Dartmouth's Norris Cotton Cancer Center has been a National Cancer Institute-designated comprehensive cancer center since 1990, a claim that fewer than two dozen institutions nationwide can make. Norris Cotton also claims something else very special—a truly collaborative culture, a sense of collegiality that transcends disciplinary bounds and that weaves together intrinsically the interests of clinicians and scientists.

Pictured on the front cover are four members of Norris Cotton's lung cancer group—from the left, radiologist William Black, MD; comparative effectiveness researcher Anna Tosteson, ScD; cardiothoracic surgeon Cherie Erkmen, MD; and demographic statistician Samir Soneji, PhD. The group brings many disciplines to bear on balancing the benefits and burdens of screening and treatment choices for patients with lung cancer.

Pictured above is Dartmouth-Hitchcock's Lebanon, N.H., campus—the home of Norris Cotton Cancer Center's administrative offices and its core scientific and clinical facilities; the Cancer Center also offers top-notch cancer care at 16 other locations all across New Hampshire and Vermont.
All Together Now
Inside the collaborative culture of Dartmouth's Norris Cotton Cancer Center

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Other portions of this book were excerpted or adapted from the following materials, all of which were produced by members of the Norris Cotton Cancer Center staff:
Norris Cotton Cancer Center History: The Early Years by Kimberly J. Murchison and Deborah S. Solomon; unbylined articles published in the Cancer Center’s quarterly newsletter, Focus, and on the Cancer Center’s website; and core grant progress reports submitted by the Cancer Center to the National Cancer Institute.

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The remaining contents were written by Dana Cook Grossman, and she also edited and designed the book. She was the director of publications for Dartmouth’s medical school and the editor of Dartmouth Medicine magazine from 1986 to 2011. Since January 2012, she has been the medical school’s director of publications emerita and a freelance writer and editor.

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Richard Barth, MD, chief of surgical oncology, confers here with a lab technician about a trial that he led of a dendritic cell vaccine for metastatic colorectal cancer.
Remarkable Strides: “Scientists and physicians, side by side”

Who can deny that today’s cancer therapy is inadequate? It’s highly toxic, it’s invariably unpleasant, and it’s not always effective. Despite truly remarkable strides in recent decades in our understanding of cancer’s molecular underpinnings, there remain numerous questions and uncertainties regarding how minute cellular changes lead to cancer and how to treat cancer once it does occur.

At Dartmouth’s Norris Cotton Cancer Center, scientists and physicians work side by side to address the spectrum of challenges that cancer presents. Story after story in this book testifies to the fact that “collaboration” isn’t a word that we merely trot out for grant applications. It’s how we live and work, how we advance the cause of combating cancer, every day.

That effort begins with a multitude of strategies to stop cancer before it starts—from community-based prevention programs, to research into better ways to communicate cancer risk factors, to clinical trials of promising chemoprevention agents.

Meanwhile, a diverse group of caregivers, including physicians in myriad specialties and subspecialties, pursues multidisciplinary efforts to deliver cancer care—in ever more beneficial, less toxic, more sustainable ways. Norris Cotton’s clinical component alone is an enormous enterprise—encompassing 17 locations in two states and addressing the needs of more than 5,200 new patients every year.

At the same time, a broad community of investigators is actively seeking to envision and create the future of cancer prevention and care—a future in which tolerable therapies can be directed with more specificity at the molecular changes that distinguish tumor cells from normal cells. Well over 200 funded research projects are ongoing at any given time at Norris Cotton. Those projects hint at what future interventions might look like: immune modulators to enhance tumor recognition by the body’s own defense systems; drugs designed to target malfunctioning signaling pathways that regulate aberrant cellular behavior; novel technologies to enhance the delivery of radiation therapy to tumor cells, while minimizing its effects on adjacent normal tissues.
This research is the part of what we do that distinguishes Norris Cotton—and the other 40 institutions in the U.S. that are designated by the National Cancer Institute as comprehensive cancer centers. We go beyond simply diagnosing cancer to developing new diagnostic techniques aimed at its early detection. We challenge conventional wisdom by doing research to understand the causes of cancer and to identify the molecular signatures of life-threatening tumors so we can optimize therapies against them. We do more than just deliver cancer care; we also devise, study, and validate interventions to improve the quality of life for cancer patients and cancer survivors.

The interconnections among all these efforts are especially evident in the conduct of clinical trials, in which patients partner with researchers—clinical investigators, physician-scientists, and experts in the basic science of cancer—to evaluate and translate laboratory advances into the clinic. Clinical trials ensure that the latest treatments are available to our patients, while helping to advance the knowledge we need to improve treatments for future patients. At any given time, up to 175 clinical trials are being conducted at Norris Cotton Cancer Center.

This is what we do. This is what keeps our clinicians and investigators, ranging from graduate students to senior faculty, focused and excited about the contributions being made at Norris Cotton. Together. Every day. In labs. In hospital rooms. In the communities we serve. In the hope that, perhaps one day, the opening question I posed will have become moot.

Mark A. Israel, MD
Director, Norris Cotton Cancer Center
The Place

The features that make Norris Cotton Cancer Center such a singular place are not simply reflective of some formula that could be easily replicated at any institution, anywhere. They are distinctive threads woven intrinsically into its past and present. They are principles born of the humanity and the passion of its physicians and scientists. They are facets of Dartmouth’s location in a setting of unsurpassed beauty. They are features of Norris Cotton’s very fiber—part of its being.
A Brief History of Norris Cotton: “What’s past is prologue”

First it was just an idea. Then it was a “little kiosk” in a parking lot in Hanover, N.H. Today, it’s a spectacular multistory building on Dartmouth-Hitchcock’s Lebanon, N.H., campus, plus a presence in 16 other locations in two states. “It”—Dartmouth’s Norris Cotton Cancer Center—has come a long way since its founding in the early 1970s.

While Norris Cotton’s visible, tangible manifestation has undergone a dramatic transformation, so, too, has its impact on the nationwide, and worldwide, fight against cancer. But at the same time, though its physical origins may have been modest, Norris Cotton Cancer Center’s aspirations have always been far-reaching. It has been said—first by Shakespeare and by many sages since—that “what’s past is prologue.” In other words, the present-day state of any organization lies in its historical roots. That is certainly true of Norris Cotton.

The Cancer Center’s origins go back to the 1950s, when Frank Lane, MD, the director of radiation therapy at Mary Hitchcock Memorial Hospital, grew concerned about the high cancer mortality rate in northern New England. Then, as now, cancer was the second leading cause of death in the United States (cancer moved into that position in 1938, dropping pneumonia and influenza to third, while heart disease, still the leading cause of death, replaced pneumonia in the top spot in 1921).

Lane ultimately concluded that New Hampshire’s cancer-treatment facilities were inadequate. Even though the state’s incidence of cancer was no higher than the national average, and the region’s cancer patients were seen initially at no later a stage in their disease than patients elsewhere, New Hampshire’s death rate from cancer was among the highest in the country.

So Lane set out on a crusade to build a cancer center. He was successful in getting grants to acquire two significant pieces of equipment, including a 45-million-volt Brown-Boveri Betatron. And Hitchcock Hospital already had some well-trained specialists who could take the lead on staffing a center. Most notable among them was hematologist Franklin Ebaugh, MD. He had arrived at Hitchcock from the National Cancer Institute (NCI) in 1958 and initiated Hitchcock’s participation in the
The portico in the center of this photo is the main entrance to Norris Cotton’s hub, housed in the Rubin Building on Dartmouth-Hitchcock’s Lebanon, N.H., campus.
prestigious Cancer and Leukemia Group B (CALGB), a national clinical trials network. When Ebaugh was recruited away in 1964 to be dean of Boston University School of Medicine, O. Ross McIntyre, MD, who had done a fellowship in hematology-oncology with Ebaugh, took over his research grants and role with the CALGB.

But despite these promising developments, Lane's efforts to raise funds for a building to house the machines and the staff ran into one dead end after another. Eventually, however, he was introduced to U.S. Senator Norris Cotton (R-NH). Cotton, a self-described "country lawyer" from Lebanon, N.H., who represented New Hampshire in Washington, D.C., from 1954 to 1975, was named minority leader of the Senate Subcommittee on Health, Education, and Welfare Appropriations in 1962. He described his work on this subcommittee as "perhaps the most satisfying experience of all my years in Congress, because you feel as if you're doing something for somebody."

So Cotton immediately understood the cause that Lane articulated and from then on was a strong advocate for the project. He worked closely with Lane on preparing a proposal that he could present to the Appropriations Subcommittee. He followed through to ensure that both Congress and the NCI supported the project. And he parlayed his close relationship with the subcommittee's chair, Senator Warren Magnuson (D-WA), into a boost for the cause that Cotton was fond of calling "the apple of my eye."

Magnuson was a natural ally, since it was he who had introduced into the House of Representatives the 1937 bill that called for the establishment of the NCI. Cotton was fond of recounting how his relationship with
Magnuson (whom he called “Maggie”) benefited the cancer center project. As the subcommittee held hearing after hearing for that project and many others all across the country, “we listened probably to some 200 or 300 witnesses during the term,” recalled Cotton. “We worked hard and sat up nights.”

During one of those late-night sessions, Cotton continued, he and Magnuson “decided that we ought to get some reward for our labors—a little something to take back to our states. Maggie asked, ‘What do you want, Norris?’ And I said what I wanted most, and what I’d been striving for, was an endowment to start a cancer center associated with the Mary Hitchcock Hospital in Hanover, New Hampshire. ‘Well, how much do you want?’ he asked. And I said—and I wanted to be reasonable on this—’Three million dollars.’ Oh, he laughed and said, ‘You can get five just as easily as three. We’ll put you down for five to start a cancer center at Hitchcock Hospital.’” (Magnuson also included a similar request for a cancer center in his own district—the Fred Hutchinson Cancer Center in Seattle.)

In the end, $3 million in federal monies were appropriated in the 1971 NCI budget to construct a cancer center at the Dartmouth-affiliated Hitchcock Hospital. The facility was also slated to receive half a million dollars a year for the next 10 years. And an additional half-million dollars was granted to Dartmouth Medical School for its general teaching program.

By 1972, the first phase of the cancer center opened—two underground stories housing the Betatron for radiation therapy, plus space for clinical oncology, nuclear medicine, radiobiology, and radiation physics research. Cotton’s support for the project didn’t end with the allocation of funding. He
also expedited the importation of the Betatron from Switzerland, where the machine had been manufactured, and helped arrange for the immigration from Germany of a woman who was one of the few technicians in the world trained to operate a Betatron.

Cotton often said that, out of all his accomplishments, his work in behalf of the Cancer Center was what he was most proud of. “Though you don’t brag about what you drag home for your district, this is the single greatest satisfaction of all my 26 years in Congress.”

Lane served as de facto director of the new center, and it was he who decided that the long-sought facility should bear Cotton’s name. But its physical presence was underwhelming. Its only visible, aboveground manifestation was—as McIntyre later described it—“a little kiosk in the middle of the parking lot” that served Mary Hitchcock Memorial Hospital. The walls of the two underground stories were three feet thick, to shield the multimillion-volt radiation therapy equipment, while the “kiosk” served as a second fire exit.

But the equipment inside the facility was of much more import than the space that housed it: a Theratron-80 Cobalt-60 unit and an Eldorado-8 Cobalt-60 unit, as well as the Brown-Boveri Betatron from Switzerland. This was state-of-the-art technology for the time; in fact, the Betatron was one of only three such instruments in the world.

In 1974, Cotton was nearing retirement from the Senate, but his enthusiasm for the Cancer Center hadn’t waned. At the last meeting of the Appropriations Subcommittee before Cotton stepped down from his seat, Magnuson asked his old friend what he would like as a “going-away present” for his constituents. “Some more money for my pet project,” Cotton answered. His request was granted. Congress allocated another $4.5 million for an addition to the Cancer Center—two aboveground stories to house medical oncology; this addition was completed in 1977 and transformed the facility into a true multidisciplinary center.

McIntyre, who by then was chief of hematology-oncology at Hitchcock, worked closely with Lane and others on the addition. The new structure sat above the underground radiation-therapy facility and contained expanded clinical space as well as facilities for research and education; it was linked to a 25-bed inpatient oncology unit within Mary Hitchcock Hospital.

In 1975, McIntyre took over leadership of the Cancer Center from Lane, becoming the first person to officially hold the title of director. He led the Center for
the next 17 years, a period during which it rose to national prominence. McIntyre explained in an oral history conducted in 2000 that despite Cotton’s help, some other early cancer centers were better funded, “while we struggled along with various patchwork [resources].” But, he adds, “if we had had more resources, we might not have been forced to be so ingenious.”

By whatever means—call it ingenuity or vision or simply hustle—Norris Cotton became the “cancer center that could.” Despite its rural location and small size relative to many urban cancer centers, a multitude of well-trained oncologists and cancer researchers trod a path to Hanover. Outreach programs brought the burgeoning expertise out into the region. A centralized, statewide tumor registry gave Norris Cotton physicians and researchers a better handle on patterns of cancer incidence. Norris Cotton specialists conducted courses and offered consultations via INTERACT—the nation’s first interstate, interactive medical television network, which had been established at Mary Hitchcock Memorial Hospital in the late 1960s. All this led, in 1978, to Norris Cotton Cancer Center receiving approval (and funding) as an NCI-designated cancer center.

There was a realization early on at Norris Cotton that cancer research needed to be interdisciplinary. “It was clearly recognized that unless you had the mouse people—who were curing leukemia in mice with drugs—talk to the clinical people—who were treating patients with drugs—that progress just wasn’t going to be as fast as it should be,” says McIntyre. “I became a proponent of the view that . . . interdisciplinary programs make more progress than single-disciplinary programs if you are talking about human medicine.”

The Cancer Center’s emergence and growing impact

1978 Year Norris Cotton was first funded as a National Cancer Institute (NCI)-designated cancer center

1990 Year Norris Cotton became an NCI-designated comprehensive cancer center; it has held the designation continuously ever since

1990 Year Ross McIntyre, MD, was named chair of the prestigious Cancer and Leukemia Group B (CALGB) research network

1995 Year the Rubin Building opened on D-H’s Lebanon campus

2005 Year Norris Cotton opened a free-standing cancer clinic in St. Johnsbury, Vt., and a medical oncology clinic in Manchester, N.H.

The Rubin Building, pictured in 1995, has since been greatly expanded.
“A meeting of the CALGB was held in Hanover in about 1961,” recalls McIntyre. “The members were Dartmouth, the National Cancer Institute, Roswell Park, Cornell, and I think maybe Mount Sinai.” McIntyre went on to serve as the national chair of the CALGB from 1990 to 1995, and today, explains the organization’s website, the CALGB is “a national network of 26 university medical centers, more than 200 community hospitals, and more than 3,000 oncology specialists.”

In fact, Norris Cotton’s membership in the CALGB serves as a marker of the outsize impact the rural and relatively small institution has had on the national cancer landscape. “A meeting of the CALGB was held in Hanover in about 1961,” recalls McIntyre. “The members were Dartmouth, the National Cancer Institute, Roswell Park, Cornell, and I think maybe Mount Sinai.” McIntyre went on to serve as the national chair of the CALGB from 1990 to 1995, and today, explains the organization’s website, the CALGB is “a national network of 26 university medical centers, more than 200 community hospitals, and more than 3,000 oncology specialists.”

McIntyre’s success in nurturing a collaborative spirit and in recruiting well-funded investigators brought the Cancer Center ever-greater national recognition. In 1990, Norris Cotton became one of the first cancer centers in the country to be designated by the NCI as a comprehensive cancer center—meaning it was strong in all spheres of cancer, from prevention and education to clinical care and research.

In 1992, McIntyre retired as director and Edward Bresnick, PhD, the chair of the Dartmouth Medical School (DMS) Department of Pharmacology and Toxicology, took over the leadership role. Research funding for Norris Cotton investigators continued to grow faster than the national average. In 1994, upon Bresnick’s departure to become vice chancellor for research at the University of Massachusetts Medical Center, he was succeeded by epidemiologist E. Robert Greenberg, MD, a longtime member of the DMS faculty.

Under Greenberg’s leadership, the Cancer Center developed a strategic plan that put considerable emphasis on regional expansion of cancer services, with the goal of providing patients with the best possible care as close to their homes as possible, throughout the region served by Dartmouth-Hitchcock.

At the same time, Greenberg faced a challenge right at “home”—to reunite the Cancer Center’s clinical facilities with the rest of Dartmouth-Hitchcock Medical Center (DHMC). In 1991, DHMC had moved from Hanover to Lebanon, to a $218-million complex designed by the Boston-based architectural firm Shepley Bulfinch Richardson and Abbot. The Cancer Center had remained behind in Hanover temporarily, while funds were raised for its new quarters on the Lebanon campus.

In 1995, the Cancer Center moved into a $25-million, three-level building named in memory of Barbara E. Rubin, the benefactor of the Amicus Founda-
tion, which made the gift that brought the building to fruition. The 115,000-square-foot facility housed the radiation oncology and hematology-oncology services, related laboratories and offices, a conference room, and a 165-seat auditorium.

But, although Norris Cotton was considered to be in the vanguard of interdisciplinary research in the 1990s, many of its basic scientists had little chance to interact with clinicians and clinical scientists. Some cancer-related labs were located in the Borwell Research Building on DHMC’s Lebanon campus, but many were still on the Medical School’s Hanover campus.

So in 2001, when Mark Israel, MD, a pediatric oncologist from the University of California, San Francisco, succeeded Greenberg as the Cancer Center’s director, he wanted to bring as many cancer researchers as possible together in one building. Planning was already under way for an addition to the Rubin Building, and Israel moved quickly to ensure that, as he explains it, the “physical lab space . . . would enhance the opportunities for interdisciplinary interactions and collaborations.”

Designing the addition—which opened in 2003—was itself a collaboration between the Shepley Bulfinch architects and members of the Cancer Center, led by Israel. Together they figured out how to create communal spaces where people would be likely to run into one another and strike up conversations—like they do at the post offices and grocery stores and soccer field sidelines throughout the small towns around Norris Cotton. The idea was that these informal interactions would spark ideas that could turn into fruitful research endeavors. That meant opening up the walls between labs and turning the research space into “neighborhoods.”

When the planning committee began its work on the addition, the architects started off by showing them the layout of some other open-space scientific buildings, including the Salk Institute and the Whitehead Institute at MIT. Although Norris Cotton’s new labs ended up being even more open than the space at Whitehead, Norris Cotton tried to avoid the warehouse-like feeling that some open-space laboratories have and instead create “neighborhoods” without sharp divisions between them.

The $40-million 2003 project went up rather than out. Consisting of four new stories, it nearly doubled the size of the Rubin Building, to 200,000
The labs ring the perimeter of the Rubin Building, so each one has windows. All the benches, shelves, and drawer units are adjustable, so the space can be easily reconfigured. The walls are brightly colored. The ceilings arch gracefully. And whiteboards are placed strategically throughout the lab areas to encourage impromptu brainstorming sessions. The two lab floors also have central corridors containing shared equipment like freezers, ultracentrifuges, and scintillation counters; environmental rooms that can be maintained at set temperatures; and communal spaces, such as glass-walled seminar rooms.

The centerpiece of the addition is a dramatic three-story atrium that serves as a crossroads for the facility. In recent decades, architects have been designing research buildings that are as beautiful as theaters, museums, and hotels. This is for very practical reasons—the goal is that people will love to go to work in such buildings and that interdisciplinary collaborations will flourish in a place where people enjoy mingling.

Atrium-style buildings are inspired, in part, by the fact that architects have been designing research buildings that are as beautiful as theaters, museums, and hotels. This is for very practical reasons—the goal is that people will love to go to work in such buildings and that interdisciplinary collaborations will flourish in a place where people enjoy mingling.

Steven Fiering, PhD, left, and Christopher Lowrey, MD, right, confer in one of Rubin’s open-space laboratories.
work of renowned architect John Portman, who designed hotels with huge central atriums ringed by balconies. “He was the one who started to put these big spaces in the center, where you could see people moving back and forth and . . . sitting down at the bottom,” says Malcolm Kent, the architect who supervised the project for Shepley Bulfinch. “They tend to be spectacular architectural spaces, and they offer the opportunity of people being able to see [others] operating at multiple levels.”

The challenge is to make sure that these “spectacular spaces” are used, not just admired—a standard by which the Cancer Center atrium can be deemed a decided success. People gather there for coffee breaks, run into each other, and take a breather from the hustle of the day. The Cancer Center’s sweeping, multilevel atrium serves as both an informal gathering place and a site for big events—here, a Medical School reunion.

Norris Cotton Cancer Center’s outsize impact

Since 1978, Norris Cotton has been continuously funded as a National Cancer Institute (NCI)-designated cancer center.

Norris Cotton is one of only 41 cancer centers in the U.S. currently designated by the NCI as a comprehensive cancer center.

In 2011, Norris Cotton was one of just 27 founding institutions of the NCI-funded Cancer Immunotherapy Trials Network.

In 2010, Dartmouth became an NCI-funded Center of Cancer Nanotechnology Excellence—1 of only 9 nationwide.

Norris Cotton ranked 45th in NCI funding in 2011 among the nation’s 74 NCI-funded cancer centers (some of them are designated cancers centers and some are designated comprehensive cancer centers).

Yet Norris Cotton is one of the smallest comprehensive cancer centers in the country. In 2011, the median membership for comprehensive cancer centers was 235, and the largest center reported a membership of 1,001; Norris Cotton currently has 150 members.

And size can be deceiving, because there are instances of cancer centers reporting four times the funding of Norris Cotton—but eight times the membership. In short, Norris Cotton is small but mighty.
Another key factor for the Cancer Center’s director, Mark Israel, is the effort to recruit bright minds to work within the beautiful facilities—to further “the process of translating Dartmouth science into making an impact on the health of people.”

Meanwhile, as Norris Cotton was consolidating and expanding its hub operations at Dartmouth-Hitchcock, it was also greatly expanding its reach and facilities throughout the region—following up on the strategic plan from the mid-1990s. Today, multidisciplinary care is offered not only in Lebanon but also at 16 additional regional locations. There are four major Norris Cotton branches—in St. Johnsbury, Vt., and Manchester, Keene, and Nashua, N.H. In addition, care is offered by Norris Cotton specialists through affiliations with 12 hospitals located throughout Vermont and New Hampshire. The goal of this regionalization is to make the best possible care available in the most convenient locations for patients, close to where they live. (See the box on page 31 for all the Norris Cotton locations.)

So, do all the regional outreach sites, the quarternary clinical facilities in Lebanon, and the beautiful research laboratories actually have an impact on cancer’s ravages? Absolutely!

Another key factor for the Cancer Center’s current director, Mark Israel, is the effort to recruit bright minds to work within the beautiful facilities—constantly reinforcing, as he puts it, “a broader foundation of physician-scientists and physician-investigators who can help with the process of translating Dartmouth science into...”
making an impact on the health of people.” That impact on people’s lives is the bottom line for any cancer center, including Norris Cotton. And at the same time, it is research that distinguishes a place like Norris Cotton. It is the ongoing effort to discover ever more effective ways to combat cancer—to advance the state of the art, not just to deliver the current standard of care—that sets apart a comprehensive cancer center like Norris Cotton.

“To cure a disease,” Randolph Noelle, PhD, observed a few years ago in an article in Dartmouth Medicine magazine, “one has to apply many different types of science.” That’s what all of Norris Cotton’s programs and facilities are aimed at—getting people in different disciplines to interact with each other. “Everybody’s busy,” continued Noelle, a longtime member of Norris Cotton’s Immunology and Cancer Immunotherapy Research Program (see page 70 for insight into his internationally recognized research). But if “you happen to walk past somebody with a cup of coffee in the middle of the day,” he said, then people are much more likely to talk with each other. “Immunology will not cure cancer,” Noelle added, “and genetics will not cure cancer, and structural biology will not cure cancer. But all of them together may.”

It is hard to quantify exactly how much progress has been made toward that goal. Certainly, some cancers that used to be deemed incurable are now highly treatable. But the way cancer data are collected has changed so much that it is difficult to accurately compare current evidence to the figures from the 1950s that motivated Frank Lane. Nevertheless, from his initial vision, to a “little kiosk,” to an NCI-designated comprehensive cancer center housed in architectural splendor is progress by any measure.

The Cancer Center’s current senior leadership

Mark A. Israel, MD  Director
Burton L. Eisenberg, MD  Deputy Director
Linda Metcalf, BS, CPA, MBA  Interim Co-Vice President for Cancer Programs and Director of Radiation Oncology
Amy Stansfield, RN, MBA  Interim Co-Vice President for Cancer Programs and Director of Hematology-Oncology
Robert W. Gerlach, MPA  Associate Director for Administration and Scientific Affairs
Linda Kennedy, MEd  Associate Director for Community Affairs
Christopher I. Amos, PhD  Associate Director for Population Sciences
Yolanda Sanchez, PhD  Associate Director for Basic Sciences
Craig R. Tomlinson, PhD  Associate Director for Shared Resources
Jason H. Moore, PhD  Associate Director for Bioinformatics
Marc S. Ernstoff, MD  Associate Director for Clinical Research
Marc Gautier, MD  Associate Director for Regional Clinical Affairs
Bradley A. Arrick, MD, PhD  Chief of Hematology-Oncology
Christopher H. Lowrey, MD  Associate Chief of Hematology-Oncology
Alan C. Hartford, MD, PhD  Chief of Radiation Oncology
Richard J. Barth, MD  Chief of Surgical Oncology
Margaret Foti, PhD, the chief executive officer of the American Association of Cancer Research, delivered a Cancer Grand Rounds talk at Dartmouth-Hitchcock in April 2012. Among the observations she has made over the years about cancer research is this insight, from an op-ed essay for the Philadelphia Inquirer: “Great science doesn’t just happen. It begins with a fundamental observation or hypothesis and develops over years into clinical advances that improve our ability to prevent and cure diseases. The gap between the laboratory and the bedside is narrowing, but the process still involves an extraordinary mix of scientific insight, curiosity, hard work, and dedication.”

All of those elements are present in abundance at Norris Cotton. For example, Craig Tomlinson, PhD, the associate director for shared resources, notes that being successful in science requires “perseverance, good ideas, and some good luck.” And, he says, “working hard and loving what you do are important, too.” He adds that many important discoveries are made “not by design but because you sort of trip over them. And you have to be able to recognize it when you trip over something good.”

Yolanda Sanchez, PhD, the associate director for basic sciences, is another Norris Cotton member who waxes eloquent about the scientific process. “When we make a discovery,” she says, “it’s like finding the piece that allows you to solve the rest of a puzzle. This may date me, but it’s analogous to the feeling you get when you score in pinball—or, for today’s audience, in a video game. Then you’re hooked and want to get to the next level.” Her greatest joy, she adds, comes from observing “in people I’ve played a role in training . . . the high of making a discovery.”

But of course it takes more than hard work to do good science. It also calls for well-designed labs, sophisticated instruments, and technological know-how.

Most of the Norris Cotton labs are in the open-design Rubin Building (see page 17 for details). It’s space that researchers find conducive to fruitful work. Immunologist Randolph Noelle, PhD, for example, has found “tremendous advantages to the labs in Rubin. The architectural design and engineering is superb. It’s bright, it’s cheery, it’s lively. That has a very significant impact on doing science. Science is a chore if you’re in unattractive
Craig Tomlinson, PhD, left, oversees Norris Cotton's shared resources and heads the Genomics Shared Resource—of which Heidi Trask, right, is microarray manager.
surroundings. Everything you can do to improve your environment is very worthwhile.” He did worry before moving into Rubin about one thing, but for naught: “The disadvantage I had perceived is not one. Each lab has its own personality. We have a rather chaotic, loud, obnoxious personality as a lab, and I thought the open space would dampen individualism. It doesn’t. It’s so well-engineered that one group can express their personalities without interfering with other groups.”

As for the necessary instrumentation and technological expertise, much of that is centralized in 14 shared resources; in addition, a 15th shared resource—Cancer Registries—is in development. Craig Tomlinson, PhD, oversees coordination among all the shared resources. The current 14, plus their directors and services, are:

- Bioinformatics—Jason Moore, PhD: bioinformatics, data mining, genomic analysis, transcriptome analysis, metabolome analysis
- Biostatistics—Tor Tosteson, ScD: clinical trial design, nonlinear dose response modeling, cost-effectiveness analysis, diagnostic test assessment, data analysis
- Clinical Pharmacology—Lionel Lewis, MB, BCH, MD: biorepository services, bioanalytical services, in vitro and in vivo modeling of combination drug effects, pharmacokinetic and pharmacodynamic assays
- Genomics—Craig Tomlinson, PhD: microarrays, whole genome sequencing, gene expression analysis
- GeoSpatial—James Sargent, MD: GIS, spatial analysis, geocoding, cluster analysis, mapping
- Immune Monitoring and Flow Cytometry—Jacqueline Smith, PhD: immunoassays, flow cytometry, cell sorting, cryopreservation
- Irradiation and Small-Animal Imaging—P. Jack Hoopes, DVM, PhD: Cs-137 irradiation, clinical irradiation, experimental irradiation, biomedical NMR, in vivo microimaging, small-animal imaging with physiological monitoring and gating
- Molecular Biology—Yolanda Sanchez, PhD: sample cycling and cleaning for sequencing, DNA sequencing, DNA fragment analysis
- Office of Clinical Research—James Rigas, MD: support for the conduct of clinical cancer research
- Optical Cellular Imaging—Craig Tomlinson, PhD: point scanning confocal microscopy, bright field and fluorescence light microscopy, image analysis
- Pathology Translational Research—Gregory Tsongalis, PhD: tissue procurement and processing, histology, molecular pathology, TMA production, laser capture microdissection, pharmacogenomics
- Proteomics—Scott Gerber, PhD: protein identi-
A few facts about Norris Cotton’s research resources

$65 million Annual funding for research conducted by members of Norris Cotton Cancer Center

200+ Number of research projects ongoing at any given time

75% Approximate percentage of Norris Cotton research funding that comes from federal agencies

$3.1 million Annual core grant funding from the National Cancer Institute for Norris Cotton’s general operations

100 to 175 Number of clinical trials ongoing at any given time—including Norris Cotton-initiated trials, national multicenter trials, and pharmaceutical industry-funded trials

200,000 Total square feet of space devoted to cancer research (including in Norris Cotton’s Rubin Building in Lebanon, N.H., as well as in Dartmouth-Hitchcock’s Borwell Research Building and in other Dartmouth research buildings in Hanover, N.H.)

14 Number of Norris Cotton-affiliated shared research resources

150 Number of members in Norris Cotton’s six research programs

In the end, however, it is the people using the resources—especially the cross-disciplinary interactions among them—that will, as Margaret Foti put it, keep on narrowing “the gap between the laboratory and the bedside.”

“That’s a fundamental reason for a cancer center,” agrees Robert Gerlach, Norris Cotton’s associate director for administration and scientific affairs—to nurture such interactions. For an institution to be designated as a comprehensive cancer center, he notes, the National Cancer Institute “has a rule of thumb that at least 20 percent of publications ought to involve faculty from multiple teams, as a sign that those interactions are taking place.” Norris Cotton so decisively exceeds that goal that “in our six programs, we have some that are even at 50 percent. Our publications are remarkably collaborative.”
It takes hard work and intelligence to succeed in science—and a bit of magic doesn’t hurt. A case in point is a service developed by James Gorham, MD, PhD, director of the Speed Congenics Shared Resource.

The service, called DartMouse, halves the time it takes a scientist to develop mice with a specific genetic profile. Gorham says the members of the DartMouse team call the high-tech machine that makes this possible the Nimbus 2000—a nod to the state-of-the-art flying broomstick in the Harry Potter series.

DartMouse uses a process called speed congenics. It’s basically a faster way for researchers to combine a strain of mouse that works well for their research with a strain that has a specific genetic trait. Gorham compares it to crossing two breeds of dogs. If, hypothetically, the high-pitched bark of a poodle was controlled by a single gene, and if, for some reason, you wanted such a bark in a German shepherd, you could breed a poodle with a shepherd. Then you’d take a pup that looked like a shepherd but had the most high-pitched bark and, again, breed it with a shepherd. Eventually, you’d get a dog genetically close to a shepherd but with the gene for a poodle’s bark. Getting there, however, could take a long time. Speed congenics makes the process go much faster by comparing the genomes of pups in every generation.

More than 50 other institutions, including several institutes within the NIH, now use DartMouse. Gorham expects demand for the service to keep growing, because its use can save a year or more of research time. “That’s a very valuable year for scientists,” he says. “They can begin to test their hypothesis sooner. They can get answers sooner. They can publish more quickly.”

So DartMouse may be just as magical as a flying broomstick—and a great deal more practical besides.
Dartmouth’s Center of Cancer Nanotechnology Excellence: A “very productive” dynamic

When the National Cancer Institute named Dartmouth a Center of Cancer Nanotechnology Excellence (CCNE) in 2010, it became one of only nine such centers in the nation. Along with the prestigious title came a $12.8-million grant to fund the center for five years.

Cancer nanotechnology is a promising research approach that makes possible a novel therapeutic method in which a magnetic field is used to heat minuscule nanoparticles that then destroy tumors. To move this concept from the lab to the clinic, Norris Cotton Cancer Center is taking the lead, in collaboration with experts from Dartmouth’s Thayer School of Engineering and Geisel School of Medicine.

In fact, Dartmouth’s grant application “had a really interesting and unique mix of clinicians, cancer biologists, and engineers,” explains P. Jack Hoopes, DVM, PhD, who heads both one of the center’s research projects and the animal research facility, where much of the CCNE work takes place. “I think our advantage was that all of the investigators came from Dartmouth.” That’s unusual on big grants like the one for the CCNE, he says. “We had materials scientists who understand particles who had never known much about a cell,” Hoopes adds. “We had biologists who understood cancer cells and clinicians who saw the big picture. . . . We could really do the whole thing at Dartmouth.”

The Dartmouth CCNE started out by focusing on breast and ovarian cancers. The first step was to design appropriate nanoparticles, explains Ian Baker, PhD, the director of the center. (Both he and Hoopes, as well as most of the CCNE’s principal investigators, are members of the Cancer Center.) The next step is to get the nanoparticles into the tumors. If a tumor lies close to the surface—as in esophageal cancer, for instance—the nanoparticles can be injected directly into the tumor. But for deep-seated cancers, delivering the particles requires a backdoor approach. Dartmouth researchers are designing antibody tags that can be attached to the surface of nanoparticles. Once tagged, Baker says, “the nanoparticles can be injected into the bloodstream and picked up by receptors on the surface of the tumors.”

Then, after the nanoparticles are concentrated in the cancerous tissue, a magnetic field is applied. The field heats the minute particles, destroying or weakening the tumor. This hyperthermia technique is likely to be used in conjunction with chemotherapy or radiation therapy, Baker adds.

So far, the CCNE research is all preclinical, says Keith Paulsen, PhD, the center’s deputy director. That’s by design. Under National Cancer Institute guidelines, the CCNE grant can’t be used to fund clinical trials. Nevertheless, the Dartmouth work is advancing quickly. Paulsen suspects trials will start within the center’s initial five-year funding period, even though they won’t be funded directly by the grant. “A lot of this is already occurring in animals, and it’s not a big stretch to push this into patients,” he says.

Both Baker and Paulsen attribute the promising pace to the collaborative spirit among the participants. There is a “very productive” dynamic, says Paulsen. “The group challenges each other in a very positive way.”
Clinical Capabilities: “When one is the biggest number”

In the world of popular music, “one is the loneliest number.” In the world of mathematics, one is the smallest prime number. And in the world of cancer care, one—the one person who has been diagnosed with cancer, when it’s you or someone you love—is the biggest, most important number imaginable.

Norris Cotton Cancer Center’s clinical enterprise encompasses 17 locations in two states and addresses the needs of more than 31,000 patients annually—5,200 of them new patients each year. But the focus at Norris Cotton is always on one—on how to meet the needs of each and every one of those thousands of patients. As individuals, not as averages. And as human beings, not as “cases.” Here are a few of the ways that happens:

• Top-notch care: This is, of course, the starting point—delivering top-notch care to every patient. Increasingly, that means care that’s precisely targeted to a patient’s own genetic profile. It means care that meets the most rigorous national standards; to give just one example of such standards, Norris Cotton was recently designated by the National Cancer Institute as a Center of Quantitative Imaging Excellence. It means offering patients a chance to take part in novel clinical trials. And it means ensuring that people don’t get more intervention than they want. The vast majority of cancer patients say that they’d prefer to spend their final days at home, but nationwide almost 25% are admitted to intensive care in the last month of their life; at Norris Cotton, that figure is only 16%.

• Regional reach: The reason for the 17 locations, stretching from the Canadian border in Vermont down to the Massachusetts border in New Hampshire, is to deliver that top-notch care as close to patients’ homes as possible—so they don’t have to drive hours and hours for treatments, so they have friends and family close at hand, so they can sleep in their own bed.

• Tumor boards: At some cancer centers, only rare or complex cases come before a tumor board—an interdisciplinary panel that discusses possible courses of treatment for a given patient. But at Norris Cotton, every newly diagnosed patient has the benefit of insight from a tumor board. All of Norris Cotton’s 13 disease-specific
Camilo Fadul, MD, center, director of the Neurology Tumor Board, leads a recent meeting of the group. At Norris Cotton, a tumor board discusses every new patient.
clinical oncology groups have an associated tumor board, made up of oncologists, radiologists, surgeons, pathologists, nursing coordinators, research scientists—anyone who might have a treatment recommendation for that kind of cancer. The commitment to this process is so strong that most of the tumor boards meet every week.

- Center for Shared Decision Making: In 1999, Dartmouth-Hitchcock (D-H) opened the nation’s first such center—to help patients, often cancer patients, factor their own preferences into treatment decisions. That’s because, very often today, there’s not just one treatment option but two or more—whether it’s choosing between a lumpectomy and a mastectomy for breast cancer, choosing whether to have PSA screening for prostate cancer, or, for a man who has prostate cancer, choosing surgery or radiation therapy or what’s known as “watchful waiting.” It used to be that patients just followed their doctors’ advice. But that meant doctors’ preferences, not patients’, guided decisions—in the case of prostate cancer, for example, willingness to accept a risk of incontinence and/or impotence due to prostate surgery over a risk that the cancer is aggressive rather than slow-growing. At Dartmouth, patients are offered detailed but user-friendly information and unbiased expert counsel to help them truly understand their treatment options. It’s an approach that has caught on nationally since it was pioneered at D-H. But even today, it’s not universal. Norris Cotton administrator Robert Gerlach says that, at a recent meeting of researchers from several cancer centers, a Norris Cotton member made a presentation about shared decision making for patients with prostate cancer. As Gerlach recalls it, an attendee from another center asked, “’How do you get the physicians to propose shared decision making?’ She had the impression,” Gerlach explains, “that there are many urologists who’ve never met a prostate they couldn’t remove.” The Norris Cot-
ton presenter replied, continues Gerlach, “‘Well, there is imbued in the clinical system here an acceptance of shared decision making.’ I think here, throughout the Cancer Center,” adds Gerlach, “people recognize the fact that patients need to have an active role in choosing the approach to their disease that best suits them.”

- Palliative care: Often confused with hospice care, palliative care is, at its core, about caring—caring for the patient, not just the patient’s disease. Ira Byock, MD, chief of the Section of Palliative Medicine (and a member of Norris Cotton’s Cancer Control Research Program), wrote this about patients’ final days in his book *Dying Well*: “While I may bring clinical skills and years of experience to the task, ultimately I am simply present, offering to help.” Both Byock and D-H have been national leaders in palliative care, and, as with shared decision making, cancer patients are often among those who benefit. They have a chance to discuss with palliative-care specialists issues like physical disability, emotional well-being, family dynamics, and death. But at Norris Cotton, palliative care isn’t reserved for those for whom all treatment options have been exhausted; indeed, it’s now incorporated into patients’ initial diagnostic visits. Evidence from clinical trials (many done at D-H) has shown that these efforts are effective—that palliative care can improve patients’ quality of life and sometimes even prolong their lives.

- Multidisciplinary and interdisciplinary care: There’s a distinction between multidisciplinary care, in which a patient sees doctors from different disciplines, and truly interdisciplinary care, in which doctors from different disciplines work closely together on patients’ behalf, seamlessly integrating their advice and recommendations and including the patient in the discussion. At Norris Cotton, all care is multidisciplinary, and increasingly it’s truly interdisciplinary.

### A few facts about Norris Cotton’s clinical capabilities

- **5,200+** Number of new patients each year
- **31,000+** Total number of patients cared for each year
- **75,000+** Visits made to Norris Cotton outpatient clinics each year
- **200+** Cancer specialists with expertise ranging from diagnostics and genetic counseling to oncology, radiation therapy, and palliative care
- **90+** Oncology nurses who coordinate patient services and master’s-level advanced practice nurses who conduct research and education
- **13** Disease-specific clinical oncology groups and tumor boards
- **70,000** Square feet (sf) of Norris Cotton clinical space at Dartmouth-Hitchcock (60,000 sf of outpatient space, 10,000 sf of inpatient space)
- **28** Beds in the inpatient oncology unit at Dartmouth-Hitchcock
Patient and Family Support Services: This is another aspect of Norris Cotton’s patient- and family-centered approach to care. An array of programs—from support groups and writing workshops to massage and music—address patients’ physical and emotional comfort. For example, Margaret Stephens, a certified harp practitioner, is a regular presence at Norris Cotton. Playing a repertoire ranging from Irish ballads to country-and-western tunes, she creates an individualized “cradle of sound” through techniques such as gradually slowing the tempo to help reduce a patient’s breathing rate. “When the music starts,” says Deborah Steele, manager of patient and family support, “it’s as if a new environment is created, a bubble of protection and healing.”

Survivorship: CARES (Cancer and Related Events of Survivorship) supports patients after their treatment ends—helping them regain control of their lives by addressing both their physical and emotional needs, from pain to self-esteem to sexual dysfunction.

Familial Cancer Program: Norris Cotton offers comprehensive genetic services, including family history analysis, risk assessment, genetic testing and counseling, and prevention recommendations.

Quality and Patient Safety Program: This is the bottom line at Norris Cotton, as at D-H generally—ensuring the quality and safety of the care that patients receive and taking unwarranted variation out of the system. A few recent initiatives that fall under this program include Operation VOICE (Voice Opportunity for Improvement of the Customer Experience); pilot projects to improve pharmacy notifications and clinic-to-infusion handoffs; and participation by several members of the Section of Radiation Oncology in a week-long Lean Six Sigma Green Belt curriculum.

Harp music creates a “cradle of sound” for cancer patients.
Carolyn Sumner was supposedly down for the count in March 2011. Diagnosed with stage IV colorectal cancer at a hospital near her home in southern New Hampshire, Sumner says her adult children were told “to just take me home and make me comfortable,” that “I had three months left.”

But Sumner wasn’t about to throw in the towel. She’d been on the ropes more than 15 years earlier, with a diagnosis of stage IV melanoma, and had gone the distance against cancer. Gone the distance to get care at Norris Cotton’s hub in Lebanon, that is, before the Cancer Center had the presence it does today throughout the region.

Here’s how Sumner tells her story: “I live in Derry, New Hampshire,” she begins. In 1994, “I was diagnosed at Hooksett Oncology with melanoma. The doctor there recommended that I go see Dr. Marc Ernstoff at Norris Cotton, because it was stage IV and they were doing research up there.

“So I made an appointment and went up there to see him. When I first met Dr. Ernstoff, I had a very comfortable—very hopeful, I guess is the word—feeling. And everybody at Norris Cotton, whether it was the nurse or the LPN or the LNA, was wonderful. You weren’t a number. I mean, I live closer to Boston than I do to Dartmouth, but [at Dartmouth] you were a person and they took time with you—there was never any rush.”

Sumner was under Ernstoff’s care through 1999. She was treated on three separate Norris Cotton clinical trials—one using granulocyte-macrophage colony-stimulating factor and one using pegylated interferon alfa-2b, both longstanding research interests of Ernstoff’s, plus a third trial using a dendritic-cell vaccine developed at Dartmouth. Today, more than 15 years after her initial diagnosis, Sumner shows no evidence of melanoma.

Then she found herself back in the ring in 2011, when a surgeon near her home delivered the haymaker of “three months left.” But Sumner, having duked it out with cancer before, was game to once more go toe-to-toe with the disease. “My daughter called Marc Ernstoff,” Sumner explains. “I knew that Dr. Ernstoff didn’t have anything to do with colon cancer, but I wanted to go up to Dartmouth.”

A matchmaker was looking out for her. “In 1996,” Sumner says, “when Dr. Ernstoff was off for a month doing research, I saw a new doctor who’d just come to Dartmouth, Dr. Marc Pipas. And, lo and behold, when I was admitted up there [in 2011], Dr. Ernstoff came to see me and said, ‘You’re going to see Dr. Pipas.’ I have been seeing him ever since, with wonderful results—absolutely wonderful. I went on a clinical trial with him, and I had two surgeries, and right now I’m doing chemo, but the prognosis looks good.”

So “here I am,” Sumner concludes, after two stage IV diagnoses, “because of the research that they do” at Norris Cotton. And once again, during her current treatments, she has been struck with the knockout care. “I hadn’t been up there since ’99,” she says, “and, my god, it’s grown so much. But you still have that same feeling—whether you’re having your blood drawn before you go to see the doctor, or when you see Dr. Pipas, or when you go in to oncology to get your treatment—they’re all just wonderful people up there.”
When Jean Kemeny, the wife of Dartmouth College President John Kemeny, titled her 1979 memoir *It’s Different at Dartmouth*, she conferred a memorable catchphrase on an imprecise concept. In fact, it took her 199 pages to pin down just what makes Dartmouth such a special place. But few have disputed the veracity of her pronouncement.

Similarly, an amalgam of ephemeral but very real qualities distinguishes Norris Cotton Cancer Center from the other excellent comprehensive cancer centers that are its peers. Here’s how Norris Cotton immunology researcher Mary Jo Turk, PhD, puts it, during an interview about her research: “I think it would be good to convey what a special place this is—and how happy I am here. I’ve never worked anywhere else,” admits Turk, who joined the Dartmouth faculty after completing her postdoctoral training in 2004, “so maybe people would say, ‘Oh, well, how do you know?’ But I have friends that work other places,” she adds, “and we compare notes.” (See page 88 for insight into Turk’s research.)

Dartmouth’s—and Norris Cotton’s—location in rural New England, amid unsurpassed scenic splendor, is certainly one of the reasons people like Turk become partial to the place. Not only are there endless opportunities for outdoor recreation, but the views out one’s windows at work and at home—and even the backdrop for one’s daily commute—are of tree-covered hills rather than concrete canyons or suburban sprawl.

Those drawn to this beautiful corner of the country come not only from all over the U.S., but from all around the world. Today, Dartmouth faculty and students represent well over 50 different countries. International interest groups abound at Dartmouth, as do overseas faculty and student exchanges and research and study abroad opportunities. And a wide array of cuisines and artistic traditions are represented both on the Dartmouth campus and in the surrounding communities, in what is known as the “Upper Valley”—that is, the small towns in both New Hampshire and Vermont along the upper reaches of the Connecticut River Valley.

Those small towns are another part of what distinguishes the place. “People are kind of laid-back around
Norris Cotton Cancer Center’s hub is on the Dartmouth-Hitchcock Lebanon, N.H., campus—which sits in the midst of a setting of unsurpassed scenic splendor.
here,” observes immunologist Turk. “It’s a small community—we see each other in the grocery store. It’s not a city, and that makes it special.”

Another distinctive factor is the size not just of the towns around Dartmouth, but of Dartmouth—and the Cancer Center. There are many people who believe the institution is just the right size—not too big, not too small—to promote effective academic collaborations. Such collaborations are especially important in carrying out translational research, in which findings made in the laboratory are moved purposefully and smoothly into patient-care applications.

Robert Gerlach, Norris Cotton’s associate director for administration and scientific affairs, worked previously at two other major cancer centers and has, over the course of his career, visited many other peer institutions. So he has a basis for saying that bigger isn’t necessarily better in the world of translational research. “You may think that numbers facilitate bumping into people with similar scientific interests,” he says, “but actually the ‘crowd noise’ can become quite distractive”—the “noise,” that is, of the vast distances from one end of a large campus to another, or of the vast numbers of fellow faculty members whom one encounters during a day.

Alan Eastman, PhD, codirector of Norris Cotton’s Molecular Therapeutics Research Program, agrees about the importance of “bumping into” colleagues. When a hypothesis shows promise in mice, for example, the next step is to test it in humans. “If a lab guy like me wants to work with human tissue,” Eastman explains, “it is critical that I have proximity to the clinicians.”

In fact, such proximity was a conscious factor in the design of Norris Cotton’s Rubin Building. “It is amazing what happens,” Eastman adds, regarding collaborations between physicians and scientists, “when we use the same coffee pot.”

Even the fact that some Norris Cotton labs are located on Dartmouth-Hitchcock’s Lebanon campus, while others are on the main Dartmouth campus in Hanover, is less of an impediment than it might be at many other places. Gerlach, who has worked at another institution with a split campus, says that at Dartmouth, “it really is no problem,” because of the free bus service that runs every 15 minutes between the two campuses. “I’ve been here five years,” Gerlach adds, “and I keep telling people it’s remarkable to have public transportation and virtually no traffic. I can set my watch and know that, five minutes before the bus is due, I can get up from my desk, walk down to the bus stop, and the
bus will be there. It’s not like you have wait around 20 minutes and wonder ‘When will the bus show up?’”

Ethan Dmitrovsky, MD, a prominent Norris Cotton physician-scientist (see page 80 for insight into his career), wrote an essay a few years ago for Dartmouth Medicine magazine, in which he extolled the institution’s “distinct strengths in size and core values. . . . Our size is an asset that our collegial and collaborative values enhance. This combination drew me to Dartmouth and has enabled me to recruit distinguished faculty from respected peer institutions.”

Not only does Dmitrovsky oversee recruitments for faculty in the Department of Pharmacology and Toxicology, which he chairs, but he’s also served on several high-level institutional search committees. He has found, he continued in the essay, that recruits are “attracted by academic values difficult to match elsewhere, values that promote interdisciplinary collaboration and scientific synergism. Scientific discovery is now a complex and highly social process involving interdisciplinary teams. Boundaries between fields are often blurred. In the future, a competitive advantage will certainly accrue to teams that assemble scientists from diverse disciplines. My own research requires close ties between basic and clinical scientists. I have found collaborators at Dartmouth because no administrative barriers exist. Our size and collaborative nature reinforce our competitive advantage in the life sciences.”

So there may be no single reason why “it’s different at Dartmouth.” But it’s clear there is a difference. “We’re very fortunate,” concludes Mary Jo Turk. “The people here are special. There’s good leadership. And a lot of it is the environment. I don’t think I would have been this successful elsewhere.”

Another distinguishing element of Norris Cotton

Norris Cotton Cancer Center isn’t a museum, but a significant piece of medical history is on permanent display there—an original copy of the 1971 National Cancer Act (pictured below). The ground-breaking act, signed by then-President Richard Nixon, provided the funding and the authority for the National Cancer Institute to lead the nation’s fight against cancer. Norris Cotton was given a copy of the act—one of only two in existence—by Marilyn Cole, the widow of former Nixon administration official Kenneth Cole, who is credited with having shepherded the Cancer Act through Congress.

“Our family felt that this was the perfect place for this document,” says Ken Cole’s brother, Brady Cole, who holds an appointment as a lecturer in psychiatry at Dartmouth’s Geisel School of Medicine and is also a member of the Friends of Norris Cotton Cancer Center. “The Cancer Center embodies the spirit and intent of the act,” Brady Cole adds, “and is a place my brother would have loved, because of its sense of inclusion, family, and community.”
The Friends of Norris Cotton Cancer Center: The Prouty as parable

Norris Cotton’s mantra might be “with a little help from my friends.” Actually, make that “with a lot of help from the Friends.” The Friends of Norris Cotton Cancer Center, that is. Ever since the group’s establishment when the Cancer Center was 10 years old, in 1982, it has engaged in many activities that benefit Norris Cotton. The group’s signature event—known simply as “The Prouty”—is in many ways a parable for the culture that distinguishes the Cancer Center.

The Prouty had humble roots, with four Dartmouth-Hitchcock nurses who were touched by the courage and can-do spirit of one of their cancer patients, Audrey Prouty of Warren, N.H. She died in July of 1982 and later that summer, in her memory, the nurses collected pledges and completed a 100-mile bicycle ride through New Hampshire’s White Mountains. They raised a grand total of $4,000 for the Cancer Center.

In the three decades since then, the Prouty has become a huge, spirited, multiday event. Bicyclists ride routes ranging from 20 miles to 200 miles; walkers stroll or jog between 3K and 30K; and rowers now take part, too, on the Connecticut River. The number of participants (who come from all over the country) has ballooned more than a thousandfold since 1982, and the amount they raise each year now tops $2.5 million.

Another significant fact about the Prouty is that this huge event, and the 30-some other events that the Friends mount or support each year, are managed by a paid staff of just six people (led by the Friends’ executive director). Many of the yellow-shirted Prouty volunteers—as well as many participants in the event—take part in honor or memory of someone they know who has battled cancer.
director, Jean Brown)—plus well over a thousand volunteers. Audrey Prouty’s can-do spirit is paying more dividends than she ever could have imagined.

“All Together Now: Dartmouth’s Norris Cotton Cancer Center

“Everybody, I think, knows an Audrey Prouty,” one of the four original nurses reflected a few years ago, “and that’s where this event has been successful: you go to the event, and you tell your stories [about cancer], and you talk to people who are riding with pictures of their mothers, of their children. It’s an honor to honor the courage that people who go through [cancer] have.”

The Prouty, observes another person who was involved with the event during its early years, “proves the power of one.” That’s one Prouty participant (or volunteer). One nurse (or four). One doctor. One researcher.

Or one patient who inspired an annual outpouring of generosity. •

A few facts about “The Prouty”

1982 Year the first Prouty was held

4 Number of participants (all of them Norris Cotton nurses) in 1982

100 Miles each rode a bicycle through the White Mountains

$4,000 Total raised in 1982 at the first Prouty

$2.5 million+ Total raised in 2012 at the 31st Prouty

5,050 Participants (cyclists, walkers, and rowers) in the 2012 Prouty

216,000+ Aggregate miles they cycled, walked, and rowed

36 States (including D.C.) represented by the 2012 participants

1,250 Volunteers who helped mount the 2012 Prouty

$17.3 million Total raised since the start of the Prouty for support services and research at Norris Cotton

$1.2 million Prouty proceeds given as pilot grants to 87 Norris Cotton researchers between 2006 and 2010

$16.3 million Amount of subsequent grant funding directly attributable to the work initiated under those pilot grants

Thousands of participants in the 2012 Prouty started and finished from this colorful balloon arch—raising more than $2.5 million for the Cancer Center.
The Programs

Six research programs bring structure and focus to the investigative work that takes place under Norris Cotton’s auspices, while myriad collaborations—both among and within the programs—knit together seemingly disparate efforts. The work covers the gamut of biomedical inquiry: from nanotechnology to massive meta-analyses; from regional community outreach to national clinical trials; from basic molecular biology to truly translational initiatives; from findings that affect Hollywood moviemaking to studies that inform federal health policy.
The goal of Norris Cotton’s Cancer Control (CC) Research Program is to reduce cancer risk and mortality and to enhance the quality of care and quality of life for cancer patients. This is accomplished through behavioral and policy research to limit cancer-causing behaviors like smoking and through comparative effectiveness research—research that is designed, according to the federal Agency for Healthcare Research and Quality, “to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options.” This goal fits harmoniously within the Cancer Center’s overall research mission, which includes fostering collaborative, interdisciplinary research into the biology, causes, prevention, and treatment of cancer.

Members of the CC Research Program constitute a diverse group of investigators. They oversee research initiatives that range from studies of basic scientific mechanisms to patient-oriented research to work involving public health policy. And they have expertise in areas as wide-ranging as the geography of cancer care, psycho-oncology, survivorship, cancer screening trials, screening registries, and community correlates of risk behaviors.

Research conducted by members of the CC Program falls into two broad focus areas—behavioral research and health services research. Within each area, members actively collaborate, whether they are working on prevention, early detection, quality of life, or quality of care. These focus areas drive both the program’s administrative infrastructure and the support services that are available to its members.

The researchers within the CC Program look at the control of cancer across the continuum of care: addressing cancer-causing behaviors among children and adolescents by studying the neuroscience of responses to advertising; seeking appropriate ways to screen for cancer through the use of screening registry research; and investigating quality-of-life and quality-of-care issues, including how best to support end-of-life care.

Cross-cutting themes within the program include bidirectional translational research and the communication and dissemination of new knowledge within the scientific community and in society at large.
Samir Soneji, PhD—who uses demographic modeling and simulation to study cancer care and outcomes—joined the Cancer Control Research Program in 2011.
Significant recent achievements of the CC Research Program

Members of the Cancer Control Research Program have recently made a number of significant findings, including the following:

- William Black, MD, a leader of the National Lung Screening Trial (NLST), coauthored a *New England Journal of Medicine* article on the effects of low-dose CT screening on lung cancer mortality among smokers. The trial enrolled 53,434 subjects and randomly assigned them to receive either three annual low-dose CT screenings or three annual chest x-rays. The CT group experienced a 20% reduction in mortality from lung cancer and a 6.7% reduction in mortality from all causes. (See page 96 for more on Black and the NLST.)

- James Sargent, MD, and colleagues are collaborating with researchers worldwide to measure the relationship between young people’s exposure to tobacco or alcohol in the popular media and their initiation of smoking or drinking. India, Scotland, and Germany number among the countries where they’ve recently worked. Sargent’s highly productive research group also continues to conduct large-scale prospective studies on the effects of media—including advertising, brand marketing, movies, and popular music—on rates of smoking and alcohol use among U.S. adolescents. (See page 46 for more on Sargent’s work.)

- Todd Heatherton, PhD, who uses functional magnetic resonance imaging to map brain activity patterns in moviegoers, reported in the *Journal of Neuroscience* that simply watching actors smoke on-screen may induce viewers to light up, by activating regions of the brain associated with planning the act of smoking.

- Tracy Onega, PhD, continues to oversee the New Hampshire Mammography Network (NHMN). Its 15-plus years of data, representing over a million mammograms, have led to more than 380 peer-reviewed publications. Currently, Onega and Anna Tosteson, ScD, are capturing risk-based breast-screening information and examining risk-based use of imaging modalities through both a Breast Cancer Surveillance Consortium project grant and a new National Cancer Institute initiative called Population-based Research Optimizing Screening through Personalized Regimens, known as PROSPR. (See page 47 for more on Tosteson’s work.)

- Carrie Hoverman Colla, PhD, is using Medicare claims data to assess changes in end-of-life chemotherapy in response to the Medicare Modernization Act.
• Samir Soneji, PhD, and colleagues used a Bayesian hierarchical forecasting model to predict mortality patterns. Among their findings were that the steady decline in the prevalence of smoking may lead to a faster than projected gain in life expectancy, especially among men 50 years of age and older.

• Suzanne Tanski, MD, MPH, has collaborated with a Dartmouth College professor of chemistry to evaluate a nanotechnology-based personal sensor for detecting and quantifying secondhand tobacco smoke exposure. Made using molecularly imprinted polymers and radiofrequency identification (RFID) technology, the sensor is about the size of the radiation badges used in operating rooms and radiology suites, so it can be worn on the shoulder or chest near the subject’s mouth and nose. The polymers are also able to detect nicotine in urine with high accuracy and precision.

• Mark Hegel, PhD, is developing telephone-delivered interventions to assist women under 60 years of age who have completed their treatment for breast cancer. The interventions are aimed at behavioral activation and problem solving in an effort to overcome restrictions on the women’s ability to perform work, social, family, or leisure activities. Hegel also received a grant to study decision making among men who have a favorable prognosis for prostate cancer; this study could support men who choose watchful waiting rather than an immediate therapeutic intervention.

• Marie Bakitas, DNSc, is evaluating the effect of offering palliative care at the time of diagnosis to patients with advanced cancer. Two companion studies involve testing the feasibility of extending this concurrent palliative-care model to patients in community-based oncology practices and evaluating a decision-making aid for patients with advanced illness.
Most pediatricians help children one at a time, in person—by keeping them well or helping them feel better when they get sick. But Norris Cotton pediatrician James Sargent, MD, has helped countless children, all around the world—by reducing the risk that they’ll fall prey to tobacco or alcohol imagery in movies.

He has done so by demonstrating, in study after study, that children who see more smoking and drinking in movies are more likely to take up smoking or to start drinking at an early age. The importance of his work has led to widespread press coverage. During a recent two-day period, for example, he was quoted on CNN and in Time, the New York Times, and the London Daily Mail.

And Sargent, the codirector of Norris Cotton’s Cancer Control Research Program, doesn’t just talk to the press about his work, but also takes an advocacy role. Here’s an example, from the New York Times: “Researchers found that exposure to smoking in movies with a PG-13 rating had essentially the same impact on adolescent smoking as exposure to smoking in R-rated movies, suggesting, they say, that it is the smoking itself . . . which causes the association. The solution offered is simple: ‘an unambiguous R rating for smoking.’ . . . That
simple policy change, writes Dr. James Sargent, who led the research, could reduce adolescent smoking by 18%.”

Sargent’s work begins with careful enumeration of smoking or drinking scenes in movies. He then tallies children’s exposure to such imagery and correlates it with whether a child takes up smoking or drinking in the future. The strength of the association has been proven time and again. And because Hollywood movies are distributed internationally, such imagery has an impact on adolescents through much of the Western world.

In recent years, researchers from all over have sought collaborations with Sargent. A study in Germany found a strong link between tobacco marketing and teen smoking; teens in the highest exposure group were almost 50% more likely to begin smoking than those in the lowest-exposure group. And Sargent recently turned his attention to a source of smoking and drinking imagery in much of the Eastern world—Bollywood movies. A 2011 study in India showed a correlation between exposure to smoking scenes in Bollywood movies and adolescent smoking.

The findings are now making a real-world impact. In 2012, the U.S. surgeon general evaluated the evidence and reported a causal association between movie smoking and onset of smoking during adolescence. And Hollywood is even reacting. In 2011, the U.S. Centers for Disease Control’s Morbidity and Mortality Weekly Report revealed substantial drops in on-screen smoking in top-grossing youth-rated films. The three major studios with published policies on smoking in youth-rated films reduced smoking imagery by 96% from 2005 to 2010. But the reduction was only 42% in the rest of the industry, so Sargent doesn’t plan to cut back on his efforts any time soon.

Anna Tosteson: Ensuring effective care

As screening, diagnostic, and treatment options have proliferated in the U.S., it has become ever harder for physicians—and their patients—to sort through all the choices. To give just one example: Who should be routinely screened for breast cancer? By what modality? And when do screening’s risks (such as radiation exposure or false positives) outweigh its benefits?

Dissecting questions like these is tough work, but Anna Tosteson, ScD, has been at it for almost two decades. She started out in the 1990s, applying her expertise in decision science and biostatistics to assessing the effectiveness of interventions to prevent and treat osteoporosis in older women. Today, she is codirector of Norris Cotton’s CC Research Program and director of the Office of Cancer Comparative Effectiveness Research. In the latter role, she oversees studies aimed at determining whether new technologies, new drugs, and new devices actually improve patient outcomes.

Currently, she is coleading a project—funded by a $6.1-million National Cancer Institute (NCI) grant, through an initiative called PROSPR (Population-based Research Optimizing Screening through Personalized Regimens)—to improve the effectiveness of breast cancer screening. Undertaken jointly with Brigham and Women’s Hospital, it is one of just three projects funded by the NCI that’s dedicated to breast cancer screening research in the U.S. •
Cancer Epidemiology and Chemoprevention Program

Norris Cotton’s Cancer Epidemiology and Chemoprevention (CEC) Research Program facilitates multidisciplinary interactions among molecular biologists, biostatisticians, epidemiologists, and clinicians. Collectively, the program’s members seek to understand the ways that cancer affects populations and the cellular mechanisms that are involved in the chemoprevention of cancer.

To do this, the CEC Program fosters the identification of major biologic targets, the discovery of novel chemopreventive agents, and the identification of markers for monitoring early biologic response. The investigators in the program use animal models of pre-neoplastic or neoplastic disease, and they also conduct hypothesis-driven clinical trials. Themes that cut across the program’s bench-to-bedside-to-community continuum include specific tumor types and potential therapeutic targets.

The program promotes investigations that identify carcinogenic factors and their effects at the molecular, genetic, and biochemical levels and directs inquiry into the environmental and biological factors that modify these effects. Collectively, these efforts encompass observational studies, in vitro studies, studies involving carcinogen-induced tumors in genetically engineered animals (primarily rodent species), and clinical trials.

The program’s long-term goal is the identification and development of interventions that inhibit carcinogenesis. Once potential strategies are found through the use of animal models, initial clinical exploration is undertaken through proof-of-principle Phase I and II trials. Findings are confirmed and ultimately extended through definitive Phase III trials.

The CEC Program seeks to continually strengthen its scientific accomplishments by organizing and encouraging both intra-programmatic and inter-programmatic interactions, as well as interactions with visiting scientists who are leaders in the fields of epidemiology and chemoprevention. These interactions foster collaborative and interdisciplinary projects among the epidemiologists, basic scientists, and clinicians who share a commitment to the scientific goals of the program.
Michael Sporn, MD, pictured with a longtime lab assistant, coined the term “chemoprevention” in the 1970s and has been a member of the CEC Program since 1996.
Members of the Cancer Epidemiology and Chemoprevention Research Program have recently logged a number of significant accomplishments, including the following:

- Ethan Dmitrovsky, MD, codirector of the CEC Program, became an American Cancer Society Professor and chair of the National Cancer Institute’s Board of Scientific Counselors for Clinical Sciences and Epidemiology. (See page 80 for more on Dmitrovsky’s career.)

- Konstantin Dragnev, MD, with Ethan Dmitrovsky and other colleagues, completed a proof-of-principle trial and a Phase II trial targeting cyclin D1 with erlotinib and bexarotene. The two drugs conferred a survival advantage against lung cancers, even in the presence of RAS mutations. The publication of this finding (in Cancer Prevention Research) was accompanied by an editorial and by a report from a team at M.D. Anderson Cancer Center that independently confirmed the Dartmouth findings in an active arm of the BATTLE Trial.

- Margaret Karagas, PhD, codirector of the CEC Program, led a non-melanoma skin cancer case-control study that resulted in the identification of an association between non-melanoma skin cancer and genus beta-type human papillomaviruses, particularly among individuals with a history of immunosuppressive drug use. The team led by Karagas—which included Judy Rees, BM, BCh, MPH, PhD; Steven Spencer, MD; and others at Norris Cotton—also identified susceptibility to these tumors determined by immunologic factors in the general population. (See page 52 for more on Karagas’s work.)

- Margaret Karagas and colleagues also identified rice consumption as a potential source of arsenic exposure among pregnant women.

- Jason Moore, PhD, and colleagues contributed to a collaborative report in Science that identified epigenomic enhancer profiles specific to colon cancers. Moore also received an $11-million award from the National Institutes of Health to establish the Institute for Quantitative Biomedical Sciences at Dartmouth.

- John Baron, MD, MSc, and colleagues are conducting ongoing multicenter, double-blind, randomized chemoprevention trials of large bowel neoplasia. The team led by Baron—which includes Douglas Robertson, MD, MPH; Richard Rothstein, MD; Elizabeth Barry, PhD; Judy Rees; and others at Norris Cotton—uses a chemoprevention model, with polyp recurrence as the
primary endpoint, to study the effects of vitamin D supplementation.

- Michael Sporn, MD, and colleagues continue their seminal work synthesizing novel chemopreventive agents such as triterpenoids and their derivatives and testing these agents in preclinical and animal models. They’ve shown that triterpenoids can prevent ER-negative breast cancers in mice. The team has also completed Phase I and II trials, and a Phase III trial is under way.

- In addition, Michael Sporn collaborated with Ethan Dmitrovsky to adapt a novel animal model for the study of chemoprevention, to assess the activity of therapeutic and chemoprevention agents in the lung. This model uses vinyl carbamate as a carcinogen because vinyl carbamate causes premalignant and malignant lung lesions, unlike the more commonly used carcinogen, urethane, which causes lung adenomas.

- Angeline Andrew, PhD, in collaboration with Ethan Dmitrovsky and colleagues, identified the deconjugase UBP43 as a novel antineoplastic target for lung and other cancers. They also uncovered microRNA-31 as an oncogenic microRNA in the lung.

- Linda Titus, PhD, and Rebecca Troisi, ScD, identified an increased risk of early-onset breast cancer in a long-term follow-up of women who had been exposed to diethylstilbestrol (DES).

- Jiang Gui, PhD, and colleagues identified new sampling approaches for the detection of gene-gene and gene-environment interactions to assess cancer prognosis.

- Brock Christensen, PhD; Carmen Marsit, PhD; Margaret Karagas; and colleagues reported a statistically significant association between RPPM methylation class and the histological subtype of glioma tumors.
Today, it’s widely known that tanning booths aren’t good for your health: In June 2012, when a New Jersey woman was arrested for allegedly bringing her five-year-old daughter into a tanning bed, the story went viral. Press accounts both online and in print spread the news, and photographs of the grotesquely tanned mother were rife on social media sites. The millions of appalled people who saw and shared that story didn’t know it, but their informed reaction was a consequence of work by Norris Cotton Cancer Center researcher Margaret Karagas, PhD.

The idea that even artificial tanning is bad for you had been debated for years, but a decade ago Karagas offered the first peer-reviewed evidence of an association between tanning beds and increased skin cancer incidence. She was the lead author on a paper in the *Journal of the National Cancer Institute* titled “Use of tanning devices and risk of basal cell and squamous cell skin cancers,” the two most common kinds of skin cancer.

The population-based, case-control study showed—contrary to longstanding safety claims made by tanning salon operators—that study participants who had used tanning lamps were more likely to develop both...
squamous cell cancer and basal cell cancer than individuals who did not have a history of artificial tanning.

Since then, Karagas has established other related associations of significant public health importance. In 2006, she reported, again in the *Journal of the National Cancer Institute*, an association between HPV (human papillomavirus) infection and the risk of developing squamous cell cancer. She also found that an individual’s cumulative exposure to radiation—such as from x-rays or radiation therapy for cancer—increased the risk of being diagnosed with either basal cell or squamous cell cancer. And she has tracked the rapid rise in the incidence of these cancers over the past 20 years, using a statewide skin cancer registry that she maintains, with collaboration from dermatologists, dermatopathologists, and pathology labs throughout the region.

In addition, Karagas has conducted a wide range of other epidemiological studies. For example, she examined the effects of consuming water containing higher than average levels of arsenic. And in 2010, she and colleagues reported that prolonged use of glucocorticoids—drugs that suppress the immune system and are often prescribed to treat inflammatory conditions, such as rheumatoid arthritis and irritable bowel disease—may increase the risk of developing bladder cancer by as much as 85%.

Karagas, who is codirector of Norris Cotton’s Cancer Epidemiology and Chemoprevention Research Program, points out that such studies are an essential first step in identifying approaches to reducing the risk of cancer. She is continuing to ferret out such associations and is currently heading a team that in 2011 received a National Institutes of Health P20 Exploratory Grant to investigate the effects of early-life exposure to arsenic.

**Jason Moore: Championing the use of bioinformatics**

If you talk to computational geneticist Jason Moore, PhD, about his work, apparent paradoxes start emerging left and right. His stock-in-trade is crunching massive amounts of data, yet he believes more is needed to parse the human genome than just additional data. He led the development of a supercomputer at Norris Cotton, made up of 1,500 processors and available for use by any researcher at Dartmouth, but he believes most geneticists have become too entranced by technology. He blogs and tweets regularly about his work, in addition to writing peer-reviewed papers and giving scholarly talks, yet he also spends a lot of time thinking about the past. “We have a lot to learn from early geneticists,” he says. “Historical context is so important... It provides a grounding, a foundation. You have to understand the history in order... to understand your place in the science.”

It soon becomes clear that Moore is deeply thoughtful rather than a self-contradiction. As Norris Cotton’s associate director for bioinformatics, he makes sure Cancer Center members know what combing through millions of genetic variations can (and can’t) do, and he supports their use of the supercomputers and sophisticated software that he’s devised and assembled.

“The Human Genome Project was way overhyped,” Moore says. But, if he has his way, the future may one day catch up to the hype.
Norris Cotton’s Cancer Imaging and Radiobiology (CIR) Research Program has two primary goals. The first is to stimulate and promote the use of biophysics and engineering to develop and evaluate new cancer diagnostic and treatment strategies. And the second is to better understand the biological and physiological factors that influence the effectiveness of cancer radiotherapy and of various imaging modalities.

To accomplish these goals, the CIR Program fosters a collaborative environment that promotes the incorporation of imaging, radiobiology, biophysics, and engineering approaches into the development and evaluation of new cancer diagnostic and treatment strategies.

The membership of the Cancer Imaging and Radiobiology Program is notable for its interdisciplinary nature. It consists of engineers, physicists, and biologists, as well as physicians and surgeons—all of whom have a demonstrated ability to translate experimental approaches from the bench to the bedside.

Research within the CIR Program currently focuses on the following areas: improving the imaging of structural and functional variables associated with malignancy, in order to better help physicians detect and characterize cancer and to better guide the administration of anticancer therapies; measuring and assessing oxygenation levels during cancer treatments; and identifying therapeutic agents and dosage recommendations to help evaluate new cancer imaging modalities, therapeutics, and exposure events.

Cross-cutting themes within the Cancer Imaging and Radiobiology Program include data fusion, multimodal imaging, and treatment guidance.
These CIR members—from the left, Ben Williams, PhD; Ann Barry Flood, PhD; and Harold Swartz, MD, PhD—show off a prototype of a dosimeter they’re developing.
The Programs
Cancer Imaging and Radiobiology

CIR Investigators are exploring intraoperative fluorescence imaging in one of the few approved clinical protocols in North America for off-label use of Levulan to guide the resection of brain tumors.

Significant recent achievements of the CIR Research Program

Members of the Cancer Imaging and Radiobiology Research Program have recently reported a number of significant achievements, including the following:

- Brian Pogue, PhD; Keith Paulsen, PhD; and colleagues found that changes in tumor angiogenesis estimated with diffuse optical spectroscopic tomography correlate to the therapeutic response of women undergoing neoadjuvant chemotherapy for invasive breast cancer.
- David Roberts, MD; Keith Paulsen; and colleagues measured fluorescence in intracranial tumors, showing that levels exist below the threshold of human visual perception.
- Ryan Halter, PhD; Alexander Hartov, PhD; and colleagues showed that passive bioelectrical properties can be used to assess high- and low-grade prostate adenocarcinomas.
- David Roberts, Alexander Hartov, and colleagues are exploring intraoperative fluorescence imaging (iFI) to guide tumor resection. This study, of iFI coregistered with preoperative MR, is one of the few approved clinical protocols in North America for off-label use of Levulan to guide the resection of brain tumors. This work is supported by the NIH; Zeiss, Inc.; Medtronic; and DUSA Pharmaceuticals.
- Ian Baker, DPhil; Keith Paulsen; Brian Pogue; John Weaver, PhD; Jack Hoopes, DVM, PhD; and colleagues received a $12.8-million National Cancer Institute U54 grant to create the Dartmouth Center of Cancer Nanotechnology Excellence. They are developing novel antibody-tagged magnetic iron-core nanoparticles to treat breast and ovarian tumors using an alternating magnetic field.
- Ian Baker and colleagues described the synthesis of core/shell-type iron/iron oxide nanoparticles for magnetic hyperthermia cancer therapy.
- Jack Hoopes and colleagues defined the time-dependent cellular uptake of intratumorally administered dextran-coated, core-shell configuration iron oxide nanoparticles in a murine breast adenocarcinoma xenograft in vivo.
- John Weaver and colleagues showed that multiple nanoparticle environmental states can be concurrently quantified using the particles’ spectral response.
- A combination of extramural and institutional support funded the consolidation of small-animal...
imaging in a new, much larger facility. The project also included the acquisition of a new 9.4-Tesla small-bore MR scanner.

- Harold Swartz, MD, PhD; Nadeem Khan, PhD; Benjamin Williams, PhD; Huagang Hou, MD, MS; Lesley Jarvis, MD, PhD; Eunice Chen, MD, PhD; Bassem Zaki, MD; and colleagues initiated the first measurements of human tumors using a unique clinical EPR spectrometer developed at Dartmouth. In preclinical studies using repeated assessments of tumor pO_2 with electron paramagnetic resonance oximetry, they found synergistic combinations of hyperoxygenation and radiotherapy.

- Harold Swartz; Benjamin Williams; Ann Barry Flood, PhD; and colleagues are developing a field-deployable physical biodosimetry device to measure radiation exposure using electron paramagnetic resonance dosimetry measurements of teeth and fingernails. This approach represents the most advanced physical biodosimetric technique. The project has been funded by two federal agencies and is being accomplished with collaboration from General Electric plus five other academic institutions in the U.S. and abroad.

- Brian Pogue and Keith Paulsen continue to develop MR-guided near-infrared spectral tomography (NIR) for diagnostic imaging of women with breast screening abnormalities. In clinical use is a 4-channel, custom MR/optical breast coil with a parallel-plate, fiber-optic tissue interface capable of remotely activated fiber positioning, which provides for the first time the option of multiplanar optical data acquisition in the MR scanner.

- Brian Pogue and colleagues continue to develop a new breast-imaging modality that combines functional parameters obtained through NIR with high-resolution 3D structural information from breast tomosynthesis.
Keith Paulsen: Collaborating his way to flabbergasting research results

Don’t try to charge Keith Paulsen, PhD, with lacking passion for his work or with having humdrum research interests. Passion is clearly not wanting in someone who regularly uses words like “eye-popping” and “flabbergasted.” And a research portfolio that includes fluorescence-guided neurosurgery can hardly be called humdrum. (It was when Paulsen first saw fluorescence defining the margins of a brain tumor that he was “flabbergasted.”)

But a charge that might stick is that of being a multitasker. Paulsen is the Robert A. Pritzker Professor of Biomedical Engineering at Dartmouth’s Thayer School of Engineering; a professor of radiology at Dartmouth’s Geisel School of Medicine; codirector of Norris Cotton’s Cancer Imaging and Radiobiology Research Program; director of Dartmouth-Hitchcock’s Advanced Imaging Center; and—the latest addition to his list of titles—codirector of the Advanced Surgical Center (ASC), a joint project of D-H, Geisel, and Thayer.

The ASC—a $20-million, 12,000-square-foot facility on D-H’s Lebanon, N.H., campus—opened in November 2012. It is the only U.S. facility of its kind dedicated to translational research. At any academic
medical center, access to operating rooms and imaging suites for research purposes is severely constrained, since patient-care priorities come first. But with a surgical center devoted to research, Dartmouth investigators have unprecedented access to space and equipment for developing and refining novel technologies and interventions.

The ASC—which Paulsen heads with Sohail Mirza, MD, MPH, the chair of orthopaedic surgery—includes two operating rooms with portable MRI and CT equipment that can be moved in and out of the ORs on overhead tracks; one OR also has space for robotic-arm angiography. This allows intraoperative imaging to be performed during surgeries, without moving the patient. The ASC also contains intraoperative ultrasound and optical imaging, data collection tools, and novel measurement technologies. With the opening of the facility, dozens of federally funded research projects are poised to benefit from its resources—projects in fields ranging from intraoperative tumor imaging to in vivo optical microscopy.

The collaboration between Dartmouth’s engineering and medical schools dates back to the 1960s. So Paulsen—who earned his doctorate in engineering at Dartmouth in 1986, after completing his undergraduate degree in biomedical engineering at Duke—has spent decades in a culture where disciplinary, departmental, and even school boundaries are fully permeable. The fluorescence-guided neurosurgery project is a case in point. Paulsen has been working on it for years with David Roberts, MD, the chief of neurosurgery at D-H. “I work with Keith more closely than I do with most of my medical colleagues,” says Roberts. “We’re part of the same team.”

Make “team player” another charge that would stick to Paulsen.

Harold Swartz: Measuring radiation in the real world

If a terrorist detonated a nuclear weapon on U.S. soil, it would be hard for emergency responders to figure out who needed treatment for radiation exposure and who didn’t. That’s because symptoms of irradiation don’t always appear right away or correlate with the degree of exposure. Lab tests can give more precise estimates, but they are “wildly impractical” after a major event, says Harold Swartz, MD, PhD, codirector of the CIR Research Program and director of the Dartmouth Biodosimetry Center for Medical Countermeasures Against Radiation (Dart-Dose).

So Swartz has been leading a team of physician-scientists and engineers in the development of devices that estimate an individual’s exposure to ionizing radiation by screening their fingernails and teeth. Swartz first suggested the concept in the 1960s. Today, thanks to support from a number of funders and collaborators, including General Electric and a $16.6-million grant from the National Institutes of Health, Dart-Dose has developed both tooth and nail dosimeters.

The more advanced device is the tooth dosimeter; it detects the concentration of unpaired electrons in tooth enamel—a measurement that correlates with radiation exposure. A tooth dosimeter is now being built for potential inclusion in the national strategic stockpile.

The group’s aim, says Swartz, is to build “real devices that fit into the real world.”
Cancer Mechanisms Program

The mission of the Cancer Mechanisms (CM) Research Program is to foster interdisciplinary collaborations and to accelerate progress along the translational continuum between gene discovery and genotype-informed molecular treatments.

The emphasis within the CM Program is on the definition of pathways that present opportunities for improved cancer diagnosis, classification, prevention, and treatment. All members of the program have scientific interests in basic cancer mechanisms, including the normal function of proto-oncogenes and tumor suppressor genes; the regulation of the cell cycle and of apoptosis (cell death); the regulation of angiogenesis and of metastasis; and stem cells and blood formation.

Members work synergistically to add value to these basic investigations by channeling their intellectual efforts, their collaborative relationships, their use of shared resources, and their developmental funds toward translational goals. These goals include molecular disease classification, the identification of basic cellular pathways and of mechanisms that provide opportunities for drug targeting, and the complex interactions of small molecules and genotypes in the processes of carcinogenesis.

The work of the CM Program runs the gamut from basic bench research to clinical research to population research, then back to the bench. Its ultimate goal is the elucidation of cellular and molecular processes that govern cell and developmental biology, and the consequences of their subversion in cancer.

The members of the program fall into three major groups—one focused on gene expression studies, one on cell and developmental biology, and one on cancer models. The membership represents experts in a range of fields, from genetics, biochemistry, and chemistry to microbiology, pharmacology, and immunology.

Cross-cutting themes within the Cancer Mechanisms Program include the identification and characterization of genetic and epigenetic lesions that correlate with or are causally related to specific features of cancer; the development of cancer models; genetic, genomic, biochemical, and proteomic analysis of carcinogenic processes; and bidirectional translational research.
Geneticist Yashi Ahmed, MD, PhD, center, pictured here with two postdocs in her lab, has been a member of the Cancer Mechanisms Research Program since 2002.
Using quantitative mass spectrometry, members of the CM Program mapped 33,017 phosphorylation sites on 6,061 different proteins during mitosis. The results generated insight into the mitotic functions of previously unknown substrates of certain kinases.

The Programs Cancer Mechanisms

Significant recent achievements of the CM Research Program

Members of the Cancer Mechanisms Research Program have recently marked a number of significant happenings, including the following:

- Yashi Ahmed, MD, PhD, and colleagues found a mechanism that regulates beta-catenin-TCF signal transduction. Ahmed and her team identified a conserved protein, called Earthbound/Jerky, that helps regulate the chromatin association of beta-catenin and TCF in response to Wnt signaling. The Wnt signaling pathway is important for developmental decisions in many tissues and, when hyperactivated, can cause colorectal cancer. Using a genetic approach in the Drosophila model system, the team found that mutations of Jerky in humans are associated with juvenile myoclonic epilepsy. This finding reveals a new mechanism for regulatory control of the conserved Wnt signaling pathway through the tissue-specific expression of Jerky.

- Patricia Ernst, PhD, the codirector of the Cancer Mechanisms Research Program, was elected to the board of directors of the Society for Hematology and Stem Cells. (See page 64 for more on Ernst’s career.)

- Scott Gerber, PhD, and colleagues identified the aurora and polo-like kinase phosphoproteomes during mitosis in human cells. The structural changes that occur in cells that are needed for chromosome segregation are driven largely by protein phosphorylation by conserved protein kinases. Using quantitative mass spectrometry, Gerber’s group mapped 33,017 phosphorylation sites on 6,061 different proteins during mitosis. They employed selective chemical inhibitors to connect 778 of these sites from 562 proteins to the activities of protein kinases of the aurora or polo-like kinase families. The results provided a comprehensive phosphorylation map of the proteome in human cells during mitosis and generated insight into the mitotic functions of previously unknown substrates of these kinases.

- Duane Compton, PhD, and colleagues discovered that CLASP1, astrin, and Kif2b form a molecular switch that regulates kinetochore-microtubule dynamics to promote mitotic progression and fidelity.

- Vincent Memoli, MD, and colleagues, including members of both the Cancer Control and the
Molecular Therapeutics Research Programs, found that the enzyme lipoprotein lipase links dietary fat to solid tumor proliferation.

- Amy Gladfelter, PhD, and colleagues identified the structural organization of septin filaments in live cells, showing that they exhibit a dynamic, paired organization that is conserved from yeast to mammals.
- James Moseley, PhD, a new member of the CM Program who trained in the lab of Nobel Laureate Sir Paul Nurse at Rockefeller University, was one of just 22 scientists nationwide named a 2011 Pew Scholar in the Biomedical Sciences, a prestigious early-career award. Moseley’s research involves the use of fission yeast as a model system to study how growth-control mechanisms are regulated during the cell cycle.
- Ethan Dmitrovsky, MD, and colleagues discovered a therapeutic approach to destabilize the PML/RAR-alpha transcription factor, inhibiting the growth of acute promyelocytic leukemia.
- Ethan Dmitrovsky, who is also a member of the Cancer Epidemiology and Chemoprevention Research Program, was appointed chair of the National Cancer Institute’s Board of Scientific Counselors for Clinical Sciences and Epidemiology. (See page 80 for more on Dmitrovsky’s career.)
- The Cancer Mechanisms Program hosted the second annual multi-center Genome Instability and Cancer Symposium in July 2011. A cooperative initiative among Norris Cotton Cancer Center, the University of Massachusetts, the University of Vermont, and the Jackson Laboratory in Maine, this annual meeting fosters interactions and collaborations among investigators associated with other cancer centers in the region. The hosting of the symposium rotates among the participating institutions.
Ernst explains that the biggest problem with cord blood transplantation “is that there’s not enough cord blood from one baby to transplant an adult.” So that’s exactly where she has been focusing her research recently.

Patricia Ernst: Exploiting a hematopoietic pathway to improve cord blood transplantation

For patients with some cancers of the blood or bone marrow—such as multiple myeloma or some leukemias—a bone marrow transplantation (BMT) may represent their best therapeutic option. But BMT’s challenges, including identification of a suitably matched donor, and side effects, including graft-versus-host disease, have limited the use of the procedure to those whose condition is life-threatening.

Enter cord blood transplantation (CBT). Like bone marrow, the blood that remains in the umbilical cord and placenta after the birth of a baby contains hematopoietic stem cells—cells from which every component of the blood can be formed. CBT “has advantages over bone marrow transplantation when it comes to identifying donors,” says Patricia Ernst, PhD, who studies the regulation of hematopoietic stem cell development and maintenance. In addition, she explains, cord blood is more immunologically naive, reducing the threat of graft-versus-host disease. And, unlike harvesting bone marrow from a donor, collecting cord blood is “totally noninvasive,” adds Ernst.

But there are also drawbacks to cord blood transplantation. The biggest problem, Ernst explains, “is
James DiRenzo: Studying the mechanisms of breast cancer

You could say that the career of James DiRenzo, PhD, was built on a strong foundation—or, make that foundations: The V Foundation for Cancer Research, for instance. The Mary Kay Ash Charitable Foundation. The General Motors Cancer Research Foundation. The Susan G. Komen Breast Cancer Foundation. The Elsa Pardee Foundation. Those are among the organizations that have supported DiRenzo’s work since his arrival at Dartmouth in 2001.

It was DiRenzo’s department chair, Ethan Dmitrovsky, MD, who advised him, because of his focus on breast cancer, to start off by going after foundation grants. DiRenzo studies normal and cancerous stem cells in the breast, the genetic control of stem cell renewal, and the cellular and genetic mechanisms of adult epithelial stem cells.

That funding approach was clearly the right strategy. “I think some of the best publications that have come out of our lab have . . . originated with private foundation money,” says DiRenzo.

Today, his work is supported by the NIH and he is the codirector—with Patricia Ernst, PhD—of Norris Cotton’s Cancer Mechanisms Program. In addition, as the scientific director since 2004 of the Comprehensive Breast Program, he plays a key role in translating research findings from the lab bench to the bedside.
The Programs
Immunology and Cancer Immunotherapy

Immunology and Cancer Immunotherapy Program

Norris Cotton’s Immunology and Cancer Immunotherapy (ICI) Research Program unites the efforts of basic and clinical immunologists in a cohesive, interdisciplinary environment. The program’s primary missions are to address important scientific questions in cancer immunotherapy and to facilitate the development of immunotherapeutic strategies for treating cancer.

The program brings together immunologists and cancer immunologists with established and experienced clinical investigators. They collaborate to design, execute, and complete Dartmouth-initiated immunotherapy trials for patients with a variety of cancers. The current focus of the ICI Program is to investigate basic mechanisms of the immune system’s interactions with tumor cells and of the nature of the tumor microenvironment, and to develop protective immune responses against malignancies.

While basic science is at the core of the ICI Program, most of the program’s members are actively involved in bench-to-bedside research to translate their findings into the clinic. Other members are hematologists, oncologists, and transplant physicians who participate in the conduct of patient trials—both passive (T cell adoptive therapy) and active (dendritic immunization)—against myeloma, melanoma, colorectal cancer, glioblastoma multiforme, and renal cell carcinoma. Although much of the work within the ICI Program is laboratory-based, the monthly meetings of the program’s members are disease-focused.

Ongoing investigations within the program include studies of natural immunity to cancer, the tumor microenvironment, the function of dendritic cells, molecular adjuvants, and scavenger receptors. This work has been translated into early-phase correlative and therapeutic clinical studies of both molecular and cellular vaccines.

In accomplishing this work, ICI members make extensive use of a number of the Cancer Center’s shared resources, including the Office of Clinical Research, Immune Monitoring and Flow Cytometry, Optical Cellular Imaging, Irradiation and Small-Animal Imaging, Pathology Translational Research, and Biostatistics.
Kenneth Meehan, MD, head of Dartmouth-Hitchcock’s Blood and Marrow Transplant Program, also codirects the Immunology and Cancer Immunotherapy Program.
Members of the Immunology and Cancer Immunotherapy Research Program have recently logged a number of significant accomplishments, including the following:

- Richard Barth, MD, continues to lead a project aimed at creating personalized vaccines for patients with colorectal cancer. The team creates vaccines from a patient’s own tumor cells—harvested after surgical resection of metastatic tumors—to try to prevent additional metastases. The vaccines use dendritic cells to induce the antitumor response. The researchers grow dendritic cells from a sample of the patient’s blood, mix them with proteins from the patient’s tumor, and inject the mixture into the patient as a vaccine. In an early clinical trial, the vaccines stimulated a T-cell antitumor response.

- Dartmouth was named a founding member of the NCI-funded Cancer Immunotherapy Trials Network. Kenneth Meehan, MD, and Marc Ernstoff, MD, are the principal investigators for this project.

- Mary Jo Turk, PhD; Edward Usherwood, PhD; and Marc Ernstoff demonstrated in a mouse model that autoimmune melanocyte destruction is required for robust CD8+ memory T-cell responses to melanoma. Such responses are sometimes accompanied by melanocyte death, leading to the development of vitiligo—white patches on the skin or hair. Melanoma patients with vitiligo have been shown to have an improved prognosis, but it’s been unknown whether the autoimmune killing of melanocytes enhances the immune responses to melanoma. Using a melanocyte-deficient mouse model of melanoma, the team found that antigens released during melanocyte destruction directly support and maintain T-cell responses to melanoma, establishing that immunotherapies can be effective even in the absence of melanocytes.

- Charles Sentman, PhD, and colleagues reported a novel bispecific reagent that can be effective in tumor immunotherapy. This bispecific molecule binds to anti-CD3 to activate T cells and uses NKG2D to bind to tumor cells. This molecule does not contain an Fc portion, so it cannot bind to FcR+ cells, and this may be a reason for its reduced toxicity. BiTEtype molecules are effective at very low doses, so toxicities are low compared to conventional bispecific reagents or larger antibody molecules. The ligands for NKG2D are expressed on a variety of tumors, so this reagent may be useful against a number of cancers; the study showed it could be used against models of colon cancer and lymphoma.

- Mary Jo Turk, PhD; Edward Usherwood, PhD; and Marc Ernstoff demonstrated in a mouse model that autoimmune melanocyte destruction is required for robust CD8+ memory T-cell responses to melanoma. Such responses are sometimes accompanied by melanocyte death, leading to the development of vitiligo—white patches on the skin or hair. Melanoma patients with vitiligo have been shown to have an improved prognosis, but it’s been unknown whether the autoimmune killing of melanocytes enhances the immune responses to melanoma. Using a melanocyte-deficient mouse model of melanoma, the team found that antigens released during melanocyte destruction directly support and maintain T-cell responses to melanoma, establishing that immunotherapies can be effective even in the absence of melanocytes.
autoimmunity is a critical component in lasting immune responses to cancer. (See page 88 for more about Turk’s work in this area.)

- Marc Ernstoff, Mary Jo Turk, and Constance Brinckerhoff, PhD, have also been studying a mutant BRAF gene in melanomas—B-RAF(V600E). A common gene mutation in melanoma, it can be treated successfully, at least for a while, with BRAF inhibitors. The team has been examining whether targeted B-RAF(V600E) inhibition alters the immunogenicity of melanoma tumors in vivo and whether B-RAF(V600E) and MMP-1/PAR-1 signaling cooperate to enhance both tumorigenesis and metastasis of melanoma cells and the expression of MAPK-induced chemokines, cytokines, and growth factors in B-RAF(V600E) cell lines as compared to BRAF wild-type melanoma cell lines.

- In a collaboration between basic scientists and clinicians, Kenneth Meehan, Marc Ernstoff, and Charles Sentman published the results of a clinical trial of myeloma patients who received a blood stem cell transplant. The patients’ own cells were grown in the lab into aggressive killer cells, which were reinfused into the patients at four points following the transplant.

- In addition, Kenneth Meehan and colleagues demonstrated that a simple blood test can predict a patient’s risk of developing complications after a blood stem cell transplant just as well as multiple bone marrow evaluations. The blood test also predicted patients’ risk of relapse.

- Dartmouth’s NIH-funded Immunology COBRE (Centers of Biomedical Research Excellence)—known as the Center for Molecular, Cellular and Translational Immunological Research—continues to support cancer immunology research, including much work within the ICI Program.
For 25 years, scientists tried to produce effective vaccines against cancer. Finally, many concluded it was an approach doomed to failure. But now, active vaccines and other targeting therapies able to unleash an immune response are revolutionizing cancer treatment.

Humans have two immune systems, innate and adaptive, explains Randolph Noelle, PhD. Both need to be engaged to trigger a therapeutic response to cancer. The innate system provides the first line of defense against pathogens, responding almost immediately when a viral or bacterial invader enters the body. This response is prompted by proteins called toll-like receptors (TLRs). When they recognize a pathogen, they bind it, leading to swelling and fever—signs that the body is trying to fight off a threat. This initial response is critical. “You’ve got to be able to initiate the immune response within minutes to hours,” says Noelle. “You’d be dead without your innate immune system.” There are now synthetic drugs, called TLR agonists, that can trigger this system.

The adaptive immune system is more sophisticated and precise and engenders specific, long-lasting immunity. Its trigger is CD40, and, as with the innate system, synthetic drugs called CD40 agonists can activate it.

Randolph Noelle, PhD, discovered an important immune system inhibitor and is now developing drugs to target it.
Using either TLR or CD40 agonists as cancer vaccines in human clinical trials has proven ineffective at inducing protective therapeutic immunity. However, studies in experimental animals have demonstrated that TLR and CD40 agonists synergistically enhance the immune response to cancer antigens and can elicit protective immunity.

Active vaccines against cancer can be likened, says Noelle, to “stepping on the gas” in an attempt to trigger the immune system to eradicate a tumor. But recent findings have shown that in cancer patients, the immune system always has its “foot on the brake.” One reason the body doesn’t naturally mount protective immune responses to cancer is that negative checkpoint regulators temper immunity; this is why previous cancer vaccines failed. The proof of principle that this is what thwarts therapeutic immune responses to cancer comes from the success of ipilimumab, an antibody that blocks negative signals through CTLA-4 (the brake) and liberates T cells to kill tumor cells; it is the first new drug approved for late-stage melanoma in decades.

Noelle’s lab has discovered another important negative regulator called VISTA. VISTA appears to be highly and widely expressed in the tumor microenvironment, and it shuts down the ability of T cells to kill tumor cells. With engagement from the pharmaceutical and biotech industries and others, Noelle is leading an effort to produce drugs that block VISTA—in the hope of generating the first therapeutics that target VISTA for the treatment of human cancers. “We have learned,” says Noelle, “how to ‘step on the gas’ and ‘take our feet off the brake’ so as to unleash and unrestrain the immune system to eradicate primary and metastatic cancer.” It may have taken a while, but a quarter-century of work is now showing spectacular clinical results.

**Marc Ernstoff: Pitching the value of clinical research**

The word “sales” is rarely, perhaps never, used in the titles of academic physicians. Marc Ernstoff, MD, is no exception. He is Norris Cotton’s associate director for clinical research, as well as a professor of medicine. But make no mistake about it, his position involves sales. And he’s good at it.

He has to be. It’s a tough climate today for clinical researchers—practicing physicians who both care for patients and do research involving patients with cancer. The challenges include money to fund studies (of which there’s less and less), time (ditto), and paperwork (of which there’s more and more, albeit for defensible reasons involving patient safety and confidentiality). Yet Ernstoff is relentlessly upbeat in his pitches to would-be clinical investigators, inviting them to become part of today’s “explosion” of knowledge.

There are also behind-the-scenes aspects to Ernstoff’s role, including overseeing the infrastructure that supports clinical research, mentoring young investigators, and fostering connections among faculty with similar research interests.

While doing all of that, he also conducts research of his own—studying the immunobiology of cancer and conducting clinical trials, primarily involving patients with melanoma and renal cell cancer. Translational research is also embedded in his clinical practice. See page 33 for the story of one of his patients; it makes it clear why he’s so good at his “sales” job. •
Molecular Therapeutics Program

The goals of Norris Cotton’s Molecular Therapeutics (MT) Research Program are to foster cooperation, collaboration, and the exchange of ideas leading to the translation of basic research hypotheses and observations into the clinic, as well as to use basic research to answer clinical questions related to improving strategies for the treatment of cancer.

The MT Program advances these goals by providing a forum for the discussion of new developments in cellular and molecular biology—with a particular focus on studying cell cycle regulation, signal transduction, apoptosis, and cellular differentiation, then subsequently on developing potentially novel therapeutic strategies within these areas of exploration.

The preclinical phase of this work includes target identification, drug discovery, and evaluation of the mechanisms of drug action. Work in the clinical phase includes correlative clinical trials to predict therapeutic outcomes; examination of the pharmacodynamics and pharmacokinetics of potential therapeutic agents; and the eventual conduct of therapeutic clinical trials.

The MT Program aims to have an impact on clinical practice through many avenues, including the study of molecular markers for diagnosis or prognosis and the stratification of patients in future clinical trials. A key cross-cutting theme guiding the program’s activities is a focus on bidirectional translational research.

Accordingly, a longterm emphasis within the program has been on conducting early translational clinical trials; for example, the MT Program’s Phase I oncology group has examined a variety of therapies in patients with normal and abnormal liver function as well as combined modality therapies.

To facilitate this work, the members of the MT Program meet in multiple settings. The membership meets in its entirety on a monthly basis. In addition, several smaller focus groups meet regularly; one of the newer focus groups, for example, brings together investigators who are interested specifically in the subject of lipogenic signal transduction. Another forum for discussion among members of the MT Program is the Phase I clinical trials group, which meets weekly.
Alan Eastman, PhD, director of the Molecular Therapeutics Program, confers here with Kristen Garner, PhD, who did her doctoral research in Eastman’s laboratory.
Members of the Molecular Therapeutics Research Program have recently reported a number of significant findings, including the following:

- Alan Eastman, PhD; Alexei Kisselev, PhD; Alexandre Pletnev, PhD; and colleagues established that inhibition of BCL2 with ABT-737 can dramatically sensitize some leukemia cell lines and chronic lymphocytic leukemia cells to vinblastine. The same study established that other purported small molecule inhibitors of BCL2 family proteins do not inhibit these proteins in tumor cells. This has resulted in a proof-of-principle trial in chronic lymphocytic leukemia led by Alexey Danilov, MD, PhD.

- Alexei Kisselev, Alexandre Pletnev, and colleagues developed a series of novel proteasome inhibitors that are selective for each of the three proteolytic sites within the proteasome, permitting analysis of the relative importance of inhibiting each site for cytotoxic activity. The antimyeloma agents bortezomib and carfilzomib primarily inhibit the chymotrypsin-like site. The team demonstrated that inhibitors of the caspase-like site sensitize malignant cells to inhibitors of the chymotrypsin-like site and developed specific cell-permeable inhibitors and an activity-based probe for the trypsin-like site. These compounds also sensitize multiple myeloma cells to inhibitors of the chymotrypsin-like site, including bortezomib and carfilzomib. Thus the trypsin-like site is now recognized as a cotarget for anticancer drugs. This provides a set of tools to separately modulate each of the proteasome sites in living cells.

- Yolanda Sanchez, PhD, and colleagues discovered novel small molecules that target neurofibromin loss in malignant peripheral nerve sheath tumor (MPNST) cells. The team identified a lead compound, plus a possible target pathway for MPNST associated with neurofibromatosis type 1 (NF1), which is caused by a mutation in the gene encoding neurofibromin. The team demonstrated a model system to identify and validate target pathways by which NF1 loss drives tumor formation.

- Michael Spinella, PhD, and colleagues discovered that a poorly characterized member of the serine/threonine kinase family, STK17A, is a novel p53 target gene. This work identified and characterized STK17A as a modulator of cisplatin toxicity and reactive oxygen species in testicular cancer cells.

- William Kinlaw, MD; Burton Eisenberg, MD; and colleagues (including members of Norris Cotton's...
Cancer Mechanisms and Cancer Control Research Programs) determined that many tumor cells can acquire essential fatty acids from circulation by secreting the enzyme lipoprotein lipase (LPL) and expressing CD36, the channel for cellular fatty acid uptake. This acquisition bypasses attempts to slow tumor growth by inhibiting de novo lipid synthesis, thus fueling tumor growth. The mechanism was studied in various tumor tissues and in HeLa cells.

- Burton Eisenberg and colleagues translated this finding into a clinical trial. They tested the hypothesis that conjugated linoleic acid (CLA) can suppress Spot 14 (S14), a central regulator of the lipogenesis phenotype. The trial was performed in a neoadjuvant setting in 24 breast cancer patients, comparing S14 expression in the diagnostic biopsy to the subsequent surgical resection following consumption of CLA for at least 10 days. The results suggest that CLA causes significant suppression in the level of S14 in breast cancer tissue, but not in the levels of fatty acid, synthase, or LPL.

- Lionel Lewis, MB, BCh, MD, analyzed plasma from the patients in this trial to measure their CLA concentrations at the time of surgery and to compare those concentrations with the observed effects on S14 expression.

- Frederick Lansigan, MD, and Mark Spaller, PhD, have expanded the program’s work on lipogenesis into additional arenas. Lansigan is investigating the role of LPL in chronic lymphocytic leukemia. And Spaller is screening for novel peptide inhibitors of LPL and CD36. Spaller’s primary focus has been synthesizing peptides that bind to PDZ domains of proteins; he has also collaborated with other Cancer Center members on testing peptide-based compounds—including with Ethan Dmitrovsky, MD, to identify inhibitors of UBP43, and with Mark Israel, MD, to identify inhibitors of Id2.
If she’s talking to an audience of scientists, Yolanda Sanchez, PhD, will describe in detail the signaling pathways that regulate cell division and the cellular mutations that lead to cancer.

But if she’s talking to an audience of nonscientists, she shifts gears as smoothly as a race car driver and explains her work using accessible analogies—for instance, comparing a cancerous cell to a race car engine. She understands, in other words, that while the advances that she makes at the lab bench are very important, so, too, is ensuring that the general public understands the implications of those advances.

She used the engine analogy in remarks to a group of Cancer Center supporters. “When you soup up an engine to make it more powerful,” she explained, “at the same time as you get more power, you also create vulnerabilities.” For example, she continued, the souped-up engine might use more fuel or might run at a higher temperature.

Then she asked her audience to imagine that a mutated cell—a cancerous cell—is a souped-up engine. Just like the altered engine, she explained, the altered, cancerous cell has vulnerabilities. “These vulnerabilities are
called the Achilles heel” of cancer, she says. The focus of her work is identifying those vulnerabilities and exploiting them to combat cancer.

In a recent study, she rewired normal cells with a cancer-causing mutation in the RAS signaling pathway, then exposed those cells, together with normal cells, to thousands of potential drug-like molecules. “The goal,” she told the audience of supporters, “was to find drugs that would kill or stop the growth of the rewired cell but would spare the normal cell. . . . The results of our studies exceeded our expectations,” she continued. “We found two dozen compounds that killed or stopped the growth of rewired cells but didn’t do anything to normal cells.”

These were significant findings, she explained, because many current treatments “are toxic to both the normal cell and the tumor cell. This is what causes the toxic effects—the side effects—of the therapies that are used today.” Of perhaps even more significance, Sanchez pointed out, is the fact that mutations in the RAS pathway are responsible for 30% of lung cancers, almost all pancreatic cancers, a subset of colon cancers, and a subset of brain cancers—“some of the most aggressive brain tumors, called gliomas.”

Many steps remain for Sanchez and her team before the findings can be applied clinically: identifying exactly what part of the cells the drugs are targeting; testing the drugs’ toxicity in animal models; and then, ultimately, conducting clinical trials. Nevertheless, Sanchez said, “we’re very excited about the implications of these findings.”

Not surprisingly, given her skill at explaining the science she does, Sanchez doesn’t spend all her time at the lab bench. She is also, in her role as associate director for basic sciences, one of the Cancer Center’s senior leaders. **Konstantin Dragnev: Improving the odds for patients**

As a thoracic oncologist, Konstantin Dragnev, MD, sees lots of patients with lung cancer. “About a third of patients with lung cancer have KRAS mutations,” he explains. “For them, targeted therapies do not work well. These patients have a bad prognosis.” But as a researcher, he has been able to do something to improve the odds for such patients. A graduate of the Higher Institute of Medicine in Sofia, Bulgaria, Dragnev came to the U.S. in 1991 for a research fellowship at the National Cancer Institute. After completing a residency at Baylor, he returned to the laboratory as an oncology fellow at Memorial Sloan-Kettering Cancer Center.

He arrived at Dartmouth in 1998 with an interest in bridging the gap between his work in the lab and his work in the clinic. Recently—in collaboration with Ethan Dmitrovsky, MD, and others—Dragnev has overseen trials for a novel drug combination that represents a promising treatment option for lung cancer patients with KRAS mutations (see page 84 for more on this work).

He calls the collaboration “true translational work. . . . as opposed to having a separate camp of laboratory researchers and a separate camp of clinical researchers. . . . You can see,” adds Dragnev, a 2012 finalist for the prestigious Schwartz Center Compassionate Caregiver Award, “how something happening in the laboratory is actually helping patients.”

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*Konstantin Dragnev, MD*
The People

It’s people who are at the heart of Norris Cotton’s success. People like clinician-scientist Ethan Dmitrovsky. Like tumor immunologist Mary Jo Turk. Like outcomes expert Bill Black. Like all 150 or so members of Norris Cotton’s research programs. Like the students, postdocs, and technicians who populate the members’ labs. Like the hundreds of physicians, nurses, and other caregivers. Whether they’re batting ideas around a seminar room, analyzing data at a lab bench, or collaborating at a tumor board meeting, Norris Cotton’s people are its core.
Ethan Dmitrovsky, MD: “A service mentality”

Everyone wants a piece of Ethan Dmitrovsky—the National Cancer Institute, the American Cancer Society, the faculty in the department he chairs, the fellow clinician-scientists with whom he collaborates, the students who populate his lab—but he never betrays an iota of impatience. His attention is always fully on whomever he’s speaking to at the moment. His tone is always measured. He exudes calm and patience.

Yet given the schedule he keeps, Dmitrovsky could be more than forgiven for an occasional expression of distraction or stress. He chairs the National Cancer Institute Board of Scientific Counselors. He holds a prestigious American Cancer Society Clinical Research Professorship. He is associate director of the Samuel Waxman Cancer Research Foundation and a member of the board of the Lance Armstrong Foundation. He chairs the Department of Pharmacology and Toxicology at Dartmouth’s Geisel School of Medicine. He holds the endowed Andrew G. Wallace Professorship. He is co-director of Norris Cotton Cancer Center’s Cancer Epidemiology and Chemoprevention Research Program. He is a practicing oncologist. He has served on a number of high-level Dartmouth search committees, including the one that recruited Cancer Center director Mark Israel, MD. And, not incidentally, he runs a very active lab that conducts bidirectional translational research.

But despite the influential circles in which Dmitrovsky moves, he seems to be most at home in his lab. And he always has time for students or postdocs who want to analyze the results of their latest experiment or mull over the next step in their career. Indeed, he seems utterly devoted to ensuring that the trainees he’s surrounded himself with get as much satisfaction out of doing research as he does.

Students are “unabashedly enthusiastic about what they do,” Dmitrovsky says. “It’s an infectious quality,” something “you can’t bottle and you can’t buy.” And his students are just as unabashed in returning the compliments. Fadzai Chinyengetere, for example, an MD-PhD student, chose Dmitrovsky as her thesis advisor because “he takes the time within his busy schedule to
Ethan Dmitrovsky, MD, right, holds many prestigious posts—but he’s never too busy to spend time with trainees like MD-PhD student Fadzai Chinyengetere, left.
interact with each and every member of the lab, to find out what's going on and how he can help.”

“How can I help?” might, in fact, be Dmitrovsky’s mantra. When Dartmouth’s president asked him to be acting dean of the medical school during the 2002-03 academic year, he agreed “out of a sense of service.” But he didn’t want to be considered for the deanship on a permanent basis because that would have taken him away from his research and his ability to “participate in the life sciences revolution.”

The purpose of scientific discoveries, Dmitrovsky firmly believes, “is to serve the public good.” For 25 years and counting—previously at Memorial Sloan-Kettering Cancer Center, where he worked from 1987 to 1998, and since 1998 at Dartmouth—his lab has been investigating the role that retinoids, natural and synthetic derivatives of vitamin A, play in cancer. Retinoids help regulate cell growth and differentiation and have shown promise in both preventing and treating various forms of the disease.

While he was still at Sloan-Kettering, Dmitrovsky’s lab and several clinical colleagues were the first in the nation to report that retinoids triggered remission in a very rare but lethal form of cancer—acute promyelocytic leukemia (APL). The team identified the biochemical pathway by which retinoids could regulate the cell cycle, helped to clone an abnormal receptor linked to the rare leukemia, and developed a molecular test to diagnose APL; the findings were published, respectively, in the New England Journal of Medicine, the Proceedings of the National Academy of Sciences, and Cell. “This was one of the first successful examples of differentiation-based therapy,” Dmitrovsky explains. “When we began, only a minority of APL patients, about 20 to 25 percent, were cured. Now, over 90 percent are cured with retinoic acid-based therapy.”

But the disease was so rare that a few years later, when he did a Medline search for “retinoic acid” and “APL,” Dmitrovsky found that “there were, frankly, more papers published than there were patients with the disease.” He figured it was time to identify another scientific challenge. “There was a large body of literature that suggested that retinoic acid could be used to prevent cancers, especially of the lung,” he explains. So he turned from investigating an extremely rare disease to investigating one that is, he says, “the most lethal malignancy for men and women in our society.” More than 150,000 Americans die each year from lung cancer—more than from any other form of cancer—and the...
A five-year survival rate hovers around 16%. It was just the kind of meaningful challenge Dmitrovsky was seeking.

A deficiency of vitamin A had long been associated with the development of lung cancer in laboratory studies. So it would stand to reason, Dmitrovsky theorized, that rectifying that deficiency might be a way to prevent the formation of lung cancer. But clinical trials with retinoids had, until that point, been mostly unsuccessful in preventing lung cancer in smokers.

Then, he says, “just as I was coming to Dartmouth, we conducted a simple and incredibly informative experiment,” the results of which were published in the Proceedings of the National Academy of Sciences. First, his team “applied the very carcinogen that causes lung cancer” to immortalized human lung cells in the laboratory, demonstrating that “we can make cancers in the laboratory.” Next, they introduced retinoic acid to the cells before applying the carcinogen. “When we gave retinoic acid,” he says, “we prevented those cancers from forming.”

“To our surprise,” he continues, “we found that the very drug that we were studying activated a protein destruction path called the ubiquitin proteasome degradation pathway.” The pathway, he explains, “is the natural process that the body uses to degrade proteins,” and the drug was engaging it.

A few years later, Dmitrovsky’s team described the mechanism by which retinoids prevent lung cancer. In November 2005, he and colleagues published a paper in the Journal of the National Cancer Institute (JNCI) that identified a previously unknown retinoic acid receptor. Targeting it, the researchers hypothesized, might restore the beneficial effects of retinoids in lung cancer patients.

**A few facts about Ethan Dmitrovsky**

**Grew up** Roslyn Heights, on the north shore of Long Island

**Education** Harvard University ’76 (BS in biochemical sciences); Cornell University Medical College ’80 (MD)

**Training** New York Hospital–Memorial Sloan-Kettering Cancer Center (residency in internal medicine); National Cancer Institute (fellowships in oncology and biotechnology)

**Ambition in college** “I was thinking of medical school at that time, but I wasn’t thinking of having science a part of my career, frankly. I thought I was going to become a doctor in the community, practicing general medicine.”

**Journals on whose editorial boards he’s served** Journal of the National Cancer Institute, Cancer Prevention Research, Molecular Cancer Therapeutics, Clinical Cancer Research, Cancer Research

**Qualities he looks for in trainees** “The answer is quite simple—a fire in the belly. I would define that as there is no external stimulus for them to do their work—it’s all internal.”

**Number of people who’ve trained in his lab** “Over 100.”
cancer cells. “It turns out that that receptor is repressed in lung cancers,” says Dmitrovsky. “So the drug we were studying—retinoic acid—couldn’t possibly work in this disease because of this defect.” However, he knew that a drug related to retinoic acid, known as a rexinoid, could activate the same protein destruction pathway but bypass the defect. So Dmitrovsky and his team initiated a clinical trial “here at Dartmouth,” he explains, using “a rexinoid in conjunction with a second drug called Tarceva,” known generically as erlotinib.

This combination of drugs was tested in a Phase I clinical trial on 24 patients; for most of them, all other treatments had failed. Although “the expected median survival in this cohort of patients was about six and a half months,” says Dmitrovsky, “the median survival for this trial was over 14 months.”

Since then, Dmitrovsky has collaborated with colleagues at Dartmouth on four more clinical trials. In two trials completed in 2011, the team treated patients with a combination of two drugs—erlotinib and bexarotene. Both drugs inhibit a protein called cyclin D1, which is involved in the regulation of the cell cycle and is often overexpressed in lung cancer cells.

One trial enrolled 10 patients slated for surgery to remove tumors in their lungs. About a week before their surgery, biopsy samples were taken from the patients’ tumors, and the patients were then treated with the combination therapy until they underwent surgery. Tissue samples were again taken from the tumors after they were removed.

An analysis of the samples showed that 8 of the 10 patients’ tumors had lower levels of key proteins after a week on the drug therapy, including six with reductions in cyclin D1. And 8 of the 10 also showed evidence that tumor cells were dying.

At the same time, the researchers conducted a Phase II trial involving 40 patients with advanced non-small-cell lung cancer. The subjects’ median age was 67, most had already been through at least one round of chemotherapy, and many had a particular mutation in a gene known as KRAS. The average survival for such patients would be expected to be about 4 months, but the 40 patients in the trial survived an average of 5.5 months. There was no group of control patients who didn’t get the combination therapy, so it’s possible the increase in survival was due to other factors. But these results, along with the earlier trial and previous research, strongly suggest that the treatment helped.

“This is a promising regimen,” Dmitrovsky says.
“It’s not a cure for lung cancer, but we’ve taken highly refractory patients that normally would not be expected to respond—as is the case when KRAS mutations are present in lung cancers—and some of them have responded.”

There were some side effects, which was expected. After the treatment, most patients had elevated levels of triglycerides—a type of fat—in their blood, and many suffered a skin rash. If triglyceride levels rise too high, it can lead to pancreatitis, but no cases of pancreatitis were seen in the study.

And it turned out there was a benefit in these side effects: among patients who exhibited a rash or elevated triglyceride levels, the survival increase was even better—an average of 6 months.

While the clinical work continues, Dmitrovsky says, “we are also studying this regimen in the laboratory, trying to see whether this could be used to prevent lung tumors. 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,” he adds, “is being able to combine these together in the same career.”

Straddling both roles can be tough, however. “This is a long process, and it’s really hard,” he said several 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 . . . human trials, to final FDA approval, can take upwards of 15 years.” But there are satisfactions as well as challenges along that winding road. An important one came in 2011, when, “the very week we published our work, the M.D. Anderson Cancer Center, who had seen our Phase I study, independently confirmed our results.”

When Dmitrovsky talks about findings like these that come from his lab, he unfailingly uses plural pronouns—“our” and “we,” rather than “my” and “I.” “I do team science,” he says, in a rare use of the first-person singular. He counts many fellow faculty members—other translational scientists, bench researchers, and clinicians—among his collaborators. In fact,
he makes a point of noting that “all of this work has essentially been done here at Dartmouth.” Pathologist Vincent Memoli, MD, and oncologist Konstantin Dragnev, MD, for example, were key contributors to the 2011 clinical trials.

And, Dmitrovsky emphasizes, “students of all stripes,” from novice undergrads to seasoned postdocs, “are foremost in this effort. I look on students as my colleagues,” he continues. “I have a partnership model, so I encourage all of them to call me by my first name. Some of them feel uncomfortable doing that, but even if they call me Doctor, I treat them as any other professional.”

That model is recalled warmly by former students. Kristen Garner, who completed her PhD in pharmacology and toxicology at Dartmouth in 2010, recalls being impressed that Dmitrovsky was so approachable and unintimidating, even though he was the chair of the department. “He says he has an open door policy, and he really means it,” she says. Garner is now a strategy consultant in the life sciences arena at Health Advances, a global biomedical consulting firm.

“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 Neil Desai, a Dartmouth College ’05 who worked in Dmitrovsky’s lab as an undergraduate Presidential Scholar. “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 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,” adds Desai, who went on to medical school at Yale and a residency in radiation oncology at Memorial Sloan-Kettering. “He always pushed me to do better, to think more critically. 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. . . . I was more motivated and learned more there than I have with any other research or academic experience.”

“He has created an environment in his laboratory that’s very supportive of young people,” agrees W. Jeffrey Petty, MD, who did an oncology fellowship at Dartmouth-Hitchcock and worked in Dmitrovsky’s lab from 2002 to 2005. “He really started with a blank slate with
In both word and deed, Ethan Dmitrovsky, MD—pictured here with Lorenzo Sempere, PhD, right, a research assistant professor—evidences his regard for the work of everyone in his lab, from undergrads to fellow faculty members.

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 2005 *JNCI* paper, is now on the faculty at Wake Forest and is still contributing to retinoid research.

In fact, it wasn’t until he left Dartmouth that Petty appreciated the extent of Dmitrovsky’s reputation. “Ethan is very highly regarded on a national level,” Petty says. “Until you’re away from the institution, you don’t see that as clearly.” Upon realizing that, Petty was all the more surprised 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 credits his love of what he does to his own experiences as a student and trainee. When he was an undergraduate at Harvard, he did an honors thesis in the lab of cell biologist Daniel Goodenough, PhD, and in the process “became intrigued by the inquiry process.” As a medical student at Cornell, he volunteered with the Indian Health Service in Claremore, Okla., and with the International Rescue Committee in a refugee camp on the Cambodian-Thai border—experiences that helped shape his commitment to service. And when he was a resident at New York Hospital-Memorial Sloan-Kettering Cancer Center, the chair of medicine was legendary physician-scientist Ralph Nachman, MD, who, says Dmitrovsky, “has been an influential person in my entire career.”

“It’s a real privilege to work as a physician-scientist,” Dmitrovsky declares. “The idea of being able to use your intellectual ability to help others is really appealing. I found my career exciting and meaningful when I started,” he concludes, “and I find it ever more so now.”

Clearly, he gets what he gives. ●
Mary Jo Turk, PhD: “The accidental immunologist”

Don’t ever accuse Mary Jo Turk of being unwilling to change course. “The one thing I was exposed to in graduate school that I’d never really liked before was immunology,” recalls Turk, a tumor immunologist. “I never liked it,” she explains, “because it was so complicated. I didn’t really understand it—B cells, T cells, antibodies.”

Today, Turk most definitely likes the field she once gave the brush-off to. And “complicated” is no longer the way she characterizes B cells, T cells, and antibodies. In fact, she was still a postdoctoral fellow at Memorial Sloan-Kettering Cancer Center, in the lab of renowned tumor immunologist Alan Houghton, MD, when she began making a mark on the understanding of the complex mechanisms that both trigger and suppress the immune system’s response to cancer.

“When I was a postdoc,” she says, “we published a paper that was pretty important for the field. We showed that if you deplete this population of regulatory T cells, tumors can be more immunogenic.” Regulatory T cells suppress the immune system, so taking them out of the picture apparently jump-started the immune system. The finding was published in 2004 in the Journal of Experimental Medicine, “a very high-impact immunology journal,” notes Turk, who was the lead author on the paper.

“That paper has been cited numerous times,” she continues. “Prior to this, there had been a very few studies looking at regulatory T cells in tumors, but we took a tumor, a melanoma, that didn’t elicit any detectable immune response. We depleted its regulatory T cells,” she explains, “and showed that now we got a very strong immune response to this tumor.

“This was the work that got me the job at Dartmouth,” adds Turk, who joined the faculty in 2004 and is now an associate professor of microbiology and immunology and a member of Norris Cotton’s Immunology and Cancer Immunotherapy Research Program.

But what led her into immunology? Turk’s accidental entry into the field she “never really liked” began when she was a grad student in chemistry at Purdue. “I started out doing drug targeting,” she says. “We were using folic acid, which binds to cancer cells. We
Mary Jo Turk, PhD, right, enjoys dealing with grad students like Shannon Steinberg, left, who is working on a project funded by the Melanoma Research Alliance.
would link drugs to folic acid to target them to the folate receptor on cancer cells. It was interesting, but it was also so simple.” The hypotheses were straightforward, she recalls. “It was just too mechanical. It got really boring.”

Then a question arose that did pique her interest. “Somebody in my lab started targeting what’s called a hapten—it’s a small molecule that causes an antibody to bind—and this caused a dramatic response against the tumor. So we started thinking about the immune response to cancer in my lab.”

Turk was intrigued enough by the finding that she began looking at the immunology literature. But she was still having a hard time with the terminology and the concepts. “My thesis advisor was not an immunologist,” she says. “He didn’t really know any immunology. So I took an immunology course.” And, suddenly, the light shone on what she’d previously found incomprehensible. “For the first time, all these things—B cells, T cells, antibodies—they all converged into this beautiful, intricate system that I suddenly liked very much.”

This occurred just as Turk was nearing the end of her doctoral studies. “So I said, ‘Well, I have to decide where my research career is going.’ I started reading Cancer Immunology, and I said, ‘This is what I want to do.’” During her last year at Purdue, she turned her work “a little more to the immune system—we started targeting macrophages, which are a type of immune cell, because we found out that folate could target activated macrophages and reduce the course of arthritis.” Concluding that she was keen on this new direction, Turk decided to switch fields and try to find a postdoctoral position in immunology—and, while she was at it, “to apply to all the best labs in tumor immunology.”

“Back then, funding was pretty good,” Turk explains, “and immunology was a really rapidly growing field. These labs had positions available, even for someone who was a nonimmunologist.” She got interviews at about half a dozen of the places she’d applied to. But when the offer came from Houghton at Sloan-Kettering, Turk “had no question—that’s exactly where I wanted to go.” She describes him as a “brilliant, amazing individual. He was a melanoma doctor originally, an MD running a very large, very productive lab.”

Most of Turk’s work since then has involved melanoma—a malignancy of the skin’s pigment-producing melanocytes. Of the three kinds of skin cancer, melanoma is the least common but the most lethal. Turk’s focus on melanoma isn’t at all uncommon, however. In fact, many tumor immunologists work on melanoma.
Mary Jo Turk believes that focus arose because of a specious belief. “Some people, even people in my field, say melanoma is an immunogenic type of cancer,” meaning it is more responsive to immune activity than other cancers. “But I say we don’t know that,” asserts Turk. “I think that’s a false argument. People say that because there are spontaneous regressions of melanoma, it must be more immunogenic. Well, you don’t know if you have a spontaneous regression of a cancer like breast cancer, because you can’t see it.” But, she points out, “melanoma is a tumor you can see. It’s right there on your skin, so you can know if it spontaneously regresses.”

The claim is also made that “there are good antigens—meaning proteins that the immune system sees—for melanoma.” That, Turk argues, is simply because melanoma was the disease that immunologists began studying first, since it’s “such a horrible disease” with “nothing that worked” to treat it. “We’ve been working on immune therapies for melanoma for years. We know what we’re looking for,” she says. “We haven’t really tried this type of therapy in breast cancer, because there are other things that work.

“So,” Turk concludes, “I don’t think that we know which tumors are more immunogenic than others. Some people claim to know, but I would say we don’t know.”

Why, then, has she focused on the disease if she doesn’t agree with those who believe that it’s the ideal model for studying tumor immunology? She began looking at melanoma for professional reasons—following the conventional wisdom in immunology and following in the footsteps of her postdoc mentor. But her reasons for staying with melanoma took a
very personal turn a few years ago, when one of her aunts was diagnosed with the disease.

“I was very close with this aunt,” says Turk, so she was devastated when her aunt’s tumor was deemed inoperable and “her doctors offered only palliative treatments.” But Turk sprang into action. She contacted melanoma experts around the country, including several at Dartmouth, and discovered that her aunt’s tumor expressed a rare mutation—a mutation that was treatable with Gleevec, a drug that had made the cover of *Time* magazine in 2001 as a “magic bullet” against cancer.

Indeed, Turk calls her aunt’s response to the drug “amazing.” She had been bedridden, but after starting on Gleevec, “within a week she was out of bed, she was back to life.” Her aunt died a year later, but because of complications from surgery for a perforated intestine, not because of a recurrence of the melanoma.

So “now it’s personal,” Turk says about her work. “I’ve been touched by this cancer, very closely. I have so many reasons to be working on melanoma now.”

That renewed commitment appears to be paying off. Turk’s lab recently made two significant observations. One concerned the fine line between stimulating an immune response to a tumor but not causing an autoimmune reaction—in which the immune system attacks the body’s own cells because it has failed to distinguish them from those of a foreign invader.

Turk likens the challenge of trying to trigger the immune system but avoid autoimmunity to fiddling with a dimmer switch. “Some of our treatment tools are like a sledgehammer,” she says, “an on-off switch. We don’t have a good dimmer switch for just tuning it. It would be nice if we could get rid of these regulatory T cells such that we could get antitumor immunity without autoimmunity.”

Finding this balance has been a major problem for cancer immunologists. When immune cells called CD8 T cells are called to action, they use cell surface molecules called antigens as a guide to which cells to kill and which to leave alone. But because tumor cells and normal cells share many antigens, killer T cells often leave tumor cells free to grow.

Scientists had found that they could create an immune response against melanoma in mice by using an antibody to stimulate an immune cell receptor called GITR—but how it occurred was unclear. Turk had grown curious about the mechanism and decided to study it. She expected to find that the antibody worked...
by depleting regulatory T cells, which suppress the immune system and keep CD8 T cells in check. Having too many regulatory T cells can lead to problems fighting off threats such as cancer, but having too few can lead to autoimmune reactions.

To investigate how the antibody worked, Turk and her colleagues injected mice with melanoma and treated them with the antibody to stimulate GITR. They then injected the mice with melanoma again to see if the combined exposure to the first tumor and the antibody would provide protection against a second tumor. Indeed, the antibody offered strong protection from a second tumor without causing an autoimmune reaction. By comparison, when they used a different antibody, one known to deplete the supply of regulatory T cells, they were still able to induce protection against a second tumor, but the mice had an autoimmune reaction.

To clarify whether the antibody was working by activating CD8 T cells or by depleting regulatory T cells, they tried a different type of melanoma for the second tumor. The antibody did not then provide protection against a second tumor—because the CD8 T cells were using the antigens of the first tumor as a guide to know which cells to attack.

It was such a significant finding that Turk had one of her graduate students, Anik Côté, repeat the experiment a couple of times. Finally she was convinced that when GITR on CD8 T cells is stimulated with an antibody, it leads to the growth of killer T cells that can spot antigens specific to tumor cells rather than to shared antigens. “You get good, long-lived immunity without autoimmunity, and that has been a big challenge in the field,” Turk says.
A recent finding casts autoimmune responses in a much more positive light, at least for some cancers. “They’re not just an unwanted side effect,” explains Turk. “They’re a good thing. It’s changed our perspective.”

The finding was published in the *Journal of Immunology*. Her lab made a related finding a few months later—showing that modest autoimmune responses may actually have beneficial effects, at least in cancers of non-essential organs. If an autoimmune attack is triggered against cancerous skin cells or breast cells, for example, it’s not catastrophic because those tissues aren’t crucial to the organism’s existence. By contrast, explains Turk, in “liver cancers, well, you can’t really afford an autoimmune response,” because the liver is an essential organ.

So she realized that the control of that “dimmer switch” didn’t need to be quite so finely calibrated in cancers of nonessential organs.

In “a difficult set of experiments,” Turk says, another graduate student, Katelyn Byrne, showed that in “mice which get a normal primary response against a tumor, then the T cells just quiet down and don’t do anything—the T cells can’t maintain a robust, long-lived response to melanoma.” But in mice which exhibit an autoimmune response—evidenced by destruction of the melanocytes—there is a good immune response against the tumor. So the autoimmune response, which was originally thought to be just a side effect, turned out to be directly related to the subsequent therapeutic immune response. In other words, says Turk, the studies showed a causal effect—“that you need constant melanocyte killing to maintain T cell responses to melanoma.” That finding, which was published in *Clinical Investigation*, now casts autoimmune responses in a much more positive light, at least for some cancers. “They’re not just an unwanted side effect,” says Turk. “They’re a good thing. It’s changed our perspective of how to look at autoimmune disease in conjunction with cancer.”

When Turk talks about working with graduate students like Côté and Byrne, she lights up. “I love working with my students,” she says. “I like solving problems with them. I like teaching them how to set up experiments. I like interpreting data with them. I like seeing them get enjoyment out of a result that’s new and something they’ve never seen before. I like meeting with the lab and being like ‘Oh, look what you’ve found! What do we do from here?’ It’s so much fun.”

She waxes just as enthusiastic about her faculty colleagues. Phrases like “most exciting thing for me” and “ideas back and forth” and “colleague next door” and “just talking about our work” tumble out as she ticks off half a dozen fellow faculty members with whom she collaborates. “I love the people here that I work with,” she concludes. “It’s fun to solve problems with them.”
So what problem is Turk looking to solve next? Lately, she has been looking at a mutation in a protein called BRAF. The mutation “occurs in about 50 percent of melanomas,” she explains, so any therapy able to target cells bearing that mutation promises to benefit a substantial number of patients with the disease. “We’re trying to understand if inhibiting this protein has an immunological consequence. I don’t think I would have been interested in it had I not seen how amazing these therapies are,” she concludes, referring to treatments that are targeted at a specific mutation, like the therapy that her aunt received.

That personal experience, she says, has “given me kind of an advantage in the field, because a lot of immunologists were not thinking about these targeted therapies.” But her year of reading the clinical literature and of talking regularly with clinicians gave her a translational perspective that she is now carrying forward.

“We just got a grant from the Melanoma Research Alliance” for the BRAF work, Turk adds. Another grad student in her lab, Shannon Steinberg, is working on this project. “She has some really interesting data,” says Turk, “showing that these inhibitors have immunological consequences. It’s been very motivating. Of course now I’m very happy to be working on melanoma.”

And very happy that she ended up deciding to go into immunology. “The immune system is so much more detailed and so much more complicated than we thought even 10 years ago,” she says. “If you read a paper from five years ago,” it seems “completely outdated” today.

So when “students come to me now and ask, ‘Do you think I can go into tumor immunology?’ I’m like, ‘Absolutely! There’s no reason you can’t totally switch fields.’”

It’s obviously a good thing that Turk herself came to that conclusion back when she was in grad school.
William Black, MD: “A call to order”

William Black hadn’t even completed his training—he was still a resident in radiology, in the early 1980s—when he began to have some reservations about his chosen specialty. He’d started to feel that the field lacked rigor. “There seemed to be a lot of variation . . . in terms of what tests were done and how patients were managed,” he says. “I was looking for some order.”

Black had majored in mathematics as an undergraduate, so he took a logical, quantitative approach to solving problems. To someone of that mindset, the problems within radiology posed an attractive challenge.

At about the time he finished his residency, Black read a journal article that concluded that screening for lung cancer using chest x-rays did not reduce the risk of dying from lung cancer. In screening, people with no symptoms of a disease are checked for findings of an early stage of the disease. A common example is mammography. Every year, millions of healthy women who have no symptoms of breast cancer have x-rays taken to look for signs of emergent breast tumors.

“I, and most everyone I knew, just sort of assumed that early detection would lead to better outcomes,” says Black. So he was surprised when he read that screening for lung cancer with chest x-rays did not, in fact, reduce mortality. That paper inspired him to learn more about the use of screening in health care—and eventually to question many of the accepted assumptions about diagnosing disease. “If we can’t figure out something this basic, like whether or not it’s good to detect a lung cancer with chest x-rays when it’s small, versus when it’s larger, what are we sure about?” he asks.

The questions Black was posing were becoming increasingly relevant, because the tools available to radiologists were rapidly improving during the latter decades of the 20th century. New technologies—computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)—were allowing doctors to see more anatomical detail than ever before. But Black realized that better images did not necessarily lead to better outcomes for patients. “We know intuitively that the pictures are pretty,” he says. “They’re
In his research, William Black, MD, has worked to shed light on thorny questions—such as tradeoffs between the risks and the benefits of certain kinds of screening.
showing us more. The big uncertainty is . . . understanding how effective our interventions, our treatments, are—as well as if, and when, they should be used.”

He continued to test and refine his ideas on the subject while serving for four years on the faculty at the University of Virginia, then for three years at the National Institutes of Health, where he conducted health outcomes research. He was recruited to Dartmouth in 1991; a full professor of radiology since 2000, he is also a member of Norris Cotton’s Cancer Control Research Program. Not long after Black arrived at Dartmouth, another newcomer, H. Gilbert Welch, MD, MPH, heard Black give a talk on his research. Welch was impressed with Black’s thoughtfulness from the start. “He’s an extremely careful researcher who really raises some fundamental questions,” Welch says. “He expresses some of the most interesting and important ideas in medicine.”

Finding that they shared an interest in understanding the benefits of screening and in studying health outcomes, Black and Welch began a long and productive collaboration. Their work includes a concept now known as overdiagnosis—the identification of “pseudo-disease,” or nascent abnormalities that may not ever go on to cause harm. The findings they and others have made run counter to the seemingly intuitive precept that it’s always best to find and treat a disease early, before it causes a problem.

But that approach creates a self-perpetuating cycle, explains Welch. “If you look harder, all of a sudden it seems like there’s more people with disease, more reason to be looking for disease.” But in fact, he says, “you may be hurting people” by treating individuals who don’t need to be treated and thus exposing them to potentially harmful side effects.

In 2010, Welch and Black collaborated on a paper for the Journal of the National Cancer Institute summarizing their thoughts on overdiagnosis in cancer. Overdiagnosis, they wrote, is “the diagnosis of a ‘cancer’ that would otherwise not go on to cause symptoms or death.” They estimated that about 25% of breast cancers detected with mammograms represent overdiagnosis, as well as about 60% of prostate cancers detected with prostate-specific antigen (PSA) tests. Many such patients receive invasive treatments that expose them to potentially devastating side effects (such as incontinence or impotence in the case of prostate surgery), or even death, all for a “cancer” that would never have caused a problem.

But the confounding factor in the concept of overdiagnosis, Welch and Black noted in the paper, is that it can be conclusively identified only if a patient is not treated for cancer and eventually dies of a different cause.
can be conclusively identified only if a patient is not treated for cancer and eventually dies of a different cause. In other words, no one knows at the time of diagnosis whether a patient is being overdiagnosed. As a result, almost everyone with a positive finding on a screening test gets treated.

Black and Welch are also careful to point out that their findings don’t imply that patients shouldn’t undergo screening tests, only that they should be aware of the potential downsides of screening. Also, they emphasize further, there is a clear distinction between a screening test on a healthy individual and a diagnostic test on an individual showing symptoms of a disease; the latter is much more often a justifiable course of action.

Black’s research on screening has at times put him in the midst of controversy. In 1993, he was a member of a committee convened by the National Cancer Institute (NCI) to assess the effectiveness of mammography. The panel reviewed the existing research and concluded that, for women aged 40 to 49, there was no definitive net benefit—that is, more potential benefit than potential harm—from routine mammography.

This report drew attention from the media, the public, and even Congress—much of it negative. Critics charged that the conclusions were an attempt to cut health-care spending, though panel members responded that they had not even included mammography’s cost in their analysis. “I just . . . called it as I saw it,” Black remembers. “But I had a very unpopular view.”

Today, whether women in their 40s should get mammograms remains a point of contention. Guidelines published in 2009 by the U.S. Preventive Services Task Force engendered widespread debate by concluding—as the
NCI panel had 16 years earlier—that, for women in their 40s, mammograms don’t offer a clear net benefit, so the decision to undergo mammography should be made by each woman, individually, in consultation with her physician. Acceptance of that recommendation has been growing but has yet to be universally understood.

For nearly a decade—from 2002 to 2011—one of Black’s primary research interests was helping to lead a major national trial of low-dose CT scans to screen for lung cancer. The National Lung Screening Trial (NLST) enrolled over 53,000 participants at 33 sites across the country (including Dartmouth-Hitchcock). For three years, about half the participants got annual low-dose CT scans and half got annual chest x-rays. The study followed participants through the end of 2009 and compared the number of deaths from lung cancer in each group to see if CT screening decreased the risk of death from lung cancer.

It turned out that it did: Participants in the CT group were 20% less likely to die from lung cancer during the study than were participants in the x-ray group, a finding that Black says is truly significant. “Even though that doesn’t seem huge in relative terms, . . . lung cancer is by far and away the leading killer among all cancers,” he says. “It kills four times more people than the next most lethal cancer [and] more women than breast cancer by far.” So in the context of lung cancer’s prevalence, he concludes, “that’s a fairly impressive finding.”

Black says the rigor with which the trial was conducted was almost as important as the reduction in mortality. All of the participants, who ranged in age from 55 to 74, were either current or former heavy smokers, meaning they were at much higher risk of lung cancer than the general population. That’s an important difference between screening for lung cancer and screening for other cancers, he says. “With lung cancer, it’s pretty easy to find the people at risk.”

Another notable element of the lung trial is that even among participants who had an initial positive CT scan, few invasive procedures—such as biopsies—were performed. Many of the positives in both groups turned out to be false positives, so a high rate of invasive follow-up procedures could have resulted in a number of people being treated unnecessarily. But only about 3% of the participants with a positive CT scan received an invasive procedure—instead, most got a follow-up CT scan a few months later—and very few complications resulted from the few biopsies that were performed. Black observes that this showed that it is possible to do large-scale

“I still believe that screening in general is a close enough call that we shouldn’t use scare tactics or just force people into it,” observes Black, “but instead explain to them as best we can what the risks and benefits are.”
screening without causing a lot of unnecessary interventions and side effects.

Finally, Black points out that the participants in the CT group had a lower rate of death from any cause—not just a lower rate of death from lung cancer. That’s important, he explains, because investigators sometimes misclassify the cause of death in screening trials, leading to an apparent reduction in death from the disease being studied but no reduction in death overall. “Death is pretty certain, but the cause is anything but,” he says. “So you really have to be careful about how you determine the cause of death.”

“I think it’s a great study,” says Welch, who was not involved in the NLST. “Any time people really go to the effort to actually try to capture the full effects of screening, everybody’s got to applaud it.”

Given Black’s history of skepticism toward screening, his enthusiasm for the NLST results may seem surprising. But he doesn’t dispute that screening and other uses of imaging technology can be beneficial—only that it’s important to carefully evaluate their effectiveness and to use them appropriately. “I still believe that screening in general is a close enough call that we shouldn’t use scare tactics or just force people into it,” observes Black, “but instead explain to them as best we can what the risks and benefits are.”

Upon the conclusion of the lung trial, Black engaged in an effort to do just that, in collaboration with two fellow Norris Cotton members—Steven Woloshin, MD, MS, and Lisa Schwartz, MD, MS—plus several other NLST investigators. Together, they produced a fact sheet to communicate the NLST’s findings to eligible individuals nationwide who are considering CT screening (which was launched at DHMC in mid-2012). Black worries that as successful as CT screening proved to be in the trial, widespread availability of the technique used in the study could lead to problems. “You wouldn’t want to exaggerate benefits or exaggerate risks,” he says. “You wouldn’t want overly aggressive follow-up of findings.”

So one lesson the former math major took from the NLST is that, as with everything else in radiology, it’s essential to approach any question in an orderly, rigorous manner. “There should be a logic,” he says. “There should be transparent and reproducible methods for reporting our observations, for interpreting our observations, and for making decisions.”
Members of the Research Programs: “Science for society”

Norris Cotton Cancer Center’s research programs aim to serve, in the words of the Cancer Center’s director, Mark Israel, MD, as a “scholarly home” for a range of researchers from across the gamut of the academic enterprise: basic scientists, translational investigators, clinician-scientists, experts in outcomes studies, population scientists, and more.

Cancer centers like Norris Cotton strive to achieve designation from the National Cancer Institute (NCI) as a comprehensive cancer center—a status that Norris Cotton has held continuously since 1990, when there were just 24 such centers (compared to 41 today).

One of the requirements for such designation is to organize the institution’s cancer investigators into research programs—at least one basic science program, one clinical program, one population science program, and so on. The members of these research programs are expected to collaborate and communicate with each other in ways that most likely would not happen were it not for the existence of the cancer center. The goal is to ensure that their scientific discoveries serve society.

The cancer research programs at Dartmouth meet not just the letter of those requirements and expectations but also their spirit. Indeed, in some areas, such as population science, they set the national bar.

Currently, the membership of Norris Cotton Cancer Center comprises 150 Dartmouth faculty members. They are drawn from nearly every one of the 17 departments at Dartmouth’s Geisel School of Medicine, from several departments in the undergraduate Arts and Sciences program at Dartmouth College, from Dartmouth’s Thayer School of Engineering, and from the world-renowned Dartmouth Institute for Health Policy and Clinical Practice. Many of them teach and/or practice medicine, too, but all of them are committed to the research process.

Listed on the following pages, broken down by research program, are all of Norris Cotton’s current members. Each entry includes the member’s name and academic titles, plus what amounts to a “tweet” about the member’s work—a description of his or her scientific interests in no more than 140 or so characters.
Radiologist Steven Poplack, MD, left, and biomedical engineer Keith Paulsen, PhD, right, exemplify Norris Cotton’s interdisciplinary, collaborative membership.
Cancer Control Research Program

Anna Adachi-Mejia, PhD • Member since 2009
Assistant Professor of Pediatrics
Assistant Professor of The Dartmouth Institute
Conducts community-based research on activity, diet, and sleep as they relate to obesity, media and community influences, and public-health policy.

Marie Bakitas, DNSc, APRN • Member since 1997
Associate Professor of Medicine
Associate Professor of Anesthesiology
Associate Professor of The Dartmouth Institute
Runs clinical trials and researches decision making and decision support in palliative oncology.

Michael L. Beach, MD, PhD • Member since 2007
Professor of Anesthesiology
Professor of Community and Family Medicine
Performs statistical analysis of longitudinal data, attributable risk modeling, and population assessment of media exposures.

Ethan M. Berke, MD • Member since 2010
Associate Professor of Community and Family Medicine
Associate Professor of The Dartmouth Institute
Uses spatial epidemiology and medical geography methodologies to understand community walkability and tobacco availability issues.

William C. Black, MD • Member since 1996
Professor of Radiology
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Studies screening for lung cancer and comparative effectiveness research in general.

Lynn F. Butterly, MD • Member since 2010
Associate Professor of Medicine
Director, Colorectal Cancer Screening
Studies colorectal cancer screening and prevention, colonoscopy quality improvement, and screening of underserved populations.

Ira R. Byock, MD • Member since 2010
Professor of Medicine
Professor of Anesthesiology
Professor of Community and Family Medicine
Chief, Section of Palliative Medicine
Investigates adjustment to life-threatening illness, symptom evaluation and management, counseling, and end-of-life care.

Carrie Hoverman Colla, PhD • Member since 2011
Assistant Professor of The Dartmouth Institute Administration
Conducts research focused on health insurance markets, insurance benefit design, and provider payment as they relate to cancer treatment.

Madeline A. Dalton, PhD • Member since 1997
Professor of Pediatrics
Professor of Community and Family Medicine

Thomas H. Davis, MD • Member since 2010
Associate Professor of Medicine
Director, Hematology-Oncology Fellowship Program
Focuses on improving the education of hematology-oncology fellows and on head and neck cancers.

Todd F. Heatherton, PhD • Member since 2007
Professor of Psychological and Brain Sciences
Lincoln Filene Professor in Human Relations
Uses cognitive neuroscience techniques to examine the neural underpinnings of self-regulatory processes in cancer-causing behaviors.

Mark T. Hegel, PhD • Member since 2006
Associate Professor of Psychiatry
Professor of The Dartmouth Institute
Director, Hood Center for Children and Families
Assesses media, family, and environmental influences on health behaviors related to cancer risk and obesity.

Ira R. Byock, MD • Member since 2010
Associate Professor of Medicine
Professor of Anesthesiology
Professor of Community and Family Medicine
Chief, Section of Palliative Medicine
Investigates adjustment to life-threatening illness, symptom evaluation and management, counseling, and end-of-life care.

Ethan Berke, MD

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Associate Professor of Community and Family Medicine
Associate Professor of The Dartmouth Institute
Studies the delivery of behavioral and palliative health services to rural cancer patients, with a focus on psycho-oncology.

Jay G. Hull, PhD • Member since 2010
Professor of Psychological and Brain Sciences
Chair, Department of Psychological and Brain Sciences
Investigates self-knowledge and the dynamics of self-regulation as they relate to cancer behaviors, with a focus on psycho-oncology.

Stephen K. Liu, MD, MPH • Member since 2010
Assistant Professor of Medicine
Assistant Professor of Community and Family Medicine
Studies pharmaceuticals for chronic diseases and associations with incident cancers in older patients, using Medicare claims data.

Meghan Longacre, PhD • Member since 2010
Research Assistant Professor of Pediatrics
Studies community, school, and family influences on adolescent overweight and food environments in rural areas.

Kathleen D. Lyons, ScD • Member since 2009
Research Assistant Professor of Psychiatry
Conducts research focused on understanding and optimizing social, emotional, and functional well-being in cancer patients.

Auden Curtis McClure, MD • Member since 2011
Assistant Professor of Pediatrics
Assistant Professor of Community and Family Medicine
Assistant Professor of The Dartmouth Institute
Concentrates on understanding and preventing cancer-causing behaviors in children, with a focus on alcohol use and obesity.

Nancy E. Morden, MD, MPH • Member since 2010
Assistant Professor of Community and Family Medicine
Assistant Professor of The Dartmouth Institute
Studies pharmacoepidemiology and cancer treatments, including adverse outcomes associated with specific medications and polypharmacy.

Joseph F. O’Donnell, MD • Member since 2010
Professor of Medicine
Professor of Psychiatry
Senior Advising Dean, Geisel School of Medicine
Focuses on medical education, the humanities in medicine, professional development, prevention, communication, and palliative care.

Ardis L. Olson, MD • Member since 1997
Professor of Pediatrics
Professor of Community and Family Medicine
Studies screening for cancer risk behaviors during adolescence, sun-tanning behaviors, and community prevention interventions.

Tracy L. Onega, PhD • Member since 2007
Assistant Professor of Community and Family Medicine
Assistant Professor of The Dartmouth Institute
Studies access to cancer care, cancer screening registries, breast cancer screening, and comparative effectiveness in cancer imaging.

Steven P. Poplack, MD • Member since 1997
Associate Professor of Radiology
Associate Professor of Obstetrics and Gynecology
Codirector, Breast Imaging/Mammography
Analyzes technologies to assess and improve breast health, including imaging, interventional procedures, mammography, and ultrasound.

James D. Sargent, MD • Member since 1997
Professor of Pediatrics
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Codirector, Cancer Control Research Program
Director, GeoSpatial Shared Resource
Studies adolescent risk behaviors, media influences, tobacco control, early-onset alcohol use, and geospatial epidemiology.

Lisa M. Schwartz, MD, MS • Member since 2007
Professor of Medicine
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Investigates how to enhance the quality of cancer communications to the public, patients, physicians, and policymakers.

Samir S. Soneji, PhD • Member since 2011
Assistant Professor of The Dartmouth Institute Administration
Focuses on research involving variations in cancer care and outcomes, demographic modeling and simulation, and forecasting.
Harold C. Sox, MD • Member since 2011
Professor of Medicine
Professor of The Dartmouth Institute
Associate Director for Faculty, The Dartmouth Institute
Investigates comparative effectiveness as it applies to cancer screening.

Susanne E. Tanski, MD, MPH • Member since 2005
Assistant Professor of Pediatrics
Studies the adoption of cancer risk behaviors during adolescence, the measurement of secondhand-smoke exposure, and smoking cessation for parents.

Anna N. A. Tosteson, ScD • Member since 1993
Professor of Medicine
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Codirector, Cancer Control Research Program
Director, Office of Cancer Comparative Effectiveness Research
Studies clinical and health-policy issues in cancer through decision-analytic modeling and comparative effectiveness research.

Tor D. Tosteson, ScD • Member since 1997
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Director, Cancer Control Research Program
Director, Office of Cancer Comparative Effectiveness Research
Focuses on research involving methodological and statistical problems in medicine.

Dale Collins Vidal, MD, MS • Member since 2002
Professor of Surgery
Professor of Community and Family Medicine
Professor of The Dartmouth Institute Administration
Chief, Section of Plastic Surgery
Focusses on informed choice in health care and oncologic plastic surgery (e.g., breast reconstruction).

H. Gilbert Welch, MD, MPH • Member since 2007
Professor of Medicine
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Assesses the risks and benefits of strategies aimed at early detection of cancer, with an emphasis on over-diagnosis and overtreatment.

Wendy A. Wells, MB, BS, MSc • Member since 2001
Professor of Pathology
Chair, Department of Pathology
Studies breast cancer diagnostic reproducibility, prognostic markers, and quantitative biophysiologic correlates to validate breast imaging.

Steven Woloshin, MD, MS • Member since 2007
Professor of Medicine
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Investigates how to enhance the quality of cancer communications to the public, patients, physicians, and policymakers.

Cancer Epidemiology and Chemoprevention Research Program
Christopher I. Amos, PhD • Member since 2012
Professor of Community and Family Medicine
Associate Director for Population Sciences, Norris Cotton Cancer Center
Director, Center for Genomic Medicine
Develops statistical methods and studies genetic and environmental factors influencing the development of lung and other common cancers.

Angeline S. Andrew, PhD • Member since 2002
Assistant Professor of Community and Family Medicine
Investigates molecular toxicology and genetic and environmental factor interactions and their impact on cancer risk and prognosis.

John A. Baron, MD, MSc • Member since 1996
Professor of Medicine
Professor of Community and Family Medicine
Studies sex hormone-related cancers (e.g., of the breast or prostate), tobacco usage, clinical epidemiology, and cancer prevention.

Elizabeth L. Barry, PhD • Member since 2008
Research Assistant Professor of Community and Family Medicine
Conducts research involving the chemoprevention of cancer and the pharmacogenetics of chemopreventative agents and nutritional supplements.
Brock C. Christensen, PhD • Member since 2011
Assistant Professor of Community and Family Medicine
Assistant Professor of Pharmacology and Toxicology
Uses molecular biology, genomics, bioinformatics, statistics, and epidemiology to describe epigenetic states in human health and disease.

Amar K. Das, MD, PhD • Member since 2012
Associate Professor of Psychiatry
Associate Professor of The Dartmouth Institute
Director of Biomedical Informatics, Geisel School of Medicine
Director, Biomedical Informatics Core, SYNERGY Center for Clinical and Translational Science
Develops novel computational methods and information technologies for clinical research and the population sciences.

Ethan Dmitrovsky, MD • Member since 1998
Andrew G. Wallace Professor of Pharmacology and Toxicology
Andrew G. Wallace Professor of Medicine
Chair, Department of Pharmacology and Toxicology
Codirector, Cancer Epidemiology and Chemoprevention Research Program
American Cancer Society Professor
Studies vitamin A derivatives (retinoids) in cancer therapy and prevention and conducts bench-to-bedside (translational) research.

Jennifer A. Doherty, PhD • Member since 2012
Assistant Professor of Community and Family Medicine
Investigates hormonal carcinogenesis and the genetic and molecular epidemiology of endometrial, ovarian, and lung cancers.

Konstantin H. Dragnev, MD • Member since 2000
Associate Professor of Medicine
Examines the molecular biology and molecular pharmacology of lung cancer and conducts proof-of-concept clinical trials.

Diane Gilbert-Diamond, DSc • Member since 2012
Assistant Professor of Community and Family Medicine
Studies gene-environment interactions related to obesity and obesity-related diseases, including cancer.

Marlene B. Goldman, MS, ScD • Member since 2006
Professor of Obstetrics and Gynecology
Professor of Community and Family Medicine
Director of Clinical Research, Department of Obstetrics and Gynecology
Studies women’s health—infertility treatment, preconception nutrition, and the effect of oxidative stress on implantation/early pregnancy loss.

Jiang Gui, PhD • Member since 2007
Assistant Professor of Community and Family Medicine
Assistant Professor of The Dartmouth Institute
Works on the development and application of statistical methods for high-dimensional data (e.g., microarrays, SNP arrays, proteomics).

Margaret R. Karagas, PhD • Member since 1996
Professor of Community and Family Medicine
Chief, Section of Biostatistics and Epidemiology
Codirector, Cancer Epidemiology and Chemoprevention Research Program
Conducts epidemiological studies focusing on the etiologic mechanisms and prevention of human cancers throughout the lifespan.

Zhigang Li, PhD • Member since 2011
Assistant Professor of Community and Family Medicine
Specializes in longitudinal and clustered data analysis, survival analysis, joint modeling of longitudinal and survival data, and measurement error.

Carmen J. Marsit, PhD • Member since 2011
Associate Professor of Pharmacology and Toxicology
Associate Professor of Community and Family Medicine
Uses epidemiologic methods to study determinants of the human epigenome and its effect on disease risk and outcomes; develops translational biomarkers.

Jason H. Moore, PhD • Member since 2004
Professor of Genetics
Professor of Community and Family Medicine
Third Century Professor
Director, Institute for Quantitative Biomedical Sciences
Associate Director for Bioinformatics, Norris Cotton Cancer Center
Director, Bioinformatics Shared Resource
Applies studies in human genetics, bioinformatics, and the analysis of complex biomedical data to theoretical aspects of computer science.
Judy R. Rees, BM, BCh, MPH, PhD • Member since 2004
Research Assistant Professor of Community and Family Medicine
Research Assistant Professor of Biochemistry
Director, New Hampshire State Cancer Registry
Focuses on disease registries, cancer epidemiology, infectious disease epidemiology, randomized controlled trial methodology, and vitamin D.

Douglas J. Robertson, MD, MPH • Member since 2001
Associate Professor of Medicine
Associate Professor of The Dartmouth Institute
Investigates colorectal cancer epidemiology and outcomes and the pharmacoepidemiology of gastrointestinal disease.

Bill D. Roebuck, PhD • Member since 1996
Professor of Pharmacology and Toxicology
Studies the chemoprevention of cancer and the modulation of toxic processes by dietary factors and nutritional status.

Richard I. Rothstein, MD • Member since 1996
Joseph M. Huber Professor of Medicine
Professor of Surgery
Chair, Department of Medicine
Investigates gastrointestinal disease and chemointerventional trials for the prevention of gastrointestinal neoplasia.

Alan R. Schned, MD • Member since 2007
Professor of Pathology
Professor of Medicine
Conducts research involving genitourinary and renal pathology (e.g., nephropathology, surgical pathology, and uropathology).

Steven K. Spencer, MD • Member since 1997
Professor of Surgery Emeritus
Focuses on dermatology and dermatopathology.

Michael B. Sporn, MD • Member since 1996
Oscar M. Cohn ’34 Professor of Pharmacology and Toxicology
Focuses on cancer chemoprevention—synthetic triterpenoids and rexinoids as anti-inflammatory, antioxidative, anticarcinogenic agents.

Linda J. Titus, PhD • Member since 1996
Professor of Community and Family Medicine
Professor of Pediatrics
Professor of The Dartmouth Institute
Conducts research involving environmental and genetic risk factors for melanoma, female cancers, and prenatal/childhood exposures.

Rebecca J. Troisi, ScD • Member since 2002
Research Assistant Professor of Community and Family Medicine
Has research interests in pregnancy and early-life exposures and their association with cancer risk in mothers and their offspring.

Scott Williams, PhD • Member since 2012
Professor of Genetics
Director, Center for Integrative Biomedical Sciences
Associate Director for Undergraduate Education, Institute for Quantitative Biomedical Sciences
Associate Director for Research, Institute for Quantitative Biomedical Sciences
Conducts research involving human population genetics, the genetics of complex diseases, and the genetic basis of health disparities.

Cancer Imaging and Radiobiology Research Program

Ian Baker, DPhil • Member since 2005
Sherman Fairchild Professor of Engineering
Senior Associate Dean for Academic Affairs, Thayer School of Engineering
Applies advanced engineering methods—mechanical behavior, phase transformations, EM, x-ray topography, and diffraction—to cancer research.

Eunice Y. Chen, MD, PhD • Member since 2011
Assistant Professor of Surgery
Assistant Professor of Pediatrics
Studies tumor hypoxia, wound healing, and head/neck cancer therapies (e.g., hypoxia-targeted theragnostic nanoparticle imaging and hyperthermia).

Eugene Demidenko, PhD • Member since 2000
Research Professor of Community and Family Medicine
Adjunct Professor of Mathematics
Uses advanced statistical methodology to analyze shapes and images, model tumor regrowth, and study electrical impedance tomography.

**Ann Barry Flood, PhD • Member since 1996**
Professor of Radiology  
Professor of Community and Family Medicine  
Professor of The Dartmouth Institute  
Associate Director, EPR Center for the Study of Viable Systems  
Director, Pilot Project Core, Dart-Dose Center for Medical Countermeasures Against Radiation  
Evaluates the comparative effectiveness of dosimetric methods in large-scale disasters and human factors in medical device use.

**Barjor Gimi, PhD • Member since 2011**
Associate Professor of Radiology  
Associate Professor of Medicine  
Director, Biomedical NMR Research Center  
Focuses on nanoporous, immunoprotective devices for encapsulated cell therapy and MRI of the fate and function of engineered therapeutic cells.

**David J. Gladstone, ScD • Member since 1996**
Associate Professor of Medicine  
Studies ultra-conformal radiation therapy to spare normal tissues from damage (e.g., image guidance and biological gating of therapeutic x-rays).

**Ryan J. Halter, PhD • Member since 2010**
Assistant Professor of Engineering  
Adjunct Assistant Professor of Surgery  
Develops clinical applications of bioimpedance for cancer screening, diagnosis, and therapy, primarily of the prostate and breast.

**Alexander Hartov, PhD • Member since 1996**
Professor of Engineering  
Studies electrical impedance imaging for breast and prostate cancer screening and fluorescence- and image-guided neurosurgery.

**P. Jack Hoopes, DVM, PhD • Member since 1997**
Professor of Surgery  
Professor of Medicine  
Adjunct Professor of Engineering  
Director, Irradiation and Small-Animal Imaging Shared Resource  
Focuses on experimental cancer therapeutics (e.g., radiation, hyperthermia, nanotechnology), animal models, pathology, and imaging.

**Huagang Hou, MD, MS • Member since 2007**
Research Assistant Professor of Radiology  
Studies the development of paramagnetic implantable resonators, tissue oxygen measurement, experimental surgery, and animal models.

**Lesley A. Jarvis, MD, PhD • Member since 2011**
Assistant Professor of Medicine  
Investigates cancer therapeutics (radiation and chemotherapy), cancer imaging for image-guided radiotherapy, and hypoxia.

**Nadeem Khan, PhD • Member since 2007**
Research Associate Professor of Radiology  
Studies free radical biology, oxygen metabolism in solid tumors, and cancer therapeutics, including antiangiogenic approaches.

**Paul M. Meaney, PhD • Member since 2002**
Professor of Engineering  
Studies microwave tomographic imaging for biomedical applications and its integration with focused ultrasound surgery applications.

**Keith D. Paulsen, PhD • Member since 1993**
Robert A. Pritzker Professor of Biomedical Engineering  
Professor of Radiology  
Director, Advanced Imaging Center  
Codirector, Advanced Surgical Center  
Codirector, Cancer Imaging and Radiobiology Research Program  
Focuses on biomedical engineering and imaging for the detection and treatment of cancer.

**Brian W. Pogue, PhD • Member since 1997**
Professor of Engineering  
Adjunct Professor of Surgery  
Adjunct Professor of Physics and Astronomy  
Dean of Graduate Studies, Dartmouth College  
Investigates light-activated or photodynamic therapy (PDT) in association with radiation therapy.
David W. Roberts, MD • Member since 1996
Professor of Surgery
Professor of Neurology
Chief, Section of Neurosurgery
Conducts research involving brain tumors, epileptic disorders, stereotactic and functional neurosurgery, and trigeminal neuralgia.

Harold M. Swartz, MD, PhD, MSPH • Member since 1993
Professor of Radiology
Professor of Physiology and Neurobiology
Professor of Community and Family Medicine
Professor of The Dartmouth Institute
Adjunct Professor of Chemistry
Adjunct Professor of Engineering
Codirector, Cancer Imaging and Radiobiology Research Program
Director, EPR Center for the Study of Viable Systems
Director, Dart-Dose Center for Medical Countermeasures Against Radiation
Focuses on in vivo EPR spectroscopy, radiation biology, radiation dosimetry for unplanned exposures, and the measurement of oxygen to enhance therapy.

John B. Weaver, PhD • Member since 1996
Professor of Radiology
Adjunct Associate Professor of Engineering
Concentrates on developing magnetic resonance elastography as a technique to measure the elasticity of tissue in vivo.

Benjamin B. Williams, PhD • Member since 2007
Research Assistant Professor of Radiology
Associate Director, EPR Center for the Study of Viable Systems
Develops and applies in vivo EPR spectroscopy to improve cancer therapies; also studies tissue oxygenation, radiation biology, and biodosimetry.

Bassem I. Zaki, MD • Member since 2002
Assistant Professor of Medicine
Studies molecular markers for response to radiation therapy, brachytherapy, unsealed radionuclide therapy, and radioimmunoglobulins.

Cancer Mechanisms Research Program

Yashi F. Ahmed, MD, PhD • Member since 2002
Associate Professor of Genetics
Studies the molecular mechanisms by which APC regulates Wnt signaling, as well as the molecular consequences of APC loss.

Angeline S. Andrew, PhD • Member since 2002
Assistant Professor of Community and Family Medicine
Investigates molecular toxicology—host genetic factors that modify cancer prognosis and response to environmental exposures.

Constance Brinckerhoff, PhD

Giovanni Bosco, PhD • Member since 2012
Associate Professor of Genetics
Studies dynamic changes in global chromosome structure and nuclear architecture and their impact on cell division and gene expression.

Constance E. Brinckerhoff, PhD • Member since 1996
Professor of Biochemistry
Professor of Medicine
Associate Dean for Science Education, Geisel School of Medicine
Focuses on the mechanisms by which matrix metalloproteinases facilitate the invasive and metastatic behavior of tumor cells.

Charles N. Cole, PhD • Member since 1997
Professor of Biochemistry
Professor of Genetics
Examines the transport of messenger RNA from the nucleus to the cytoplasm and its impact on normal and abnormal cell biology.

Michael D. Cole, PhD • Member since 2003
Professor of Pharmacology and Toxicology
Professor of Genetics
Investigates transcriptional mechanisms and distal regulatory elements regulating c-myc expression and other genes relevant to cancer.

Duane A. Compton, PhD • Member since 1996
Professor of Biochemistry
Senior Associate Dean for Research, Geisel School of Medicine
Analyzes chromosomal instability and aneuploidy in human tumors.

Ethan Dmitrovsky, MD • Member since 2002
Andrew G. Wallace Professor of Pharmacology and Toxicology
Andrew G. Wallace Professor of Medicine

Page 110 • All Together Now: Dartmouth’s Norris Cotton Cancer Center
Chair, Department of Pharmacology and Toxicology
Codirector, Cancer Epidemiology and Chemoprevention
Research Program
American Cancer Society Professor
Studies vitamin A derivatives (retinoids) in cancer therapy and prevention and conducts bench-to-bedside (translational) research.

James DiRenzo, PhD • Member since 2001
Associate Professor of Pharmacology and Toxicology
Codirector, Cancer Mechanisms Research Program
Scientific Director, Comprehensive Breast Program
Conducts research involving the genetic control of stem cell renewal and applies tumor stem cell theory to translational breast cancer research.

Patricia A. Ernst, PhD • Member since 2005
Associate Professor of Genetics
Associate Professor of Microbiology and Immunology
Codirector, Cancer Mechanisms Research Program
Studies pathways regulating hematopoietic stem cell development and maintenance, leukemia, and the epigenetic regulation of both.

Steven N. Fiering, PhD • Member since 1996
Professor of Microbiology and Immunology
Professor of Genetics
Director, Transgenics and Genetic Constructs Shared Resource
Applies novel approaches, including nanoparticles and tumor vaccines, as well as mouse models to the detection and treatment of cancer.

Scott A. Gerber, PhD • Member since 2006
Associate Professor of Genetics
Associate Professor of Biochemistry
Director, Proteomics Shared Resource
Studies the mechanisms by which mitotic kinases contribute to cancer initiation and maintenance, using novel proteomics methods.

Amy S. Gladfelter, PhD • Member since 2006
Associate Professor of Biological Sciences
Studies the control of cell cycle progression, the mechanisms of nuclear asymmetry, and cell cortex organization by septins.

Henry N. Higgs, PhD • Member since 2002
Professor of Biochemistry
Investigates cell motility and the actin cytoskeleton in normal cell physiology and disease.

Mark A. Israel, MD • Member since 2001
Professor of Pediatrics
Professor of Genetics
Director, Norris Cotton Cancer Center

Focuses on the role of nervous system differentiation in tumorigenesis, including the creation and study of novel animal models of human brain tumors.

Vincent A. Memoli, MD • Member since 2007
Professor of Pathology
Investigates endocrine, neuroendocrine, bone, pulmonary, and surgical pathology.

Dale F. Mierke, PhD • Member since 2011
Professor of Chemistry
Studies the structural basis and the mechanism of action of different peptide hormones.

James B. Moseley, PhD • Member since 2010
Assistant Professor of Biochemistry
Conducts research involving the basic mechanisms that coordinate cell growth and division.
Mary Jo Mulligan-Kehoe, PhD • Member since 2002
Associate Professor of Surgery
Investigates angiogenesis in mouse models of atherosclerosis and the function of PAI-1 proteins as anti-angiogenesis agents.

Lawrence C. Myers, PhD • Member since 2008
Associate Professor of Biochemistry
Designs studies to reveal the basic mechanisms that facilitate positive/negative eukaryotic gene regulation at the molecular level.

C. Harker Rhodes, MD, PhD • Member since 2007
Professor of Pathology
Professor of Neurology
Conducts research that involves the molecular biology of gliomas, the molecular genetics of neuropsychiatric disorders, and neuropathology.

Richard M. Saito, PhD • Member since 2005
Associate Professor of Genetics
Focuses on identifying the genes and mechanisms used to regulate cell-cycle entry in the context of normal animal development.

Radu V. Stan, MD • Member since 2011
Associate Professor of Pathology
Associate Professor of Microbiology and Immunology
Studies the role of endothelial cells in permeability, angiogenesis, and diapedesis of leukocytes in cancer and inflammation.

Michael L. Whitfield, PhD • Member since 2004
Associate Professor of Genetics
Examines the regulation of gene expression during cell division and the identification and mechanisms underlying scleroderma subsets.

Margaret A. Crane-Godreau, PhD • Member since 2007
Research Assistant Professor of Microbiology and Immunology
Director, Cigarette Smoke Exposure Analysis Laboratory
Studies innate immunity in the respiratory and reproductive tracts, especially as it relates to tobacco-induced disease.

Marc S. Ernstoff, MD • Member since 1991
Professor of Medicine
Conducts research that involves psoriasis, atopic dermatitis, photodynamic therapy, laser therapy, and melanoma immunotherapy.

Immunology and Cancer Immunotherapy Research Program

Richard J. Barth, MD • Member since 1996
Associate Professor of Surgery
Chief, Section of Surgical Oncology
Chief, Section of General Surgery
Studies the immune response to tumors in vivo by characterizing cytokines expressed by lymphocytes infiltrating tumors or by tumors themselves.

Brent L. Berwin, PhD • Member since 2004
Associate Professor of Microbiology and Immunology
Director, Molecular and Cellular Biology Graduate Program
Investigates macrophage phenotype, function, and contribution within ovarian cancer.

M. Shane Chapman, MD • Member since 2005
Associate Professor of Surgery

Brent Berwin, PhD
Associate Director for Clinical Research, Norris Cotton Cancer Center
Focuses on cancer immunotherapy, especially as it relates to melanoma and renal cell carcinoma.

Camilo E. Fadul, MD • Member since 1996
Professor of Medicine
Studies neurologic complications of systemic cancer and primary brain tumors.

James D. Gorham, MD, PhD • Member since 1999
Professor of Pathology
Professor of Microbiology and Immunology
Director, Speed Congenics Shared Resource
Investigates the regulation of tolerance, inflammation, and autoimmunity in the liver.

William R. Green, PhD • Member since 1983
Professor of Microbiology and Immunology
Chair, Department of Microbiology and Immunology
Studies T cell immune responses to viral diseases, including cell-mediated immunity to mouse retroviruses that cause leukemia or immunodeficiency.

Paul M. Guyre, PhD • Member since 1983
Professor of Physiology and Neurobiology
Professor of Microbiology and Immunology
Studies the hormone and cytokine regulation of macrophage function.

Kenneth R. Meehan, MD • Member since 2001
Professor of Medicine
Codirector, Immunology and Cancer Immunotherapy Research Program
Director, Blood and Marrow Transplant Program
Conducts research involving hematology and bone marrow transplantation, including autologous grafts and adoptive cellular immunotherapy.

David W. Mullins, PhD • Member since 2011
Assistant Professor of Microbiology and Immunology
Studies cancer immunology and lymphocyte trafficking; develops immunotherapy approaches for the treatment of metastatic cancers.

Randolph J. Noelle, PhD • Member since 1984
Professor of Microbiology and Immunology
Focuses on regulatory T cell biology, B cell memory/plasma cell development, immune tolerance in transplantation, and cancer vaccines.

William F. C. Rigby, MD • Member since 1996
Professor of Medicine
Professor of Microbiology and Immunology
Conducts research involving the regulation of gene expression, such as post-transcriptional regulation of cytokine gene expression.

Charles L. Sentman, PhD • Member since 2002
Professor of Microbiology and Immunology
Codirector, Immunology and Cancer Immunotherapy Research Program
Investigates new cancer immunotherapies based on immune receptors, how they function in tumor models, and innate immunity and NK cells.

Jacqueline Y. Smith, PhD • Member since 1992
Research Assistant Professor of Microbiology and Immunology
Director, Immune Monitoring and Flow Cytometry Shared Resource
Studies biomarkers for multiple sclerosis to predict responders versus nonresponders.

Zbigniew M. Szczepiorkowski, MD, PhD • Member since 2004
Associate Professor of Pathology
Associate Professor of Medicine
Focuses on novel cellular therapies applied across the field of medicine and evidence-based approaches to the use of apheresis in clinical practice.

Mary Jo Turk, PhD • Member since 2004
Associate Professor of Microbiology and Immunology
Studies tumor immunology, T cell memory to tumors, the role of autoimmunity, and the immunology of molecularly targeted cancer therapies.

Edward J. Usherwood, PhD • Member since 2002
Associate Professor of Microbiology and Immunology
Studies cell responses to viral infections and how the process offers protection against tumor development.

Charles R. Wira, PhD • Member since 1983
Professor of Physiology and Neurobiology
Studies how female sex hormones influence immunity in the female reproductive tract, using animal models and human tissues.
Michael E. Zegans, MD • Member since 2010
Professor of Surgery
Professor of Microbiology and Immunology
Conducts research involving ocular microbiology and bacterial biofilm formation.

Molecular Therapeutics Research Program
Bradley A. Arrick, MD, PhD • Member since 1996
Associate Professor of Medicine
Chief, Section of Hematology-Oncology
Investigates the genetics and clinical management of familial breast cancer.

Catherine Carriere, PhD • Member since 2007
Research Assistant Professor of Medicine
Studies the molecular dissection of cancer initiation and the role of the tumor microenvironment, particularly in pancreatic cancer.

Ruth W. Craig, PhD • Member since 1996
Professor of Pharmacology and Toxicology
Focuses on antiapoptotic MCL1, including its role in normal cell differentiation and its exploitation as a target in cancer.

Alexey V. Danilov, MD, PhD • Member since 2011
Assistant Professor of Medicine
Studies chronic lymphocytic leukemia, including the role of p53 family members in disease progression and chemotherapy resistance.

Alan R. Eastman, PhD • Member since 1989
Professor of Pharmacology and Toxicology
Codirector, Molecular Therapeutics Research Program
Director, Program in Experimental and Molecular Medicine
Develops novel cancer chemotherapeutic strategies that target cell cycle checkpoint regulators and the process of apoptosis.

Burton L. Eisenberg, MD • Member since 2003
Professor of Surgery
Deputy Director, Norris Cotton Cancer Center
Conducts research involving sarcoma, breast, and gastrointestinal malignancies.

Gordon W. Gribble, PhD • Member since 1993
Professor of Chemistry
Focuses on the synthesis of biologically active natural products, including novel indoles and anticancer triterpenoids.

Peter A. Kaufman, MD • Member since 1995
Associate Professor of Medicine
Conducts research on HER2-positive breast cancer.

William B. Kinlaw III, MD • Member since 1997
Professor of Medicine
Investigates lipid synthesis and uptake as potential therapeutic targets in breast and other cancers.

Alexei F. Kisselev, PhD • Member since 2004
Associate Professor of Pharmacology and Toxicology
Studies targeting the proteasome for treatment of cancer, polysome-associated proteasomes, and their role in proteostasis.

Manabu Kurokawa, PhD • Member since 2012
Assistant Professor of Pharmacology and Toxicology
Studies how cancer cells survive and evade programmed cell death to acquire chemoresistance.

Frederick Lansigan, MD • Member since 2009
Assistant Professor of Medicine
Investigates hematologic malignancies, with a primary focus on lymphoma.

Lionel D. Lewis, MB, BCh, MD • Member since 1996
Professor of Medicine
Professor of Pharmacology and Toxicology
Codirector, Molecular Therapeutics Research Program
Director, Clinical Pharmacology Shared Resource
Specializes in early-phase clinical trials, clinical pharmacology, and the toxicology of antineoplastic agents.

Gustav E. Lienhard, PhD • Member since 1997
Professor of Biochemistry
Focuses on cellular signaling pathways and the hormonal regulation of membrane trafficking.

Christopher H. Lowrey, MD • Member since 1996
Professor of Medicine
Professor of Pharmacology and Toxicology
Associate Chief, Section of Hematology-Oncology
Vice Chair for Clinical Affairs, Department of Medicine
Develops novel pharmacologic therapies for sickle cell disease.
cell disease, thalassemia, and leukemia involving epigenetics and cell stress signaling.

**Todd W. Miller, PhD • Member since 2012**
Assistant Professor of Pharmacology and Toxicology
Investigates the translational application of novel drugs targeting cell signaling pathways for breast cancer therapy.

**William G. North, PhD • Member since 1983**
Professor of Physiology and Neurobiology
Studies vasopressin, oxytocin-related neuropeptides, and NMDA receptors in breast cancer, small-cell carcinoma, and other solid tumors.

**Deborah L. Ornstein, MD • Member since 2009**
Associate Professor of Medicine
Associate Professor of Pathology
Focuses on hematopathology and diagnostic and clinical blood coagulation.

**J. Marc Pipas, MD • Member since 2007**
Associate Professor of Medicine
Conducts research involving colon, gastrointestinal, and pancreatic cancers.

**Alexandre A. Pletnev, PhD • Member since 2007**
Research Assistant Professor of Chemistry
Studies the organic synthesis of novel compounds in support of biomedical research.

**James R. Rigas, MD • Member since 1996**
Associate Professor of Medicine
Director, Office of Clinical Research
Focuses on research involving thoracic oncology.

**Yolanda Sanchez, PhD • Member since 2006**
Associate Professor of Pharmacology and Toxicology
Associate Director for Basic Sciences, Norris Cotton Cancer Center
Director, Molecular Biology Shared Resource

Studies cell-cycle checkpoints in the etiology of cancer and as drug targets for cancer; uses chemical genetic screens for drug discovery.

**Gary N. Schwartz, MD • Member since 2001**
Associate Professor of Medicine
Investigates chemotherapy and endocrine therapy for breast cancer, signal transduction pathways, and new drug development.

**Kerrington D. Smith, MD • Member since 2012**
Assistant Professor of Surgery
Focuses on surgical oncology, including an active translational research direct tumor xenograft program in pancreatic cancer.

**Mark R. Spaller, PhD • Member since 2008**
Associate Professor of Pharmacology and Toxicology

Focuses on the development of peptides and organic small molecules that target proteins in cancer research, drug discovery, and protein biochemistry.

**Michael J. Spinella, PhD • Member since 1998**
Associate Professor of Pharmacology and Toxicology
Studies mechanistic links between stem cell pluripotency, differentiation, and chemotherapy response and resistance.

**Michael B. Sporn, MD • Member since 1996**
Oscar M. Cohn ’34 Professor of Pharmacology and Toxicology
Oscar M. Cohn ’34 Professor of Medicine
Focuses on cancer chemoprevention—synthetic triterpenoids and rexinoids as anti-inflammatory, antioxidative, anticarcinogenic agents.

**Craig R. Tomlinson, PhD • Member since 2007**
Assistant Professor of Medicine
Assistant Professor of Pharmacology and Toxicology
Associate Director for Shared Resources, Norris Cotton Cancer Center
Director, Genomics Shared Resource
Director, Optical Cellular Imaging Shared Resource
Studies aryl hydrocarbon receptor signaling in obesity, cancer, and atherosclerosis and genomics approaches in development and disease.

**Gregory J. Tsongalis, PhD • Member since 2007**
Professor of Pathology
Director, Pathology Translational Research Shared Resource
Develops molecular diagnostic technologies and applications for rapid diagnosis of human cancers.

**Matthew P. Vincenti, PhD • Member since 1998**
Research Associate Professor of Medicine
Studies the role of inflammation in regulating matrix metalloproteinase gene expression in cancer.
About Norris Cotton Cancer Center
Norris Cotton Cancer Center combines advanced cancer research at Dartmouth College and Dartmouth’s Geisel School of Medicine with patient-centered cancer care provided at Dartmouth-Hitchcock Medical Center in Lebanon, N.H., at Dartmouth-Hitchcock regional locations in Manchester, Nashua, and Keene, N.H., and St. Johnsbury, Vt., and at 12 partner hospitals throughout New Hampshire and Vermont. It is one of only 41 institutions nationwide that hold the National Cancer Institute’s Comprehensive Cancer Center designation.

Norris Cotton’s Mission
To prevent and cure cancer through pioneering interdisciplinary research, to translate new knowledge into better prevention and treatment, and to provide effective and compassionate clinical care that improves the lives of patients with cancer and their families. We are committed to excellence in our research, dynamic partnerships between our laboratories and clinics, robust outreach and education throughout our region, and outstanding education and training programs for future cancer scientists and clinicians.

Norris Cotton’s Vision
Norris Cotton Cancer Center will discover new worlds of cancer medicine, lead efforts to prevent and cure cancer in Northern New England, and contribute to solving the problems of cancer worldwide, while providing the highest level of safe, innovative, compassionate care for patients with cancer.

To Learn More About Norris Cotton
Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, 1 Medical Center Drive, Lebanon, NH 03756
603-653-9000 • http://cancer.dartmouth.edu • www.facebook.com/dartmouthcancer
Dartmouth’s Norris Cotton Cancer Center has been a National Cancer Institute-designated comprehensive cancer center since 1990, a claim that fewer than two dozen institutions nationwide can make. Norris Cotton also claims something else very special—a truly collaborative culture, a sense of collegiality that transcends disciplinary bounds and that weaves together intrinsically the interests of clinicians and scientists.

Pictured on the front cover are four members of Norris Cotton’s lung cancer group—from the left, radiologist William Black, MD; comparative effectiveness researcher Anna Tosteson, ScD; cardiothoracic surgeon Cherie Erkmen, MD; and demographic statistician Samir Soneji, PhD. The group brings many disciplines to bear on balancing the benefits and burdens of screening and treatment choices for patients with lung cancer.

Pictured above is Dartmouth-Hitchcock’s Lebanon, N.H., campus—the home of Norris Cotton Cancer Center’s administrative offices and its core scientific and clinical facilities; the Cancer Center also offers top-notch cancer care at 16 other locations all across New Hampshire and Vermont.