



# Digest

## Cloak of Medicine Presented

**E**ighty first-year students were welcomed into the medical profession with the white coat ceremony October 26, which introduced the new students to the privileges and responsibilities associated with becoming a physician.



Dean John C. Baldwin, MD, welcomes MD/PhD candidate Hai Sun into medicine.

Associate Dean for Medical Education, David Nierenberg, MD, expounded on the symbolism of a white coat, stating that they stood for “the uniform of a profession, a medical caregiver, cleanliness, skill, training, expertise and qualities of professionalism.” Wearing a white coat should express professionalism, he said, such as “subordination of one’s self-interests, response to society’s needs, adherence to high ethical and moral standards and demonstration of core humanistic values of empathy, integrity and altruism.” He did, however, warn against possible negative connotations to a white coat, such as formality, authority, arrogance, superiority, power and condescension.

DMS Dean John C. Baldwin, MD, commented that “the experience

of medical school is going to be quite different from anything you’ve done before. It’s not going to be like high school and it’s not going to be like college.” He characterized this period as an important transition in the students’ lives, an experience that is not only intellectual but also profoundly emotional. “It’s an attitudinal transition,” he said, “for you will notice a change in the way you study and a change in the way you think about people.”

Baldwin said that medical training prepares physicians to perform two basic tasks: relieve suffering and prolong life. Physicians, therefore, have limited expertise and are not meant to be judges, policemen or moral guides for their patients. “Be grateful to your patients,” Baldwin said, “because patients give meaning, purpose and gratification to the physicians’ lives.” He concluded by saying, “That is why this is such a great profession, symbolized by putting on a white coat.”

White coats were presented along with a pin from the Arnold P. Gold Foundation, dedicated to fostering humanism in medicine.

—Tanisha Keshava, Dartmouth '05



Katrina Mitchell '05 accepts her white coat.

## Biomedical Research Excellence Funded

**D**artmouth Medical School has received an \$11.6 million award from the National Institutes of Health (NIH) to establish a nationally recognized center of biomedical research excellence in immunology and inflammation. The five-year grant will support collaborative projects at DMS in conjunction with the University of New Hampshire (UNH), promoting research opportunities for biomedical investigators in New Hampshire with broad potential for understanding and treating diseases of the immune system and cancer.

The funds are awarded through a special program called COBRE, an acronym for centers of biomedical research excellence that NIH designed to cultivate research expertise among junior faculty and strengthen the research infrastructure of states that do not receive as much NIH funding as some large states.

“This award enables the medical school to build on its productivity and leadership in an area of far-reaching importance for health and disease. And as importantly, it affords an opportunity to forge alliances in a consortium with life scientists at UNH,” says DMS Dean John C. Baldwin, MD.

The program encompasses five integrated research projects, under the umbrella of “immune mechanisms controlling inflammation and cancer.” The projects are “multidisciplinary in breadth, characteristic of a center of

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## Dean's Column

In this country, as of last summer, more than 50 million people had no health insurance, and at least 30 million more were underinsured. According to the US Census Bureau, at least 75 percent of the uninsured people were actually working. Still, in the absence of a right to healthcare in this country, they were uninsured and relegated to the "safety net" of struggling inner city hospitals, free clinics, emergency wards and teaching hospitals. Clearly, those without jobs have no hope of obtaining traditional insurance, and they fare even more poorly in accessing the health system. This serious problem clearly demands attention if America is to move into the new century remaining the most powerful nation in the world. We must recognize that the uninsured are vitally important to the healthcare system as a whole, for their costs must, in the long run, be borne by us all as their lack of treatment negatively affects society. It is our moral duty to see that every person in this great nation has access to this basic human right.

At DMS, we are working actively to combat this problem. Through our Center for Evaluative Clinical Sciences, and in concert with the Rockefeller Center at Dartmouth, we are actively pursuing new solutions to this crisis, and are working with others around the nation to implement changes in public policy. I am very proud that DMS is a national leader in this area, and I strongly encourage each one of you to think about ways in which you might become involved with this important cause.



John C. Baldwin, MD  
Dean, Dartmouth Medical School  
Vice President for Health Affairs, Dartmouth College



## Protein Passengers Find Seats on Cellular Bus

For some proteins made deep within a cell, those that work elsewhere in the body have a complex journey aboard carrier vesicles with many possible stops before they exit the cell and reach their destination. DMS biochemists have discovered a key receptor for sorting which proteins stay and which leave, documenting for the first time what many scientists theorized but had not confirmed about how proteins travel through cells for export.

The results, published November 16 in *Science*, by Charles Barlowe, PhD, associate professor of biochemistry and William J. Belden, a graduate student, help resolve a major piece of the cell traffic puzzle. They pave the way for further understanding of how hormones such as insulin and other important factors are conveyed through cells for secretion into the bloodstream.

Transporting proteins that need to leave the cell to function is essential. After they are manufactured on membranes in the cell interior, the proteins are captured in little vesicles that take them to the cell boundary for discharge. Packaging the proteins to board the vesicles takes a series of steps not yet well delineated.

"Internal membranes have thousands of proteins in them and some of those proteins depend on vesicles to travel to another location. But the first

step is getting into a vesicle. That's called sorting," says Barlowe. He makes the analogy of a bus. "If there is a bus to carry passengers and the passengers need seats, then if we look at the bus carefully we should be able to find some seats."

Using baker's yeast as a model system, Barlowe found a seat on the cellular bus. He discovered a "transport receptor," the first of its kind to select a soluble protein and help ferry it out of its compartment.

Yeast, like many animals, gives off pheromones when mating. Barlowe found that one little yeast pheromone binds to a protein, Erv29p, for its journey through the cell, and that without that receptor protein, the pheromone is not secreted. "If you knock out Erv29p, you still make the bus and it still goes to the right place. But it's missing the seat for this passenger to get on, so the passenger stays off." The vehicle moves along, but it can't carry passengers.

The Erv29p receptor may have parallels in higher cells or there may be other receptors as well, and diseases related to faulty secretion could be linked to flawed receptors. In humans, evidence suggests that a protein similar to Erv29p is required to get a blood clotting factor out of cells, so genetic mutation that causes a form of hemophilia is linked to a protein like the one documented in yeast.



Charles Barlowe, PhD

## Team to Develop Psychosocial Support for Mars Mission

What would you do if you were stuck in a small room with half a dozen people for two and one-half years? Would you be exasperated? Would you function efficiently? This is the dilemma facing the National Aeronautics & Space Administration (NASA) as it plans for a long-distance space trip to Mars. The foundation for such a mission rests on more than designing and building a sophisticated spacecraft capable of getting to Mars. Just as important is the need to make sure that the astronauts on board remain mentally fit.

The National Space Biomedical Research Institute (funded by NASA) recently funded a research team at Dartmouth to come up with a solution for this unique problem—to develop a prototype of computer software that could someday diagnose each astronaut's mental health and conduct therapeutic exercises.

James A. Carter, PhD, instructor in community and family medicine, and Jay C. Buckey, MD, research associate professor of medicine, lead the team. They will be working with Leonard Greenhalgh, PhD, Amos Tuck School of Business, an expert on business situation conflicts, Mark Hegel, PhD,

associate professor of psychiatry and of community and family medicine, an expert on problem-solving treatment for depression, and Albert W. Holland, PhD, chief psychologist at NASA-Johnson Space Center.

The prototype will be a computer-based system to assist astronauts in preventing, diagnosing and managing psychological and social problems that could arise on a long-duration space mission. This project will merge the fields of psychotherapy and multimedia to develop self-help programs for prevention and treatment of psychosocial problems. A completed Smart Medical System for Psychosocial Support (SMS-PS) will contain diagnostic, treatment and educational programs geared toward every foreseeable psychosocial problem, particularly conflict resolution and depression.

Using videos of mentors and hosts in the various modules will help make the tone of the modules less clinical and the SMS-PS will be accessible to any space or ground-crew member at all times. Designed to serve multiple functions in its complete form, it could be used for: diagnosing psychosocial problems, providing psychotherapy, guiding medication

management, giving educational support for crew-members-turned-care providers, pre-mission training support, and providing a resource to ground personnel.

A mission to Mars would take two and one-half to three years, including the travel time and the time spent on Mars waiting for a suitable exit window. Buckey, a former astronaut who was a member of a 16-day space shuttle mission in April 1998 says, "What we are dealing with is not people who have psychological problems; really quite the opposite. We want to help people who are psychologically strong, but are put in surroundings that are very demanding."

Carter said that they would also shoot video segments with screen actors in the space station simulator at NASA-Johnson Space Center in Houston to make the SMS-PS into a more attractive resource.

An important factor for any doctor-patient relationship is confidentiality. This applies to the SMS-PS as well. Hence, the SMS-PS is designed to be completely confidential. "When people know that the system is confidential they will seek preventive help early and keep a situation from becoming worse," Buckey explained.

The potential of a system for self-administered psychotherapy is tremendous. It would be beneficial in isolated working conditions such as offshore oilrigs, research camps at the poles, or ships and submarines at sea, and similar programs could be developed for general public use in a variety of settings, such as at public health centers, schools, social service offices, employee assistance programs, or prisons. In general, such a tool could perhaps revolutionize psychotherapy, as it is known today.

—Shahana Jamil, Dartmouth '04



Jay Buckey, MD, (left) and James Carter, PhD.

# The Psychiatrist and *The Sopranos*

Hollywood hasn't been kind to psychiatrists. Since the birth of filmmaking their profession has been cast in an unflattering light from the buffoonery of *Analyze This* to the outright sinister portrayal in *One Flew Over the Cuckoo's Nest*.



Ronald L. Green, MD

Enter HBO's *The Sopranos*, with Lorraine Bracco playing Dr. Jennifer Melfi, the psychiatrist treating Tony Soprano, a middle-aged New Jersey mobster suffering panic attacks. Their sessions together are compelling, accurate and often tense as Tony explores his conflicts about his mother, his suburban family, and his mafia cohorts. *The Sopranos*, if critics and ratings are to be believed, does it better than anyone ever has.

So, to what do the writers of *The Sopranos* owe such original insight and perspective? Robin Green, co-executive producer and one of the show's writers, credits the expert counsel of her brother Ronald L. Green, MD, Dartmouth Medical School professor of psychiatry and director of training and education for psychiatry. With research interests in brain morphology in schizophrenia and dyslexia, Green might seem an unlikely advisor on the treatment of a ham-fisted Jersey wise

guy, but he grew up in Providence, Rhode Island, the domain of infamous Mafia kingpin Raymond Patriarca. Green recalls tales of the notorious mob boss being forced by his wife to smoke his cigars in the backyard so he wouldn't stink up the house.

Robin says of Ron's role, "He's guided me and my writing partner co-executive producer Mitchell Burgess all along—prescribed psychotropic drugs for Tony, dosages, advised on treatment of anxiety attacks and on general issues in psychotherapy and he has referred us to specialists in the behavioral branches of the field. Talking things out with him and then sharing his thoughts with show creator David Chase and the other writers has given rise to ideas for stories." Robin and Mitchell call Ron when they want to know where to go with drugs or therapy or how to handle a situation such as a panic disorder or how a psychiatrist would react when Tony seduces a woman he met in the waiting room.

"We check with Ron a lot to keep things in the realm of reality—he keeps us honest," says Burgess. Green offers his help nights and weekends, on a pro bono basis, even supplying the three-pronged approach Melfi used to treat Tony: medication for the depression, dynamic psychotherapy, and cognitive behavioral therapy. Last season's entire story line stemmed from an hour-long conversation between Ron and Robin.

Though only about two scenes out of 35 each episode typically involve Tony's therapy, Robin Green emphasizes, "it is the spine—the conscience of the show."

Incidentally, "Employee of the Month," an episode Robin Green co-wrote with Mitchell Burgess, took this year's Emmy award for outstanding writing for a drama series. Nevertheless, Green is humble about his role on the hit show, saying that he often has to consult with or defer to other doctors. When it's behavioral treatment, he'll consult Robert Ferguson, PhD, assistant professor of psychiatry, or when Tony's girlfriend tried to kill herself, he turned to Norman Yanofsky, MD, associate professor of medicine and of community and family medicine, for ER advice.

Green also shrugs off questions about his unpaid status on *The Sopranos* given the show's meteoric rise in popularity and critical acclaim, hastening to add with a laugh that he did receive a *Sopranos* cast jacket. HBO also sent him to the Emmy's ceremony in LA this year where he had the thrill of being at Robin and Mitchell's side when they won their award.



Emmy award winners Robin Green (left) and Mitchell Burgess, executive producers of *The Sopranos*, discuss psychiatry's portrayal in television and film at a recent psychiatry department grand rounds.

## New Gene Class Found

Geneticists at Dartmouth Medical School have discovered a new family of unusually small genes that act in the finely tuned yet remarkably versatile orchestration of development and behavior, adding still another dimension to the diversity and complexity of the cell.



Victor Ambros, PhD

Unlike most genes, these new-found ones do not encode for proteins, but rather produce tiny regulatory RNAs, dubbed “microRNAs” because they are so small. If as abundant and varied as they seem, this novel class of regulators offers promising and potentially far-reaching opportunities to understand critical steps in development.

The new molecules were reported October 26 in *Science* by Victor Ambros, PhD, professor of genetics, and Rosalind C. Lee, a research associate. The team identified the first little RNA, the product of the *lin-4* gene in a microscopic roundworm, a decade ago.

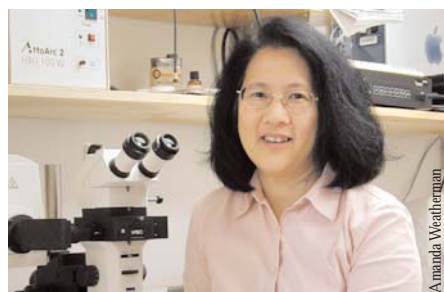
RNA (ribonucleic acid) comes in numerous forms. Each RNA is a copy of a gene, part of the cell’s DNA (deoxyribonucleic acid). Organisms have thousands of genes that collectively hold information for all their components. The Dartmouth team found 15 new genes that fit the microRNA family in the worm, *C. elegans*, and documented evidence for many more. Two of those genes are also found in humans, including one related to heart tissue development.

“These little RNAs are unusual; they don’t make protein, (but) inter-

fere with the messenger RNAs that do make protein. The key is that here is a match between the little RNA and its target, and the microRNA binds to the target and makes it incompetent to translate its message into protein,” Ambros said.

MicroRNAs, also called miRNAs, are extensive and diverse. “Each miRNA is probably matched to one or more other genes whose expression it controls. Their potential importance to control development or physiology is really enormous. There could be many hundreds of genes whose activity is being regulated this way. It’s important to find all the human miRNA genes and understand what they do.” Ambros added.

Such studies became possible since the genomes—the total package of hereditary information—of humans and other species have been sequenced, and bioinformatics advances have facilitated computer analysis of vast genetic data stores. The field of genomics, which encompasses volumes of information and poses computational challenges, is rich for collaborative investigations with intriguing and useful outcomes.



Rosalind Lee

In the commonality of life, *C. elegans*, with its relatively simple genetic apparatus, is a stepping stone to discovering gene products probably performing similar functions in humans. Comparing sequences in worms, insects, mice and humans, scientists can zero in on those that are functionally important, since they are often

similar or identical across species.

One of the small RNAs, mir-1, identified in worms, flies and humans, appears specific to heart tissue, and may play a role in heart development and diseases.

Ambros first compared the genomes of *C. elegans*, sequenced in 1999 and a related worm, *C. briggsae*, completed in June. The work illustrates how quickly genetics is moving. “Suddenly we could compare these two genomes, and that broke a logjam in gene discovery.” The two worms, 10 million years apart, are close enough in evolutionary time to develop the same way, he continued, “so when we see identical DNA sequences, we infer that this signifies genetic machinery doing the same thing.”

The findings built on work over the past decade in roundworm mutants with striking developmental defects. In 1991, Lee and Ambros found *lin-4*, a surprisingly small gene that produced a particular hook-shaped RNA. This little gene seemed to be a temporal switch in development, but unlike most timing controls, instead of synthesizing protein, it repressed protein production from certain other genes.

“We’ve developed and applied a way of finding many of a new class of genes and think that in a year we may have found all of the *C. elegans* miRNAs. “We’re not focussing on one gene like we used to, but a whole class of genes,” Ambros said. “We’d like to answer broad questions about how they work as well as specific questions about individual genes. The challenges escalate as the number of genes increase and the analyses become more complex. With lots of data we have to be able to weed out what’s garbage and what’s real so computer tools and bioinformatics expertise are essential.”

## Non-Surgical Therapy for Leg Pain Cheaper, Easier

Using angioplasty and stents to treat a common cause of leg pain is not only as effective as surgery, it also is easier for patients, has an equivalent effect on quality of life and costs about half as much, according to a study by Michael A. Bettmann, MD, professor of radiology, presented November 27 at the Scientific Assembly and Annual Meeting of the Radiological Society of North America.

Crampy pain while walking, called claudication, is a common symptom of peripheral vascular disease (PVD), an underdiagnosed condition that affects approximately 10 million people in the US. PVD is caused by arteriosclerosis (hardening and narrowing of the blood vessels), and sufferers are at higher risk of other cardiovascular problems, such as heart attack and stroke. Claudication can be treated surgically, typically with bypass grafting, or radiographically with angioplasty and stents.

“We found the cost differential between surgery and minimally invasive intervention is huge, while there is no sig-



Michael Bettmann, MD

nificant difference in the effectiveness of the treatment,” said Bettmann, an interventional radiologist and director of clinical research for radiology at DHMC. “Also, minimally invasive therapy is far easier on the patient, with a much shorter recovery time compared to surgery.”

In the study, 64 patients received radiographically guided minimally invasive therapy and 33 had surgery. The cost of minimally invasive treatment averaged \$6,502 vs. an average of \$12,422 for surgery.

Study co-authors include Bertrand Janne d’Othee, MD, adjunct assistant professor radiology, Richard J. Powell, MD, associate professor of surgery, and Michael F. Morris DMS ’03.

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excellence, with a common theme of modulating immunity,” explains William Green, PhD, professor of microbiology and immunology, who heads the program. Collectively they can help define new ways to harness the immune system to combat tumors and bacterial infections or to subdue immune responses to control inflammation or autoimmunity.

Hallmarks of the program include faculty mentoring by pairing junior level faculty with established senior colleagues, training for graduate students and postdoctoral fellows, and support for core facilities. Faculty

from DMS as well as from UNH serves as investigators, leaders or mentors. Program co-directors include William Hickey, MD, senior associate dean at DMS, and Andrew Rosenberg, PhD, dean of life sciences and agriculture at UNH.

The projects range from basic studies to delineate immune processes and pathways, to strategies for tailoring vaccines and immune therapies against cancer and infectious diseases. They (with leaders and mentors) are:

- Factors that play a central role in inflammatory processes and autoimmune disease (Ralph Nichols, PhD; William Rigby, MD);
- Cellular, molecular and physiologic mechanisms involved in septic shock and other inflammatory responses (James Gorham, MD, PhD; Paul Guyre, PhD; Thomas Pistole, PhD, —UNH);
- Defining processing pathways of novel tuberculosis antigens to develop new vaccines against antibiotic resistant strains (Mark Lang, PhD; Grant Yeaman, PhD; William Wade, PhD; Vernon Reinhold, PhD, —UNH);
- Strategies to amplify T cell responses for use in immunotherapy for prostate cancer (Paul Wallace, PhD; Michael Fanger, PhD; Paul Guyre, PhD);
- Preclinical studies and clinical trials of vaccines for colorectal cancer (Richard Barth, MD; Randy Noelle, PhD).



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