesn't mean that I'm not devoted to developing new and improved therapies. It's just that, from a societal standpoint, I think more emphasis should be placed on preventing disease."

Over the past few years, Dannenberg has been working to spread the word about the causal relationship between infection and cancer: he says that more than 20 percent of cancer cases worldwide can be traced to viruses, bacteria, or parasites. "It's quite a startling number. I don't think the public is sufficiently aware of the link between chronic infection and cancer." With the advent of the Gardasil vaccine to protect young women from four types of human papillomavirus (HPV), Americans have become more aware of the relationship between HPV and cervical cancer. But they may not know that the same virus is closely connected to throat and oral cancer (an argument for vaccinating boys as well), that chronic hepatitis B and C can lead to liver cancer, or that *Helicobacter pylori* can cause stomach cancer.

What do those underlying conditions have in common? Inflammation, the body's response to infection. Dannenberg has become one of the world's leading authorities on the link between chronic inflammation and cancer—a relationship that he says goes far beyond the one-fifth of cancer cases caused by infectious diseases. Long-standing inflammation of virtually any tissue increases the risk of cancer, and a clearer understanding of the mechanisms underlying the inflammation-cancer connection should provide the basis for strategies to reduce cancer risk.

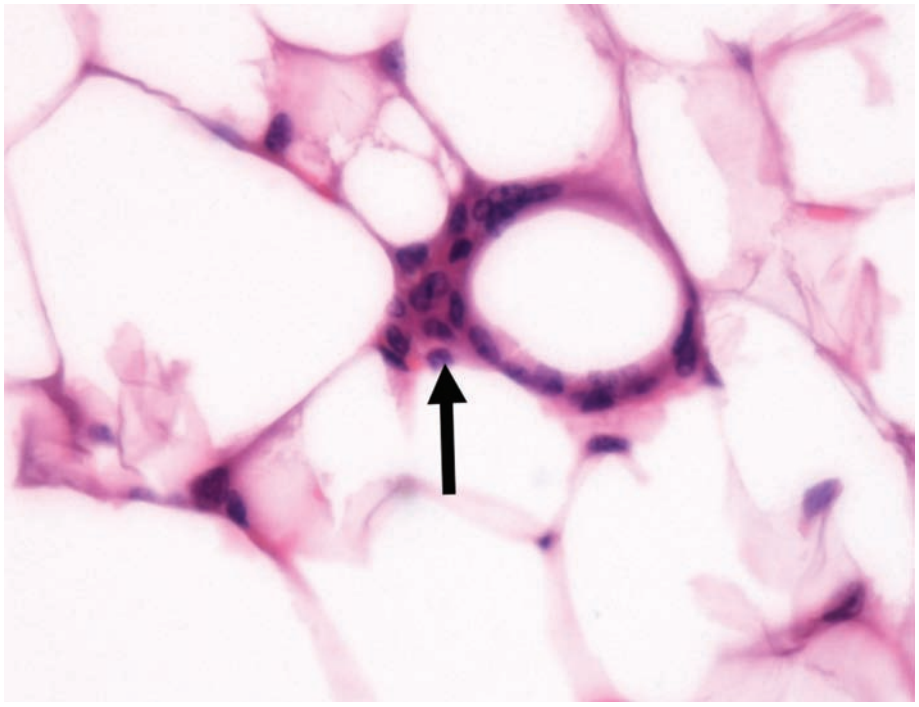
Dannenberg's lab has focused its efforts on a network of genes that control the synthesis (COX-2, mPGES-1) and inactivation (15-PGDH) of pro-inflammatory prostaglandins (PGs). Working with a multidisciplinary team of investigators including his longtime collaborator Kotha Subbaramaiah, PhD, the Jack Fishman Associate Professor of Cancer Prevention, Dannenberg's lab discovered that the COX-2 gene was over-expressed in a variety of premalignant and malignant conditions leading to increased levels of PGs—and that inhibiting the COX-2-PG pathway protected against the formation and growth of experimental tumors. PGs promote tumorigenesis by a number of mechanisms. For example, Dannenberg and colleagues described how the COX-2 enzyme's production of PGs increases formation of aromatase—which, as the producer of estrogen, plays a vital role in breast cancer.

In 2004, their work made national headlines after an article in the *Journal of the American Medical Association* reported that use of aspirin—an inhibitor of COX-derived PG synthesis—could dramatically lower the risk of developing hormone receptor-positive breast cancer, which makes up about 70 percent of cases in postmenopausal women. They began working in cell culture and confirmed their findings in a mouse model—concluding that over-expression of COX did indeed lead to an increase in aromatase. The researchers then wondered whether the findings could be extended to women.

"The question became, how the heck would I test this idea in real time?" Dannenberg recalls. "I struggled. I did not know what to do. And then I thought to myself, I have colleagues at Columbia who have just completed this well-known breast cancer study. I knew they had collected a wealth of data concerning use of aspirin, so I went to them with a molecular hypothesis. Based on our preclinical studies, we hypothesized that use of aspirin, an inhibitor of PG production, might suppress aromatase levels and thereby protect against hormone receptor-positive breast cancer." Dannenberg asked the epidemiologists to interrogate their database. The findings: women who reported having ever taken aspirin showed a 26 percent reduction in hormone receptor-positive cancer, but no meaningful drop in the receptor-negative version. "As a physician-scientist, I found it gratifying," Dannenberg recalls. "Here we were demonstrating, albeit in a retrospective study, that use of aspirin, an inhibitor of pro-inflammatory PG production, led to a statistically significant reduction in hormone receptor-positive breast cancer—but it had no effect on hormone receptor-negative breast cancer, consistent with our preclinical findings."

"This work has tremendous potential for public health impact," says Clifford Hudis, MD, chief of the Breast Cancer Medical Service at Memorial Sloan-Kettering Cancer Center, a professor of medicine at Weill Cornell, and one of Dannenberg's longtime collaborators. Still, Hudis and Dannenberg stress that they don't recommend that all women take aspirin specifically for breast cancer prevention. Despite the drug's potential benefits—also protecting against heart disease—it can have serious side effects, such as stomach ulcers and brain hemorrhage. "What I can say is that for those who are taking aspirin for other reasons, there is likely to be a benefit in reducing cancer risk," Dannenberg says. He and his collaborators continue to work on the link between pro-inflammatory PGs and aromatase with the goal of developing pharmacological or dietary strategies to reduce breast cancer risk.

In a related line of investigation, Dannenberg and his collaborators are working on inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), a condition that predisposes the patient to colorectal cancer. The mechanisms underlying the inflammation-cancer connection are being defined. "Many of the pathways that are aberrant in colitis are also altered in colorectal tumors," Dannenberg says. "In the short term, these mechanisms promote wound healing—but left unchecked, they lower the threshold for tumor formation." The ongoing work promises to provide new insights into the link between colonic inflammation and colorectal cancer that may result in risk reduction strategies. Another goal is to develop a personalized approach to reduce colonic inflammation.



PROVIDED BY DR. DANNENBERG

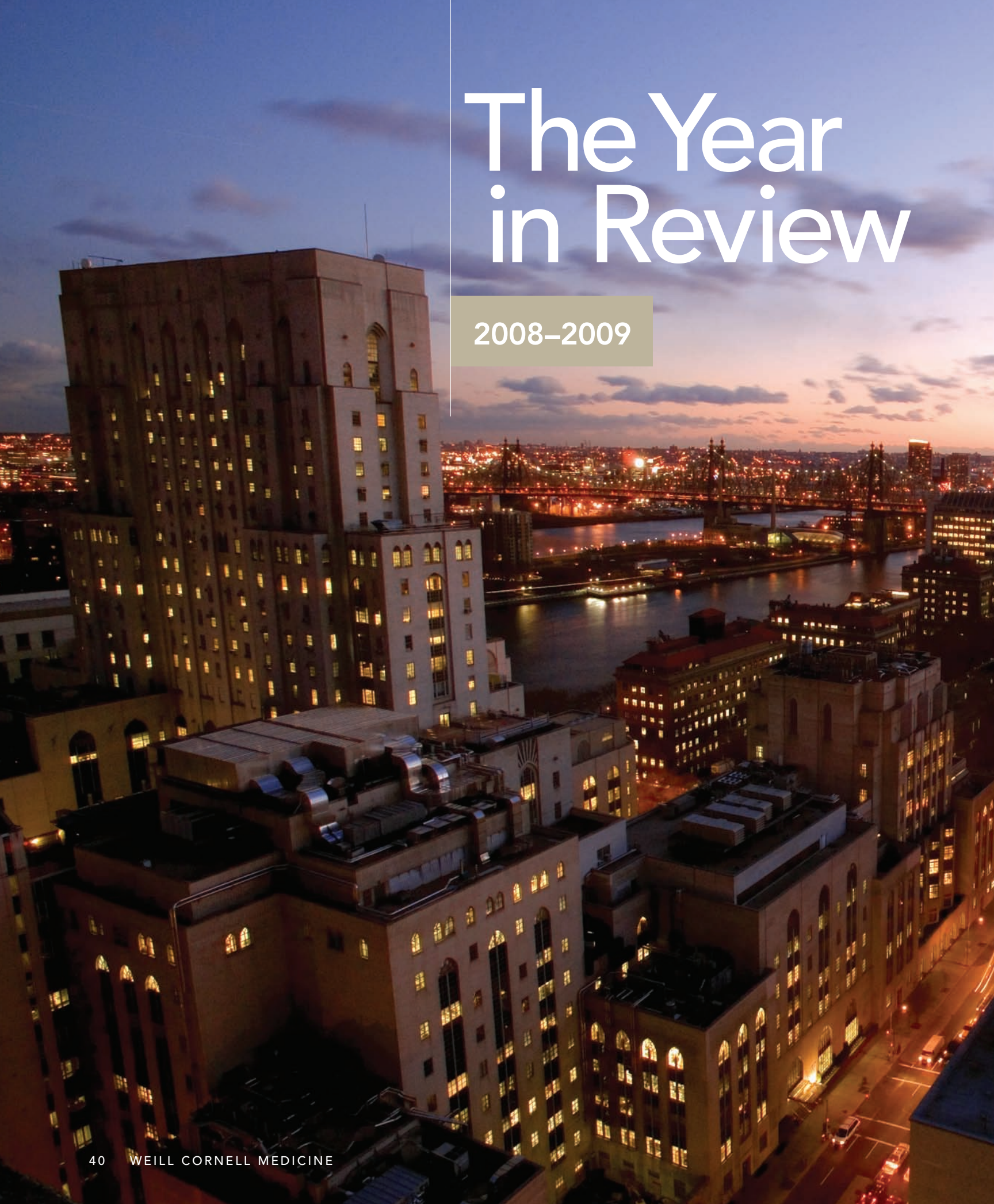
Cancer cause?: Dannenberg is investigating the role of substances released by inflammatory cells—such as these (marked by an arrow) in the breast tissue of obese mice—as promoters of cancer.

Dannenberg's current work also includes exploring how one of America's most pressing health issues—the fact that a third of the population is overweight and another third is obese—may also portend a rise in cancer diagnoses. "One of the things that we're interested in pursuing now is obesity as a public health crisis," says Dannenberg. "Most people don't appreciate that obesity isn't just a risk factor for diabetes or heart disease, but also for cancer." Obese patients, he notes, are predisposed to a number of different cancers, including those of the breast, colon, endometrium, pancreas, and esophagus. "Obesity causes a sub-clinical inflammatory state," he says. "It's not like having a hot knee—if you have arthritis in your knee, you know about it. But in fact obesity can lead to inflammatory cells infiltrating tissues. So in addition to weight control there may be pharmacological or dietary strategies to suppress inflammation and thereby assist in reducing the personal risk of developing cancer."

Production of PGs, he notes, is sensitive to diet—so ingesting some types of fish and other foods that contain omega-3 fatty acids could reduce PG levels and suppress inflammation. By contrast, other types of dietary fat may be pro-inflammatory. "Working in close collaboration with Louise Howe, PhD, associate research professor of cell and developmental biology at Weill Cornell, and Dr. Subbaramaiah, we are actively investigating the effects of different dietary lipids on PG levels and related inflammatory mediators in preclinical models," says Dannenberg. "Of course, the long-term goal of this work is to be able to make evidence-based dietary recommendations. It is absolutely reasonable to believe that diets can be tailored to modify personal risk, but careful, mechanistic bench-to-bedside studies are required. It's our view that, on a population basis, this type of work illustrates the potential of employing diet to reduce cancer risk."

Trained as a gastroenterologist, Dannenberg earned his MD from Washington University in St. Louis and did his residency and fellowship at Weill Cornell. Although he no longer sees patients, he is every inch the physician-scientist, colleagues say. "He is a remarkable person and has amazing energy," says Babette Weksler, MD, professor of medicine at Weill Cornell. "He organizes a complicated laboratory—people coming from all over the world, young scientists, young surgeons who often have had no background in the lab—and everyone goes away well trained and with a good paper under his or her belt. It's a lot of different people working together and all learning a great deal. Going to his lab meeting every week is one of my pleasures."

Both Hudis and Weksler laud Dannenberg for his skills as a collaborator, as well as for his ability to place his work into a broader context. "He is driven and passionate beyond belief—in a very good way," Hudis says. "He's also extremely and appropriately self-critical. When he's presenting an idea, he's the first person to point out if there's something potentially wrong with it, which is the way good scientists work. I find him inspiring to collaborate with, because he works so hard, in such a tightly focused way, and pursues a specific problem to the end. When you're with Andy, the system that his lab is focused on becomes the most important thing on Earth." ●



The Year in Review

2008–2009

DISCOVERIES THAT MAKE A DIFFERENCE

Thank You for Partnering with Us

The *Discoveries that Make a Difference* Campaign at Weill Cornell Medical College has a singular goal: to translate our excellence in research into the most advanced treatments for patients as quickly as possible. Our physician-scientists are already in the vanguard of some of today's most profound medical discoveries, thanks to our world class position in teaching, research, and patient care, as well as our fertile collaborations across disciplines with researchers at Cornell University in Ithaca.

As of September 2009, $865 million has been raised toward the $1.3 billion goal for the *Discoveries* Campaign. Each gift moves us closer to our goal. We will succeed only with the continuing generosity of our alumni and friends, such as the donors whose names you see in the following pages. We are deeply grateful.

The 69th Street Medical Research Building

At the center of our *Discoveries that Make a Difference* Campaign is a new Medical Research Building, a 480,000 square-foot, sixteen-floor facility on the Weill Cornell campus. It is a close neighbor to the Weill Greenberg Center, our award-winning outpatient care facility.

The Medical Research Building heralds a new era in the landscape of Weill Cornell, doubling its current research space and fostering collaboration to promote scientific innovation. Its unique open floor plan will maximize collaboration among our renowned physician-scientists. Core facilities on each floor of the Medical Research Building will provide centralized access to state-of-the-art technology used by faculty across all research areas, increasing efficiency and reducing costs.

The Medical Research Building, a state-of-the-art blueprint for twenty-first-century science, will serve as a catalyst for pushing the boundaries of discovery to find solutions to some of our most significant health issues.

The *Discoveries that Make a Difference* Campaign will also fund additional research laboratories, scientific program development, faculty recruitment, student scholarships, and fellowships.

Key research areas include: Cancer; Cardiovascular Disease; Children's Health; Global Health and Infectious Disease; Neurodegenerative/ Neuropsychiatric Diseases and Aging; Diabetes, Metabolic Disorders, and Obesity; and Stem Cell, Developmental Biology, Reproductive, and Regenerative Medicine. To date, $290 million has been raised toward the funding goal of $350 million for the Medical Research Building.

The Weill Challenge

The Campaign received a significant boost when Joan and Sanford I. Weill established the *Weill Challenge*, a program that offers matching funds for gifts to the Medical Research Building. The *Weill Challenge* will allow more donors to maximize the impact of their gifts: every $1.50 given to the Research Building will be matched with $1.00 from Mr. and Mrs. Weill. The *Weill Challenge* has been launched at a critical time, when so many of the Medical College's supporters are feeling the effects of the economic downturn.

This is a historic moment in scientific discovery. With your support, this groundbreaking Campaign will leverage the world-class expertise of our faculty and propel next-generation breakthroughs in prevention, treatment, and cures for some of our most debilitating and urgent health conditions. Thank you for joining us.

We are grateful to all the generous friends who have supported Weill Cornell over the past year. Special thanks are extended to the following donors whose gifts of $1,000 or more were recorded during the fiscal year July 1, 2008, through June 30, 2009:

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

Entering medical students

Total applications received	5,577
Male	2,953
Female	2,624
Under-represented minorities	679
Total applicants interviewed	732
Total acceptance letters sent	290
Matriculating students (Fall 2009)	101
Male	55
Female	46
Under-represented minorities	25
New York State residents	33
Out-of-state residents	66
International students	2
Age range in years	20–36
Average age	23.6
Average science GPA	3.73
Cumulative GPA	3.75
Average MCAT score	11.5
Verbal	10.6
Physical science	11.7
Biological science	12.1

Entering PhD students

Matriculating students (Fall 2009)	40
Male	10
Female	30
Under-represented minorities	8
New York State residents	7
Out-of-state residents	19
International students	14
Average science GPA	3.6
Average GRE scores (percentiles)	82.5 %
Verbal	82 %
Quantitative	83 %

Tri-Institutional MD-PhD Program

Matriculating students (Fall 2009)	14

Total enrolled students

Medical students	363
Graduate students	545 *
MD-PhD students	43

*Includes: 352 PhD; 20 PhD Tri-I Chemical Bio; 18 PhD Tri-I Computational Bio; 20 MS Clinical Epidemiology; 36 MS Clinical Investigation; 99 MS Physician Assistant

Degrees conferred (May 2009)

MD	92
PhD	58
MS	17
MD-PhD	13

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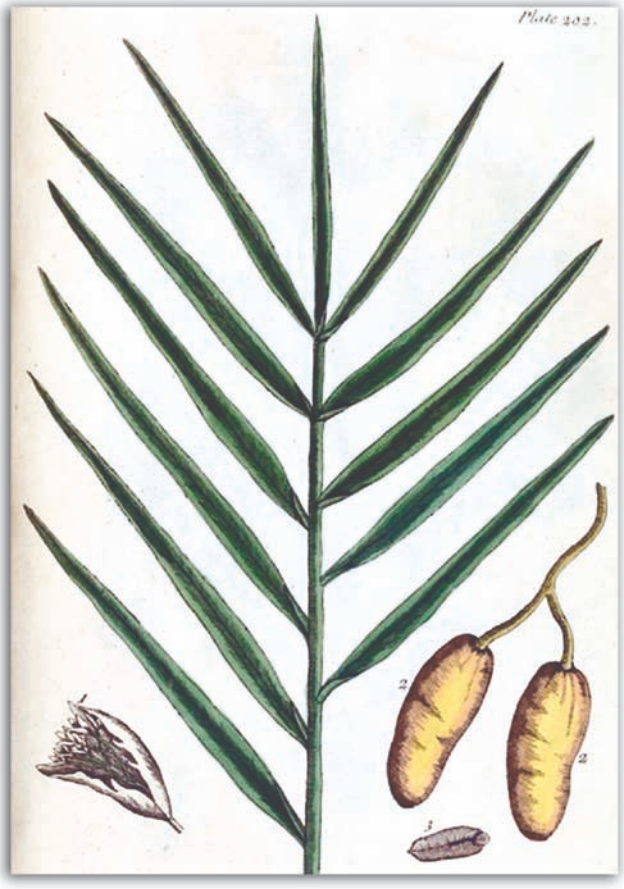
Post Doc

Save the Date

WCMC-Q maps the genome of the Middle East's signature crop

Dates are to the Middle East what apples are to America—not only a staple crop but a cultural symbol. So when researchers at Weill Cornell Medical College in Qatar cast about for a plant with which to test the capabilities of their new Genomics Laboratory, they didn't have to look far. "It's such an important crop in this part of the world, because it's one of the few trees that can withstand the environment—extreme heat, wind, sandstorms—and still produce nutritious fruit," says Joel Malek, MS, the lab's director. "It's one of those crops that the rest of the world would not necessarily be interested in studying. But historically, this region has relied heavily on dates in all kinds of ways."

In February, Malek and a team of four technicians began unraveling the secrets of the date palm using the latest technology, known as next-generation DNA sequencing. While such technology has generally been used for resequencing—in which researchers already have a reference and are looking for small differences between samples—using it to map a genome from scratch was uncharted territory. Of the 3,000 varieties of date, they chose the Khalas (*Phoenix dactylifera*), considered one of the finest. "Apparently it's the quintessential date, not too sweet or salty," says Malek, a native of the Boston area who has developed an appreciation for the fruit in the year and a half he's been in Doha. "It has just the right flavor, and because of that it's expensive. Now, when I go to the store I keep my eye out for it."



FROM: A CURIOUS HERBAL , ELIZABETH BLACKWELL, 1737

Tree of life: The date palm, seen in an eighteenth-century illustration, has been a vital crop in the Middle East for millennia.

Although the date palm genome is small compared to that of other plants, it still comprises about 300 million bases—only about 3,000 of which had previously been sequenced. But within a few months, the researchers announced that they had completed a draft of the genome. They're currently preparing their work for publication and will continue the project as funding becomes available. "We've probably decoded 90 to 95 percent of the 300 million bases, and we know what their general neighborhood is," Malek says. "We have the sequence, but where exactly the genes sit on the genome and in what order—we have a rough view of that."

The work, Malek says, could offer major advances in the ancient practice of date cultivation—particularly in making them hardier. "A lot of domesticated date palms are not very resistant to disease, whereas wild trees are," he says. "We're trying to figure out why. Have the ones that have been cultivated for thousands of years lost certain immunity genes?" The research could also facilitate propagation. Date palms come in male and female versions, with only the latter producing fruit; growers need a single male to pollinate every fifty to one hundred females. To ensure the right balance, they can't just plant from seed; they have to wait for a female tree to sprout a shoot, allow it to grow for several years, then transplant it. "It's decades before they can regenerate an orchard," Malek says. "Our goal would be to find the genetic difference between male and female and come up with a test for the seeds."

In addition to aiding local agriculture, the date palm project was launched to prove the capabilities of the biomedical research program at WCMC-Q. The program is funded by support from the Qatar Foundation, which aims to make it a hub for research throughout the Middle East. "Many people don't set out to do these larger projects because they don't believe the technology exists here," Malek says. "The goal is to get the country and the region up to speed. Because once people see that it can be done, they'll start envisioning what they could accomplish."

A TIME OF HOPE

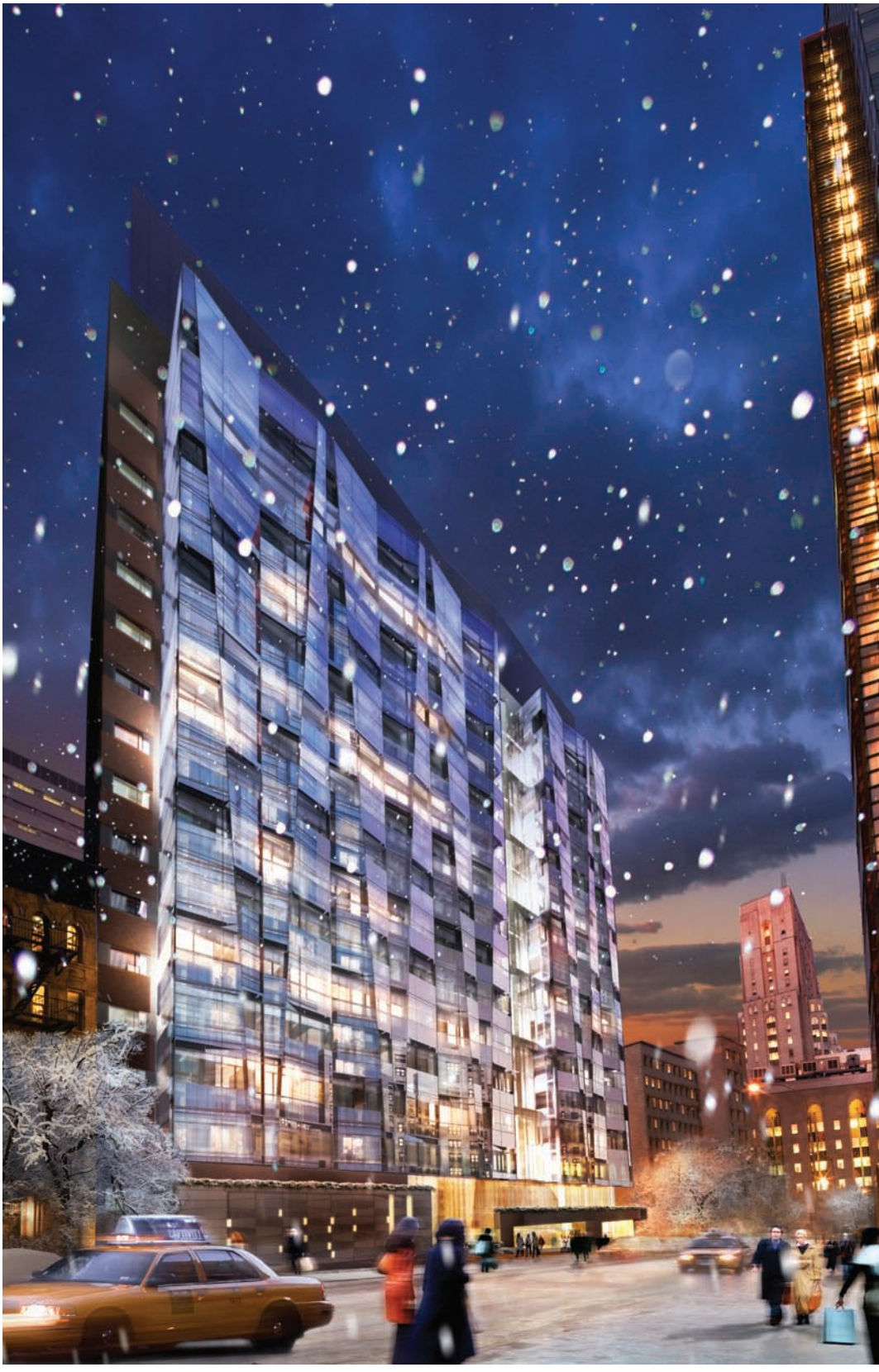
The holiday season is a time of celebration, expectation, and a measure of the promise of things to come.

There has been much to celebrate over this past year, including recognition of the research spearheaded by our basic science and clinical faculty in the form of new and renewed contracts and grants during an increasingly difficult time of constrained federal resources. But in the face of a struggling economy, our donors have continued to step forward to ensure that we will continue our mission of unexcelled medical education and breakthrough research, both contributing to a pledge to provide the highest quality patient care. Our new Medical Research Building will serve as a cornerstone for our future as a world-renowned "bench to bedside" institution. One can only look to the future with much hope and expectation.

Wishing you peace and good health in the year ahead,

Antonio M. Gotto

Dean Antonio M. Gotto Jr.



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FAMILY DAY 2010

SAVE THE DATE **Friday, March 26, 2010**

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