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A Strike Against ALS

Vital: The Magazine of The University of Massachusetts Medical School



The Real Thing



Early Intervention

Vitae: L., the plural of life

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

University of Massachusetts Medical School

The University of Massachusetts Medical School was created in 1962 by an act of the Massachusetts Legislature and today is comprised of three schools. Since accepting its first class in 1970, the School of Medicine has provided students with an accessible, comprehensive and personally rewarding medical education of the highest quality, one which optimally prepares them to excel as physicians. The Graduate School of Biomedical Sciences, opened in 1979, is a faculty-initiated PhD program that trains scientists in a specialty area with a broad background in the basic medical sciences, in preparation for conducting research with direct relevance to human disease. Opened in 1986, the Graduate School of Nursing, through its master's, post-master's 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.



Vita_{ae}: Contents

News and Notes	2
Features	7
Grants and Research	21
Alumni Report	23
The Last Word	28

A Strike Against ALS

7

A UMMS researcher uses the revolutionary gene-silencing technique, RNA interference, to go on the offensive against Lou Gehrig's disease.



Nothing Like the Real Thing

12

UMMS laboratories partner with a local high school to increase achieving students' seriousness about science.



Early Intervention

17

UMMS leads a multisite study of the effects of supplemented baby formula on cystic fibrosis disease progression.

UMMS Initiates Ground-breaking Clinical Trial of HIV Vaccine

Scientists at UMass Medical School are recruiting volunteers for a clinical trial to test the safety and effectiveness of a new vaccine for human immunodeficiency virus, HIV. The vaccine was developed by scientists at UMMS and Advanced BioScience Laboratories, Inc. (ABL) after years of intense research and testing. The U.S. Food and Drug Administration designated the vaccine as an investigational new drug in March 2004.

HIV, the virus that leads to acquired immune deficiency syndrome (AIDS) remains a global epidemic. With the rate of infection accelerating in many parts of the world, the search for an effective HIV vaccine is one of the highest public health priorities. Yet, development of an HIV vaccine has been challenging because HIV mutates rapidly, making it an elusive target for traditional vaccine strategies that focus on one strain of the virus. UMMS and ABL have made significant progress by creating a novel “polyvalent” HIV vaccine based on

multiple strains of HIV collected directly from infected people living in five locations around the globe, representing five different strains of the virus.

The approach developed at UMMS uses elements of HIV’s DNA to induce an immune response to the virus. The DNA is then boosted by an injection of recombinant viral proteins developed by ABL that have been shown to enhance the host’s immune response to the DNA elements of the vaccine in animal models. So far, the DNA and protein combination has been tested in two animal models with very promising results. Antibodies produced by the immunized animals effectively neutralized live HIV isolates collected from several parts of the world. That success facilitated taking the novel vaccine to the next step, a clinical trial in humans.

Both the vaccine research and the clinical trial are funded by a National Institute of Allergy and Infectious Diseases contract

awarded in 2000 to ABL and UMMS. The award was part of a \$70 million

commitment by the National Institutes of Health to just four public-private partnerships worldwide in an effort to accelerate the development and testing of promising HIV vaccines. ©

Volunteers for the HIV vaccine clinical trial are needed; volunteers must be 18-50 years old, in good health, with no history of HIV infection and no previous enrollment in an HIV vaccine clinical trial. The study’s duration is one full year and participants will be reimbursed for their time and donation of multiple blood samples. For more information, visit http://www.umassmed.edu/cidvr/clinical_trials/ or call toll-free, 1-888-687-5757.



Associate Professor of Medicine Shan Lu, MD, PhD (left) heads the HIV vaccine effort at UMMS. Jeff Kennedy, MD, UMMS assistant professor of medicine, directs the clinical trial.

Mello Invested as Blais University Chair

UMMS formally invested Howard Hughes Medical Institute Investigator and Distinguished Professor of Molecular Medicine Craig C. Mello, PhD, as the *Blais University Chair in Molecular Medicine* at its fifth annual Investiture ceremony, held June 5 at the Hoagland-Pincus Conference Center on the Worcester Foundation campus. The academic event also featured guest speaker Judah Folkman, MD, Harvard Medical School professor and pioneer of angiogenesis, the study of the formation of blood vessels and their connection to tumor growth.

The Blais Chair represents the first University Chair to be established at the Medical School and was endowed by philanthropists Jack and Shelley Blais, who have contributed significant leadership gifts to UMMS over the past four years. Inspired by Dr. Mello’s keen understanding of genetic function and his enthusiasm for scientific progress, the Blaises established the chair to

support the scientist’s continued research into RNA interference (RNAi), heralded as the 2002 “Breakthrough of the Year” by *Science* magazine.

“For Jack and Shelley Blais to pledge their support to one of our stellar young faculty is a true testament to their continued commitment to the Medical School’s future as a premier research institution,” said Chancellor and Dean Aaron Lazare.

UMMS currently has 25 named professorships. Seventeen have been established since 1999, including eight through the generosity of donors to the Worcester Foundation for Biomedical Research. According to Dr. Lazare, the *Celia and Isaac Haidak Professor of Medical Education*, “Endowments speak to the faith our benefactors have in us, as individuals and as an academic research institution, to understand and find the answers to life’s most perplexing medical questions.” ©

UMMS Ranks Third in Primary Care Education in *U.S. News*

UMass Medical School was ranked third in primary care education among the nation's 125 medical schools by weekly news magazine *U.S. News & World Report* in its annual review, "America's Best Graduate Schools," published in April. UMMS, which has held a spot near the top of the category since the magazine began its rankings in 1994, was tied with the University of Wisconsin-Madison for third; the University of Washington and Oregon Health & Science University were first and second, respectively. *U.S. News'* rankings of the nation's accredited medical schools are based on measures of academic quality which are weighted by reputation among faculty and residents, research activity, student selectivity and faculty resources.

UMMS was founded by an act of the state legislature in 1962 to provide highly trained primary care physicians. Today, the campus includes the School of Medicine, the Graduate School of Biomedical Sciences,

opened in 1979, and the Graduate School of Nursing, opened in 1986.

"This Medical School was founded by the Commonwealth to train outstanding primary care physicians for its citizens," said Chancellor and Dean Aaron Lazare. "The *U.S. News* ranking underscores our institution's success in answering the Commonwealth's call, and I am exceptionally proud of the faculty and staff."

Jack Wilson, president of the University of Massachusetts, said, "It's clear that UMass Medical School has earned its place among the top medical schools in the nation, an achievement that reflects well on higher

public education in the state. The Medical School sets the standard of quality for all of the state's universities, and we extend our congratulations to Dr. Lazare and his colleagues."

UMMS was also ranked 53rd in the *U.S. News* list of research schools. Beyond its core mission of distinction in medical education, the past decade has seen UMMS explode onto the national scene as a major center for research. The institution also

ranks near the top among public medical schools in the Northeast in the amount of funding awarded by the National Institutes of Health. Federal and private research grants and contracts at UMMS rose from about \$2 million in 1977 to more than \$154 million in 2004, making it one of the fastest-growing research institutions in the country. 🕒



Commencement Celebrates Accomplishments, Advocacy



UMass Worcester awarded 151 degrees at its 31st Commencement exercises held June 6 at Mechanics Hall in Worcester. Chancellor and Dean Aaron Lazare presented 98 MD degrees, including one MD/PhD, to graduates of the School of Medicine; 21 PhD degrees from the Graduate School of Biomedical Sciences; and, from the Graduate School of Nursing, 27 master's degrees, three post-master's certificates and, with UMass Amherst, two doctoral degrees.

Distinguished 1979 School of Medicine graduate Carolyn M. Clancy, MD, delivered the Commencement address. Dr. Clancy is the director of the U.S. Department of Health and Human Services Agency for Healthcare Research and Quality, supporting research to improve health care access, quality, safety and cost-efficiency. She is also an associate clinical professor at the

George Washington University School of Medicine, and specializes in internal medicine and women's health.

An honorary degree was presented to R. Norman Peters, Esq. Peters has been a loyal supporter of the Medical School since 1990, when he advocated on the institution's behalf during a fiscal crisis in the Commonwealth. His efforts were helpful in the reinstatement of state funding and led to an enhanced relationship between UMMS and the executive branch. As a member and past chair of the UMass Memorial Foundation, Peters was instrumental in fostering relationships between individuals and UMMS that support the Medical School's efforts to promote the health and well-being of the Commonwealth's residents. 🕒

Norm Peters, honorary degree recipient

Innovative GSN Graduate Entry Program Addresses Nursing Shortage



GSN Dean Doreen Harper, PhD, with the new Graduate Entry Pathway's director, Kathleen Thies, PhD

The Graduate School of Nursing (GSN) and the UMMS initiative Commonwealth Medicine have launched an innovative, accelerated Graduate Entry Pathway (GEP) to respond to the nursing workforce shortage in Central Massachusetts.

The GEP is the first program of its kind in the region, and the first offered by a public university. Leading to a master's degree in nursing, the program will facilitate graduate study and careers in nursing for recent college graduates as well as other adults with

bachelor's degrees in areas outside nursing. Students enrolled in the GEP will be qualified to become licensed registered nurses after completion of the first of the three-year program; once they earn the master's degree, they will be qualified to become nurse practitioners and nurse educators. "The GEP brings talented individuals to nursing who will greatly enhance our profession," said GSN Dean Doreen Harper, PhD.

The GSN is accepting applications for the first class, scheduled to commence this August, under the guidance of the GEP's new director, Kathleen M. Thies, PhD, RN. Dr. Thies will use her extensive experience in community-based student nursing practice and in program development to build a curriculum that will emphasize both hands-on technical skills and essential nursing knowledge, preparing students to take the National Council Licensing Exam for Registered Nurses in their second year of the three-year program.

"The Graduate Entry Pathway is our institution's response to pressing needs in particular nursing specialties, such as geriatrics and critical care, as well as in the field of nursing instruction," said Thomas Manning, deputy chancellor for Commonwealth Medicine. "We're very excited about introducing highly trained individuals to new opportunities that benefit themselves and their fellow citizens." ©

The positive economic impact of the nation's medical schools and teaching hospitals was highlighted in February with the published results of a study that found that the 125 U.S. medical schools and some 400 teaching hospitals had a combined national economic impact of over \$326 billion in 2002, employing one out of every 54 wage earners in the country's labor force. The study, "The Economic Impact

of Medical College and Teaching Hospital Members of the Association of American Medical Colleges," measured the financial contributions of the association's member institutions in the regions in which they are located and in the nation as a whole.

Due in part to the contribution of UMass Medical School, the study found a nearly \$21 billion total economic impact in Massachusetts during that same time period. Public medical schools like UMMS indirectly generate revenue through income taxes paid by staff and through sales tax and corporate net income taxes paid by businesses providing goods and services to the school.

One of the report's major findings is that the medical schools and teaching hospitals are major employers in their home states, accounting for 2.7 million jobs directly or indirectly in 2002. More than half of these—1.5 million—were full-time positions. UMMS alone employed 3,872 people in FY '02 (3,383 full-time and 489 part-time), a payroll of more than \$213 million annually. ©

Study Finds Medical Schools and Teaching Hospitals to be Major Economic Contributors

Irwin Inducted as President of American College of Chest Physicians

UMass Medical School Professor of Medicine Richard S. Irwin, MD, FCCP, was inducted as president of the prestigious American College of Chest Physicians (ACCP) at CHEST 2003, the College's 69th annual international scientific assembly, held in October. ACCP is a medical specialty society of physicians, surgeons and allied health professionals who specialize in diseases of the chest: pulmonology, cardiology, cardiovascular and cardiothoracic surgery, hypertension, critical care medicine and related disciplines.

Dr. Irwin announced that, as president, he intends to encourage the ACCP to formally and actively embrace the concept of patient-focused care. "Medical education and clinical practice have entered into a revolutionary period, the period of patient-focused care," he said in his inaugural

address. "[It] is the care we want our families to receive all the time. And, as physicians and medical professionals, I believe this is the care we want all of our patients to receive."

Chief of the Division of Pulmonary, Allergy and Critical Care Medicine at UMass Memorial Health Care, Irwin has been an active ACCP Fellow since 1979. He is editor-in-chief of *ACCP-SEEK* and an editorial board member and department editor of *CHEST*, the official peer-reviewed journal of the ACCP. His research interests include the pathogenesis, diagnosis, and treatment of cough; asthma management; risk factors of severe asthma; and gastrointestinal and respiratory system interactions. He has authored over 150 peer-reviewed articles, nearly 200 textbook chapters, and edited 28 books and monographs. ©



Richard Irwin, MD

UMMS Faculty Highlighted in Ad Campaign

The University of Massachusetts produced a new series of 30-second television advertisements that emphasize UMass research and illustrate ways in which these efforts are making the world a better place, and two UMMS faculty members were squarely in the television spotlight.

One of the spots focuses on the work of John L. Sullivan, MD, professor of molecular medicine and pediatrics, and director of the Office of Research at UMMS, who has pioneered a treatment now being used throughout the developing world to prevent mother-to-child transmission of HIV. Dr. Sullivan played a key role in the discovery of nevirapine, conducted the first testing of the drug and pioneered its use in the area of preventing mother-to-child transmission.

Another of the advertisements focuses on the emerging work of UMass faculty members, including Howard Hughes Medical Institute Investigator Craig C. Mello, PhD, the *Blais University Chair in Molecular Medicine*, who co-discovered RNA interference, a tool that has revolutionized biomedical research techniques. The ads aired on a host of Boston and Central Massachusetts television stations throughout the months of April and May. ©



John Sullivan, MD, was filmed during a visit to South Africa. Craig Mello, PhD, recorded his segment in the lab.

Campus Modernization Update

After a successful first year, Campus Modernization is moving forward this summer with projects in a number of areas around the UMass Medical School site and the hospital facility of clinical partner UMass Memorial Health Care. Students, faculty, staff and visitors are being urged to use

the Clip-On will provide much-needed swing space to accommodate the later stages of the façade replacement project.

This spring also witnessed the start of granite removal and replacement on the hospital. Campus Modernization teams removed granite panels from the south face of the hospital in April and May and are scheduled to begin the installation of limestone and window system curtainwall in June.

A drive along the east side of campus will also expose visitors to the impressive progress of the UMass Memorial Lakeside Expansion, which will revitalize and redefine UMass Memorial activities on the University Campus. After the relocation of general and trauma entrances and the installation of utility and sewer lines in the spring, construction will concentrate on the Expansion's concrete foundation and steel structure.

At the south end of the hospital, around the outpatient entrance, major changes are underway to prepare for the creation of a new, impressive entry into the facility. To facilitate the construction, the Benedict Building entrance has undergone a number of alterations, including the placement of construction fencing, relocation of the valet service, relocation of handicapped self-parking spaces, and the improvement of auto and pedestrian traffic flow in and out of the area. ©

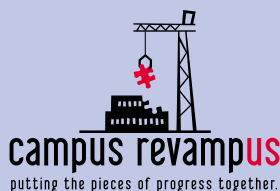


The "Clip-On" receives its "topping-off."

extra caution as they travel around the University Campus as various projects of the initiative's key elements cause an increase in construction activity and traffic.

Significant construction progress has been made around the main Medical School entrance and lobby. There, the steel frame of an office space addition, called the "Clip-On," rose quickly this spring. Scheduled to open in fall 2004,

For details and tips on navigating the campus, visit www.umassmed.edu/campusrevampus



Walk to Cure Cancer's New Date: Sunday, September 26, 2004

Last year, over 7,000 walkers and 400 teams came together to Walk to Cure Cancer, raising over \$596,000 to support cancer research at UMass Medical School. Beginning this year, the event will take place on the fourth Sunday of September, rather than on Labor Day, as it has since the inaugural Walk in 1999. Event organizers, including the Massachusetts AFL-CIO, determined that the Walk would grow even more significantly if it did not coincide with other Labor Day activities.

Carol Hull will be at the Walk on the UMMS campus September 26—she and her "Cape Crew" wouldn't miss it (see photo below). "Walking to cure cancer gives us all a feeling of hope. If it weren't for cancer research, I may not have been so lucky in my battle against breast cancer," said Hull. "My goal is to continue to raise funds to support research to benefit others." ©



Join the thousands of individuals and teams at the Walk to Cure Cancer, Sunday, September 26 and help create a future filled with hope. For more information, call the UMass Memorial Foundation at 508-856-1634 or visit www.walktocurecancer.com, which now features on-line fund-raising capabilities and personalized Web page creation for walkers and teams.





A Strike Against ALS

A UMMS researcher uses the revolutionary gene-silencing technique, RNA interference, to go on the offensive against Lou Gehrig's disease.

By Michael I. Cohen

The disease strikes otherwise healthy adults, destroying their ability to walk, talk, and eventually, to breathe. Its most famous victim gave not only his life, but also his name to it.

Commonly called Lou Gehrig's disease, amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that kills nerve cells, robbing its victims of the ability to control their muscles. The cause and destructive mechanisms of ALS remain largely unknown, but research at UMass Medical School has revealed a way to shut down a gene that causes a particular form of ALS.

This advance, the first of its kind to stop

any variety of ALS in lab tests, may open the door to treatment for people stricken with this disease and other neurodegenerative disorders. "My goal is to help people suffering with ALS by finding a cure," said Zuoshang Xu, MD, PhD, associate professor of biochemistry & molecular pharmacology and cell biology, who developed the gene-silencing approach for ALS. "If we are successful, a byproduct of this effort will be a technology very useful in research toward treatment for other diseases."

Approximately 30,000 Americans have ALS and some 5,600 new cases are diagnosed each year. (Global figures are

sketchy, but some groups estimate 160,000 people worldwide get ALS annually.) The disease is always fatal, claiming 80 percent of its victims within five years.

Most cases of ALS are sporadic, meaning they strike seemingly at random, but about 10 percent of ALS cases have a hereditary component. In this group of "familial" ALS, researchers have identified mutations of a gene called SOD-1 that is linked to about 25 percent of the familial cases. The mutant gene creates a toxic protein that initiates a cascade of biochemical reactions leading to nerve cell death.

The subset of familial ALS linked to the mutant SOD-1 gene is the target of Dr. Xu's

Zuoshang Xu, MD, PhD, checks the progress of a Polymerase Chain Reaction (PCR) machine, equipment that aids his investigations by amplifying strands of DNA for experimental use.



lab. "Focusing on the familial cases is valuable because it allows us to establish an animal model of the disease and study the disease pathways across many generations," Xu said. People afflicted with familial ALS have a normal copy of the SOD-1 gene and a mutant copy of the SOD-1 gene, which differs only slightly from the normal type. For several years, Xu's strategy has been to search for a way to stop the mutant gene from producing the toxic protein, while leaving the normal gene unaffected.

Xu began his work locally in 1994 when he joined the Worcester Foundation for Biomedical Research, which merged with UMMS in 1997. Xu has explored a variety of biochemical means to try and block the mutant gene. The big leap in his work came in 2001 when Xu integrated the emerging technology of RNA interference (RNAi) into his research. "I was reading papers about how RNAi was being applied to mammalian cells, and I saw that one of the authors was here at UMass Medical School," he said. That author was Phillip D. Zamore, PhD, associate professor of bio-

chemistry & molecular pharmacology. “I met with Phil and it became immediately clear that this could be applied to ALS. So our collaboration began,” Xu said.

RNAi is a biological process discovered in 1998 by the Medical School’s Craig C. Mello, PhD, the *Blais University Chair in Molecular Medicine* and Howard Hughes Medical Institute Investigator, and colleague Andrew Fire, PhD, of the Carnegie Institution of Washington at the time. Since Mello and Fire’s seminal publication describing their breakthrough in 1998, RNAi



“Dr. Xu is clearly the leader on this technology and we’re trying to do whatever we can to help it along.”

– Robert Brown Jr., MD, shown left

Dr. Robert Brown is a world-renowned leader in ALS research. He directed the team that discovered the mutant gene responsible for some familial ALS cases. He and UMMS’ Zuoshang Xu, MD, PhD, are now collaborators.

has emerged as one of the most important methods used in cutting-edge biomedical research. Dr. Zamore and his colleagues have made significant advances in understanding the mechanisms of RNAi and have developed technologies that allow researchers to apply RNAi to a variety of cells.

RNAi interrupts the way genes create proteins, the substances that activate and regulate the body’s metabolic functions. It has the ability to block the creation of harmful proteins spawned by mutant genes—hence its use as a vital tool in laboratories around the globe working to battle diseases such as ALS.

To use an analogy baseball great Gehrig may well have appreciated, RNAi works like the cut-off man in a baseball game. Imagine there’s a runner on second base and the batter hits a line drive to center field. The center fielder is the gene. He picks up the ball and throws for home—the ball is the RNA message created by the gene. The catcher is the cell organelle, or recipient of the message. He’s waiting for

the ball so he can make the play at home plate—make a protein. But before the ball reaches home plate, up pops the shortstop who cuts off the throw—that’s the RNAi effect. By grabbing the ball as it passes, the shortstop prevents the play at the plate. The center fielder is unaffected, as is the catcher. But there’s no play at the plate. No protein is created.

Of course, silencing only the one gene that can cause problems is much more complicated than throwing out a runner in a baseball game. There are approximately 30,000 genes in human DNA. To use RNAi to silence just one of those genes, researchers must create small stretches of RNA that mimic the exact message sent by the targeted gene. It’s a complicated biochemical task, undertaken at the molecular level.

Xu’s breakthrough involves the production of bits of RNA that silence the mutant SOD-1 gene, but leave the normal copy of the gene alone. The results of his initial tests of the technology were first published in August 2003 in the journal *Aging Cell*. “We were able to stop production of the

toxic protein in cultured cells,” Xu said. “Now we are taking the strategy to the next phase of testing.” In this next phase, Xu is studying methods to deliver the ALS gene-silencing construct into the cells of the central nervous system—primarily the cells of the spinal cord—in a way that can be effectively transferable to human patients. He is also testing an approach to prompt cells to produce their RNAi effect against the mutant gene on their own and continuously, thereby permanently silencing the mutant SOD-1 gene.

“Dr. Xu’s success with RNAi and ALS is a breakthrough,” said Robert H. Brown Jr., MD, director of the Day Neuromuscular Research Laboratory and the Muscular Dystrophy Association clinic at the Massachusetts General Hospital. Dr. Brown, who is also a professor of neurology at Harvard Medical School, is a world-renowned leader in ALS research. He led the team that discovered the mutant SOD-1 gene as the cause for some familial ALS cases.



RNA interference revolutionizes disease research and future treatment

The work began as a quest to cure amyotrophic lateral sclerosis (ALS). But the technological advance developed by Zuoshang Xu, MD, PhD, associate professor of biochemistry & molecular pharmacology and cell biology at UMass Medical School (see story starting on page 7), may prove to be an effective weapon in the fight against other neurodegenerative diseases, including Alzheimer's and Parkinson's.

"The common element in many of these diseases may well be misfolded or aggregated proteins," said C. Robert Matthews, PhD, the *Arthur F. and Helen P. Koskinas Professor of Biochemistry & Molecular Pharmacology* and chair of the Department of Biochemistry & Molecular Pharmacology at UMMS. "With the tools of RNAi, scientists are able to remove the messenger so the protein never gets made. If Dr. Xu's technology works as hoped, it could have far-reaching applications. "

RNAi, or RNA interference, is a process that silences genes by degrading the messages those genes send. RNAi was discovered in 1998 by Craig C. Mello, PhD, the *Blais University Chair in Molecular Medicine* at UMMS and an investigator of the Howard Hughes Medical Institute, with colleague Andrew Fire, PhD, of the Carnegie Institution of Washington at the time.

Since Mello and Fire's findings were published in *Nature* in 1998, the application of RNAi has swept through laboratories around the world, changing the way many biomedical researchers work. Outside UMMS laboratories, companies at the forefront of pharmaceutical innovation have purchased licenses to RNAi technology, co-owned by UMMS and the Carnegie Institution, to aid in their development of treatments for disease. As of February 2004, 37 licenses have been issued to companies including Novartis AG, Bristol-Myers Squibb, CytRX Corp., Sirna Therapeutics, Monsanto Co., GlaxoSmithKline and Pfizer.



Brown and Xu are now collaborators and meet regularly to share ideas and review approaches to the ALS research. “This effort is very exciting,” Brown said. “Dr. Xu is clearly the leader on this technology and we’re trying to do whatever we can to help it along.”

According to Brown, the confluence of events that leads to nerve cell death from ALS is incredibly complex. A multitude of biochemical interactions are involved, with many of those processes remaining unclear. That’s why he’s so interested in the RNAi approach. “It opens up the prospect of treating first principles,” Brown said. “This attempts to abort the cascades that lead to cell death before they gain momentum, and that is incredibly exciting.”

As a neurologist, Brown treats people afflicted with ALS and other neurodegenerative diseases and sees the suffering wrought by ALS firsthand. “All ALS is devastating, but the dominant form of the familial ALS is particularly destructive. It leads to death in a matter of months,” Brown said. “I have 500 families in my clinic affected by ALS—I say families, because the impact goes well beyond the patients.”

The current phase of Xu’s research will take approximately one year to complete. If the ongoing round of studies are successful, and the gene-silencing construct continues to perform as hoped, then Brown would advocate moving the technology quickly into a clinical trial with a small number of ALS patients, and would offer his lab as host to a clinical trial of Xu’s technology.

Even though the SOD-1 mutation is implicated in a small percentage of ALS cases, Brown believes Xu’s research, and similar work being done at the Day Laboratory, will ultimately lead to findings that will help people with other forms of ALS. “The downstream events that make the dominoes topple in all cases of ALS have significant overlap. So one could predict that the same drugs that work against one form of ALS could work against other sporadic forms,” Brown said. “Even if Dr. Xu’s work cures only the familial form of ALS, it would be a stunning achievement in medical science, a dream come true for those families. But I think this work may have even broader applications.” ©

At UMMS, researchers are taking full advantage of RNAi technology to speed investigation into a variety of diseases, including diabetes, HIV/AIDS and cancer, as well as ALS. Leveraging the new tools of RNAi is just one example of the Medical School’s collaborative approach to research, Dr. Matthews said. “This entire institution, at all levels, supports and advocates for communication among faculty, staff and students. That’s how science needs to be done. These are complex problems and by bringing together groups that span the scientific spectrum, to share insight and ideas, we have the best possible chance to have a real impact,” he said.

“The Journal Club” group, which includes Xu’s team and scientists from four other labs studying elements involving neurological diseases, exemplifies that collaborative culture. The group meets every two weeks to discuss their research and current publications in a range of journals. From those conversations, ideas flow, and concepts are applied in new ways. “I don’t know if we’ll ever

understand the original causes of all these neurodegenerative diseases. There could be multiple genes and environmental factors involved,” Xu said. “But if we work together to dissect the pathways of the disease, and understand what elements are involved that lead to nerve cell death, then we can try to stop one element along that pathway, giving us the potential to prevent the disease altogether.” ©



Nothing Like the Real Thing

UMMS laboratories partner with a local high school to increase achieving students' seriousness about science.

By Andrea L. Badrigian



A multiple choice quiz: Please read the following passage and then select the most appropriate statement from the choices that appear below:

When research is mentioned in the media, they only show faceless figures behind white lab coats and goggles. It makes the whole research area seem technical and impersonal. The field is actually very involved and emotional. The process is dynamic, with ups, downs and even 180° turns. Yet, what drives this process is the fact that every step, the biggest downs and the smallest ups, is a discovery. Research is very true to the dogma of science: whether it brings breakthroughs, mistakes, successes or failures, it's about learning and doing from what you learn. The reality of experimentation, and of most other things in life, is you never know what to expect. Making mistakes is OK and failures can only add to success. Errors are part of the process; being able to explain the errors and figuring out how to avoid them next time is the important part.

The author of this passage is:

- A. A former Worcester North High School student.
- B. A student who scored a 5, the highest possible score, on the Advanced Placement Biology Examination prior to his entrance to Cornell University.
- C. A participant in the program that brings exceptional high school students to the labs of UMass Medical School researchers to advance their scientific knowledge through hands-on experimentation with the most advanced equipment available.
- D. All of the above.

Loc Van will tell you, the answer is D. He is all of the above and much more, as are each of the students that have, over the past five years, joined their North High Advanced Placement (AP) Biology teacher Jane Raabis in UMMS laboratories to view the processes of mitosis and meiosis, enzyme catalysis, and genetic and molecular development in all their splendor. “Doing labs in class is great, but nothing beats seeing the real thing,” said Loc.

Kevin Quang, a North High graduate and junior at UMass Amherst, is just as enthusiastic about the hands-on exposure he gained at UMMS. “I’ve always known that I wanted to pursue a career in the scientific field, since biology always interested me. How can’t the study of life interest you? Visiting the UMass Medical School labs let me experience biology as a ‘scientist’ first-hand and not just as a student reading it out of a book. I actually had the opportunity to squeeze eggs out of a frog and work with live fruit flies. A book definitely can’t beat that learning experience.” At UMass Amherst, Kevin found he was a step ahead in his Biology 100 and 101 labs. “The labs done at the Medical School, such as transforming bacteria to become resistant to an antibiotic or working with enzymes, are also done here at UMass Amherst. I was able to help other students who didn’t understand the lab, and it made the lab report much easier for me.” The North High-UMMS collaboration requires students to keep detailed lab notebooks, chronicling the experimental “ups and downs” Loc Van described. “Manuals weren’t required for my labs at UMass Amherst,” said Kevin, “but I found myself scribbling down information in my notebook anyway and this helped me when it came to doing the lab report.”

UMass Medical School’s Stephen J. Doxsey, PhD, and North’s Raabis beam when they hear former students—now studying science in college—attribute part of their academic

success to the program the two have maintained since 1999. They mention others that characterize the caliber of learners they've been privileged to shepherd through the collaboration: Melissa Jacquez, who scored an impressive 3 on the AP test and is now majoring in biology at Holy Cross; Maria Black, a nursing major at Fitchburg State College; and Wemoor Randolph, a current North High student who plans to be an obstetrician.

Dr. Doxsey, associate professor of molecular medicine, biochemistry & molecular pharmacology and cell biology (a title that reflects not only the fields in which the scientist is well-versed, but also his suitability as a designer of the program),

brought the idea of students in full-fledged labs to North High's principal, Robert Boulé; science department head, the late Robert Davis and biology teacher Raabis in the spring of 1999, based on his experience as a post-doctoral fellow at the University of California/San Francisco. "I was involved in a science education program at UCSF, initiated by Dr. Bruce Alberts who is now president of the National Academy of Sciences, that connects researchers with students," said Doxsey, who assisted middle school pupils with their science projects. "One of the first things I did when I came to UMass Medical School was to reach out to North in the same way." One of North's former students, Nora Aboody, went on to win the state Science Fair competition

after working with UMMS. "I then wanted to get involved at some other level," said Doxsey, and the AP Biology class concept came to be.

"It started small," said Raabis, North's current Science Department chair, who noted that six students—all female—first entered the UMMS labs with the objective to complete a portion of their required course material there, using sophisticated equipment North simply couldn't provide. "This program was an answer to several things for us," said Raabis. "Not only did the UMass labs give us the advanced equipment that allowed us to complete gel electrophoresis, transformation and enzyme catalysis, but the program also served as a response to the state's mandate



Left, Jane Raabis, North High's Advanced Placement Biology teacher, demonstrates the proper technique for coaxing frog eggs for North senior Francis Adu-Gyamfi. Below, students Sylvia Roman and Jermaine Collins-Watkins retrieve a frog to try it themselves. The frog eggs are then encouraged to undergo cell division, while students watch with the naked eye. The process can also be magnified; Steve Doxsey, PhD (page 12), views the slides he has prepared for students to analyze via the computer screen. The monitor shows the colorful, fluorescent expression of a living cell protein, revealing microtubule fibers in the mitotic spindle during cell division.





“...I actually had the opportunity to squeeze eggs out of a frog and work with live fruit flies. A book definitely can’t beat that learning experience.”

– Kevin Quang, North High graduate
and student at UMass Amherst

that high schools restructure the school day to increase student achievement.” North High had moved to block scheduling of courses and a semester system, allowing students to carry fewer classes, yet spend more time in each. “AP Biology would now meet for 99 minutes each day all year,” Raabis enthused. “What a great opportunity for our students—this new partnership fit

the mission of North as well as UMass Medical School in terms of outreach.” (See related story, below.)

And what a great selling point for Raabis, as she worked to recruit an increasing number of students, from a variety of diverse backgrounds, to the challenging AP Biology course. Achieving students take the course to prepare for the Advanced Placement


Biology Examination and, if they score successfully, for a freshman year in college exempted from prerequisite science classes. “The partnership with UMass was successful from the start; the kids were very excited. No other high school in Worcester has this opportunity,” said Raabis. Her class numbers grew, from six, to nine, (males now joining in), to a high of 19 in

Pipeline promotes opportunities for thousands of area students

Bringing North High School students to UMMS laboratories isn’t the first and only connection between the two educational institutions. North’s Health Science Academy was established through the Medical School’s Worcester Pipeline Collaborative, a decade-old outreach initiative that has introduced the varied opportunities inherent in the health and science fields to thousands of local students, primarily those from minority and economically disadvantaged backgrounds. Jane Raabis, the AP Biology teacher at North, is grateful to the Pipeline for supplying transportation for her students to the world of UMMS research. “With the Health Sciences Academy and AP Biology class at UMass, our school has covered all of the bases for all its students, no matter where they are in their academic level.”

The Pipeline is nationally recognized as a successful educational partnership between the Medical School and local health care institutions, scientific companies, colleges and the Worcester Public Schools. As it

strengthens overall educational efforts to promote scientific literacy in the community, the Pipeline prepares the workforce for jobs in biotechnology, health care and research through mentoring, internships and job shadowing programs for students, and professional development and curriculum assistance for teachers.

Many students who participated in the early years of the Pipeline are now graduating from college and seeking careers in the life sciences field. According to Deborah Harmon Hines, PhD, UMMS associate vice chancellor for school services, the Medical School is waiting with anticipation at the end of the Pipeline to hire its “graduates” whenever possible. At a recent UMMS Job Fair, qualified Pipeline participants were given preference for many of the available positions. According to Dr. Harmon Hines, “This institution decided to support Pipeline programs some 10 years ago, and it’s now starting to pay off in the employment realm.” 

September 2002. “At that point, we had to break the class into two groups when we visited the Medical School,” said Raabis, who this past year brought 14 students to the labs of Doxsey (mitosis and meiosis) and his colleagues David Lambright, PhD (enzyme catalysis); Craig Peterson, PhD (molecular biology) and Tony Ip, PhD (genetics of organisms).

Dr. Ip joined Doxsey and Raabis’ program as “the only fruit fly biologist on the campus at the time,” he said. “The students come to my lab to do short

have as much of the enzyme to break down alcohol as other ethnic groups, and the kids just thought that was really cool, that he would even talk about that.” Such openness encourages the students to ask questions at the same time it dispels myths about “the scientist.”

“I usually start from the top, describing how research at UMass Medical School complements the work of our clinical partner, and how I fit in as a scientist—what is my day like?” explained Doxsey about his initial approach to each new

Doxsey and his colleagues find the program “so satisfying. When the kids leave we know they’ve learned something—what makes us tick. They realize that this is a cool environment where people are trying to figure things out using these different tools and it can be very attractive.”

“Steve and the other investigators really give the kids the sense that they can see themselves doing something like this,” said Raabis. She watches the students’ confidence grow throughout the year, as they complete each of the labs. “They

North High 10th-grader Yuee Liu in the Doxsey lab

“These kids really appreciate this opportunity, which always exceeds their expectations. ...It makes it the best that it can be for them.”

— Jane Raabis, North High Science

Department chair



experiments on mating behavior and alcohol sensitivity. They always show their curiosity and interest, truly budding minds in science. It’s rewarding to know that one day they may remember they did some interesting experiments at UMass Medical School.”

Raabis is certain they’ll remember, in part because the scientists themselves are accessible people, who dress in jeans and speak to the students on their level, without a trace of condescension. “Tony came right out and told the students that Asian people, he being one of them, don’t

class of students. “I introduce the post-docs and assistants in my lab and describe where they are in their careers as well. This really provides a sense of progression for the students.” When Doxsey details his work in cancer research, he establishes an immediate connection. “The kids start talking—they say ‘yeah, I have a relative with cancer.’ Soon they understand why the cell division they’ll witness in the lab is a step toward seeing that abnormal processes in our bodies can cause cancer.”

enter the AP Biology class with experience in science rooms that have no sinks, no tables, and then enter the labs at UMass with full equipment and someone working in the field to guide them. It makes all the difference.” And, Raabis noted, the time and effort the investigators put in is not lost on the students. “These kids really appreciate this opportunity, which always exceeds their expectations. And, they know they are special because they have been chosen to be part of this. It’s like icing on the cake. It makes it the best that it can be for them.” ©



Early Intervention

UMMS leads a multisite study of the effects of supplemented baby formula on cystic fibrosis disease progression.

By Alison M. Duffy



“We found that individuals who carry one copy of the CF gene but are disease-free [the parents] have levels of AA and DHA midway between normal controls and CF patients.”

– Brian O’Sullivan, MD

Blood samples from New England’s newborns, drawn to determine a number of metabolic disorders, are sorted and stored at the UMMS Newborn Screening Program. In 1999, the program piloted an optional test for cystic fibrosis and today, 99 percent of parents opt for the test.

Every day in maternity wards

throughout New England, a simple drop of blood is taken from the heels of newborns to be tested for a host of metabolic disorders that, if left undetected and untreated, could cause irreversible brain damage, lifelong disability or death. Such testing, conducted daily for some 500 infants born in the region by the UMass Medical School New England Newborn Screening Program, provides a clear benefit: early detection and the opportunity to prevent the ramifications of the disease altogether.

The picture for prevention is not quite so clear for cystic fibrosis (CF), a chronic and ultimately fatal genetic disorder, usually diagnosed before age three, that results in the production of abnormally thick mucus in the lungs and pancreas and affects more than 30,000 young people

nationwide. In 1999, the UMMS Newborn Screening Program piloted an optional test for CF and today, 99 percent of parents opt for the test. Yet, even though CF can be detected before symptoms appear, there is still no cure and no preventive measures to offer patients.

There is a glimmer of hope, however, regarding the symptoms of CF. Brian O’Sullivan, MD, UMMS associate professor of pediatrics, and other researchers this year identified in CF patients an imbalance in two particular fatty acids, arachidonic acid (AA) and docosahexaenoic acid (DHA). This discovery, viewed against previous animal studies, has served as the impetus for a clinical trial that may provide important clues to staving off the onset of symptoms and perhaps lessening their severity.

The fatty acid study, published in the February 5, 2004 issue of the *New England Journal of Medicine* (NEJM) by Dr. O’Sullivan and lead author Steve Freedman, MD, of Beth Israel Deaconess Medical Center, found that CF patients had abnormal levels of AA, which is associated with causing inflammation, and DHA, which is known to suppress inflammation. The study helped answer questions raised by Dr. Freedman’s earlier work showing that genetically altered mice with CF had low levels of DHA and high levels of AA, an imbalance that resulted in uncontrolled and excessive inflammation. Additional studies indicated that higher levels of DHA in the diet could help restore the balance and mitigate effects of the disease in mice. It wasn’t yet clear, however, whether the fatty acid imbalance was present in



Two-year-old Andrew Coccio was diagnosed with cystic fibrosis through the UMMS New England Newborn Screening Program. According to Dr. Brian O'Sullivan (above, right), his patient is “a thriving, happy and playful boy in part due to early diagnosis and treatment and because his mother, Amy, is a saint!” Andrew has an older brother, Anthony, who does not have CF.

humans with CF and, if so, whether it was a cause or result of the inflammation seen in CF.

The NEJM study included as control groups individuals with asthma, upper respiratory infections or inflammatory bowel disease, and parents of CF patients. By comparing the fatty acid levels and inflammatory responses in the groups, “We found that individuals who carry one copy of the CF gene but are disease-free [the parents] have levels of AA and DHA midway between normal controls and CF patients,” said O'Sullivan, results indicating that the fatty acid defect is a basic problem of CF, not a reflection of the disease state.

O'Sullivan and Freedman collaborated on the landmark study after being introduced to each other by Eliza Parker, MD '01, who

had worked in the Freedman lab prior to studying at UMMS. It was Dr. Parker who provided the method by which DHA could be introduced to patients selected for the clinical trial soon to get underway.

Parker, now a second-year pediatrics resident at New York's Weill Cornell Medical Center, had expressed an interest in conducting a CF-related project between her first and second years of medical school. She knew that Freedman had seen differences in CF mice fed DHA—she also knew that mouse and human breast milk contain DHA. For her study, Parker decided to seek a link between breastfeeding and the onset of symptoms of CF in humans.

“I remembered that CF mice did well until they were weaned from breastfeeding, and then the disease kicked in,” said Parker.

Though it wasn't clear whether the disease progression was tied to weaning or a coincidence of age, she thought, “Why wouldn't this be the same in humans? And wouldn't that be an easy way to potentially have an effect on the disease's progression?”

With O'Sullivan and Freedman, Parker created a questionnaire regarding breastfeeding practices and distributed it through CF centers across the country, generating some 800 responses from parents of CF children of all ages—infants, teens, young adults. The researchers found that there was a statistically significant decrease in the need for intravenous antibiotics—a common therapy for CF lung infection—in those children who had been exclusively breastfed for six months or more. Another

finding, although not of statistical significance, indicated that the infants who were breastfed also experienced onset of CF symptoms at a slightly later age. The results of the questionnaire study were published in the April 2004 issue of *Pediatric Pulmonology*, with Eliza Parker as the lead author.

“It was those three pieces of the puzzle—knowing that DHA made a difference in mice; knowing that humans had the same defects; and having a hint through Eliza’s *Pediatric Pulmonology* paper that breastfeeding is beneficial for infants with CF—that led us to think that feeding early in life with DHA-supplemented formula might be helpful,” said O’Sullivan.

O’Sullivan is now leading a multisite study of the effect of DHA-supplemented formula on the disease progression in CF infants identified through newborn screening and whose parents have chosen not to breastfeed. Traditionally, infant formulas available in the United States have not contained any DHA, although some manufacturers have added small amounts of the fatty acid to their formulas to capitalize on its purported benefit for neurologic development, an advantage that remains unproven. The formula O’Sullivan is using, provided by Mead Johnson Nutritionals, contains three times as much DHA as the company’s commercially available fortified formula, and a higher concentration than is found in the breast milk of the average American mother.

O’Sullivan’s study is funded by the Cystic Fibrosis Foundation and Mead Johnson, the manufacturer that is providing the study formula for free—“no small cost,” according to O’Sullivan. He expects to enroll 80 to 100 infants at 16 to 20 sites: there are currently five sites in Massachusetts and 11 in New York, two of the nine states that already screen for CF at birth. Other states may join the study as

well. (Approximately 35 cases of CF are detected annually among the Commonwealth’s infants; New York sees nearly 50. Nationwide, about 1,000 cases of CF are identified annually, either through newborn screening or clinical diagnosis.) Infants will be monitored for 12 months, from identification via newborn screening through their first birthdays.

Although lung disease causes death in 90 percent of CF patients, in the first year of life few patients have dramatic respiratory problems while most do experience pancreatic symptoms. Prior to the advent of newborn testing, the majority of CF diagnoses were made based on a child’s failure to thrive (poor growth), a result of pancreatic insufficiency and improper digestion of food. Because pancreatic damage occurs earliest, the study will rely on monthly stool samples to monitor human fecal elastase (FE-1) levels, a measure of pancreatic function that indicates the degree of inflammation and destruction in the pancreas. “What we’re hoping to see is preservation of pancreatic function and higher FE-1 levels in the group getting DHA, a sign of less inflammation and destruction of the pancreas,” said O’Sullivan. “If we see even a small difference now, we’d want to follow it to see if the difference is maintained or lost over time.”

O’Sullivan would like to obtain funding to follow the same cohort of children to age 5, 6 or 7, when they’re old enough to participate in pulmonary function tests to detect any long-term benefit of intervention with the DHA-supplemented formula. “With good care and nutritional support, and aggressive antibiotic therapy for minor respiratory illnesses, a lot of kids don’t develop problematic lung disease until they’re into high school and beyond,” said O’Sullivan. “We have some kids who are track or basketball stars;

activities that weren’t dreamed of 25 years ago.” In fact, the life expectancy for children with CF has increased dramatically over the years. When O’Sullivan graduated medical school in 1980 and began doing CF research, life expectancy was about 25 years; today is it up to 33 years. But if 33 years seems an improvement, early intervention to make more of those years disease-free would be even better. (O’Sullivan admits he is unsure about newborn screening for CF, and remains concerned about the ethical and moral conundrum raised when parents are provided with a diagnosis of a disease

**“Until now, the answer
to the question**

**‘can we offer something to
parents of children with CF?’**

**has been a no—this study
may give us a yes.”**

— Brian O’Sullivan, MD

they can’t avoid.) If the infant formula study provides further evidence that early intervention with DHA can help delay the onset of CF, even by a few years, O’Sullivan’s concerns will be allayed. “Until now, the answer to the question ‘can we offer something to parents of children with CF?’ has been no—this study may give us a yes,” he said. “If this does turn out to be a yes, then there’s a very strong argument indeed for nationwide, mandatory newborn screening for cystic fibrosis.” ©

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

Reid Gilmore, PhD, professor: Assembly and Transfer of N-linked Oligosaccharides, one year, \$350,756; recommended for three more years, \$1 million.

Tariq M. Rana, PhD, professor: Dynamics of Transcriptional Activation in HIV, one year, \$178,875; recommended for four more years, \$1.4 million.

Charles G. Sagerström, MD, assistant professor: Molecular Analysis of Hindbrain Formation, one year, \$325,850; recommended for three more years, \$906,300.

Celia A. Schiffer, PhD, associate professor: HIV-1 Vif: Another Potential Target, one year, \$238,500; recommended for one more year, \$238,500.

National Science Foundation

C. Robert Matthews, PhD, the *Arthur F. and Helen P. Koskinas Professor of Biochemistry & Molecular Pharmacology* and chair: Folding Mechanisms of Dihydrofolate Reductase and the Response Regulators, one year, \$179,240; recommended for one more year \$183,168.

CELL BIOLOGY

National Institutes of Health

Jeanne B. Lawrence, PhD, professor: Nuclear and Genomic Organization of Gene Expression, one year, \$312,224; recommended for three more years, \$1 million.

Greenfield Sluder, PhD, professor: Centrosomes in the Control of Mitosis and Interphase, one year, \$397,500; recommended for three more years, \$1.2 million.

Gary S. Stein, PhD, the *Gerald L. Haidak, MD, and Zelda S. Haidak Professor of Cell Biology* and chair: Identification of Histone Gene Regulatory Sequences, one year, \$457,848; recommended for three more years, \$1.4 million.

Janet L. Stein, PhD, professor: Short-term Training for Minority Students, one year, \$126,509; recommended for four more years, \$506,036.

George B. Witman III, PhD, the *George F. Booth Chair in the Basic Sciences*: Flagellar Motility and Assembly, one year, \$444,123; recommended for three more years, \$1.4 million.

FAMILY MEDICINE & COMMUNITY HEALTH

Department of Health and Human Services

Daniel H. Lasser, MD, MPH, professor and chair: Academic Administrative Units in Primary Care, one year, \$218,577; recommended for two more years, \$557,677.

Mark E. Quirk, EdD, professor: Faculty Development in Primary Care, one year, \$261,504; recommended for two more years, \$540,000.

Robert Wood Johnson Foundation

Linda F. Weinreb, MD, professor: Depression in Primary Care: Linking Clinical and System Strategies, two years, \$550,000.

MEDICINE

Andrew's Buddies

Elliot J. Androphy, MD, the *Barbara and Nathan Greenberg Chair in Biomedical Research*: Screening of Drugs

That Modify SMN2 Splicing, one year, \$176,696; recommended for one more year, \$173,000.

National Institutes of Health

Francis A. Ennis, MD, professor: Flavivirus Infection: Pathogenesis and Prevention, one year, \$1.3 million; recommended for four more years, \$6 million.

Dale L. Greiner, PhD, professor: Genetics of Autoimmunity in BB Rats, one year, \$327,755; recommended for three more years, \$1 million.

Joan B. Mannick, MD, assistant professor: Nitrosylation of Cytochrome C during Apoptosis, one year, \$278,250; recommended for four more years, \$1.1 million.

Aldo A. Rossini, MD, the *William and Doris Krupp Professor of Medicine*: Mechanism of Islet Transplantation Tolerance, one year, \$1.1 million; recommended for four more years, \$4 million.

Frederick A. Spencer, MD, associate professor: Monitoring Trends in Venous Thromboembolism, one year, \$661,833; recommended for three more years, \$2 million.

Gyongyi Szabo, MD, PhD, associate professor: Alcohol and Monocyte Signaling, one year, \$394,845; recommended for four more years, \$1.6 million.

Robert B. Zurier, MD, professor: Cannabinoid Acids as Anti-inflammatory Agents, one year, \$318,000; recommended for two more years, \$636,000.

MOLECULAR GENETICS & MICROBIOLOGY

The National Science Foundation

Anthony R. Poteete, PhD, professor: Genetics of Bacteriophage Lambda Red-Mediated Recombination, one year, \$120,000; recommended for two more years, \$240,000.

MOLECULAR MEDICINE

American Diabetes Association

Zhen Y. Jiang, PhD, research assistant professor: Using Small Interfering RNA (siRNA)-induced Gene Silencing to Analyze Insulin Signaling on Akt Pathway and its Role in Glucose Transport in Insulin-sensitive Cells, one year, \$137,802; recommended for two more years, \$276,000.

National Institutes of Health

David G. Lambright, PhD, assistant professor: Structural Basis of G Protein Mediated Signaling, one year, \$332,993; recommended for three more years, \$933,729.

Craig C. Mello, PhD, the *Blais University Chair in Molecular Medicine* and Howard Hughes Medical Institute Investigator: RNA Mediated Genetic Interference in *C. elegans*, one year, \$318,000; recommended for three more years, \$954,000.

NEUROLOGY

National Institutes of Health

David Paydarfar, MD, associate professor: Physiology of Swallowing and Airway Protection, one year, \$278,250; recommended for three more years, \$835,000.

NEUROBIOLOGY

National Institutes of Health

Hong-Sheng Li, PhD, assistant professor: Functional Analysis of the dCAMTA Transcription Factor, one year, \$382,281; recommended for four more years, \$1.4 million.

PATHOLOGY

National Institutes of Health

Cynthia Chambers, PhD, assistant professor: Mechanisms of CTLA-4 Function, one year, \$357,750; recommended for four more years, \$1.4 million.

Kenneth L. Rock, MD, professor and chair: Immunobiology of MHC Restriction of T Cells, one year, \$159,000; recommended for four more years, \$1.2 million.

PHYSIOLOGY

National Institutes of Health

Mitsuo Ikebe, PhD, professor: Function of Small G-Protein Binding Myosin, one year, \$373,650; recommended for four more years, \$1.4 million.

Motor Function and Regulation of Myosin VII, one year, \$302,100; recommended for four more years, \$1.2 million.

Michael J. Sanderson, PhD, professor: Calcium Signaling in Airway Smooth Muscle, one year, \$362,690; recommended for four more years, \$1.3 million.

Yu-Li Wang, PhD, professor: Dynamic of Actin in Normal and Transformed Cells, one year, \$390,745; recommended for four more years, \$1.7 million.

PSYCHIATRY

National Institutes of Health

William H. Fisher, PhD, professor: Modeling CJ Involvement Among PMI, one year, \$313,479; recommended for two more years, \$600,000.

Jean A. King, PhD, associate professor: Imaging Unconditioned Fear, one year, \$300,300; recommended for three more years, \$800,000.

RADIOLOGY

National Institutes of Health

Michael A. King, PhD, professor: Beowulf Cluster for Computer-Intensive Research, one year, \$460,295.

Patient Motion Detection and Compensation in Spect, one year, \$559,206; recommended for four more years, \$2.3 million.

U.S. Department of Energy

Donald J. Hnatowich, PhD, professor: Targeting Cancer with Radio-labeled Antisense Oligomers, one year, \$160,582; recommended for three more years, \$1.1 million.

SURGERY

National Institutes of Health

Giacomo P. Basadonna, MD, PhD, professor: Protection of Pancreatic Islets by Survivin, one year, \$159,000; recommended for one more year, \$159,000.

Jodie Maranchie, MD, associate professor: Impact of Renox on HIF-alpha in Renal Cancer, one year, \$129,060; recommended for four more years, \$520,000.

I've just celebrated my 14th Commencement as Chancellor with the UMass Worcester community of students and faculty. The stirring processions and flowing robes—so key

MESSAGE FROM THE CHANCELLOR/DEAN

to the grandeur of the occasion—remind me of how fortunate I am to be in my position at this campus. As we celebrate with our graduates, the men and women who are beginning their careers as physicians, nurses and researchers, we are reminded of what a privilege it is to have a role in their education. They are bright, energetic and full of idealism for the future.

Each year, the UMass Worcester Commencement brings an exceptional speaker to our midst. Dr. Carolyn Clancy, this year's speaker, is proof of that fact. This 1979 graduate of the School of Medicine is director of the U.S. Department of Health and Human Services Agency for Healthcare Research and Quality. She is responsible for supporting research designed to improve the quality of health care, reduce its cost, improve patient safety, decrease medical errors and broaden access to essential services. Her agency does so by providing information that helps policy leaders, providers and consumers make more informed health care decisions.

Dr. Clancy said that her experience as a student at UMass Worcester shaped her mindset as well as her career, with the emphasis on community medicine reinforcing the notion of service to our fellow citizens. Beyond her education here, she learned to love medicine even more because, as she says, "medicine draws on the best of science to customize health care to an individual's needs and preferences."

On the following pages, you'll read about three other alumni who have come to their own understandings about the potential of medicine and science as Dr. Clancy has, and as, I'm certain, our latest group of graduates will as time goes by:

Charles Wolleben, PhD '86, was a member of the first class enrolled in the Graduate School of Biomedical Sciences. Today, as director of Global Regulatory Strategy for neuroscience compounds at Bristol Myers-Squibb, Dr. Wolleben finds that his career answers his "drive to apply research to outcomes....At [UMass Worcester] I was forced to never forget what the ultimate goal was—to apply basic science to clinical medicine."

It was here that Marcia Ormsby, MD '82, came to understand the link between the mind, lifestyle and health. She says, "I began a



lifelong study of nutrition, as it relates to health and healing. Stress also leads to healing problems; I'm convinced that the body-mind connection exists and it was at UMass that this connection was taught and learned."

Kathleen Jackson, MS '99, found the Graduate School of Nursing's program "demanding and rigorous." With this foundation, she devised a program to ensure continuity of care for patients at home after hospitalization for congestive heart failure and was honored for her ingenuity by Partners HealthCare and its Innovation Award. She says, "Improving quality, access and delivery of care to patients is what all nurses strive for!"

A handwritten signature in blue ink that reads "Aaron Lazare". The signature is fluid and cursive, written in a professional style.

Aaron Lazare, MD



Charles D. Wolleben, PhD '86

Charles Wolleben had the early Graduate School of Biomedical Sciences all to himself—almost. He was one of just eight students to first enroll in the PhD Program in Medical Sciences, the precursor to the GSBS. Although the group shared the campus with medical students, the hospital's floors and patient

rooms were largely empty, reflecting the facility's fledgling status in 1979. Dr. Wolleben recalls leaving his sixth floor laboratory to cut through the cavernous hospital corridors to reach the cafeteria, an unhindered trip then that would be maze-like today.

Such trailblazing is analogous to the effect the first class had on the future GSBS. "It wasn't clear how this group of anomalies was going to fit into the bigger picture. We molded the path as we went," said Dr. Wolleben of the inaugural students and their faculty. "There may have been a political debate at one time about a hospital, medical school and graduate school together in Worcester, but it certainly has evolved into a real fixture characterized by rapid growth."

Dr. Wolleben learned of the new graduate program immediately—he was a research technician in founding Dean Thomas Miller's biochemistry lab. "I knew many of the faculty outside of the academic realm because of my work experience. Graduate students like myself became another outlet for the faculty's objective to answer clinical needs through their basic science research."

According to Dr. Miller, his former employee turned student



Marcia V. Ormsby, MD '82

Dr. Marcia Ormsby acknowledges that her path to medical school was peppered with obstacles. At 29, she was a

single parent receiving federal assistance who dreamed of applying her talents as a painter to the art of healing. Unwavering in this vision, she sold her home and most of her belongings to attend the University of Pennsylvania, where she completed the courses necessary to pursue a medical degree. Following two years of diligent study, and the achievement of a near perfect grade point average, Dr. Ormsby still faced difficulty in achieving admission into medical school; given her personal obligations and untraditional student profile, several schools voiced concern about her ability to succeed.

Not UMMS. Dr. Ormsby was gratified when she received a call from the Medical School's registrar, who personally invited her to join UMMS, and started a pattern of help when she needed it. "I'll always remember the librarian at UMass who allowed me to take home reserved books as long as I returned them by the opening hour in the morning," she recalled. "She knew that I was struggling with a son at home and couldn't spend long hours on campus."

The belief in Dr. Ormsby was well-founded. Today, she is one of only a few women in the country to have established a successful solo surgical practice that specializes in aesthetic cosmetic surgery. According to Dr. Ormsby, this pursuit combines her knowledge of "healing, artistry and surgery, with a focus on total well-being." She explained, "It was at UMass that I began a lifelong study of nutrition, as it relates to health and healing. Today, I actually defer surgery for

a patient who displays evidence of toxins until their lifestyle has improved. Stress also leads to healing problems; I'm convinced that the body-mind connection exists and it was at UMass that this connection was taught and learned."

Dr. Ormsby also credits the high ratio of female students in her medical school class with fueling her awareness of women's issues, both medically and politically. She recognizes this experience as the basis for her activism in lobbying for issues affecting women's health. "As an artist and a healer, I bring to the specialty of plastic surgery a great focus and determination to heal the exterior and the interior. I'm grateful to UMass Medical School for being forward thinking and for its appreciation of a unique situation that has allowed me to become an asset to my community." —LCB

“proved outstanding in the classroom. He was diligent, highly intelligent and motivated. He is one of our best and brightest.” It’s not surprising then, that Dr. Wolleben says coming to Worcester was “the seminal event in my life leading to my current career.”

That career is at Bristol-Myers Squibb, where Dr. Wolleben provides research teams with the regulatory context for their investigations, ensuring that they comply with applicable laws and principles pertaining to the development and commercialization of pharmaceuticals. As director of Global Regulatory Strategy for neuroscience compounds, Dr. Wolleben is guiding a portfolio of compounds in the pre-clinical and late stages of development, and a few poised for the marketplace. “This position answers my drive to apply research to outcomes. There is a tremendous medical need to address in areas like depression, psychosis and dementia.”

Dr. Wolleben works extensively with health authorities in the U.S., Europe, Australia and Asia. “The goal of our company is to develop novel therapeutic agents to address the enormous medical challenges that confront patients, their families and physicians, and ultimately provide broad access to those therapies.” He noted that his regulatory discussions with health authorities are “80 percent about basic science. Few people know that; they hear about drug approvals or withdrawals, but really those decisions are driven by fundamental scientific principles.”

Since it typically takes 10-15 years to bring a new drug to patients, Dr. Wolleben must be a man of determination. That trait blossomed at UMMS, a unique setting where he was surrounded by medical students and a burgeoning hospital, and was “forced to never forget what the ultimate goal was—to apply basic science to clinical medicine.” —ALB



Kathleen Jackson, MS '99, NP

Kathleen Jackson spent 19 years as a bedside nurse in Metrowest Medical Center’s intensive care unit, earning

growing autonomy and respect along with increasingly sophisticated nursing skills and knowledge. As her responsibilities for critical care decisions grew, Jackson realized that, “Functioning in the advanced practice role can bring opportunities beyond our traditional practice settings. I knew I could do more for patients as a nurse practitioner.” It was time to go back to school.

“The GSN program was demanding and rigorous—improving quality, access and delivery of care to patients is what all nurses strive for!” Jackson appreciated the Graduate School of Nursing’s trimester program that allowed her to complete her studies while working full time and raising two teenagers. Earning her master’s in adult

acute/critical care from the GSN enabled Jackson to create a unique new role for herself that bridges the best of high-tech medical care and personal nursing care. In collaboration with the internists and cardiologists at Charles River Medical Associates of Natick, Mass., she established an innovative program to ensure continuity of care for patients at home after hospitalization for congestive heart failure (CHF). Jackson travels throughout the Metrowest area to visit patients, many of whom are homebound elders with physical limitations that hinder their ongoing medical care. “As a nurse practitioner, I can bring the benefits of a traditional doctor visit to their doorsteps. Patients benefit tremendously from the social interaction, education, health care and prescriptive abilities an NP can provide.”

The success of this approach has been tangible: “I have a CHF patient I’ve been seeing for three years. He has not been re-hospitalized once during that time,” Jackson said. Recognizing the program’s widespread support from physicians,

patients and families, Partners HealthCare, parent company of Charles River Medical Associates, honored Jackson with its Innovation Award in 2001.

The CHF program has since expanded to include homebound patients with other chronic diseases, like multiple sclerosis, diabetes, hypertension and chronic obstructive pulmonary disease. Jackson also sees ambulatory outpatients in clinic each morning before setting out for home visits in the afternoon.

Complementing her commitment to excellent patient care is Jackson’s interest in advancing the nursing profession. While she doesn’t have as much time as she’d like to devote to advocacy, membership in the Massachusetts Coalition of Nurse Practitioners keeps her hand in legislative issues that address public health and nursing policy. “I’m interested in both broadening and redefining nurse practitioner roles, adding value for patients and caregivers alike.” —SLG

1976

Michael T. Foley, MD, is chief administrative officer for the medical staff at Caritas St. Elizabeth's Medical Center in Boston. Dr. Foley has practiced as a gastroenterologist at the hospital since 1981 and was a trustee of the University of Massachusetts.

1978

Ethan B. Russo, MD, took a full-time position in natural products research with GW Pharmaceuticals of Porton Down, United Kingdom, after practicing neurology for 20 years. Dr. Russo continues to live in Montana with periodic trips to England. His latest book is *Women and Cannabis: Medicine, Science and Sociology* (Haworth Press, Inc., 2003).

1981

Joseph R. DiFranza, MD, professor of family medicine & community health at UMMS, received the Society of Teachers of Family Medicine 2004 Best Research Paper Award at the society's annual conference in May for his paper, "Development of Symptoms of Tobacco Dependence in Youths: 30 Month Follow-Up Data from the DANDY Study." Dr. DiFranza's report, co-authored by Judith A. Savageau, MPH, UMMS assistant professor of family medicine & community health and pediatrics, was originally published in *Tobacco Control* in 2002.

1984

Michael A. Coyne, MD, was named the 2003 Volunteer of the Year by the National Hemophilia Foundation at its annual meeting in November. Dr. Coyne, an emergency department physician at Berkshire Medical Center, has served on the foundation's board of directors and its Medical and Scientific Advisory Committee, advocated on a number of related medical and research issues, and conducted lectures and written articles on emergency care for patients with hemophilia. According to the foundation, Dr. Coyne has "contributed significantly to helping the organization meet its mission and goals," and the foundation's president, Jordan Lurie, praised Dr. Coyne for being "diligent and dogged in pursuing improved therapies for our community."

1987

Charles S. Hemenway, MD, PhD, an associate professor of pediatric hematology/oncology at Tulane University and a member of the Tulane Cancer Center, has been named the Mauverney Research Excellence Scholar for his research into the Rational Development of an Inhibitor of t(4;11) Leukemia.

Murray C. Norcross Jr., MD, returned to the United States in July 2003 after a three-year assignment as medical director at the Naval Hospital in Yokosuka, Japan. Dr. Norcross is now serving as the director for Current Operations and Platform Readiness of the Office of the Navy Surgeon General. He resides in Burke, Virginia with his wife Ann and children Monica, 17, and Nathaniel, 16.

1988

Luis A. Sanchez, MD, is the chief medical examiner for Harris County, Texas. After graduating from UMMS, Dr. Sanchez established the position of HIV program coordinator for the Department of Pediatrics at the former UMass Medical Center. In coordination with Worcester's Department of Public Health, he implemented a comprehensive AIDS risk prevention program focused on the Hispanic community. Dr. Sanchez went on to complete his residency in anatomic pathology at Columbia University College of Physicians and Surgeons in New York and his fellowship in forensic pathology at the Dade County Medical Examiner's Office in Miami. He served as deputy chief medical examiner for the District of Columbia for over six years, and in 1998, became acting chief medical examiner. During his tenure in Washington, Dr. Sanchez was a frequent lecturer at the Department of Criminal Investigation Homicide School of the Metropolitan Police Department. He has been an active consultant in forensic medicine for the International Criminal Investigative Training Assistance Program (ICITAP) under the aegis of the Criminal Division of the U.S. Department of Justice. As an instructor for the ICITAP, Dr. Sanchez has taught all aspects of forensic medicine—and the on-scene role of the medical examiner—to police officers, physicians and attorneys in regions throughout the world, including Central and South America, the Caribbean and Central Asia.

1989

Ronald N. Adler, MD, was appointed medical director of the Hahnemann Family Health Center in Worcester after serving as the health center's education director since 2000. He is the only UMMS faculty member to have been recognized by graduating residents as the program's "Inpatient Teacher of the Year" (1998-99) and as its "Outpatient Teacher of the Year" (2000-01). In addition to his clinical activities at Hahnemann Family Health Center, Dr. Adler provides care to patients at the Plumley Village Health Center.

Tammy B. Bottner, MD, is co-founder of Riverside Pediatrics in Newburyport, Mass. on the campus of Anna Jaques Hospital.

1991

Patrick R. McSweeney, MD, is a family physician at Franklin Family Practice and at Milford-Whitinsville Regional Hospital, where he serves as medical director of the Tri-County Medical Associates. Dr. McSweeney lives in Medway with his wife and three children.

Karen P. Szczechowicz, MD, recently left a group practice to open an office as a solo practitioner in Peabody, Mass. According to a February newspaper article in *North Shore Sunday*, Dr. Szczechowicz “started from the ground up, serving as office cleaning crew and doing the bulk of her own billing. To this day, Szczechowicz’s practice retains an overwhelmingly hands-on feel: She administers her own vaccines, runs lab tests herself and she’s weighed and measured every patient in her practice personally.” Though she now has help with a part-time billing staffer and nurse, Dr. Szczechowicz is quoted in the article as saying, “I keep reassuring my patients I have no intention of growing this into a group practice. ...What’s great about a solo practice is you see every patient for every visit.” Affiliated with Salem Hospital and North Shore Children’s Hospital, Dr. Szczechowicz is the mother of two boys, ages 10 and 6.

1997

Khoa D. Do, MD, practices internal medicine with Gastrointestinal Physicians in Salem, Mass. His clinical interests include liver disease and diseases of the esophagus and pancreas.

Joseph P. Rossacci, MD, recently completed his medical fellowship in nephrology at Beth Israel Deaconess Medical Center in Boston. He is a clinical nephrologist at Saint Vincent Hospital at Worcester Medical Center.

1998

Jacquelyn M. Reilly, MD, is a physician with North Shore Ear, Nose and Throat Associates in Salem, Mass. At Albert Einstein College of Medicine, Dr. Reilly was chief resident of otolaryngology, sinus disease and head and neck surgery.

Matthew Russell, MD, a specialist in geriatric medicine, is a staff physician for Caritas Medical Group of Caritas St. Elizabeth’s Medical Center. Dr. Russell practices in Waltham and is also pursuing his master’s degree in clinical epidemiology at Boston University.

2000

Bruce E. Condit, MD, is an internal medicine specialist on the staff of Central Maine Medical Center. He is the center’s first hospitalist, providing care for inpatients at the request of their primary care physicians. While at UMMS, Dr. Condit was presented with the Gary G. Winzelberg, MD, Memorial Award for his “warmth, compassion and dedication” and received a Student Leadership Award for Community Service. Dr. Condit lives in Auburn, Maine with his wife Whitney.

Cara Douville Kaupp, MD, is a pediatrician with Partners in Pediatrics of Nashua, New Hampshire and is on the staff of Southern New Hampshire Medical Center.

Jean Siddall-Bensson, MD, practices internal medicine at Attleboro Medical Associates.

2003

Jaimie Kane, MD, married Jay Candelmo on June 7, 2003 in Providence, Rhode Island. Dr. Kane is a pediatric resident at UMass Memorial Medical Center; her husband is a second-year MBA student at the Sloan School of Management at MIT.

The following physicians have joined the medical staff of UMass Memorial Health Care — Marlborough Hospital:

1986

Abraham Fischer, MD, obstetrics/gynecology

1992

James M. Flynn, MD, cardiology

1993

Valerie R. Price, MD, nephrology

1998

John S. Martin-Joy, MD, psychiatry

1999

Kerri E. Osterhaus, MD, obstetrics/gynecology

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

Vitae: The Last Word

By Michele P. Pugnaire, MD

Vice Dean for Undergraduate Medical Education at UMMS

Prompted by a renewed emphasis on patient safety, preventing medical errors and assuring quality in health care, the School of Medicine recently revised its approach to medical education. This revision shifts the Medical School's curriculum from an objective-based model to one promoting fundamental "competencies" that UMMS students must demonstrate upon completion of their education—competencies that are necessary to best serve patients through today's multifaceted occupation of "physician." Below, Dr. Michele Pugnaire describes the framework of this new approach to teaching that will allow medical school graduates to even more effectively apply their knowledge and skills "in practice."

The Competencies for Medical Education are described in a document officially adopted by UMMS last year, yet by no means is that document simply a "to-do list;" rather, it embodies our educational philosophy and the distinctive and unique attributes of our institution, our faculty and our students. It also reminds us that we are not training our students for graduation alone, but for their whole professional life, compelling us to incorporate components into the curriculum that help define, track and monitor their progress well beyond the time they are with us.

and future demands of undergraduate medical education, to best prepare today's students for practice in tomorrow's health care environment. We required that each Competency be "measurable," allowing educators to assess student progress as well as mastery, and that the document that outlines them be structurally sound and user friendly—one that continually inspires us as we refer to it.

This document also addresses our student-centered educational viewpoint, one that sees our charges as more than the sum of the courses they take or their performance on tests. Given the demands of the profession, we have an obligation to speak to our students' individuality and well-being while giving them the resources they need to succeed. In addition, the entire set of Competencies addresses trends emphasized in the medical profession such as life-long learning, service, communication and teamwork.

The Competencies document is a launching point for further development of the curriculum and its assessment. Work is currently underway to "map" the Competencies against the existing curriculum, to fill gaps, remove redundancies and make changes across all disciplines and all years with the Competencies as our guide. This effort will be both retrospective and prospective, given that our curriculum is naturally evolving. These adaptations will also allow us to establish a framework to evaluate the levels of mastery that our students should achieve at particular points in their medical education—from simply reporting on a topic learned, to educating others on the subject.

Our goal as medical educators can best be conceptualized this way: when a patient, perhaps someone in our own medical practice or even a member of our family, is in need of medical care, we want to know that a thoughtful, caring—and fully competent—physician is attending to them. If that individual is a UMMS graduate, then our pledge as educators is that this physician is a compassionate healer, whose natural desire to care for others has been reinforced and assessed by our Competency-driven curriculum. ☉

The Competencies for Medical Education have their foundation in the six roles of the physician—Professional, Scientist, Communicator, Clinical Problem Solver, Patient and Community Advocate and Person. These roles are represented in visual form through posters that enhance corridors, clinics and classrooms at various UMMS educational sites. The Physician as Advocate and as Person posters are shown here.

The cornerstone of the Competencies curricular innovation is the concept of training an "undifferentiated" graduate who has prepared for the multiple roles of the physician. These roles—Professional, Scientist, Communicator, Clinical Problem Solver, Patient and Community Advocate and Person—are supported by specific proficiencies that represent the knowledge, skills, attitudes and behaviors that our educational program aims to teach and assess.

Determining these Competencies required the collective wisdom of many UMMS contributors; each Competency was carefully considered for its merit and relevance to both the current needs



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