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Revisiting the Brudnick

Vitae:

The Magazine of
The University of Massachusetts Medical School

The RNAi Revolution is Here.

Beyond the Routine

Crossing the T's

Vitae: L., the plural of life

The name of this magazine encompasses the lives of those who make up the UMMS community, for which it is published. They are students, faculty, staff, alumni, volunteers, benefactors and others who aspire to help this campus achieve national distinction in education, research and public service.

University of Massachusetts Medical School

The University of Massachusetts Medical School was created in 1962 by an act of the Massachusetts Legislature and today is comprised of three schools. Since accepting its first class in 1970, the School of Medicine has provided students with an accessible, comprehensive and personally rewarding medical education of the highest quality, one which optimally prepares them to excel as physicians. The Graduate School of Biomedical Sciences, opened in 1979, is a faculty-initiated PhD program that trains scientists in a specialty area with a broad background in the basic medical sciences, in preparation for conducting research with direct relevance to human disease. Opened in 1986, the Graduate School of Nursing, through its master's, post master's, doctoral degree and Graduate Entry Pathway programs, provides professional education and training for advanced practice nurses within three specialties: adult acute/critical care nurse practitioners, adult ambulatory/community care nurse practitioners and advanced practice nurse educators.

Commonwealth Medicine

Commonwealth Medicine is UMass Medical School's innovative public service initiative, providing expertise to public sector agencies so they may optimize their efficiency and effectiveness. By offering access to its unparalleled breadth of academic, research, management and clinical resources, Commonwealth Medicine assists agencies to enhance the value and quality of expenditures, and improve access and delivery of care to at-risk and uninsured populations.

UMass Memorial Foundation

The UMass Memorial Foundation, established in May 1998, is the charitable partnership created through a merger of the former University of Massachusetts Medical Center Foundation and the Memorial Foundation. The mission of the Foundation is to support the academic and research enterprises of UMass Medical School and the clinical initiatives of UMass Memorial Health Care.

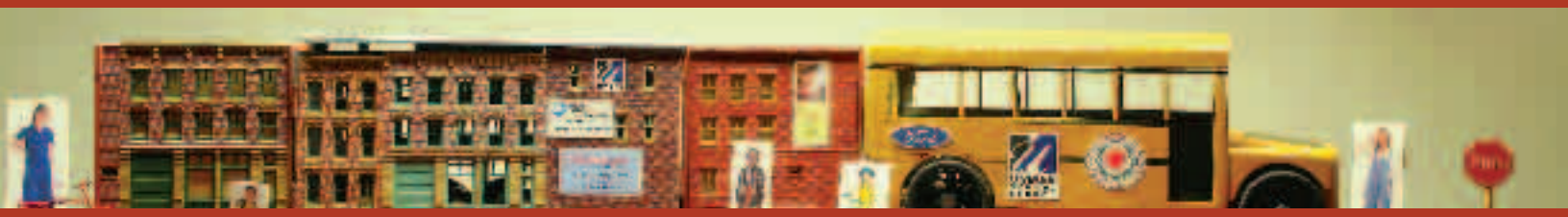
Worcester Foundation for Biomedical Research

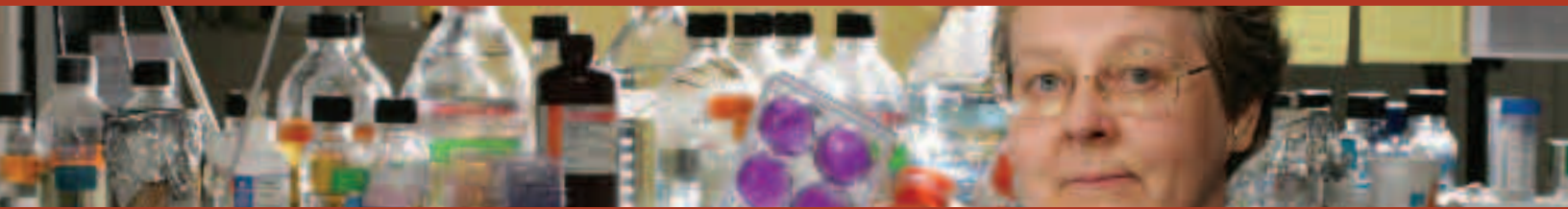
The Worcester Foundation for Biomedical Research is a nonprofit organization devoted to the support of research and the education and training of tomorrow's scientists at the University of Massachusetts Medical School. Founded in 1944 as an independent basic biomedical research institute, with research accomplishments that include the birth control pill and the work that led to *in vitro* fertilization, the Worcester Foundation merged with UMass Medical School in 1997.

UMass Memorial Health Care

UMass Memorial Health Care is Central Massachusetts' largest nonprofit health care delivery system, covering the complete health care continuum with teaching hospitals, affiliated community hospitals, free-standing primary care practices, ambulatory outpatient clinics, long-term care facilities, home health agencies, hospice programs, a rehabilitation group and mental health services. UMass Memorial is the clinical partner of the University of Massachusetts Medical School.

Vitae: Contents





Tariq Rana, PhD, and his lab have increased the effectiveness of RNAi gene silencing from two percent to 65 percent in their targets.

UMMS Researcher Enhances Gene Silencing Technology

The ability to silence genes by RNA interference (RNAi), co-discovered by UMass Medical School researcher and Howard Hughes Medical Institute Investigator Craig C. Mello, PhD, the Blais University Chair in Molecular Medicine, has emerged as one of the most important advances in biomedical research, giving scientists a method to understand what genes do in the body and a means to interrupt how they direct the creation of proteins that regulate biologic functions—theoretically blocking the effects of disease-causing genes. As effective as RNAi has proven to be, some genes are hard to silence. Now, a UMMS research team, led by Tariq M. Rana, PhD, professor of biochemistry & molecular pharmacology and director of the Program in Chemical Biology, has made the genes in question more susceptible to silencing by making the messages they send more readable by the RNAi machinery.

Some of those messages are easy to read, like a memo typed on a flat piece of paper, while others are harder to see, as if the memo were folded and placed in an envelope. Dr. Rana's lab developed a way for the RNAi tools to "open" the envelope, then read the message inside. If the message matched the one the RNAi tool was trying to silence, it was destroyed. "We are pleased that this concept seems to work in a dramatic way," said Rana. "By improving the target accessibility of the messengers the genes make, we increased the silencing effect from just two percent to 65 percent in the targets we studied. That's enough to make a difference." The results of the experiments were recently published in the journal *Nature Structural & Molecular Biology.*

Associate Dean Carole Upshur, EdD, established the CPHR faculty, curriculum and program policies and contributed to recruitment efforts for the first class, whose members are now taking courses.

New PhD Program in Clinical & Population Health Research Attracts Established Scientists

The first courses of the Graduate School of Biomedical Sciences' new PhD Program in Clinical & Population Health Research (CPHR) are underway this fall, and, judging by the backgrounds of its students, the program is attracting a variety of established scientists as they embark on the next phases of their careers.

The CPHR program prepares students to conduct research on issues of health care access, screening, treatment, quality and outcomes. It develops researchers with strong core competencies in statistics, epidemiology and research methodologies applicable to clinical trials and population health studies, and has a specific emphasis on public sector issues and vulnerable populations.

Mayra Tisminetzky and Ginny Briggs are two examples of active researchers whose knowledge and skills will be broadened by the new program. Tisminetzky practiced psychiatry in her native Buenos Aires before she came to the United States with her husband, a psychiatrist at Worcester State Hospital. She began work as a research assistant at the New York State Psychiatric Institute, where she helped design protocols for clinical trials and collaborated on research into the gender differences in responses to antidepressants. "I was

UMMS Advances Potential New Approach in Cancer Therapy

Calling it "an exciting development in an area of great need," Dario C. Altieri, MD, UMMS professor and chair of Cancer Biology and director of the UMass Memorial Cancer Center,

Dario Altieri, MD, and colleagues engineered shepherdin, represented in red in the image above as it binds to and inhibits the tumor-facilitating protein Hsp90. Shepherdin kills tumor cells while sparing nearby normal cells, making it a potentially attractive drug for targeted therapy.

along with colleagues in Italy and at the Moffitt Cancer Center in Florida, announced the development of a molecular anti-cancer agent, called shepherdin, that selectively kills tumor cells while sparing normal cells nearby. Shepherdin was described in a study published in the journal *Cancer Cell.*

In 1997, Dr. Altieri discovered survivin, a protein abundant in cancer cells, which contributes to uncontrolled proliferation of cancer cells and tumor growth. He sought a way to interfere with the function of survivin and its partner protein—Heat shock protein 90, or Hsp90—that chaperones survivin to ensure its durability and its delivery into cells. He engineered the compound shepherdin to bind to Hsp90 and block its ability to work with survivin, resulting in destruction of cancer cells and inhibition of tumor growth. The anti-tumor activity of shepherdin does not affect normal tissues and organs, and prolonged use of shepherdin in animal models is tolerated with no signs of toxicity. These features may make shepherdin an attractive drug for targeted cancer therapy.

Altieri, noting that traditional cancer treatments do not distinguish between cancerous and non-cancerous cells, said, "We have learned so much about how cancer works and yet we have few targeted therapies for patients. This may be a very effective model through which therapeutic agents can seek out and destroy only the malfunctioning, cancerous cells, leaving normal, healthy cells unaffected."

always interested in combining my clinical practice with the development of a deeper knowledge in research," Tisminetzky said. "It was during my work in New York that I realized the importance of epidemiology to developing a career that joined clinical and statistical work and led to a deeper comprehension of mental illness." Tisminetzky earned her master's in public health from UMMS.

Ginny Briggs' vast knowledge of epidemiology comes from her master's course work at UMass Amherst and experience at Liberty Mutual Research Center in Hopkinton, where she has been involved in several studies of workplace injury. The CPHR program will prepare her to explore a new focus in her research, that of the health-related problems of people with spina bifuda and other related disabilities. "From orthopedics to learning disabilities, I am anxious to begin the search for answers that will ultimately help this population live longer, healthier and happier lives," wrote Briggs in her personal essay when applying to the CPHR program. "The program offers a unique curriculum that will…allow an opportunity to participate in an intellectually rigorous pursuit of the deeper understanding of epidemiological science and research methods needed to accomplish my goals."

Briggs and Tisminetzky join five other students, including two MD/PhD students, who will start CPHR doctoral course work after completing two years of medical school. "We're truly excited by the caliber of this class and by the potential of these students to expand clinical research at UMass Medical School," said Associate Dean Carole C. Upshur, EdD.

James McNamara, PhD, has returned to Central Massachusetts from a position in business development at SRI International, originally affiliated with Stanford University.

Office of Technology Management Welcomes New Executive Director

Fitchburg-native James P. McNamara, PhD, an experienced leader in biomedical technology development and commercialization, recently joined UMMS as the new executive director of the Office of Technology Management (OTM). "I'm happy to come home to Massachusetts at a time when so much world-class research is happening right here at the Medical School," he said. In his new role, Dr. McNamara will lead the UMMS team that works to commercially develop the many innovations produced by faculty and staff, as well as secure funded partnerships that support the work of the research enterprise.

McNamara came to UMMS from his position as senior director of business development for the Biosciences Division at SRI International, the prestigious California-based research and technology development organization originally affiliated with Stanford University. After earning his bachelor's degree in chemistry from the College of the Holy Cross and both a master's in organic chemistry and a doctorate in medicinal chemistry from the University of Connecticut, McNamara headed west for a postdoctoral fellowship in the bio-organic chemistry program at SRI, staying on after completing his fellowship. He eventually rose to direct the business development and intellectual property functions for SRI's Pharmaceutical Drug Discovery Division and was most recently responsible for a division with annual revenue of $30 million.

A Better Solution for Rabies Treatment Through MBL/CDC Partnership

In findings that may lead to a more cost-effective, easier-to-produce biologic that can be given to people who have been bitten by rabid or potentially rabid animals, a team of scientists at UMass Medical School's Massachusetts Biologic Laboratories (MBL) and the U.S. Centers for Disease Control (CDC) has developed a novel human monoclonal antibody called HuMAB 17 C7 that can neutralize multiple variants of rabies virus. Details of the new antibody and the results of the tests—in which the antibody neutralized 25 different rabies viruses in culture—were presented in June at an international conference in Kiev, Ukraine.

Six to 10 million people worldwide are exposed to rabies every year and as many as 70,000 die. Ideally, individuals exposed to rabies receive a vaccine regimen that includes rabies vaccine and human rabies immune globulin (hRIG). But because hRIG is derived from human blood, it is expensive and often in short supply, especially in developing countries. Researchers are hopeful that HuMAB 17 C7 addresses both the supply and side effects issues since monoclonal antibodies can be produced in large quantities at much lower costs than blood products and are easier to distribute and store. "We were pleased to join with the CDC to search for a better and more accessible product for people who are exposed to rabies, which continues to be a major health problem around the world," said Donna Ambrosino, MD, director of the MBL and professor of pediatrics at UMMS.

Looking ahead, the team at MBL and CDC is evaluating potential collaborations to prepare for a phase 1 clinical trial to test the safety and tolerance of the antibody in otherwise healthy people.

UMMS Students Say 'We Care'

UMass Medical School students are trained to be compassionate caregivers to their patients and advocates for the communities they serve. Their advocacy and compassion were evident in their responses to victims of Hurricane Katrina, and, closer to home, their wishes for UMMS Chancellor and Dean Aaron Lazare's speedy recovery from recent surgery. At their annual Arts Night (left), students gathered donations to the American Red Cross toward a goal of $10,000 by Thanksgiving. At right, they gathered with members of the faculty to send a special message to Dr. Lazare.

UMMS Study Reveals Marker for Familial Alzheimer's Disease

Investigators from the UMMS Department of Neurology have discovered that levels of a protein in spinal fluid that is a known marker for Alzheimer's disease are abnormally low at least four to 12 years before the expected onset of symptoms in a group of subjects with a gene mutation that gives them an almost 100 percent risk of developing the early-onset familial form of the disease. The study, conducted with colleagues from the University of Toronto and called "Familial Alzheimer's disease: Decreases in CSF $A\beta_{42}$ levels precede cognitive decline," appeared in the July 25 issue of *Neurology.*

Researchers have previously determined that the earliest detectable signs of the brain pathology in Alzheimer's patients are deposits of amyloids such as the protein $A\beta_{42}$, which may interfere with normal brain function. The most common early-onset familial form of the disease is caused by an inherited mutation in a gene identified as PS1, which increases the level of $A\beta_{42}$ in the brain, with a concurrent decrease in the level in the spinal fluid. While such purely genetic cases of Alzheimer's disease comprise perhaps five percent of the total number of cases, the expectation is that treatments for this form of the disease will eventually apply to all forms as well. This new finding provides a window of opportunity for researchers to investigate the impact of therapies in the years before such high-risk individuals might develop symptoms of the disease.

The study was designed and conducted by Majaz Moonis, MD, associate professor of neurology, and Daniel A. Pollen, MD, professor of neurology. "We were surprised to find the same low levels of $A\beta_{42}$, seen in individuals with advanced disease, in people many years younger than the age at which they could expect symptoms to appear," noted Dr. Moonis. "This finding should lead to numerous clinical trials to identify interventions which will correct abnormalities in the metabolism of $A\beta_{42}$ long before symptoms would otherwise occur, potentially delaying the onset of symptoms and improving the length and quality of life for individuals faced with early-onset familial Alzheimer's."

‘Pulling Together’ for New Emergency Department

At the June campaign kick-off gala, Arthur Remillard III, a director of the Remillard Family Foundation and a UMass Memorial Foundation board member, received a water color painting representing the new main entrance and lobby of the Medical Center’s University Campus—the Remillard Family Pavilion.

UMass Memorial Medical Center’s $40 million Emergency Care Campaign to support the state-of-the-art emergency facilities currently under construction overlooking Lake Quinsigamond on the University Campus was officially launched at a gala on June 29. The campaign features a “pulling together” theme that uses rowing as a metaphor for the teamwork encouraged amongst hospital leadership, staff and the Central New England community. The kick-off event, emceed by WCVB-TV news anchor Liz Brunner, was hosted by John O’Brien, president and CEO of UMass Memorial Health Care; Chancellor and Dean Aaron Lazare; Sumner Tilton Jr., chair of the UMass Memorial Board of Trustees; and Arthur Pappas, MD, the Emergency Care Campaign chair.

The highlight of the evening was the formal announcement of a $10 million gift from the Remillard Family Foundation, a gift that underscores the sentiment behind the campaign theme and continues the momentum created in January by Commerce Bank and Trust Chairman David “Duddie” Massad, who gave $12.5 million to the campaign. On behalf of the foundation, Arthur Remillard Jr. said, “It is our hope that this gift will contribute to the important relationship between this remarkable medical center and the people of the region who have come to rely on UMass Memorial.” CEO O’Brien called the gift a “gesture that will resonate for generations.” In recognition of the leadership gift, the main entrance and lobby of the Medical Center’s University Campus will be named the Remillard Family Pavilion.

Cancer Walk Reaps Thousands in Walkers and Funds

The annual Walk to Cure Cancer, held Sunday, September 25, 2005, brought a record 10,000 walkers to the UMass Medical School campus and approximately $800,000 to the coffers that help support cancer research programs at UMMS. Members of the Department of Pediatrics walked with teams of patients and their families this year, including Ali and Dad’s Army (above), led by team captain Anna Ling Pierce; Greg’s Gang, with captains Chris and David Mandara; Jessica’s Journey, led by Marion Mauro; Eddie’s Echelon, with Jen and Ed Urbanowski; and Drew’s Crew, captained by Nancy Stassi.

Investiture Honors Researchers, Physicians; Provides Forum for Announcement of New Endowments

UMass Medical School's sixth annual Investiture Ceremony, held at the Hoagland-Pincus Conference Center on the Shrewsbury Campus on June 4, celebrated the extraordinary research of faculty and the generosity of supporters who champion their work. Three faculty members were formally invested into endowed professorships and the establishment of two new endowments was announced.

Azra Raza, MD, professor of medicine and chief of the Division of Hematology/Oncology, was invested as the Gladys Smith Martin Chair in Oncology, established in 2001 to honor the late Gladys Smith Martin, sister of Worcester Foundation for Biomedical Research benefactor H. Arthur Smith. Dr. Raza was recognized for her dedication to the cause of treating and curing cancer.

Peter E. Newburger, MD, professor of pediatrics, cancer biology and molecular genetics & microbiology and director of Pediatric Hematology/Oncology for the Department of Pediatrics, was invested as the Ali and John Pierce Chair in Pediatric Hematology/Oncology, established in memory of Ali Pierce, who succumbed to liver cancer in 1996, and her father John Pierce, who died less than a year later while raising funds in Ali's name. Dr. Newburger is well-known for his dedication to the health and well-being of young people and provided compassionate care to Ali.

Also honored was Linda F. Weinreb, MD, professor and chair of family medicine & community health, who was selected as the first Joy McCann Professor for Women in Medicine for her role as a mentor, advisor and leader. The three-year professorship is funded by the Joy McCann Foundation and honors female faculty for excellence in medical education leadership, research, patient care and community service.

The two new endowments announced at the ceremony are the Gretchen Stone Cook Chair in Biomedical Sciences, which is to be held by an outstanding faculty member chosen by the UMMS Chancellor/Dean without restriction, and the Leo P. and Teresa M. LaChance Chair in Mental Retardation and Behavioral Health, which will support research into the causes and treatment of mental retardation, pending University of Massachusetts Board of Trustee approval.

Reflecting on the increase in the number of endowed positions from just seven in 1997 to 28 today, Chancellor Aaron Lazare said, "This dramatic growth is a clear indication of the maturity the University has attained along its path to national distinction in research, education and public service."

The three esteemed scientists and physicians who received endowed professorships at the ceremony are (front row) Peter Newburger, MD, Linda Weinreb, MD, and Azra Raza, MD. They are joined by Matthew Erskine, Esq. (back row, left), chairman of the H. Arthur Smith Charitable Foundation, University of Massachusetts President Jack Wilson, PhD, UMMS Chancellor and Dean Aaron Lazare and Anna Ling Pierce.

Revisiting the Brudnick

Investigators at UMass Medical School's Brudnick Institute are pursuing a common interest in addiction while they continue to explore the origins of schizophrenia, affective disorders and dementia.

By Kelly A. Bishop

Brudnick Institute faculty are known for their range of expertise and collaborative spirit, according to Director Steven Treistman, PhD. They include (from left): Evgeny Rogaev, MD, PhD; Haley Melikian, PhD; Treistman; Jean King, PhD, of the Center for Comparative Neuroimaging; CCNI Director Craig Ferris, PhD; Paul Gardner, PhD; and Schahram Akbarian, PhD.

Long considered a consequence of personal weakness, addiction to drugs or alcohol has historically been viewed as a social rather than a medical problem. But while personality, peer pressure, stress and curiosity influence the decision to experiment, these factors become less important over time as the physiological effects of drugs and alcohol cause profound changes in the brain. Many scientists now believe that these significant alterations to brain chemistry and function—rather than social factors—are what make the treatment of addiction so challenging.

The scientific faculty of UMass Medical School's Irving S. and Betty Brudnick Neuropsychiatric Research Institute believe that research into the neurobiology of addiction is critical to the development of successful therapies that can block the reinforcing characteristics of drugs and alcohol, eliminate an addict's craving and even mediate the neurological changes associated with abuse. Led by Director Steven N. Treistman, PhD, professor of psychiatry and neurobiology, Brudnick Institute faculty are pursuing a common interest in addiction. In addition to disease-related research, they are also researching normal neurological function and basic biological processes with the hope that this research will provide the basis for understanding psychiatric disorders.

The Brudnick Institute opened in May 2000 for the comprehensive study of the brain and behavior through basic and clinical research, and was made possible in great part by the generosity of Betty Brudnick and her late husband Irving, whose struggle with depression inspired a dedication to neuroscience research.

"Addiction is a psychiatric disorder." Dr. Treistman said. "Although it is somewhat difficult not to blame addicts for their actions, if you take the reasons

why someone first tried a drug out of the equation, you find that there are significant reasons to treat addiction as an illness." One is that the brain and nervous system are changed in response to exposure to a drug. In addition, research has demonstrated that there may be a genetic predisposition toward substance abuse.

When naturally activated—for example, through exercise—the brain's reward systems produce changes ranging from slight mood elevation to euphoria, directing an individual's behavior toward future natural rewards. However, addictive drugs work in much the same way: they activate brain reward mechanisms directly and chemically alter the natural functioning of these systems, often leading to compulsive drug use.

Brudnick Institute investigator Haley E. Melikian, PhD, assistant professor of psychiatry and biochemistry & molecular pharmacology, explores how addictive drugs change the brain at the molecular level. She studies neurotransmitter transporters, a family of proteins that regulate the chemicals that transmit information across the junction (synapse) that separates one nerve from another.

Drugs such as cocaine, amphetamine and Ecstasy target these transporters. For example, cocaine inhibits the uptake of dopamine, a neurotransmitter involved in the brain's reward systems, by blocking the transporter; the result—an abnormal buildup of dopamine in the synapse that produces the elation associated with cocaine use.

Dopamine has garnered particular attention from researchers because of its role in the regulation of mood, motivation and reward. Because of this, the study of dopamine and addiction often has bearing on the study of other mental illnesses such as schizophrenia and depression. A practicing clinician and basic scientist, the Brudnick Institute's Schahram Akbarian, MD, PhD, associate professor of psychiatry, is interested in the long-term changes that dopamine and other neurotransmitters create in neuronal gene expression and how drugs induce chemical changes in the brain.

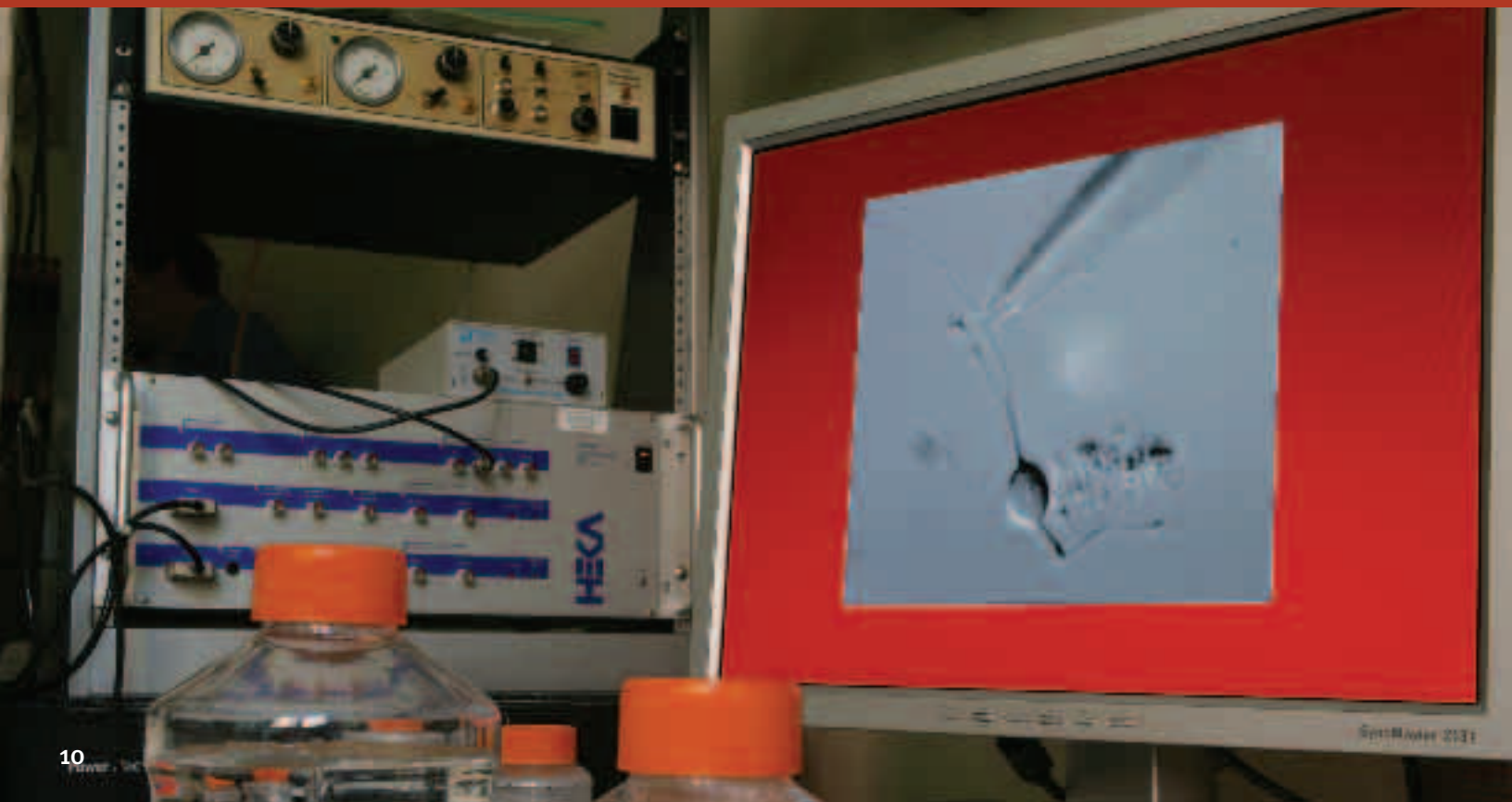
Many of these critical changes take place in the portion of the cell nucleus that contains DNA, affecting gene expression and the process of DNA repair. Dr. Akbarian's lab examines changes in the cell nucleus after administration of stimulant drugs.

"Genetics can only give so much information," Akbarian explained. "We need to look at the changes that can result in psychosis and addiction."

Like Akbarian, Treistman is interested in the neurological changes wrought by drugs of abuse, specifically the effect of alcohol on the brain and the long-term consequences of alcohol consumption.

Because alcohol affects many molecules within the brain, identifying a specific molecular target for it has been more difficult than for drugs such as cocaine and heroin, for which targets are less

In the Treistman laboratory, Research Assistant Professor of Neurobiology Gilles Martin, PhD, has perfected techniques to record electrical signals from individual dendrites of neurons (seen in magnified image below) isolated from the reward pathway of the rat brain. This knowledge may be vital in the development of therapeutic treatments for craving and addiction.



abundant, and better defined. Treistman has centered his research on "ion channels"—brain proteins that are critical for normal brain function—that may provide insight into alcohol's action on the brain.

The Treistman lab has found that prolonged exposure to alcohol has two effects on these channels—first, they become less sensitive to alcohol, and second, channels located in the cell membrane are internalized (where they are nonfunctional), so more alcohol is required to produce the same response. The adapted brain is now "dysfunctional" in the absence of alcohol, possibly contributing to relapse. Treistman hopes that by defining the action of alcohol on channels, researchers can develop a therapeutic agent to block the craving that accompanies alcohol addiction.

Neuroimaging is also playing a vital role in the research into addiction. With the imaging technology and faculty expertise of the Center for Comparative Neuroimaging (CCNI), a collaborative effort of the Brudnick Institute and Worcester Polytechnic Institute, addiction research can be visualized, not just studied at the cellular and molecular levels. Researchers can examine a drug's pattern of activation globally over the entire brain, identifying those areas that are specifically affected by drugs of abuse.

CCNI Director Craig F. Ferris, PhD, professor of psychiatry and physiology, is interested in both the short- and long-term effects of these drugs and conducts a number of developmental studies that are shedding light on their impact. A unique strength of non-invasive imaging is the ability of investigators to identify and locate brain activity without harming the organisms with which they are working; scientists can also detect the changes wrought by drug use and addiction over time.

In recent years, for example, the use of Ecstasy has become more pervasive, particularly among young people who view the substance as a harmless "club drug." To determine the cumulative impact of Ecstasy on the brain, Dr. Ferris and colleagues are conducting a National Institute on Drug Abuse-funded study, based on research that found Ecstasy users typically take two doses on both Friday and Saturday evenings. Investigators reproduce this usage pattern and image both the effect of the drug shortly after use and the organism's social and cognitive behavior during the remainder of the week.

"Imaging is another powerful tool in the study of addiction," said Ferris. "Each investigative tool, whether it examines action at the molecular, cellular or systemic level, is an important part of the overall effort to understand the physiological and behavioral changes that result from addiction. That is where the Brudnick Institute allows for the highest level of integration."

The CCNI's non-invasive imaging equipment allows researchers to detect the changes wrought by drug use and addiction over time.

Brudnick Institute research into the neurobiology of addiction is critical to the development of therapies that can block the reinforcing characteristics of drugs and alcohol, eliminate craving and mediate the neurological changes associated with abuse. "Addiction is a psychiatric disorder," says Director Steven Treistman, PhD (above).

The late Irving Brudnick and his wife Betty (above) contributed $2.5 million to help fund construction of the Brudnick Institute, one of only a handful of facilities in the country devoted to studying the biological causes of mental illness. Mr. Brudnick said at the time of the Institute's opening in 2000: "Betty and I have long wished to establish such a facility that would have as its mission the objectives of not only seeking the causes of and cures for mental illness, but also advancing the latest in effective treatments for patients and their families."

Mind Matters at the Brudnick Institute

Although the interest in addiction is a common one among Brudnick Institute faculty, it is far from the only area of study. Current investigations are underway to identify the genes and mutations that underlie schizophrenia, depression and other affective disorders, and dementia, while others are continuing to determine how biological and environmental factors influence the onset of mood disorders such as fear and anxiety.

As a large segment of the American population ages, Alzheimer's disease has evolved into a major area of interest in the research community, and Brudnick Institute investigators want to uncover the molecular mechanisms for Alzheimer's disease as well as its risk and protecting factors. Professor of Psychiatry Evgeny I. Rogaev, MD, PhD, is interested in the regulation of proteins called "presenilins."

Presenilins, which were discovered by Dr. Rogaev and his colleagues, are critically important genes in the pathogenesis of Alzheimer's disease; they bear mutations that are evident in the early onset of the disorder. Rogaev is pursuing the theory that it is not only these mutations, but also the regulation of the activity of these presenilins that may modulate the progression of Alzheimer's disease. Rogaev is also searching for specific genes and DNA variations that may be risk factors for schizophrenia, depression and other diseases of abnormal behavior.

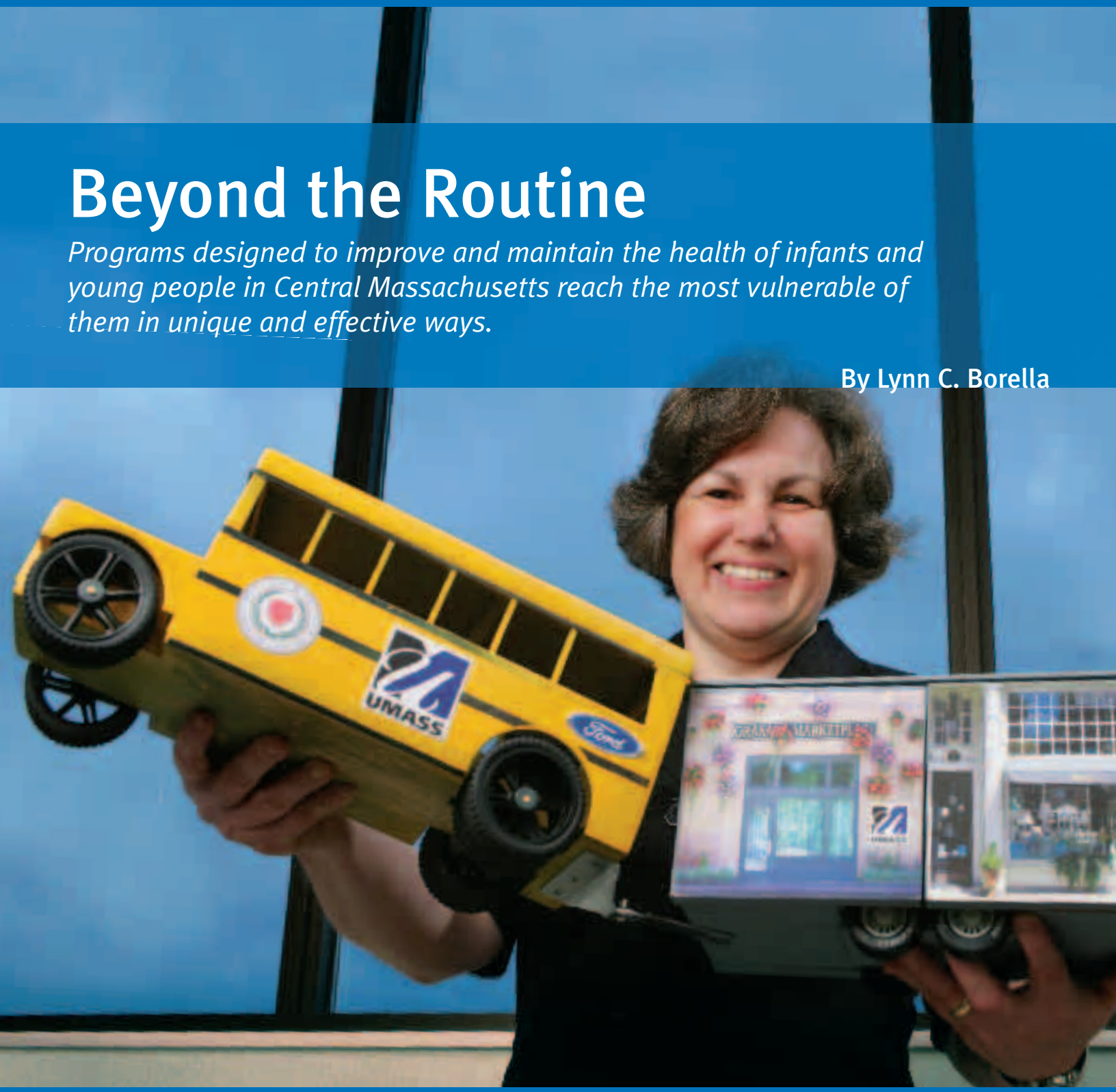
Associate Professor of Psychiatry Paul D. Gardner, PhD, has focused his research on the molecular analysis of ion channels, with implications for neurological development in a variety of disease states. Ion channels play a central role in signal generation within the nervous system, and disruption of this signaling can lead to severe consequences in terms of neuronal function. Dr. Gardner is particularly interested in understanding the molecular events that control the expression of a particular class of ion channels that have been implicated in a variety of brain processes and pathologies, including nicotine addiction, learning and memory, aging, anxiety, nocturnal frontal lobe epilepsy, schizophrenia, analgesia and dementia.

"With our focus on addiction, and research on such diverse areas as neuronal development, Alzheimer's disease, obesity, schizophrenia and mood disorders, the true strength of the Brudnick Institute and its faculty is our range of expertise, coupled with a synergistic and collaborative spirit," said Brudnick Institute Director Steven Treistman, PhD.

Beyond the Routine

Programs designed to improve and maintain the health of infants and young people in Central Massachusetts reach the most vulnerable of them in unique and effective ways.

By Lynn C. Borella



Mariann Manno, MD, is co-principal investigator for the Worcester site of the national Injury Free Coalition for Kids, an organization dedicated to reducing childhood injuries, the leading cause of childhood death and hospitalization in the United States. Dr. Manno holds a scale model of one of the Coalition's most popular teaching tools, the mobile Safety Streets museum (pictured here and on page 16). The life-size museum on wheels can be driven into any parking lot to unfold into a mini-town that promotes safety behaviors to children.

There are a number of UMass Medical School and UMass Memorial programs designed to improve and maintain the health of infants, children and teenagers in Central Massachusetts that go far beyond routine studies and visits to the doctor. These programs reach into the community, exemplifying the definition of public service by promoting public health and educational awareness in distinctive ways. The following highlights three such initiatives.

Confronting the challenge of infant mortality

What's behind the higher than predicted mortality rate of children under the age of 1 in Central Massachusetts? It has remained above both the state and national averages for more than a decade, according to the Commonwealth's Department of Public Health. This galvanized a group of community agencies and advocates, including faculty and clinicians from UMass Medical School and UMass Memorial Health Care, who came together in the mid-1990s to find answers. In doing so, they formed the foundation for today's Worcester Infant Mortality Reduction Task Force. The Task Force's recent findings have it poised to make a significant impact on the city's youngest residents.

"Infant mortality is, to many, a reflection of the health of a community and, therefore, of great concern to us," said Marianne E. Felice, MD, professor and chair of the UMMS Department of Pediatrics and chair of the Task Force. "My initial thought when I became chair of the Task Force in 2002 was that we had to find answers to two predominant questions: Why are our rates higher than predicted and who is dying?"

The Task Force began by averaging statistics in three-year blocks rather than on an annual basis to improve data collection. (While the rate of infant mortality is higher than predicted, one death can raise the rate significantly: In 2002, the rate in Worcester was 8.8 deaths per 1,000 children younger than 1 versus 4.9 in Massachusetts and 7.0 in the United States.) Members also looked at the known risk factors for infant mortality—being a smoker, a teenager, a single mother and/or poor—and were taken aback when it turned out that these risk factors did not apply to the population of women whose babies were dying. Finally, Task Force member Dale B. Magee, MD, MPH, clinical assistant professor of obstetrics & gynecology, single-handedly examined each death certificate of an infant from the region who died before age 1. From this data, the Task Force determined that the majority of infants who died in sample year 2003 were in their first month of life and resided in Worcester. In addition, many of these babies had been born to immigrant women from Western Africa—predominantly Ghana.

The Task Force organized focus groups of Ghanaian women of child-bearing age to try to understand the high rate of infant death. While these focus groups were fruitful, Dr. Felice—who presented the Task Force's findings to the Health Committee of the Worcester City Council at the close of 2004—now believes that a full-scale scientific study is needed to analyze the heart-wrenching problem. And, she is turning to the Ghanaian community for insight. "Whatever we do, we have to attack this problem in many different ways and get out the message that the best way to healthy babies is to ensure that women are healthy before they become pregnant. This is not just a challenge for the Task Force, or for a subset of women, but also for the community at large."

Dr. Felice (pictured) believes that a full-scale scientific study is needed to analyze the heart-wrenching problem [of infant mortality]. "This is not just a challenge for the Task Force, or for a subset of women, but also for the community at large."

The state's Department of Social Services (DSS) requires that every child entering foster care have a medical exam within seven days of entering a new home and a full evaluation within 30 days. But many children don't receive these exams for several reasons, including unavailability of previous medical records, transportation and child care concerns and difficulty scheduling timely medical appointments.

Prompted by this lack of medical attention given to foster children—arguably some of the most vulnerable of pediatric patients—Linda D. Sagor, MD, MPH, associate professor of pediatrics and director of General Pediatrics at UMass Memorial Medical Center, became impassioned by their plight.

"According to DSS, only 11 percent of these children were receiving the health care screenings required in 2001; even fewer were receiving dental or mental health consultations," said Dr. Sagor. "This made me wonder why we couldn't develop a system that met the needs of these kids and made sure that, at the very minimum, we started their health care in foster care the right way."

In her capacity as chair of the Foster Care Committee for the Massachusetts Chapter of the American Academy of Pediatrics, Sagor met with many concerned individuals in the Worcester community. Their commitment, coupled with significant logistic and philanthropic support from the Children's Leadership Council of United Way of Central Massachusetts, Fleet Bank, Allmerica, Fallon Community Health Plan, UnumProvident and the UMMS Office of Community Programs, produced the Foster Children Evaluation Services Clinic (FaCES), which opened at UMass Memorial in fall 2003.

FaCES—an ongoing collaboration of the Department of Pediatrics, the Office of Community Programs, DSS, and the Massachusetts Department of Medical Assistance—provides foster children up to age 11 with a repository to house their medical records, as well as a clinic, staffed by Dr. Sagor and Heather Forkey, MD, for evaluations and screenings that promote consistent and streamlined health care. All children under age three are referred to the UMass Memorial Medical Center Early Intervention and Family Support Program. Children over three are referred for mental health and dental evaluation and treatment. Laboratory evaluations are also completed and immunizations updated as needed.

"A key benefit of the FaCES program is that all information, including previous medical information and immunization records, is kept at the clinic. A copy is sent to the primary care physician who will follow the child while in foster care," said Sagor. "Our clinic also addresses dental and behavioral and developmental issues, and that's really important to this population."

Sagor particularly credits the work of Taína Pabón, the administrative coordinator of the program's operation. "Taína is really a case manager for these kids, with responsibilities that range from finding missing medical records to providing toys for the children who attend their first exams."

The UMass Center for Adoption Research is conducting an evaluation of the clinic to study the program's success in meeting its objectives. Sagor hopes that this analysis will quantify how the clinic is fulfilling its mission and lead to expansion of services to adolescents in foster care. She also hopes that the program will eventually be replicated statewide. "Wouldn't it be great that it started with UMass Medical School?" Sagor enthused.

As part of her daily pediatric practice, Linda Sagor, MD, MPH, sees many patients, including four-year-old Bobby Duquette of Shrewsbury. She and many health care and community partners developed the FaCES program to ensure that the state's foster children, arguably some of the most vulnerable of patients, receive the comprehensive care they deserve, as well.

Keeping kids safe through education

Injury is the leading cause of childhood death and hospitalization in the United States. Each year in Worcester alone, hundreds of children under age 19 are injured seriously enough to require medical treatment.

Michael Hirsh, MD, brought the educational programs of the national Injury Free Coalition for Kids to Worcester.

Michael P. Hirsh, MD, joined UMMS and UMass Memorial five years ago with an aim to address these statistics through education. Armed with experience at two Pittsburgh hospitals, the pediatric trauma surgeon set out to establish an Injury Free Coalition for Kids in the region that would provide educational awareness programs designed to keep kids safe.

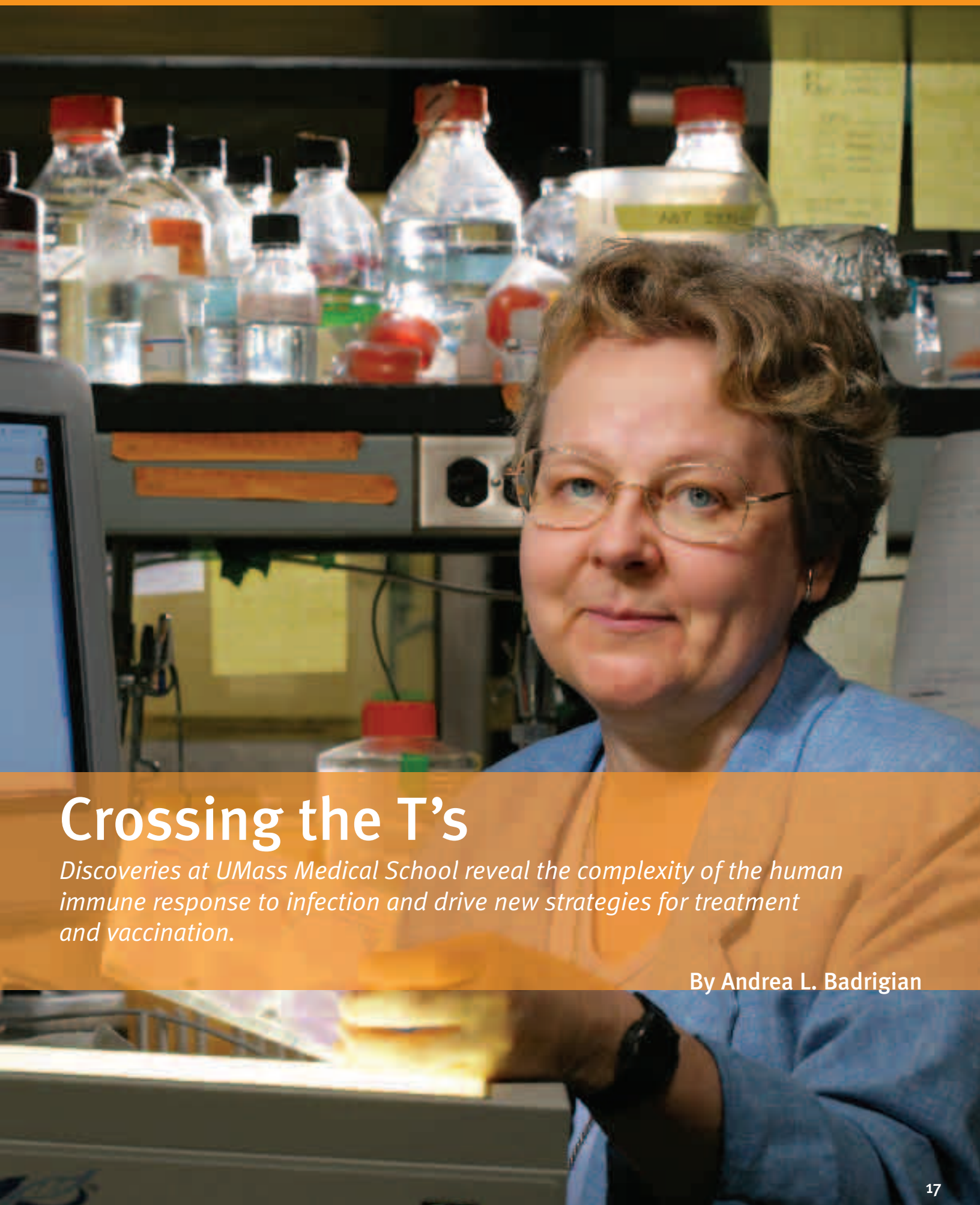
"The concept of wearing seat belts was foreign 25 years ago; it took lots of education and legislation to make it an accepted practice. That's the kind of long-term focus on education about injury prevention that I wanted to initiate in Massachusetts," explained Hirsh, a professor of surgery and pediatrics at UMMS.

The Injury Free Coalition for Kids is a nationwide organization of hospital-based injury prevention programs aimed at reducing the number and severity of childhood injuries by providing education to parents and caregivers about health hazards, eliminating dangers in the community and providing children with free or low-cost social activities led by adult role models. The Coalition currently has 40 sites in cities throughout the country, all supported by the Robert Wood Johnson Foundation; Worcester was the 15th site, designated in 2001.

Hirsh works collaboratively with co-principal investigator Mariann M. Manno, MD, clinical associate professor of pediatrics and emergency medicine, and recruits medical students and residents to make the Injury Free Coalition for Kids a success for the community. Following are several highlights of the program:

- **Goods for Guns** – Established in 2002 to promote gun safety, this two-day annual program gives the public an opportunity to turn in operable firearms to the local police department in exchange for a gift certificate redeemable at retail stores. Over the last three years, the program, sponsored by Wal-Mart, has collected about 800 firearms. "The purpose is not to be anti-gun, but instead to get unlocked, loaded, improperly stored guns out of homes where there are children," explained Dr. Manno. "In addition, Goods for Guns offers us tremendous opportunity to raise community awareness about gun violence."
- **Ski Helmets** – Initiated in 2004, this effort to promote helmet use among skiers was galvanized by a teenage patient cared for at the Medical Center who suffered a severe head injury. Manno created a video incorporating footage taken by the child's family—documenting his ordeal from the ED through rehabilitation—that is mailed to ski schools, along with offers to speak to students about helmet use and safety on the slopes.
- **Safety Streets** – This mobile museum is based on a stationary exhibit established by Hirsh in Pittsburgh. Developed with the assistance of a bioengineer from the UMMS Department of Surgery, as well as funding from corporate and public sponsors, the mobile unit is pulled by a school bus and can drive into any parking lot to unfold into a mini-town that promotes 40 safety behaviors, including pedestrian and bike safety. Another feature of the "street" is **Safety Home**, which teaches children how to avoid injuries such as burns, furniture tip-overs and stairway falls. "One of the hallmarks of this program is that it's very visible," Hirsh explained. "It 'puts a face' on what injury-free is all about. We're hoping it will take off and be a model for other Injury Free sites nationwide."

In addition to these and many other programs offered through the Coalition, Hirsh and Manno are teaching injury prevention as a model of preventive medicine to first-year medical students through a standardized clerkship. "Injuries kill more children under 21 than all other causes combined, yet they are considered 'accidents' rather than a preventable, public health concern," said Manno. "These programs give us endless opportunities to teach patients and the public about risky behaviors and ways to prevent injury."



Crossing the T's

Discoveries at UMass Medical School reveal the complexity of the human immune response to infection and drive new strategies for treatment and vaccination.

By Andrea L. Badrigian

About two weeks after fall orientation at UMass Medical School's sister campus in Amherst—and at colleges and universities around the country—the symptoms start to show in the student body: severe fatigue, headache, sore throat, chills, fever, muscle aches. Like the colors of autumn, acute infectious mononucleosis has arrived: swollen lymph nodes, jaundice, a measles-like rash and soreness in the abdomen due to an enlarged spleen. Though a miserable experience, the "kissing disease" still provokes snickers and rolling of the eyes as it symbolizes a rite of passage for many college students. But for researchers at UMMS involved in a National Institutes of Health program project grant, the onset of "mono" season brings fresh opportunity to analyze human antiviral immune responses, particularly those to Epstein-Barr virus, the causative agent of acute infectious mononucleosis.

Liisa Selin, PhD, (below) and Professor Raymond Welsh, PhD, demonstrated that infection-fighting CD8+ T-cells specific for one virus can become activated during infection with an unrelated virus, a discovery that changed the fields of immunology and virology. This "cross-reactivity" of T-cells, as well as the sequence of infections over time, Dr. Selin later found, plays a key role in whether an outcome is immunity or sickness.

Epstein-Barr virus (EBV) is one of the largest of the viruses to infect humans, with over 200 genes (as compared to, for example, HIV, which has only nine genes). Over 90 percent of the world's population acquires EBV at some point in their lives. EBV is classified by virologists as "persistent" because it remains in the body's B lymphocytes—one of the immune system's groups of infection-fighting white blood cells—after a person's first exposure.

Yet, the title of the NIH grant at UMMS, "Evolution and Maintenance of Memory CD8+ T-cells," reveals something intriguing: There is a key dimension to this immune response that has valuable implications for the treatment of infection and the development of vaccines. The current study of mono in students at UMass Amherst builds on discoveries at UMass Medical School that have revolutionized the fields of immunology and virology. The research, led by Liisa Selin, PhD, Katherine Ruiz de Luzuriaga, MD, and Alan Rothman, MD, is particularly exciting because it addresses one of the oldest puzzles of the immune system: how your body recognizes an infectious substance and orchestrates a response.

Immune system cells—the B-cells and T-cells and a host of others—each have a highly specific origin and purpose, but all work together to help an organism recognize and fight infections. T-cells are a type of white blood cell, that, like B-cells, are born in the bone marrow. T-cells then migrate from the marrow to mature in the thymus gland, after which T-cells can respond directly to the part of an infectious agent called an antigen, or they can help B-cells to produce antibodies. CD8+ T-cells, in particular, play an important role in antiviral immunity by attacking and clearing virus-infected cells.

"The original theory about CD8+ T-cells and how they saw antigens was that when you had an infection, your immune system generated T-cells that were very, very specific for the original antigen they saw," explained Dr. Selin, an associate professor of pathology. So specific, in fact, that it was widely held that the CD8+ T-cells retained a "memory" to react to that infection and that antigen alone. "So if the infection was flu, then the T-cells should only be reactivated if you had flu again, and those T-cells

Katherine Luzuriaga, MD, hypothesizes that "heterologous immunity"—the activation of memory T-cells for one infection during infection with an unrelated virus—helps explain the variability in the severity of symptoms experienced by persons infected with mononucleosis.

would only work against flu, in a lock and key fashion." When Selin arrived at UMMS in 1991, she began a collaboration with Professor of Pathology Raymond Welsh, PhD, who had recently discovered that he could activate the memory CD8+ T-cells for one type of infection in a mouse by infecting it with a second, unrelated, virus.

"This was surprising," said Selin, as the finding went against the traditional notion about CD8+ T-cell responses to specific antigens: Welsh and Selin went on to demonstrate convincingly in mice that memory CD8+ T-cells specific for one virus can become activated during infection with an unrelated virus.

Selin started working on what the mechanisms could be for that activation and how those mechanisms might influence disease outcome. "In fact," she continued, "that's just what we found—that these mice had immune protection against a second, powerful, virus. Not total protection, the way they would if they had had a vaccination and then were exposed to an infection, but they did have partial protection."

Selin also found, however, that some of the mice, instead of developing protection against infection, got sick with a rare condition called acute fatty necrosis.

According to Selin, it took almost ten years for most immunologists to accept the idea that memory CD8+ T-cells developed from one infection could be activated by a different infection. "Why would memory cells to one infection influence the outcome of another infection?" she said. "One of the reasons, it turns out after the studies we've done, is that some CD8+ T-cells are cross-reactive."

Selin and Welsh invented the term "heterologous immunity" to describe this phenomenon. And not only have they been able to show that CD8+ T-cells are not nearly as specific as previously thought, Selin has also discovered that the order in which mice are exposed to infections is key to whether they develop immunity or get sick.

"For instance, in the lab, we do experiments with two different viruses—one called LCMV, and the other, vaccinia. It turns out that a mouse that has LCMV first is protected against vaccinia, but a mouse that has vaccinia first is not protected against LCMV," said Selin.

Selin and Welsh's work in mice led them to collaborate with Dr. Katherine Luzuriaga, professor of pediatrics and molecular medicine, to study whether heterologous immunity may help to explain the variability of disease severity observed after many viral infections. Selin and Luzuriaga are studying the UMass Amherst students with acute infectious mononucleosis with the hypothesis that pre-existing cross-reactive CD8+ T-cells may provide some protection against EBV infection but may also contribute to some of the symptoms of mono.

CD8+ T-cells scan the surfaces of infected cells for little pieces of protein ("peptides," made up of building blocks called amino acids) that are produced when the virus infects the cell. "When cells are infected with a virus, these peptides of about 8 to 10 amino acids in length are expressed on the cell surface along with self proteins—this combination provides a signal to the immune system that an infection is present," explained Luzuriaga. "With Epstein-Barr virus, for example, we have now defined several peptides that elicit huge CD8+ T-cell responses in patients with mono."

But what is amazing is that some of those CD8+ T-cells, once thought to be highly particular in what they responded to, can in fact, cross react with CD8+ T-cells that respond, for example, to a nine-amino acid peptide in influenza. Work conducted under the auspices of the program project has demonstrated that these EBV-flu cross-reactive CD8+ T-cells are expanded in individuals experiencing mono. "It turns out that hundreds of different T-cell receptors can recognize one single part of the antigen on a virus, and viruses can have 15 or more of these recognizable parts," said Selin, meaning 15 chances for cross-reactivity. Moreover, patterns of reactivity can differ from person to person, so each individual will have different patterns of cross reactivity. "Our hypothesis is that outcome following infection is determined by an individual's pattern of cross-reactivity," said Selin.

"Understanding how cross-reactive CD8+ T-cells can contribute to protection or disease following viral infection is not only important to understanding disease pathogenesis but also has important implications for vaccine development," said Luzuriaga. "As our ability to develop vaccines against a wide variety of pathogens grows, we have to know how to combine or sequence these vaccines to optimize protection and minimize potential side effects." To further explore how cross-reactive CD8+ T-cells may be activated by vaccines, Selin and Luzuriaga have collaborated with Dr. Alan Rothman, a professor at the UMMS Center for Infectious Disease and Vaccine Research and an expert in studying memory CD8+ T-cells to viruses and vaccines. "Our research is interested in the issue of how your body is able to maintain memory for a long time when it's not constantly getting nudged," said Rothman. How are CD8+ T-cells generated to vaccines? Are the mechanisms surrounding T-cell memory the same in persistent and non-persistent viruses? "How does a vaccine affect the memory your body has for other viruses you had before?" he said.

"One of the challenges is now that we know how complicated the system is and how many different things can affect the response in the end, we as immunologists need to start drawing the lessons from those observations and make an effort to predict what's going on, to someday guide vaccination or treatment strategies," said Rothman. "All of this research will in essence feed into that—once we know how the sequence of viruses you get exposed to over time affects your immune response, how your body reacts to one exposure versus ongoing exposure to the virus, we will hopefully have a better picture of all of these processes."

Alan Rothman, MD, an expert in infectious disease and vaccine research, explores how cross-reactivity may be activated by vaccines in order to advance development of those that provide optimal protection with minimal potential side effects. "How does a vaccine affect the memory your body has for other viruses you had before? All of this research will in essence feed into" guiding vaccination or treatment strategies.

Vitae: Grants and Research

New and competitive renewal grants of $100,000 or more are listed here according to department or center and funding sources.

BIOCHEMISTRY & MOLECULAR PHARMACOLOGY

National Institutes of Health

William R. Kobertz, PhD, assistant professor: *K+ Channel Complexes: Assembly, Trafficking and Function,* one year, $312,379; recommended for four more years, $1 million.

Alonzo H. Ross, PhD, professor: *Role of Doublecortin in Glioma Cell Invasiveness,* one year, $139,320; recommended for one more year, $139,643.

IRVING S. AND BETTY BRUDNICK NEUROPSYCHIATRIC RESEARCH INSTITUTE

National Institutes of Health

Schahram Akbarian, MD, assistant professor of psychiatry: *Chromatin Alterations in Rett Syndrome,* one year, $291,600; recommended for four more years, $1.2 million.

Evgeny I. Rogaev, PhD, professor of psychiatry: *Molecular-Genetic Mechanisms for Early-onset Obesity,* one year, $155,800; recommended for two more years, $325,000.

CANCER BIOLOGY

American Cancer Society

Leslie M. Shaw, PhD, assistant professor: *Mechanism of alpha6/beta4 Integrin-dependent Metastasis,* three years, $540,000.

National Institutes of Health

Lucia R. Languino, PhD, professor: *Beta1 Integrins and IGF-I Receptor in Prostate Cancer,* one year, $287,955; recommended for four more years, $1.2 million.

U.S. Army Medical Research and Materiel Command

Lucia R. Languino, PhD, professor: *In Vitro and in Vivo Modulation of Prostate Cancer Cell Proliferation by Integrins and Type 1 Insulin-like Growth Factor Receptor,* two years, $596,250.

CELL BIOLOGY

National Institutes of Health

Elizabeth J. Luna, PhD, professor: *Cytoskeleton-Membrane Interactions,* one year, $411,240; recommended for three more years, $1.2 million.

CENTER FOR INFECTIOUS DISEASE AND VACCINE RESEARCH

Department of Health and Human Services

Jennifer S. Daly, MD, professor of medicine: *Categorical Grant Program to Provide Outpatient Early Intervention Services with Respect to HIV Disease,* one year, $481,468; recommended for four more years, $1.9 million.

National Institutes of Health

Robert W. Finberg, MD, the Richard M. Haidack Professor of Medicine and chair: *Innate Immunity and Herpes Simplex Pathogenesis,* one year, $358,500; recommended for four more years, $1.3 million.

Katherine F. Ruiz de Luzuriaga, MD, professor of pediatrics: *Killer Cells & Viral Load in Vertical HIV Infection,* one year, $364,500; recommended for four more years, $1.3 million.

EMERGENCY MEDICINE

National Institutes of Health

Steven Bird, MD, assistant professor: *Assessment of Organophosphate Neurotoxicity,* one year, $128,273; recommended for three more years, $366,209.

FAMILY MEDICINE & COMMUNITY HEALTH

Department of Health and Human Services

Robert A. Baldor, MD, professor: *Residency Training in General and Pediatric Dentistry,* one year, $130,653, recommended for two more years, $228,733.

MEDICINE

Families of Spinal Muscular Atrophy

Ravindra N. Singh, PhD, assistant professor: *Characterization of a Novel Intronic Element as the Potential Therapeutic Target for SMA,* two years, $194,314.

National Institutes of Health

Zheng Zheng Bao, PhD, assistant professor: *Expression and Regulation of the Axon Guidance Cues,* one year, $327,300; recommended for four more years, $1.5 million.

Uri Galili, PhD, professor: *Increase/gp120 Immunogenicity/Linked Alpha-Gal Epitopes,* one year, $243,000; recommended for one more year, $243,000.

Elizabeth A. Jackson, MD, assistant professor: *Diet and Exercise Counseling Among Patients with Coronary Heart Disease,* one year, $127,035; recommended for four more years, $500,000.

Vitae: Grants and Research

MEYERS PRIMARY CARE INSTITUTE

Agency for Healthcare Research and Quality

Jerry H. Gurwitz, MD, the Dr. John Meyers Professor of Primary Care Medicine and professor of medicine: *Health Information Technology in the Nursing Home,* one year, $475,566; recommended for two more years, $1 million.

MOLECULAR GENETICS & MICROBIOLOGY

National Institutes of Health

Allan Jacobson, PhD, professor and chair: *Messenger RNA Metabolism in Yeast,* $589,822; recommended for three more years, $1.9 million.

John M. Leong, MD, PhD, professor: *Actin Pedestal Formation by EHEC O157: H7,* one year, $416,018; recommended for four more years, $1.7 million.

Janet M. Stavnezer, PhD, professor: *Molecular Basis of Immunoglobulin Heavy Chain Switch,* one year, $405,000; recommended for four more years, $1.6 million.

MOLECULAR MEDICINE

American Cancer Society

Michael H. Brodsky, PhD, assistant professor: *DNA Damage Response Genes and Drosophila Telomere Function,* three years, $720,000.

National Institutes of Health

Usha Acharya, PhD, assistant professor: *Ceramide Metabolism and Photoreceptor Homeostasis,* one year, $350,550; recommended for four more years, $1.5 million.

Michael P. Czech, PhD, professor and chair: *Properties of the High Affinity Insulin Receptors,* one year, $497,440; recommended for three more years, $1.6 million.

Nathan Lawson, PhD, assistant professor: *Role of Plcg1 in Vegf Signaling,* one year, $319,950; recommended for four more years, $1.3 million.

Mario Stevenson, PhD, the David J. Freelander Professor of AIDS Research: *Role of Monocytotropism in HIV/SIV Pathogenicity,* one year, $361,036; recommended for four more years, $1.8 million.

William E. Theurkauf, PhD, professor: *RNA Localization and Translational Control,* one year, $509,117; recommended for four more years, $2 million.

NEUROBIOLOGY

National Institutes of Health

David R. Weaver, PhD, associate professor: *Genetic Analysis of Circadian Oscillator Hierarchy,* one year, $187,313; recommended for one more year, $225,238.

Smith Family New Investigator Awards Program of the Richard and Susan Smith Family Foundation

Marc R. Freeman, PhD, assistant professor: *Characterizing Core Components of the Glial Cell Machinery,* two years, $200,000.

NEUROLOGY

ALS Association

Lawrence J. Hayward, MD, PhD, associate professor and **Ashutosh Tiwari,** PhD, instructor: *Aberrant Hydrophobicity of ALS Mutant Cu/ZN Superoxide Dismutase (SOD1) Variants and its Relation to Toxicity,* two years, $146,000.

National Institutes of Health

Vivian Budnik, PhD, professor: *Development of Neuromuscular Junctions,* one year, $374,625; recommended for four more years, $1.5 million.

PATHOLOGY

National Institutes of Health

Leslie J. Berg, PhD, professor: *Tec Family Tyrosine Kinases in T-cell Signaling,* one year, $364,500; recommended for four more years, $1.5 million.

Joonsoo Kang, PhD, assistant professor: *Regulation of T-cell Development by SOX13,* one year, $319,500; recommended for four more years, $1.3 million.

Yan Shi, PhD, research assistant professor: *Molecular Identification of an Endogenous Adjuvant,* one year, $202,500; recommended for one more year, $243,563.

PEDIATRICS

Department of Health and Human Services

Charles D. Hamad, PhD, associate professor: *Continuing Education/Distance Learning,* one year, $129,751; recommended for two more years, $255,975.

PSYCHIATRY

William T. Grant Foundation Distinguished Fellow Grant

Joanne Nicholson, PhD, associate professor: *Transforming the Child Welfare System to Improve Outcomes for Children and Youth Whose Parents Have Mental Illness,* one year, $212,657.

It is not uncommon for alumni to tell me that their education opened many doors for them. Our dedicated faculty, innovative programs of study and accomplished student body combine to make their diplomas uniquely valuable. Now we've opened another door, so to speak, that beckons everyone who visits our campus into an improved facility for learning.

MESSAGE FROM THE CHANCELLOR/DEAN

Campus Modernization continues on the Worcester campus, and this fall a major milestone of the project will be reached—our opening of the new Medical School entrance and lobby, as well as the opening of a new south hospital entrance and lobby for patients and visitors. The Medical School entrance and lobby, easily distinguishable and immediately noticed with its impressive awning and accents in blue, will usher faculty, students, staff and visitors into a modern foyer that leads to new and renovated areas within.

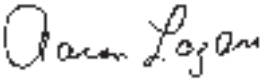
The new UMass Memorial entrance and lobby, which will be called the "Remillard Family Pavilion" to acknowledge the generous $10 million gift made by the Remillard Family Foundation to the UMass Memorial Emergency Care Campaign, is a distinctive and functional entrance for the hospital and a beautiful complement to the new emergency department, scheduled to open in 2006. The emergency department will be known as the "Duddie Massad Emergency and Trauma Center," in acknowledgement of a $12.5 million gift by longtime Worcester businessman David "Duddie" Massad.

The opening of the Medical School entrance and lobby and the Remillard Family Pavilion will make a marked improvement in the accessibility to educational programs and health care services. We thank our students, faculty and staff for the patience and cooperation they have shown during Campus Modernization. Throughout it all, they've helped us uphold our national reputation for distinction in education, research, public service and clinical care.

On the following pages, you'll learn about three alumni who are making a difference in their communities everyday. Pediatrician Cara Kaupp, MD, specializes in caring for internationally adopted children at her practice in New Hampshire. This summer she traveled to China with a group of adoptive families to medically prepare their new children for life in the United States.

Graduate School of Nursing alumna Kristine Ruzycki is chief of nursing services at MIT Medical, which delivers care to the Massachusetts Institute of Technology community. She was instrumental in MIT Medical's decision to offer patients a choice of designating a nurse practitioner as their primary care provider, as an alternative to a physician, and in September 2004, was the first nurse to be appointed director of student health at MIT.

Finally, Dr. Thomas Fabian met a need in his community by opening a free-standing imaging center—Advanced Imaging of Port Charlotte, Florida—earlier this year. "The lack of medical services in this region of southwest Florida was creating a great hardship for patients," he says. Dr. Fabian found that his medical education was directly relevant to his business endeavor. "I remember taking a community medicine class that focused in part on evaluating the health care needs of a community with an eye toward developing and providing services. The knowledge from that class was essential… ."



Aaron Lazare, MD

Vitae: Alumni Profiles

Kristine A. Ruzycki, APRN, BC, '88, '93

Two-time Graduate School of Nursing alumna Kristine Ruzycki has enjoyed expanding roles in diverse health care settings, serving a spectrum of patient populations from hospital- to community-based, employees to students, adolescents to elders. Each stage of her education prepared her for the next step: "The GSN paved the way for me to be innovative and experimental, learning from experience and outcomes, and applying them to practice," she said. "Having worked with nurse practitioners from every graduate nursing school around, I've discovered that the education and preparation I received at UMass Worcester is equal to or better than any other."

A 1972 diplomate of Worcester's St. Vincent Hospital School of Nursing, in 1980 Ruzycki earned her bachelor's degree in nursing from Worcester State College, where future GSN Professor and Dean Lillian Goodman founded the first baccalaureate nursing degree program in Central Massachusetts. Upon deciding to pursue a master's degree, Ruzycki called Dr. Goodman for a reference. "She told me UMass Worcester was starting its own nurse practitioner program, so I decided to wait."

A member of the GSN's first class, Ruzycki graduated with a concentration in nursing administration/management, one of three tracks the school originally offered. As she advanced in management, there was just one problem: "I missed the direct patient care, which is why I became a nurse in the first place." So she returned to the GSN in 1992, again as one of an inaugural class, this time in the school's post-master's certificate program for community health/adult nurse practitioner. She supplemented her educational activities with a role as the GSN's first Alumni Association president, an office she held for ten years, and eventually received the Association's award for significant contributions to the GSN.

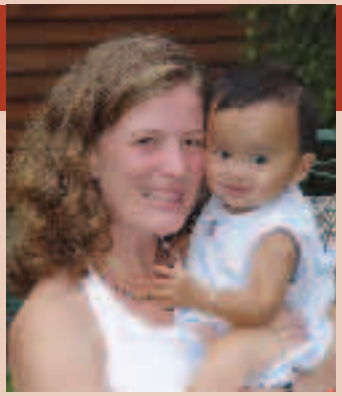
Today Ruzycki blends clinical care with management as chief of nursing services at MIT Medical, a multi-specialty ambulatory group practice, an inpatient unit and an HMO serving students, faculty, staff and retirees of the Massachusetts Institute of Technology community. In addition, in September 2004, she was appointed director of student health, the first nurse to hold that position at MIT. (Prior to joining MIT, Ruzycki served as director of Employee Health Services at UMass Memorial, as well as executive director of the UMass Memorial Home Health & Hospice Department.) In another first, Ruzycki was instrumental in MIT Medical's decision to offer patients a choice of designating a nurse practitioner as their primary care provider, as an alternative to a physician.

"People are starting to understand nurses' unique abilities to provide primary care," she said. "Those of us with advanced degrees have contributed to this." -SLG

Thomas Fabian, MD '76

When Dr. Thomas Fabian opened his free-standing imaging center—Advanced Imaging of Port Charlotte, Florida—earlier this year, it was the realization of a professional dream. "The motivating factor was need in the community," Dr. Fabian said. "When my father-in-law was suffering from cancer, he had to travel 200 miles for treatment. The lack of medical services in this region was creating a great hardship for patients."

The 12,000-square-foot facility, with its $10 million in equipment, is a world show site for cutting-edge imaging technology and attracts patients from as far away as Miami and Orlando. Through partnerships with GE, Siemens and Hologics, Dr. Fabian is able to offer a comprehensive range of services, including bone density scanning, mammography, ultrasound and breast MRI, as well as general imaging services such as X-ray and nuclear medicine exams. "With a full range of diagnostic tools under one roof, patients in the surrounding communities now have much quicker access to services they normally had to wait months for." In addition, the film-less Picture Archiving



Cara Douville Kaupp, MD ’oo

Perhaps one of the most striking aspects of the scene Dr. Cara Kaupp witnessed this summer in a Chinese government building was the silence. Nannies passed babies to dozens of their new adoptive parents in one massive transfer, yet few of the children cried. Dr. Kaupp realized this unexpected reaction was a result of the children’s time in an orphanage, where the human bond rarely forms. When no attention would be paid, “the children learn very quickly that crying doesn’t help,” Dr. Kaupp explained.

But the lack of attention is over for the children Dr. Kaupp met as the pediatrician traveling with parents adopting through China Adoption With Love, Inc. Her trip was her first to China, but instrumental in preparing the children medically for their new lives in America. Dr. Kaupp says that the experience transformed her as well, adding “so much depth to me as a pediatrician and a person…a family doesn’t have to be biological; giving birth is a small part of being a parent.”

At Partners in Pediatrics in Nashua, New Hampshire, Dr. Kaupp specializes in the care of internationally adopted children. She medically evaluates them on behalf of agencies, and patients include children who were born in Romania, Ethiopia and China. During her time in Changsha, Hunan Province, her skills as a pediatrician were put to the test, as she had no advanced medical equipment to use during exams. “I brought a stethoscope, otoscope, growth curve charts, a basic first aid kit and donated antibiotics. We used the hotel bathroom scales to weigh the babies. It was frustrating because with one of the sick children, I had to ask myself, ‘Where do we go from here?’” The rural hospital posed the danger of new infection.

The parents and Dr. Kaupp expected the babies would have problems, but some were more severe than even she had anticipated. Yet, one grateful parent, Leslie Granese, director of marketing for the University of Massachusetts President’s Office, says Dr. Kaupp was key to enabling her to take her baby home. “Maya had gotten sick at the orphanage and lost about a third of her body weight. She was emaciated and dehydrated,” said Granese. “But Cara was able to discern that Maya could be healthy again with the right care. Cara was unrelenting in her commitment to Maya [pictured with Dr. Kaupp] and deserves much of the credit for her recovery.”

Dr. Kaupp developed her interest in international adoption while a resident at University of Rochester, but her love of pediatrics grew from the example of her UMMS faculty advisor, Dr. Linda Sagor. As a student, Dr. Kaupp enjoyed the community outreach and patient advocacy programs UMMS exposed to her—and she met her future husband here, Gregory Kaupp, MD ’98. He also has a practice in Nashua, Medicine Pediatrics, where he sees adult and pediatric patients. The couple plan to adopt internationally when they start their own family. “We always knew we would adopt, but this experience in China really cemented it for us.” -ALB

and Communications System (PACS) technology gives patients and their doctors access to test results quickly. “A radiologist from UMass Medical School could log on to our system and view their own patient’s scans on a monitor immediately after an image is created.”

As Dr. Fabian was developing the business side of Advanced Imaging, he found that his medical education was directly relevant. “I remember taking a community medicine class [now the Community Health Clerkship] that focused in part on evaluating the needs of a community with an eye toward developing and providing services. The knowledge from that class was essential in setting up this business and complemented the expertise my business partners brought to the project.” He also credits Dr. Carl D’Orsi with teaching him about strong leadership by example. And he built lifelong relationships while at UMMS, including with Robert Leone, MD ’77, with whom Dr. Fabian worked in Massachusetts prior to developing Advanced Imaging. “I had opportunities to go to med school in Boston, but I chose UMMS because I knew I would be a part of a community and be known by my professors and classmates. It seemed like the ultimate education.” -EC

Vitae: Class Notes

Photo by Ed Wozniak. Printed with permission.

Dr. Johnson before her office shrine to the Red Sox.

1975

Erica E. Johnson, MD, was appointed chief of the Division of General Internal Medicine at Newton-Wellesley Hospital in January 2005. With nearly 100 internists in the division, she has several immediate challenges, the most pressing being universal implementation of an electronic medical records system. Dr. Johnson, an assistant professor of medicine at Tufts University and adjunct assistant professor at UMass Medical School, was profiled in the *Wellesley Townsman* on February 3 regarding her new role and her career as a primary care physician and teacher. She was quoted in the article, "I'm convinced that my patients get better care when medical students and residents are involved because they are looking at patients and illnesses in a new light." Dr. Johnson was the 2004 recipient of Newton-Wellesley's Locke Award for Excellence in Primary Care Teaching in Medicine. She has served on the Partners Community Healthcare, Inc. Board of Trustees for the last five years.

Anita Karcz, MD, MBA, is chief medical officer for the Institute for Health Metrics (IHM), a nonprofit organization she co-founded. IHM automates the process of extracting data from hospital information systems for quality and operational indicators, allowing clinical personnel to spend their time improving clinical practice rather than gathering data and generating reports. Dr. Karcz also serves as an advisor or board member for early medical companies and is an active volunteer in entrepreneurial business organizations such as the Commonwealth Institute and the MIT Enterprise Forum.

1977

Robert A. Klugman, MD, clinical associate professor of medicine at UMass Medical School, is vice chair and chief quality officer for the Department of Medicine and medical director for managed care at UMass Memorial Health Care. He keeps a busy practice in Westborough, Mass. and is active in local community organizations. Dr. Klugman's daughter, Ashley, attends law school in New York City, while daughter Allison is a senior at Providence College.

Robert G. Leone, MD, is chairman of Northeast Radiology Associates, serving Anna Jaques Hospital in Newburyport, Mass., as well as two radiology offices and two free-standing MRI centers. He and his wife, Janet, celebrated their 32nd wedding anniversary July 14. Their 24-year-old daughter, Melissa, teaches computer science at a private boys school in Asheville, North Carolina, as she studies for her master's degree in information technology at George Washington University. Their son, Andrew, is 21 and finished his junior year at Boston College with a 3.8 GPA. "Despite my telling him all about current medical practice, he is in the process of applying to medical schools," says Dr. Leone.

1979

Eric D. Leskowitz, MD, recently received a two-year grant from the Langeloth Foundation to establish the Spaulding Rehabilitation Hospital Integrative Medicine Project. "I'm doing a lot of talking and writing about various forms of energy medicine," he says. His daughter, Shari, moved to San Francisco and son, David, to Boulder, Colo., so Dr. Leskowitz and his wife, Doreen, look forward to visiting some "nice places in the months ahead. All is well."

Christopher H. Linden, MD, professor of emergency medicine at UMass Medical School, practices emergency medicine at Milford Regional Medical Center and covers the toxicology service at UMass Memorial one week per month. The service, which now has four fellows and five faculty, provides physician-to-physician telephone consults and outpatient evaluations, and can accept inpatient transfers, both adults and children. Dr. Linden encourages physicians to call the service regarding their patients with real or suspected poisoning (in-state: 800-441-4131; out-of-state: 800-242-1554).

Andrew J. Miller, MD, in his 23rd year as a primary care physician in Douglas, Mass. and whose practice trains third-year UMass Medical School students and post-graduate residents in internal medicine, serves as associate professor of clinical medicine at UMMS and is chief of the Division of Community Internal Medicine in the Department of Medicine. He has served on multiple committees at the institution in order to enhance its primary care mission and continues to enjoy an active

role in the School of Medicine's Alumni Association, serving as vice president/treasurer. Wife Tina is a speech pathologist working with special needs children in preschool. Their son, Matt—born during Dr. Miller's fourth year in medical school—recently married and works as a computer engineer for Sun Microsystems. Daughter Jen recently graduated from Wheelock College with her master's degree and is a kindergarten teacher in Shrewsbury. "If this sounds too much like a Marcus Welby-like dream...it really is! And I owe it all to UMass Medical School!!" says Dr. Miller.

1980

Spouses **Abigail Adams, MD,** and **Brian Hennessy, MD,** both recently received promotions to the rank of clinical associate professor at UMass Medical School, she in internal medicine and he in anesthesiology. "We are very happy in our work here," they report, adding that outside the job, they have had recent visits with their daughter, Christy, and grandson, Cole, 6, who now live in Tanzania.

Ronald J. Hurley, MD, is newly appointed executive vice chairman of the Department of Anesthesiology, Perioperative and Pain Medicine at Brigham and Women's Hospital. His daughter, Meghan, just graduated from Boston College, while daughter Emily is a junior at Boston University. "Neither shows any inclination to follow dad's slowing footsteps," Dr. Hurley says. His wife, Beth, a former ICU nurse at UMass, runs a thriving garden design business.

1994

Jeffrey Cukor, MD, assistant professor of emergency medicine at UMMS and an emergency medicine physician at UMass Memorial Medical Center, was recently honored by the Worcester Police for his extensive involvement in the city's annual "Give Kids a Fightin' Chance" Celebrity Boxing Night held at the Worcester Palladium.

Dr. Cukor, who was recognized for coordinating a volunteer team of 36 emergency department residents to help him with the boxing program, said he was surprised and humbled by the award. "I feel honored to have received this plaque, and I'm proud to participate in a program that reaches out to kids in the Worcester community. The vision for the project comes from the Gang Unit, and I respect their enthusiasm and commitment."

The boxing event was created by the Worcester Police to raise money for programs that benefit inner city children—$250,000 has been raised over a three-year span. This year's fundraiser featured a 12-bout card of grudge matches between local celebrities, business leaders, politicians and law enforcement officials. "The biggest hurdle we faced putting this program together was medical clearance for the kids to fight and to have medical personnel on site," Police Sgt. Steven Roche said. "Jeff Cukor from day one has been there when we needed him and has gone above and beyond for these kids."

1998

Patrick McEnaney, MD, a specialist in minimally invasive surgery, has been appointed to the active medical staff at Milford Regional Medical Center and performs laparoscopic surgical procedures at the Medical Center's new Surgical Center. While a resident at UMass Memorial Medical Center, Dr. McEnaney received numerous awards, including the H. Brownell Wheeler Award for exceptional performance as a surgical resident, twice; the Outstanding House Officer Teaching Award; and the Resident Teaching Award.

Alumni of the School of Medicine, Graduate School of Biomedical Sciences and Graduate School of Nursing may send their latest news to alumni@umassmed.edu

Dr. Jeffrey Cukor holds the plaque the Worcester Police surprised him with at a recent Emergency Medicine department meeting.

Vitae: The Last Word

By Robert W. Finberg, MD, *the Richard M. Haidack Professor of Medicine and Chair of the Department of Medicine at UMass Medical School*

Dr. Finberg was a featured speaker at the September symposium, "Plague, An Abiding Scourge," presented by UMMS and the Worcester Art Museum in conjunction with the museum's celebrated exhibition, Hope and Healing: Painting in Italy in a Time of Plague, 1500-1800, which concluded on September 25. The symposium examined the responses to medical and economic catastrophes wrought by the plague—relevant today as the threat of contagion by disease persists. Dr. Finberg, an internationally renowned expert in infectious diseases, is pictured at left before one of the exhibit's most powerful pieces, St. Michael the Archangel Overcoming Satan.

Giovanni Andrea Sirani, oil on canvas from the Bob Jones University Collection, Bob Jones University Museum and Gallery

If we define plague by one of its more common usages, "a highly infectious, usually fatal, epidemic disease; a pestilence" (The American Heritage® Dictionary, Fourth Edition), then we have had plagues since we have had life. How, as a species, have we dealt with this kind of adversity? As doctors, what is our record?

In 1346 at the battle of the Genovese trading post of Caffa on the Black Sea, an army from Mongolia was being decimated by a mysterious disease. The Mongol commander catapulted bodies of the dead soldiers into the besieged city. In 1347 sailors on Genovese trading ships arriving in Sicily were noted to be dying as the ships docked. These sailors had a disease characterized by swellings in the armpits and groin and their clinical course was characterized by fever and hemorrhage. Within 18 months this disease would spread across the European continent and kill 20 million—one-third of the population. Whether the "Black Death" was actually bubonic plague is still debated. (A recent popular book argues that it was actually caused by an unusual strain of *B.antracis*, the cause of anthrax.)

Regardless of the actual cause of the horrific calamity that overwhelmed Europe, the exhibition "Hope and Healing" illustrates, literally, the response of humans, and to some extent, doctors to an infectious disaster. What can we learn from this experience, and how has it changed the way we face (and will face) such plagues?

Medical thought in the 14th century was still based on the concepts of Hippocrates, whose theory of Medicine was based on the body's own healing powers: he taught that it was the task of the physician to aid this natural process. This concept, which was a thousand years old in medieval times, led to the advice of the Greek physician Galen, who suggested that in times of plague, it was best for the physician to leave the area as quickly as possible. Many did exactly that. At the time, many of these distant medical scholars suggested that "miasmas," or unhealthy air, was the cause of the pestilence. Galen's Book of Fevers, which dealt with the interactions of different biles and humors in determining health, and still widely read at the time, was of little use.

Fortunately, the observation that the disease spread with people and animals was made by the people of the time. As a result, many walled cities acted to prevent the entrance of plague sufferers. The concept of quarantine, a 40-day prohibition on entry, was introduced, and the first public health board was founded in Florence in 1347. The plague years resulted in the institution of sanitary measures, the building of hospitals and importantly, in the understanding of the notion of "contagion," or the infectious nature of epidemics.

In our own time, the advent of the plague of HIV has led to fuller understanding of basic immunology (host defense) and virology, to the point that when two new plagues, Hantavirus Pulmonary Syndrome and SARS, were described in the late 20th and early 21st century, the organisms were identified within weeks and largely controlled within months. It is hoped that as we face plagues in the future, such as the influenza epidemics likely to come, we will be able to learn enough to advance medical knowledge and aid in the triumph over plagues.

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