

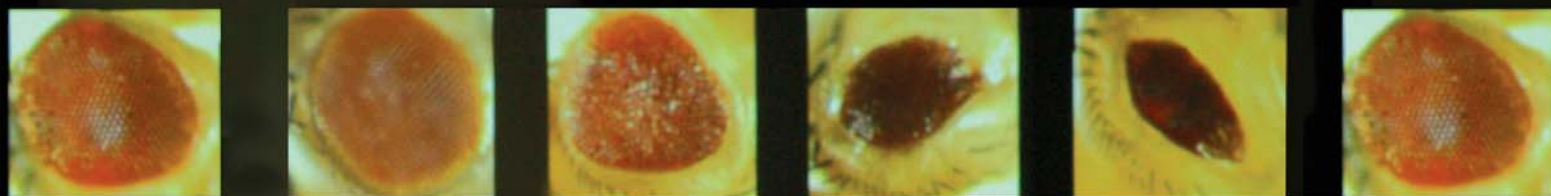
fall/winter 2004, vol. 27 no. 1



Diabetes Pre-emption

# Vitae:

The Magazine of  
The University of Massachusetts Medical School



Raising the Bar on Toll



A Place of Their Own

## **Vital** e: 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 and doctoral degree 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.



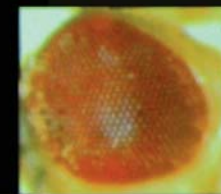
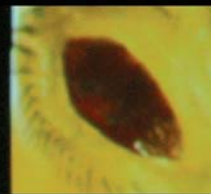
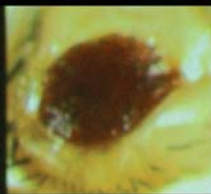
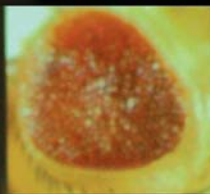
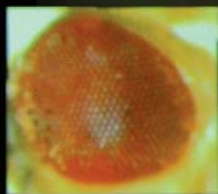
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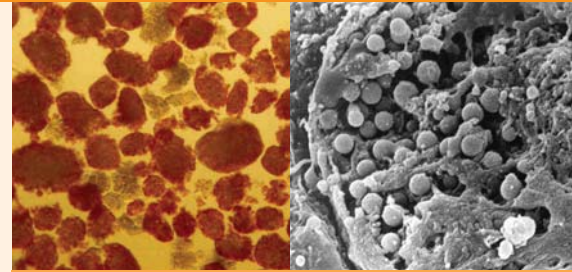
## Research Team to Test New Protocol for Islet Cell Transplantation

Taking new steps in research aimed at a better treatment for the most severe form of diabetes, two new clinical trials at UMass Medical School and UMass Memorial will soon transplant insulin-producing islet cells into a limited number of patients with type 1 diabetes. These transplant trials will use a novel protocol for therapy that may help the patients live free of insulin dependence—and in the latest advance, one of the trials will use insulin-producing cells isolated and cultured at UMMS.

“Our ultimate goal is to be able to transplant islet cells without the need for the patients to stay on powerful immunosuppressive drugs for the rest of their lives,”


said Aldo A. Rossini, MD, the William and Doris Krupp Professor of Medicine and chief of the Division of Diabetes at UMMS, leader of one of the teams preparing for the islet transplantation. “We hope this next round of trials will take us one step closer to that goal.”

The new protocol, funded by the National Institutes of Health, is based, in part, upon the experience leaders in the field gained while participating in the international Edmonton Protocol in 2002. At that time, UMMS was among 18 centers worldwide to participate in the clinical trial which tested a transplant protocol first developed at the University of Alberta in Edmonton, Canada to reverse



Islet cells (left) and insulin molecules within them

the insulin dependence of diabetics through islet cell transplantation.


As this issue of *Vitae* went to press, Cristiana Rastellini, MD, associate professor of surgery, and an expert in the field of islet cell isolation, received approval from the U.S. Food and Drug Administration to isolate and culture islet cells for use in a transplantation clinical trial, making UMMS one of just 10 such centers in the country with permission to culture these insulin-producing cells. 

## UMMS Scientist Receives ADA Renold Award

Michael P. Czech, PhD, UMMS professor and chair of molecular medicine, was awarded the American Diabetes Association’s 2004 Albert Renold Award in June. The award, named for the renowned physician and researcher, is given annually to an individual whose career is distinguished by outstanding achievements in the training of diabetes research scientists or the facilitation of diabetes research.

“I am honored to receive the Albert Renold Award in recognition of my role in mentoring the many students and postdoctoral fellows who have passed through my lab,” Dr. Czech said. “I know that each and every one of them has made a contribution to further advancing our knowledge of diabetes and obesity.”

Throughout his career, Czech has studied type 2 diabetes, which currently afflicts over 18 million Americans and is on the rise; his lab has made essential strides in understanding the fundamental mechanisms of the disease. An integral member and associate director of the UMMS Diabetes Endocrinology Research Center, one of 15 across the country funded by the National Institutes of Health, Czech directs a lab group of 20 scientists who are at the leading edge of research on diabetes, insulin

action and signal transduction pathways involved in metabolic diseases. In 2000, Czech received the prestigious Banting Medal from the ADA. 

Michael Czech, PHD, mentors Graduate School of Biomedical Sciences student Nana Hagan.




## Commonwealth Medicine Executive Wins Carballo

Jean Sullivan, JD, special assistant to the Deputy Chancellor for Commonwealth Medicine at UMass Medical School, is the latest UMMS employee to win the Manuel Carballo Governor's Award for Excellence in Public Service. The Carballo Award is presented annually to 10 state workers who exemplify "the highest standards of public service through exceptional accomplishment, exemplary leadership, creativity and productivity." UMMS employees have received this honor in four of the past six years.

Sullivan shares her extensive knowledge of Medicaid law and federal reimbursement through her responsibilities at Commonwealth Medicine, where she serves as the key liaison with the state Executive Office of Health and Human

Services. She was pivotal in the passage of the 2002 Act for a Healthy Commonwealth, implemented to stabilize the health care safety net by increasing support for Medicaid and for the Uncompensated Care Pool, which pays for medically necessary services provided by acute care hospitals and community health centers to low-income uninsured and underinsured individuals.

Sullivan also played a critical role in the development of the legislation that created the Division of Medical Assistance (DMA) and, most notably, was a leader in developing the Medicaid waivers that created MassHealth, the state health insurance program responsible for directly reducing the number of uninsured residents in the state. 




Jean Sullivan, JD

## Renowned Cell Biologist Joins Cancer Biology

Arthur M. Mercurio, PhD, whose career has focused on the mechanisms of invasive and metastatic cancer, has been appointed vice chair of the Department of Cancer Biology. Formerly the director of the Division of Cancer Biology and Angiogenesis in the Department of Pathology at Beth Israel Deaconess Medical Center and Harvard Medical School, Dr. Mercurio joined UMMS as a professor of cancer biology this fall.

"Art Mercurio is a leader in the field of breast cancer research and brings to our cancer program more than 20 years of experience in tumor cell biology," said Dario C. Altieri, MD, the Eleanor Eustis Farrington Chair in Cancer Research and chair of the Department of Cancer Biology. "He has a long history of translational oncology research and a vision to further build our research program and its interface with our clinical efforts."

Mercurio, whose research is focused on understanding the biology that contributes to the metastasis, or spread of solid tumors, particularly breast and colon cancers, will work closely with Azra Raza, MD, chief of the Division of Hematology-Oncology in the Department of Medicine, to spearhead the clinical cancer research initiatives at UMass Memorial Medical Center. Mercurio will also become the program leader of the solid tumor initiative at UMMS.

"My goal is to use the outstanding basic science here as a foundation for building programs that unravel mechanisms of metastasis and to work with oncologists and pathologists to translate this knowledge into more effective approaches for the clinical management of solid tumors," said Mercurio. 



Arthur Mercurio, PhD

## Accreditation Visit Reveals GSN Achievements

The Graduate School of Nursing completed a successful accreditation visit in early October by the Collegiate Commission on Nursing Education, an official accrediting body for U.S. baccalaureate and higher degree nursing programs. This on-site review followed several weeks and months of a self-study process undertaken by the GSN to evaluate the effectiveness of the graduate nursing education programs, assess the program's broad educational goals and examine the teaching environment of the graduate nursing students.

The CCNE validated that the GSN has met and is in compliance with each of the four areas: Mission and Governance, Institutional Commitment and Resources, Curriculum and Teaching Learning Practices, and Student Performance and Faculty Accomplishments. ©



Students interact during a Graduate Entry Pathway class, one of the GSN's innovative programs.

## MERIT Award Recognizes UMMS Professor's Sustained Excellence

Professor of Pathology Raymond Welsh, PhD, first received the grant, "Immunity and Virus Disease," in 1975 while at the Scripps Clinic in California. He brought the grant with him when he joined UMMS in 1980 and, in a recent letter to the National Institutes of Health (NIH), described a number of discoveries about basic mechanisms of viral immunology and immunopathology gleaned over the past 29 years from the grant's studies of viral infections in mouse models.

For this sustained record of scientific productivity, the NIH has awarded Welsh a highly selective extension on the grant for 10 years—in the form of back-to-back, five-year grants—totaling approximately \$4 million. The Method to Extend Research in Time, or MERIT Award, recognizes investigators whose research

competence and productivity are distinctly superior, and who are likely to continue to perform in an outstanding manner.

The MERIT Award also acknowledged Welsh's contributions in teaching; he has trained the most UMMS PhD graduate students, 11, of any GSBS faculty member to date and credits the graduate students, post-doctoral fellows and junior faculty who have worked in his lab with assisting in the development of the data that helped secure the MERIT Award.

Other UMMS investigators who have received NIH MERIT Awards include Mario Stevenson, PhD, the David J. Freeland Professor of AIDS Research, and Steven N. Treistman, PhD, professor of neurobiology and anesthesiology. ©

## On Apology a Critical Success

UMMS Chancellor and Dean Aaron Lazare received critical acclaim for his book *On Apology*, published by Oxford University Press in late August. The book explores the components of an effective and

sincere apology and how apology can be a healing act of honesty, humility and generosity in both interpersonal and international relations. Calling it a "jewel of a book that reveals the many facets of


the seemingly simple act of apology," *Publisher's Weekly* gave *On Apology* a starred review in its Sept. 27 issue. "Drawing on a vast array of literary and real-life examples...Lazare succeeds in

## Radiation Oncology Department Established

The growth of the UMass Medical School and UMass Memorial cancer research and care programs, and the increased interaction between radiation oncologists and their colleagues in departments such as Cancer Biology, led to the recent establishment of the Division of Radiation Oncology as a department.

“The members of the division are widely regarded for their expertise,” noted Chancellor and Dean Aaron Lazare.

“While their primary appointments in a number of different departments and divisions speak to the multidisciplinary nature of the specialty, having a common academic department makes good sense, and enhances our ability to recruit and retain academic physicians in this specialty.” The administrative change is expected to promote future research, academic and clinical care achievements in a vital area of cancer research and treatment.

Thomas (T. J.) FitzGerald, MD, leads the department as its chair. A 1980 graduate of UMMS and incumbent chief of the Division of Radiation Oncology, Dr. FitzGerald is a noted academic radiation therapist who is widely published and serves as director of the Quality Assurance Review Center, a National Cancer Institute-funded program for several important treatment protocols. 


## ‘Blue Ribbon’ Honors Lamar Soutter Library

The Lamar Soutter Library has received a 2004 Blue Ribbon Consumer Health Information Recognition Award for Libraries from the National Commission on Libraries and Information Science




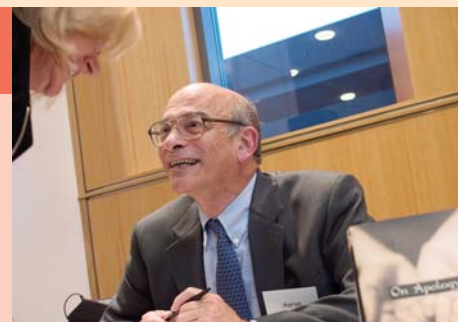
(NCLIS). The award recognizes one library in each state that best promotes a healthy lifestyle for its citizens; the libraries are nominated by state library agencies and winners are chosen based on the overall success of the library’s consumer health information services program, with emphasis on the program’s potential impact, innovativeness and adaptability.

The Soutter Library was one of three Massachusetts libraries nominated. It was particularly recognized for its role in providing information to the families of chronically ill children through the establishment of a pediatric library and for its training and outreach services provided through the Regional Medical Library

grant program. In the award letter, sent to Director of Library Services Elaine R. Martin, MSLS, the commission’s Chair Beth Fitzsimmons, PhD, wrote, “The Lamar Soutter Library’s...innovative creation and distribution of consumer health information has enabled Massachusetts to strengthen and build its consumer health information services, resulting in a healthier, well-informed community of users. The Library...epitomizes the concept of knowledge development and knowledge sharing, one of the basic tenets of professional librarianship.” 

showing that a true apology is among the most graceful and profound of all human exchanges,” the review read. “When it is sincere, [an apology] is not an end but a new beginning....Everybody on earth could benefit from this small but essential book.”

In addition to *Publisher’s Weekly*, *On Apology* has been reviewed or featured by *Oprah* magazine, *The Forward*, the *San Francisco Chronicle*, *Real Simple* magazine, ESPN’s “Outside the Lines” and Boston’s ABC affiliate WCVB-TV. 



Aaron Lazare, MD, at a recent book signing

## Corporate and Community Sponsorship Ensures Successful Walk to Cure Cancer

Blue Cross Blue Shield of Massachusetts returned this year as the presenting sponsor for the sixth annual Walk to Cure Cancer, held Sunday, September 26. The company also pledged \$50,000 per year for the next three years, beginning with the 2004 Walk.


Blue Cross Blue Shield participated in the inaugural Walk in 1999 and again in 2000 as a water stop and team sponsor. "In 2001, we were particularly inspired by the Massachusetts AFL-CIO's impressive participation in the Walk to Cure Cancer and compelled to match that commitment with our own contribution," said Senior Vice President of Corporate Relations Fredi Shonkoff. "We applaud the collaboration between the Mass. AFL-CIO and UMass Medical School with its clinical partner, UMass Memorial Health Care, in the effort to battle cancer, and are thrilled to continue our partnership with the Walk."

Over the years, Blue Cross Blue Shield employees who make up the "Blue Crew" have become integral to the success of the Walk, volunteering at water stops and along the route, as well as raising funds as they walk for a cure. Many of the 700 employees on the team have felt the impact of cancer—one is a nine-year survivor of brain cancer, for example. For this and many other similar reasons, members of the Blue Crew will continue to be a strong presence.

Blue Cross Blue Shield of Massachusetts, in partnership with the Mass. AFL-CIO, was joined by other corporate and media sponsors of the Walk, including Verizon, FleetBoston, NSTAR, Raytheon, Polar Corporation, Stop & Shop, New England Cable News, Worcester *Telegram & Gazette* and WSRS-FM/WTAG-AM. Flagship sponsors were: UMass Memorial Health Care, CWA Local 1301, Mailhandlers of N.E.



Members of presenting sponsor Blue Cross Blue Shield of Massachusetts' "Blue Crew" joined some 8,000 other participants at the 2004 Walk, which raised approximately \$660,000 for UMMS cancer research programs. Top, from left: Tom Cabral, Elaine Ermanski, Eileen Marsh, Teri Doucette and Dave Rudick; bottom, from left: Diana Poole, Karie Lee, Deb Mikelonis and Patricia Peters

Local 301, UFCW Local 1445, College of the Holy Cross and Worcester Fitchburg Building Trades Council. 

## Miller Named UMass Memorial Foundation Chief Executive




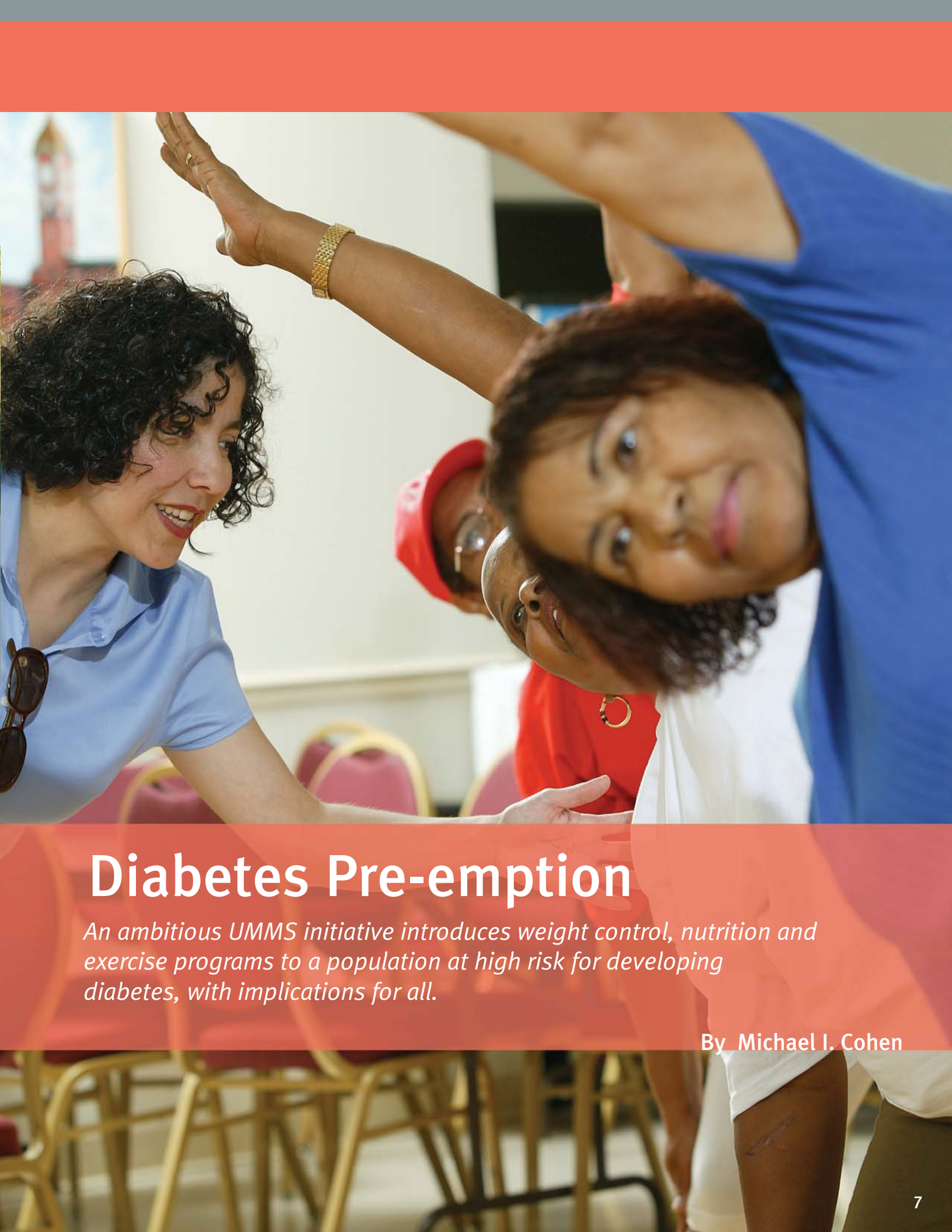
Rod Miller, a highly regarded development professional, was named chief executive of the UMass Memorial Foundation in June. He is leading the joint development and outreach functions of the school and clinical system as UMMS Vice Chancellor for Development and UMass Memorial Health Care Vice President for Development.

"Rod's accomplishments as a fundraiser

are impressive, but his talent for engendering involvement and nurturing support in a way that builds long and mutually productive relationships strikes us as his real strength," said Chancellor and Dean Aaron Lazare.

Miller joined the UMass Memorial Foundation from his most recent position as vice president for institutional advancement at the Cold Spring Harbor Laboratory in New York, one of the world's eminent biomedical research institutions. Previously, he developed comprehensive fund-raising and alumni programs at Polytechnic University in Brooklyn and Queensland University of Technology in his native Australia.

"With the fruits of the Human Genome Project in hand, the challenge to treat many debilitating diseases is no longer theoretical or technical, but financial," said Miller. "I am delighted to be joining the effort to develop opportunity for philanthropic investment that furthers the biomedical discovery and health care at UMass Medical School and UMass Memorial." 



# Diabetes Pre-emption

*An ambitious UMMS initiative introduces weight control, nutrition and exercise programs to a population at high risk for developing diabetes, with implications for all.*

By Michael I. Cohen

**Elliot Joslin, founder** of the famed diabetes clinic that bears his name, said nearly 100 years ago that with diabetes, genetics loads the cannon, but obesity pulls the trigger. Today, among the Latino population of the United States, the cannons of diabetes are booming.

To address the soaring incidence of diabetes among Latinos, both in the Commonwealth and across the country, UMass Medical School and the Greater Lawrence Family Health Center (GLFHC) have embarked on an ambitious clinical trial to test a program that researchers hope will prevent the onset of type 2 diabetes among members of the Latino population in Lawrence, Massachusetts. And if the trial succeeds there, it could point the way to a cost-effective approach for preventing type 2 diabetes in all populations.

“If we show that we can prevent diabetes among Latinos in Lawrence, then I would hope third-party payers would start covering this kind of intervention for anyone who needs it,” said Ira S. Ockene, MD, principal investigator of the clinical trial and the David J. and Barbara D. Milliken Professor of Preventive Cardiology and professor of medicine at UMMS. “Right now third-party payers are willing to pay \$50,000 to have stents placed in your heart when you are sick, but they’re not willing to pay \$1,000 for the counseling that



“A confluence of factors here add up  
to diabetes being much worse  
for Latinos in Lawrence.”

– Trinidad Tellez, MD (above center, and on page 7),

who will oversee the clinical trial’s operations on a daily basis.

She’ll be helped by Alexandra Luciano (left) and Nelida Vatcher (right).



Nutritionists like Migna Alecon (left) will take participants in the clinical trial food shopping, to help them select items that fit the protocol for diabetes prevention. She visits the El Pilon market in Lawrence, owned by Cesar Arias (right).

might prevent you from becoming sick. That’s unfortunate, and I hope if our study is successful, that will change.”

Dr. Ockene’s reference to heart disease in the context of a diabetes prevention program is hardly casual. The consequences of diabetes left unchecked are severe, including heart disease, stroke, blindness and kidney failure. “Diabetes is an extraordinary risk factor for heart disease,” Ockene said. “The major cause of death among diabetics is heart disease. So as a cardiologist, I have every reason to be interested in diabetes, just as I have every reason to be interested in smoking, high blood pressure and cholesterol.”

Conversely, diabetes can be managed with great success. Well understood measures, such as weight control, proper nutrition and increased physical activity can help most diabetics avoid the severe complications of the disease. So Ockene and his colleagues will attempt to translate that body of knowledge to help people who do not yet have diabetes remain free of the disease. “Based on all the studies we have done previously on how you get people to change their nutrition and physical activity, we believe we can develop an intervention that will be simple and workable in the real world—even in a very challenging environment like the one in Lawrence,” said Ockene.

John P. Mordes, MD, professor of medicine, a diabetes researcher and clinician at UMMS, worked as a consultant with Ockene to craft the clinical trial. “I see many Latinos in my clinic, so I know first-hand the magnitude of this problem,” Dr. Mordes said. “The goal of intervening before diabetes is present is, by far, preferable to providing care for someone who already has the disease. So it was a privilege for me to be asked by Dr. Ockene to be involved in the design of this trial.”

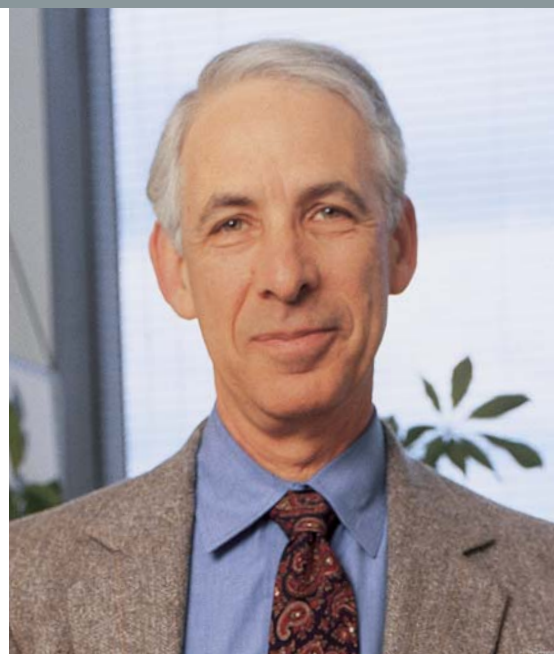
The effort is called the Lawrence Latino Diabetes Prevention Project (LLDPP), a four-year, \$2.6 million randomized clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (NIH). The study brings together an array of community groups including the Lawrence Council on Aging/Senior Center, which will be the host site for much of the programming; the YWCA of Greater Lawrence, which will help with recruitment and advise on community issues; UMass Lowell, which will analyze the blood samples from participants in the study; and the clinical and research resources of UMass Medical School and the GLFHC. “This is an excellent partnership between the academic researchers and the

community,” said Trinidad Tellez, MD, a clinician-researcher at the GLFHC, and an instructor in family medicine & community health at UMMS.

Dr. Tellez is a co-principal investigator of the prevention study. She’s also a member of the Executive Advisory Committee for the Massachusetts Diabetes Prevention and Control Program, which is working on a statewide diabetes action plan. “The burden of diabetes in Lawrence is high and there are a lot of challenges delivering this intervention,” Tellez said. “We believe that if we can prevent diabetes here, anybody should be able to do it anywhere.”

According to the American Diabetes Association (ADA), some 18 million Americans now have type 2 diabetes (often called adult onset diabetes, though the spike in obesity among children is driving a similar increase in diabetes among young people). More troubling is the rate of increase in the prevalence of the disease. According to federal statistics, the number of people diagnosed with type 2 diabetes jumped nearly 30 percent between 1997 and 2002.

While type 2 diabetes affects all segments of the population, it hits certain groups harder. Latinos, Asians, African Americans and Native Americans are genetically more



As principal investigator of the Lawrence diabetes study, Ira Ockene, MD, hopes it will yield dramatic results that can translate into a national model for diabetes prevention.

susceptible to diabetes, and that predisposition is enhanced by environmental or behavioral factors such as poverty and obesity that can hasten onset of the disease. The result: these minority groups suffer from diabetes at two to three times the rate of the majority population in the United States. In Massachusetts, the prevalence of type 2 diabetes among Latinos is 8.4 percent, compared to 4.7 percent for the Caucasian population.

Increasing daily physical activity is a key component of the clinical trial. Below, Lawrence residents representing a range of ages work out at the Senior Center.





The Lawrence Latino Diabetes Prevention Project is not just a series of classroom sessions filled with facts and figures. Participants will cook together and dine together for several months at the Lawrence Senior Center, learning recipes and eating habits that are both satisfying and healthful.

In Lawrence, one of the poorest communities in the Commonwealth, the problem is even worse, with the prevalence rate now pegged at 11.8 percent for Latinos of Puerto Rican and Dominican origin. “There’s a confluence of factors here that add up to diabetes being much worse for Latinos in Lawrence,” Tellez said.

As it tracked the soaring incidence of type 2 diabetes in Lawrence, the GLFHC began working several years ago to help patients better manage their diabetes. Funded by a REACH 2010 grant from the U.S. Centers for Disease Control and Prevention, the health center developed educational and clinical protocols aimed at diabetic Latinos. Under the leadership of Dean Cleghorn, EdD, UMMS associate professor of family medicine & community health and a director of one of the GLFHC clinics, the REACH program has built an infrastructure of diabetes education and care within the health center. A cornerstone of

that effort is the Diabetes Self-Management Education Program that was recently awarded “Education Recognition” from the ADA. “REACH is very important and very successful,” said Tellez, who also works on the REACH project. “We know it helps people who have diabetes. Now we’re trying to expand our scope and help the 42,000 Latinos in Lawrence who don’t have the disease, but who are at risk for developing diabetes.”

The Lawrence study will enroll a total of 400 Latinos who fall into this category. The participants will be split into two groups of 200 each, with one group (the control group) being given the usual care for non-diabetics now practiced in the Lawrence area. The other group (the intervention group) will participate in a 23-month-long series of programs designed by the research team to help reduce the risk of developing diabetes—primarily through weight loss and increased physical activity. Both groups will be followed for a year after the intervention classes end.

The preventive programs for the group will include cooking classes, exercise classes, strategies for food shopping and eating out at restaurants. There will be educational sessions about diabetes, the risk factors that lead to diabetes, and the consequences of the disease if left unchecked. The program will also include several psychosocial elements to help people deal with issues such as self-efficacy and depression that play a pivotal role in a person's ability to change behaviors. "Long-term adherence is the key to the success of this program," said Milagros C. Rosal, PhD, assistant professor of medicine at UMMS and co-principal investigator of the study. "When you want people to change, you have to make the changes easy and appealing, otherwise they won't adhere to them long-term. So we will try to build skills in situations that resemble their day-to-day activity."

Dr. Rosal works in the UMMS Division of Preventive and Behavioral Medicine. In the Lawrence study, Rosal will lead the effort to develop the programs that will convey the educational information on diabetes prevention to the intervention group. She will also develop practical literacy- and culturally sensitive strategies to facilitate attitudinal and behavioral change. "The Lawrence population presents multiple challenges, including language, culture and literacy level," Rosal said. "We'll need to use very little printed material, and we're planning to deliver the entire intervention in Spanish."

In that effort, Rosal will draw on insights she's gleaned from several years of work studying factors that facilitate or inhibit diabetes self-management among low-literate Latinos. That population typically suffers higher complication rates and higher death rates from diabetes as compared to Caucasians, Rosal said.

"Interestingly, we found that the problem was not access to health care; nearly everyone in the groups we studied had access to health care and was seeing their doctor several times a year. So the key issue, I believe, is that patients may not be receiving the information they need about diabetes in ways they could process and integrate into their daily lives."

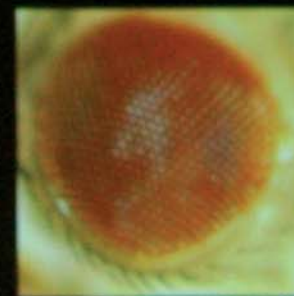
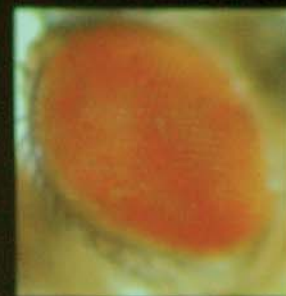
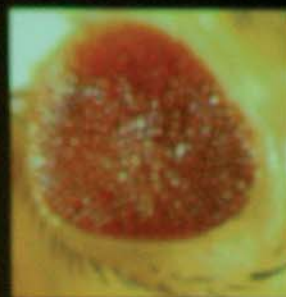
Rosal is now working closely with clinicians, nutritionists and counselors from UMMS and the GLFHC to finalize the methods and materials to be used in the Lawrence clinical trial. Plans call for a variety of group sessions, individual sessions, and follow-up phone calls to participants' homes. Recruitment for the study will begin this fall, and the first intervention classes are scheduled for January 2005.

Throughout the study, researchers will track participants' weight, body/mass index, blood pressure, cholesterol and blood glucose levels. That data will be used in a well-established formula that can predict a person's chance of developing diabetes within seven years, based on their metabolic profile. The test of the Lawrence study will be to see if the intervention group significantly reduces its risk of diabetes, compared to the control group. "Years ago when we studied cholesterol and heart attacks, we had to track people and prove we reduced the incidence of heart attacks in the group. We don't do that anymore because the linkage is a given—now we just focus on reducing cholesterol, knowing that will reduce heart attacks," Ockene said. "The same is true with diabetes. We don't have to follow the people in this study for 10 years to see what will happen. Our goal is to gain the knowledge that if we reduce these risk factors, the incidence of diabetes will be reduced." ©



**"When you want people to change, you have to make the changes easy and appealing.... We will try to build skills in situations that resemble their day-to-day activity."**

*— Milagros Rosal, PhD (left), has studied behavioral patterns of Latinos with diabetes in Springfield, Massachusetts and drew upon the experience to design program materials and methods for the Lawrence clinical trial.*



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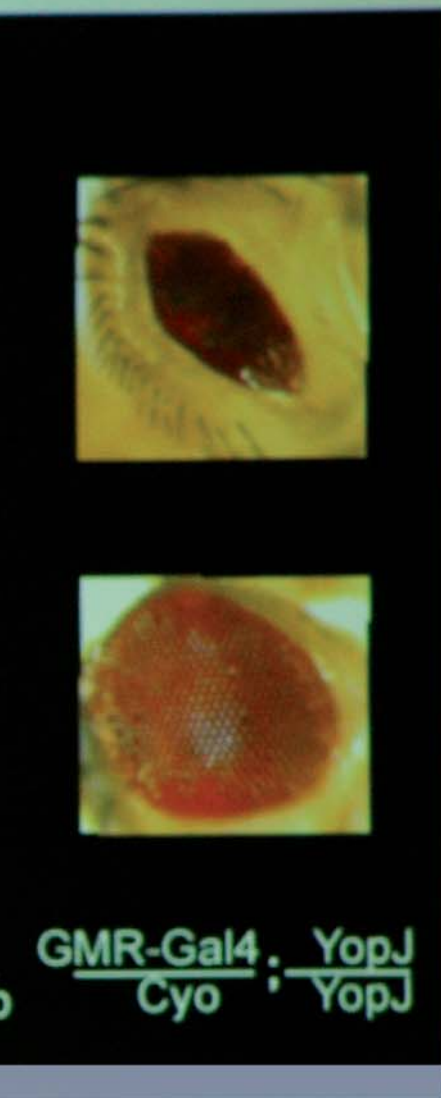
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# Raising the Bar on Toll

*The discovery of immune response ‘Toll-like receptors’—and the leadership of UMMS researchers in exploring their significance—is revealing potential impact on a range of diseases.*

By Kelly A. Bishop



For years, scientific inquiry into immunity was dominated by the study of the adaptive immune system—how the body fights infection with the complex production of antibodies that specifically target an invading pathogen. In recent years, however, a series of new discoveries has reinvigorated the study of the innate immune system, one with much in common among plants, insects and mammals. With the recent discovery that the gene Toll from the fruit fly (*Drosophila*) plays a critical role in insect immunity, and the identification of mammalian Toll counterparts called “Toll-like receptors,” innate immunity is becoming one of the hottest areas of current research. Leading the way, UMass Medical School is rapidly building a core group of investigators who are further elucidating how Toll-like receptors (TLRs) work as a means to gain insight into the innate immune response.

The innate immune system—the only form of immunity in insects and the precursor to the adaptive immune system in mammals—acts as the first line of defense against a range of pathogens. Whereas adaptive immunity involves the body’s response to an invading microorganism with the production of specific antibodies and lymphocytes that precisely target and combat the invader, the innate immune system reacts non-specifically immediately upon infection, before adaptive immunity is triggered. When signaled, the body’s cells respond to pathogens by secreting “cytokines,” proteins that function as mediators in the generation of an immune response. Recent research has shown that TLRs somehow recognize pathogens right away, activating the critical signaling pathways that stimulate this initial immune response. A number of new investigations at UMMS—a representative few of which are described in the following pages—are targeted at understanding the mechanisms

by which TLRs recognize pathogens, how they activate signaling pathways, and, ultimately, how TLRs can be manipulated to limit or promote the immune response.

A developmental biologist, UMMS Associate Professor of Molecular Medicine and Cell Biology, Y. Tony Ip, PhD, was working on the embryonic development

“...one hypothesis is that the body needs some sort of ‘danger’ signal, a signal that activates the immune response. Current research indicates...Toll-like receptors.”

– Neal Silverman, PhD (pictured left)

of the fruit fly when he became interested in the Toll gene. First identified in Germany in 1980 as a gene in the pathway that controls dorsoventral patterning—the development of the fruit fly from the back to the belly—it soon became apparent that there were similarities between the Toll pathway in tiny fruit flies and a mammalian pathway (the Interleukin 1 Inflammatory Pathway) that was known to play a significant role in immunity. “We found that both pathways use a similar family of transcription factors [NF-kappaB],” said Dr. Ip. “So we asked, ‘Why is a transcription factor for inflammatory gene expression and the regulation of T cells and B cells in mammals so similar to a protein that controls dorsoventral development in *Drosophila*?’ ”

Ip's research focused on the *Drosophila* equivalents of NF-kappaB (three fly genes called, in the whimsical way of fruit fly gene-naming, Relish, Dorsal and Dif) to answer that question. "We started working on the Toll-Dorsal pathway and we showed that Dorsal was not only similar in sequence to NF-kappaB, but it also functions in a similar way. In the fly embryo, Dorsal binds to sites that are akin to the mammalian NF-kappaB signaling pathways, similarly regulating the genetic response that controls the developmental process as well as inflammation and immunity." Subsequent investigations proved that all three NF-kappaB-related proteins, Dorsal, Relish and Dif, play key roles in the *Drosophila* immune response. Toll, it was shown, was an important contributor to the fly's immune response.

Ip is continuing his research into the Toll pathway to determine whether all of the Toll genes in *Drosophila* (nine have been identified in the fruit fly; 11 TLRs have been identified in mammals) play a role in the innate immune response and also whether they have additional function in *Drosophila* beyond immunity.

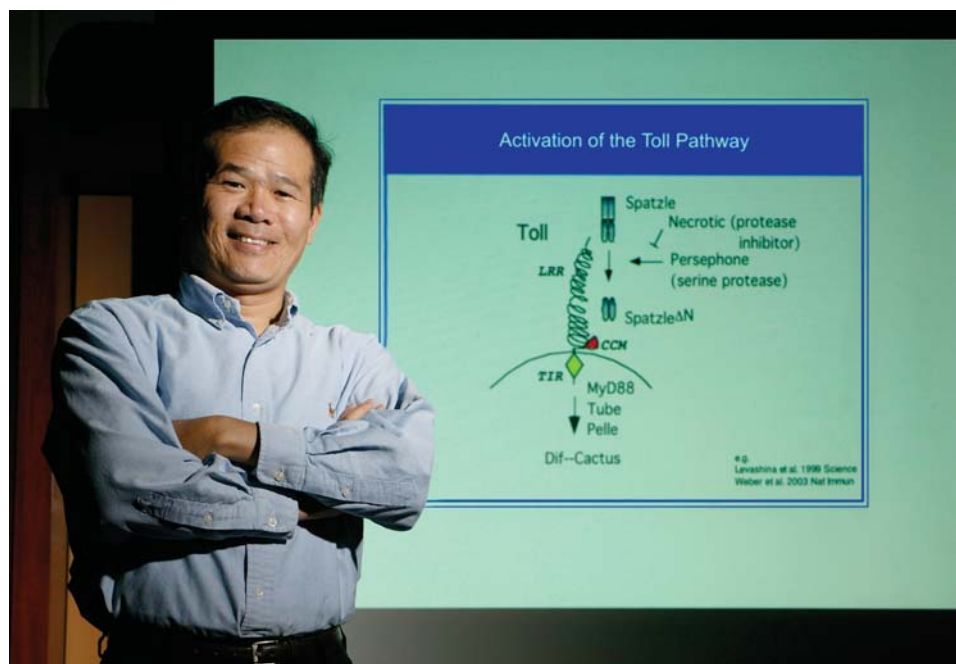
Like Ip, UMMS Assistant Professor of Medicine Neal Silverman, PhD, is using *Drosophila* as a model system to study the mechanisms that allow pathogens to lead to specific immune responses and to see what's responsible for transmitting a signal from the site of infection to the nucleus of an immune responsive cell. "Immunologists have always asked the question, 'How does the body recognize something as being a pathogen so it knows to attack it?'" Dr. Silverman said. "It turns out there are a lot of different answers to that question, but one hypothesis is that the body needs some sort of co-stimulatory or 'danger' signal, a signal that activates the immune response. Current research indicates that such signaling is most likely accomplished through Toll-like receptors."

One model that Silverman is interested in is the plague agent *Yersinia pestis*. Certain pro-

teins made by *Yersinia* can effectively stop the innate immune response. "*Yersinia* can make proteins and then when it infects a mammal, it can nuzzle up to its cells and inject bacterial protein into them, at which point it wreaks havoc. In particular, *Yersinia* makes six of these proteins that get injected and together they collaborate to effectively stop the immune response," Silverman explained. One of these proteins, in fact, has been shown to prevent the activation of NF-kappaB and the production of cytokines. To understand how this protein inhibits

the immune response, Silverman is examining how it blocks the signaling pathways to prevent the cytokine response and is trying to determine what genes it is targeting in the *Drosophila* innate immune response pathways.

"I think this is a really exciting area of research in terms of possible clinical advances, bench to bedside," said Silverman, "That's because a whole raft of diseases—some might even go so far as to say all diseases—have in their pathology a contribution from the innate immune



Tony Ip, PhD (above), is pictured against the illustration of the *Drosophila* Toll Pathway, which has been shown to play an important role in both the developmental process and immunity. At right, cancer biologist Michelle Kelliher, PhD, is investigating the effect of protein RIP1, on the signaling of Toll-like receptors 3 and 4. Previously implicated in the signaling of tumor necrosis factor, an important pro-inflammatory cytokine affecting many inflammatory diseases, Kelliher's research has shown that RIP1 may also play an important role in innate immunity.



Prior page: Neal Silverman, PhD, is poised before a series of images demonstrating the effects of YopJ, a protein of plague agent *Yersinia pestis*, as manifested through the fruit fly eye (above). Through *Drosophila*'s optical instrument, Dr. Silverman is investigating the mechanism by which YopJ can inhibit the immune response.

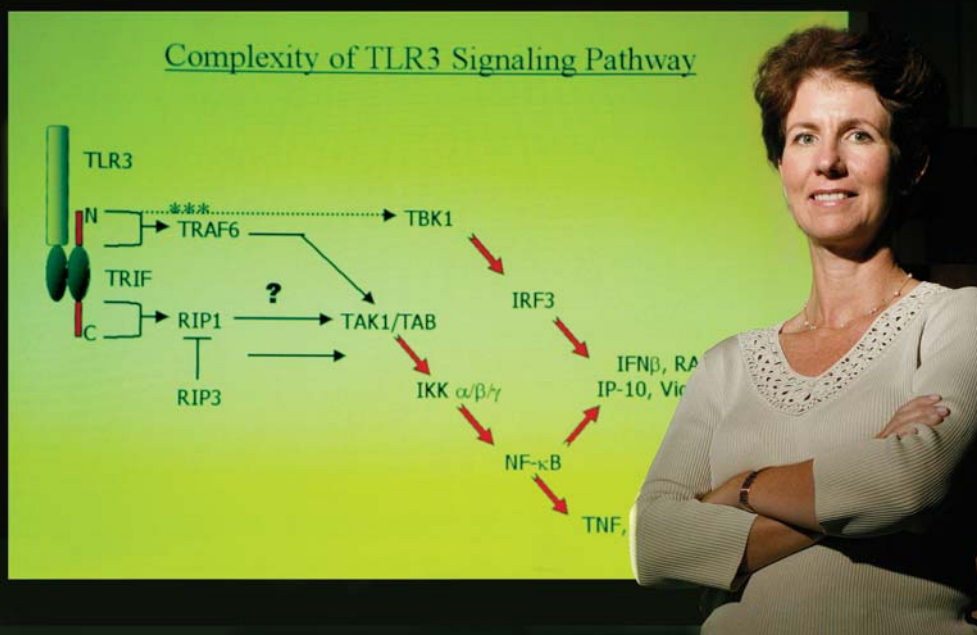
response—something that was not fully appreciated just five or 10 years ago. But with the discovery of these Toll-like receptors, it's really blossomed into a dynamic area of research with the potential to have impact in a range of diseases.”

With cancer as one such potential disease, Michelle A. Kelliher, PhD, associate professor of cancer biology, has recently expanded her own research into the TLR realm. Dr. Kelliher's research into TLRs developed from a collaboration with Jurg Tschopp of Switzerland's University of

Lausanne. Kelliher and Dr. Tschopp have been working on a protein (RIP1) that participates in the NF-kappaB response to the signaling of TNF, or tumor necrosis factor, a cytokine that is produced by tumors and contributes to muscle breakdown, weakness and loss of appetite in cancer patients. TNF is also a very important pro-inflammatory cytokine affecting many inflammatory and immune diseases. “It is hard to find a disease that TNF doesn't influence,” Kelliher said.

Her studies indicate that RIP1 also exists in a pathway with Toll-like receptor 3 and potentially, Toll-like receptor 4. “That prompted us to test whether TLR 3 or 4 signaling is affected in mice that lack RIP1. We found that RIP1-deficient cells fail to activate NF-kappaB or produce cytokines when exposed to molecules that typically evoke a response from TLR 3.” Continuing research is focused on exploring what happens to the signaling and to inflammatory gene expression in the absence of RIP1. “While we previously thought that RIP1 was a specific mediator for TNF only, we now see that it is also a mediator for TLR 3 and possibly TLR 4 and that it may play a very important role in regulating innate immunity.”

To further investigate these questions, Kelliher's laboratory is working on developing a RIP1-deficient mouse model. “In the absence of RIP1 itself, mice don't survive, so it's an essential gene. We still don't know why those RIP1-deficient mice die, but one idea that has developed from TLR research is that the mice are very susceptible to infection because they cannot activate the cytokine response to pathogens.”



Although the innate immune system functions as a protective response, an overactive response can be a detriment. One investigation studies TLR response to a particular virus and the devastating effect inflammation can have.



Although the innate immune system functions as an important protective response, the opposite—an overactive immune response—can be a detriment to organisms. The manifestations of cytokine production, such as intense fever, shock-like symptoms and inflammation, can prove dangerous and all too often fatal. Evelyn A. Kurt-Jones, PhD, research associate professor of medicine, and Chair of Medicine Robert W. Finberg, MD, the Richard M. Haidack Professor of Medicine, are investigating the mecha-

tion associated with viral infection can be beneficial to the host, if that inflammation occurs in a closed compartment like the brain and skull it can actually be detrimental.”

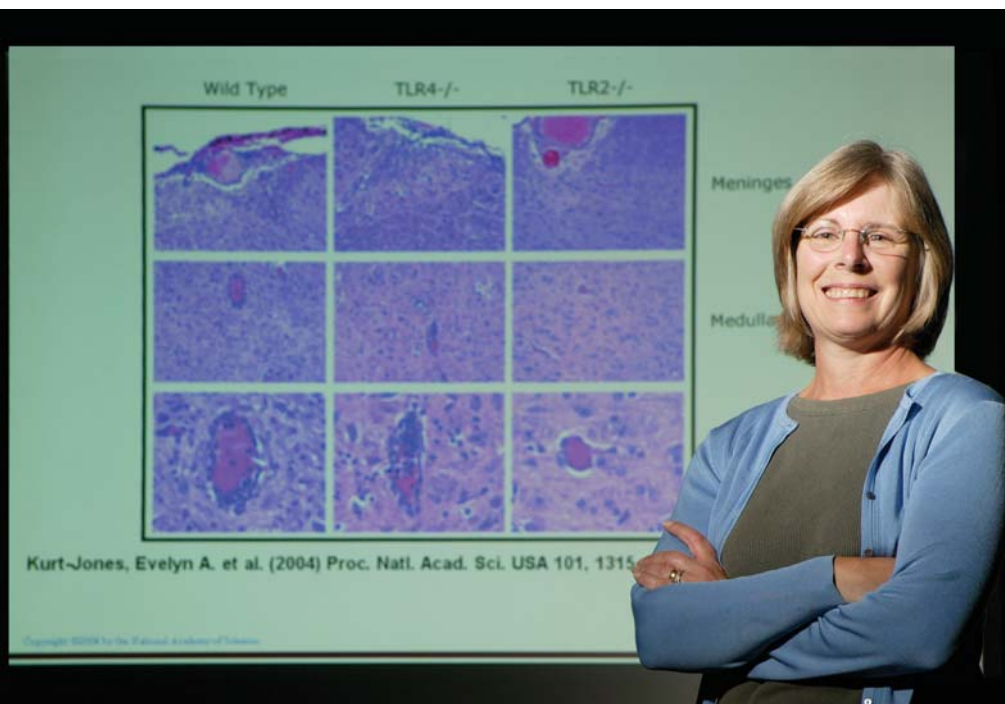
One investigation underway is studying TLR response to a particular virus and the devastating effect that such inflammation can have. “The herpes simplex virus 1 (HSV 1) can cause a disease in neonates and it has the clinical features of a shock-like syndrome,” Kurt-Jones explained. “In previous research, we

into the brain, but they didn’t develop any inflammation. “These mice survived and eventually the adaptive immune system cleared the virus but without the inflammation. So, it was a distinct advantage to those mice that didn’t have TLR 2. As long as you don’t have TLR 2 you can survive long enough to make an adaptive response that will clear the infection.” These findings have led to clinical studies that are examining the response of neonatal blood cells to HSV which seems to indicate that these blood cells are more reactive to the virus and have a much more exuberant cytokine response. “The eventual goal would be to modulate or dampen the TLR 2 response and prevent the encephalitis,” Kurt-Jones said.

Reflecting on the Toll and Toll-like receptor researchers currently at UMMS, Kurt-Jones noted that they are an invaluable source of support and information. “We have frequent conversations through a recently established Innate Immunity Group. And, we have so many exceptional people working on the many aspects of Toll and Toll-like receptors that we are becoming a major center for Toll research.”

As evidence of UMMS’ growing reputation in the field, Kurt-Jones joined colleagues Finberg, Ip and Silverman with presentations at Toll 2004, an international conference that attracted over 300 scientists from around the world. UMMS expertise in TLRs was prominently featured at the conference, which was co-organized by UMMS Professor of Medicine Douglas T. Golenbock, MD. A renowned TLR researcher and a leader in this emerging field, Dr. Golenbock also presented at the conference.

Kelliher looks forward to continuing work with Toll-like receptors with the support of the UMMS Toll community. “There is such expertise to call upon here that we are all very excited about future research in this area.”



Pictured with slides showing the inflammatory response triggered by the herpes simplex virus in the brains of infected mice, Evelyn Kurt-Jones, PhD, has demonstrated that the absence of Toll-like receptor 2 and the consequent lack of inflammation is actually beneficial to those mice.

nisms associated with this overreaction of the innate immune response.

In studying TLRs, Dr. Kurt-Jones and colleagues recognized that viral diseases often had many of the same initial clinical features that are seen in a bacterial infection such as fever and inflammation. Their subsequent research found that TLRs did indeed recognize viral pathogens. “It turns out that a number of viruses do engage Toll-like receptors and this is important in ‘fighting-off’ an infection. However, while the inflamma-

found that TLR 2 was involved in activation of the immune response, so it occurred to us that HSV 1 might also engage TLRs.” A series of studies confirmed that HSV 1 did engage TLR 2 to provoke an activation of cytokines. However, the cytokine activation was surprising. While mice with TLR 2 who were exposed to the virus became infected and the virus traveled into the brain—resulting in a massive inflammatory response, encephalitis and severe illness—mice without TLR 2 became infected, the virus went



# A Place of Their Own

*UMMS and its clinical partner gain space for conducting clinical research trials, key to expansion and potential designation as a General Clinical Research Center.*

By Alison M. Duffy

**The newly opened** Clinical Trials Unit on the seventh floor of UMass Medical School is one of the more visible components of a concentrated multi-year effort by the Office of Clinical Research (OCR) to expand the clinical research enterprise at UMMS in conjunction with its clinical partner, UMass Memorial Health Care. While the Medical School focused considerable energies in creating a successful and widely respected basic sciences research enterprise, the institutions' clinical trials capabilities have lagged behind. That will soon change.

"Both the school and the clinical system aspire to be one of the top ten academic health centers and research medical schools in the country, and if you look at the top 20 or 30 now, they all have very strong, very well developed clinical research enterprises," said John L. Sullivan, MD, director of the Office of Research and UMMS professor of pediatrics and molecular genetics &

microbiology. "Ours is really in its infancy and if we want to be an outstanding academic health center and one of the top 25 research medical schools in the country, our clinical research enterprise simply has to be robust."

Director of the Office of Clinical Research Sheila B. Noone, PhD, notes that two of the factors that faculty have said hamper their efforts to grow the enterprise are a lack of space in which to conduct clinical studies and a shortage of well-trained clinical research nurse coordinators readily available to staff those studies. Without this essential support, Dr. Noone said, researchers often miss out on highly competitive clinical trials, particularly those sponsored by industry that require immediate start up. In answer to these needs, UMMS has invested \$500,000 in the new Clinical Trials Unit (CTU), which provides dedicated space, well trained staff and a menu of important services from which clinical investigators can choose to help

expand, enhance and expedite high quality clinical research studies.

The 2,600-square-foot suite is designed much like an ambulatory clinic, with four patient exam rooms for study visits, an infusion room with two recliners, and a quiet, comfortable waiting room. It also houses a conference room, four staff offices, and workspace and computers from which investigators and study coordinators can retrieve laboratory results and other necessary documents. The CTU also features a kitchenette and a small laboratory with a centrifuge, a freezer and a hematocrit machine, as well as an area for packing and shipping of trial samples to comply with strict transport regulations. In addition, there is a secure area for study files and case reports and, working with the existing investigational pharmacy located in the hospital, the CTU can accept delivery of study drugs to be used during the day.

Prior page: Sheila Noone, PhD, and John Sullivan, MD, are a welcoming sight in the new Clinical Trials Unit. In the unit's infusion room (below), four essential individuals who carry out key components of any clinical trial: (left to right) Lucie Lajeunesse, RPh (investigational pharmacist); Bernie White, RN (clinical research nurse coordinator); Donna Christian (regulatory specialist); and Michael Brennan (clinical contracts specialist).



Of particular value to the investigators will be the availability of highly skilled clinical research nurse coordinators, such as Bernadette “Bernie” White, RN, CCRC, who serves as the CTU’s research manager. White, who oversees clinical trials for investigators in the current Clinical Research Center tucked away in the hospital, is one of two full-time certified clinical research nurse coordinators who will staff the new CTU. The second coordinator is being recruited and a third *per diem* coordinator will be added as the number of studies facilitated by the CTU increases.

“The support of well-trained, experienced research nurse coordinators is probably the key to the CTU,” said Noone, who holds a joint appointment as assistant professor in the Graduate School of Nursing and the Department of Obstetrics of Gynecology. “It’s time consuming for investigators to recruit and train their own coordinators, especially for divisions in which there are sporadic trials. By staffing coordinators, the CTU takes the recruiting and training onus off the researchers so they can focus on the study and get it started quickly.”

“This is a different kind of nursing,” noted White, who has been a clinical research nurse coordinator at UMMS since 1989. These coordinators must have at least two years of research experience and “an intimate knowledge of regulatory information” in addition to skills in basic life support, infection control, phlebotomy, EKG, IV insertion, and packaging and shipping of sensitive materials. While all areas of nursing require strict attention to detail and high quality patient care, White noted that in research nursing, “you have to be precise in not only what you do but how you do it and how you document it, because the validity of the data can determine the outcome and the value of the research.”



Through the CTU, investigators can request coordinator support as either a “percent of effort,” depending on the intensity of the study, or on a per-visit basis. Because some studies enroll a small number of patients, or because investigators may need assistance with only one part of their study, the coordinators can simultaneously manage studies for several different investigators. Fees for the services are factored into the study budget.

Peter N. Riskind, MD, PhD, professor of clinical neurology, is one such investigator who expects to utilize the CTU’s a la carte menu. He already relies on White to administer a novel, once-a-month infusion of a study drug to treat multiple sclerosis, something Dr. Riskind has neither the clinic space nor the staff time to accomplish. He agrees that the CTU’s flexibility will serve a critical need: “We can add trials easily knowing that through the CTU we will have the space and the coordinator available.” In Riskind’s experience, a CTU “offers tremendous time savings in terms of streamlining paperwork and lining up knowledgeable staff, and can get us

The new Clinical Trials Unit provides dedicated space, well trained staff and important services from which clinical investigators can expedite high quality clinical research studies.

to a study’s starting line much more quickly. It helps to not have to hire and train someone for each trial.” Riskind notes that with enough space and appropriate coordinator support, he and his colleagues “could double the number of clinical trials we’re doing in neurology.”

Aside from physical space and staff time, the services offered by the Office of Clinical Research include the support of an investigational pharmacist, Lucie LaJeunesse, RPh, who also serves as vice chair of the Institutional Review Board (IRB). LaJeunesse consults with clinical researchers, reviews new study protocols, manages the dispensing of investigational drugs and handles drug-related documentation. Investigators also benefit from regulatory support—help with the sometimes overwhelming but important crossing of *i*’s and dotting of *i*’s during the many steps preceding the start of any clinical trial. The negotiation of contracts, budgeting process and, in particular, the IRB submission process, can be onerous, according to Noone, especially for investigators who have busy clinic schedules and are managing concurrent clinical

trials. Donna Christian, the CTU's on-site regulatory specialist, is available to assist clinical investigators with study initiation by drafting their IRB submission and consent form, organizing their regulatory documents for the sponsor, and, if needed, assisting with the investigational new drug applications to the FDA.

In the past two years, Christian has supported 38 investigators in 55 projects. Departments that have sought regulatory or research coordinator assistance from the Office of Clinical Research include neurology, pediatrics, dermatology, endocrinology, gastroenterology, radiology and psychiatry, indicating an across-the-board need for the CTU.

"2004 saw the number of industry-sponsored clinical trial agreements nearly double, to 114," said Noone, thanks to the office's concerted efforts to streamline the process of review and negotiation of clinical trials agreements. (In comparison, the average number of trials opened from 1995 to 2003 was 64 per year.) Noone developed a new database to track the process of contract receipt, review and negotiation that is proving invaluable in reducing the time that will be needed to process an agreement to two or three weeks instead of the months it currently takes. She is assisted in the communica-

tions and negotiation of industry-sponsored clinical trials by Michael Brennan, clinical contracts specialist for the Office of Clinical Research.

Cognizant that clinical trials units at other institutions have struggled with an overwhelming response by their researchers—about three-quarters of academic medical centers in the United States have opened similar units in the last several years, according to Centerwatch, a clinical trials listing service—Noone plans to carefully manage the growth of the CTU. Seven to nine studies will move to the CTU this fall, and Noone projects approximately 25 to 30 clinical trials will utilize the unit in its first year while also providing relevant training for faculty.


"There's an education and training component that I feel very strongly about," she said. "By training faculty to prepare more accurate study proposals and understand the budgeting process a little better, we can be more efficient in the start up of trials, thereby increasing the number of trials we can manage." Noone has presented to faculty several sessions on budget planning and regulatory issues and is currently planning one on industry-sponsored clinical trials with representatives from the Mass Biotech Council. She also

hopes to have an FDA representative present a session on the regulatory issues regarding device studies.

One final component Noone wishes to develop through the CTU is a useful pool of study volunteers, which would require two things: raising public awareness about what participation in a clinical trial entails, and a workable database of volunteers, particularly for healthy studies. Many clinical studies recruit patients who suffer the disorder being studied, but there is an increasing need for healthy people in phase 1 trials, something a volunteer database could facilitate.

In providing an array of services, Noone and Dr. Sullivan expect the CTU to serve clinical researchers from across the entire institution, enabling faculty to pursue more National Institutes of Health-sponsored clinical research studies and eventually positioning UMMS and UMass Memorial for a successful application for development of a General Clinical Research Center. According to the NIH, there are currently 78 such centers at university-based hospitals in the country, facilities that offer centralized and highly specialized resources for inpatient and outpatient clinical research. Right now, Sullivan said, UMMS stands out among its peer institutions for not housing a center.

"While we've been extraordinarily successful in developing a rich talent pool in the basic sciences, physician-scientists are a rare breed and very difficult to attract," he said. "One would expect to see a more robust clinical research facility here, akin to the vibrant basic science work currently underway. With the consensus among leadership in both institutions, that's what our efforts are now directed toward."

"I believe we have the pieces in place," agreed Noone. "With the collaboration of the Medical School and its clinical partner, we are primed to elevate the scale, scope and complexity of the clinical research enterprise across our campuses." 



**"We have the pieces in place. We are primed to elevate the scale, scope and complexity of the clinical research enterprise across our campuses."**

— Sheila Noone, PhD

# Vitae: Grants and Research

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

## BIOCHEMISTRY & MOLECULAR PHARMACOLOGY

### *National Institutes of Health*

**Job Dekker, PhD**, assistant professor: Structural Annotation of the Human Genome, one year, \$366,820; recommended for two more years, \$800,000.

**Kai Lin, PhD**, assistant professor: Structural Basis of Regulation of IRF, one year, \$383,340; recommended for three more years, \$1.2 million.

**C. Robert Matthews, PhD**, the *Arthur F. and Helen P. Koskinas Professor of Biochemistry & Molecular Pharmacology* and chair: Folding Mechanisms of TIM Barrel Proteins, \$344,475; recommended for three more years, \$1 million.

**William E. Royer, PhD**, associate professor: Ultrafast Time-resolved Crystallography on Scapharca Hb, one year, \$227,724; recommended for three more years, \$651,000.

**Scot A. Wolfe, PhD**, assistant professor: Dimeric Cys2His2 Zinc Finger Proteins for Gene Targeting, one year, \$274,003; recommended for four more years, \$1.2 million.

**Zuoshang Xu, MD, PhD**, associate professor: Understanding Mechanism and Therapy of ALS Using RNAi, one year, \$367,688; recommended for four more years, \$1.5 million.

## CANCER BIOLOGY

### *National Institutes of Health*

**Dario C. Altieri, MD**, the *Eleanor Eustis Farrington Chair in Cancer Research* and chair: Control of Apoptosis in Cancer by Survivin, one year, \$298,920; recommended for four more years, \$1.2 million.

## CELL BIOLOGY

### *National Institutes of Health*

**Harvey M. Florman, PhD**, professor: Regulators of the Sperm Acrosome Reaction, one year, \$343,000; recommended for four more years, \$1.3 million.

**Timothy Henion, PhD**, research assistant professor: Notch Signaling in Olfactory Progenitor Cell Fate, one year, \$141,500; recommended for one more year, \$141,500.

**Andre J. Van Wijnen, PhD**, associate professor: Bone Cell Growth Regulation by Runx2/Cbfa1, \$293,374; recommended for four more years, \$1.1 million.

## FAMILY MEDICINE & COMMUNITY HEALTH

### *Department of Health and Human Services*

**Darlene M. O'Connor, PhD**, associate professor: Real Choice Systems Change, three years, \$499,992.

**Carole C. Upshur, EdD**, professor: Treatment of Chronic Pain—Consumer and Provider Concerns, one year, \$100,000.

## MEDICINE

### *National Institutes of Health*

**Elliot J. Androphy, MD**, the *Barbara and Nathan Greenberg Chair in Biomedical Research*: Functions of Human Papillomavirus E6, one year, \$293,355; recommended for four more years, \$1.2 million.

**Egil Lien, PhD**, assistant professor: The Role of LPS and Toll-like Receptors in Plague, one year, \$382,160; recommended for four more years, \$1.5 million.

**Shan Lu, MD, PhD**, associate professor: Multi-gene Plague Vaccine With Expanded Protection, one year, \$550,179; recommended for one more year, \$540,000.

**Aldo A. Rossini, MD**, the *William and Doris Krupp Professor of Medicine*: Interdisciplinary Studies of Hormone Function, one year, \$248,054; recommended for four more years, \$1.3 million.

**Neal Silverman, PhD**, assistant professor: Activation of Insect Immunity by Gram-negative Bacteria, one year, \$357,750; recommended for four more years, \$1.4 million.

**Michele Trucksis, PhD, MD**, associate professor: Accessory Cholera Enterotoxin, Mechanism of Action, one year, \$119,250; recommended for three more years, \$1.1 million.

**Robert B. Zurier, MD**, professor: Treatment of Rheumatoid Arthritis—Marine/Botanical Oils, one year, \$551,061; recommended for three more years, \$2.2 million.

## MOLECULAR GENETICS & MICROBIOLOGY

### *National Science Foundation*

**Dannel McCollum, PhD**, associate professor: Regulation and Function of Clp 1p Protein Phosphatase, one year, \$283,713; recommended for three more years, \$800,000.

## MOLECULAR MEDICINE

### *American Diabetes Association*

**Laxman D. Gangwani, PhD**, research assistant professor: To Define the Function of the Zinc Finger Protein ZPR1 in Spinal Muscular Atrophy, one year, \$110,805; recommended for two more years, \$223,000.

## *National Institutes of Health*

**Joel D. Richter, PhD**, professor: Polyadenylation and Translational Control, one year, \$339,962; recommended for three more years, \$1 million.

**Rossella G. Tupler, MD, PhD**, research assistant professor: Investigating the Molecular Basis of FSHD, one year, \$367,688; recommended for four more years, \$1.5 million.

## *U.S. Army*

**Stephen J. Doxsey, PhD**, associate professor: Centrosome-based Mechanisms, Prognostics and Therapeutics in Prostate Cancer, three years, \$596,250.

**Keith W. Mikule, PhD**, a postdoctoral fellow in the laboratory of **Stephen J. Doxsey, PhD**, associate professor: Building Breast Cancer: Dissecting the Contribution of Pericentrin and its Binding Partners to Chromosome Instability and Tumorigenesis, three years, \$171,000.

## NEUROBIOLOGY

### *National Institutes of Health*

**Vivian G. Budnick**, professor: The Wingless Transduction Pathway in Synapse Development, one year, \$321,975; recommended for four more years, \$1.3 million.

**Patrick Emery, PhD**, assistant professor: Circadian Photoreception in *Drosophila Melanogaster*, one year, \$291,946; recommended for four more years, \$1 million.

**Steven M. Reppert, MD**, the *Higgins Family Professor of Neuroscience* and chair: Circadian Clock: Transcriptional Control, one year, \$367,688; recommended for three more years, \$1.1 million.

**Scott Waddell, PhD**, assistant professor: How Does the Amnesiac Gene Product Aid Memory, one year, \$315,993; recommended for four more years, \$1.3 million.

## NEUROLOGY

### *National Institutes of Health*

**William Schwartz, MD**, professor: Neurobiology of Circadian Dysrhythmias, one year, \$294,150; recommended for three more years, \$882,000.

## PATHOLOGY

### *National Institutes of Health*

**Kenneth L. Rock, MD**, professor and chair of pathology: Immunobiology CTL Responses to Exogenous Antigens, one year, \$403,125; recommended for four more years, \$1.2 million.

### *Richard and Susan Smith Family Foundation*

**Francis K. Chan, PhD**, assistant professor: Smith Family New Investigator Award; TNF-Induced Programmed Cell Death in Immune Responses, two years, \$200,000.

## PEDIATRICS

### *National Institutes of Health*

**Peter E. Newburger, MD**, professor: Gene Expression in Mature Neutrophils, one year, \$562,035; recommended for four more years, \$2.4 million.

### *U.S. Department of Education*

**Charles D. Hamad, PhD**, associate professor: Fund for the Improvement of Postsecondary Education, one year, \$149,864; recommended for two more years, \$300,000.

## PHYSIOLOGY

### *National Institutes of Health*

**John V. Walsh, MD**, professor: Local Ca<sup>2+</sup> Signaling in Smooth Muscle, one year, \$465,542; recommended for four more years, \$2 million.

## PSYCHIATRY

### *Alzheimer's Association*

**Evgeny I. Rogaev, PhD**, professor: Interaction Between Presenilin-related Putative Proteases and Alzheimer's Disease Pathway, three years, \$250,000.

### *National Institutes of Health*

**Timothy Q. Duong, PhD**, assistant professor: Layer-Specific Functional and Perfusion Imaging of Retina, one year, \$344,475; recommended for three more years, \$1 million.

**Karen Lionello-Denolf, PhD**, assistant professor: Developing a Model of Transitive Behavior, one year, \$127,350; recommended for one more year, \$127,350.

## SURGERY

### *U.S. Army*

**Shuk-mei Ho, PhD**, professor: Estrogen Receptor-beta Hypermethylation and Prostate Carcinogenesis, three years, \$596,251.

# Vitae: Alumni Report

Do you recall your Commencement? Can you picture UMMS biomedical research at that time? We were justifiably proud of our achievement. We were delighted to boast researchers of the highest

## MESSAGE FROM THE CHANCELLOR/DEAN

caliber and graduate students whose work was at the leading edge of research. Our students and faculty were capturing national attention for their research. Fifteen years ago, the Program in Molecular Medicine was just an emerging idea. The Graduate School of Biomedical Sciences had grown to recruit 25 students annually and our alumni had almost reached 100.

Fast forward to Commencement 2004 and the growth is truly astonishing! Entering our 25th year of the GSBS, we now recruit more than 80 students annually. We number more than 250 alumni. Our school stands at 350 students and 250 research faculty. We house half of our faculty and students in a new, state-of-the-art, 360,000-square-foot research building and our basic science research program is ranked 18th among the nation's medical schools. The numbers speak volumes but only begin to capture the excitement that circulates about our school. We feel this excitement in many ways. Our students eat, drink and breathe their research. They work long hours to drive their progress forward, ever aware that their competition is close at their heels. Our students understand the importance of their work and are determined to experience the thrill and recognition of bringing their discoveries to press first. We encourage this attitude and celebrate each success they enjoy. More significantly, our students understand that every inch of progress brings new hope to those whose health is inexorably linked to research success and they are determined to succeed where others have not.

Each mid-winter heralds the annual GSBS recruitment weekends. Here, prospective students experience our collective excitement for graduate studies. Faculty, students and staff organize and execute a weekend of science, interviews, education and social mixing which, for all participants, captures the essence of the GSBS—collegiality, passion for research, ambition, teamwork, unquenchable intellectual curiosity, competition, friendships, hard work and fun! These qualities encapsulate the graduate experience which, when combined with a nurturing hand from one or more of our gifted faculty, transforms talented undergraduates into the scientific leadership of tomorrow.

For the researcher, the ultimate measure of an institution is the quality of the research that bears the institution's name.



The quality, diversity and impact of the research carried out by GSBS students and their guiding faculty over these 25 years is stunning. We are recognized at the highest levels of peer review for our contributions to the areas of diabetes, AIDS, RNA interference, cancer, immunology, neuroscience and neurodegenerative disease, to name just a few. This success has catalyzed further recruitment of outstanding new faculty and graduate students to the school. We have the overwhelming sense that our work and growth have only just begun.

We have risen to national distinction through the efforts of many at all levels of this institution. The leadership team of my office and the chairs has worked to foster an environment that promotes biomedical research and the development of tomorrow's scientific leaders. We are thrilled by the success that our junior faculty and graduate students enjoy today and we continue to work diligently to promote an environment in which research can flourish.

As we look to the future with a sense of accomplishment and in anticipation of exciting discoveries and growth yet to come, we should also recognize the great debt we owe our founding faculty who include the first dean of the graduate school, George Wright, and his successor, Thomas Miller Jr. Each shaped this school and cultivated an environment in which faculty and students can thrive. If I may quote the current dean of the GSBS, Anthony Carruthers, "The first 25 years have produced astounding achievement by our school. The next 25 years will be breathtaking."

*Aaron Lazare*

Aaron Lazare, MD



## Alla Grishok, PhD '01

Dr. Alla Grishok was in the right place at the right time. A graduate student in the UMass Medical School laboratory of Craig C. Mello, PhD, Howard Hughes Medical Institute Investigator and the Blais University Chair in Molecular Medicine, Grishok was involved in many of the first investigations that unlocked the possibilities of RNA interference (RNAi), one of the most important methods used in cutting-edge biomedical research today.

Yet Grishok almost didn't attend UMMS. With her bachelor's degree in molecular biology from Kiev State University, Grishok worked for a decade as a research assistant in her native Ukraine and as a research technician at the Medical College of Wisconsin before deciding to pursue her PhD. Admitted into the Graduate School of Biomedical Sciences (GSBS) in 1995, she says that if she hadn't entered the program, she probably wouldn't have gone back to school for her doctoral degree at all.

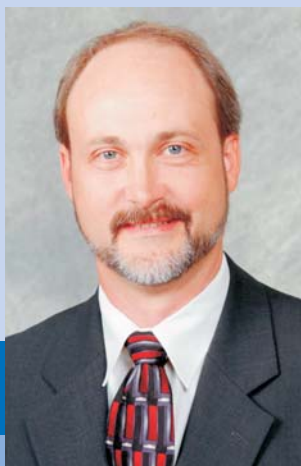
"I chose the GSBS because it was flexible and offered more interdisciplinary opportunities. I was also very interested in the work being undertaken at the time in Jeanne Lawrence's laboratory on regulatory RNAs. I was fortunate that, although there were no opportunities in Dr. Lawrence's lab, I was able to find out more about Dr. Mello's lab from a student, Sam Driver, who is actually one of the authors on the original RNAi paper published in *Nature*."

Although graduate school was difficult—given that she was a single parent pursuing her degree later in life—Grishok credits her success at the GSBS to the warm environment and constant support she received from her fellow students and the administration.

Currently a postdoctoral fellow at the Center for Cancer Research at MIT, Grishok is pursuing her passion for genetics and microRNAs in *C. elegans*—work she directly attributes to her experience in Mello's lab. In recognition of her outstanding research, she was named one of 17 recipients of the 2002 Weintraub Graduate Student Award by the Fred Hutchinson Cancer Research Center, and was awarded a three-year Damon Runyon Cancer Research Foundation postdoctoral fellowship, presented to young scientists whose research focuses on cancer prevention and therapies.

"It's rare to have the opportunity to do work in a field that is just developing," Grishok said.

"When I look back on our discussions of the first mutants identified in the RNAi pathway, it's like a miracle. If I had pursued a different path, I would definitely have been less successful in my own research. The GSBS allowed me to work independently and design my own experiments. And, that's why I went to graduate school—to formulate my own scientific questions and to find answers." —LCB



## Kenneth Wright, PhD '90

Dr. Kenneth Wright is gratified to be conducting cutting-edge cancer research at a prestigious institute, in his home state, no less. The GSBS graduate is Member-in-Residence at the H. Lee Moffitt Cancer Center & Research Institute, located on the campus of the University of South Florida (USF) in Tampa—the youngest institution ever to receive comprehensive National Cancer Center accreditation from the National Cancer Institute.

Wright's journey to the forefront of cancer biology has taken him full circle professionally as well as geographically. His current, NIH-funded inquiries into how the immune system can be harnessed to fight tumors build on his first explorations into how cells work in the lab of Gary Stein, PhD, and Janet Stein, PhD (both then at the University of Florida, now at UMMS as the Gerald L. Haidak, MD, and Zelda S. Haidak Professor of Cell Biology and chair, and professor of cell biology, respectively).

Wright was an undergraduate at the University of Florida when he first met the Steins; he progressed from volunteering in their lab, to commencing doctoral studies there. When Gary Stein was invited to become chair of cell biology at UMMS in 1987, Wright also made the move. "It was a great opportunity and an easy decision. UMMS already had a strong reputation."

His decision to focus on cancer research was cemented after Wright completed a post-doctoral fellowship with Jenny Ting, PhD, at the

Lineberger Comprehensive Cancer Center at the University of North Carolina. Today Wright is assistant professor of interdisciplinary oncology in the immunology program at the Moffitt Cancer Center. His inquiries into the normal and abnormal function of immune cells led to his lab's breakthrough discovery of a key molecule required for the development of cancer-fighting immune cells. The molecule modifies histone proteins—the same proteins he studied as a student at the GSBS. "Having histones on my radar helped in our discovery."

Wright's commitment to training the next generation of scientists has evolved along with his research. He again credited the Steins' influence. "They have a love for science and they make it fun. They taught me that mentoring students is a very important part of what we do." In response to the shortage of trained investigators in the still-young field, Wright was instrumental in establishing a Cancer Biology PhD Program at Moffitt and USF. "Our students start learning about cancer from day one. Scientific discovery takes time. Our job is to keep working at it so the breakthroughs will keep coming."—SLG



## Daniel N. Hebert, PhD '92

According to Dr. Daniel Hebert, “life just doesn’t get any better.” With the support of enthusiastic students and sufficient grant funding, the associate professor of biochemistry & molecular biology at the University of Massachusetts Amherst is pursuing his *own* research riddles. And, he credits his experience at the Graduate School of Biomedical Sciences (GSBS) with leading him to embrace this career choice. “In academia, you can truly formulate your own scientific questions and engage in investigations specifically geared toward answering those questions,” he said.

Hebert currently oversees a research group within the UMass Amherst Program in Molecular and Cellular Biology, monitoring how proteins mature and degrade in the cell. “When proteins don’t fold correctly, it can lead to a number of disease states,” Hebert said, “Our lab investigates this chemical question in the context of living cells, focusing on the factors that assist these processes. Although very basic biology, its connection to disease is evident.”

Following receipt of his bachelor’s degree in chemistry from the University of New Hampshire, Hebert worked for a year in his family’s business, which manufactures ion-selective electrodes. However, his brother’s positive impressions of UMMS while a student at nearby Worcester Polytechnic Institute, coupled with Hebert’s own interest in the biological sciences, led him to the GSBS.

Still in its infancy in 1985 when Hebert entered the program, the GSBS was preparing to graduate its first students. One of a dozen in his class, Hebert noted the closeness among students—who all knew and supported each other—as well as the immediacy with which he was able to pursue his interest in biochemistry. Hebert worked as the first member in the newly formed lab of Anthony Carruthers, PhD; the current GSBS Dean was then a junior investigator who had just completed his own postdoctoral experience. “It was a very attractive program; you were able to focus on your research from the get-go. After my first lab rotation, I co-authored a paper with Tony Carruthers,” noted Hebert. “We had incredible access to the faculty.”

Following receipt of his PhD, Hebert pursued his postdoctoral work in the Department of Cell Biology at Yale Medical School. Like his experience at UMMS, the spirit in his lab was communal. And, it’s this type of environment—one that Hebert continues to foster today—that garners fruitful results. “The stereotype of the scientist as introverted couldn’t be farther from the truth,” concluded Hebert. “Researchers must be strong communicators, willing to interact with colleagues. It’s collaboration that leads to success in science; no one individual can do it alone.” —LCB

Alumni of the School of Medicine, Graduate School of Biomedical Sciences and the Graduate School of Nursing may send their latest news to [alumni@umassmed.edu](mailto:alumni@umassmed.edu)

## 1975

**Claudio Delise, MD**, no longer practices obstetrics, but continues his work in the field of gynecology. He and his wife, Joan, are relocating to Sudbury, Mass. from Hingham and are enjoying their 20-month-old grandson.

## 1979

**Robert M. Haddad, MD**, was appointed president and chief executive officer of Caritas Christi Health Care in May, after serving since 2001 as president of Caritas St. Elizabeth's Medical Center in Boston, a teaching hospital affiliated with Tufts School of Medicine and the Caritas system's flagship institution.

## 1982

**David Liberman, MD**, is president and founder of Computer Trust Corporation of Boston, which develops, installs and supports the WinSURGE family of information systems used in hospitals and commercial laboratories performing anatomic pathology (surgical pathology, cytology, autopsy, histology and nuclear medicine). Dr. Liberman lives in Brookline, Mass. with his wife, Judy, and their daughters, Cindy, 10, and Debbie, 7.

**Bruce D. Minsky, MD**, recently received an honorary medical degree from the Friedrich Alexander University in Erlangen, Germany. He is a professor of radiation oncology in medicine at the Weill Medical College of Cornell University, as well as the vice chairman of the Department of Radiation Oncology and chairman of Quality Assessment at Memorial Sloan-Kettering Cancer Center. His wife, Connie Kissinger, is a vocalist in Hawaii; the couple lives in Manhattan and Kauai.

## 1983

**Susan Auerbach-Ferdman, MD**, is joined by her husband, Mauro, and daughter, Dina, at an August Parents' Orientation at UMMS. Dina is a first-year medical student. Dr. Auerbach-Ferdman practices in Winchester, Mass. and resides with her family in Cambridge.

## 1989

**Susan C. Schiavi, PhD**, is a principal scientist leading a discovery team at Genzyme Corp. of Framingham, Mass. Dr. Schiavi completed her post-doctoral work at Harvard Medical School. She lives in Hopkinton with her husband, **David S. St. Laurent, MD '85**, and their son and daughter.

**Gregory A. Taggart, MD**, has joined UMass Memorial Medical Center as chief of the Foot and Ankle Program in the Department of Orthopedics & Physical Rehabilitation. Dr. Taggart has also been appointed assistant professor of orthopedics & physical rehabilitation at UMMS. Most recently he practiced at the Center for Orthopaedics of New Haven, Conn., and served as an assistant clinical professor of orthopedics and rehabilitation at Yale University School of Medicine. A major in the U.S. Army Reserve, Dr. Taggart has been deployed in Bosnia, Afghanistan and Kuwait, and recently returned from deployment in Iraq.

## 1990

**Dmitry Blinder, PhD**, is president of ViroGen Corporation of Watertown, Mass., a manufacturer of recombinant viral antigens and monoclonal antibodies for research and diagnostic applications. Dr. Blinder is a recipient of the U.S. Civilian Research & Development Foundation's "Next Steps to the Market" Program Awards for the development of a biotechnology group for the production of Monoclonal Antibody Kits and the New Approach for Modulation CD-95-Mediated Apoptosis. Dr. Blinder resides in Boston and is on the faculty of Northeastern University.

## 2000

**Geneve Allison, MD**, is in her first year of a fellowship in infectious diseases at Tufts-New England Medical Center, after serving her internal medicine residency at Alameda County Medical Center in Oakland, California. She writes: "I live in Malden, Mass. with the greatest guy ever, my husband, Michael Murphy. We were married on November 28, 2003, in California. **Katharine Cornell, MD '00**, and her husband, Daron, and daughter, Lucy, braved the 3,000 mile trip to celebrate with us. I would love to hear from folks—[gallison@tufts-nemc.org](mailto:gallison@tufts-nemc.org)."

**Adam Feldman, MD**, and his wife, Jennie Kroopnik Feldman, are the proud parents of a new baby boy who has been named after Adam's late father, Robert Feldman.

**Jeffrey B. Hopkins, MD**, has joined the medical staff of Milford-Whitinsville Regional Hospital. While in residency training at UMass Memorial Medical Center, Dr. Hopkins served as a Life Flight physician.



# Vitae: The Last Word

By Thomas Manning, Deputy Chancellor for Commonwealth Medicine and Strategic Facilities Planning, and Timothy Fitzpatrick, Associate Vice Chancellor for Master Space Planning

*For the past two years, the UMass Medical School community has come to embrace the challenges and opportunities of Campus Modernization—a four-year initiative to revitalize and renovate the Medical School's main campus in Worcester. With the approach of the half-way mark in the schedule of projects, Thomas Manning (below, left) and Timothy Fitzpatrick offer their perspectives on the success of Campus Modernization to date and the vision for future growth on campus.*



When you combine the number of years we've worked here, it totals more than 50; yet, we have never been more enthusiastic about the campus's progress than over the last two. The multi-faceted projects that comprise the strategy to

modernize the campus—replacement of the main building's granite façade with limestone and a new window system; the construction of new lobbies and entrances for the Medical School and hospital; construction of the Clip-On office addition; reconstruction of the Faculty Conference Room; the enclosure of the Chancellor's Courtyard; and a new parking garage and a 256,000-square-foot hospital addition, including a new Emergency Department—are exciting, and yes, immensely challenging. But as we see limestone and glass replace the granite façade, we are invigorated by the change from a gray, aging facility to a light, bright building.

In recent months, construction of the hospital entrance and lobby has accelerated and the new Medical School lobby has taken shape. Visitors to the campus will be able to quickly recognize the hospital and school, whose entrances have, seen now in retrospect, been rather obscure over all of these years. With two-story configurations, the lobbies distinguish main entrances that are appropriate for a nationally recognized medical school and health care leader. Furthermore, the shared elements of the entrances will reinforce that UMass Medical School and UMass Memorial are united in partnership, while the subtle design differentiation will distinguish the organizations as entities with individual, yet complementary missions.


One of the most gratifying elements of Campus Modernization has been the cooperation shown by faculty, staff and the visiting public. Their remarkable patience and good cheer in the face of extensive construction and, at times, disruption without any immediate benefit, is a tribute to our institutional culture and the people we serve. Yet, we are now approaching the time when the benefits will begin to be revealed. With the opening of the new garage this fall, employees who were shuttled from off-site locations have returned to parking on campus. Congestion on campus roadways

has decreased, and our Office of Public Safety is now positioned at the front of the new garage facing South Road, our most heavily traveled thoroughfare, to underscore our commitment to safety.

The new year will bring additional benefits. Addressing a critical shortage of space, Campus Modernization will give us the opportunity to add valuable conference rooms and offices. With the completion of the Clip-On, a number of smaller conference rooms will provide teaching venues in demand from all three schools, while medium and large rooms will meet a variety of administrative and instructional needs. In addition to creating two conference rooms, the enclosure of the Chancellor's Courtyard will enlarge the Chancellor's Office operating area and will allow Dr. Lazare to bring additional senior staff into the vicinity, enhancing both functionality and communication. And, although its footprint won't have changed, the essential Faculty Conference Room will feature significant structural, organizational and audiovisual improvements. To reinforce its functionality, the room is also being constructed in such a way that it can be opened up into the new Medical School lobby for large events.

We have grown so much and so quickly over the years that the organization, signage and greenery on campus has suffered. At the completion of various phases of Campus Modernization, we look forward to bringing a greener environment to our shared constituencies. Moreover, a comprehensive signage program will be implemented in phases to make traveling on and through campus safer and easier.

To top it off, as the UMass Memorial Lakeside Expansion takes shape on the east side of campus, it is thrilling to witness our clinical partner's continued investment in quality patient care and education through the introduction of a state-of-the-art technological infrastructure.

While Campus Modernization progresses and meets some of the immediate needs of our institutions, it is imperative that we continue planning additional initiatives for enhancement of the Worcester campus. By January 2005, we expect to have in hand an updated campus master plan that addresses our future infrastructure and programmatic needs and identifies areas of growth that will contribute to our continually energized academic and clinical enterprises. 

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