

Profiles in Innovation

# Research

# DOWNSTATE

2016

## Profiles in Innovation: The Anthology Edition

# Over

## a Century and a Half of

# Innovation

# Research DOWNSTATE

## Profiles in Innovation: The Anthology Edition

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# A Biotech Park Grows in Brooklyn

Despite its wealth of scientific and biomedical talent, New York City has long lagged behind areas like Boston and San Francisco in attracting and retaining small and mid-sized biotechnology companies.

The reason is simple, says Eva Cramer, PhD, Downstate's vice president of biotechnology and scientific affairs and a distinguished service professor of cell biology. "There's a lack of affordable lab space."

Envisioning a solution that could benefit emerging biotech firms, and Downstate and New York City scientists as well, Dr. Cramer and colleagues devised in 2000 a plan for a biotechnology incubator, a lab facility that provides already-built bench and office space at reasonable prices. "We started with no real estate, no money, just the idea that we could capitalize on the synergy between companies and our faculty and students," Dr. Cramer recalls.

That idea has grown into a Biotechnology Park adjacent to the campus, a larger facility on the Brooklyn waterfront called BioBAT, plus an educational program that prepares college science majors for jobs in biotechnology.

The Biotechnology Park, featured



Eva Cramer, PhD

in a March 2010 article in Crain's New York Business, is one of only two biotech incubators in the whole of New York City. It includes the 24,000-square-foot Advanced Biotechnology Incubator and a state-of-the-art synthetic chemistry facility. The proximity of both helps facilitate interactions between the companies and Downstate's faculty and students. BioBAT, a 486,000 square-foot facility for more mature biotech companies, is based at the former Brooklyn Army Terminal. Tenants include the International AIDS Vaccine Initiative, a developer of HIV

vaccines; BioCangen, which designs assays for cancer detection; and Bio-Signal Group, a producer of devices that record brainwaves. "Having these different kinds of spaces means we can provide smaller companies with larger facilities as they grow," Dr. Cramer says.

Because "science courses do not adequately equip science majors for employment in biotech labs," Dr. Cramer says, the incubator's one-month workforce development component teaches undergraduate students biotech job skills. To date, the program has helped more than 90 students find work in the field. "These students are well received by a wide range of employers, from the City's Medical Examiner's Office and the New York Blood Center, to the American Museum of Natural History," Dr. Cramer says. A number of graduates are employed at the incubator itself.

"Faculty members now have a place to pursue their entrepreneurial projects right next to the school," Dr. Cramer says. "Our medical and graduate students can experience the excitement of working at biotech start-ups. And the dream we had ten years ago has been built, and continues to grow, right here in Brooklyn." ■

# Teasing Influences Apart: A New Model for In-Utero Crack Exposure

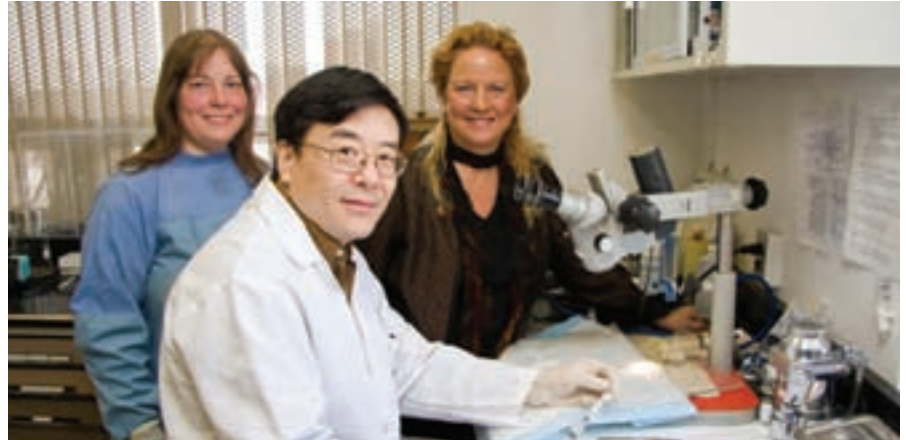
One doesn't hear much about the crack-cocaine epidemic these days. The news articles about crack-exposed newborns, so common at the epidemic's outset in the mid-1980s, have disappeared from the front pages of the nation's newspapers. And the epidemic itself peaked in 1990.

Nevertheless, every year in the United States, an estimated 165,000 women smoke crack while pregnant, according to the federal Substance Abuse and Mental Health Services Administration. In the last decade, more than a million crack-exposed babies have been born.

Clinicians have studied the development of children exposed in utero to this purified, smoke-able form of cocaine since the epidemic began. They have documented problems with behavior and attention, deficits in language and cognition, lower academic achievement, and lower IQs. Neuroimaging has revealed anatomical differences in brain development between crack-exposed and otherwise healthy children. But, because many children exposed to crack in utero are raised in homes with drug-using and/or mentally unstable parents, separating the impacts of prenatal crack cocaine exposure from other influences on brain development, behavior, and cognitive function is difficult.

Studies with animal models can help answer questions about crack's impact on exposed offspring. But to date, the only models available to researchers conducting studies in pregnant rats and their progeny have been ones that mimic maternal nasal cocaine use rather than crack bingeing, which gives users a faster and more intense "high."

Diana Dow-Edwards, PhD, is attempting to rectify that problem. A professor of physiology and pharmacology and of cell biology, Dr. Dow-Edwards is using funding from the National Institute of Drug Abuse to develop a first-of-its-kind model of crack bingeing in pregnant rats. "If we can establish this model," says Dr.



From left: Susanna Popp, PhD, research associate; Ning Zhao, MD, senior research associate, with Dr. Dow-Edwards.

Dow-Edwards, "we can set in motion a series of experiments that will inform our scientific understanding of the effects of in utero crack exposure on offspring."

Dr. Dow-Edwards has been using rat models, albeit imperfect ones, to study crack's impacts since the epidemic started more than 25 years ago. "Crack was a huge public problem then. As someone who had been researching the effects of in utero alcohol exposure, I had the tools to join other researchers in investigating this new problem," she says about her early involvement in the field.

Crack bingeing is the most common form of cocaine use among pregnant women. Yet, to date, the evolution of a rat model of bingeing behavior has been slowed by difficulties in determining appropriate dosing levels and the complexity of certain surgical techniques. "A more accurate model can move the research in this field forward," Dr. Dow-Edwards says.

Nasal cocaine use differs from crack use in that nasal cocaine is metabolized more slowly and is less likely to lead to drug cravings. By contrast, "crack leads to very rapid increases and decreases in drug levels in the brain," Dr. Dow-Edwards explains. Crack users frequently binge for 12 hours or more. "In the fetus, these two phenomena may influence the

development of those same brain areas that cause cravings in adults," Dr. Dow-Edwards observes.

To better explore these effects, Dr. Dow-Edwards and her lab have devised a model that employs a difficult-to-implant jugular cannula in combination with frequent intravenous dosing. The cannula allows Dr. Dow-Edwards and her research group to inject cocaine directly into the rats' bloodstream.

Now, they are working to achieve the kinds of crack-use sequelae that human mothers develop: severe weight loss, miscarriage, and premature birth. "If we can identify a sub-toxic but very robust dosing pattern, then we will be sure we have an accurate model of human in utero exposure," Dr. Dow-Edwards says. Offspring from such a model could enable her lab to more accurately explore crack's impacts. "We also want to examine whether enriched environments improve outcomes for offspring," she says, "and to look at reward circuits and cognitive function."

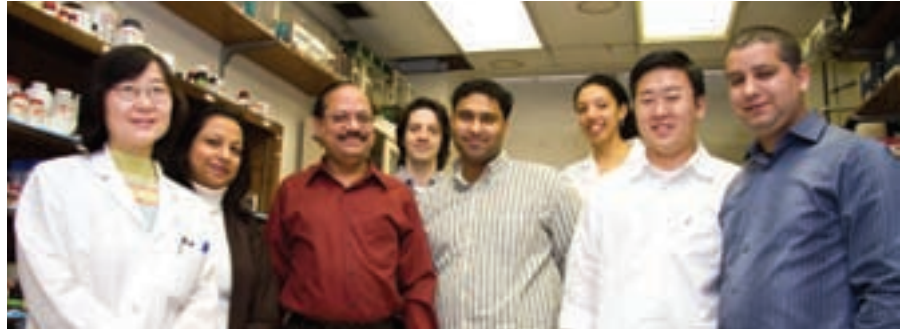
All this research is aimed at helping doctors and social service providers understand crack-exposed children's specific needs and challenges. "Ultimately, the information we uncover," Dr. Dow-Edwards says, "will end up helping kids." ■

# Midnight Oil: Sleep Disturbances' Impact on Lipoprotein Production

Night-shift workers — everyone from nurses to police officers to researchers at the British Antarctic Survey Station — suffer from cardiovascular disease and metabolic syndrome at rates that are sometimes five times greater than their peers working the day shift. Metabolic syndrome is a cluster of medical conditions which includes high cholesterol and is linked to heart disease and stroke.

Though researchers have documented this phenomenon, to date, they have had trouble understanding its causes. But now, with funding from the National Institute of Diabetes and Digestive and Kidney Diseases, Mahmood Hussain, PhD, a professor of cell biology and pediatrics, appears to have brought its etiology to light. Using laboratory mice, Dr. Hussain has recently discovered that circadian rhythms — our 24-hour activity/sleep cycles — and the genetically controlled mechanisms that regulate them play a significant role in the production of lipoproteins. Lipoproteins are a group of soluble proteins that combine with and transport fats (lipids) in the bloodstream. Excess accumulation of these low-density lipoproteins in the plasma is a major contributor to heart disease. “When our circadian rhythms are disrupted,” Dr. Hussain explains, “we absorb more lipids and have more lipoproteins in the blood.”

Dr. Hussain, who has spent much



Dr. Mahmood Hussain's lab (from left): Xiaoyue Pan, PhD, research assistant professor; Irani Khatun, candidate for PhD; Dr. Hussain; David Bowman, BS, research support specialist; Joby Josekutty, candidate for MD, PhD; Joyce Queiroz, MS, research support specialist; James Soh, candidate for MD, PhD; Jahangir Iqbal, PhD, research assistant professor.

of his career researching lipid formation, came to the question of how disruptions in circadian rhythms influence lipid production when Xiaoyue Pan, PhD, one of his post-doctoral fellows, approached him with the previously unexplored idea. She had studied circadian rhythms as part of her PhD thesis. “I said, ‘That’s fantastic! Let’s get started,’” Dr. Hussain recalls.

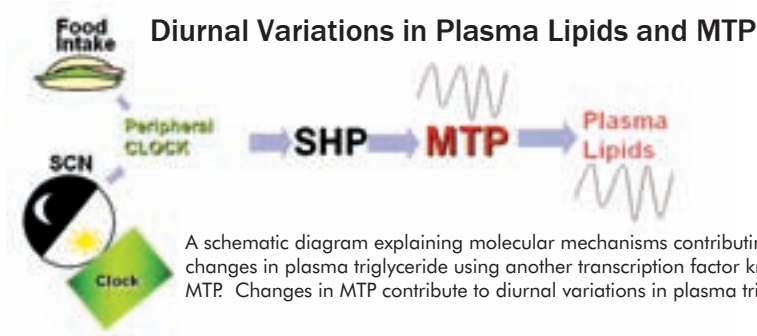
Drs. Hussain and Pan with members of their lab first experimented in normal mice, disturbing their natural sleep/wake cycles and measuring the resulting changes in lipid levels. Mice are naturally nocturnal. And “when we fed them during the day instead of during the night, they switched the timing of their activity and their lipid production from nighttime to daytime,” Dr. Hussain explains. “But when we kept them in constant light for five whole days, they

lost this diurnal regulation of lipoprotein production,” and continued to produce lipoproteins around the clock.

To further explore the day/night cycles’ impact on lipid production, Dr. Hussain turned to mice that had mutations in the Clock gene. Clock is a member of a group of “genes found in every cell that regulate the body’s 24-hour cycle,” Dr. Hussain explains. Clock genes are themselves switched on and off within a part of the brain called the suprachiasmatic nucleus, which is sensitive to light. “Clock mutant mice cannot sense properly when daytime is and when nighttime is,” Dr. Hussain explains. Rather than having to keep his mice awake 24 hours a day, the Clock genetic mutation did the work for him. As a result, like many night-shift workers, the mutant mice were active and eating for many

more hours than their normal counterparts. The animals' plasma lipid levels — especially their levels of so-called triglyceride-rich APOB-containing lipoproteins — increased “to very high levels and remained high throughout the day” when compared to their normal siblings. Dr. Hussain’s research also led to the observation that “Clock mutant mice are prone to atherosclerosis” — hardening of the arteries — indicating that “disruptions in circadian rhythms may predispose individuals to this disease,” he says.

Dr. Hussain’s experiments have illuminated the pathways by which these APOB-containing lipoproteins are formed. “We found that the Clock gene actually regulates another transcription factor called SHP (small heterodimeric partner), and SHP regulates MTP (microsomal triglyceride transfer protein),” a transfer protein that plays a pivotal part in the formation of APOB-containing lipoproteins. In earlier research, Dr. Hussain was the first to identify MTP as a key protein involved in the diurnal



regulation of plasma triglyceride.

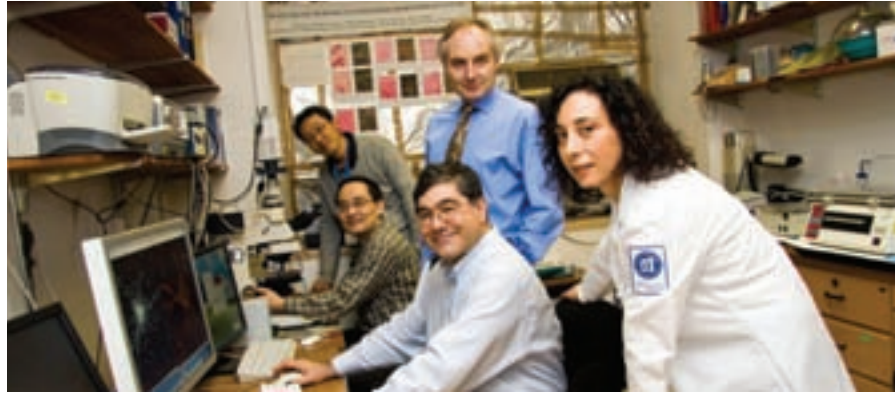
Having teased apart the mechanism by which sleep disruptions increase circulating lipid levels in laboratory mice, Dr. Hussain hopes to explore further the implications of those findings. How might sleep disruptions affect heart and kidney function? And, are there processes that can reduce lipid accumulation and lipoprotein formation in mice that are active almost 24 hours a day? He has another ongoing research project supported by the National Heart, Lung, and Blood Institute to look into ways to inhibit MTP as a means to lower plasma lipids.

“Sleep disruption is a hallmark of our age,” Dr. Hussain notes. Social changes brought about by the television, the Internet, and frequent air travel, as well as the global marketplace, have increased the numbers of people with interrupted and insufficient sleep. For example, some traders wake up at 3 a.m. to watch the European markets, and there is a steadily increasing number of transcontinental business travelers, who frequently cross time zones. “It’s important to understand,” Dr. Hussain says, “how this lack of sleep is affecting our cardiovascular health.” **R**

# Travel to the Junction: RNA's Journey from Nucleus to Synapse

**H**ow does the brain interact with its environment? What is the process through which internal and external stimuli influence brain cell activity, and with that activity, brain function?

For years, these questions have fascinated Henri Tiedge, PhD, a professor of physiology and pharmacology, who explores them at their most basic scientific level. In particular, Dr. Tiedge is enthralled by the subject of neuronal RNA translation. That's the complex and largely mysterious process by which the genetic information stored in brain cells' DNA is used to create ribonucleic acid (RNA) molecules that are the instructions for creating proteins. In neurons, the RNA itself can travel to remote parts of the cell where synapses are located, and build proteins on site. "These proteins — neurotransmitter receptors, ion channels, protein kinases



Dr. Tiedge, standing in the center, and members of his laboratory (from left): Jun Zhong, PhD, research assistant professor; Taesun Eom, PhD, research scientist; Ilham A. Muslimov, MD, PhD, research scientist; and Anna Iacoangeli, PhD, research assistant professor.

— are involved in synapse structure and function," Dr. Tiedge explains. "They underlie the whole panoply of higher brain function."

Dr. Tiedge wants to understand what enables the genetic information that is stored in a neuron's DNA to find its way

to the synapse. And, given that large amounts of this genetic information travel to synapses and are stored there until, often much later, the need arises for the information to be synthesized into protein: what controls how this genetic information gets to remote sites,

and what controls the use of this information to build proteins on site?

These are essential questions. “The process of reacting to stimuli by translating RNA into proteins is basically what allows the brain to interact with the outside world,” explains Dr. Tiedge. The localization of proteins at synapses enables communication among brain cells. This communication, in turn, is responsible for many of the basic processes in which the brain is involved — learning, memory, language, emotions, to name just a few. Deciphering the neuronal RNA translation process may explain much, not only about normal brain function, but also about abnormal brain function. Malfunctions in neuronal RNA translation appear to underlie autism, Alzheimer’s disease, and a form of mental retardation known as Fragile X syndrome, researchers say. Certain drugs of abuse may have long-term effects on consciousness and behavior by altering the ways brain cells make critical proteins. “Brain function,” Dr. Tiedge says, “depends on how these RNAs are localized and translated at synapses over time.”

Knowing that lay audiences may have trouble understanding molecular brain research, Dr. Tiedge is fond of analogizing the process of neuronal RNA transport to a New York City commute. How do straphangers know which subway to board in Manhattan in order to arrive at SUNY Downstate in Brooklyn? What information, in what form, allows them to catch the right train, get off at the

right stop, and arrive at their desks at the beginning of the workday? Is there something that prevents the commuters from disembarking too soon and wandering aimlessly around downtown Brooklyn?

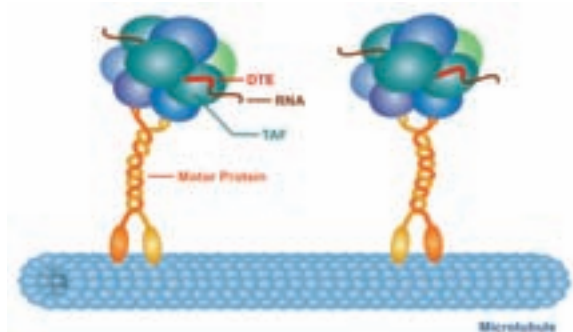
To learn the answers to these questions, Dr. Tiedge and his team perform experiments in cultures of rat brain cells, small pieces of brain tissue (“brain slices”), and postmortem human brain tissue. They have also developed mouse models. “We have found,” Dr. Tiedge explains, “that gene expression at the synapse is governed by a type of RNA called” — not surprisingly — “regulatory RNA.” Using knock-out mice that are missing certain of these regulatory RNAs, Dr. Tiedge has demonstrated that synaptic RNA translation into local proteins is instrumental in normal brain function; his knock-out mice have hyperexcitable brain cells, and the animals themselves are prone to seizures.

Much more research in this area remains to be done. The traveling instructions that RNAs receive come in the form of ensembles of nucleotides — molecules made up of nitrogenous bases, sugars and phosphates — called “codes.” “At the moment, we only understand some of the codes that get certain classes of RNA out of the cell’s nucleus where they’re made, to the synapses, where they

function,” Dr. Tiedge says.

His new research in this area, funded by the National Institute on Drug Abuse, explores how drugs of abuse, such as opiates, impact neuronal RNA translation.

“Once we understand all of the components in this process of neuronal RNA translation, we can think about how to address diseases such as autism and Alzheimer’s,” Dr. Tiedge says. His research on how drugs of abuse impact neuronal RNA translation may help explain mechanisms of action of these drugs and aid researchers in developing more effective treatments to reverse addiction. But his research has broad implications for all of neuroscience. “Basically,” Dr. Tiedge says, “this type of research has the ability to explain how brain cells function as a person interacts with his or her environment. This work may one day help explain a fundamental part of who we are.” ■



RNA transport along dendritic microtubules. Trans-acting factors (TAFs) interact with dendritic targeting elements (DTEs) that are contained within transported RNAs. RNA-containing particles are thought to be transported by molecular motors such as kinesins.



# Once Around the Block: Decoding the Causes of Ischemic Injury

**M**ore than 1.25 million Americans suffer from heart attacks each year. Another 800,000 are affected by stroke. A rare form of blood-flow blockage in the intestines that affects about 35,000 people annually has a fatality rate of more than 70 percent. All these conditions have one thing in common: ischemia — inadequate

or disrupted blood supply — followed by reperfusion injury.

Until recently, scientists believed that the tissue damage these ischemic events precipitate is mostly the result of blood-flow blockage. But, Ming Zhang, MD, PhD, a research assistant professor of anesthesiology and cell biology, has discovered there is another cause

as well: inflammation that results from a post-ischemic autoimmune response that follows reperfusion. “When I came to Downstate in 2005, I began discussing this new concept with cardiologists and other clinicians,” Dr. Zhang recalls. “It was quite a novel idea for them. But now that we have more research to back up this concept, clinicians are becoming

interested in how the process works." Indeed, Dr. Zhang's research in humans and in laboratory animals may soon lead to the development of an agent that can help minimize the damage this autoimmune response generates.

Dr. Zhang's interest in the causes of ischemic injury stems from research he conducted as a post-doctoral student at Harvard. "My mentor had a project on autoimmunity and inflammation," he recalls. "As I became involved, I saw the many potential applications of this research." In 2004, Dr. Zhang and colleagues were the first to publish on the subject, using laboratory animals to document the phenomenon in cases of intestinal ischemia.

"We discovered that with ischemia, cell membranes get damaged and intracellular components" — cell contents, in other words — "are suddenly exposed to the immune system," Dr. Zhang explains. "When blood vessels are reperfused, the body's innate immune system, which has never before encountered these 'self' components, goes on the attack. Certain antibodies dock onto the injured cells and destroy them." These antibodies are a variant of the immunoglobulin, IgM. Since Dr. Zhang first discovered this process in intestinal ischemia, he and other researchers have documented it in animal models that include other types of ischemic injuries, such as heart attack, trauma, burns, and surgery.

With funding from the National Heart, Lung, and Blood Institute, Dr. Zhang is currently testing whether humans have similar responses. To conduct this research, he has enlisted several of Downstate's cardiac surgeons. "In cardiac surgery, you have a kind of



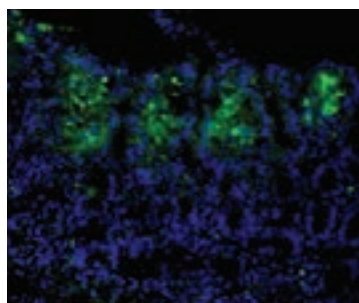
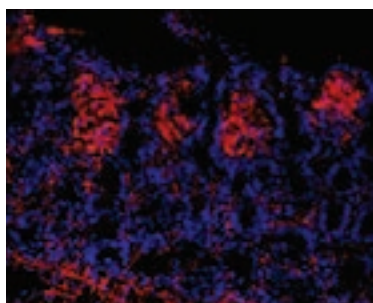
Dr. Ming Zhang and members of his laboratory (from left): Chihyuan Mark Lai, PhD student; Haekyung Lee, PhD student; Amie Kim, MD student; Dr. Zhang; Georges Labaze, MD, clinical research coordinator; Yunfang Joan Hou, MD, instructor, ECRIP fellow; Julie Rushbrook, PhD, professor (Dr. Zhang's collaborator); and Karan Gulaya, BS, research assistant.

ischemia, too," he explains. "The blood vessels are clamped off to allow the surgeon to operate on the heart." When the clamps are removed, blood flow to the area is reestablished. "To help us ascertain whether IgM plays a role in post-ischemic injury, these surgeons are collecting samples of blood from patients' hearts before surgery and after," Dr. Zhang says. His lab then tests the IgM levels in those samples in an effort to ascertain whether this phenomenon is also a significant problem in humans.

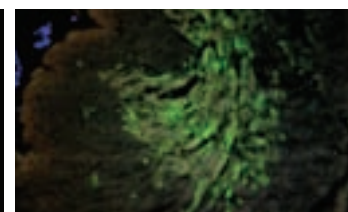
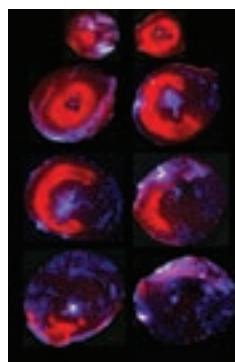
Dr. Zhang believes his research has tremendous translational potential. "Imagine that a high-risk person — someone who had already had a heart attack or a stroke — could carry an injection 'pen,' like the EpiPens that people who have severe allergies carry," he says. "If the person had another ischemic

event, paramedics or emergency room personnel could inject this agent to block the autoimmune response." Likewise, surgeons and anesthesiologists could administer such an agent during surgery, prior to reperfusion.

Dr. Zhang has already been working to make that possibility a reality. "While I was at Harvard, I developed a short peptide that can target the early reaction between the autoimmune antibody and the self antigen," Dr. Zhang says. (His mentor has started a biotech concern to further develop and market this treatment.) Now, Dr. Zhang is designing and testing potential chemical reagents to block this autoimmune response as well. "We have great hope," he says, "that targeting this pathogenic IgM will help minimize injury in a whole host of ischemic events."



Autoimmune natural IgM (red fluorescence) and complement C3 (green fluorescence) are present within the intestinal tissue following ischemia.



Myocardial infarction is tracked by red fluorescent dye and non-ischemic tissue is traced by blue fluorescent dye. Inflammation in the myocardial tissue is tracked with green fluorescent staining of complement C3.

# Mission: To Vanquish Cervical Cancer

Cervical cancer is a largely preventable disease.

Pap smears, which assess cervical cells for signs of cancer or precancerous growth, have enabled doctors “to find lesions early, when they’re close to 100 percent curable,” notes gynecologic oncologist Ovadia Abulafia, MD. In fact, Pap smears and newer generation tests have all but eliminated cervical cancer in the industrialized world.

Except among the poor. Their limited access to medical care means they

often miss out on cervical cancer screenings and the health benefits they provide. “Unfortunately, patients frequently come to us with cervical cancer that is in the advanced stages,” says Dr. Abulafia, a professor and chair of Downstate’s Department of Obstetrics and Gynecology. “They often haven’t had a Pap smear in ten years.”

That regrettable situation is also an important research opportunity. Though the disease’s prevalence in the United States is down steeply from the highs of the pre-Pap test 1940s — about

11,000 cases are now diagnosed annually, according to the National Cancer Institute — worldwide, cervical cancer remains the second-most common malignancy among women. Two hundred and eighty-eight thousand women die of the disease each year.

Dr. Abulafia has played an important role in researching cervical cancer screening and treatment, both as a principal investigator for the Gynecologic Oncology Group (GOG), a National Cancer Institute-funded cooperative clinical trials group, and as a former member of GOG’s cervical committee, which determines the standard of care for cervical cancer patients in the United States.

“What we know about gynecological cancers today is considerably more than what we knew 15 or 20 years ago,” he says. “And as a result, we’ve made significant progress in treating certain GYN malignancies, particularly cervical cancer.”

Dr. Abulafia is a strong advocate of the clinical trials system. “We offer participation in GOG trials to every patient who medically qualifies for a trial, regardless of ability to pay,” he notes.

Under his leadership, Dr. Abulafia and his colleagues have explored new types of cervical cancer screening, evaluating methods such as ThinPrep® (liquid-based cervical cytology), a more advanced Pap test. In fact, in a 2003 study published in the journal *Gynecologic Oncology*, Dr. Abulafia reported that ThinPrep® was more sensitive and accurate than the traditional Pap smear.

Dr. Abulafia has also pursued research into possible connections between HIV and cervical cancer. Because the vast majority of cervical cancers are viral in origin — caused by

Ovadia Adulafia, MD





Members of the Division of Gynecologic Oncology (from left): Wen-Ching Lee, PhD, Institutional Review Board administrator for GOG studies; Allison Wagreich, MD, senior gynecologic oncology fellow; Dr. Abulafia; Joyce McGuire, RN, clinical trials coordinator; Yi-Chun Lee, MD, gynecologic oncology division chief; Ghadir Salame, MD, junior gynecologic oncology fellow.

persistent infections with carcinogenic strains of the human papillomavirus — and because HIV hinders immune responses, some in the medical community have been concerned that HIV-positive women may be at greater risk for precancerous cervical lesions and for cervical cancer itself.

Dr. Abulafia’s studies have tested whether cervical cancer screening methods are effective in HIV-positive women and whether a surgical technique called cervical conization can prevent progression to invasive cancer among HIV-positive women with precancerous cervical lesions.

“We found these methods were less effective in HIV-positive women than in healthy women, and those results emphasized the need for increased vigilance in testing HIV-positive women for

cervical cancer,” Dr. Abulafia explains. “But now, with the widespread introduction of antiretroviral therapy for HIV-positive women, the incidence of both precancerous lesions and invasive cervical cancer has declined significantly.”

Dr. Abulafia has also collaborated with Downstate radiation oncologist Marvin Rotman, MD, in testing cervical

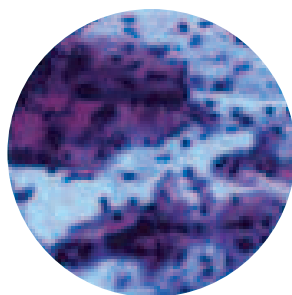
approach. “Our research with Dr. Rotman has enabled us to make significant progress in treating women at high risk for recurrent cervical cancer,” Dr. Abulafia says. “And we have vastly increased our knowledge about the complications and side effects of treatment.”

In fact, Dr. Abulafia says, “every GOG trial we participate in results in

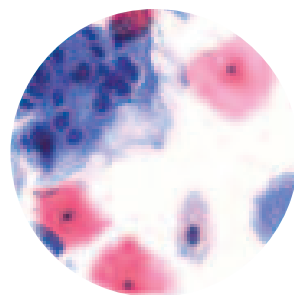
**Every trial we participate in results in some important new knowledge, even if the trial proves the new treatment isn’t successful.**

cancer treatments that combine radiation and chemotherapy. (See Dr. Rotman’s profile on page 6.) One such trial found a 15 percent increase in five-year survival using the combined

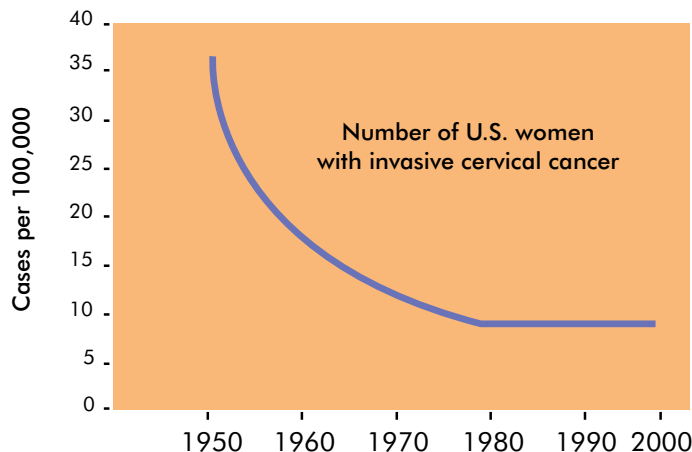
some important new knowledge, even if the trial proves the new treatment or the new technique isn’t successful. That, too, is an important way we make progress.” ■



With the conventional Pap smear method, cells can be obscured by blood, mucus, and inflammation.



The ThinPrep® Pap Test method preserves the cells and minimizes cervical cell overlap with blood, mucous, and inflammatory cells.





Members of the Cardiovascular Imaging Research team (from left): Haroon Kamran, MD, research associate; Oladipupo Olafiranye, MD, fellow; Ather Mansoor, MD, fellow, Empire Clinical Research Investigator Program; Dr. Jason M. Lazar; and Louis Saliccioli, MD, assistant professor of medicine and director of advanced cardiac imaging.

# Heart Disease Treatment is Crucial in HIV Care

**T**he advent, in the mid-1990s, of Highly Active Antiretroviral Therapy (HAART) has changed the nature of HIV infection. Rather than the short, harrowing, and fatal disease it was in the early days of the AIDS epidemic, HIV infection has become a chronic illness, with many individuals living for 20 or more years after diagnosis. Like many chronic illnesses, it includes a number of complications. One of them is heart disease.

In fact, today, cardiovascular disease ranks among the leading causes of death in HIV-positive people, says Associate Professor of Medicine Jason Lazar, MD, director of the University

Hospital of Brooklyn's program in non-invasive cardiology.

Building upon Downstate's longstanding expertise in both HIV and cardiovascular medicine, Dr. Lazar and his team are pursuing the causes and potential treatments of heart disease in HIV-positive women. "Our job is two-fold," says Dr. Lazar. "First, to identify the factors that raise cardiovascular risk for HIV-infected women, and then, quite simply, to find better ways to treat them."

Dr. Lazar's investigations are part of the multi-site Women's Interagency HIV Study (WIHS), initiated at Downstate in 1993. WIHS is one of the world's most comprehensive HIV stud-

ies; study sites have enrolled more than 3,000 participants since its inception.

The study examines all aspects of HIV disease in women. There are three groups of participants: HIV-positive women on HAART, other HIV-positive women, and healthy controls. The groups are socioeconomically matched. "With WIHS, we have an enormous database of biological and psychological information, as well as information about participants' economic status and educational attainment," says Dr. Lazar.

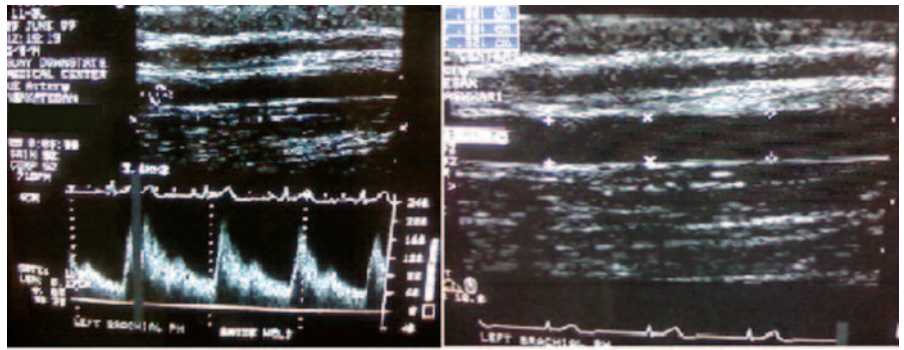
The fact that HIV-positive women are at increased risk of heart disease comes as no surprise to Dr. Lazar. "HIV

infection is associated with biological changes, such as inflammation and chronic activation of the immune system, which in other medical models are associated with increased incidence of heart disease," he notes.

Indeed, among the study group's HIV-positive women, Dr. Lazar's team has documented a number of increases in heart-disease risk: a five-fold increase in cardiomyopathy (heart muscle weakness); higher levels of a heart stress-related biomarker called NT-pro-BNP, usually caused by HIV-positive women's higher rates of Hepatitis C; and diminished dilating abilities in major blood vessels. Moreover, he observes, "our data confirm that poverty and low educational attainment more than double the risk of heart disease, just as they do in non-HIV-infected populations."

The medical literature documents that HAART can increase cholesterol plaque build-up, a major contributor to heart disease. But HIV itself is an important cause of heart disease in HIV-positive women, Dr. Lazar has discovered. "Our studies show that high cholesterol caused by HAART is not related to cardiomyopathy," he says. "Instead, the cause is HIV itself."

Dr. Lazar has also found that HIV is responsible for the diminished dilating abilities of blood vessels in HIV-positive women. "HIV causes blood-vessel inflammation — vasculitis — and that



Ultrasound of the brachial artery showing the blood flow to increase (left) and the artery to dilate (right) in response to various stimuli.

vasculitis impairs the ability to dilate," he explains. So-called progenitor cells in the bone marrow may also play a role in keeping blood vessels flexible.

In healthy people, progenitor cells help repair the linings of blood vessels,


vessels repair themselves in general."

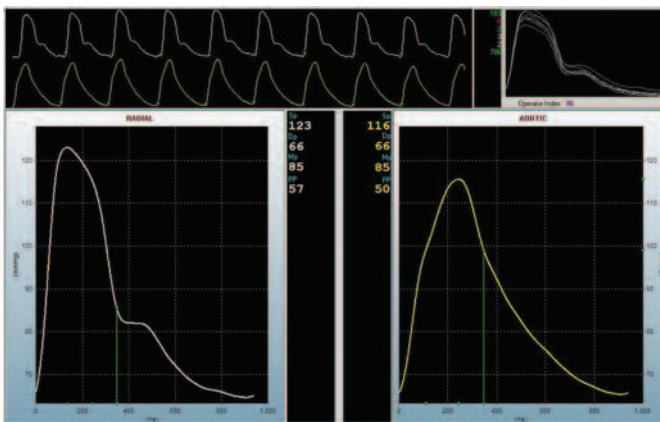
Dr. Lazar's work represents the best in the rapidly emerging field of translational research — the quick transformation of scientific discoveries into clinical applications. Indeed, at Downstate's

## Today, cardiovascular disease ranks among the leading causes of death in HIV-positive people.

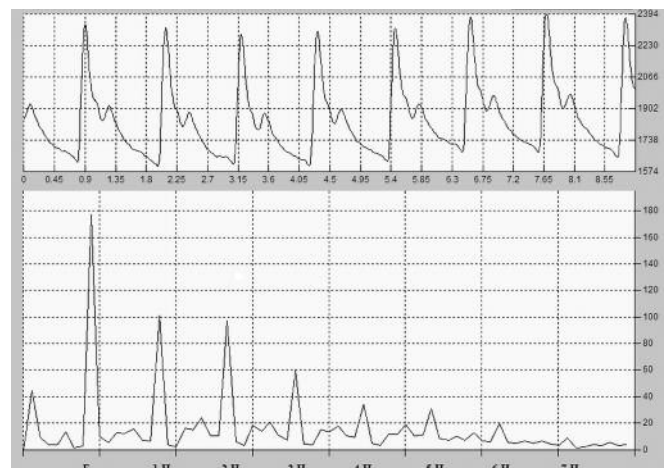
improving their ability to dilate under stress. HIV-positive women produce "greater numbers of KDR-positive progenitor cells and fewer numbers of CD34-positive progenitor cells" than HIV-negative women, Dr. Lazar has discovered. "These differences in progenitor cell production may explain some of the differences in dilation, as well as provide new insight into the process by which blood

Cardiovascular HIV Affiliate Clinic, a heart-disease treatment program designed for HIV-positive patients, Dr. Lazar uses his team's findings to optimize patient care.

"We're altering treatment regimes to best protect our patients' cardiovascular systems," Dr. Lazar says. "We want to intervene before heart disease presents itself." 



Non-invasive recording of blood pressure from the radial artery (left) used to determine arterial stiffness and blood pressure in the central aorta (right) near the heart.



Non-invasive arterial blood pressure recording (top) and breakdown by mathematical technique into basic signal components (bottom).

# Medicine vs. Microbes

**B**acteria evolve to overcome obstacles to their spread. That fact is part of their very nature. Indeed, in the late 1940s, only a few years after penicillin's introduction to the United Kingdom, approximately half of the staphylococcus (staph) infections there developed a resistance to the world-changing drug.

These days, multidrug-resistant (MDR) bacteria can "outwit" almost any of the antibiotics doctors use to treat them. Several of these bacteria have taken up residence in hospitals, unfortunately. In these healthcare settings, they put at risk some of the most vulnerable patients — infants and elders in intensive care units, immuno-compromised

individuals already weakened by chemotherapy or disease.

Accurate statistics about death rates from hospital-acquired infections are difficult to come by. But "patients who get these bugs have very high mortality

non-MDR form of the infection.

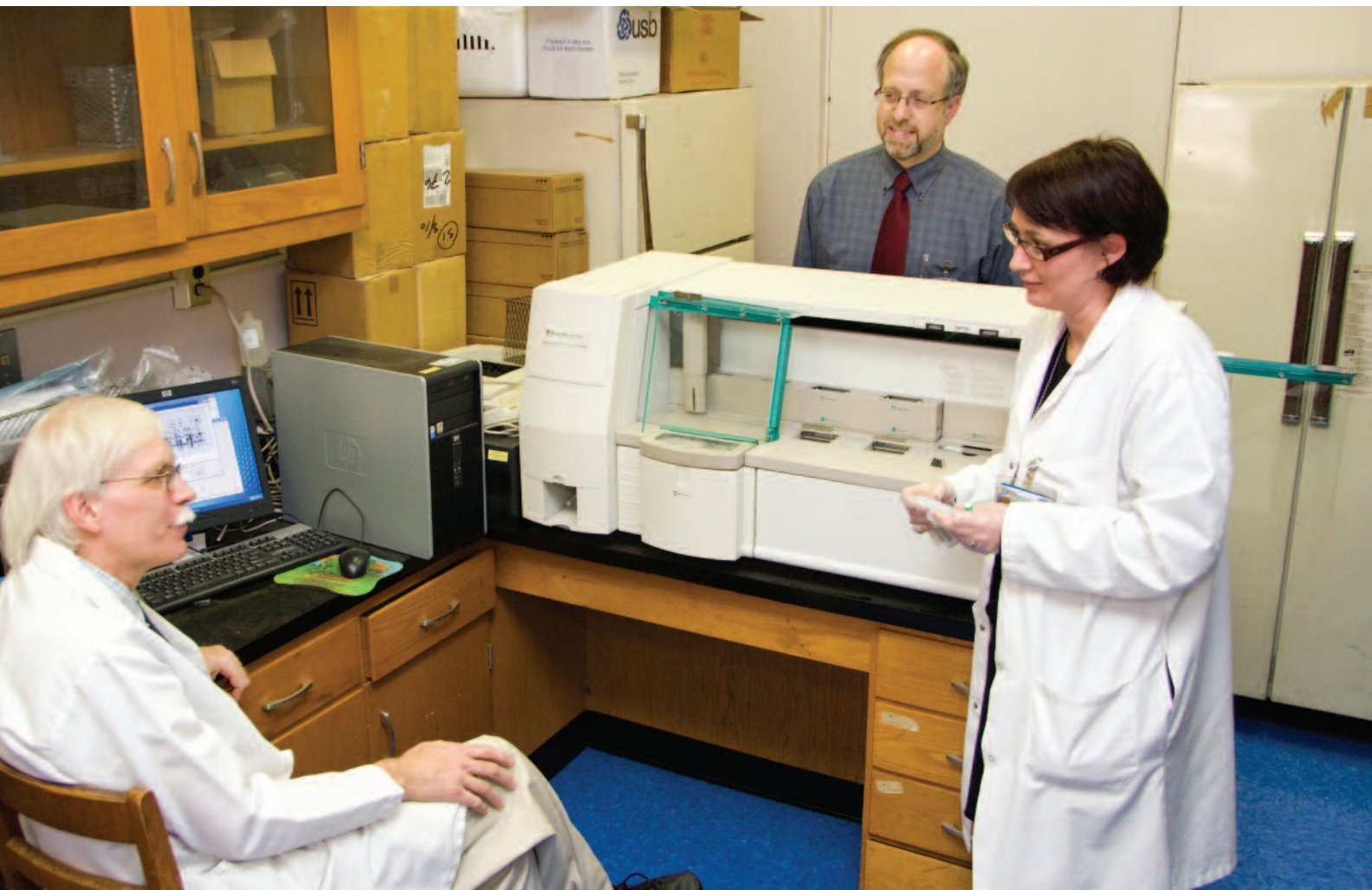
Whether those high mortality rates result from MDR infections themselves or "from the fact that these patients are very sick to begin with" is still unclear, Dr. Quale says. But a dramatic rise in

**Dr. Quale and his colleagues hope to outsmart multidrug-resistant bacteria by finding their Achilles' heel in the enzymes and proteins they produce.**

rates," notes infectious disease specialist John Quale, MD, an associate professor of medicine. In one study, patients with one type of MDR bacterium — *Klebsiella pneumoniae* — had a three-fold greater risk of death compared to patients with a

the prevalence of MDR *K. pneumoniae* infections in New York City hospitals from 2001 through 2006 highlighted the need for research into enhanced surveillance, detection, and infection control measures.

Dr. Quale (seated) and his collaborators David Landman, MD, associate professor of medicine, and Simona Bratu, MD, assistant professor of medicine.



For several years now, Dr. Quale, has been collaborating with Simona Bratu, MD, assistant professor of medicine, and David Landman, MD, associate professor of medicine, to explore the molecular biology of antibiotic resistance in *Klebsiella pneumoniae* and another MDR bacteria, *Acinetobacter baumannii*. These are two of the world's most prevalent and dangerous hospital-acquired infections.

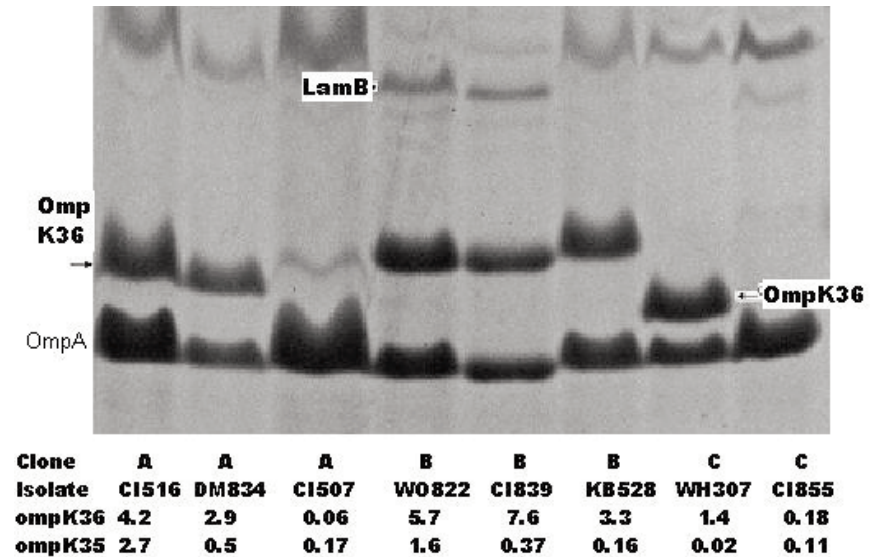
The group, which is funded by the National Institute of Allergy and Infectious Diseases, a division of the National Institutes of Health, has two goals: to uncover the primary causes of antibiotic resistance in these two MDR bacteria and to identify new sites that antibacterial drugs can attack.

"To combat these infections, we really need new classes of antibiotics," Dr. Quale explains. "But short of that, there are proteins and enzymes these bacteria produce that could be inhibited. We're looking for the Achilles' heel of the bacteria."

In hospitals, MDR bacteria linger on surfaces and on infected patients, spreading through some of the most mundane types of contact. "In the intensive care unit," Dr. Bratu explains, "a staff member might touch a patient who has the infection or pick up the germ by touching a patient's bed." That staff member might then pick up a chart at the nurse's station, touch a phone, a computer or an IV pole. Through those points of contact, "another staff member can spread the bacteria to a different patient," she explains. The fact that patients can harbor the infection but have no symptoms – and that clinical cultures cannot be relied on to identify patients who are infected – adds to the difficulty of control.

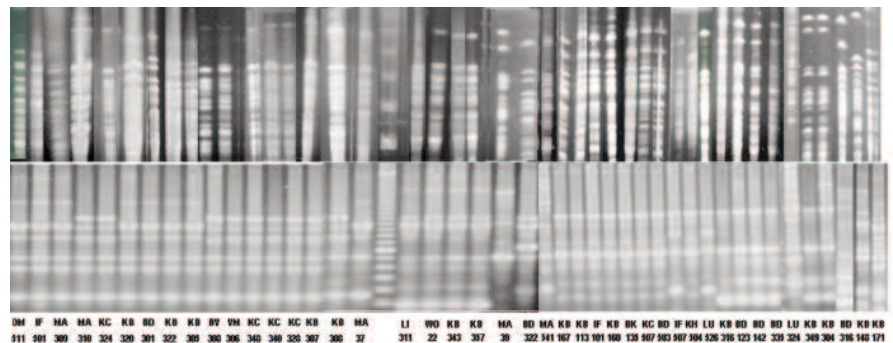
The research and clinical staff at Downstate have developed infection control protocols for intensive care units that, in one study, have more than halved *Klebsiella* infections. As documented in an article in the May 2009 issue of *Infection Control and Hospital Epidemiology*, an aggressive program that includes contact isolation, daily cleaning of environmental surfaces and patient-related items, education, and a team effort involving

**FIG 1**



**FIG 1.** (KpPorins) Proteins isolated from the cellular membranes of *Klebsiella pneumoniae* and subjected to electrophoresis. Some isolates can lose a porin (demonstrated by the isolate in the third column, which has reduced production of a porin called OmpK36) that contributes to antimicrobial resistance.

**FIG 2**



**FIG 2.** DNA fingerprint patterns of isolates of *Acinetobacter baumannii*. Highly resistant isolates from hospitals throughout Brooklyn tend to share similar fingerprint patterns, suggesting the spread of clonally related isolates throughout medical centers in our region.

nursing and infectious disease staff can produce significant results.

But further limiting the spread of *K. pneumoniae* and *A. baumannii* requires research into the fundamental causes of their resistance.

One of the causes, the group has discovered, is beta-lactamase, "an enzyme that eats up some of the penicillin-type medications before those drugs can kill the bacteria," Dr. Quale explains. Also under examination is the function of porins, "little pores in the cell membrane that allow antibiotics to get inside." In MDR infections, porins' function may

be compromised in some way. Moreover, adds Dr. Bratu, "some of the bugs have what are called efflux pumps. When an antibiotic gets inside the cell, the efflux pump renders it ineffective by pumping the antibiotic back out again."

The group is also measuring gene expression in the two MDR bacteria, in an effort to understand how gene regulation plays a part in antibiotic resistance and how its manipulation might enable new types of treatment.

"We need new drugs," Dr. Quale says. "Our research can lay the groundwork for creating them." **R**



# Getting Ready for the Unthinkable

**P**andemic flu. Chemical leak. Terrorist attack.

Disasters like these require a special type of medical expertise, a special type of planning — so much so that New York City’s Department of Health and Mental Hygiene (DOHMH) has mandated that each of the city’s acute-care hospitals appoints an emergency preparedness coordinator.

At University Hospital of Brooklyn (UHB) that position has been ably filled by Michael Augenbraun, MD, a professor of medicine. Dr. Augenbraun collaborates on emergency preparedness activities with Bonnie Arquilla, DO, Downstate’s director of disaster management and an assistant professor of emergency medicine. Together, they have developed innovative disaster-preparedness programs that can serve not only UHB’s central Brooklyn neighborhood, but, through replication by other hospitals, the larger city, and indeed, the wider world.

With support from DOHMH’s Fund for Public Health in New York, Drs. Augenbraun and Arquilla have created protocols for mass screening and triage, delivering critical care, and controlling infection during a public health emergency. They’ve designed and conducted drills to help hospitals, churches, and schools throughout the

One of the keys to emergency preparedness is coordination among area healthcare providers. When Drs. Augenbraun and Arquilla took up the task of readying UHB for disasters, “one of the first questions we asked ourselves was, How do we create a coordinated response among medical providers in our neighborhood?” Dr. Augenbraun recalls.

**Hospitals are called upon to do such vital work during disasters that implementing these programs successfully is central to mitigating a disaster’s impact.**

city prepare for disasters. And now, they are sharing their expertise with medical centers and universities in the developing world.

“Hospitals are called upon to do such vital work during disasters,” Dr. Augenbraun says, “that implementing these programs successfully is central to mitigating a disaster’s impact and guaranteeing the best possible outcomes.”

The pair quickly developed a network of area hospitals — UHB, Kings County Hospital, Kingsbrook Jewish Medical Center, and Kingsboro Psychiatric Center — to participate in joint disaster-preparedness activities. Together, these hospitals have collaborated on at least 18 drills in the last seven years, each one modeling responses to possible disasters such as subway explosions and toxic chemical leaks.



Bonnie Arquilla, DO



Michael Augenbraun, MD

“Last summer, we ran a drill with 350 volunteer ‘patients’ to test our protocols for a pandemic influenza,” Dr. Augenbraun explains. One of the group’s goals was to ensure that “infected” and “uninfected” volunteers were kept apart, to avoid further infection.

“We learned a lot about what we can anticipate,” Dr. Augenbraun says. For instance, institutions “may underestimate the need for space in case of a large number of patients,” Dr. Augenbraun says. “The drills have helped us refine our protocols.”

Another of Dr. Augenbraun and Dr. Arquilla’s accomplishments is the development of disaster response protocols for hospitals. Their manual, “Children in Disaster: Hospital Guidelines for Pediatric Preparedness,” is likely the first of its kind in the nation. The handbook is available for free online, and details, among other things, the pharmaceuticals hospitals should keep on hand, psychosocial interventions that might aid children, and security and tracking procedures for pediatric patients.

“I’m proud that the manual is accessible to any hospital that wants to use it,”



(From left) Dr. Bonnie Arquilla; Patricia M. Roblin, MS, administrator; Charles Parker, BA, drill coordinator; Dr. Augenbraun; George Allen, RN, PhD, director of infection control.

says Dr. Augenbraun, who is also developing a guide to the disaster-related needs of the geriatric population.

The team’s influence has spread beyond New York City to the developing world. Dr. Arquilla has been collaborating with officials in South Africa to organize disaster preparedness protocols for the upcoming 2010 soccer World Cup there. She also consults regularly with medical officials in India. “The collabora-

tion with South Africa is new,” Dr. Arquilla says. “But in my longstanding work in India, I’ve learned how health-care workers can better handle large crowds and communicate with large numbers of patients.”

“What we’re doing,” Dr. Augenbraun says, “is creating a larger safety net. That net will enable hospitals to fulfill their roles as healthcare providers at the times when they are needed most.” **R**

**EMERGENCY PREPAREDNESS EXERCISES**



# Tiny Patients, Terrible Pain

**N**ewborns and premature infants in neonatal intensive care units (NICUs) are subject to a host of painful procedures: intubation, heel sticks, blood draws, and intravenous lumbar punctures, to name just a few. These babies may also experience significant pain as a result of their underlying medical conditions.

Pain is not just a quality of life issue for these sick children. Ongoing pain is associated with an increased likelihood of death in NICUs.

Unfortunately, “there is very limited analgesia available to newborns,” observes neonatologist and pharmacologist Jacob Velasco Aranda, MD, PhD, a professor of pediatrics and head of Downstate’s neonatal unit. In fact, only three drugs are used to manage pain in

infants — acetaminophen (Tylenol), morphine and fentanyl — and both morphine and fentanyl carry with them significant risks: respiratory depression, and, in some cases, death. “Managing pain safely and effectively is one of the major issues we face as neonatologists,” says Dr.

**Managing pain safely and effectively is one of the major issues we face as neonatologists.**

Aranda, who is one of a handful of experts in the country on drug efficacy and safety in newborns.

He is also a pioneer in his field, having made a number of important discoveries that have led to improved survival and health outcomes. One of those, about the use of caffeine for the treatment of apnea

in premature infants, has led to sizeable decreases in both mortality and illness. A 2007 study in the *New England Journal of Medicine* found that among severely premature newborns — those with birthweights between 500 to 1250 grams — the administration of caffeine increased

survival from 53.8 to 59.8 percent. Caffeine-treated babies were also 40 percent less likely to develop cerebral palsy and almost 12 percent less likely to experience developmental delays.

“Caffeine stimulates the mechanism in the brain that controls breathing,” Dr. Aranda explains. “And, of course, breathing is crucial to survival. But appropriate breathing and adequate ventilation are also essential for proper neurological development, which is probably why we see fewer cases of cerebral palsy and developmental delays in caffeine-treated babies.”

Today, Dr. Aranda, who maintains an academic affiliation with Wayne State University in Detroit, leads a multi-site clinical trial aimed at expanding analgesia options for newborns. The trial emerged from the planning process of the Pediatric Pharmacology Research Unit (PPRU), a National Institutes of Health-funded network of 13 university pediatric departments that explores pharmacological questions relevant to children. Through Dr. Aranda’s Wayne State affiliation, Downstate has become the only PPRU site in New York City.

The trial will examine codeine’s effects as a painkiller in newborns and explore how factors such as genetics, ethnicity, and age may determine how individual infants respond to the drug. “Codeine is easy to administer,” Dr. Aranda says, “so it could be a great addition to our therapeutic arsenal.”

Jacob Velasco Aranda, MD, PhD





The Neonatal Clinical Research Team (from left): Nadine Lahage, MD, assistant professor of pediatrics; Gloria Valencia, MD, clinical professor of pediatrics and director of neonatal intensive care; Antoni D'Souza, MD, assistant professor of pediatrics; Sara Higgerson, BA, clinical research coordinator; and Dr. Aranda.



Dr. Aranda with two members of the Neonatal Translational Laboratory: Charles Cai, MD, MS, research associate, and Nadine Lahage, MD, assistant professor of pediatrics.

"Children — babies especially — react to drugs differently than adults do," Dr. Aranda says, explaining the need to test codeine on infants. The trial, funded by the National Institutes of Health's National Institute of Child Health and Human Development, is titled "Absorption and Metabolism of Oral Codeine in Mechanically Ventilated Neonates."

"The questions we're asking are very simple ones," Dr. Aranda notes. The first is whether newborns can absorb codeine at all. They may simply eliminate it from their systems. "The second question is," he says, "If they do absorb it, can they activate it metabolically? Because codeine itself is not the active drug. The active drug is morphine, which is metabolized from codeine by two enzymes called CYP2D6 and UGT2B7." Though morphine doses used in previous clinical trials are associated with an increased risk of death among pre-term babies, Dr. Aranda believes codeine will not present similar risks because it is absorbed less efficiently.

To answer these questions, Dr. Aranda and his fellow investigators will administer a single dose of codeine orally and test for the drug and its metabolites in the babies' urine and blood. To gauge the painkiller's effectiveness, they will also study babies' facial expressions and tongue movements.

Dr. Aranda's study will examine whether genetic variations that control

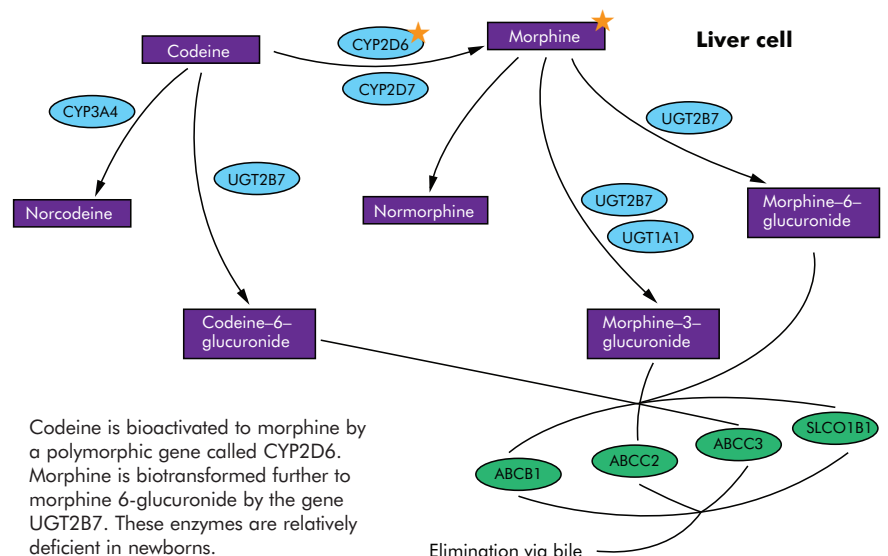
CYP2D6 and UGT2B7 expression "explain why some kids who are in pain get a drop of morphine and they're very happy, and other kids, with the same disease and severity, get high doses of morphine and they're still crying," he says. In the future, such genetic information could lead to more individualized pain management.

Dr. Aranda also hopes to determine the role an infant's age plays in codeine's efficacy. "Newborns, notoriously, don't express CYP2D6 and UGT2B7" he notes. "But with this study, we may be able to discover at

what age a premature infant begins to express these genes and whether a baby born at term expresses them earlier than a pre-term baby," Dr. Aranda explains.

The hopes for the study are high. "There's a lot of heartache in the NICU," Dr. Aranda says. "But if we can expand the safe pain management options available to these infants, we can improve their lives significantly while they are in the NICU, improve their health outcomes, and relieve their families' stress at knowing their children are in pain." ■

## Metabolic pathway of codeine and morphine



# When the Immune System Confuses Self and Other

The way Christopher Roman describes it, a well-functioning immune system is a splendid thing. "There is a beauty to the natural world," says the associate professor of molecular biology and immunology, "but some of that beauty can only be witnessed indirectly or through a microscope."

When the immune system works properly, its efforts are amazing. "Imagine: You have this huge collection of T cells and B cells, which are major immune system components, and they can recognize threats they've never, ever seen before — just about anything you can throw at them," says Dr. Roman. "It doesn't matter whether those threats are molecules from bacteria, viruses, or parasitic worms."

When the immune system malfunctions, however, the results can be devastating. Lupus is an example. In the United States, alone, this autoimmune disease affects as many as 1.5 million people; 90 percent of its sufferers are

women. The illness, sometimes fatal, can cause kidney failure, heart disease, pulmonary problems, and disorders of the central nervous system. At present, lupus has no cure.

Much remains unknown about the disease. But, inspired by the promise that his work may contribute to an effective treatment for lupus and other autoimmune problems, Dr. Roman is

**Dr. Roman is teasing apart the complex regulatory pathways of the immune response on a molecular and genetic level. This, he believes, will lead to a greater understanding of what malfunctions in autoimmune disease.**

teasing apart the complex regulatory pathways of the immune response on a molecular and genetic level. This, he believes, will lead to a greater understanding of what malfunctions in autoimmune disease.

"What really motivates me," he says, "is the idea that what we discover

could have an impact on how we think about autoimmune diseases and how, one day, we treat them."

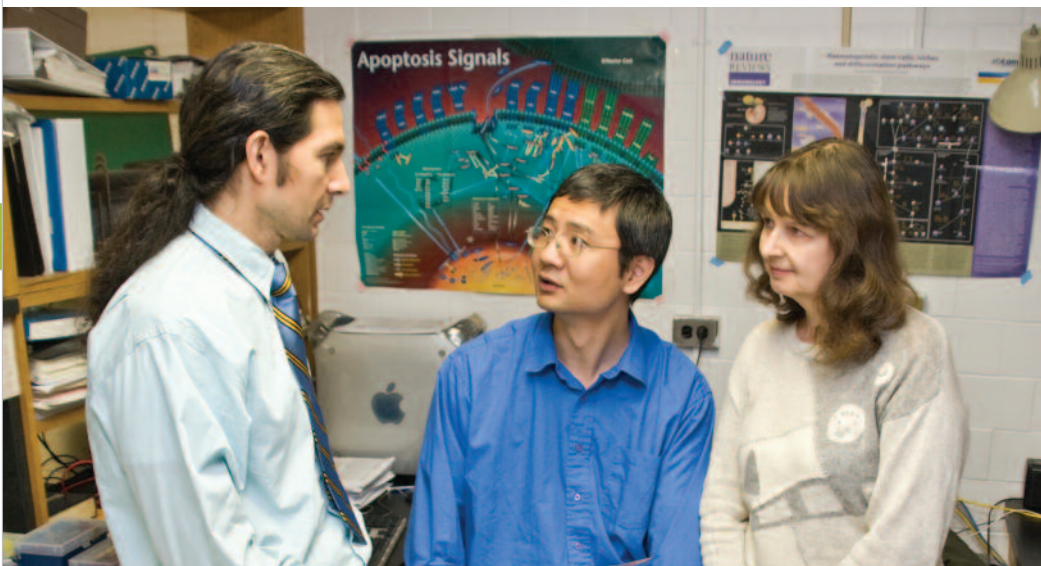
When Dr. Roman appeared in *Profiles in Innovation* in 2006, his research focused, then as now, on communication among various constituents of the immune system. In particular, his lab had begun investigating a molecule known as CD40 ligand. The molecule is a signaling

protein produced by the immune system's T cells to relay information to other important immune components.

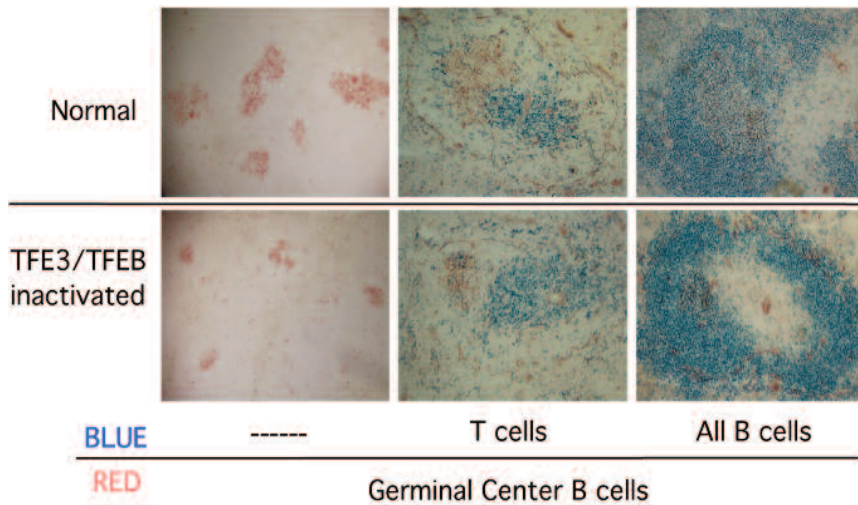
"T cells are like mission control," Dr. Roman explains. "They figure out when there's been a breach of the system, and what type of organism is responsible." CD40 ligand is made when the breach is detected, which serves to messenger information to the immune cells that do the dirty work of killing invaders and cleaning up the damage. "CD40 ligand is what T cells use to rally the troops and send them into action," he says.

In a well-functioning immune system, T cells make CD40 ligand only when there's a foreign entity to attack. "A happy T cell just hanging around doesn't make much CD40 ligand at all," Dr. Roman explains. But in lupus, as in other autoimmune disorders, the immune system has difficulty distinguishing between self and other. It misconstrues the signals the body transmits. As a result, says Dr. Roman, "T cells end up making CD40 ligand all the time."

That constant CD40 ligand production creates a flood of antibodies of a



Dr. Roman with members of his lab: Chongmin Huan, MD, PhD, senior molecular immunologist and research scientist, and Igljika Batova, PhD, postdoctoral associate.



**Two almost identical molecules, called TFE3 and TFEB, are critical for the production of protective antibodies.** These images illustrate a key observation made by Dr. Huan, Dr. Gottesman, and Dr. Roman to support the discovery that TFE3 and TFEB are instrumental in CD40 ligand production. In the spleens of experimental mice that Dr. Huan created at SUNY Downstate in which TFE3 and TFEB molecules were inactivated in T cells, antibody-producing B cells are not properly activated by T cells to become Germinal Center B cells. This is because the T cells are unable to make CD40 ligand, which is required for them to activate B cells. The result is smaller and fewer Germinal Centers compared to normal mice, which results in immune deficiency characterized by the lack of protective IgG antibodies. In the images, a cluster of discreet Germinal Centers defined by the red Germinal Center B cells is on the left. The middle and right panels show a close-up of one Germinal Center with the activated Germinal Center B cells still in red but with T cells (middle) or all B cells (right) in blue.

type that the immune system usually destroys. These antibodies attach themselves to free-floating DNA and other “self” molecules in the blood stream. “You then get these big, inflammatory complexes,” Dr. Roman observes. Though these complexes find their ways into many types of tissue, one of the organs hardest hit is the kidneys. “The complexes get deposited there and cause a catastrophic inflammatory response that destroys them,” he says.

In the last two years, Dr. Roman has focused his investigations on the process by which T cells manufacture CD40 ligand. With support from the Lupus Research Institute, the National Institutes of Health, and the dean of SUNY Downstate’s College of Medicine, Dr. Roman’s lab has discovered that two almost identical molecules, called TFE3 and TFEB, are instrumental in CD40 ligand production. By designing an artificial protein that lacks the machinery to bind to the DNA responsible for producing these two molecules, Dr. Roman and his team were able to stop CD40 ligand production almost entirely. Dr. Roman believes this finding may one day be useful to developers of a CD40-ligand inhibitor for people with lupus.

All these investigations were accomplished by Dr. Roman’s research team, which includes senior molecular immunologist and research scientist Chongmin Huan, MD, PhD, and Susan R. S. Gottesman, PhD, MD, Downstate’s director of hematopathology and an expert in cellular immunity. Ellen Ginzler, MD, MPH, distinguished teaching professor and chief of rheuma-

tology, is now a collaborator on the new lupus studies.

“Dr. Ginzler is a nationally known expert on lupus,” Dr. Roman notes. “She’s been a terrific sounding board, keeping us informed about the clinical manifestations of the disease. She’s also offered to help recruit some of her patients to volunteer blood that we can study.”

Despite the progress made in Dr. Roman’s lab, much remains to be learned about the functioning and malfunctioning of the immune system in lupus. “We know relatively little about the checks and balances within the immune system and how that system functions at the molecular level,” he explains. “And, of course, we want to know why lupus T cells produce so much CD40 ligand in the first place.”



# PKMzeta, Sentinel of Memory

It's not often that scientists are featured on "This American Life," the thoughtful and sardonic Showtime TV documentary series.

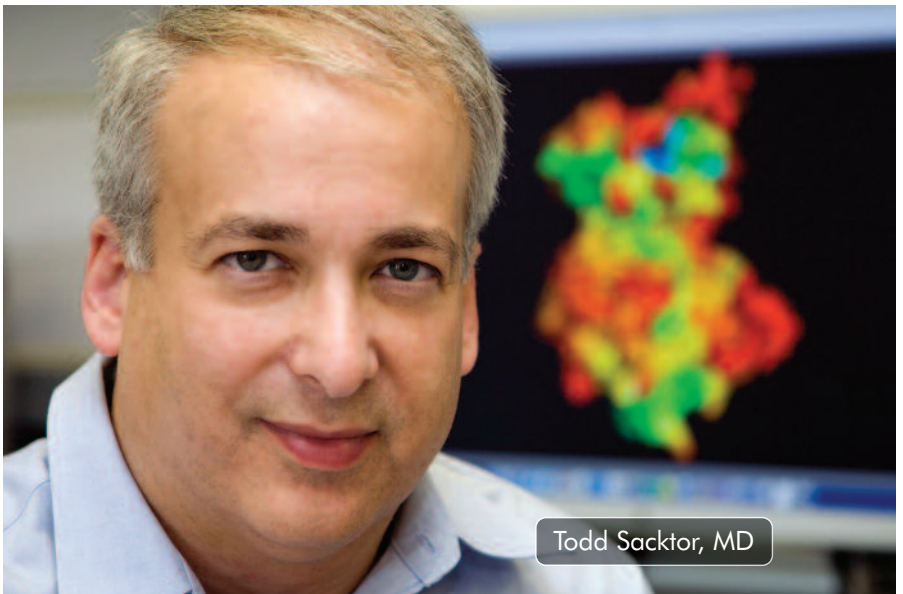
Yet, there was Todd Sacktor, MD, professor of physiology and pharmacology, with his collaborator André Fenton, PhD, discussing how the two had erased traumatic memories from the minds of laboratory rats. (For information about Dr. Fenton's other research, see "How the Hippocampus Multitasks to Avoid Confusion," p. 4)

In 1993, Dr. Sacktor was the first to posit that a neuroenzyme called PKMzeta was the molecule that fixed memory in the brain. His work did not meet with universal acceptance, however; other scientists had other theories. Since then, even as Dr. Sacktor's ideas began to gain credence, many researchers came to believe that PKMzeta was responsible only for the initiation of memory, not for its long-term maintenance, as Dr. Sacktor had proposed. "For 16 years," he says, "I worried, 'Was I right?'"

To answer that question, Dr. Sacktor enlisted the collaboration of Dr. Fenton. Their idea was to teach laboratory animals to avoid, on a rotating turntable,

**Dr. Sacktor was the first to posit that a neuroenzyme called PKMzeta was the molecule that fixed memory in the brain.**

an area in which they received a mild shock. Then, the scientists planned to inject a PKMzeta-blocking drug into the rats' hippocampi, the part of the brain that makes sense of spatial location. Dr. Sacktor believed the animals would no longer remember the area where they had received shocks, so they would no longer try to avoid them.



His and Dr. Fenton's theory proved to be correct: PKMzeta is, in fact, the molecule that maintains memory in the hippocampus. *Science* published the results of their experiments in August 2006. Since then, in a similar experiment in 2007, Dr. Sacktor and colleagues from Israel's Weizmann Institute of Science once again used this PKMzeta-blocking compound to erase unpleasant memories from the minds of

formation and maintenance throughout the brain. "What is the physical substance of the memory trace?" he asks. While that answer is not yet completely clear, Dr. Sacktor, whose work on the molecular underpinnings of memory was first profiled in this publication in 2006, continues to make progress in understanding this compelling question.

PKMzeta's uniqueness initially drew Dr. Sacktor's attention. "Unlike other enzymes in the brain, which turn on and off," he says, "PKMzeta is different. Once created, it's continually active, which makes sense for a memory molecule." Yet, it was difficult to get many in the neuroscience community to embrace the idea that PKMzeta played a pivotal role in memory maintenance. The commonly accepted notion has been that what maintains memory is a change in brain anatomy.

experimental animals, this time in the neocortex, the outer layer of the brain. Drs. Sacktor's and Fenton's colleagues at the University of Wisconsin have documented PKMzeta's role in maintaining memory in the amygdala as well, the part of the brain associated with fear and smell.

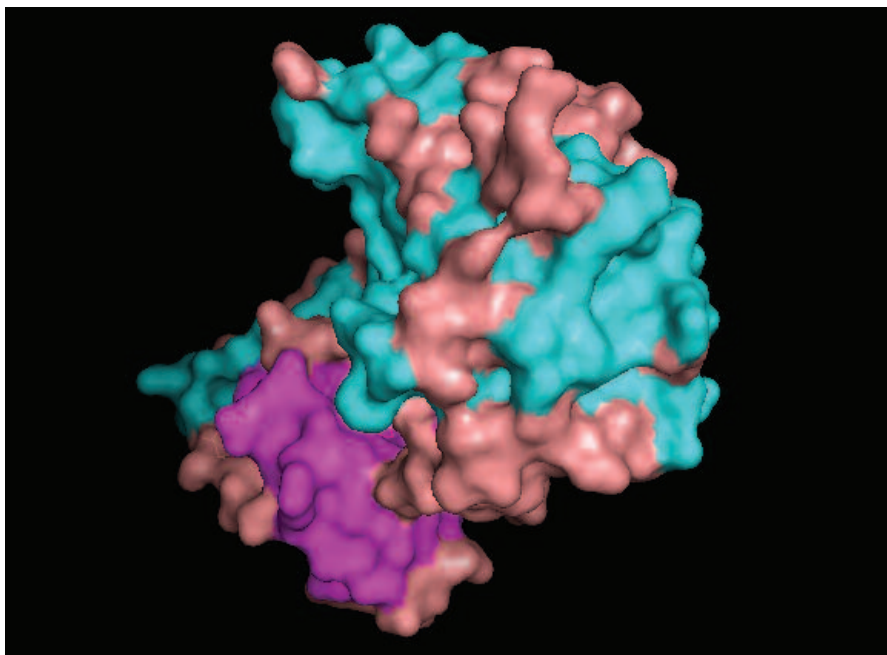
Dr. Sacktor's goal now is to understand fully PKMzeta's role in memory

In fact, since the 1960s, neuroscientists have observed a physiological change in which the strength of the

synaptic connections between brain cells increases after their stimulation. This phenomenon is called long-term potentiation (LTP) and for decades was thought of as a potential model for memory. The discovery that PKMzeta cemented both these strengthened synaptic connections and long-term memories provided the crucial link showing that LTP was indeed the underlying mechanism for memory storage.

The crucial experiment required several years of preparation. First, Dr. Sacktor developed a compound that would block the action of PKMzeta without destroying brain function. Then, though “most scientists believed that it was almost impossible to erase memories that were well established,” Dr. Sacktor set out to prove otherwise.

Much as Dr. Sacktor predicted, the laboratory animals in his experiments with blocking PKMzeta have consistently forgotten learned behaviors, both in experiments at Downstate and at the Weizmann Institute. In his animals, the number of receptors on certain brain



Crystal structure of PKMzeta. (Image by Dr. Rongbao Li, Southern Research Institute, Birmingham, Ala.)

cells was reduced by half, to their pre-LTP count, after Dr. Sacktor administered the PKMzeta-blocking compound.

Having made the major discovery of PKMzeta's pivotal role in both the formation and the maintenance of memory in several key areas of the brain, Dr. Sacktor

continues to explore the function of what some have called “the memory molecule.”

“There’s so much to learn about the molecular underpinnings of memory,” Dr. Sacktor says. “Right now, we can do that best by focusing on the workings of PKMzeta.” ■

Members of Dr. Sacktor’s laboratory: (from left to right) Peter Serrano, PhD, research assistant professor; Deana Pinkhasova, research associate; Andrew Tcheranopov, MSc, research support specialist; Rachna Sondhi, MD/PhD student; Dr. Sacktor; Yudong Yao, PhD, post-doctoral fellow; Dezhi Tian, PhD, post-doctoral fellow.





# Unique GABA Receptors Trigger Teen Anxiety

**N**euroscientist Sheryl Smith, PhD, spent a lot of time in front of TV cameras last year.

The professor of physiology and pharmacology was featured on CBS News with Katie Couric; on the BBC World News; and on ABC News in primetime, where the cameras showed her putting mice through a challenge and talking with her 14-year-old daughter, Ashley.

The attention was well deserved. After all, how often does a scientist unravel one of life's more elusive mysteries?

That mystery? Why formerly easygoing and agreeable children become moody and unpredictable teenagers.

The answer, Dr. Smith says, is that adolescents' brain cells are covered with a unique kind of receptor. The receptor, called the alpha4-beta2-delta GABAA receptor, first appears at puberty and disappears again as adulthood sets in. Its presence causes teens to become significantly more anxious in the face of stress than do either adults or children.

Dr. Smith's discovery has the potential to smooth out domestic relations around the globe. In fact, don't



Sheryl Smith, PhD

know there's a physiological reason teenagers respond much more intensely to stress than adults do."

Sheryl Smith hadn't set out to study moodiness in teenagers — though, as a parent, she has had opportunities to watch that kind of

experiments on prepubescent mice. "Using young mice enabled us to manipulate the hormones," she explains. "We didn't want the mice's own hormonal cycles to interfere with our research."

During one set of experiments, the results were the opposite of what Dr. Smith anticipated. Mice that one would have expected to be calmed by allopregnanolone became much more agitated when faced with a complex challenge. "It turns out that one of our technicians used pubescent mice instead of the young ones," Dr. Smith explains. "I thought, 'This is a lucky break. Let's follow it up.'"

So she and her colleagues "worked like crazy for the next two years," documenting the existence of alpha4-beta2-delta GABAA receptors and the ways they interact with allopregnanolone. The paper chronicling their work was published in *Nature Neuroscience* (10:469-477, 2007).

The paper's main finding was that because of the presence of these unique GABA receptors during adolescence, allopregnanolone agitates rather than calms. When exposed to the hormone, Dr. Smith says, her mice became more anxious and less willing to explore, but also more attentive to their environment and, thus, more apt to learn.

Dr. Smith believes that even though her research subjects are rodents, what she has discovered is relevant to people. "All the changes that we see accompanying this receptor in mice also occur in humans," she notes. "And allopregnanolone is released in both mice and humans."

Dr. Smith's findings indicate that adolescence is an important stage of human development. "Our study

## Why formerly easygoing and agreeable children become moody and unpredictable teenagers

be surprised if, in response to an outburst, your teenager soon offers up the following apology: "It's not me, Mom! It's my GABA receptors."

The impact of Dr. Smith's discovery may be far-reaching. The finding illuminates the relatively unexplored subject of mood disorders in teens, and opens the door to new studies on learning and memory among adolescents. Says Dr. Smith, "It's good to

volatility in action. Instead, her discovery got its start in what she considers "a happy accident."

Here's what happened: For many years, she has studied the calming impact a hormone metabolite called allopregnanolone has on the brain when it comes into contact with GABAA receptors, which are involved in quieting neural electrical activity.

Often, Dr. Smith performed her



Dr. Smith and members of her lab: (from left) Shweta Varshney, Ph.D. student; Nicole Lapadura, BS, research specialist; Dr. Smith; Nicole Sabliuskas, Ph.D. student; and Ahmer Ishtiaq, BS, research specialist.

shows that adolescents are not just young adults. Their physiology and moods are different," she says.

Moreover, her findings may explain why some anti-depressant medications effectively treat anxious and depressed adults but may backfire in teenagers, at times with tragic results.

"Drugs like Prozac and Zoloft increase the amount of allopregnanolone in the brain," Dr. Smith observes. "Since allopregnanolone increases anxiety in teens, these may not be the best drugs to give to teenagers who are having problems with instability."

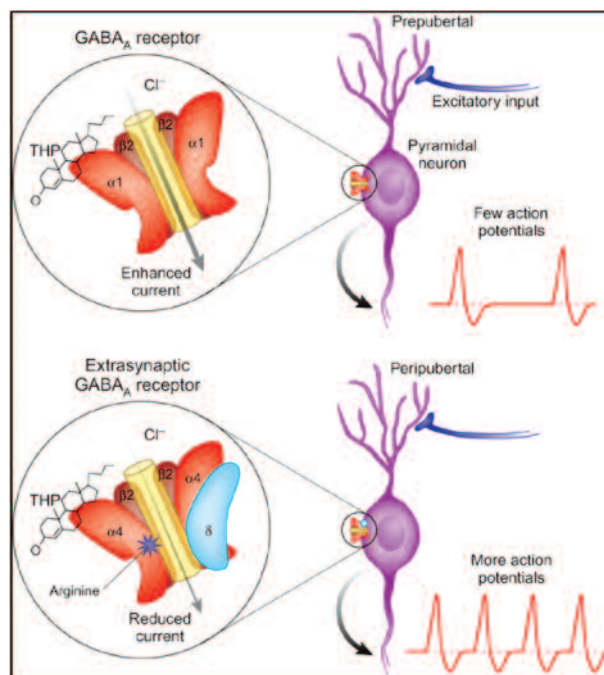
Dr. Smith thinks there's an evolutionary reason why formerly placid children turn into moody fifteen-year olds: "A heightened sense of anxiety may keep them focused and learning new skills" — the skills needed for independent living. "Maybe this increased response to stress forces them to figure out their own solutions," she speculates.

To test her theory that pubescent anxiety enhances learning and thus offers "an evolutionary advantage," Dr. Smith is now collaborating with

Downstate researcher Armin Stelzer, MD, an expert in learning and memory. "Being at Downstate," where many researchers focus on learning and memory, "is great, because it facilitates collaboration," Dr. Smith says. "I can walk into a colleague's lab and

learn the techniques I need to perform these experiments."

These techniques and experiments may further elucidate the workings of the adolescent brain, and bring Sheryl Smith some well-deserved attention, yet again. ■



**A stress steroid reverses its effect at puberty in female mice.**

Before puberty (upper panel), the stress steroid THP enhances the function of target GABA receptors (upper left) on neurons in CA1 hippocampus (upper center) and decreases action potentials (upper right), thereby reducing anxiety as a compensation for prolonged stress. However, at puberty (lower panel), novel types of target GABA receptors ( $\alpha4\beta\delta$ , lower left) emerge on these neurons (lower center), which THP inhibits, thereby increasing action potentials (lower right). This novel action of the steroid increases anxiety in response to prolonged stress in the adolescent.

# An Eye Into Parkinson's Disease

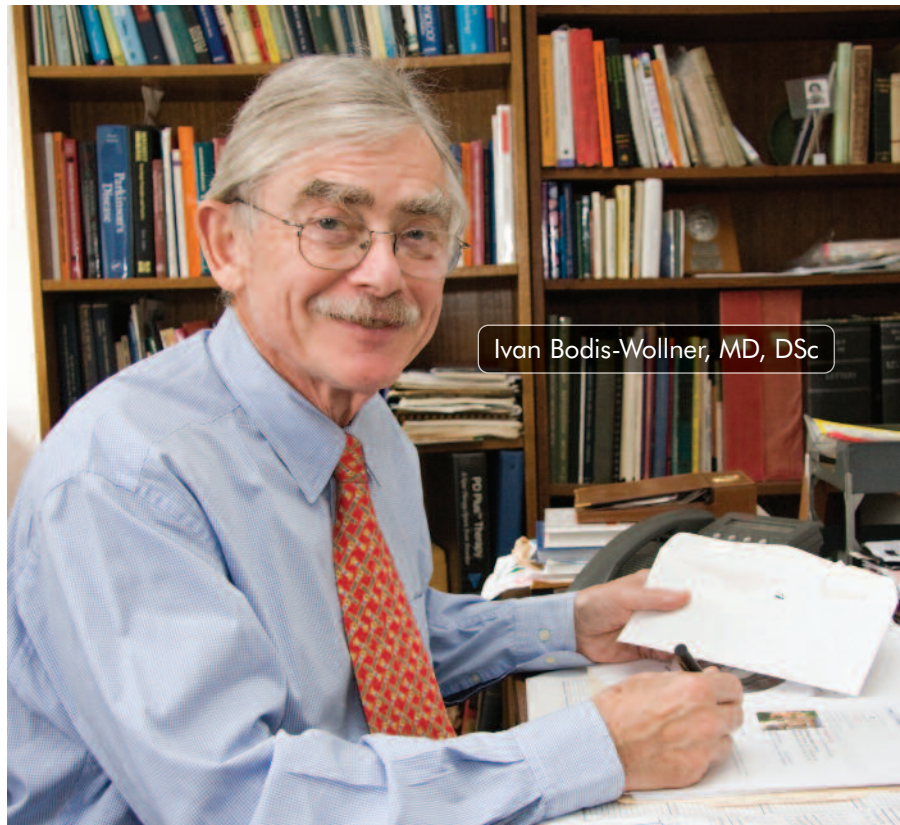
**L**ike many illnesses affecting the nervous system, Parkinson's disease is difficult not only to treat but also to monitor.

New evidence suggests that the degenerative motor disorder begins in the peripheral nervous system and then works its way to the central nervous system — most importantly, to the brain. Once established there, this disease can cause a host of neurological problems: tremors, motor impairment, communications difficulties, and mental disturbances.

Visual problems were not thought to be part of Parkinson's disease, however. From the time the illness was first described in the early 1800s, until more than 150 years later, the loss of visual acuity and the difficulty in distinguishing contrast many Parkinson's patients experience were attributed to other causes, such as aging, cataracts, and glaucoma.

But in the late 1970s, Ivan Bodis-Wollner, MD, DSc, professor of neurology and ophthalmology and director of University Hospital's Parkinson's Disease and Related Disorders Center, one of the National Parkinson Foundation's Centers of Excellence, showed that Parkinson's disease itself can have a negative impact on vision.

In 1978, using electrophysiology — brain-wave monitoring through externally applied electrodes — he was the first to document delayed visual processing in the brains of individuals with Parkinson's disease. Following



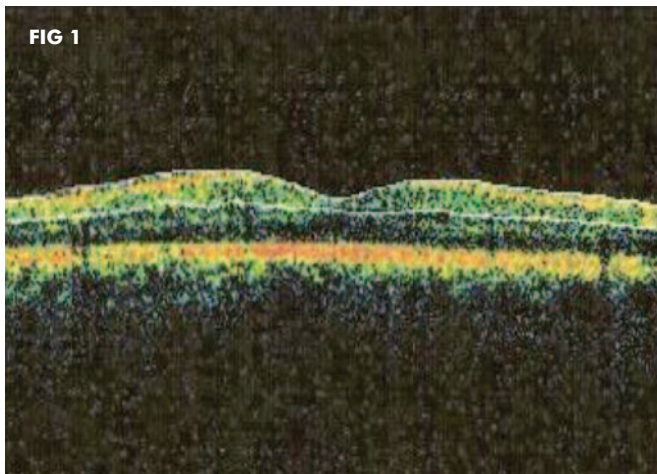
that, he used the method again, this time discovering among Parkinson's patients deficits in contrast-sensitivity — difficulty distinguishing an image from its background.

Importantly, as part of that research, he showed that vision changes in tandem with neurological functioning. "When a patient doesn't move well," Dr. Bodis-Wollner explains, "he doesn't see well."

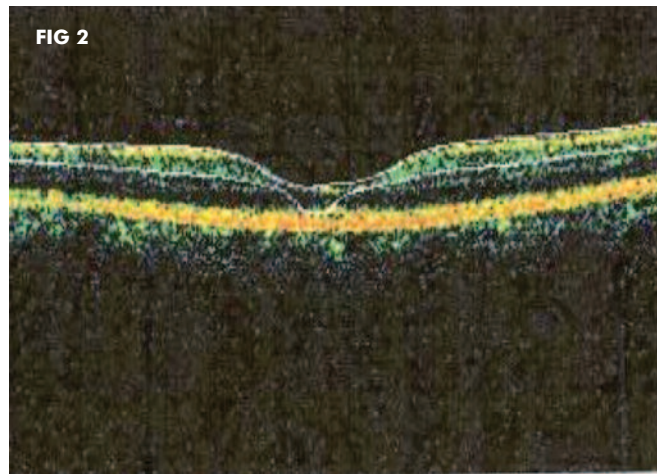
Motor problems in Parkinson's disease are caused by the death of neurons that secrete and process an important neurotransmitter called dopamine. Dr. Bodis-Wollner's research established that the death of these neurons, called "dopaminergic" cells, is also responsible for Parkinson's-related visual problems. "Without dopaminergic cells, dopamine-sensitive cells are deprived of dopamine" he notes, "and are no longer able to make very important decisions that relate to vision and to motor execution."

In the late 1990s, intrigued by the role dopaminergic cells play in the vision of Parkinson's patients, Dr. Bodis-Wollner developed a quantita-

**"The ability to image the retina may revolutionize the process of evaluating and monitoring the neuronal changes that occur in Parkinson's disease."**



**Fig 1** The OCT of the retina of a healthy subject (46 years of age). The bottom of the picture represents the outer layers of the eye; the top, the inner layers. The dip, or "valley", in the center is normal: retinal neurons are pushed to the side to allow light to penetrate to the outer layers, where photoreceptors are located.



**Fig 2** The OCT of the retina of a Parkinson's disease patient (50 years of age). The "valleys" - top and center - represent the loss of neurons in the inner retina, including the nerve cells which transmit visual information to the brain.

tive description of the relationship between the retina's dopaminergic and dopamine-sensitive cells. A major advance in the Parkinson's disease field, the model has been used to predict the retina's response to new and existing Parkinson's treatments.

In the last several years, Dr. Bodis-Wollner has employed a new imaging technology called Optical Coherence Tomography (OCT) to detect microscopic changes in the retina. Says Dr. Bodis-Wollner, "the ability to image the retina may revolutionize the process of evaluating and monitoring the neuronal changes that occur in Parkinson's disease."

Using OCT, he has been among the first to measure the retinas of individuals with Parkinson's disease. Often, they are 15 to 20 percent thinner than normal. "This loss may be a major reason why Parkinson's patients have trouble detecting contrast," Dr. Bodis-Wollner says. "And we've learned that the area of the retina affected in Parkinson's may impair visual cognition," the ability to respond to and categorize visual images.

Dr. Bodis-Wollner looks forward to furthering this research by acquiring the latest generation OCT equipment. "With these machines, we hope to be able to specify dopaminergic cells, in addition to measuring the retina's thickness," he notes. Giving researchers

access to cell counts could dramatically alter the course of clinical trials for new Parkinson's treatments.

Until recently, "investigators have had to rely on clinical observations and wait a minimum of 18 months to discover the impacts of potential neuroprotective treatments on the brain's dopaminergic pathways and, thus, on disease progression," Dr. Bodis-Wollner explains. With the detailed counts of retinal dopaminergic cells and information on

retinal thinning that advanced OCT equipment can provide, researchers may be able to assess much more quickly and accurately whether a new treatment has arrested neuronal degeneration.

Dr. Bodis-Wollner notes, "OCT should be able to help quite a lot in our quest for neuroprotective agents — agents that can stop the dying-off of dopaminergic cells." And with that, help stop the progression of Parkinson's disease itself. ■



Dr. Bodis-Wollner with M. Asim Javaid, MD, postdoctoral research fellow, Sofya Glazman, MD, coordinator, Parkinson's Disease and Related Disorders Center of Excellence of the National Parkinson Foundation.

# Decoding Diabetic Retinopathy

**B**etween 12,000 and 24,000 Americans go blind each year as a result of diabetic retinopathy.

Diabetic retinopathy usually develops over several years and has its origins in the body's poor control of blood sugar levels. At the onset, the tiny blood vessels in the retina begin to swell and leak. Next, some of these vessels close off. Then, as more of them are blocked, the retina sends molecular signals that initiate a frenzied formation of new and fragile blood vessels. In the advanced stages, called proliferative retinopathy, these weakened vessels invade the vitreous gel that fills the eye; when they leak, severe vision loss or blindness results.

To date, a high-tech vision-saving technique called scatter laser surgery can, when administered early, improve the vision of people with diabetic retinopathy. But the procedure has limitations. Often, it can lead to the loss of peripheral vision, and, because new blood vessels continue to grow, the procedure must be repeated.

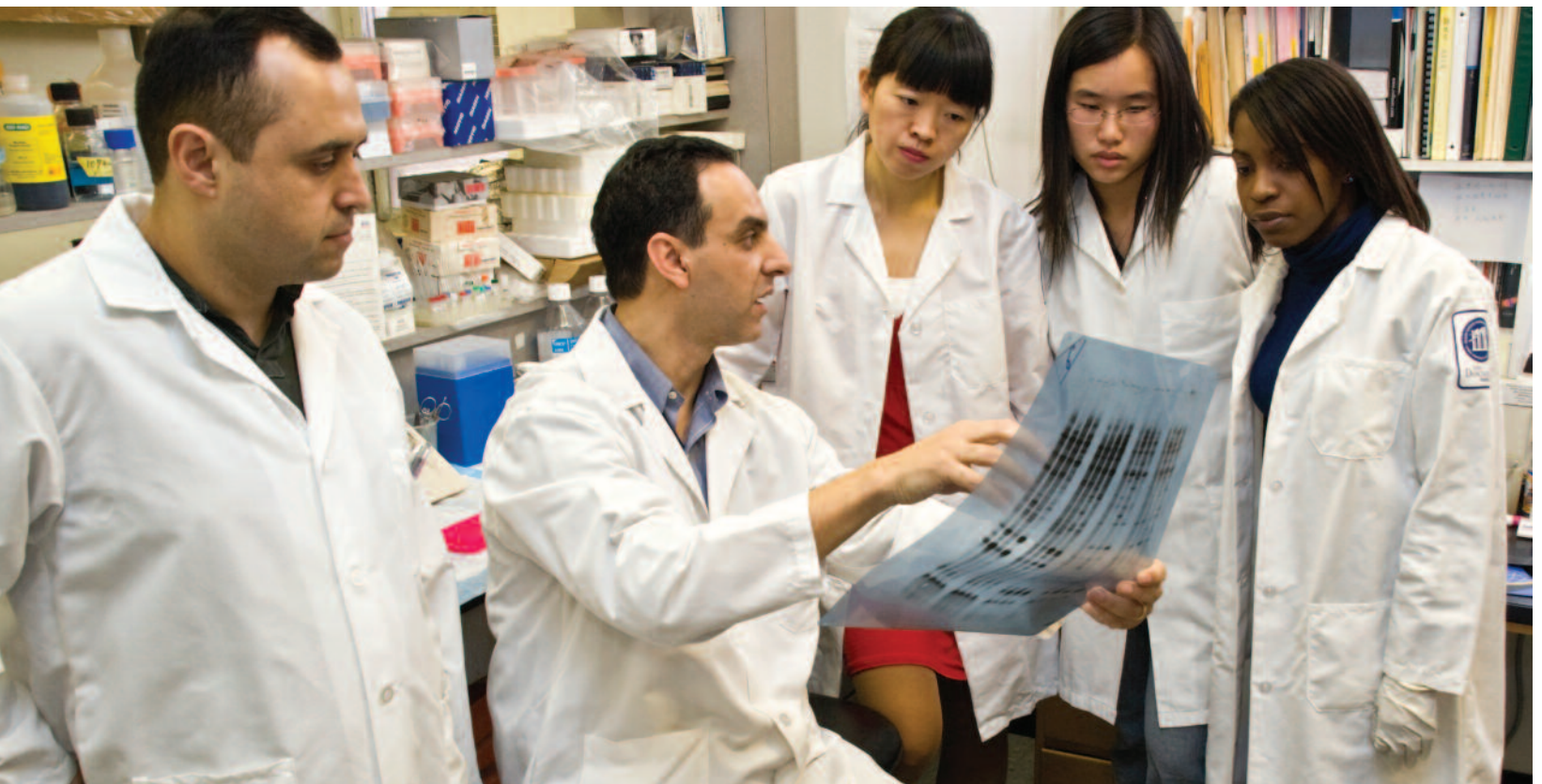
To develop better treatments for this vision-impairing disease, Brahim Chaqour, PhD, an assistant professor of anatomy and cell biology at SUNY Downstate, is decoding the molecular processes that underlie diabetic retinopathy. "My goal is to understand a number of mechanisms that affect

blood vessel growth and degeneration," he says. These include the role of angiogenic factors, which lead to the proliferation of new blood vessel branches, and the role of anti-angiogenic factors, which lead to the destruction of pre-existing blood vessels and the formation of new blood vessel branches.

"A better understanding at the molecular level will help us learn how to control the process, both in the early and later stages of the disease," he says.

Dr. Chaqour has made great progress towards this goal. He has identified a "small family of genes," that, in the presence of hyperglycemia (high

Members of Dr. Chaqour's lab: (from left to right) Jorge Espinoza, PhD student; Dr. Chaqour; Haibo Liu, PhD, postdoctoral fellow; and Hunter College interns Michelle Lee and Tyesha Williams.



blood sugar levels), plays a crucial role in all phases of diabetic retinopathy. Working in tissue culture and with laboratory animals, he has documented how these genes, normally active only during embryonic and fetal development, initiate the weakening of healthy retinal blood vessels and promote the formation of new, leaky ones.

On a fundamental level, Dr. Chaqour is interested in the ways that cellular environment affects cell behavior. In the hyperglycemic milieu of the diabetic retina, the pericytes, the smooth muscle cells forming the outer layer of capillaries, begin to die. That process further deprives the retinal tissues of oxygen. Dr. Chaqour and his colleagues discovered that when this oxygen deprivation occurs, two long-dormant genes, Cyr61 and CTGF, from the family Dr. Chaqour has identified begin to express themselves in the retina. Their proteins accumulate in the space surrounding blood vessel cells, further exacerbating pericyte death.

That's not the only role Cyr61 and CTGF play in diabetic retinopathy. During the most advanced stage of diabetic retinopathy, their over-expression contributes to the uncontrolled proliferation of new, leaky blood vessels, Dr. Chaqour has concluded. "The proteins these genes express even cause blood vessels to grow into the eye's vitreous gel, which, under normal conditions, is completely free of blood vessels. There's no control mechanism in these newly activated genes that allows them to stop."



Brahim Chaqour, PhD

Dr. Chaqour's lab discovered that vasculogenesis, the creation of entirely new blood vessels from stem cells, is promoted by the Cyr61 protein as well. Until recently, scientists believed that angiogenesis — the branching off of

**Dr. Chaqour has identified a "small family of genes," that, in the presence of hyperglycemia, plays a crucial role in all phases of diabetic retinopathy.**

new blood vessels from existing ones — was the only blood vessel-formation mechanism involved in the disease. In fact, "scientists believed vasculogenesis took place only during embryonic development and then stopped alto-

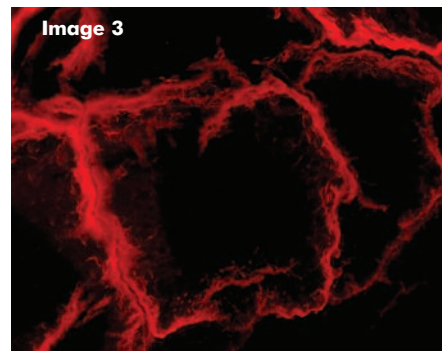
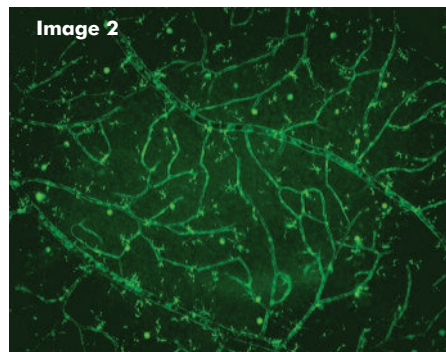
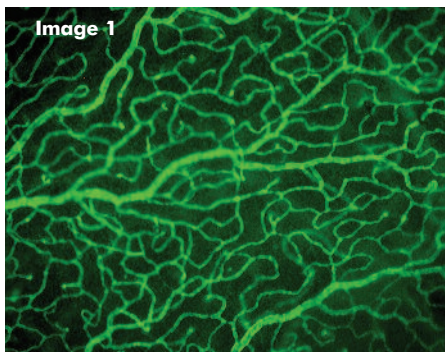
gether," he says. By exposing stem cells to Cyr61 in tissue culture, Dr. Chaqour and his colleagues demonstrated "this protein promotes the process of vasculogenesis involved in diabetic retinopathy."

Another of his important discoveries is a protein called MMP-2. "In the normal retina," Dr. Chaqour explains, "there's almost no MMP-2. But in diabetic animals, Cyr61 and CTGF induce expression of MMP-2." The protein destroys the extracellular matrix, the biological scaffolding that stabilizes and connects cells. "This further degrades the pericytes."

Dr. Chaqour is using these discoveries to develop pharmacological treatments that may derail diabetic retinopathy, even in the absence of tight blood sugar control. "We're trying," he says, "to put together recombinant peptides that will interrupt the growth of abnormal blood vessels and allow healthy retinal activity to occur."

Already, Dr. Chaqour and his colleagues developed several compounds, still unnamed, that block the destructive action of MMP-2. "That's not

enough to stop diabetic retinopathy, yet," Dr. Chaqour says. "But it's a start. One day, we may discover a pharmacological treatment that enables patients to avoid the current surgical one." ■



**Image 1:** A well-organized and functional network of blood vessels in the retina of an adult rat.

**Image 2:** A disorganized and dysfunctional network of blood vessels in the retina of an adult diabetic rat.

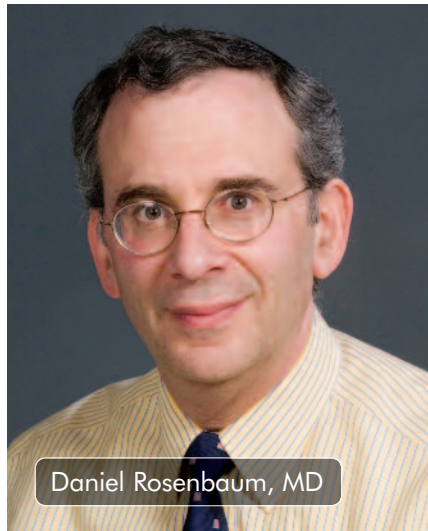
**Image 3:** An extensive degradation of blood vessels in the retina of a diabetic rat. Diabetes activates specific proteases responsible for the destruction of retinal vessels during diabetes.

# The Eye: Gateway to the Brain

**W**hoever said the “eyes are the window to the soul” never met Daniel Rosenbaum, MD, chairman of neurology at SUNY Downstate.

Given the nature of Dr. Rosenbaum’s research into the retina, the light-sensitive inner layer of the eye, the phrase might be slightly amended to: “the eyes are the window to the soul and the gateway to the brain.”

The retinas are actually outcroppings of brain tissue. For Dr. Rosenbaum, intent on better understanding the causes of major strokes and developing treatments that may one day ameliorate or even prevent them, the eye has proven to be an ideal, if unanticipated, area of study. “Originally, I began my research in the brain itself,” says Dr. Rosenbaum. “But, because of the eye’s accessibility, there are certain topics that are much



Daniel Rosenbaum, MD

more readily researched there than in the brain itself.”

Among those topics are the types of damage that occur in neural tissue

when it’s deprived of oxygen and glucose, as happens during a stroke. Using rodent models, Dr. Rosenbaum is making important breakthroughs, discovering that some stroke-induced brain damage can be limited through the use of strategies that interrupt cell death. In addition, his research suggests the body’s own protective mechanisms may be mobilized to protect those at highest risk for strokes.

What type of death do brain cells undergo during a stroke? Researchers assumed it was necrosis, a passive form of cell death “in which the cells simply explode,” Dr. Rosenbaum explains.

In the early 1990s, however, Dr. Rosenbaum demonstrated that necrosis was far from the only type of cell death involved. “In cerebral ischemia,” a consequence of a stroke or other condition causing inadequate blood supply, “the brain area that’s most significantly ischemic, the core, will undergo necrotic cell death,” Dr. Rosenbaum notes. “But there’s a region surrounding the core, the penumbra, where the damage may not be severe enough to actually kill the cells immediately.”

However, many of those cells eventually die off. Why? Because of apoptosis, or so-called programmed cell death.

Dr. Rosenbaum was among the first to demonstrate this phenomenon in neurons outside a stroke’s core area of impact. Apoptosis is the body’s “systematic and planned dismantling of cells,” Dr. Rosenbaum explains. (In the study that led to this discovery, as in many others, Dr. Rosenbaum induced ischemia in his laboratory animals by restricting blood flow to the retina.)

“The distinction between apoptosis and necrosis is a vitally important one,” Dr. Rosenbaum continues, “because if it’s an active form of cell death, we can

Frank Barone, PhD, director, basic research in cerebrovascular disease; Joel David, lab technician; and Dr. Rosenbaum.



intervene and prevent cells from dying. With necrosis, we can't."

Indeed, in a study published in 1997 in the journal *Vision Research*, Dr. Rosenbaum was the first to demonstrate that during an ischemic event in the retina, the application of a compound called aurintricarboxylic acid halted apoptosis and thus preserved retinal function.

Ultimately and unfortunately, aurintricarboxylic acid proved to present serious life-risk when used systemically. But Dr. Rosenbaum's finding was important because it was proof of principle. "We now know for sure that if you find the right strategy, you can limit some of the apoptosis that occurs after stroke," he says.

Dr. Rosenbaum's research has led to a major discovery: Yet another type of cell death that occurs during stroke. Called necroptosis, this type of cell death shares characteristics with both apoptosis and necrosis. (The study of cell death involves the use of an inflammatory cytokine called TNF. In the presence of inhibitors of programmed cell death, or apoptosis, a TNF variant called TNF-alpha activates and exposes necroptosis for detailed analysis.) It is a finding that may increase the arsenal of stroke-fighting drugs because the agents that will one day block necroptosis "are going to be different than the agents that block apoptosis and necrosis."

In fact, future stroke-blocking agents may be based on molecules produced by the body itself, Dr. Rosenbaum has begun to learn. "One

of the most exciting ways to limit apoptosis is with a compound called erythropoietin (EPO), which the retina begins to express when it becomes ischemic, as if to protect itself," he explains. Dr. Rosenbaum hopes EPO,

with a severe insult, we see much less stroke injury."

This finding may eventually help prevent strokes in cardiac bypass patients, who are at high risk for ischemic events. "Perhaps 24 hours

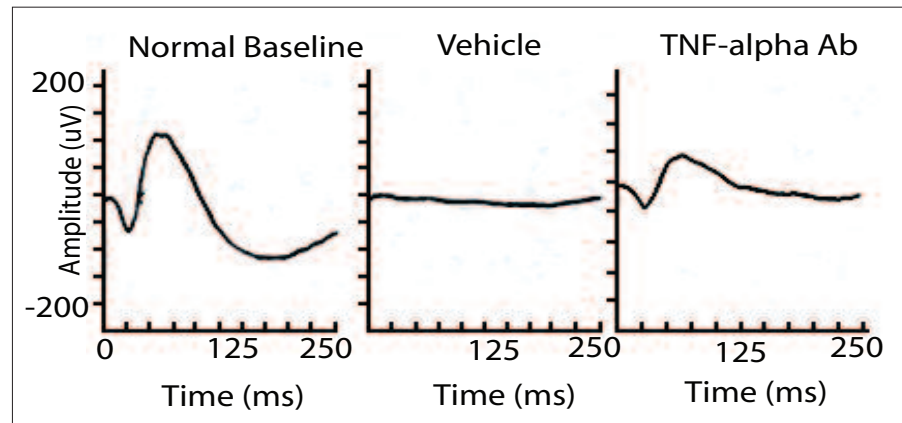
## Using rodent models, Dr. Rosenbaum is making important breakthroughs, discovering that some stroke-induced brain damage can be limited through the use of strategies that interrupt cell death.

or a modified version of it, will play a clinical role in limiting cell damage after stroke.

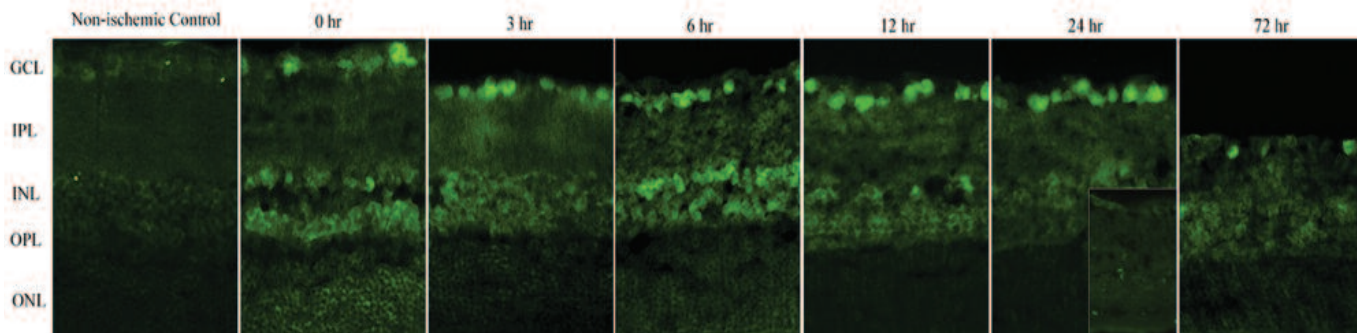
Similarly, his lab is exploring a phenomenon known as remote preconditioning, in which minor ischemic events protect brain cells from damage during later, more severe strokes. "In our animals, we found that if we make the hind legs ischemic for a short time and then come back 24 hours later

before surgery, we could mimic preconditioning, and thereby increase protection against major strokes," Dr. Rosenbaum explains.

These discoveries could potentially change the course of stroke treatment and the lives of millions of stroke sufferers. They have been enabled as much by Dr. Rosenbaum's keen, observing eye as by the eye itself — window to the soul and gateway to the brain. ■



Electroretinography (ERG) tests retinal function. By blocking TNF-alpha activity before and even after the ischemic insult, one can see protection of retinal function following the ischemic insult.



Cryosections of rat retina at different time points subsequent to 60 minutes of retinal ischemia. One can see that TNF-alpha is expressed following ischemic injury to the retina. By blocking TNF-alpha activity, one may be able to protect the retina against cell death.



# Talk Therapy Eases Depression in Dialysis Patients

Life isn't easy for patients with end-stage renal disease (ESRD). Because their kidneys function at less than one-tenth normal capacity, these individuals must undergo hemodialysis three times a week.

The procedure removes wastes, toxins, and excess fluids from their blood streams. But attending the four- to five-hour sessions makes it difficult for patients with ESRD to hold regular jobs or participate in social activities. The majority also suffer from other illnesses, such as diabetes and high blood pressure, which can further curtail their daily activities. Often, ESRD patients are elderly, poor, and have limited mobility.

"It can be a very difficult life, in addition to the time they spend on the machine," says Daniel Cukor, PhD, assistant professor of psychiatry and behavioral sciences, who has a long-standing interest in the impact of physical illness on emotional well-being. Yet, there has been little research conducted on the mental health and men-



tal health-treatment needs of people with ESRD.

Dr. Cukor, who has studied this issue, has found very high rates of untreated depression, anxiety, and other mental disorders among patients at University Hospital of Brooklyn's Parkside Avenue outpatient dialysis center. "More than 70

percent had some form of psychiatric diagnosis," Dr. Cukor relates. "But only 13 percent were in treatment with a mental health provider."

These findings spurred Dr. Cukor to implement a pilot study of a drug-free treatment plan for depression that can be delivered chairside during dialysis. Now funded by the National Institute of Diabetes and Digestive and Kidney Diseases, he hopes to refine and test this treatment so it can be used in dialysis centers nationwide. Dr. Cukor's goal is to offer the kind of help for depression that so many people undergoing dialysis need, without additional medications or doctors' appointments.

Daniel Cukor didn't start off as a researcher. In 2002, after receiving his doctorate in clinical health psychology from Yeshiva University, he came to SUNY Downstate as a postdoctoral fellow to further his training in cognitive and behavioral therapy (CBT). That form of psychotherapy, he says, "aims to help people evaluate how they think about problems and then change inappropriate behavioral responses to those problems."

CBT can sound abstract, but the therapy has been proven to be effective in treating depression, anxiety, and several other forms of mental illness.

Dr. Cukor's interest in psychology led him to visit patients at the outpatient dialysis center. "I wanted to see what the patients' issues were and what kind of psychological burdens they faced."

Those initial meetings led Dr. Cukor to conduct a more formal assessment of patients' mental health needs. He discovered that 20 percent met the criteria for major depression, "the kind where you don't have the emotional energy even to get out of bed," he explains. Another 9 percent suffered from dysthymia, a milder form of the illness. By

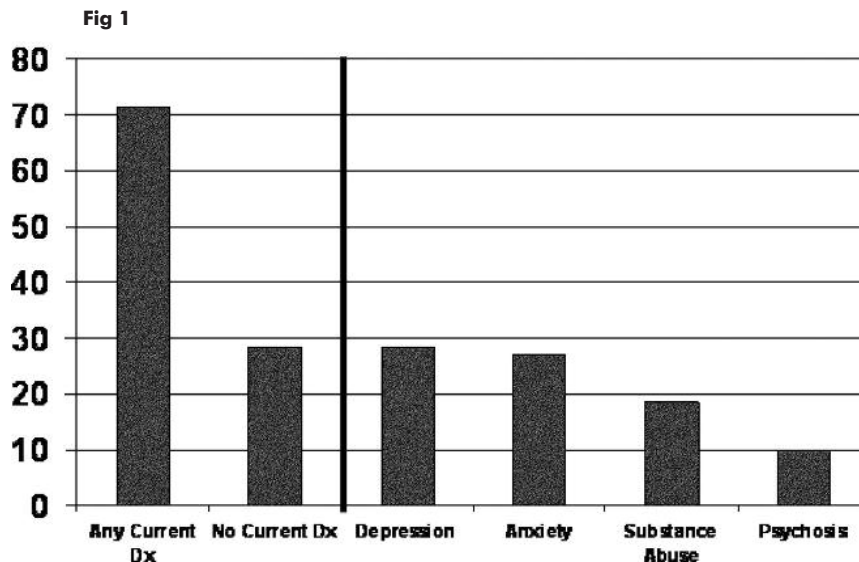


Fig 1. Psychiatric diagnostic categories. Percent of samples with SCID diagnoses (N=70)

Fig 2

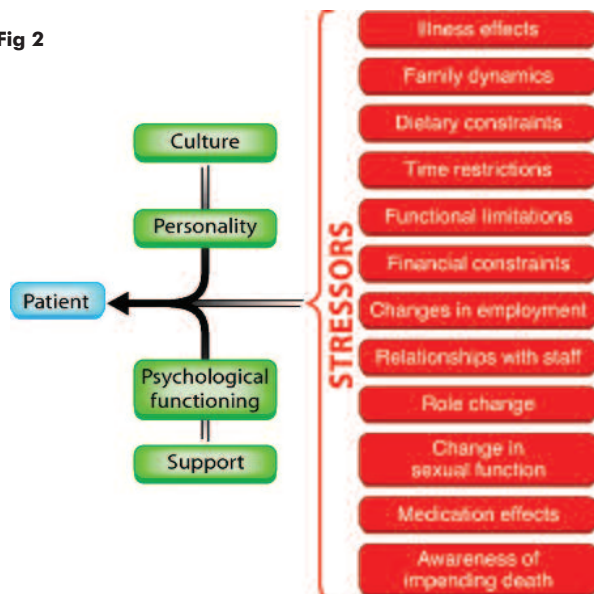


Fig 3

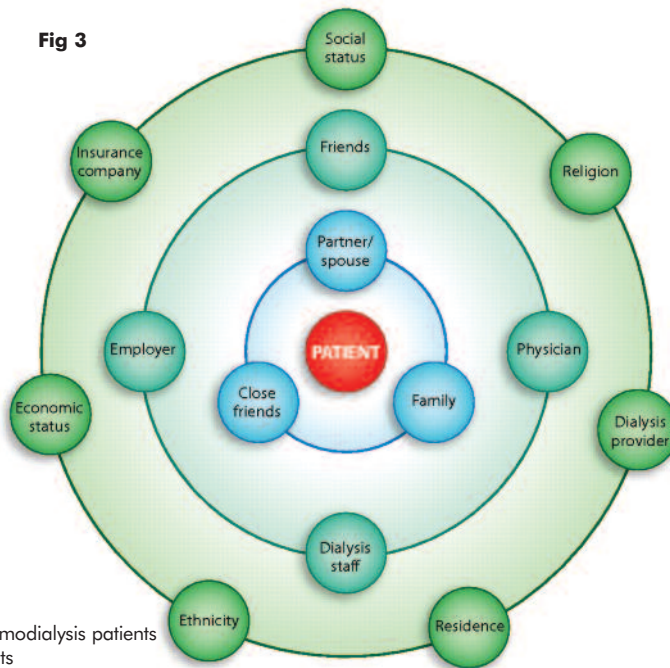


Fig 2. Patient characteristics and stressors that may affect perceived stress in hemodialysis patients  
Fig 3. Psychosocial parameters: spheres of influence for hemodialysis patients

comparison, between 6 and 7 percent of adults in the United States suffer from major depression in any given year; 1.5 percent experience dysthymia.

Nevertheless, patients and doctors alike are reluctant to use antidepressant medications. “The last thing most of these patients want is another pill and another side effect,” Dr. Cukor explains.

Hence the pilot study on CBT, which provided one-on-one therapy to 16 individuals during their dialysis sessions.

At first, people were a little uncomfortable. “But because at the initial meetings I was mostly offering education about depression, the participants became more relaxed,” Dr. Cukor says. As part of his introduction to cognitive therapy, Dr. Cukor explained that “the way you perceive life is often much more important than the way life actually is.”

Later sessions included behavioral therapy — teaching people to improve their mood by doing things they enjoy. “It could be a small thing, like going to the movies or playing music in the house when you’re alone,” Dr. Cukor says.

In fact, in his study the average depression scores dropped from 29 points on the Beck Depression Inventory to 18.5 points at the conclusion of the 15-week treatment. Three months later, the scores were only slightly higher — 18.8 points — indicating a sustained benefit from the CBT approach.

Among medically ill patients, 14 points and above is considered

### Dr. Cukor’s goal is to offer the kind of help for depression that so many people undergoing dialysis need, without additional medications or doctors’ appointments.

depressed. Thus, though many of the 16 patients in Dr. Cukor’s study remained depressed, they were far less depressed than before. “In trials for antidepressant drugs,” he notes, “five or six points of benefit is defined as remission.”

Now, Dr. Cukor hopes to refine the treatment and test it on a larger scale. Eventually, he hopes to conduct a multisite trial to compare chairside CBT to

pharmaceutical interventions. This will allow him to test for a statistically significant difference between the two approaches and to determine whether CBT can improve physical health outcomes as well.

“By its very nature, end stage renal disease means hard times and harder times. I’m glad my work may contribute to making patients’ lives a little easier.”

Dr. Cukor with Deborah Rosenthal (seated) and Yael Mayefsky, psychology trainees at SUNY Downstate and PhD candidates at Albert Einstein College of Medicine.



# Between Cells: Diffusion in the Brain's Extracellular Space

**W**hat if the phenomenon you study is so minute and multi-dimensional that it defies observation through traditional scientific methods? And what if the techniques available for researching the subject are unable to separate the component parts into their individual domains?

Those are some of the problems Sabina Hrabetova, MD, PhD, faces in trying to understand the dynamics of the diffusion of molecules through the brain's little-understood extracellular space (ECS).

The brain ECS is the part of the brain between the cells. Filled with fluid and something called the extracellular matrix, a kind of scaffolding made of proteins and sugars that anchors cells and synapses and provides receptors onto which molecules can bind, "the brain ECS makes up about 20 percent of the brain by volume," Dr. Hrabetova explains.

The dynamics of diffusion play a pivotal role in the ability of ions, neurotransmitters, and therapeutic agents to make their way through the brain's gnarled landscape — travels that enable and control many life processes.

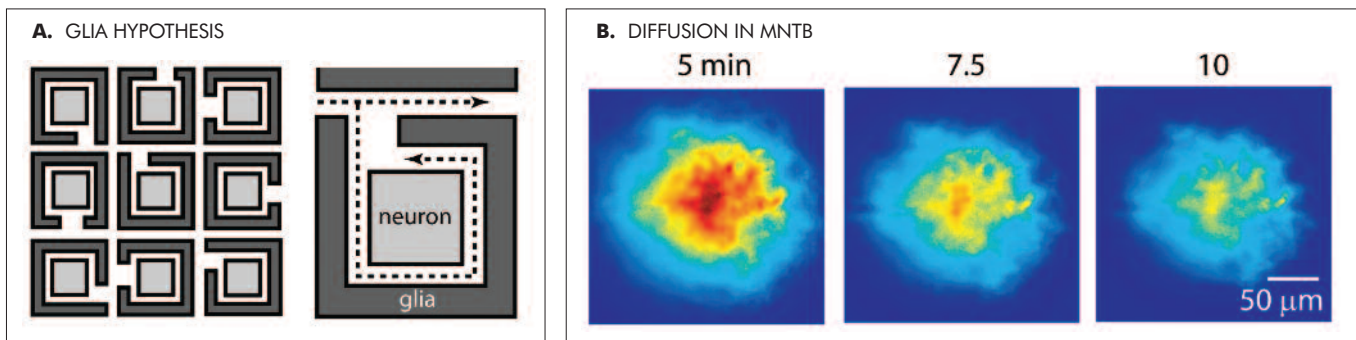


Nevertheless, diffusion through the brain ECS remains an enigma. To solve this puzzle, Dr. Hrabetova, assistant professor of anatomy and cell biology, employs a unique combination of computer modeling, theoretical biophysics, and good old-fashioned bench science.

Dr. Hrabetova has been fascinated by the inner workings of the brain since her days as a medical student in Czechoslovakia. As a doctoral candidate in Dr. Todd Sacktor's lab (see "PKMzeta, Sentinel of Memory," p. 8), she studied

synaptic plasticity and the role in memory formation played by certain enzymes in the brain known as protein kinase C isoforms.

When she finished her doctoral degree in 1998, however, she "wanted to learn something new, something completely different." Attracted to the work of Charles Nicholson, the world's leader in brain ECS research, she joined his lab at New York University as a postdoctoral researcher. "There, I learned how important the brain ECS is for commu-



## Glia processes may form a major diffusion barrier in brain extracellular space (ECS).

**A.** Thin glia processes wrap themselves around neuronal bodies, processes, and synapses, and form pocket-like dead-space microdomains (DSM) in the ECS. The DSMs can significantly influence the communication between the brain cells and drug delivery by transiently trapping signaling molecules and therapeutic substances diffusing in the ECS.

**B.** Brainstem auditory nucleus MNTB containing giant axosomatic synapses — the calyx of Held synapses — provides a model brain region to study the DSMs. Fluorophore-labeled macromolecules show inhomogeneous distribution in the rat MNTB, possibly caused by the trapping of macromolecules in the DSMs. (S. Hrabetova, unpublished)

nication between brain cells and for drug delivery," she says. "It was also an under-explored area, and I realized there was a lot I could discover."

In 2007, she set up her own lab at Downstate. The research has not been easy. "It's not yet possible to release a molecule in one part of the ECS and follow its movement to another," she

## The dynamics of diffusion play a pivotal role in the ability of ions, neurotransmitters, and therapeutic agents to make their way through the brain's gnarled landscape — travels that enable and control many life processes.

explains. Tools for measuring the brain ECS cannot easily separate the extracellular matrix from the area's other component parts. And electron microscopy, often effective in imaging tiny objects such as cell components in fixed tissue, is not suited for documenting "molecules moving in three-dimensional spaces in living tissue."

The difficulty in imaging diffusion is compounded by the question central to Dr. Hrabetova's research: "What happens when the brain's glial cell processes — the long, thin extensions of glial cells — wrap themselves around neuron bodies and around synapses?" Glial cells are the brain's second major cell type and their processes often create barriers that complicate rapid or easy diffusion of various neurotransmitters and therapeutic agents.

"In the past 10 years, there's been more and more evidence that glial processes can respond to neurotransmitters, release neurotransmitters themselves, and influence the signaling between neurons. It seems that glia are a more active cell type than we thought. And I want to find out whether these cells also regulate transport in the brain ECS," she explains. To address these questions, Dr. Hrabetova and her collaborators are using a series of mathematically based, computer-enabled simulations. "The experimental work of rigorously testing our hypothesis is still ahead of us," Dr. Hrabetova says.

While still in Dr. Nicholson's lab, Dr. Hrabetova discovered that molecules making up the extracellular matrix can have a significant impact on the diffu-

sion of signaling molecules. "Some of the extracellular matrix molecules can slow down diffusion of calcium, a molecule that's very important for axonal regeneration after injury," she notes.

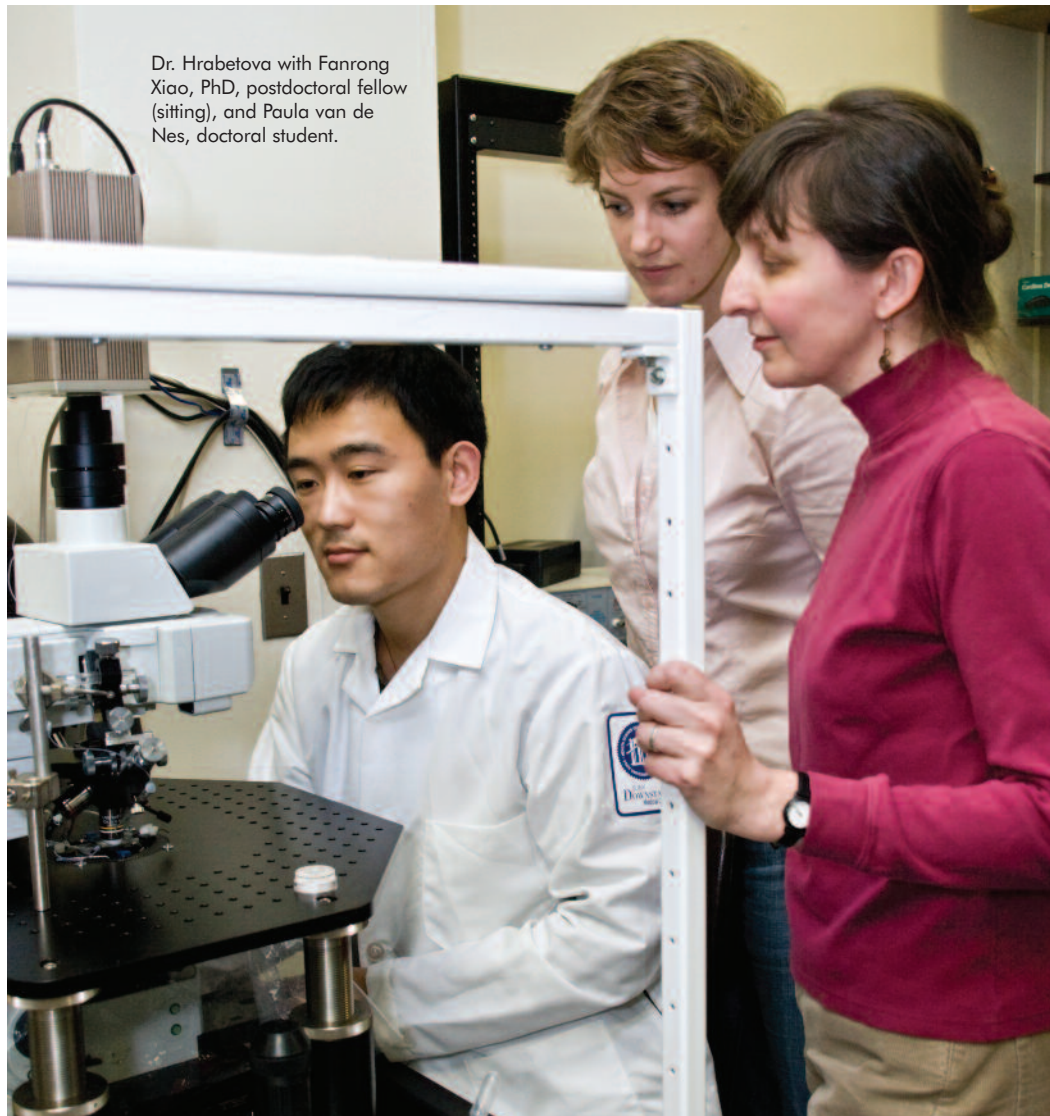
Likewise, she has learned that the structure, as well as the size, of molecules released into the brain ECS has a significant impact on diffusion. "If you

structure a very heavy molecule as a chain, it will have the same ability as a small ion to move through the brain ECS," she explains. "But a round molecule of the same weight will move more than five times as slowly."

Using data from her computer simulations and lab experiments, Dr. Hrabetova and her colleagues are able to quantify the rate at which different substances diffuse through the brain ECS.

"This is very useful as a way to test drugs in development, so that we can tell how far a drug is going to diffuse in an hour, or a day," she says. The technique should enable drug makers to better gauge and tailor the efficacy of their treatments, and is an important byproduct of the research questions that compel Dr. Hrabetova, despite many methodological difficulties: "What is the geometry of the extracellular space? What are its components? How does the brain ECS influence the normal signaling between brain cells?"

These are some of the challenging questions Dr. Hrabetova says that she needs to answer if her research is to help patients. **R**



Dr. Hrabetova with Fanrong Xiao, PhD, postdoctoral fellow (sitting), and Paula van de Nes, doctoral student.

# Strategies that Work: Information and Access to Care Reduce HIV Transmission

In the absence of a cure for the human immunodeficiency virus (HIV), prevention is the most effective tool healthcare professionals have for reducing the infection.

According to Tracey E. Wilson, PhD, associate professor in the Graduate Program in Public Health at SUNY Downstate, multiple strategies are necessary to prevent transmission of the virus that causes AIDS. This is especially true among urban minority populations, who are at greater risk for infection, but often lack access to medical care and health education.

One of the most important ways to

reduce HIV infection is to expand HIV testing. "After being diagnosed with HIV, people are more likely to reduce their level of sexual risk behavior," explains Dr. Wilson.

It is estimated, however, that nearly half of new sexually transmitted HIV infections are transmitted by HIV-positive partners who know they are infected. Therefore, prevention must also focus on helping people with HIV reduce the risk of transmission. Dr. Wilson has worked closely with colleagues at University Hospital of Brooklyn's STAR Health Center, which provides outpatient care to HIV

patients, to develop, implement, and evaluate such programs.

One initiative, funded by the Centers for Disease Control and Prevention, evaluated risk reduction interventions delivered by medical providers to HIV patients during routine HIV primary care. The program successfully integrated risk reduction education with HIV care. Six months after the intervention, unprotected sex among patients was reduced from 42 to 26 percent.

Following this work, the CDC funded Dr. Wilson's proposal to increase patient retention in HIV primary care. As part of this project, she

From left to right: Marilyn A. Fraser - White, MD, associate director for research and training, Arthur Ashe Institute for Urban Health; Michael Joseph, PhD, MPH, assistant professor, Graduate Program in Public Health; Grace Macalino, PhD, deputy director of research and programs, Arthur Ashe Institute for Urban Health; Ruth C. Browne, ScD, chief executive officer, Arthur Ashe Institute for Urban Health; and Dr. Wilson.



is developing clinic-based approaches to increase the likelihood that patients with HIV access care regularly. Dr. Wilson notes that studies demonstrate that retention in care is associated with improved quality of life, as well as reduced HIV-transmission risk behaviors.

Another key approach to HIV prevention involves working with those who are at risk for HIV infection. This includes injection drug users and individuals who engage in high-risk sex behaviors. It also includes members of groups who have suffered from a disproportionate burden of HIV infection, such as African-Americans or men and women living in geographic areas with a high prevalence of HIV.

Dr. Wilson and her colleagues in Downstate's Division of Infectious Diseases have developed and tested programs to reduce HIV risk in Brooklyn, including a partner notification program for men and women diagnosed with sexually transmitted infections (STI's). In this randomized controlled study, patients were encouraged to notify their sexual partners of their condition and supported in their efforts to do so. Not only did the program increase the percentage of patients who informed their partners, it reduced subsequent STIs. Six months after initial diagnosis, the rate of new STIs was cut nearly in half, from 11 percent among the control group who received the standard level of care to 6 percent among those who received the intervention.

Dr. Wilson is now working with colleagues in her department and with longtime partners at the Arthur Ashe Institute of Urban Health (AAIUH) to develop approaches to risk reduction for African- and Caribbean-American men living in Brooklyn. The program, based on a model developed by the Ashe Institute for providing health education in nontraditional settings, will deliver HIV risk-reduction education through barbershops in Central Brooklyn and Flatbush.

According to Ruth C. Browne, ScD, co-principal investigator for the project and chief executive officer of AAIUH, "while most black men regularly go to



Tracey Wilson, PhD

the barbershop, many lack a regular source of health care. Community-based venues such as these can be supportive environments for promoting behavioral change."

Drs. Browne and Wilson have collaborated on a similar program for a different target group and disease: women and breast cancer. Through beauty parlors, health educators taught women about the importance of mam-

to the needs of those at risk. The latter can only be achieved by working closely with the target population to identify prevention needs and appropriate strategies. "When people believe that we want to help their community, they are more willing to share information about behaviors that are often stigmatized," says Dr. Wilson.

Equally important, adds Dr. Wilson, the programs must work for

**"When people believe that we want to help their community, they are more willing to share information about behaviors that are often stigmatized."**

mography, demonstrated breast self-examination, and provided referrals for follow-up care.

Dr. Wilson believes the key to developing effective programs involves combining strong public health methods with knowledge of and sensitivity

care providers, as well as patients. "If, at the end of the day, these programs are too expensive or too time consuming to be adopted by clinics and community-based organizations, then our efforts to fight the spread of HIV will not be effective." ■

# Pioneers of Alcoholism Research: Henri Begleiter and Bernice Porjesz

Sometimes, someone comes along who changes everything. In the field of alcoholism research, that someone was Henri Begleiter, PhD, a distinguished professor of psychiatry and neuroscience at SUNY Downstate Medical Center.

Dr. Begleiter, who died in April 2006, at age 70, was internationally revered as an innovator who redefined medical science's view of alcoholism.

"Before Henri came along," says his longtime collaborator Bernice Porjesz, PhD, professor of psychiatry and behavioral sciences, and director of SUNY Downstate's renamed Henri Begleiter Neurodynamics Laboratory, "the dominant view in the field was that anomalies and dysfunctions found in the brains of alcoholics were the result of drinking."

Dr. Begleiter was the first to conceptualize the important role genetics plays in the development of alcoholism and related disorders. One of his major accomplishments, Dr. Porjesz says, was in thinking, "Maybe the dysfunctions we see in alcoholics' brains are something that these alcoholics had prior to becoming alcoholics. Maybe these dysfunctions put them at risk for alcoholism."

Throughout his celebrated career, Dr. Begleiter dug deep into the complex relationship between genetics and behavior, laying groundwork that continues to provide insights into alcoholism's genetic links.

As a young scientist, Dr. Begleiter explored the workings of the healthy brain — how humans hear, see, and think. To conduct such research, he needed to compare healthy and abnormal brains, and thus chose to study the brainwave activity of alcoholics.

"We wanted to know what functions are affected by alcoholism, what functions recover with abstinence, and so on," Dr. Porjesz explains. "We studied this by comparing the brainwave activity of alcoholics with that of non-alcoholics."

Together, Drs. Begleiter and Porjesz identified a type of neural hyperexcitability that didn't exist in the brains of non-alcoholics. That piqued their scientific curiosity and their research interest shifted, from normal brain function to alcoholism.

Drs. Begleiter and Porjesz found that one measure of a certain type of brainwave activity, called P3, "was very low in alcoholics," Dr. Porjesz says. When they began to look into this phenomenon, "We thought, of course, it was the function of drinking alcohol for so many years," she adds.

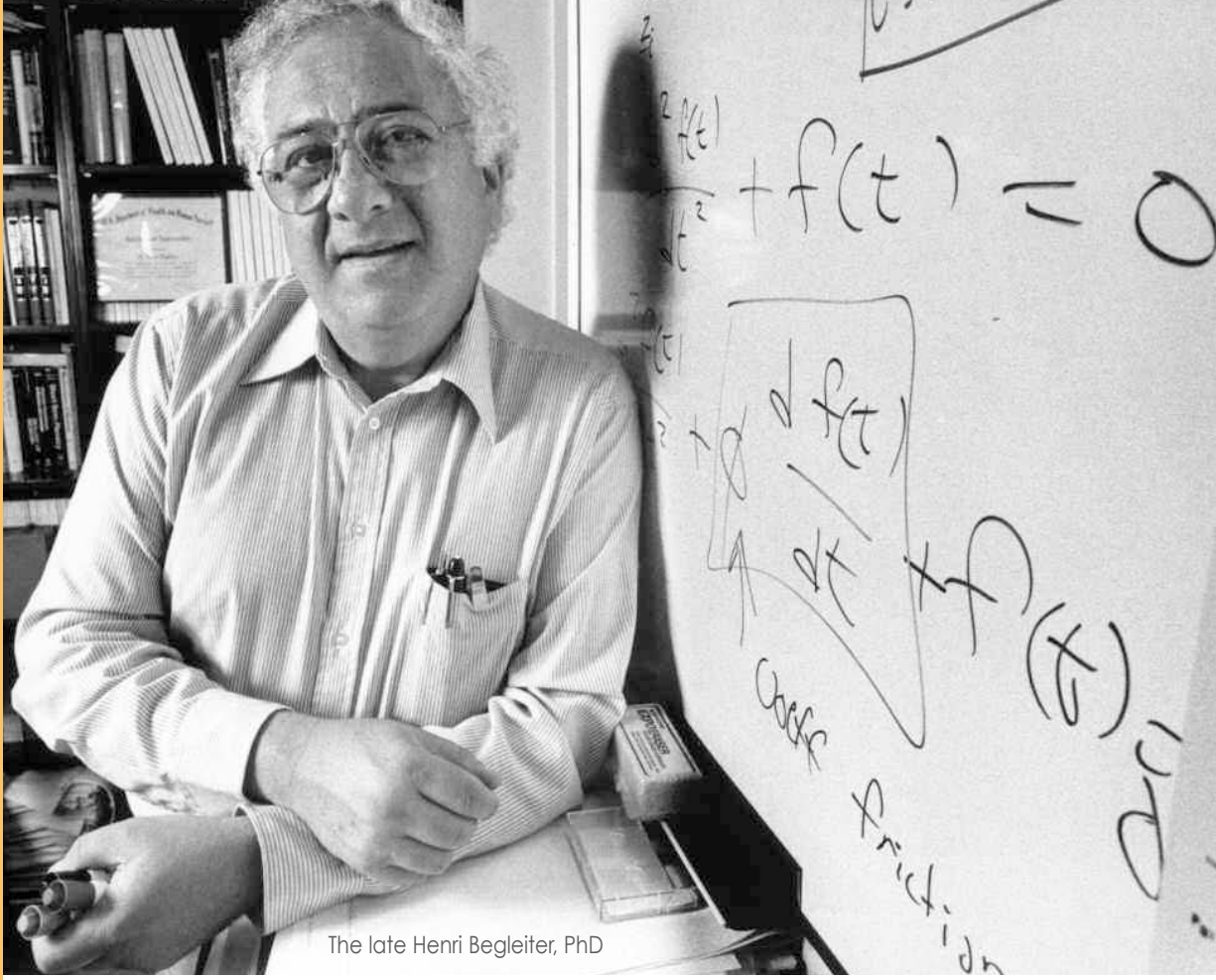
Drs. Begleiter and Porjesz next tested recovering alcoholics who had been sober for significant lengths of time. They found the same activity — a very low P3 response.

Concurrently, studies coming out of Scandinavia indicated that boys whose biological fathers were alcoholics were four times more likely to develop alcoholism than boys whose fathers weren't alcoholics. This was true even for the sons of alcoholics adopted as newborns by non-alcoholic families.

This startling finding led Dr. Begleiter to wonder whether the irreversible brainwave deficits he and Dr. Porjesz saw in alcoholics — the low P3 — existed before these individuals developed alcohol dependence.

"So we looked at the sons of alcoholic fathers," Dr. Porjesz recalls. The pair specifically chose sons of alcoholic fathers, rather than alcoholic mothers, to ensure that any anomalous brain wave activity hadn't resulted from prenatal alcohol exposure. The boys were between 7 and 13 and had never been exposed to alcohol or drugs.

"Lo and behold," Dr. Porjesz recalls, "they too had this low amplitude P3, which, given everything that was known about alcoholism at that point, was astonishing." Using this data, Dr. Begleiter proposed that these brain-



The late Henri Begleiter, PhD



Bernice Porjesz



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wave deficiencies put the biological children of alcoholics at significantly higher risk of developing alcoholism.

The data, published in 1984 in the prestigious journal *Science*, changed the way many researchers and professionals think about alcoholism. “Until then,” says Dr. Porjesz, “we believed alcoholism ran in families solely because children would see their parents drinking and, basically, alcoholism is what they learned.”

These results spurred Drs. Begleiter and Porjesz to study the relationships between genetics and alcoholism. In 1989, Dr. Begleiter founded and led, until his death, the nine-site Collaborative Study on the Genetics of Alcoholism (COGA), examining families heavily affected by alcoholism. In its 18th year, the study, which Dr. Porjesz now leads, includes almost 25,000 individuals and remains the world’s largest study of genetics and alcoholism.

A major focus for the COGA project is the underlying genetic causes of brainwave patterns that distinguish individuals at risk for alcoholism and other so-called externalizing disorders, such as drug abuse, conduct disorder, and anti-social personality disorder. This approach, which COGA adopted many years ago, has been instrumental in identifying several genes involved in alcohol dependence and related disorders in the COGA families.

“With these ‘risk genes’ in hand,” says Dr. Porjesz, “we’re now running prospective studies in the next generation of children in these families. We’re comparing children with and without these genetic variants as they go through the age of risk. That way, we can study the interaction of these genes and the development of alcoholism and other related disorders.”

Today, the Henri Begleiter Neurodynamics Lab is at the forefront of alcoholism research. Says Dr. Porjesz, “We’re learning new things from our studies all the time.” The multidisciplinary staff continues to discuss their research and new ideas weekly, much as they did, at Dr. Begleiter’s initiation, while the distinguished professor was still alive.

Dr. Porjesz recalls, “Lots of times, everyone would be on one track and Henri would come up with something, some great idea, out of left field. It would be something no one else would have thought of. And that’s something about Henri – an incredible creativity and ability to think outside of prescribed categories – that I particularly miss.

“Even though we have to move ahead without Henri’s vision, ground-breaking ideas, enthusiasm, and charisma, we’re moving forward. We are dedicated to continuing his innovative approach.” ■

**Bottom right:** Bernice Porjesz, PhD, and her team. From left to right: Arthur Stimus, project coordinator; Dr. Porjesz; David Chorlian, senior scientific programmer; Madhavi Rangaswamy, PhD, assistant professor; and Kamarajan Chellappan, PhD, assistant professor, during a weekly lab meeting.



## Opioids and the Central Nervous System

More than 1.5 million Americans are addicted to narcotics. Heroin claims an estimated 1 million regular users, while hundreds of thousands more abuse morphine, codeine, Oxycontin®, and Vicodin®.

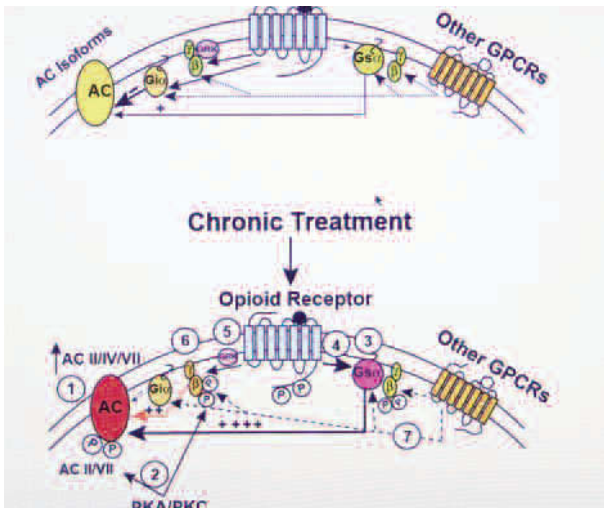
Alan Gintzler, PhD, chair of the Department of Biochemistry at SUNY Downstate Medical Center, is trying to understand why. Funded by the National Institute on Drug Abuse, Dr. Gintzler and his colleagues are exploring how cells in the central nervous system respond to the ongoing presence of opium-derived drugs. “If you really understood the adaptations that chronic morphine use elicits,” says Dr. Gintzler, “you would be able to understand the dependence on narcotics that people develop, and what happens when you take the drug away.”

It could also help medical professionals intervene in the process of narcotic addiction itself, both by preventing addiction to pain-relieving narcotics, and blocking drug cravings in users. His research, Dr. Gintzler believes, “could be used to detox. It could also be used as an

adjunct for pain therapy to prevent patients from becoming addicted.”

Specifically, Dr. Gintzler has focused his attention on one mechanism of the addiction process – the fact that animals and humans develop a well-documented tolerance for narcotics. In cancer patients, “if you give them morphine, initially it controls their pain very well,” Dr. Gintzler explains. Over time, however, the patient needs higher doses to achieve the same relief. “After a couple of months, you can give as much as several grams of morphine and it’s barely enough,” Dr. Gintzler notes. “Several grams are enough to kill someone who is just starting to use morphine.” A similar phenomenon occurs with drug addicts.

Dr. Gintzler’s research shows how this adaptation occurs. “Cells in the central nervous system communicate by releasing chemicals called neurotransmitters that are then received by receptors on the surfaces of other cells,” he says. Many cells in the brain transduce their signals once the receptor is activated by using G proteins. Dogma in Dr. Gintzler’s field



Schematic representation of the discovery by Dr. Alan Gintzler and colleagues of changes in signaling molecules and their associations in response to chronic morphine.



Dr. Alan Gintzler and members of his laboratory. Clockwise: Michael Shy, MD, PhD, student; Nai-Jiang Liu, PhD, research assistant professor; Tarak Sharma, PhD, research associate; Dr. Gintzler; Arati Panda, laboratory manager; and Sumita Chakrabarti, PhD, research assistant professor and senior laboratory scientist.

dictates that after habitual exposure to opioids, communication between the opiate receptor and the G protein becomes interrupted. When the opioid activates the opiate receptor, the signal that is generated can no longer get through.

Dr. Gintzler’s work challenges this view. “The conversation” between opioid receptors and G proteins “is still going on, but it changes,” he explains.

During initial opioid exposure, one part of the G protein, called the alpha subunit, communicates with the receptor. After chronic exposure, another part, the beta gamma subunit, takes over. The previously silent beta gamma subunit now is suddenly heard and signals opioid exposure.

Adaptations to the habitual presence of opioids don’t stop there. During initial exposure, Dr. Gintzler discovered, opioid receptors communicate with one type of G protein, an inhibitory type. After long-term exposure, they switch to another, excitatory type.

These adaptations may save cells. But they don’t help people who take opioids for either pain relief or pleasure. “From the cell’s point of view, tolerance is protective and adaptive,” Dr. Gintzler notes. After all, the drug’s presence disrupts the cell’s equilibrium. But once the drug is present on a regular basis, a new equilibrium develops. Should these drug levels drop, the adaptations become unbalanced and withdrawal ensues.

While much of Dr. Gintzler’s work examines this process on a cellular level, he hopes his research will help prevent and treat narcotic addiction in living, breathing human beings. “The understanding of adaptations that are elicited by the chronic use of morphine,” he says, “will enable us to identify the pivotal changes that underlie the craving phenomenon, and then target them to weaken their effect.” ■

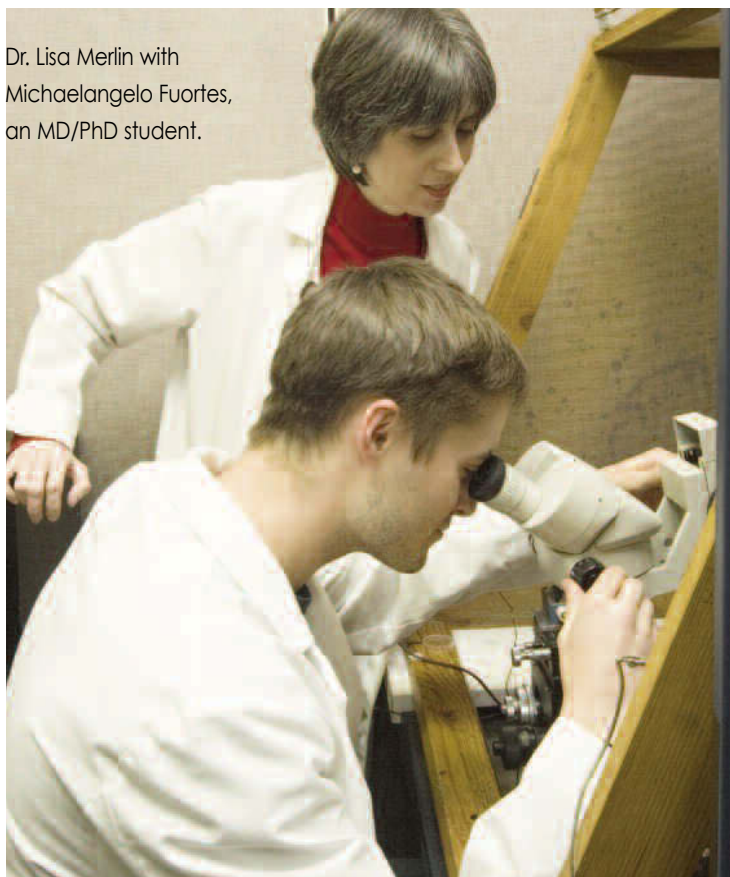


## the origin of seizures

Lisa Merlin, MD, wants to understand what causes epilepsy. Not what causes seizures, per se. Seizures are something about which medical science already knows a fair amount: High fevers can cause them, as can uncontrolled diabetes and alcohol abuse. Remove these causes and the brain returns to its normal, relatively undisturbed state.

But epilepsy is a different problem – a neurological disorder characterized by recurrent episodes of seizing. Each year, nearly 200,000 Americans are diagnosed with the disorder. Dr. Merlin, both a professor of neurology and of physiology and pharmacology, wants to understand why. How, she says, “the normal brain becomes permanently predisposed to producing electrical discharges that cause seizures.”

Dr. Lisa Merlin with  
Michaelangelo Fuortes,  
an MD/PhD student.



Though there are different types of epilepsy, many who suffer from the disorder were first put at risk by a head injury, stroke, meningitis, or other damage to the brain. Using techniques pioneered by her mentor and colleague, Robert Wong, PhD, [see page 20], Dr. Merlin has found the basic pathway that turns a relatively normal brain into an epileptic one. She is testing compounds that may block that pathway, and thus block the development of the disease in high-risk individuals. “The hope is that someday, these interventions will be clinically applicable,” Dr. Merlin explains.

On the surface of human brain cells are three groups of receptors known as mGluRs, metabotropic glutamate receptors. “The hyperactivity” of one of those groups, Dr. Merlin has discovered,

“seems to have a particular ability to persistently enhance the excitability of the brain.”

In other words, epilepsy in brain-injured and other high-risk people may be caused by the over stimulation of a certain set of receptors by a neurotransmitter called glutamate. This process sets off a cascade of events within networks of brain cells, resulting in long-lasting changes in channels within the cells, “opening them, closing them, and modifying them in a permanent way,” Dr. Merlin explains. Such changes make the brain cells, in essence, epileptic.

To block that process, and thus prevent the disease in high-risk people, Dr. Merlin and her colleagues are testing the efficacy of certain chemical compounds. In experiments using guinea pig brain tissue, an amino acid called L-cysteine sulfinic acid (CSA) appears to do the trick. So does a blocker of a particular kind of mGluR. “It’s very preliminary,” says Dr. Merlin, but it seems these compounds may “interfere with the pathway that produces the epilepsy.”

That’s particularly exciting to Dr. Merlin, who works not only as a researcher but also as a clinician at Brooklyn’s Kings County Hospital, across the street from SUNY Downstate. “Currently, all the available drugs only suppress seizures once the person already has epilepsy,” Dr. Merlin explains. “But a drug that would prevent the development of epilepsy could decrease the population of epileptics worldwide.” ■



Robert Wong

# fragile x syndrome and epilepsy

**r**obert Wong, PhD, distinguished professor and chair of physiology and pharmacology at SUNY Downstate Medical Center, is motivated as much by a keen intellectual interest in the basic workings of the brain as by a desire to help those who suffer from seizure disorders.

“My habit of studying the brain is more like observing the brain,” says Dr. Wong. “I don’t start with theories I try to test. I don’t try to predict things. I’m just interested in observing various brain activities and figuring out what they are.”

That approach has led to one of the most highly acclaimed careers in modern epilepsy research. And with good reason: Dr. Wong’s findings have shaped the field since the late 1970s, when, working with colleague Roger Traub, MD [see page, 26], he first identified the mechanism that causes seizures. Dr. Wong also developed many of the techniques that underlie epilepsy research worldwide.

Now, using his observational approach, Dr. Wong is pursuing a new facet of his research interest: why 30 percent of children with the genetic developmental disorder known as Fragile X syndrome also suffer from epilepsy. “In Fragile X,” says Dr. Wong, “there’s just one genetic defect,” one protein that’s missing. By studying how this mutation leads to epilepsy, Dr. Wong may once again spur major breakthroughs in epilepsy research.

As a postdoctoral fellow, Dr. Wong wanted to learn how brain cells worked together to cause seizures.

So, in collaboration with Dr. Traub, he applied his observational method. Dr. Wong explains that they discovered that when a brain cell, a neuron, gets excited “it sends a signal out to a few other neurons.

Those communications are very strong and have a high probability of exciting many other neurons.”

Excited neurons can then excite their neighbors, which, in turn, excite the neurons that surround them. As the process mushrooms, a kind of neuronal “hyper-synchronization” ensues, Dr. Wong says. The excited neurons “discharge in unison,” generating the abnormal electrical activity that results in seizures.

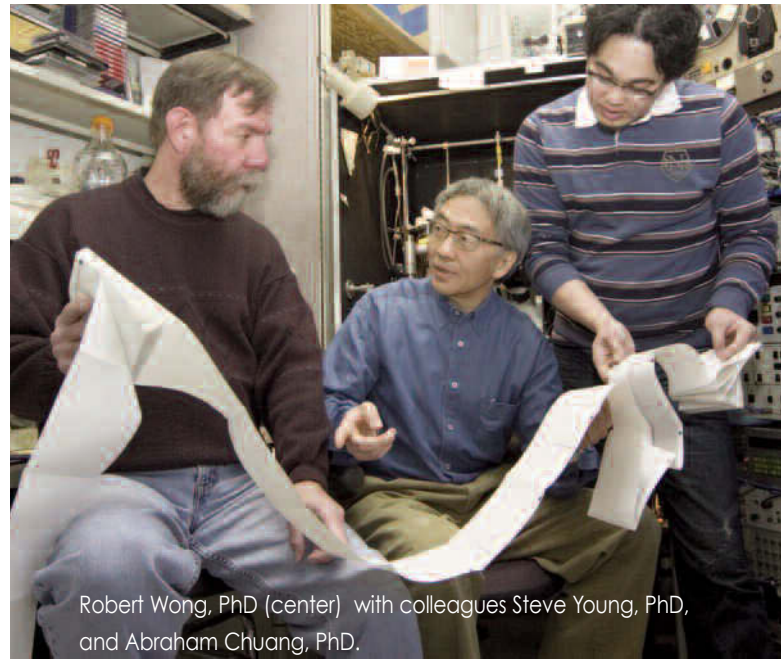
Building on this important finding, Dr. Wong went on to discover that in the normal brain, the excitatory process described is usually inhibited by a neurotransmitter called GABA, gamma-aminobutyric acid. But GABA production can be curtailed by the repeated excitation of the cells that produce it. “So one way that epilepsy occurs is when the excitation becomes too strong or when inhibition is not strong enough,” he explains.

Dr. Wong’s collaboration with Lisa Merlin, MD (see page 18) and Greg Taylor, a SUNY Downstate MD/PhD student, resulted in the discovery of how interictal spikes, synchronized electrical discharges shorter than one second, evolve into discharges of longer duration and more clinical significance, termed ictal discharges. This process occurs when a neurotransmitter called glutamate stimulates a group of receptors on the surfaces of brain cells, known as metabotropic glutamate receptors. The glutamate transforms the cells in a way that allows for long-lasting excitatory activity. “Changing the communication between cells is fundamental to the process by which normal brain cells become prone to epilepsy,” Dr. Wong says.

Now, using these findings, Dr. Wong is examining the causes of epilepsy and developmental disorders in children with Fragile X syndrome. Says Dr. Wong, “Fragile X is a very well-defined disorder. Only one gene and one protein are involved, and these produce huge changes in the brain.”

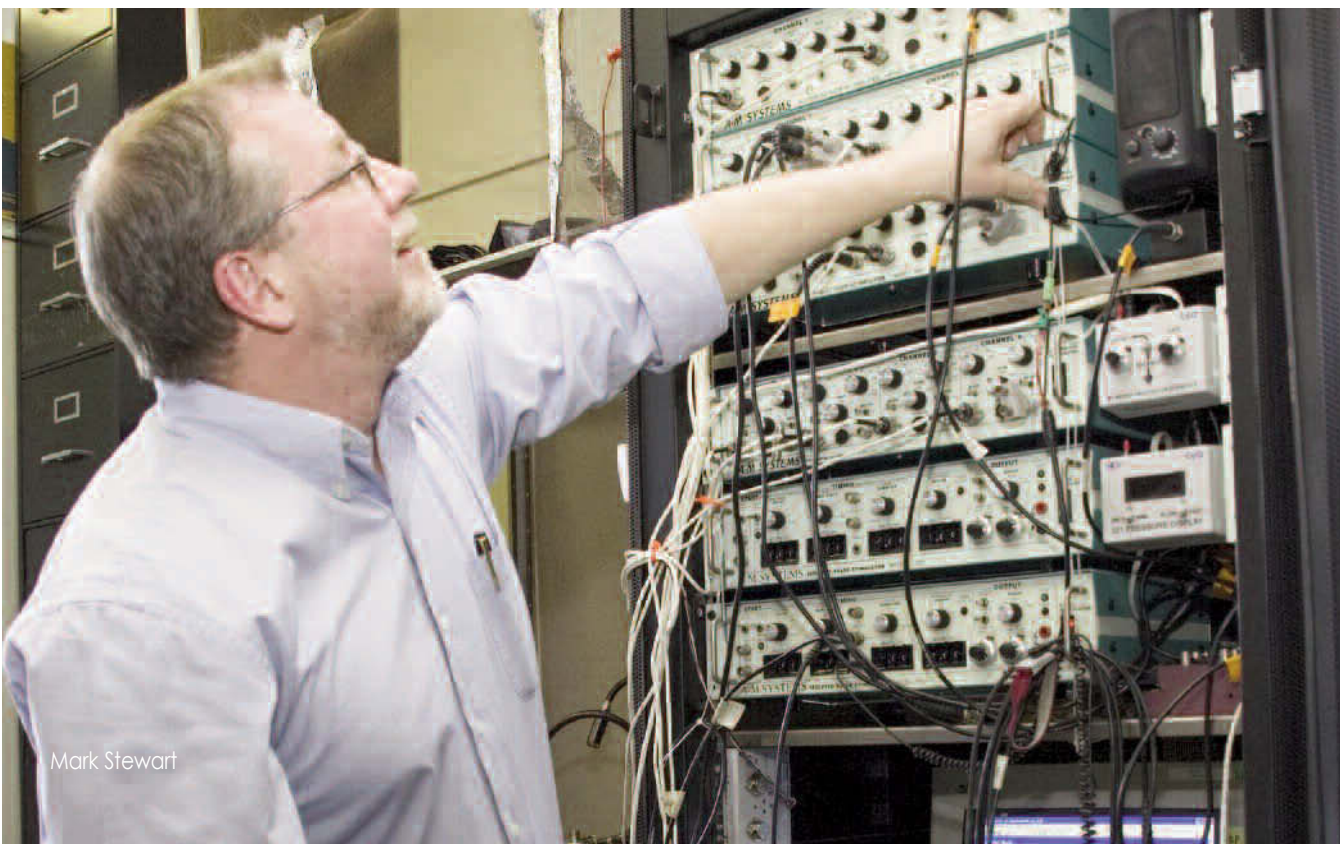
Not only are children with Fragile X mental retardation syndrome prone to epilepsy, but more than 30 percent suffer from autism. Dr. Wong believes that by exploring the alterations that result from these genetic changes, he and his collaborators may learn to better understand epilepsy and the profound, often devastating developmental disorders that Fragile X can cause. Says Dr. Wong, “Fragile X is a great key to the puzzle of how the brain works.”

That’s a puzzle Dr. Wong continues to piece together through his ongoing and careful observation of the brain. “If you concentrate on selective details,” Dr. Wong says about his method, “those small details might become applicable to a very big picture.” The very big picture that is epilepsy ■



Robert Wong, PhD (center) with colleagues Steve Young, PhD, and Abraham Chuang, PhD.





Mark Stewart

# sudden unexplained death in epilepsy (sudep)

**S**udden Unexplained Death in Epilepsy (SUDEP). The name is almost as dramatic as the event itself, which is usually precipitated by a generalized, full-body seizure. Such seizures, termed tonic-clonic seizures in medical literature, don't normally lead to death. Why, then, do as many as 10,000 of the nation's more than 2.5 million epileptics succumb to SUDEP each year, with no other identified cause?

Until now, medical science devoted relatively little energy to this question. It's uncovered few answers and found no way to prevent the wrenching event. Neuroscientists studying seizures have focused on understanding how the abnormal electrical activity in the brain responsible for seizures is generated, and how to stop or prevent it.

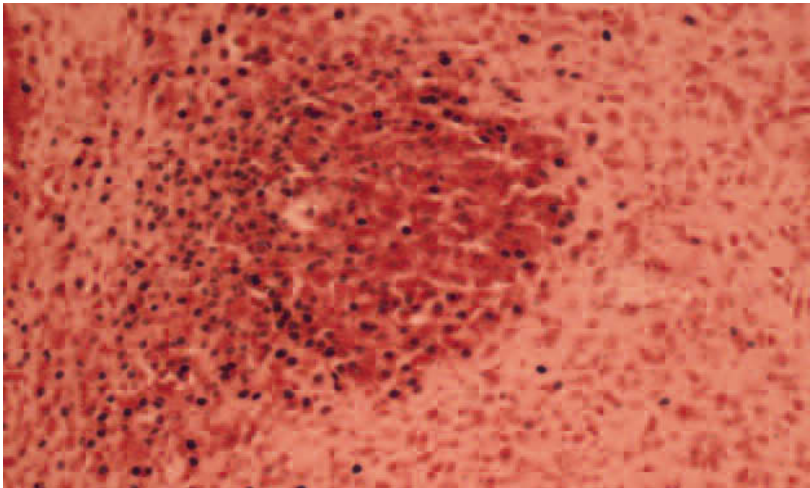
But now, Dr. Stewart's group at SUNY Downstate is trying to address these questions both benchside and bedside. Using new techniques developed in his lab, and data collected from patients in the Epilepsy Monitoring Unit at SUNY Downstate's University Hospital of Brooklyn, Dr. Stewart and his colleagues hope to have answers to the problem soon.

"This is an area where the consequences are dire," he says, "and, for me, as a researcher, there's a chance to have an effect on a patient's life."

To better understand the causes of SUDEP, it's important to know how seizures happen. Generalized seizures come about when abnormal electrical activity spreads throughout a large portion of the brain's outer layer, called the cerebral cortex. This activity can cause the entire body to stiffen and convulse. Epileptic activity can happen on a smaller scale, too. In so-called focal seizures, smaller brain areas are affected, generating more limited results. Focal seizure can cause, among other responses, goose bumps, visual auras, and olfactory sensations.

Generalized or focal seizure activity frequently involves the limbic system, a group of brain areas that are critically important for making memories and expressing emotions, but are also prone to seizure activity. The limbic system can strongly influence a much more basic set of brain structures: the autonomic nervous system. These “low-level” brain areas regulate heart rate, blood pressure, and respiration.

SUDEP is thought to result when seizure activity spreads from the cortex and limbic system into the autonomic nervous system (ANS) in a peculiar way. “All seizures have some impact on the ANS, but life-threatening changes in heart rate or blood pressure are uncommon,” Dr. Stewart explains. “Death is likely to be caused by some very peculiar involvement of the ANS as seizure activity spreads through the brain.”



A section of rat brain tissue showing the paraventricular nucleus, a part of the hypothalamus. Darkly stained cells are evidence of elevated levels of c-fos, a protein marker used to indicate activity. The increase in c-fos expression in the paraventricular nucleus after seizures indicates that these cells were strongly activated by the seizures.



Mark Stewart, MD, PhD, is reviewing seizure activity recorded during experiments on rats with Kiyomi Koizumi, MD, PhD, distinguished professor of physiology & pharmacology, and Rena Orman, PhD, a postdoctoral fellow.

Until recently, it’s been difficult to study precisely how this happens, because researchers were unable to control where seizures occur or follow the paths of seizures from cortex or limbic areas into lower parts of the brain. But about a year ago, Dr. Stewart’s lab developed a technique that for the first time allows them to cause seizure activity in the limbic area of a laboratory animal’s brain without involving the cortex, and to follow this activity through the ANS and into the periphery.

“With this tool for studying animals and our ability to study seizure activity in patients in the hospital epilepsy unit, we can essentially define the patterns of brain activity that cause specific changes in the autonomic nervous system,” Dr. Stewart says.

Dr. Stewart believes his lab will soon identify the type of brain activity associated with SUDEP and how it may vary from patient to patient. By so doing, they may eventually enable epileptics who sense a seizure coming on to treat themselves with medications that control heart rhythms and/or blood pressure. “In those cases,” Dr. Stewart says, “they could administer something which would dramatically lower the chances they would suffer an abnormal heart rhythm, a spike in blood pressure, or respiratory distress that could result in sudden death.”

“Those are real therapeutic targets,” Dr. Stewart notes, explaining that many existing medicines have the potential to protect patients “once we establish what they need to be protected from.” In the meantime, he and his colleagues are making much progress toward their goal of identifying the brain patterns that foretell SUDEP. “The tools to predict seizures and their impact on the body for an individual patient are coming,” he says. “And with them, a chance to save many lives.” ■



Katherine Perkins

## is GABA a culprit?

**k**atherine Perkins, PhD, is on the trail of a mystery. That mystery? The role the neurotransmitter GABA, gamma-aminobutyric acid, plays in causing epileptic seizures.

What makes this a mystery is that for a very long time, neuroscientists have believed that GABA's major role in the adult brain was as the chief inhibitory neurotransmitter, calming brain cells down and thereby decreasing the electrical activity that can result in seizures.

But in 1991, Robert Wong, PhD, and fellow SUNY Downstate researcher Hillary Michelson, PhD, made what was then a startling discovery: GABA could be used by the brain cells that release it, called interneurons, to excite other interneurons. In so doing, GABA can cause a large group of interneurons to become active simultaneously.

"The finding that interneurons could use GABA among themselves as an excitatory transmitter was very controversial and very exciting," says Dr. Perkins, who was a graduate student in Dr. Wong's lab at the time and is now an associate professor of physiology and pharmacology at Downstate. "And I've been interested in the excitatory action of GABA ever since."

Dr. Perkins is interested in the mechanisms of neuron-to-neuron communication. To study how brain cells communicate – how they excite or calm each other down – she and her colleagues record electrical activity in slices of hippocampus taken from the brains of healthy laboratory guinea pigs. These brain slices are treated with a chemical that makes them fire in ways similar to the ways human brain cells fire during epileptic seizures. “In fact, electrical recordings from the brain tissue of people with epilepsy look an awful lot like the guinea pig recordings we do in the lab,” Dr. Perkins says.

Through this recording process, Dr. Perkins learned that “under certain conditions, when an interneuron releases GABA onto a principal neuron, it excites that neuron and can trigger an epileptiform seizure.”

These discoveries in guinea pig brain slices were confirmed recently by other labs that conducted studies on the brain tissue of human beings with severe epilepsy: GABA can play an excitatory role in the generation of epileptic seizures. “Seeing the data from the human brain tissue studies has made me excited about what I could do to help people with the disease,” she says.

In her studies, Dr. Perkins has seen that “the same cell can receive both calming, inhibitory GABA-mediated input and excitatory GABA-mediated input.” Now, with funding from the National Institutes of Health, she and her colleagues hope to discover which kinds of interneurons are responsible for the excitatory and the inhibitory types of GABA responses. “Right now, it’s not clear whether these different types of GABA responses are produced by different types of interneurons,” Dr. Perkins explains. “Our early data suggest that they are.”

Such a discovery could help unravel the mystery of GABA’s role in causing epileptic seizures, and may elucidate the role the neurotransmitter plays in other important brain functions such as learning and memory. Discovering the source of GABA’s excitatory action could also help in developing treatments for the difficult-to-control disease of epilepsy.

“We might be able to enhance GABA’s calming effect without also enhancing the excitatory effect,” Dr. Perkins explains. “That,” she says, “would be especially good news for patients with epilepsy.” ■



Katherine Perkins, PhD, with Jonathan Lopez, a fourth-year medical student.

# training and

HIV Clinical Scholars  
Amanda Swan, NP,  
and Katherine Marx, NP,  
with Dr. Jack DeHovitz.



It happens mostly behind the scenes. But “one of the most important things we do at the HIV Center,” says Director Jack DeHovitz, MD, MPH, professor of medicine and of preventive medicine and community health, “is to train new researchers, healthcare practitioners, and leaders.”

In fact, health professionals come to SUNY Downstate Medical Center from throughout the world to receive specialized training in HIV medicine, prevention, and research. “Because of our expertise in these areas,” Dr. DeHovitz says, “we can offer instruction and mentorship that would be hard to replicate elsewhere.”

One group of trainees — Nicholas A. Rango HIV Clinical Scholars — receives two years of specialized instruction as part of a program created and funded by the New York State Department of Health’s AIDS Institute. To date, SUNY Downstate has trained 19 HIV Clinical Scholars.

Nurse practitioners Amanda Swan and Katherine Marx are the newest HIV Clinical Scholars. Until their fellowships end in June 2008, they’ll treat patients, deepen their knowledge of HIV medicine, attend weekly seminars on public health and AIDS policy issues, and explore research methods. “For me, as a new nurse practitioner,”

# EDUCATION

says Ms. Swan, “having a preceptor – a clinician who serves as my mentor – has really helped.”

Ms. Marx agrees. “I’m able to meet with my preceptors weekly to go over patient questions and issues. If I need someone to look at something – a rash I’m not sure about – the preceptors are right there. That kind of support is a really important part of my training.”

But not the only important part. The Clinical Scholars from SUNY Downstate meet weekly with fellow HIV Clinical Scholars from around New York to discuss policy issues and public health. “We have seminars on international AIDS issues, on epidemiology, on youth work – a whole variety of topics,” says Ms. Marx. “These seminars have allowed me to put my clinical work in context and to think about how to become more active in public health issues.”

Still, these Clinical Scholars say the most important part of their training is the relationships they develop with patients at Downstate’s HIV clinics for adults and adolescents. Says Ms. Swan, “Especially in HIV work, patients tell you things about themselves that a lot of other people don’t know. You play a big part in their life. When I finish this program, that will be what I remember most – my relationships with the patients here.”

Of course, those relationships may continue if Ms. Swan, like a number of the HIV Center’s trainees, remains at SUNY Downstate after her fellowship is complete. That’s what Tracey Wilson, PhD, a cognitive psychologist, did after finishing two years of post-doctoral training at SUNY Downstate in 1997.

Sponsored by the Association of Teachers of Preventive Medicine and the Centers for Disease Control and Prevention (CDC), Dr. Wilson was able to apply her interest in individual behavior change to the field of HIV

prevention. “A large part of my post-doc training was in different areas of public health – basic epidemiology, infectious disease epidemiology, and the design and evaluation of prevention programs,” she says.

That training enabled her to design and implement programs to help stop the spread of HIV and other sexually transmittable diseases – programs she continues to develop today as an associate professor in SUNY Downstate’s Department of Preventive Medicine and Community Health.

The HIV Center provides similarly intensive training to researchers and healthcare professionals from Central and Eastern Europe as part of the Fogarty AIDS International Training & Research Program started in the 1990s. Funded by the National Institutes of Health, the program is named after a former member of Congress.

“It was a means of linking up academic medical centers to centers in the developing world that were gearing up to fight HIV,” Dr. DeHovitz explains. To date, the Fogarty program at SUNY Downstate has provided short-term training to more than 5,300 professionals in HIV-related fields and long-term training to more than 70 others.

A number of the first Fogarty researchers trained by SUNY Downstate faculty came from the Czech Republic, Hungary, and Poland. “Some of them were basic science researchers; some were public health researchers,” Dr. DeHovitz explains. “And some did clinical research within healthcare settings.”

Now, as the AIDS epidemic has spread to the former Soviet Union, so has the Fogarty program, creating educational partnerships with researchers and healthcare providers in Russia, Estonia, Georgia, and Armenia. “We bring people over here for training,” says Dr. DeHovitz, who directs the project, “and help create relationships and partnerships within a cadre of individuals who can work together and who continue once they return to their countries.”

In that way, SUNY Downstate offers its considerable HIV expertise to Brooklyn, N.Y., and beyond. ■



The **WITS** (Women and Infants Transmission Study) team (left to right): Magalie Joseph, RN, Dr. Sheldon Landesman, Ava Dennie, RN, Anna O'Neal, Gail Joseph.

# HISTORIC FIRSTS IN research

Despite making up almost 30 percent of all HIV/AIDS cases in the United States, women and children are the disease's least recognized faces. In most places, that is. But not at SUNY Downstate Medical Center.

In fact, since the pandemic began in the early 1980s, "our major research accomplishments have come in the area of HIV's impact on women and children," notes HIV Center Director Jack DeHovitz, MD, MPH.

SUNY Downstate's faculty are at the leading edge of research in the risks and causes of perinatal human immunodeficiency virus (HIV) transmission, the natu-

ral history of HIV disease in women, and the impact on children born with the virus. In fact, this research is changing the standard of care in many areas, and with it, the course of the HIV epidemic as a whole.

In some ways, SUNY Downstate's Brooklyn location made this research a natural fit. "Very early in the epidemic," recalls Sheldon Landesman, MD, professor of medicine and assistant dean for clinical education, "we started seeing babies with the disease."

Realizing that those on the front lines needed to understand how this new and rapidly spreading disease

impacted HIV-positive women and their children, Dr. Landesman teamed with Howard Minkoff, MD, distinguished service professor of obstetrics and gynecology, Joan Hittelman, PhD, clinical associate professor of psychiatry and pediatrics, and Hermann Mendez, MD, professor of pediatrics, to design and implement the nation's first study of perinatal HIV transmission, the Maternal and Infant Transmission Study (MITS) that ran from 1985 through 1993.

Contrary to earlier reports, the study showed that only about 25 percent of babies born to HIV-positive mothers developed the disease, and that "prematurity and low birth weight seemed to enhance the risk of infection," says Dr. Landesman. The research also suggested that cesarean section and/or the time between a woman's water breaking and her infant's delivery had significant bearing on whether the child would become HIV positive; the more quickly the child was delivered, the lower the risk.

MITS led to important policy recommendations as well. At the time MITS began, doctors only tested women for HIV who had self-identified risk factors, such as injection drug use or a drug-using partner. But "something like 30 percent of the women in the study had risk factors for acquiring HIV that they didn't identify," Dr. Landesman says. "So, Howard Minkoff and I published a paper saying you shouldn't offer HIV testing to pregnant women based on the HIV risk factors they identify. You should offer it to all pregnant women."

Later studies confirmed that using risk factors alone would fail to identify many HIV-positive pregnant women. The American College of Obstetricians and Gynecologists adopted Drs. Landesman and Minkoff's position; routine HIV screening for all pregnant women is now the standard of care in the United States.

To find answers to the questions raised by their initial research in MITS, the SUNY Downstate team developed and implemented a next-generation study called the Women and Infants Transmission Study (WITS),

which ran from 1989 through 2006. The study examined a number of issues that have had great bearing on the lives of women and infants with HIV, including: how does HIV disease progress in pregnant women? Are there specific factors that increase the risk of perinatal HIV transmission? What course does HIV infection take in infants?

Dr. Minkoff explains, "One of the things that WITS showed is the relationship between viral load [the amount of HIV in the blood] and fetal transmission. A high viral load increases the risk of maternal-infant transmission. But if the viral load is undetectable as a result of medication, there's a very low risk of transmission." Dr. Landesman and other WITS investigators demonstrated that a shortened time between a woman's water breaking and her child's delivery reduced by 50 percent the risk of perinatal HIV transmission. Because elective cesarean section cuts the time between membrane rupture and delivery to zero, the practice of elective cesarean section, too, is now the standard of care.

The result of these and related research: Maternal-infant HIV transmission has been virtually wiped out in the developed world. Says Dr. Landesman, "That's a very real and substantive accomplishment. Antiviral therapy is important, but it's no cure for people with HIV. This stopping of maternal-infant transmission represents a powerful means of HIV prevention." Twenty years ago, that was almost unimaginable.

The Women's Interagency HIV Study, based at SUNY Downstate Medical Center and other locations throughout the country, is one of the world's most comprehensive studies of HIV disease. "This study tries to look at the effect of the disease on all aspects of women's health," says renowned HIV researcher and co-principal investigator Howard Minkoff. The study examines not only the immune functioning of the women enrolled, but their cardiovascular health, their cognitive abilities, and their gynecological problems.

Since 1993, when the study began, Dr. Minkoff and his staff at SUNY Downstate have explored these ques-





Howard Minkoff, MD

tions, finding differences in the ways women and men metabolize some HIV treatments, and documenting HIV's effects on areas such as gynecological health, where HIV increases rates of cervical dysplasia, precancerous growths in the cervix.

"Now the women in our study are getting older," Dr. Minkoff says, "so in a way, our next funding cycle is really about HIV and aging." Many of the women in the observational study are undergoing perimenopause, which triggers hormonal changes that may have an effect on the virus. Many have been HIV-positive for more than a decade, and have taken potent medications for long periods of time. "There may be long-term toxicities associated with chronic exposure to these medications," Dr. Minkoff explains.

Conclusions drawn from the study alerted medical professionals to the special health issues women with HIV face. But Dr. Minkoff is equally proud of the policy changes the study prompted. "I remember being at a meeting where one of the Army's chief physicians said to

me, "Thanks for your article," Dr. Minkoff recalls. Before the article came out, the U.S. Army wouldn't allow pregnant women enrolled in its health services access to anti-retroviral therapies. Says Dr. Minkoff, "It's nice to know that a single article based on our research and the ethical issues it raised can make such a difference in the lives of women with HIV."

"Early on in the epidemic," says Joan Hittelman, PhD, clinical associate professor of psychiatry and pediatrics, "we realized that in children there was a serious neurodevelopmental component of HIV infection. "The children we saw then were spastic. It was terrible to watch them lose their motor abilities and slip backwards on cognitive milestones. And then, of course, many of them died."

It was a bleak situation that many turned away from. But not Dr. Hittelman, who, as director of Downstate's Infant Behavior Laboratory, had created Downstate's Infant and Child Learning Center early in the epidemic expressly to address developmental delay

and regression in HIV-positive infants and children. Understanding how important it was to track and treat HIV in young children, she and pediatrics professor Hermann Mendez, MD, pioneered studies into the disease's impact on that age group. "Before the medications were developed, HIV was devastating to these children's brains," Dr. Hittelman recalls. "Their muscles would become tight. They couldn't move. And they lost the ability to speak."

Many children born to HIV-positive mothers were also drug-exposed. The Maternal and Infant Transmission Study (MITS) and the Women and Infants Transmission Study (WITS) separated out the effects of prenatal drug exposure from those of HIV. "The drug-exposed infants," Dr. Hittelman says, "manifested some neurological insult, but it was mild compared to that of HIV. And often they outgrew its effects. The HIV-positive infants looked perfectly normal at birth, but they became progressively worse. It was terrible to watch."

As the AIDS epidemic advanced, Dr. Hittelman's studies focused on the impact that HIV and HIV medications had on children's development. Surprisingly,

many children who were HIV-positive and undergoing treatment progressed as well as their uninfected peers, Dr. Hittelman and her colleagues found. Only those with what are called AIDS-defining illnesses (illnesses the Centers for Disease Control and Prevention uses to validate an AIDS diagnosis) experienced developmental problems. "That's when the virus goes to the brain and we start seeing developmental delays," Dr. Hittelman says. Such delays were also linked with increased mortality, she and her colleagues found.

Today, with the exception of a study looking into the long-term consequences that perinatal antiretroviral therapy may have on children born to HIV-positive women, there's little research going on at SUNY Downstate into HIV's impacts on children. That's because, thanks in large part to the earlier research conducted by SUNY Downstate faculty, almost no cases of perinatal HIV transmission exist any more in Brooklyn, or, for that matter, in the developed world.

"It's a completely different experience now," Dr. Hittelman says. "It's a success story." SUNY Downstate's HIV researchers can be proud of the role they played in making this success story happen. ■

“*Almost no cases of perinatal HIV transmission exist any more in Brooklyn, or, for that matter, in the developed world.*”

IAVI Immunobiology group  
examining HIV vaccine  
antibody data.

Picture from left to right:  
Aaron Wilson,  
senior research associate;  
Jacqueline Miller, research associate;  
Adrian McDermott, PhD,  
principal scientist;  
Brenna Kelly, research associate.



# INTERNATIONAL AIDS VACCINE INITIATIVE *ia vi*

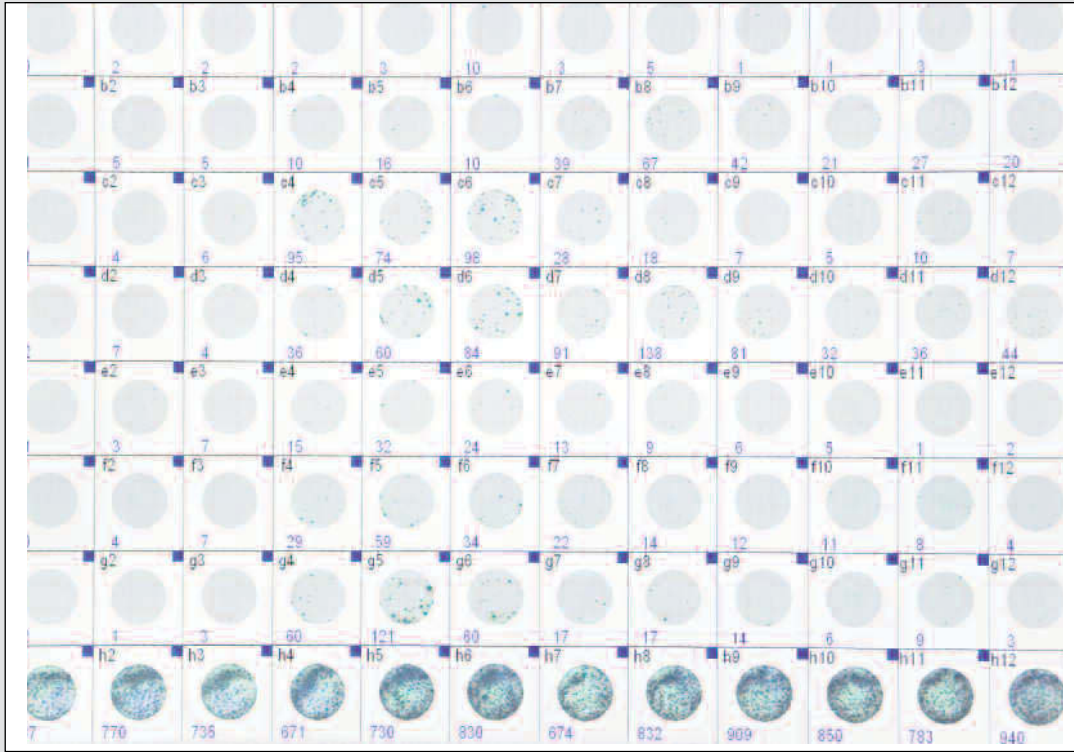
If ever there was a disease in need of a vaccine, it's AIDS. The illness, caused by the human immunodeficiency virus (HIV), has killed more than 25 million people worldwide since 1981; almost 3 million died in 2006 alone. Globally, an estimated 40 million people are living with HIV infection.

Other viruses – polio, smallpox, hepatitis A and B – have yielded to vaccines that build immunity to specific viral agents. But HIV remains elusive, due in large part to the nature of the virus. HIV is a retrovirus, and like other retroviruses, it inserts copies of its genetic

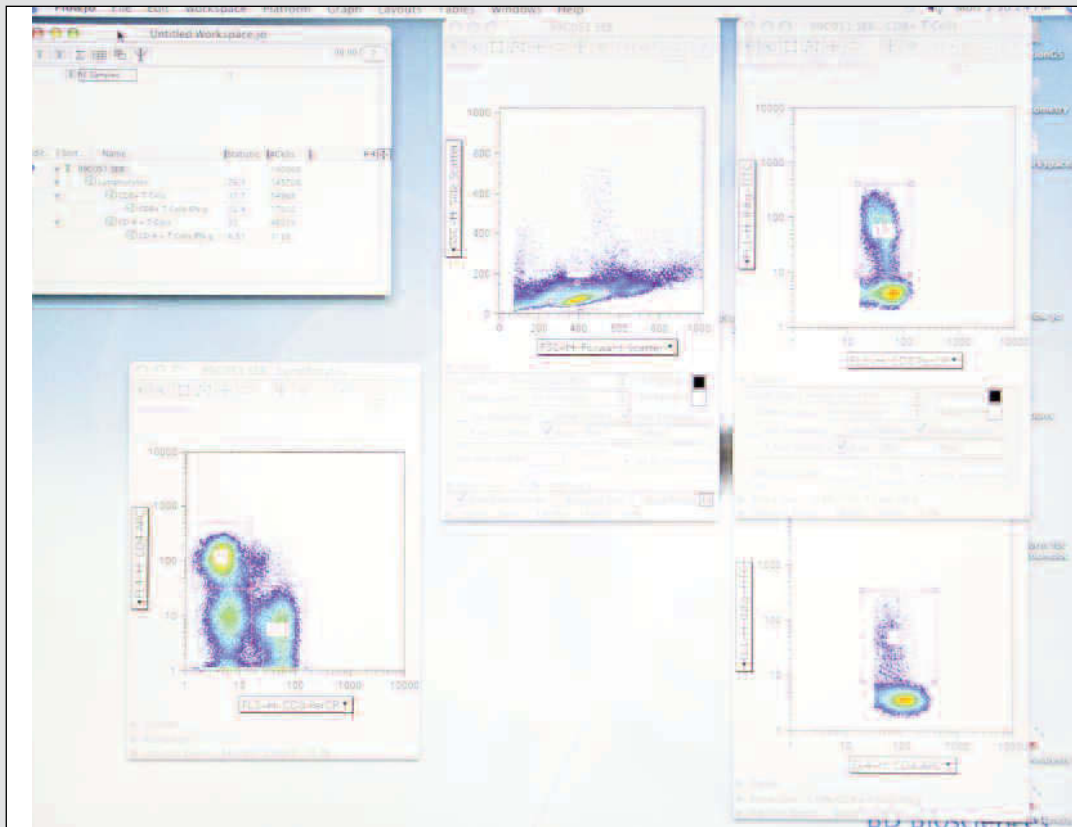
material into cells in a way that makes them less visible to the body's immune system. In addition, HIV mutates rapidly. And, there's no single HIV – various subtypes thrive in different parts of the world.

Nevertheless, scientists believe an AIDS vaccine is not only possible, but necessary. A vaccine is the best way, they believe, to eradicate a disease that is spreading rapidly in areas with minimal healthcare infrastructure, such as Sub-Saharan Africa, India, and the former Soviet Union.

“Even though there are a lot of challenges,” says Adrian McDermott, MSc, PhD, an assistant professor of



Preclinical assessment of a prototype vaccine using a screening technique called IFN $\gamma$  ELISPOT. Data in each square represents the immune responses of vaccinated test subjects and aids in the evaluation of potential vaccine candidates. The number of spots correlates to the ability of the subject's immune cells to recognize HIV vaccine proteins.



Preclinical assessment of a prototype vaccine using a technique known as 4-color flow cytometry. The panels displayed represent the analysis of data generated by a flow cytometer, which uses lasers to accurately count immune cells from vaccine recipients that have been tagged with a number of fluorescently labeled antibodies. This information enables researchers to determine the quality of the immune response generated in test subjects and ultimately the potential success of a particular vaccine.



## About IAVI

The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 24 countries, IAVI and its network of collaborators research and develop vaccine candidates, conduct policy analyses, and serve as advocates for the field. In its first 10 years, IAVI translated innovative technologies into six vaccine candidates that entered human trials in 11 countries in Asia, Africa, Europe, and North America; established major new clinical trial capacity in Africa and Asia; and mobilized more than \$500,000 in new funding for AIDS vaccine research and development.

IAVI recently received \$12 million from the City of New York and signed a Memorandum of Understanding with SUNY Downstate to develop a world-class research and development facility at the Brooklyn Army Terminal. IAVI's AIDS Vaccine Development Lab will be the anchor bioscience tenant for a 486,000-square-foot biotechnology center called "BioBAT," a collaboration between the New York City Economic Development Corporation and SUNY Downstate through the SUNY Research Foundation. IAVI's new lab will significantly expand AIDS vaccine research and development efforts in New York City.

IAVI's Jacqueline Miller and Teddy Warria working in biosafety cabinets. The cabinets protect Ms. Miller and Mr. Warria from potentially dangerous pathogens present in the samples processed from preclinical vaccine studies.

pediatrics at SUNY Downstate Medical Center and the principal scientist for immunobiology for the International AIDS Vaccine Initiative (IAVI), a non-governmental, public/private partnership, “we believe this is the way to go.”

IAVI has the only applied research and development lab dedicated solely to AIDS vaccine development. Scientists at IAVI are aggressively working to produce the next generation of novel and improved vaccine candidates and to rapidly translate these advances into new vaccines for human testing. Developing safe, effective, and accessible HIV vaccines is not just IAVI’s mission; it is Dr. McDermott’s calling in life.

In pursuit of that calling, Dr. McDermott leads IAVI’s Preclinical Core Immunobiology Lab, which evaluates the efficacy of emerging vaccine candidates. He also heads up IAVI’s Live Attenuated Consortium (LAC), which is researching so-called immune correlates – biological indicators of immunity to HIV.

Immunity to HIV? Is such a thing possible?

There are individuals who, though repeatedly exposed to the virus, remain uninfected. Similarly, a group termed “elite non-progressors” tests positive for the virus but never develops immune deficiencies.

One group of non-progressors, an Australian cohort identified in the 1990s, is missing a type of HIV gene called *nef*. To investigate this phenomenon, scientists developed a mutant simian immunodeficiency virus (SIV) that is also missing the *nef* gene. After ini-

tial exposure to this mutant virus, the SIV delta *nef* vaccine elicits a protective response in 95 percent of the animals tested.

At present, the mechanism that offers this protection is unknown. “Something’s protecting them, though,” Dr. McDermott says, “so we’re trying to find out what that is.” Toward that end, Dr. McDermott is examining these animals’ immune responses and their genetics.

Dr. McDermott’s research hasn’t stopped there. His lab has helped standardize assays – scientific tests – that researchers in the LAC Consortium use to judge “different experiments in the context of the same assays,” he says. “It’s about standardization across many different investigators.”

Finally, he and his colleagues work closely with IAVI’s Vector Design group that researches biological agents, such as benign viruses that might deliver an HIV vaccine to the area of the immune system that can best use it to provide immunity. One possible vector is the reovirus that would carry the vaccine to the gut, to which HIV migrates soon after entering the body. “Once the individual becomes infected,” says Dr. McDermott, “you would have immunity in the spot where the depletion of [immune] cells takes place.”

“So the immune correlates and the vectors program are very closely linked,” Dr. McDermott explains.

With 4 million people annually infected with HIV, Dr. McDermott feels these programs can’t come to fruition soon enough. ■

**Families, Adolescents, and Children's**

**Experiences at SUNY staff (left to right):**

Ericka Woods, PhD; Dr. Birnbaum;

Theresa Gayle, RN; Hermann Mendez, MD;

Tom Panzella, PA; Kate Grossman,  
fourth year medical student.



# community SERVICE and OUTREACH

the HEAT, ICLC, and FACES programs

When you look at all the HIV statistics, 50 percent of all the newly infected cases are in people below the age of 25,” says Jeffrey Birnbaum, MD, MPH, assistant professor in the Department of Preventive Medicine and Community Health at SUNY Downstate Medical Center. “To meet their special needs, Health & Education Alternatives for Teens – HEAT – is there.”

HEAT provides HIV-positive and high-risk youth with medical and mental health services, case management, support groups, and outreach and education. Its staff of 12 offers a variety of support groups for teenagers and off-site HIV counseling and testing, in addition to other services. “We also constitute a network of other adolescent service providers who are con-

cerned about HIV prevention,” Dr. Birnbaum says. Among the HEAT staff, he notes, are two young people who “do direct street outreach and speak to other youth at schools and youth programs.”

Funded by the New York State AIDS Institute and the federal Ryan White Program, HEAT is unique in Brooklyn. It is the only program in the borough specifically designed to meet the medical, mental health, and social service needs of HIV-positive and high-risk youth. But a program that offers world-class medical expertise to a community in need is hardly unique at SUNY Downstate.

Among SUNY Downstate’s HIV-related projects that directly benefit the community are the Infant and Child Learning Center, once New York State’s only pre-school and early intervention program providing services to HIV-positive children. And, the FACES clinic (Families, Adolescents and Children’s Experiences at SUNY) offers tailored services to HIV-positive children, parents, and their families.

HEAT’s emphasis on specialized services for HIV-positive teens is unusual. “There are a lot of people in the pediatric AIDS world and in the adult field, too, who think they can just squeeze teenagers into their programs,” Dr. Birnbaum says. “But unless you’re set up to work with teens, you’re not going to be that successful.”

Adolescents have special needs related to the developmental stages of the teenage years, Dr. Birnbaum says. It’s those needs, and the lifestyle issues they create, that HEAT was designed to meet. “Ostracized gay youth. Ostracized transgender youth. Teenage moms,” Dr. Birnbaum says. “They each come with different sets of issues. We’re equipped to deal with those issues in ways that pediatric providers or adult providers probably are not.”

In the 1980s, Joan Hittelman, PhD, clinical associate professor of psychiatry and pediatrics, had a problem. The HIV-positive children she saw in her clinic had nowhere to receive the early-intervention services



Dr. Jeffrey M. Birnbaum.

they desperately needed to ameliorate their HIV-related developmental delays and obstacles. In her capacity as director of Downstate’s Infant Behavior Laboratory, Dr. Hittelman worked with early-intervention providers. But with the inception of the AIDS epidemic, “Nobody wanted to accept a referral from us,” she says. “With the intense AIDS phobia at that time, all the early intervention providers could think was that they were going to get an HIV baby.”

So Dr. Hittelman started her own program: the Infant and Child Learning Center (ICLC).

Begun in 1987, the ICLC was, says Dr. Hittelman, “a special education pre-school,” then serving 24 HIV-positive children. In those days, when treatments were few and most children with HIV died before finishing





Dr. Joan Hittelman, Director, Infant and Child Learning Center.

elementary school, “we taught sign language so the kids would be able to communicate with us after they lost their ability to speak,” Dr. Hittelman recalls. “And we spent a lot of time talking with them about death and dying.” The Infant and Child Learning Center offered special education, physical, occupational and speech therapies, counseling, and nursing services. “We tried to get the children back to normal, or at least to become their best-functioning selves,” Dr. Hittelman says.

Within a couple of years of its founding, the ICLC began serving children and premature infants with other medical problems. The ICLC also provided a program for school-aged children who had been temporarily forced out of the public school system because of their HIV status.

By the mid-1990s, as a result of scientific breakthroughs that helped prevent perinatal HIV transmission, relatively few HIV-positive babies were being born in Brooklyn. The stigma around HIV began to abate and antiretroviral therapy started to improve the well-being and extend the lives of HIV-positive children. So the program expanded its mission to include an early intervention and preschool program for medically involved children with developmental delays, with a special emphasis on premature infants. The program has grown to a point where it is building its own facility.

“We now serve over 500 families in their homes and another 100 in our center,” Dr. Hittelman explains. “And I’m very happy to say that only a few of those kids have HIV.”

Hermann Mendez, MD, was a resident in pediatrics when babies with an unknown immune deficiency started being born at SUNY Downstate in the early 1980s. “I think we had one in 1981, and one in 1982,” says Dr. Mendez, now a professor of pediatrics at SUNY Downstate. Soon the problem snowballed. By the end of 1984, he says, “we had 70 or 80 cases in children.”

As part of SUNY Downstate’s pioneering work in HIV, Dr. Mendez collaborated with SUNY Downstate

faculty, including Sheldon Landesman, MD, Howard Minkoff, MD, and Joan Hittelman, PhD, to establish the FACES (Families, Adolescents and Children's Experiences at SUNY) clinic for HIV-positive children and their families. "The clinic's mission was then, as it is now," Dr. Mendez says, "to provide the best possible care to HIV-infected children, adolescents, and their families, and to conduct clinical research to advance that care."

Toward those ends, the FACES clinic offers medical and mental health services, case management, and nutritional advice; it runs clinical and observational trials that detail the impact on children of HIV exposure, infection, and medication. Because antiretroviral drugs can be difficult and complicated to take, "We also have a mental health worker who deals with medication compliance," Dr. Mendez explains.

The FACES clinic involves the community it serves in all aspects of its work. "We have the largest community advisory board in the country," Dr. Mendez proudly states. The group numbers more than 60.

One of the staff's most important jobs is to work with HIV-positive pregnant women. "Many of these women don't have an indication for treatment," Dr. Mendez says, explaining that their HIV-infection has not progressed to a point where they need medication. "When they get pregnant, we put them on antiretrovirals. They have planned cesarean sections, which, we've learned, significantly reduce the risk of perinatal HIV transmission. And these women are having babies who are healthy." The FACES clinic follows these infants and offers them medical services as well.

The FACES staff also provides care to long-term survivors of HIV, young people who, years ago, were perinatally infected. "But we're losing our business," Dr. Mendez says with a smile. "The rate of HIV infection among children has declined at an amazing rate. In a few years, I'm looking forward to closing up shop.■"

*"We're losing our business... the rate of HIV infection among children has declined at an amazing rate."*



Mary Ann Banerji

# clinical advances

In the mid-1990s, Mary Ann Banerji, MD, professor of medicine, helped pioneer a novel approach to the treatment of patients with newly diagnosed type 2 diabetes – the kind that occurs when the body is unable to use the insulin it produces, or to meet the increased demand for insulin that can result from obesity.

Instead of prescribing what was then the standard treatment – drugs such as metformin and sulfonylureas – Dr. Banerji, with colleagues Samy McFarlane, MD, MPH [see page 48], Rochelle Chaiken, MD, and Harold Lebovitz, MD, offered patients a short course of injectible insulin.

The result? Amazing. “About 40 percent of our patients had their blood sugar return to normal,” recalls Dr. Banerji. “They were able to stop taking insulin. In fact, they didn’t need any diabetes medications at all.”

By contrast, none of the patients who received standard care had their blood sugar return to normal. And only one third were able to meet “target” blood sugar levels. Moreover, Dr. Banerji’s insulin treatment put patients with type 2 diabetes into remission for an average of three years. “Normalizing blood sugar levels allowed the pancreas’ insulin-producing beta cells to recover and start producing insulin again,” she explains.

Dr. Banerji and her team have been on the forefront of other medical breakthroughs. In 1994, they identified a previously unreported form of diabetes in people of African descent. Termed “Flatbush diabetes” after

SUNY Downstate’s Brooklyn neighborhood, the illness has an unusual presentation. It primarily affects adults and presents with ketoacidosis, a state of insulin deficiency characterized by high levels of acids and sugar in the blood.

Since ketoacidosis was involved, clinicians believed that patients “needed to be treated with insulin forever,” Dr. Banerji recalls. Her research helped prove “this type of diabetes usually needs insulin only for a short while and then can be treated with pills for years thereafter.”

As director of the SUNY Downstate Endocrinology Clinic and Diabetes Center, Dr. Banerji is an advocate of research into scientific questions that have a direct impact on clinical care. She uses her clinical experience to pose basic research questions that advance care for the growing population of people with diabetes.

To understand the causes of diabetes, Dr. Banerji studies the connection between diabetes and fat storage in the body. “People’s bodies store fat in different places,” she explains. Fat can be stored in the abdominal cavity, or in the liver; it can be marbled in muscle. Storing fat on the hips, being “pear-shaped,” appears to have little bearing on the development of diabetes, Dr. Banerji says. But “from our early work using CT (computed tomography) scans, we’ve learned that storing fat in the abdomen or the viscera is a central component of type 2 diabetes.”

Dr. Banerji and her colleagues also demonstrated that South Asians who have the same body-mass index as whites – body mass index is a ratio of weight to height – often have more fat and less lean muscle mass, leading to higher rates of diabetes and cardiovascular disease.

Dr. Banerji and her team of nurse practitioners and diabetes educators are participating in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the National Institutes of Health’s largest clinical trial involving people with type 2 diabetes. The trial is designed to determine whether cardiovascular events (heart attack, stroke, or cardiovascular death) can be prevented in individuals with type 2 diabetes through intensive control of blood sugar, blood pressure, and lipid levels.

The medical realities of diabetes aren’t Dr. Banerji’s only concern. She believes lifestyle interventions can address many of the underlying causes. “The diabetes epidemic will require public health measures and lifestyle changes to combat our current state of excessive food intake and physical inactivity,” Dr. Banerji observes.

With funding from the Centers for Disease Control and the State of New York, Dr. Banerji is investigating novel approaches to treatment and prevention. “Our mission,” she says, “is to educate people – both those at risk and those with diabetes – out in the community.”

Toward this end, she works with Downstate’s Center for Health Promotion and Wellness and the non-profit Brooklyn Diabetes Task Force, a coalition of hospitals and healthcare organizations, on educating people at health fairs and houses of worship. The Task Force also sponsors an annual diabetes fitness walk.

Dr. Banerji chooses to see diabetes in a broad context, hoping to understand both its physical and its social causes. “To me, that’s critical,” she says. “You have to understand diabetes’ various presentations and its social context in order to know where to focus research efforts.” ■

*“Dr. Banerji is an advocate of research into scientific questions that have a direct impact on clinical care.”*

# controlling diabetes through lifestyle changes

Samy McFarlane



**Can diabetes be prevented? Or, what about the heart attacks and strokes that prematurely take the lives of about 65 percent of all diabetics? Samy McFarlane, MD, MPH, wants to know.**

His questions aren't merely academic, but fundamental to overall health, not only for individuals but also for the nation as a whole. Right now, more than 21 million Americans – a full 7 percent of the population – have the disease. Another 41 million between the ages of 40 and 74 are at risk. Public health experts anticipate those numbers will double by 2030, with an attendant increase in personal, social, and financial costs.

“This is quite serious,” says Dr. McFarlane, professor of medicine and chief of SUNY Downstate’s Division of Endocrinology, Diabetes and Hypertension, and editor-in-chief of *Therapy*, published by Future Medicine Inc. “The epidemic is claiming the lives of myriads of people and leaving others blind and amputated. I hope my research will help do something about this.”

Ninety five percent of people with diabetes in the United States suffer from type 2 diabetes. The illness, formerly known as adult-onset diabetes, is highly preventable, related, in large part, to obesity and inactivity.

“If I have a patient who’s at risk,” Dr. McFarlane says, “my first recommendation will be diet and exercise.”

But such lifestyle interventions are notoriously difficult to maintain. Even highly motivated patients have trouble keeping weight off and exercising on a regular basis. Moreover, the risk of diabetes increases with age, with the dying off of the pancreas’ insulin-secreting beta cells [see page 50]; many older adults aren’t able to exercise with the intensity necessary to prevent diabetes. “Because of that,” Dr. McFarlane says, “we want to investigate other ways to prevent not just the disease but the complications arising from it, such as strokes and heart attacks.”

Dr. McFarlane is doing just that, spearheading SUNY Downstate’s participation in several large-scale, multi-site international clinical trials to test drugs that might prevent diabetes-related complications in people at high risk. Among these is the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial, which is looking at whether giving the drug glargine, a long-acting insulin, early in the course of diabetes will help prevent heart attacks and strokes.

He is also looking at the relationship of diabetes to metabolic syndrome (characterized by a collection of symptoms that include obesity, impaired glucose tolerance, hypertension, elevated triglycerides, and low HDL) and their interplay with cardiovascular disease. “Diabetes is considered a cardiovascular disease equivalent,” he notes, “so the effects of treatment on both illnesses can not be overlooked.” For example, recent studies have shown that diuretics and beta blockers, which are used to treat cardiac disease, decrease glycemic control and increase the risk of developing diabetes. Because of this, “the risk profile for both diseases has to be evaluated in totality,” Dr. McFarlane cautions.

Dr. McFarlane has been extremely successful in attracting and enrolling large numbers of African-Americans and Caribbean-Americans to take part in his studies, despite a longstanding distrust of clinical trials by many in these communities. On the walls of his office hang certificates of appreciation from several churches that worked with him to recruit trial participants. How did he manage this where other researchers failed?

Dr. McFarlane sees clinical trials as a service to the surrounding community, which has a high prevalence of diabetes, hypertension, hypercholesterolemia and other chronic illnesses at disproportionately high rates. “Of the 1,000 supposedly healthy people we screened for one trial, 23 percent had diabetes and didn’t know it,” he says. “A lot of these individuals didn’t have doctors. We enrolled them in our clinic and provided them with care much, much earlier than we would have if they had waited until symptoms were evident.”

“Quality of care and treatment outcomes are closely linked,” continues Dr. McFarlane. “A short or sporadic patient encounter doesn’t provide the time needed to address patient motivation or to have an impact on complex behaviors. Enrolling patients in clinical trials is one way to help address this.”

Dr. McFarlane hopes his research and the advances he pioneered in clinical care will help stem the tide of the diabetes epidemic, a tide that is rising all around him. “One thing that clinical research has taught me,” he says, “is that in dealing with this disease, we can find methods that work.” ■



# xian-cheng JIANG

In the United States alone, almost 700,000 individuals each year die from atherosclerosis and related cardiac problems.

In China, too, atherosclerosis is a major killer, one that felled researcher Xian-Cheng Jiang's father at a young age. "It was very quick," Dr. Jiang, associate professor of anatomy and cell biology, recalls. "This is my motivation to study this problem."

Atherosclerosis results, in large part, from the build-up of lipids—fats and fat-like materials—in the bloodstream and along the artery walls, causing blockages and life-threatening deposits known as plaques.

Dr. Jiang's research into the subject of lipid metabolism, from lipids' beginnings in the digestive system through their elimination, may lead to new drugs that can treat atherosclerosis and may help individuals currently unaided by the popular cholesterol-lowering statin compounds. With great enthusiasm, Dr. Jiang says, "We are trying to find a new drug target."

Many lipids are familiar from discussions in the popular press—HDL and LDL cholesterol (the good kind and the bad kind, respectively), as well as triglycerides, which are simply fats.

But as a biochemist, Dr. Jiang understands that these well-known lipids are not the sole source of the problem. “Some people have normal cholesterol levels, but they still suffer from atherosclerosis,” he explains. “In other words, there is another mechanism; other lipids are involved in the process.”

These other lipids, including sphingomyelin and a phospholipid called phosphatidylcholine, are what Dr. Jiang studies. To get a sense of just how important these lipids are in the development of atherosclerosis, Dr. Jiang and his colleagues compared sphingomyelin levels in 600 chest-pain patients. Those whom doctors determined had stenosis, a plaque-induced narrowing of the arteries, had significantly increased sphingomyelin levels compared to those without stenosis.

“So the real question is, ‘why?’” Dr. Jiang asks. What elements of sphingomyelin metabolism lead to hardening of the arteries?

Using bioengineered mice, Dr. Jiang has studied the five-step process of sphingomyelin formation. Already, he and his colleagues have identified a drug that, at least in the mouse population, acts on the first part of the process, lowering levels of circulating sphingomyelin. “We found a dramatic decrease due to the inhibition of biosynthesis,” Dr. Jiang says. “Also, we found that atherosclerosis in these mice is dramatically decreased.”

Dr. Jiang says he and his colleagues still have much work to do in understanding sphingomyelin metabolism. Could an intervention closer to the end of the five-step process offer better results? This is, after all, a complex research area.

As are the other areas Dr. Jiang is exploring: molecular communication between lipids, which researchers call “cross-talk,” and phospholipid metabolism. “We find that in cardiac cases, a protein called plasma phospholipid-transfer protein is increased,” Dr. Jiang notes. He hopes he and his colleagues can develop communication inhibitors that stop the development of life-threatening plaques.

“The immediate goal,” he says, “is drug discovery.”

*When Xian-Cheng Jiang was a medical student in China, he had a mentor: a tutor whose field of study was lipid metabolism.*

*In the United States, Dr. Jiang has taken up that role for the four graduate students and two post-docs in his lab. “Dr. Jiang is so special,” says Tiruneh Hailemariam, who, under Dr. Jiang’s guidance, has focused on the area of sphingomyelin metabolism.*

*While some researchers take more of a hands-off approach with grad students, “Dr. Jiang follows my work every day and supports me,” Mr. Hailemariam says. “Almost every morning we have a brainstorming session and argue about research problems.”*

*Mr. Hailemariam expects to continue to learn from Dr. Jiang even after his graduate studies are over. “He’ll definitely continue to be a mentor once I’m done here,” he says. “He gives a lot of support. He is a very approachable person.”*





# todd SACKTOR

Why do we remember? What causes things to stick in the brain, or, conversely, to fall away from consciousness?

These are questions that have always fascinated neurologist Todd Sacktor, MD, professor of physiology and pharmacology. As a boy, he read everything he could about neuroscience and even tried, with limited success, to perform a memory experiment on his 3-year-old brother.

Dr. Sacktor has used this life-long fascination to become an international leader in the field of memory research. His most important discovery—that a single enzyme called protein kinase M zeta (PKM zeta) is the molecule that fixes memory in the brain—may have wide-ranging implications. Dr. Sacktor's efforts to understand memory may change the way we think about the complex subject and revolutionize many of the ways medical science treats its disorders.

“What is it in the brain that is storing information?” That is a question that Dr. Sacktor has pursued for more than two decades. Most of Dr. Sacktor's initial work has been on a process called long-term potentiation—the mechanism by which connections between brain cells are strengthened, and which is widely considered the physiological basis of memory.

“Each brain cell is hardwired, probably through evolution, to be connected to certain other brain cells,” Dr. Sacktor explains. This is why the brain has a propensity to store visual information, for instance, in the back of the brain. Or to store decision-making information in the front.

The more individual connections are reinforced, the stronger they become, and the more intensely they are remembered. The question of memory, Dr. Sacktor explains, really boils down to: “What is the basis for the permanent enhancement of these connections? What is the molecule that causes it?”

In 1993, Dr. Sacktor found what many neuroscientists now believe to be the answer to that question: an enzyme called PKM zeta. “Its unique structure allows the enzyme to be persistently active, thus sustaining increases in the strength of the synaptic connections between neurons, and causing long-term increases in the response to the same stimuli.”

Dr. Sacktor’s discovery will likely have wide-ranging implications, particularly in the area of Alzheimer’s disease. The degenerative brain disorder afflicts 4.5 million Americans, at great personal and financial cost—\$100 billion annually in the United States alone. Working with SUNY Downstate’s chairman of pathology, neuropathologist Suzanne Mirra, they found PKM zeta in the neurofibrillary tangles that are the hallmark of Alzheimer’s disease.

Says Dr. Sacktor, “We asked a very simple question: ‘Is this molecule screwed up in the brains of Alzheimer’s disease patients?’ And the answer is, it is.”

The mechanism for memory loss in Alzheimer’s disease may be the binding of PKM zeta to the neurofibrillary tangle, he explains. Blocking that binding process through new drug treatments or other interventions may help stop memory loss in those with early symptoms of Alzheimer’s. “This would be an entirely new way to approach the problem,” Dr. Sacktor says.

The neuroscientist’s work with PKM zeta may also be instrumental in developing new treatments for the shattering chronic pain syndrome known as reflex sympathetic dystrophy (RSD). In RSD, researchers believe, the nervous system constantly re-experiences—replays—the pain first felt during a simple trauma, such as a fall, a bone break, or minor surgery.

Using information about how PKM zeta works, one could potentially “flip all those pain pathways from being supersensitized to being normal,” Dr. Sacktor says.

Dr. Sacktor likens his work to the field of computer science. “What we are studying is the hard disk,” he says.

“We are trying to figure out how the zeros and ones are stored—the physical substrate of memory. Once you understand that,” he says about his field of neuroscience, “a great many other emergent properties of the brain will follow.”



*Dr. John Chapin with Lei Li, his PhD student; Shaohua Xu, MD, PhD, a post-doc fellow; and technician David Rodriguez.*

# john CHAPIN

**T**o John Chapin, PhD, professor of physiology and pharmacology, the brain is the most important thing. It is what makes us what we are, but how does it work? Though the brain has been considered as a kind of computer, it is much more powerful because it is *intelligent*. It can instantly recognize subtle expressions in a human face, coordinate the fine movements of a gymnast, and even appreciate art. Why are brains so much smarter? If we could answer that question, we could make better robots, cure neurological diseases, and understand our own behavior.

In the 1980s, many scientists thought that information in the brain was stored in single neurons, just as bits of information in a computer are stored in tiny transistors. Dr. Chapin, however, proposed that information in the brain is not stored in single nerve cells, but instead is distributed across millions of them.

To prove this idea, he developed a method for implanting arrays of electrodes in the brains of rats, allowing him to record the signals from each of a large number of nerve cells simultaneously. This completely changed the way neurophysiologists did their experiments. Previously they would record information from one neuron at a time and then average across many trials. Now they could record from so many neurons simultaneously that they could extract clear and accurate information from the brain in real time.

This approach has proved to be useful not just for understanding how information is processed in distributed brain networks, but also for helping people with paralyzing brain diseases such as spinal cord injury and Lou Gherig's disease (ALS).

In 1999, Dr. Chapin and his colleagues were the first to use this multi-neuron recording method to extract "motor commands" from the brains of experimental animals, allowing them to directly control the movement of a robot arm, "by thought alone!" as reported by the BBC. This demonstration has since spawned the new science of "brain-machine interfaces (BMIs)" and with it, a whole new area of biomedical technology. Scientists and corporations around the world are now working on various methods to use brain interfaces to restore motor function in paralysis victims.

Meanwhile, Dr. Chapin's lab is going to the next level by developing another brain interface that will restore the sense of touch to patients with spinal cord injuries who have lost both motor and touch-sensory function. This involves using electrodes to stimulate regions in the brain involved in perceiving touch and arm position. Recent experiments suggest that such stimuli do indeed produce perceptions of touch or arm movement. When this "somatosensory prosthesis" is fully developed it will be combined with a motor prosthesis (BMI), and patients with spinal cord injuries may be able to use their brains not only to directly control a robot arm (or their real arm) to reach and grasp a cup of water, but also to "feel" that cup.

In the process of developing this sensory prosthesis, Dr. Chapin stumbled on another innovation that could have profound implications in law enforcement and national security.

While studying whether rats can "feel" as if their whiskers are being touched when an electrode stimulates their cortical whisker area, Dr. Chapin found that such stimuli can not only be felt, but can be used to train the rat to go left, right, or straight—just as a rat would turn to the right if his right whisker were touched. When Dr. Chapin and colleagues put a wireless brain stimulator and video camera on a rat's back, they found that the rat could be remotely guided through virtually any indoor or outdoor space that a rat can enter. Finally, they trained the rats to use their highly acute sense of smell to detect explosives.

As a result, a project originally intended to benefit paralysis victims has now yielded a novel technology that can be used to help find victims buried in rubble caused by a natural disaster or terrorist attack.

# MIRIAM feuerman



*Dr. Miriam Feerman with two of her MD/PhD students: James Park and Eric Anderson. Both have already received their PhD degree and will graduate from medical school in May 2006.*

“I’VE ALWAYS  
BEEN INTERESTED  
IN CANCER.”

**S**o says molecular biologist Miriam Feerman, PhD, associate professor of biochemistry, an internationally recognized researcher in the field of liver regeneration.

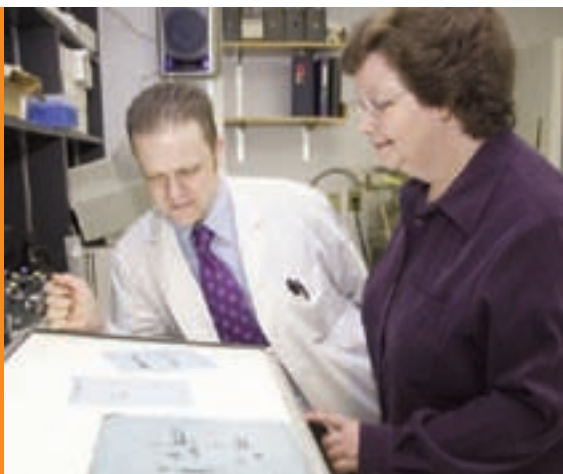
For years, Dr. Feerman has been involved in painstaking research into the basic science of liver growth and the cancer-causing disruptions that occasionally mark the liver’s growth pattern. Now, in collaboration with clinicians at Downstate’s University Hospital of Brooklyn, she’s taking her knowledge “from the bench to the bedside,” in an effort to understand why individuals on methadone maintenance who are infected with the hepatitis C virus (HCV) appear to have lower liver-cancer rates than those who don’t take methadone.

The potentially protective effect of methadone is a curious finding that, on its face, might not seem particularly earth-shattering. But only to people without a clear understanding of liver cancer and of one of its primary causes, HCV. In the United States alone, liver cancer causes 3 percent of the total number of cancer deaths among men. Anywhere from 2.7 million to 5 million Americans suffer from chronic HCV infection. Of those, between 1 and 5 percent will die of HCV-induced hepatocellular carcinoma. Worldwide, as many as 200 million people—a staggering 3.3 percent of the world’s population—have contracted the disease.

Understanding and locating the cause of methadone’s potentially preventative effects could lead to life-saving treatments. “The potential for this research is big,” Dr. Feuerman says, with some understatement. “We just have to get on it.”

The liver is the ideal organ to study for someone who has always been interested in cancer, Dr. Feuerman says. That is because the liver is unique in its ability to replicate itself—to regrow—after trauma, surgery, or exposure to toxins. Imagine a section of kidney or intestine removed during surgery. The wound heals, but the part removed will forever be missing. The liver, on the other hand, can reproduce itself almost entirely.

“What attracted me to using the liver as a model for cancer was that you could think of regeneration as a normal growth process and cancer as a growth process gone a little bit berserk,” Dr. Feuerman explains. Finding what is different in the two processes might help explain liver cancer and perhaps other cancers as well.

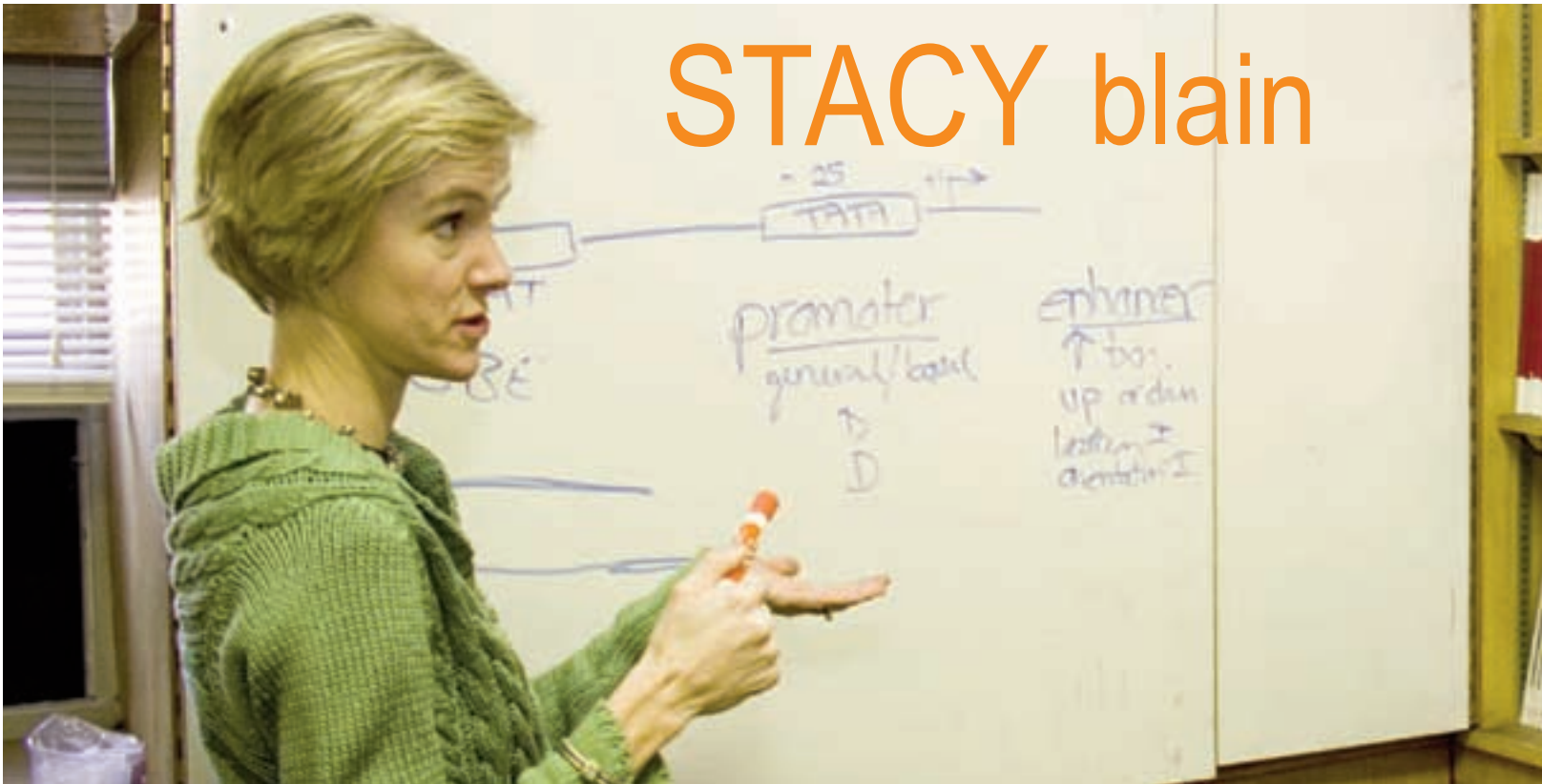


“THE POTENTIAL FOR  
THIS RESEARCH IS BIG.  
WE JUST HAVE TO GET  
ON IT.”

In her lab, Dr. Feuerman has endeavored to do just that. With collaborators, she identified a heretofore unknown gene called MCM8, which is implicated in the complicated mechanism of tumor growth. Now, instead of looking at the liver and the way its genetic material creates building blocks for both normal and deranged cells, Dr. Feuerman and her Downstate colleagues, Drs. Nora Bergasa and Cherif El Younis, will take a new tack. Rather than looking at the liver itself, they will explore the protective effects of an external substance, methadone.

In this exploration, there are once again complicated questions of molecular biology in play, some of which Dr. Feuerman translates into more understandable English: “How is it that exposure to methadone influences the development of liver cells and the cell division property of those liver cells?” she asks.

The answers could save millions of lives.



# STACY blain

The protein molecules cancer researcher Stacy Blain, PhD, assistant professor of pediatrics and anatomy and cell biology, is interested in share an unusual quality: both function sometimes as tumor suppressors and other times as tumor activators.

“That wasn’t my original reason for studying them,” Dr. Blain says. “I’m interested in these proteins because they are multifaceted, as cancer is.” Indeed, with the goal of helping better diagnose and treat breast cancer and other malignancies, the molecular biologist has focused on two "Janus-like" compounds (Janus was a Greek god who had two faces)—one a gene called p27 and another a protein called TGF-beta—both of which may be implicated in the vast majority of human cancers. For instance, p27, found always in normal cells, appears to be missing in 60 percent of all carcinomas. TGF-beta, which is involved in several biological processes, such as involution (tissue repair and immune modulation), can arrest tumor growth or promote it.

“These molecules are master regulators,” Dr. Blain notes. “That makes them more interesting from a scientific point of view and potentially more rewarding from a clinical perspective.”

In order for cancer cells to develop and replicate, they need to pass through a series of regulatory checkpoints and roadblocks, one of which is p27. When working properly, it halts a cancer cell’s progress. But when something is awry, p27 waves the potentially malignant cell through to the next checkpoint.





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as cancer is.

*Dr. Stacy Blain  
with technician  
Dina Leznova and  
PhD student  
Sarah Nataraj.*

Often “checkpoint” problems come in the form of genetic mutations, Dr. Blain observes. Indeed, genetic mutations cause most tumor-suppressor problems. But something odd happens when p27 malfunctions. “Very rarely do you find mutations in p27 at the genetic level,” she explains. “Usually, it’s made properly but it’s degraded. Or it’s put into the wrong compartment of the cell—it’s present in the cytoplasm when it should be in the nucleus.”

That malfunction serves not only to promote cancer, but also, interestingly, to identify its most aggressive forms. “In breast cancer,” Dr. Blain continues, “the loss of p27 appears to correlate very closely with poor prognosis.”

Dr. Blain believes p27’s most immediate use is as a prognostic marker for women with breast cancer, especially for the majority, whose cancer has not yet spread to the lymph nodes. “In 30 percent of these women, the cancer recurs within five years,” Dr. Blain notes. But because medical science doesn’t yet know which 30 percent are at greatest risk, many women who don’t need it receive unnecessary and potentially harmful chemotherapy and radiation treatment.

Dr. Blain says, “If we could screen for p27, and you didn’t have any, the clinicians could probably tell you ‘You have a very bad cancer and we need to treat it aggressively.’” Women whose tumor tissue showed high p27 levels might be spared additional therapies. Likewise, the gene might serve as a treatment target itself. “Because it’s not mutated,” Dr. Blain says, “it may be more conducive to therapeutics.”

TGF-beta is another compound with a complex action. “Our body makes and uses it all the time to control almost all cellular processes,” Dr. Blain observes. Functioning normally, TGF-beta not only stops cell division, it also promotes the destruction of cells the body no longer needs. But when malfunctioning, Dr. Blain says, “it causes cancer cells to become mobile and leave the primary tumor,” resulting in metastasis. Dr. Blain recently received a grant from the Susan G. Komen Breast Cancer Foundation to study whether the TGF-beta signaling pathway might be harnessed to treat or even prevent breast cancer metastasis, the cause of more than 333,000 annual breast-cancer deaths worldwide.

“This is a long way away,” Dr. Blain says about the possible fruits of her research. “But you’ve got to think big.”



# CHRISTOPHER roman

Christopher Roman, PhD, assistant professor of microbiology and immunology, wants to understand how your immune system works. Not just how it works, but what can go wrong with it.

“T-cells are the mastermind cells of the immune system. And what we have developed is a line of research that tries to understand how T-cells’ biology is regulated,” says Dr. Roman. “That is, how their involvement in immune response is controlled.”

The immune system is elaborate, almost military in structure, with chains of command and separate battalions organized around specific tasks. “Normally, in the immune system, there are these alarms that are caused by foreign invaders,” Dr. Roman explains. “That gets the T-cells going and the T-cells garner the troops.” Other types of white blood cells, Dr. Roman says, “do the ‘dirty’ work of recognizing the mess, cleaning it up, and eventually clearing it from the body.”

In particular, Dr. Roman is interested in a molecule that T-cells make called CD40 ligand. “What this molecule does is endow other cells with the power to kill or to do something to get rid of infection,” he says.

“YOU’RE NOT JUST ASKING ‘HOW CAN I MAKE THIS PATIENT BETTER?’ BUT, ‘WHAT’S CAUSING THIS DISEASE?’”

*In Dr. Roman's lab, Brendan Smith is finishing the PhD portion of his combined MD/PhD program. "I've been working on the role that two molecules have in regulating B-cell development," he explains.*

*At SUNY Downstate, as at many MD/PhD programs, students do their first two years of medical school first, then their PhD work, followed by the final two years of medical school with its focus on clinical work.*

*Brendan is not sure whether, after finishing the combined degree program, he will choose to be a researcher, a clinician, or both. "I'm going in with an open mind," he says. In an ideal world, "I'd like to do basic science research with some translational component"—research with some element that moves basic science out of the lab and into the doctor's office.*

*Still, even if he decides to become a clinician, entering the MD/PhD program was the right choice for Mr. Smith. "It gets you to think about things you're doing in the clinic on a molecular level," he says. "You're not just asking 'How can I make this patient better?' but, 'What's causing this disease?'"*

Because of the immune system's integral involvement in so much of human health, its dysfunctions can cause severe, often life-threatening diseases—rheumatoid arthritis, lupus, and multiple sclerosis, to name just a few. In the United States alone, an estimated 14 to 22 million people suffer from autoimmune disorders.

"If we learn more about what tells T-cells do to make CD40 ligand, then we can come up with strategies to intervene," he says. "There are lots of illnesses where this might play a role, like Crohn's disease, inflammatory bowel disease, and atherosclerosis. CD40 ligand has even been implicated in Alzheimer's disease."

According to Dr. Roman, immune disorders are often caused by T-cell malfunctions. "Either the T-cells don't send out any instructions, they don't send out the right instructions, or they send out instructions all the time." They identify something that is internal to the body as foreign and fight it constantly.

That is what happens in the case of rheumatoid arthritis and lupus. "CD40 ligand gets made when it is not supposed to be—in the absence of infection—and drives the development of B-cells [another type of infection-fighting white blood cell] that make self-reactive antibodies. These auto-reactive complexes are actually what is dangerous."

Dr. Roman and his collaborators have not limited their investigations to CD40 ligand, however. They are also exploring other aspects of immune functioning: "We are trying to understand where B-cells come from," he says, matter-of-factly. These major players in the immune system share a common ancestor with T-cells, but serve a vastly different function, Dr. Roman explains. "B-cells make special molecules, antibodies, that coat foreign material and allows other killer cells to glom on to microbes and destroy them."

Dr. Roman's research may also lead to new understandings of white-blood-cell cancers—lymphomas and leukemias. "Many of the processes that we study that control lymphocytes-developmental decisions are actually deranged in cancer," he says. "We are studying the normal process to learn how it can get messed up."

For Dr. Roman, whose interest in the functioning of the human body began in childhood, investigating the immune system's minute workings is a source of constant fascination. "I have a natural curiosity about how things work," he says. And there is an even greater reward for his work: "With the information we generate, we can hopefully get new ways to treat immune system diseases."

# MATTHEW pincus



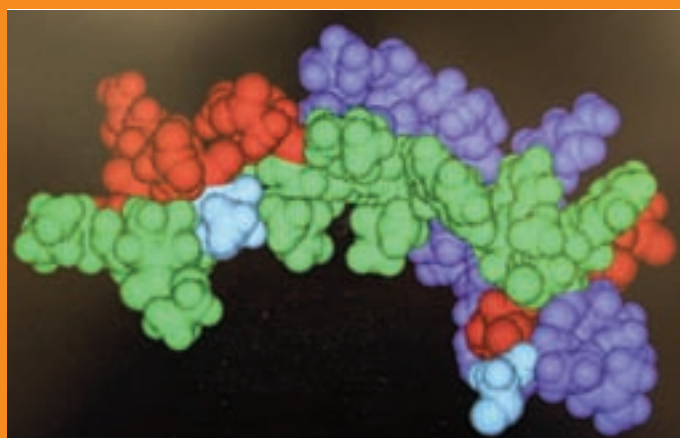
“OUR PRIMARY INTEREST WAS IN ADDRESSING PROBLEMS WITH **RAS-P21**. THIS PROTEIN HAS BEEN IMPLICATED IN ONE OUT OF THREE HUMAN CANCERS.”

**P**athology professor Matthew R. Pincus is curing mice of cancer, using bioengineered peptides, parts of a protein called p53 that control cell division. And not just mice that are a little sick, but mice whose bodies are riddled with human pancreatic tumors.

What is so impressive about the results of Dr. Pincus's research is that of all human cancers, pancreatic cancer has the worst prognosis. Almost 34,000 Americans will be diagnosed with the disease in 2006; only 24 percent will live out the year, and fewer than 5 percent will survive for five years after their cancers were first detected. In mice implanted with human pancreatic tumors, the outlook is similarly bleak.

Yet Dr. Pincus's mice are fine, he says. Not only are they tumor-free, but "their weight gain is exactly what you'd expect in a normal mouse, and they behave completely normally." What is even more startling about the work Dr. Pincus and his colleague Josef Michl, MD, associate professor of pathology, have done is that their treatments

*A peptide molecule, PNC-27, bioengineered by Dr. Matthew Pincus. In mice, this experimental drug kills cancer cells, leaving the healthy cells intact.*



involve none of the punishing chemotherapy and radiation that today are the hallmark of most cancer treatments. Instead, their new peptides kill only cancer cells and leave normal cells undisturbed.

Dr. Pincus's and Dr. Michl's work in the lab shows that the peptide approach may apply not only to the devastating problem of pancreatic cancer, but to a large number of human cancers including those of the lung, breast, colon, and prostate—in other words, many of cancer's leading killers. Dr. Pincus is also applying his peptide approach to malfunctions of another important protein involved in many cancers, called ras-p21. "Our primary interest was in addressing problems with ras-p21," he explains. "This protein has been implicated in one out of three human cancers. It causes more than 90 percent of pancreatic cancers, about 75 percent of colon cancers, and about a third of lung cancers."

His approach, should it prove successful in human clinical trials, could revolutionize the way cancer is treated and transform our expectations of what a cancer diagnosis may mean. "While our results are very promising, I don't want to make any false

claims,” he cautions. “We’re eager to begin clinical trials as soon as possible.”

Back in the early 1980s, when Dr. Pincus was a scientist at the National Institutes of Health, he and the rest of the scientific world learned an important new fact. In a cell’s DNA, “a single amino substitution”—the presence of one type of amino acid when another is appropriate—“makes that protein oncogenic,” that is, it allows the protein to cause cancer. “It meant there was a link between protein structure in cells and cancer,” he says. “That’s when I became interested in the problem.”

So far, that interest has had impressive results. Using a vector—a biochemical vehicle that helps replace damaged proteins with the new ones he and Dr. Michl have created—the two scientists have succeeded in treating cancers in human cancer cells in Petri dishes. Their approach has killed cancers in cell lines not just for pancreatic cancer, but for colon cancer, one type of brain tumor, cervical cancer, breast cancer, and a cancer of the blood vessels.

The peptides kill the cancer cells without damaging healthy cells. “The peptides are causing very selective cancer cell death,” Dr. Pincus explains. “There is no adverse effect from the peptides at all.” The same has happened in their experiments using laboratory mice.

Dr. Pincus’s greatest hope now is that he can raise the money to get these peptides into human clinical trials within the next year. “We want to emphasize them in terms of real treatment,” says Dr. Pincus, who initially came to Downstate in its first class of MD/PhD students. “We want to push right now.”

*Dr. Matthew Pincus (l)  
and Dr. Josef Michl.*



# ALAN gintzler



*Dr. Alan Gintzler and Nai-Jiang Liu, PhD, a BIRCWH scholar.*

## HERE'S A CONUNDRUM IN THE FIELD OF PAIN RELIEF: WOMEN ARE SIGNIFICANTLY LESS SENSITIVE TO PAIN THEN MEN ARE. YET, WHEN IT COMES TO CHRONIC PAIN SYNDROMES, WOMEN SUFFER AT A FAR HIGHER RATE.

Pain researcher Alan Gintzler, PhD, professor and interim chair of biochemistry, has been trying to understand why. “The statistics are staggering,” he says. “In chronic pain syndromes such as temporomandibular joint syndrome, or TMJ, something like 80 to 90 percent of the cases are in women.”

Dr. Gintzler, who is also a program director of a Women's Health Research Training Grant (BIRCWH), hopes his research into women's paradoxical experiences of pain will help improve the treatment of pain in both women and men. “Pain treatment continues to be very primitive,” he explains. Unfortunately, “there are lots of pain syndromes that are very poorly managed.”

Dr. Gintzler didn't set out to be a pain researcher. But as a young scientist he made a startling finding: Pregnant laboratory animals were far less sensitive to pain than animals that weren't pregnant. Eventually, he tested the pain thresholds of pregnant rats and found it increased as their pregnancies progressed, peaking just before childbirth. Such is the case in pregnant women, as well. Why does this happen? High levels of estrogen and progesterone released during pregnancy, Dr. Gintzler explains, “act on spinal neurons to activate analgesia.”

But Dr. Gintzler didn't think hormonal differences alone accounted for the dissimilarity between women's and men's experiences of pain. To test that hypothesis, he made male rats hormonally “pregnant”—giving them hormones that mimicked the hormones female rats produce internally during gestation. “Low and behold,” he says, “they had very, very robust analgesia. As great, if not greater, than the females.”

That result might seem to contradict Dr. Gintzler's original hypothesis. But in the process of conducting his experiments, he and his collaborators have discovered that the central nervous system's pain pathways aren't entirely the same in females and males. Females have an additional system that processes pain. And not only that. The receptors that females and males have in common work differently. Observes Dr. Gintzler, “the components in the female are multiplicative.” In other words, they work together synergistically. Give a female a small amount of pain relief, and she's likely to get a disproportionate benefit. In males, pain relief “is purely additive,” Dr. Gintzler says. The same analgesic input gives far less relief.



Dr. Gintzler is one of several researchers pursuing the question of why, then, women suffer from chronic pain at disproportionate rates.

“Nobody has a complete handle on why women experience much more chronic pain,” he says. Indeed, the medical literature offers no firm conclusions. But Dr. Gintzler theorizes that the synergistic pathways that aid women in late pregnancy and childbirth may be the same ones that plague them when they develop chronic pain. Just as a small increase in the activity of the analgesic system gives females greater relief, so a small deficiency “has a much bigger effect in the opposite direction,” Dr. Gintzler says.

Dr. Gintzler’s interest in women’s and men’s differing experiences with pain dovetails with his other major research interest: how the body becomes tolerant of opioid-based narcotics. “One of the more intriguing aspects” of the analgesic effects of increased estrogen and progesterone exposure “is the noticeable decrease of tolerance development,” Dr. Gintzler explains. “This could suggest sex-based differences in tolerance and perhaps even addiction mechanisms.”

Dr. Gintzler’s twin interests may well increase medical science’s knowledge of sex-based differences in pain and analgesia. Perhaps one day, he says, “that difference can be exploited to optimize pain treatment.”



*Dr. Gintzler with Sumita Chakrabarti, PhD, and laboratory technician Arati Panda.*

# SHERYL smith

HORMONALLY-RELATED MOOD CHANGES, SUCH AS PREMENSTRUAL SYNDROME (PMS), HAVE RARELY BEEN THE FOCUS OF SERIOUS SCIENTIFIC INQUIRY.

This despite the fact that a full 30 percent of American women experience PMS on a regular basis, with 10 percent being severely affected and an additional 5 to 7 percent undergoing such intense symptoms as to warrant the psychiatric diagnosis of premenstrual dysphoric disorder.

Neuroscientist Sheryl Smith, PhD, professor of physiology and pharmacology, is out to change all that. In her lab, PMS is the major priority. And what she's found may come as a surprise, and as a kind of recognition, to millions of PMS sufferers and non-sufferers alike: The set of brain cell receptors involved in PMS, called GABA receptors, are the same ones affected by tranquilizers such as Valium, Xanax and Ativan, as well as by alcohol and the hormonal changes that can accompany menopause and childbirth.

"All this happens in the part of the brain called the limbic system," Dr. Smith explains, "which is important for things like spatial memory as well as for mood. So there are repercussions on mood, on memory, and learning."

What causes PMS? Dr. Smith and her team have learned that during the second half of the menstrual cycle, after ovulation, a metabolite of the naturally occurring hormone progesterone, called allopregnanolone, binds to GABA receptors. “When allopregnanolone is at high levels,” Dr. Smith says, “there’s less brain excitability in a normal person.” Researchers have reported, for example, fewer instances of epileptic seizures during this so-called luteal phase of the menstrual cycle.

At the very end of the cycle though, progesterone’s soothing effects come to an abrupt stop. Dr. Smith explains, “The progesterone levels become very low, and this progesterone metabolite is also declining. That’s when many women have a change in mood.” Similar declines in allopregnanolone levels also occur during the period immediately following childbirth, which in some mothers results in postpartum depression; after repeated stress; and during menopause, when changes in mood and cognition are also common.

Dr. Smith and her fellow researchers think what happens at the end of the menstrual cycle is a type of withdrawal. “Amazingly, what you see in the brain looks a lot like alcohol withdrawal,” Dr. Smith says. In fact, as in withdrawal, one type of building block in the affected GABA receptor, called the alpha 4 subunit, increases markedly during PMS, and levels of the more soothing alpha 1 subunit decrease. “In rats, when you see alpha 4 increasing, the rats have increased anxiety and it’s easier to produce a seizure. There are also changes in learning.”

Dr. Smith is currently investigating how to prevent increases in the alpha 4 subunit in the face of changing hormone levels. A compound called antisense appears to prevent such withdrawal symptoms. “In laboratory animals,” Dr. Smith says of her research, “you can put antisense into their brains and it prevents alpha 4 from being increased. Normally, these animals would be very anxious. But the antisense prevents the formation of alpha 4 subunits. And when that happens, you don’t see the anxiety or seizure activity.”

Dr. Smith’s research has led her to a few important conclusions about PMS and other related problems. Because GABA receptors that contain higher levels of alpha 4 are sensitive to low levels of alcohol, women experiencing the mood changes associated with PMS or menopause might well benefit from an occasional drink, when symptoms are most severe. But only one drink.

“There is some increased response to very low doses” of alcohol, she says. In fact, women who experience severe PMS are at higher risk for alcoholism, perhaps as a result of self-medication in the face of increased sensitivity to alcohol.

Dr. Smith hopes to further explore the basic science of PMS. For women who suffer from PMS, and for the millions of others with the related mood changes and cognitive impairments that occur during menopause and after childbirth, that research will be a welcome prospect.



WHAT IF THERE WERE A WAY TO SCREEN FOR AND DETECT BREAST CANCER THAT COULD FIND THE DISEASE IN ITS EARLIEST STAGES, COULD AVOID EXPOSING PATIENTS TO THE POTENTIALLY CARCINOGENIC EFFECTS OF THE X-RAYS NOW USED IN MAMMOGRAPHY, AND WAS SIGNIFICANTLY MORE ACCURATE THAN CURRENT MEDICAL IMAGING TECHNOLOGIES?

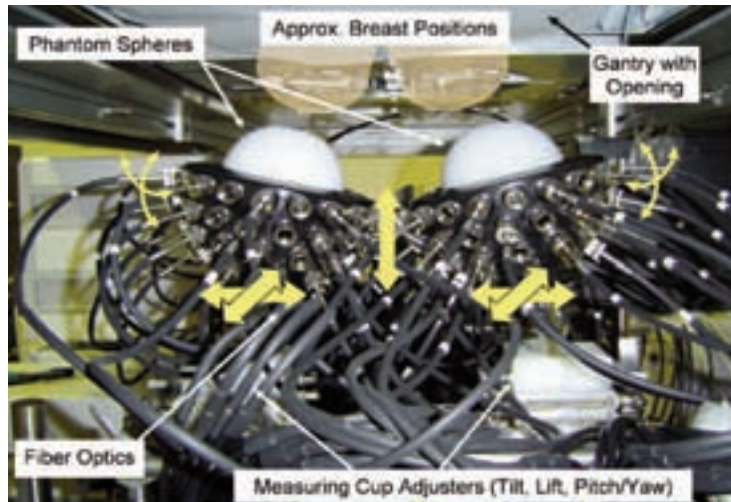
## barbour

Pathology professor Randall Barbour, PhD, may have found a way to do all that and more. Dr. Barbour, who is also research professor of electrical engineering at Polytechnic University, is the inventor of a relatively new field of medical imaging technology called diffuse optical tomography (DOT). DOT is a noninvasive approach that uses near-infrared light and computer algorithms to visualize tissue.

DOT has vast potential, including the diagnosis of the multiple health problems faced by extremely premature infants and improved visualization of degenerative neurological disorders. Georgetown University researchers are even using it to study what happens in the brain when individuals commit acts of deception.



*Left:  
Experimental imager  
setup for simultaneous  
dual breast optical  
mammography*



*Right:  
Fiber-optic connections  
used in the simultane-  
ous dual breast optical  
mammography*

Nowhere is DOT's potential greater than in the diagnosis of breast cancer and the assessment of treatments. "The likelihood is," says Dr. Barbour, "optical tomography is going to almost certainly be the preferred way to monitor the response to chemotherapy and the preferred technique, period, for breast cancer screening."

Randall Barbour had an epiphany. One day, while adjusting his car's headlights in the dense fog, he realized that light from a distant source was better at penetrating the low-lying cloud than light from a nearby source. Familiar with pulse oximetry, a non-invasive medical technology that uses near-infrared light to monitor the oxygen content of a patient's blood, Dr. Barbour thought he might be able to use near-infrared light to penetrate the dense cloud that is human body tissue. "In effect, we took the basic idea of pulse oximetry and extended it to a functional imaging tool," he says.

But that wasn't easy. The problem was how to read the light that penetrated the tissue. Light, after all, diffracts in complicated ways. Dr. Barbour's scientific quandary was "How could you possibly unscramble those randomly scattered patterns of light to allow you to reform the information, if you will, to get an image?"

Dr. Barbour, a biochemist by training, presented his ideas at a scientific forum in the mid-1980s; a few months later, a physicist friend explained how that might happen. Shortly thereafter, Dr. Barbour and his collaborators wrote the first computer code that enabled the process. "Sure enough," Dr. Barbour recalls, "within a short period of time, we knew it would work."

Indeed, since the late 1980s, the innovations have raced forth. "Typically, it takes about 20 years to work out all the bugs and come up with a new imaging scan," Dr. Barbour explains.

Now, working onsite at SUNY Downstate and at its nearby Advanced Biotechnology Incubator, using funding from such innovative sources as the Susan G. Komen Breast Cancer Foundation and the United States Department of Defense's breast cancer research program, Dr. Barbour and his team are ready to move their technology into the future. This year, Dr. Barbour's imaging venture, NIRx Medical Technologies, has begun to enroll healthy women and women with breast cancer in clinical trials that will compare DOT's accuracy to that of currently available detection technologies, including mammography and magnetic resonance imaging. "Already, we have sensitivity and specificity values"—measures of accuracy—"over 90 percent, which is considerably better than x-ray," he says.

The trial results won't be available for another year or so. "But right now," Dr. Barbour says, "I'm quite optimistic."