



## Wired for Success at DMS

It is no secret that technology has changed the practice of medicine. With the advent of computers, technological leaps have advanced digital imaging for diagnosis and accelerated the mapping of the human

genome. Now the Dartmouth Medical School faculty have taken steps of their own to harness new technologies to enhance the medical curriculum and better serve the students.

Students at DMS are indoctrinated into a technological mindset even before they arrive

on campus. Laptop computers, already strongly recommended, will be required for the entering class for the first time beginning in August 2004. In addition to accessing online textbooks and health care programs, researching medications, referencing the drug-related information in Clinical

Pharmacology Online and reviewing journals on MEDLINE, DMS students will rely on their laptops in ways more immediate to DMS community.

Those computers will come in handy when the students begin to review the hundreds of slides that make up "Cells, Tissues, and Organs (CTO)," a required class for all first year students. Over 700 histology slides were digitized and posted on the DMS website this fall to supplement the class and provide a reliable resource for students to review, sans

microscope. The digital images have become a popular learning tool because arrows appear when a different label is highlighted, showing the students exactly where each component is located, and

most can be inspected at varying degrees of magnification.

"I initially designed the site as a review program so students could see these images as often as possible," said assistant professor of anatomy and CTO director

Dr. Matthew Heintzelman, who

believes that repetition is the key to learning histology. "I pictured students curling up with their laptops and plugging through a few dozen images at a time." But Heintzelman and his colleagues soon noticed that students were bringing in their laptops to class and comparing what they

saw on the microscopes to the labeled slides online. "The number of students raising their hands to ask about details under the microscope dropped dramatically," said Heintzelman.

At a lab earlier this fall, more than half of the first year students were consulting laptops next to their microscopes, their eyes bouncing

between the eyepieces and the computer screens. "The slides on the website make it easier to review the different slides and bringing my laptop to lab ensures that I am studying exactly what I am supposed to be learning," said first year student Shannon Myer. Classmate Khushal Latifzai said that he feels more prepared for class because,

"I can take the initiative and review the slides before I step into the lab."

Heintzelman is quick to point out that digital slides could never fully replace the hands on study with a microscope. "I am very old school in terms of the way I approach anatomical education. I think of it like looking at a Monet painting in an art book and then going to an art museum and seeing the real thing. ... It's essential to differentiate between subtle hues and textures of cells and tissues and you just can't get that digitally."

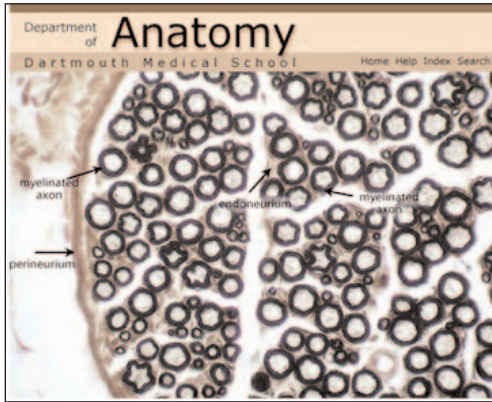
Other innovative advances adding to the scope of the curriculum are virtual programs developed by Dr. Joseph Henderson and his team at the Interactive

Media Laboratory (IML). Their laboratory offers a program, Clinical Genetics, which centers on four simulated patients who have, or are at risk of developing, diseases where knowledge of clinical genetics can affect outcomes. "The simulated office visits and the interviews with



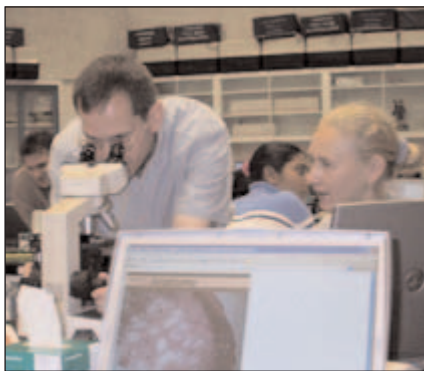
Susanne Griffin, '07 compares a slide online to a slide on the microscope.

Andy Nordhoff



Details of a single nerve fascicle, one of hundreds of magnified histology slides now accessible on the DMS website.

Paul Genzano



Dr. Matthew Heintzelman assists first year student Meredith McCoy, '07 in a CTO lab.

Andy Nordhoff



real patients were extremely helpful," wrote one DMS student in her evaluation.

Another IML program is Primary Care of the HIV/AIDS Patient, which offers the user a chance to play the long-term physician, and gives a first hand sense of the emotional impact of HIV/AIDS on individual patients at a virtual clinic that includes an orientation, a learning resources room, and encounters with a virtual "patient." Both programs, requirements for third year students, involve discussions with faculty

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## Deans Column

The faculty of Dartmouth Medical School has been expanding at a rapid pace over the past five years.

We read about the accomplishments, skills and interests of new recruits regularly in the DMS and DHMC publications. Likewise, we routinely hear of the research successes of specific faculty members. While all of this is exciting and well-deserved, there is a hidden component behind most of the stories that is rarely noted: collaboration.

The time of individual scientists and physicians making major breakthroughs or attaining great ends by struggling on their own in an isolated lab or clinic has almost completely vanished. We are in an era of multidisciplinary research, complex techniques, narrowly defined areas of expertise, and increasingly complex problems. The current model for success in research and patient care involves a team of individuals assembled for a specific task, each person bringing to the problem a narrowly defined, but superbly performed, set of skills. Such teams are assembled across departmental boundaries, and frequently include members at other academic institutions from this country and abroad.

One notable feature at Dartmouth is the breadth of our collaborative efforts. Not only does this extend from department to department, it also carries across all the various components of Dartmouth. Thriving interactions exist between the medical faculty and members of Thayer, Tuck and the Faculty of Arts and Sciences. This is by no means routine in academia. During a recent visit to Dartmouth by Dr. Thomas Cech, president of the Howard Hughes Medical Institute, this aspect of our research endeavors was recognized in a highly laudatory manner.

DMS has been most fortunate in its ability to attract physicians and scientists of the highest caliber, and these days the process of recruitment goes on continuously. While the department chairs always seem to be seeking new candidates with outstanding talent and achievement in their disciplines, the question that is increasingly becoming the critical factor in deciding to whom to offer a position is: with whom will they collaborate?

William F. Hickey, M.D.  
Senior Associate Dean for Academic Affairs  
The Constantine and Joyce Hampers Professor

## New Pathway Found to Enhance Cancer Treatment

Recent DMS research points to a potentially larger role for retinoids in the treatment and prevention of cancer. Retinoids, compounds derived from Vitamin A, work by turning on proteins called retinoid receptors that increase the abundance of a panel of retinoid "target genes." The new study, in the November 7 issue of the *Journal of Biological Chemistry*, builds on the prior DMS discovery that a potential retinoid receptor inhibitory protein called RIP140 is a byproduct of one of these target genes.

Now the research team has found that RIP140 is responsible for repressing the retinoid receptors, adversely affecting the ability of retinoids to differentiate cancer cells and slowing tumor growth in experiments using testicular cancer cells.

"Once RIP140 was removed, growth of cancer cells was repressed by retinoids at a faster rate compared to experiments where RIP140 was present," said Kristina White, who performed the experiments with Mark Yore, both graduate students in pharmacology and toxicology.

Retinoids are known to have anti-tumor properties in the clinical setting. Laboratory findings indicate retinoids have

the potential to treat and prevent a variety of leukemia and solid cancers, primarily by causing cancers to "mature" or "differentiate" and thus more closely resemble normal cells. This strategy may have less severe side-effects compared to conventional chemotherapy and may be a particularly

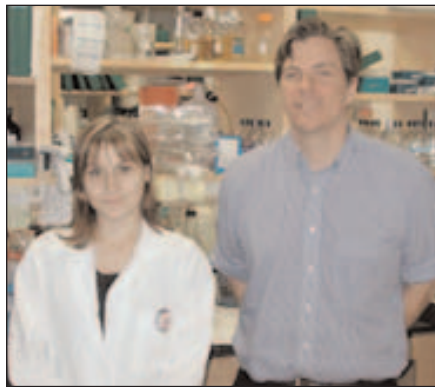
valuable strategy in preventing cancer in high-risk individuals.

However, thus far retinoids have only proven to be useful toward a small subset of cancer types in people.

"We were surprised at how much better retinoids worked in RIP140-free cells," said Dr. Michael Spinella, assistant professor of

pharmacology and toxicology and a member of the Norris Cotton Cancer Center. "When we knocked RIP140 out of the cancer cells, they began to differentiate within two days; it usually takes five days to see any change in the cells."

More work lies ahead, Spinella added. The team hopes to use these findings to develop better differentiation-based strategies for the treatment of human cancer. Initial studies on RIP140 were conducted by Joanna Kerley, a graduate student in pharmacology and toxicology. Other DMS researchers who contributed include Shannon L. Warburton, Angelina V. Vaseva, Erica Rieder and Dr. Sarah J. Freemantle.



Kristina White and Dr. Michael Spinella

Andy Northhoff



Tom Kosowski

### Blood Pressure Screening

First year medical students Jimmy Carroll, (left) and Andrew Siesennop offered free blood pressure tests to local residents at K-Mart during National Primary Health Care Week. Several members of the Dartmouth chapter of American Medical Students Association (AMSA) took part in this effort to educate people on the risks of high blood pressure and increase vigilance in maintaining general health.

## Team Fights HIV/AIDS and TB in Africa

Contagious diseases still wreak havoc, especially in developing nations, and often when tamable, yet entrenched diseases converge with recently emerged infections. So it is that tuberculosis (TB), a treatable and preventable airborne infection is growing dramatically, fueled by the increased susceptibility to TB of people living with HIV. Still the largest single infectious cause of death worldwide, TB is also becoming the biggest killer in HIV/AIDS. The global problem prompted the International Aids Trust, a non-governmental organization, to call for fighting HIV/AIDS and tuberculosis simultaneously.

Meanwhile DMS researchers have been at the forefront of such an international effort to improve the outlook for a particularly vulnerable group: those with HIV and TB in Africa. Dr. C. Fordham von Reyn, professor of medicine, heads programs in Tanzania to develop and test an effective TB vaccine for people with HIV/AIDS and to train local scientists and health care workers.

The work, said Dr. Stephen P. Spielberg, dean of Dartmouth Medical School, “exemplifies the strengths of the Dartmouth medical enterprise: collaboration, inclusion, and the practical application of research and training outside our walls here in Hanover. Dr. von Reyn and his team are simultaneously bridging cultures, exchanging knowledge, training physicians

here and in Africa, and tackling the very real problems of one of our world’s newest and most devastating epidemics—HIV/AIDS—and one of the oldest and most persistent—tuberculosis. And they’re doing it not just in laboratories, but in the regions where its effects are most devastating. The lasting legacy for our students, our colleagues and collaborators, and on patients with HIV/AIDS and tuberculosis is incalculable.”

Recently, the DMS-lead team received \$1.5 million from the National Institutes of Health’s Fogarty International Center to provide HIV and tuberculosis research training to health care workers in Tanzania in collaboration with Boston University (BU) School of Public Health, Muhimbili University College of Health Sciences (MUCHS) and the National Public Health Institute of Finland. The new partnership, the Dartmouth/Boston University AIDS International Training and Research Program (AITRP), aims to increase knowledge and enhance research skills and capacity in Tanzania to reduce deaths from HIV and TB.

The five-year award builds on previous NIH-funded studies by von Reyn and Dartmouth colleague Dr. Richard Waddell that were the first to demonstrate the high rate of unrecognized and untreated bloodstream tuberculosis infections among HIV infected patients in Africa. The findings spurred them to update a vaccine strategy to prevent the severe TB complication in HIV patients.

Preliminary trials of their vaccine in the United States and Finland have been promising. The new booster, a killed vaccine, enhanced TB immunity in HIV patients whose weakened immune systems make the current TB vaccine, which is a live vaccine, more risky. In most countries where TB is widespread, children generally receive a vaccine made from live *Mycobacterium bovis*, Bacille Calmette-Guerin (BCG), used to reduce the risk of TB for more than half a century.

“Since there is no evidence that the current BCG vaccine protects patients with HIV against TB, we have been working on a new strategy to immunize persons with HIV against TB safely and effectively,” said von Reyn.

In a “back to the future” approach, he and colleagues revived a strategy used successfully prior to BCG: administration of killed vaccines against TB. The team dusted off the concept to employ a multiple dose series of a contemporary killed mycobacterial vaccine to prevent TB. Results of their study in Finland, where BCG vaccine is routinely administered at birth, were reported in the November 7 issue of the journal AIDS.

“The multiple-dose course of the inactivated vaccine boosted immunity against TB both in those with HIV and those without HIV. The vaccine was also safe and did not adversely affect the patients’ underlying HIV infection,” von Reyn said.

Added Dr. Robert Horsburgh, chair of epidemiology at BU School of Public Health and a co-director of the AITRP, “These findings give hope to the search for a vaccine against TB. This killed preparation would also be safe for use in persons with HIV infection. Thus, if it proves to be effective in preventing TB, it could help millions of people with HIV infection.”

The Finnish study was the basis for a large-scale trial Dartmouth researchers have been conducting since 2001 in Dar es Salaam, Tanzania with Muhimbili Medical Center. The five-year \$4 million NIH-funded study is the only efficacy trial of a new TB vaccine under way in the world. It will enroll more than 2,000 HIV-infected patients to determine if TB among high risk HIV-infected people in Tanzania can be reduced.

AIDS was first reported in Tanzania in 1983, according to Dr. Kisali Pallangyo, professor at MUCHS and co-investigator in Tanzania. “By the end of 2002, over 2.4 million people in Tanzania were estimated to have HIV and the rate of tuberculosis cases increased four to five-fold during the same period. The Fogarty training grant will strengthen our ability to investigate methods to control these dual epidemics in Tanzania,” Pallangyo said.

Through the AITRP Tanzanian trainees will enroll in DMS degree programs, directed by Dartmouth faculty, including Drs. Lisa Adams, Charles Wira, Bernard Cole and Gerald O’Connor, and at BU School of Public Health and the National Public Health Institute of Finland.

### MPH Program Accredited

After its first year, Dartmouth Medical School’s program for the master of public health degree (MPH) has been awarded the maximum accreditation term of five years (through December of 2008) from the Council on Education for Public Health.

MPH program director Dr. Gerald O’Connor, professor of medicine and of community and family medicine, said the maximum term accreditation “reflects the strength of Dartmouth’s evaluative clinical sciences graduate program and its commitment to training and research that meet broad regional and national health needs.”

DMS awarded the first MPH degrees to 32 students in June 2003.

## Biofilm Antibiotic Resistance May be Susceptible to Genetic Approach

**B**iofilms, slimy clusters of bacteria that are resistant to antibiotics, may have a genetic chink in their armor that could be exploited to combat the infections they cause, say DMS researchers who are using a genetic-based approach to investigate how biofilms can withstand antibacterial treatments.

Their study, published in the November 20 issue of *Nature*, provides an innovative model for the investigation of biofilms that may lead to the development of new methods to hamper their resilience. "We are beginning to get at some of the mechanisms that might be important to understanding the antibiotic resistance of biofilms, which is the first step in the long journey to developing a treatment," said lead author Dr. George O'Toole, assistant



Dr. Thein-Fah Mah

professor of microbiology and immunology.

Biofilms are complex communities of bacterial cells that can survive environmental stresses including the presence of antibiotics. These populations can form on industrial equipment, medical implants, teeth (plaque) and internal organs, and are estimated to be involved in 65 percent of human bacterial infections.

Conventional antibiotic therapy is frequently ineffective once pathogens have formed biofilms: these surface-attached communities are up to 1,000-times more resistant to antibiotics. Biofilms are of particular interest to those who study periodontal disease and pneumonias associated with cystic fibrosis.

The study questions prior assumptions that the structure itself confers resilience

suggesting that one day, clinicians may be able to program the bacteria to be less resistant to antibiotics. "This is the first time anyone has used an unbiased genetic



Dr. George O'Toole

approach to understand why biofilms are resistant to antibiotics," said principal author Thien-Fah Mah, a postdoctoral fellow at DMS.

Using a common pathogen, *Pseudomonas aeruginosa*, the researchers developed a genetic screen to look for mutant strains that were more sensitive to antibiotics. "The idea was to let the bacteria tell us which genes were important," said Mah. "We were able to identify a mutant of *P. aeruginosa* that, while still capable of forming biofilms, did not develop the high-level biofilm-resistance to three classes of antibiotics."

*Continued from page 1*

members to further enhance the computer-based format.

Not that the medical school has limited its applications to laptop computers. It has also encouraged the use of personal data assistants (PDAs), which can be found in the pockets of a growing number of residents and students. DMS made PDAs available to students a few years ago and, after polling the users, began to investigate various applications of these hand-held devices. "The school has been very supportive of PDAs," said Todd Burdette '04, alluding to DMS support for PDA purchases, installations of programs, and even

technical support if problems arise. The school is also working on a new patient encounter tracking program available for PDAs, which, predicts Burdette, "will make owning a PDA nearly essential over the next few years."

Indeed, building on a successful project in a related area, a group of DMS faculty and students has almost completed D-MEDS, a powerful new web-based software application that will allow students to document their interactions with patients and clinical preceptors in all clinical situations, in detail, using any desktop, laptop, or nearly any PDA. (See September/October Digest.) DMS

students will be able to document their progress throughout four years at DMS in the six broad competencies that all medical students, residents, fellows, and practicing physicians need to develop and then augment. "When D-MEDS comes online in January 2004," predicts Dr. David Nierenberg, senior associate dean for medical education, "it may be the most complete clinical encounter documentation system in any medical school in the country." He adds that DMS will continue to train its students at the peak of technology, paving the way toward many new advances in the medical field.

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