

First Years Shoulder White Coats and New Responsibilities

Seventy-eight first year medical students went through a ceremonious right of passage in their journey to become physicians on September 19 as they donned gleaming white coats for the first time. Family and friends of the class of 2007, who through a series of faculty presentations received a detailed overview of what the Dartmouth Medical School curriculum entails, applauded loudly with their newfound appreciation for what it means to wear a cloak of medicine.

Kicking off the ceremony, Medical School Dean Stephen Spielberg, MD, PhD, described the white coat as the “embodiment of our profession.” Quoting an array of societal leaders from Louis Pasteur to Mr. Rogers, he cited accomplishments in medicine, including the 50th anniversary of the discovery of DNA as well as the more recent successful mapping of the human genome. Spielberg said that by wearing

a white coat, the students have accepted the responsibility to bring the enormous advances of medicine out of laboratories and into patients’ lives.



Sophia Califano, Dorothea Tórti and Maricruz Merino (from left) pose in their new coats at the reception.



Folasade Ajayi, Patrick Ladapo, Khushal Latifzai, and Bjorn Engstrom (from left) model their new garb after the ceremony.



Jennie Hyojin Chung receives congratulations from Dr. Alvord as classmates Marc Akashi and Seyi Akinbobola applaud.

Photos: Flying Squirrel Graphics

“The goal of actually developing science in the interest of society should be achieved by each of us, as we care for our patients day to day,” Spielberg told the crowded Kellogg Auditorium. “Our white coats,” he concluded, “represent our highest aspirations for science and learning in the service of our fellow human beings.”

Next, speaking as a DMS alumnus, a professor, a practicing physician and a parent of a recent DMS graduate, Senior Advising Dean Joseph O’Donnell, MD, assured the family and friends of the class of 2007 that the goal of DMS is to nurture exceptional people as well as exceptional physicians. He also introduced the class mission

statement, to which every member of the class had the opportunity to contribute and personalize. The class mission, said O’Donnell, “is a way to get at what it is the students aspire to and we hope the students take their mission statement and use it as a resource 10, 20 and 30 years down the road, to keep focused on the reasons they entered the medical field.”

Then, Senior Associate Dean David Nierenberg, MD, led a discussion on the importance of compassion, understanding and dedication in being a physician and stressed personal one-on-one relationships with patients. “Be the kind of physician your patients want you to be,” he advised. “Picture yourself sitting in a hospital waiting room and imagine who you want to walk through that door, and you will know instantly who you want to be.”



Nicholas Demartini signs the class mission as Kevin Desrosiers looks on.

Lori Alvord, MD, associate dean for student and multicultural affairs, and Sue Ann Hennessy, assistant dean for student affairs, presented white coats to the students as they received congratulations from several second and third-year students who took time to celebrate with them.



William Tseng “takes off” with his new white coat.

Deans Column

If the answer is D-MEDS, what are the questions? How can students track the patients they see, their diagnoses and the clinical procedures they learn at clerkship sites across the country? How can the amount and quality of feedback from preceptors to students be tracked? How can students, faculty and clerkship directors expand their focus to include the (six) major areas of training and competency? How can the medical school convince the LCME (our national accrediting body) that all our clerkship sites offer comparable, high-quality clinical learning experiences?

D-MEDS, the Dartmouth Medical Encounter Documentation System, may be the answer for these challenges facing medical schools across the country. Building on earlier successful efforts to develop a simple software system to document the encounters among DMS students, their patients and their preceptors in several outpatient clerkships, a group of DMS faculty and students is nearly done developing a powerful new software application that will allow students to document in detail the richness of their interactions with patients and preceptors in all clinical situations — using any desktop, laptop or nearly any PDA. In a few months, this may be the most complete documentation system in any medical school in the U.S.

This tool will help students create their own personal portfolios of experiences during clinical rotations, and keep DMS students and faculty focused on the six broad competency areas: expanding medical knowledge, improving clinical skills, strengthening communication skills, practicing professionalism, measuring and improving what they do, and learning how to practice within a complex health care system. For the first time, faculty and preceptors can examine how students experience these areas in daily practice.

We look forward to launching D-MEDS in all our clerkships and On Doctoring this winter and spring. By documenting and examining what our students see and do during all their clinical rotations, we hope to improve the way our students, preceptors and patients experience clinical education.

David Nierenberg

David Nierenberg, MD
Edward Tulloh Krumm Professor
Senior Associate Dean for Medical Education



Mark Austin-Washburn

Discovery Advances Prion Disease Research

Adding to the paradox of prion diseases, DMS researchers have discovered that RNA plays a role in converting a normal prion protein into a mutant that leads to mad cow disease and other fatal brain illnesses. Their study, reported in the Oct. 16 issue of *Nature*, provides important clues to understanding the role of prions, unorthodox infectious agents whose ability to transmit disease has confounded physicians and scientists.

The work, by Dr. Surachai Supattapone, assistant professor of biochemistry and of medicine, opens new avenues of exploration for diagnosis and treatment of a perplexing group of neurodegenerative disorders called prion diseases. Prions lack RNA or DNA, the nucleic acids that contain genetic information to replicate. No one knows what spurs conversion of a normal prion protein to a disease-causing counterpart. Supattapone, with coauthors Nathan Deleault and Ralf Lucassen, has discovered that RNA may be a catalyst for transformation.

"It has been well proven that nucleic acids, including RNA, are not part of the infectious agent, so it's an ironic twist that a catalyst for the reaction may be RNA," said Supattapone. He emphasized, however, that the findings are consistent with the "protein-only" hypothesis because the nucleic acids are in the host and are not contained in the disease spreading particle.

Prions related to infectious brain diseases such as Creutzfeldt-Jakob disease in humans, chronic wasting or scrapie in animals have long been known, but research to piece the process together has moved slowly. The discovery more than 25 years ago that prions were proteins, devoid of nucleic acids, upended what scientists assumed not only about disease transmission, but about life itself. All mammals have a gene to make a prion protein, but the normal prion is a different shape than the infectious prion.

Somehow, this normal protein is modified into an abnormal counterpart that accumulates exponentially in the brain until death.

"It's a curious thing, because this protein is able to stimulate its own formation and change, without nucleic acids. It's been a fascinating question for people to come

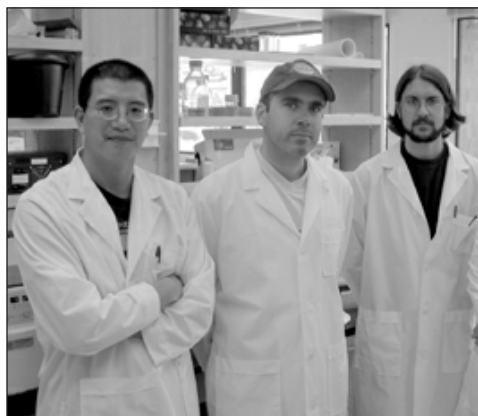
to grips with scientifically in addition to being the central reaction in an important medical problem," Supattapone said.

Now, his team has discovered that specific RNA molecules are required to transform prion proteins into their abnormal shapes. They devised a technique to observe how the normal prion protein, called PrPC, effi-

ciently converts into the abnormal infectious protein, PrPSc (scrapie), in a test tube. They found that adding enzymes that slice RNA blocked accumulation of abnormal prion protein. Taking it further, the researchers purified RNA and reconstituted the activity they had abolished with the RNA-cleaving enzymes. Adding enzyme knocked down scrapie protein and adding RNA brought it back up, indicating that RNA is really a stimulator.

The existence of RNA-converting factors could aid early detection of prion diseases, now incurable and invariably fatal. Ideal treatment time would be in the nascent stages of symptoms, before development of permanent brain damage. Current diagnosis requires a small brain biopsy, which may not provide much abnormal protein, but a technique where RNA can be added to boost the signal of abnormal proteins may offer quicker diagnosis.

The next step is to pinpoint the RNA molecule, which seems to be only in mammals. "This stimulatory RNA appears to be a specific one which makes it exciting to study," Supattapone said. If we can identify, clone and produce this specific RNA, it may be useful as therapeutic target or a diagnostic tool. In addition, it may offer clues to the mechanism of conversion."



Dr. Surachai Supattapone, Ralf Lucassen and Nathan Deleault, from left.

Andy Nordhoff

Lung Disease Research Center Funded

A team of scientists, led by Dartmouth Medical School, has been awarded \$12 million from the National Institutes of Health (NIH) to establish an interdisciplinary research center on lung diseases in New Hampshire. The five-year grant will support studies at DMS, Dartmouth College and Keene State College, in collaboration with New Hampshire's Departments of Environmental Services and of Health and Human Services.

NIH established the funding program, known by the acronym COBRE (Centers of Biomedical Research Excellence), to augment and strengthen the biomedical research capabilities of small or rural states and to enhance the scientific expertise of junior faculty in those regions.

"The COBRE grant to further research into mechanisms of lung disease is a tribute to the investigators in the program, and an exemplar of the kinds of research in which Dartmouth excels," said Dr. Stephen P. Spielberg, DMS dean. "It enables investigators across disciplines, including basic, translational and clinical scientists, to collaborate with a goal of bringing advances in scientific understanding of disease mechanisms and treatments to patients in need. This grant will have a major impact for faculty development, research, education of young scientists and clinical application of new knowledge to patients."

Projects will investigate several lung diseases including lung cancer and cystic fibrosis (CF), an inherited, life-threatening disorder that causes severe lung damage and nutritional deficiencies. Some of the studies will focus specifically on New Hampshire.

"The funding will create the infrastructure to enable Dartmouth and Keene State investigators to conduct state-of-the-art research on lung diseases," said Dr. Bruce Stanton, professor of physiology, who heads the program. "This is an opportunity to better understand not only how these diseases are caused, but to translate those insights to new therapeutics."

The program includes five multidisciplinary research projects under the umbrella of "cellular and molecular mechanisms of lung disease." Three projects that focus on

cystic fibrosis will investigate the biology of the cells affected, the structure of the molecules involved and the infections common in people with CF, one of the most prevalent genetic diseases in the US where one in 25 individuals is a carrier. Two other projects to study environmental factors that contribute to lung diseases including lung cancer, which accounts for over 30 percent of all cancer deaths in New Hampshire, will work with state agencies to examine the effects of agents such as arsenic, radon, nickel and diesel exhaust.

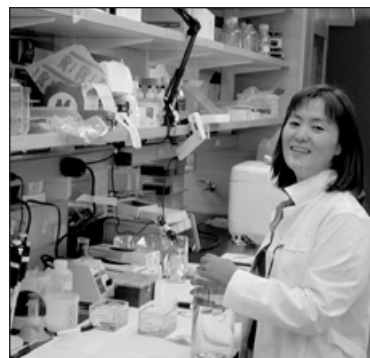
Funds will also support faculty recruitment and development of a new, state-of-the-art proteomics facility to study the location, structure and function of the proteins involved in these lung diseases.

Program co-directors are Dr. Joshua Hamilton, professor of pharmacology and toxicology, and Dr. James Leiter, professor of physiology. The program supports faculty mentoring by pairing junior level faculty with senior colleagues, training for graduate students and postdoctoral fellows, and developing closer research ties among the collaborating groups in New Hampshire.



Dr. Bruce Stanton

Jon Gilbert Fox



Dr. Kyoson Yun, a research associate in pediatrics, enjoys her new lab space at NCCC.

Andy Nordhoff

Expansion Opens

The Norris Cotton Cancer Center (NCCC) recently celebrated the expansion project that doubled the size of its facility and helps pave the way for efforts to enhance cancer research opportunities for DMS and DHMC. The celebration coincided with an announcement that the National Cancer Institute has approved another five years of support to NCCC as a comprehensive cancer center, almost doubling its current \$1.8 million.

The expanded center is ideal for "integrating science in the interest of patients," said DMS Dean Stephen Spielberg in his address at the formal opening of the center's new research labs and offices. The \$34 million expansion adds four floors of state-

of-the-art research and administrative space, doubling the square footage in the Barbara E. Rubin Building to 200,000 square feet. The project brings the number of labs to 16, each of which has the capability to accommodate research teams of three to 12 people.

The expansion project will conclude with the renovation of patient treatment areas next year.

Preceding the ceremony was a symposium, "Discovering New Worlds of Medicine," which featured keynote speaker Dr. Olivera J. Finn who heads the immunology program at the University of Pittsburgh Cancer Institute. Cancer center investigators and assistant professors, Dr. Yashi Ahmed (genetics), Dr. James DiRenzo (pharmacology and toxicology), and Dr. Lawrence Myers (biochemistry), also presented their new research on tumor suppression and gene expression processes.

The dedication ceremony began with a welcome from NCCC Director Mark Israel. Speakers, in addition to Spielberg, included Hospital President James Varnum, Clinic President Thomas Colacchio and former NCCC director Ross McIntyre, followed by a ribbon cutting with city and state officials.

COBRE Investigators and Projects

- George O'Toole, PhD, (DMS), how bacteria infect the lungs of CF patients;
- Agnieszka Swiatecka-Urban, MD (DMS), how mutations in CFTR, the gene that is altered in CF patients, cause the disease;
- Dean Madden, PhD, (DMS), structural analysis of proteins that modulate the function of the CFTR protein;
- Melinda Treadwell, PhD (Keene State College), effects of air pollution in New Hampshire on lung disease, including cancer;
- Eric Duell, PhD, (DMS) and Xun Shi, PhD, (Dartmouth College), environmental epidemiology study of lung cancer in New Hampshire.

Research Offers Insight on Treatment for Hereditary Eye Disease

Findings of a Dartmouth Medical School study may provide a step for treating as well as understanding an incurable debilitating eye disease that can eventually lead to blindness. The research targets the mutation of a specific gene that can trigger retinitis pigmentosa (RP), a hereditary disease that affects 1.5 million people worldwide, many of whom are legally blind by the age of 40.

The study, which appeared in the October 3 issue of the *Journal of Biological Chemistry*, highlights research conducted on rhodopsin, a protein located in the back of the eye that is credited with helping sight in dim or low-light conditions. It is one of several proteins in the retina that controls how light is detected.



Dr. John Hwa

The mutation linked to RP can be traced to the photoreceptor rhodopsin. A single mutation, state the researchers, can cause a cascade of retinal events that leads to retinitis pigmentosa and eventual blindness.

“We wanted to concentrate on the reasons why rhodopsin is prone to misfold; that way we have the best chance of correcting that distortion before the disease can worsen,” said lead author, Dr. John Hwa, assistant professor of pharmacology and toxicology.

Retinitis pigmentosa is a degenerative disease that affects the photoreceptors in the retina. It begins with a single mutation within the rhodopsin protein that triggers a domino effect and, over a period of years,

the mutation is responsible for aggregation of the protein, death of the individual retinal cells, destruction of the retina and eventually blindness.

“We needed to understand the problem at the level of the protein; then we can design a ligand or drug to stabilize the abnormal protein to make sure it is destroyed properly.” Hwa and DMS co-authors Aleksander Stojanovic and Irene Hwang used compensatory mutations and crystal structure, which enabled them to decipher which of rhodopsin’s 348 amino acids were distorted.

“We now have a molecular understanding of the abnormal proteins,” said Hwa, “so we can move ahead to the ultimate goal of designing effective drugs to delay the degeneration that occurs to people suffering from RP.”

Gender and Geography Increase Racial Disparities in Health Care

Past studies have shown racial disparities in health care treatment around the US, but new Dartmouth research published in the October 2 *New England Journal of Medicine* shows that the disparities are even larger when geography and gender are added to the equation.

Looking at the most commonly performed joint replacement surgery, total knee replacements, researchers from DMS and DHMC found widely varying rates of surgery among blacks, whites and Hispanics. Surprisingly, they found that gender and geographic location seem to have a major impact on rates, even within the same racial or ethnic group.

“We know that knee replacements are a more common operation for women

than for men,” says Dr. James Weinstein, professor and chair of orthopaedics and professor of community and family medicine, an author of the article. “But even adjusting for that, the differences in the rates for black men and black women in the same cities are dramatic.”

Looking at Medicare statistics from 1998-2000, Weinstein and Dartmouth co-authors Drs. Jonathan Skinner and John Wennberg, professors of community and family medicine, and former DHMC resident Dr. Scott Sporer were able to analyze data from 430,726 knee arthroplasties according to region, sex, race, and ethnic group.

“An important message of this study is that disparities exist not just because of the color of your skin or the language you

speak, but also because of your zip code,” said Skinner. Even among white women, rates ranged from 2.0 per thousand in New York City to 7.2 per thousand in St. Louis.

In other findings, the article notes that nationally, rates of knee replacement were higher for whites overall than for Hispanics, with the gap most pronounced when looking at rates among men. Some of this gap could be explained by differences in income and by patterns of residential segregation.

This latest study, funded by the National Institutes of Health and the Robert Wood Johnson Foundation, builds on decades of research by Wennberg and his colleagues at the Center for the Evaluative Clinical Sciences, aimed at improving the delivery of health care.

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DMS Communications

1 Rope Ferry Road (HB 7065)

Hanover, NH 03755-1404

Tel: (603) 650-1492 • Fax: (603) 650-1730

Email: dms.communications@dartmouth.edu

www.dartmouth.edu/dms/news

Hali Wickner, Editor

Andy Nordhoff, Associate Editor

Mark Cookson, Layout & Design