

Ethan Dmitrovsky, M.D.: A people person

By Laura Stephenson Carter

"I love you daddy," proclaim the chalk letters scrawled on a blackboard in Ethan Dmitrovsky's office. Dmitrovsky may be a busy physician-scientist—he's the chair of DMS's Department of Pharmacology and Toxicology, nationally recognized for his work, active in countless professional organizations, and the head of a busy lab—but he always has time for the people in his life: his wife and four children; his friends; and his colleagues, especially those in his lab.

Dmitrovsky exudes the calmness, patience, and kindness of a wise teacher. And he creates an environment in his lab that brings out the best in people—ensuring that they get as much satisfaction out of doing research as he does.

"He has a very genuine quality in his interactions with people in the lab that [attests to] his great interest in both his research and his pupils," says Neil Desai, a Dartmouth College '05 who worked in Dmitrovsky's lab as an undergraduate Presidential Scholar. "With that kind of environment in place," adds Desai, now a medical student at Yale, "it's easy to enjoy what you do."

It's clear that Dmitrovsky enjoys all aspects of his work—from hashing out thorny questions in the lab to mentoring young scientists to interacting with peers nationally. And he instills enthusiasm and a sense of purpose in those around him. He also takes pride and pleasure in the fact that what he does is in service to others—patients, DMS, and medicine as a whole.

For example, when asked by Dartmouth President James Wright to be acting dean of the Medical School in 2002-03, Dmitrovsky agreed "out of a sense of service." But he didn't want to be considered for the permanent job because that would take him away from his research and his ability to "participate in the life sciences revolution."

The purpose of scientific discoveries "is to serve the public good," Dmitrovsky firmly believes. For nearly 20 years—previously at Memorial Sloan-Kettering Cancer Center, where he worked from 1987 to 1998, and since then at DMS—his lab has been investigating the role that retinoids, natural and synthetic derivatives of vitamin A, play in treating cancer. Retinoids help regulate cell growth and differentiation. Vitamin A deficiency has been associated with the development of lung cancer in laboratory studies. It would stand to reason, he theorized, that rectifying that deficiency might be a way to prevent lung cancer. But clinical trials with retinoids were, for the most part, unsuccessful in preventing lung cancer in smokers.

While he was still at Sloan-Kettering, Dmitrovsky's lab was the first in the nation to report that retinoids triggered remission in a rare but lethal form of cancer—acute promyelocytic leukemia. He and colleagues identified the biochemical pathway by which retinoids could

"I really feel Dr. Dmitrovsky was a special sort of mentor and researcher. I was more motivated and learned more there than I have with any other research or academic experience."

regulate the cell cycle, helped clone an abnormal receptor linked to the rare leukemia, and developed a molecular test to diagnose the disease. That work led him to explore new ways to treat and perhaps prevent lung cancer, which he describes as "the most lethal malignancy for men and women in our society."

At Dartmouth, his team found a retinoid mechanism linked to lung cancer prevention and identified a retinoid target gene that triggers cell death. In November 2005, he and colleagues published a report in the *Journal of the National Cancer Institute (JNCI)* that identified a previously unknown retinoid receptor. Targeting it, the researchers hypothesized, may restore the beneficial effects of retinoids in lung cancer cells.

"It turns out that that receptor is repressed in lung cancers," explains Dmitrovsky. "So the drug we were studying—retinoic acid—couldn't possibly work in this disease because of this defect. We knew that a related drug to retinoic acid, called a rexinoid, would be able to activate this same protein destruction pathway, but could bypass this defect that we hypothesized would exist. So about three years ago, we began working on a clinical trial here at Dartmouth to use a rexinoid in conjunction with a second drug called Tarceva." This combination of drugs was tested in a Phase I clinical trial on 24 patients, for most of whom other treatments had failed. Phase I trials seek to determine the maximum tolerable dose of a drug. Although "the expected median survival in this cohort of patients would be about six and a half months," says Dmitrovsky, "the median survival for this trial was over 14 months." A corroborative Phase II trial is under way at DHMC, in collaboration with investigators at Mount Sinai Hospital in New York City.

"We are also studying this regimen in the laboratory, trying to see whether this could be used to prevent lung tumors," continues Dmitrovsky. "This is an example of bidirectional translational research—work from the bench to the clinic and then back again. The appeal of being a physician-scientist is the ability to contribute both scientifically and clinically. The pleasure, the real joy, is being able to combine these together in the same career of a physician-scientist."

Straddling both roles can be tough, though. "The domain of the physician-scientist is often about drug discovery and development. This is a long process, and it's really hard," he told an audience two years ago when he was invited to give Dartmouth's annual Presidential Lecture. "From the moment of target identification in the laboratory, to early preclinical testing in cells and in animal models, to the three phases of trials, human trials, to final FDA approval, can take upwards of 15 years."

Dmitrovsky insists that he can't take all the credit for his lab's accomplishments and that they are largely due to the efforts of his in-

Laura Carter is the associate editor of DARTMOUTH MEDICINE magazine.



JOHN GLEIBERG FOR DARTMOUTH MEDICINE

terdisciplinary team of basic and clinical scientists, postdoctoral fellows, and students. But he puts a lot of effort into training and supporting these members of his team, from undergraduates to seasoned scientists.

"The clearest examples of Dr. Dmitrovsky's mentorship and supportive personality for me came from his invaluable help in all my research presentations at Dartmouth," recalls Desai. "On one occasion, he attended a rather unimportant undergraduate poster session on an early Saturday morning. I still remember my surprise at seeing him come by to hear my explanation of the poster the morning after he surely spent a late night in his office revising grants for postdocs and reviewing papers for major journals."

"He always pushed me to do better, to think more critically, and to practice more," continues Desai. "It is a high standard that he sets for his students, but it is one he is very prepared to help them reach. I really feel Dr. Dmitrovsky was a special sort of mentor and researcher. I was more motivated and learned more there than I have with any other research or academic experience."

Kristen Garner, a pharmacology-toxicology doctoral student (as well as a regular writer for DARTMOUTH MEDICINE), is impressed that Dmitrovsky is so approachable. "He says he has an open door policy, and he really means it," she says, noting that she and other students don't hesitate to ask for his advice. No one finds him intimidating, she adds, even though he's the head of the department.

"He has created an environment in his laboratory that's very supportive of young people," agrees former oncology fellow W. Jeffrey Petty, M.D., who worked in Dmitrovsky's lab for three years. "He really started with a blank slate with me. I had no experience in the laboratory. He taught me what I needed to learn and also created an environment in his lab where I could succeed." Petty, who was first author on the November JNCI paper, left DMS in 2005 to become an assistant professor at Wake Forest School of Medicine. Dmitrovsky has given Petty a chance to do part of the retinoid research there.

It wasn't until he left Dartmouth that Petty realized the extent of Dmitrovsky's national reputation. "Ethan is very highly regarded on a national level," he says. "Until you're away from the institution, you don't see that as clearly." That made it all the more surprising, adds Petty, that "he invested a lot of time in me and my training, helping me learn how to write grants and journal articles. It was a lot of work for him to do that." But that's a part of his job that Dmitrovsky clearly treasures. "When he was acting dean, he always enjoyed spending

his time back in the lab," adds Petty. "That time I could tell was really important for him to recharge his battery, to be in the mix of the science, to come through the lab and see what was going on, keep his finger on the pulse of the science."

Dmitrovsky considers contributing to science to be one of many ways he serves the public good. Service in many forms has marked his career. As a medical student at Cornell, he volunteered for the Indian Health Service in Claremore, Okla., and for the International Rescue Committee in a refugee camp on the Cambodian-Thai border.

After graduating from Harvard in 1976 and earning his M.D. in 1980, Dmitrovsky did his residency at New York Hospital-Memorial Sloan-Kettering Cancer Center and further training at the National Cancer Institute. In 1987, he joined Sloan-Kettering, where he headed the Laboratory of Molecular Medicine. He came to Dartmouth in 1998 as the Andrew G. Wallace Professor and the chair of pharmacology and toxicology. He has built up the department, doubling its research funding—from \$4.3 million in fiscal year 1998 to \$8.6 million in 2005—and increasing the size of the faculty.

He's served on the editorial boards of several major oncology journals, including the *JNCI* and *Cancer Research*, and on numerous scientific advisory panels, including at the Lance Armstrong Foundation. He was elected in 1994 to the American Society for Clinical Investigation, the preeminent organization for physician-scientists, and in 2004 to the Association of American Physicians and Surgeons. In 2005, he was invited to testify before the President's Cancer Panel about overcoming barriers to translational research. At Dartmouth, Dmitrovsky is the president's senior advisor for science and technology and a trustee of the Hitchcock Foundation. He has served on several high-level search committees and cochaired the committee that recruited Dr. Mark Israel to head the Norris Cotton Cancer Center. He's also a trustee of the Upper Valley Jewish Community.

"It's remarkable that as much as he does, and as hard as he works, that he's able to enjoy it still," says Petty.

"I think that it's a real privilege to work as a physician-scientist," Dmitrovsky says. "I'm grateful to have the career that I have and look forward to continuing to contribute. The idea of being able to use your intellectual ability to help others is really appealing."

And it's also really appealing that no matter how busy he is, he always has time for all the people in his life. ■