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 intimately 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.
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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.

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All Together Now: Dartmouth’s Norris Cotton Cancer Center • Page 5
Pediatric oncologist Mark Israel, MD, has headed Norris Cotton since 2001.

**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—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 reverse 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.

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 early detection. We challenge conventional wisdom by doing research to understand the cause 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 derive, 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, this 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.
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

A Brief History of Norris Cotton: “What’s past is prologue”
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.”

Cotton immediately understood the cause that Lane articulated and from then on was a strong advocate for the project. He parlayed his close relationship with the subcommittee’s chair into a boost for the cause that Cotton was fond of calling “the apple of my eye.”

The Cancer Center’s genesis and early incarnation

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1957</td>
<td>Frank Lane, MD, director of radiation therapy at Hitchcock, began to compile regional cancer mortality statistics.</td>
</tr>
<tr>
<td>1970</td>
<td>Lane first met with U.S. Senator Norris Cotton to explore federal support for a cancer center at Dartmouth-Hitchcock.</td>
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<tr>
<td>1971</td>
<td>$3 million was appropriated by the National Cancer Institute to construct such a facility at Dartmouth-Hitchcock. Groundbreaking occurred on July 3.</td>
</tr>
<tr>
<td>1972</td>
<td>The facility, a two-story underground structure, opened.</td>
</tr>
<tr>
<td>1977</td>
<td>A two-story aboveground addition opened.</td>
</tr>
<tr>
<td>1985</td>
<td>Dartmouth granted Cotton an honorary degree.</td>
</tr>
</tbody>
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In 1972, the Cancer Center consisted of two underground stories and a “little kiosk,” at left in the photo on the left. By 1977, two aboveground stories, in the foreground of the photo on the right, had been added.

Magnuson (whom he called “Maggi”) 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 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 programs.

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. Cottons support for the project did not end with the allocation of funding. He
instruments in the world. From Switzerland was one of only three such instruments in the world.

Brown-Boveri Betatron was far more important than the space that housed it: a 52-foot-tall kiosk in the middle of the parking lot that 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—a little kiosk in the middle of the parking lot” that served Mary Hitchcock Memorial Hospital. The walls of the 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 importance than the space that housed it. In fact, the Betatron was one of only three such instruments in the world.

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 item I’d思念 of all my 26 years in Congress.”

He was most proud of the money that went to the Cancer Center. “Some more money for my pet project,” Cotton answered. Magnuson asked his old friend what he would like as a “going-away present” for his constituents. “Some cancer research,” Cotton had answered.

He requested that Congress appropriate $4.5 million for an addition to the Cancer Center—two underground 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, 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 simple.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 took 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. Norris Cotton became a “going-away present” for his constituents. “Some cancer research,” Cotton had answered.

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 program than single-disciplinary programs if you are talking about human medicine.”

Johnsbury, Vt., and a medical oncology clinic in Manchester, N.H.

The Rubin Building opened on D-H’s Lebanon campus in 1995.

The Rubin Building, pictured in 1995, has since been greatly expanded.
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, McIntyre was recruited to become the 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, through 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 Foundation, 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.

All Together Now: Dartmouth’s Norris Cotton Cancer Center  •  Page 16

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 Bolwell Research Building on DHMC’s Lebanon campus, but many were still on the Medical School’s Hanover campus. Today, the Cancer Center’s hub facility in Lebanon has its own dedicated entrance and administrative space in the Rubin Building.

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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. Artisan-style buildings are inspired, in part, by the 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 attend departmental meetings and departmental meetings and departmental meetings.

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—a standard by which the Cancer Center has been deemed a decided success. People gather there for coffee breaks, run into each other, and attend departmental meetings and departmental meetings and departmental meetings.

Yet Norris Cotton is one of the smallest comprehensive cancer centers in the country. In 2011, the median membership for comprehensive cancer centers was 255, 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.
other while traversing the building’s various levels, hold informal meetings at its clustered seating areas, and schedule more formal meetings in the conference rooms located just off the soaring space. In addition, the atrium has come to be a popular site for retirement receptions, and formal meetings in the conference rooms. Informal meetings take place at its clustered seating areas, and other while traversing the building’s various levels, hold informal meetings at its clustered seating areas, and schedule more formal meetings in the conference rooms located just off the soaring space. In addition, the atrium has come to be a popular site for retirement receptions, and formal meetings in the conference rooms.
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 this 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 waxed 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 have been, 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 “as 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 choice if you’re in an unattractive environment.”

Research Resources: “An extraordinary mix”

Yolanda Sanchez, 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 Rubn 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, looseness 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 menacing with other groups.”

As for the necessary infrastructure and technological expertise, much of that is centraled 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: 

- Biostatistics—Tor Tosteson, ScD: clinical trial design, nonlinear dose response modeling, cost-effectiveness analysis, diagnostic test assessment, data analysis, mapping, cluster analysis, geographic analysis, geocoding, spatial epidemiology
- Genomics—Craig Tomlinson, PhD: microarray, whole genome sequencing, gene expression analysis
- Biophotonics—Jane Sargent, MD, GIS, spatial analysis, geochemical analysis, mapping, targeting, pharmacoeconomic modeling, mapping
- Transgenic and Genetic Constructs—Steven Fiering, PhD: design, generation, and maintenance of transgenic mouse lines
- GeoSpatial—James Sargent, MD: GIS, spatial epidemiology
- Immune Monitoring and Flow Cytometry—Jacqueline Smith, PhD: immunoassays, flow cytometry, cell sorting, cryopreservation
- Toxicology—Yolanda Sanchez, PhD: toxicology monitoring and gating
- Tissue Core—Gregory Tsongalis, PhD: tissue procurement, processing, histology, molecular pathology, TMA production, laser capture microdissection, pharmacogenomics
- Proteomics—Scott Gerber, PhD: protein identification, protein post-translational modification analysis, general proteomics/poly- peptide liquid chromatography-mass spectrometry services
- Speed Congenics—James Gorham, MD, PhD: speed congenic mouse development, mouse genetic mapping (see page 26 for more on this service)
- Transplant and Genetic Constructs—Steven Fiering, PhD: design, generation, and maintenance of transgenic mouse lines
- Cancer and Leukemia Group B (CALGB)
- Eastern Cooperative Oncology Group (ECOG)
- Gynecologic Oncology Group (GOG)
- Radiation Therapy Oncology Group (RTOG)

I think, indeed, 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. “It nurtures such interactions. For an institution to be designated as a comprehensive cancer center, he notes, the National Cancer Institute “has a rule of thumbs 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 . . . at 50 percent.”

The Place

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Research Resources

The Place

“at 50 percent.”

The Place

Research Resources

Research Resources

The Place

Research Resources

The Place

Research Resources

The Place

Research Resources

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 Bowell 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

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All Together Now: Dartmouth’s Norris Cotton Cancer Center • Page 25
a very valuable year for scientists," he says. "They can begin to cut their horizon 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.

"That's a very valuable year for scientists," he says. "They can begin to cut their horizon sooner. They can get answers sooner. They can publish more quickly."

More than 50 other institutions, including several 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 cut their horizon sooner. They can get answers sooner. They can publish more quickly."

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 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.”

Two members of the staff in Gorham’s lab put the machine they’ve dubbed Nimbus 2000 through its paces.

"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 your German shepherd, you could breed a poodle with a German 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. Then 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.

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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.”

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S t i f t, the CCNE research is all preclinical, says Keith Paulsen, PhD, the center’s deputy director. That’s by design. Under National Cancer Instit- ute guidelines, the CCNE grant can’t be used to fund clinical trials. Never- theless, the Dartmouth work is advancing quickly. Paulsen expects 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 anim- als, and it’s not a big stretch to push this into patients,” he says.

Both Baker and Paulsen attribute the promising pace to the collabora- tive spirit among the participants. There is “a very productive” dynamic, says Paulsen. “The group challenges each other in a very positive way.”

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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—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 nationally almost 25% are admitted to intensive care in the last month of their lives; 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 tumor boards meet weekly to discuss patients’ cases and ensure that patients receive the care they need and want.

**Clinical Capabilities: “When one is the biggest number”**

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 in 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, or choosing whether to have PSA screening for 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 surgeons who’ve never met a prostate they couldn’t remove.” The Norris Cotton administrator Robert Gerlach, 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. The commitment to this process is so strong that most of the tumor boards meet every week.

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. Evidence from clinical trials (many done at D-H) has shown that palliative care can improve patients’ quality of life and sometimes even prolong their lives.
Two stage IV diagnoses vs. four clinical trials: “Here I am, because of the research that they do” at Norris Cotton

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 was 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 out to see Dr. Ernstoff. I had a very comfortable—very hopeful—experience. And everybody at Norris Cotton, whether it was the nurses 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. She received 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.

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What Distinguishes the Place: “It’s different at Dartmouth”

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
What Distinguishes the Place

The Place

The same coffee pot. “When we use the same coffee pot,” adds “when we use the same coffee pot,” adds, “when we use the same coffee pot.” 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.”

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 institution 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.”

Another distinctive factor is the size not just of the institution is just the right size—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. He says, “So there may be no single reason why ‘it’s different at Dartmouth.’ But it really is no problem, because of the free bus service that runs every 15 minutes between the two campuses. ‘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.” Dartmouth Medicine

“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 (picture 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 wife of former Nixon administration official Kenneth Cole, who is credited with having shepherded the Cancer Act through Congress.

“Our family felt 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 Gastro 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, “it 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, 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, Jean Brown)—plus well over a thousand volunteers. Audrey Prouty’s can-do spirit is paying more dividends than she ever could have imagined.

“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 facing 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.

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.

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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

CHELSEA GEOFFREY

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.

DAN GROSSMAN
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.
Cancer Control Program

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 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 are among the countries where they’re currently working. Sargent’s highly productive research group also continues to conduct large-scale prospective studies on smoking or drinking. India, Scotland, and Germany number among the countries where they’re currently working. Sargent’s highly productive research group also continues to conduct large-scale prospective studies on smoking or drinking. India, Scotland, and Germany number among the countries where they’re currently working.

- Todd Heatherton, PhD, who uses functional magnetic resonance imaging to map brain activity patterns in marijuana users, 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 Omega, PhD, continues to oversee the New Hampshire Mammography Network (NHMN). In 15-plus years of data, representing over a million mammograms, there have led to more than 300 peer-reviewed publications. Currently, Omega and Anna Tosteson, ScD, are capturing task-based breast-screening information and examining risk-based use of imaging modalities through a consortium called Population-based Research Optimizing Screening through Personalized Regimens, known as PROSPR. (See page 47 for more on Tosteson’s work.)

- Carrie Flormann Collins, PhD, is using MultiCare claims data to assess changes in end-of-life chemotherapy in response to the Medicare Modernization Act.
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 James Sargent: Taking on the tobacco, alcohol, and movie industries

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.

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.

James Sargent, MD, studies how tobacco and alcohol imagery affects teens’ likelihood of smoking and drinking.

Anna Tosteson, ScD
Ensuring effective care

As screening, diagnostic, and treatment options have proliferated in the U.S., it has become ever harder for physicians 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 what new technologies, new drugs, and new devices actually improve patient outcomes.

Currently, she is leading 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

The Norris Cotton Cancer Epidemiology and Chemoprevention (CEC) Research Program facilitates multidisciplinary interactions among molecular biologists, bioinformatics, 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 focuses on 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.
Significant recent achievements of the CEC Research Program

Members of the Cancer Epidemiology and Chemoprevention Research Program have recently reported 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 Genes, Chromosomes and Cancer) was accompanied by an editorial and by a report from a team at M.D. Anderson Cancer Research Center that independently confirmed the Dartmouth findings in an active arm of the BATTLE Trial.
- Brock Christensen, PhD; Carmen Marsit, PhD; Margaret Karagas; and 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 Karagas’s work.)
- Ethan Dmitrovsky and colleagues 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 arsenic 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 p53-inhibitor phenotype specific to colorectal cancer. Moore also received an $11-million award from the National Institutes of Health to establish the Institute for Quantitative Biosciences.
- 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 degradates 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 carcino- gen, urethane, which causes lung adenomas.
- Angelitee 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 onco-genic microRNA in the lung.
- Linda Tintu, 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).
- Jason Guo, 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 methyltransferase cl and the histological subtype of glioma tumors.

A few facts about the CEC Research Program

- 28 Number of members of the Cancer Epidemiology and Chemoprevention (CEC) Research Program (see page 106 for a list of all the members of the program)
- 8 Number of primary department representatives by those members

Codirectors

- Margaret Karagas, PhD, and Ethan Dmitrovsky, MD

1996 Year the six most senior members of the program became members of Norris Cotton Cancer Center

2012 Year the five newest members of the program became members of Norris Cotton Cancer Center

Community and Family Medicine

Department in which the most members of the CEC Program (12) hold their primary faculty appointment

14 Number of members of the CEC Program who hold an appointment in more than one department

18 Number of members of the program who hold a PhD, ScD, or DSc

4 Number of members of the program who hold a named chair

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<th>Number of members of the program who hold a named chair</th>
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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 news accounts that in 2011 received a National Institutes of Health P20 Exploratory Grant to investigate the effects of early-life exposure to arsenic. She is continuing to ferret out such associations and is currently heading a statewide, case-control study that in 2011 received a National Institutes of Health P20 Exploratory Grant to investigate the effects of early-life exposure to arsenic. She is continuing to ferret out such associations and is currently heading a population-based, case-control study that showed 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.
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. Also notable is the wide array of techniques used by members of the program—including spectroscopic tomography, magnetic spectroscopy, fluorescence imaging, and electron paramagnetic resonance, to name just a few modalities. This range of resources provides a novel framework for combining conceptual and practical approaches to clinical decision-making associated with the identification and management of cancer patients.

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.
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:

- Ian Baker, PhD; Keith Paulsen; Brian Pogue; John Weaver, PhD; Jack Hoopes, DVM, PhD, and colleagues found that changes in tumor angiogenesis estimated with diffuse optical spectroscopic tomography correlates with 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 Haber, 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 intravenous 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, Zeva, Inc.; Medtronics; and DUSA Pharmaceuticals.
- Ian Baker, David Roberts, Keith Paulsen; Brain 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 Nanoradiology 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; Hoong Hoon, MD, MS; Lloyd Jervis, 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 pO2 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 biosensor device to measure radiation exposure using electron paramagnetic resonance dosimetry measurements of teeth and fingernails. This approach represents the most advanced physical biosensor 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 colleagues continue to develop MR-guided near-infrared spectral tomography (NIRI) for diagnostic imaging of women with breast screening abnormalities. In clinical use is a 6-channel, custom MR/optical breast coil with a parallel-plate, fiber-optic tissue interface capable of naturally activated fiber positioning, which provides for the first time the option of multiplex optical data acquisition in the MR scanner.
- Brian Pogue and colleagues continue to develop a novel 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.

Keith Paulsen, PhD, is officially based at Dartmouth’s engineering school but has offices in many Norris Cotton floors.

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.”

Harold Swartz, MD, PhD

GEOFFREY HOLMAN
The ultimate goal of the work in the CM Program is the elucidation of cellular and molecular processes governing cell and developmental biology and the consequences of their subversion in cancer.

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 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.
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 model system Drosophila melanogaster, the team found that mutations of Jerky in human cells are associated with juvenile myoclonic epilepsy. This finding reveals a new mechanism for regulatory control of the conserved Wnt signaling pathway through the time-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 Cell Research. (See page 64 for more on Ernst’s career.)

- Scott Gerber, PhD, and colleagues identified the aurora and polo-like kinase phosphorylation sites on 6,061 different proteins during mitosis. They employed selective chemical inhibitors to connect 778 of these sites from one of the two departments in which the most members of Norris Cotton Cancer Center work. (See page 328 for more on the departments.)

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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. It builds on her previous work, particularly a notable 2007 paper in the journal Cell Stem Cell, which reported that a gene known as MLL (mixed lineage leukemia) is essential for the maintenance of the proper number of stem cells in the bone marrow. Since then, Ernst has been trying to define the molecular pathways that MLL controls—one that regulates normal stem cell function and one that leads to leukemia. She’s now using studies to distinguish “the pathway that controls normal stem cells” from “the pathway that’s used wrongly to produce leukemia.”

She hopes this will have therapeutic implications in two ways. The first is that it may be possible to “target the part of the pathway that is dysregulated in leukemia,” she explains. The second relates to cord blood transplants. Her latest, as-yet-unpublished finding is that the normal version of the pathway is responsible for the development of stem cells, including in the developing embryo. “So,” she says, “we’re trying to explore the pathway and figure out how to turn it on a bit to expand cord blood for cord blood transplantation.” It’s “a really burgeoning field,” she adds.

In addition to directing a lab, Ernst collaborates with breast cancer researcher James DiRenzo, PhD, to direct the Cancer Mechanisms Research Program. Though they arrived at Dartmouth independently of one another, Ernst and DiRenzo both trained at Dana-Farber Cancer Institute in Boston. “I didn’t know him there,” Ernst says, but because of their shared background, “we had sort of a natural affinity.” Which makes them naturals to nurture affinities among their fellow members of the CM Program.

José DiRenzo: Studies 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 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 co-founder—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.
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.

The 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, the function of regulatory T cells, 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.

Immunology and Cancer Immunotherapy Program

Kenneth Meehan, MD, head of Dartmouth-Hitchcock’s Blood and Marrow Transplant Program, also codirects the Immunology and Cancer Immunotherapy Program.
Programs

The Immunology and Cancer Immunotherapy Research 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 aiming 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, then 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 vaccine 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.

- Charles Sentman, PhD, and colleagues reported a novel bispecific reagent that can be effective in tumors. 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. BiTE-type 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 killing of melanocytes enhances the immune responses to melanoma. Using a melanocyte-deficient mouse model, the team found that antigens released during melanocyte destruction directly support and maintain T-cell responses to melanoma, establishing that 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 melanomas, it can be treated successfully, at least for a while, with BRAF inhibitors. The team has been examining whether targeting B-RAF inhibition alters the immunogenicity of melanomas 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 infused 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.

A few facts about the ICI Research Program

- Number of members of the Immunology and Cancer Immunotherapy (ICI) Research Program (see page 112 for a list of all the members of the program)

- Number of primary departments represented by those members

- Codirectors Charles Sentman, PhD, and Kenneth Meehan, MD

- Year the three most senior members of the program became members of Norris Cotton Cancer Center

- Year the newest member of the program became a member of Norris Cotton Cancer Center

- Number of members of the Immunology and Cancer Immunotherapy Research Program (ICI) Research Program (see page 112 for a list of all the members of the program)

- Number of primary departments represented by those members

- Codirectors Charles Sentman, PhD, and Kenneth Meehan, MD

- Year the three most senior members of the program became members of Norris Cotton Cancer Center

- Year the newest member of the program became a member of Norris Cotton Cancer Center

- Number of members of the ICI Program who hold an appointment in more than one department

- Number of members of the ICI Program who hold an appointment in more than one department

- Number of members of the ICI Program who hold an appointment in more than one department
Randolph Noelle: Triggering (and liberating) the immune system to attack human tumors

For 25 years, scientists tried to produce effective vaccines against cancer. Finally, more than a decade ago, it was an approach doomed to failure. But now, active vaccines and other targeting therapies able to unleash an immune system 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 ‘take our feet off the brake’ so as to unleash and unrestrain the 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 engages specific, long-lasting immunity. It triggers CD40, and, as with the innate immune system, synthetic drugs called CD40 agonists can activate 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 already has its “foot on the brake.” One reason the body doesn’t naturally mount protective immune responses to cancer is the negative checkpoints that regulate immune responses. 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 therapeutic immune responses 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 title 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 effortlessly upbeat in his pitches to would-be clinical investigators, inspiring 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 55 for the story of one of his patients; it makes it clear why he’s so good at his “sales” job.
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 long-term 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.
fatty acid uptake. The channel for cellular LPL and expressing CD36, circulating by secreting essential fatty acids from tumor cells can acquire 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.

M 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 Plantes, PhD, and colleagues established that inhibition of BCL2 with ART-737 can dramatically sensitize some leukemic 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.
- Members of the Molecular Therapeutics Research Program and colleagues developed a series of novel proteasome inhibitors that are selective for each of the three proteolytic sites primarily inhibit the chymotrypsin-like site. This work identified a lead compound, plus a possible target pathway for MMP13 associated with neurofibromatosis type 1 (NF1), which is caused by a mutation in the gene encoding neurofibromin. This work demonstrated a model system to identify and validate target pathways by which NF1 loss drives tumor formation. This mechanism was studied in various tumor tissues and in HeLa cells. It 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 tissues, but not in the levels of fatty acid synthase, or LPL.
- Lionel Lewis, MB, BS, PhD, 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.
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A few facts about the MT Research Program

- 30 Number of members of the Molecular Therapeutics (MT) Research Program (see page 114 for a list of all the members of the program)
- 7 Number of primary departments represented by those members
- Alan Eastman, MD, and Lionel Lewis, MB, BS, 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 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 these 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 Care Award, “how something happening in the laboratory is actually helping patients.”
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.
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 whoever 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 compliment. 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: “A service mentality”
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 Darmouth’s president asked him to be acting dean of the medical school during the 2002-03 academic year, he spoke “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 science revolution.”

“Fire in the belly. I would define that as there is no external stimulus for doing something. It is an inner drive, a need to explore. And I think that is a key driving force in science.”

The People
Ethan Dmitrovsky, MD
Cornell University Medical College ’80 (MD)
New York Hospital–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, 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 retinoic acid 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, helping to correct 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.”

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 retinoids 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.”

And women in our society.”

“… of the most rare but lethal forms of cancer to investigate,” 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 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.

In November 2005, he and colleagues published a paper in the Journal of the National Cancer Institute (JNCI) that identified a previously unknown retinoid acid receptor. Targeting it, the researchers hypothesized, might restore the beneficial effects of retinoids in lung cancer patients, resulting in cancer prevention.

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 retinoid acid receptor. Targeting it, the researchers hypothesized, might restore the beneficial effects of retinoids in lung cancer patients, resulting in cancer prevention.

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Ethan Dmitrovsky, MD

Ethan Dmitrovsky, MD, right, collaborated on two clinical trials with pathologist Vincent Marini, MD, left, and oncologist Konstantin Dragnev, MD, center.

It’s not a cure for lung cancer, but we’ve taken highly refractory patients that normally would not be expected to respond—no 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 those side effects: among patients who exhibited a rash or elevated triglyceride levels, the survival increase was even better—an average of 6 months.

When 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.”

When Dmitrovsky talks about findings like those that came 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.

The People

Ethan Dmitrovsky, MD

When Dmitrovsky talks about findings like those 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 makes a point of noting that “all of this work has essentially been done here at Dartmouth.” Pathologist Vincent Menisch, MD, and oncologist Komminats Drag-
nev, MD, for example, were key contributors to the 2011 clinical trial.

And, Dmitrovsky emphasizes, “students of all stripes,” from novice undergrad to seasoned postdocs, “are foremost in this effort. I look on students as my col-
leagues,” 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, even if they call me Doctor, I treat them as any other professional.”

That model is scaled weekly by former students.

Kristen Garner, who completed her PhD in phar-
maceutical sciences in 2010, recalls that 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
really means it,” she says. Garner is now a strategy con-
sultant in the life sciences arena at Health Advances, a

global biomedical consulting firm.

And, Dmitrovsky emphasizes, “students of all

The People

Ethan Dmitrovsky, MD

It wasn’t until he left Dartmouth that Petty appreciated the extent

That model is recalled warmly by former students.

Ethan Dmitrovsky, MD, for example, were key contributors to the
2011 clinical trials. On one occasion, he attended a rather important oncology seminar 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 spent a late night in his
office revising grants for postdocs and reviewing papers for major journals.

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 David 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 Clare-
more, Okla., and with the International Rescue Committee in a refugee camp
on the Cambodian-Thai border—experiences that helped shape his commit-
tment to service. And when he was a resident at New York Hospital-Memorial
Sloan-Kettering Cancer Center, the chair of medicine was legendary physi-
cian-scientist Ralph Nachman, MD, who, says Dmitrovsky, “has been an in-
fuential person in my entire career.”

“it’s a real privilege to work as a physician-scientist,” Dmitrovsky de-
clares. “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 gains what he gives.

In both word and deed, Ethan Dmitrovsky, MD—pictured here with Lorenzo
Sempere, PhD, right, a research assistant professor—advocates his regard for
the work of everyone in his lab, from undergrads to fellow faculty members.

Page 86 • All Together Now: Dartmouth’s Norris Cotton Cancer Center

Page 87 • All Together Now: Dartmouth’s Norris Cotton Cancer Center

The People

Ethan Dmitrovsky, MD

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. Upon realizing that, Petty was all the more surprised that “he in-
volved 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 David 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 Clare-
more, Okla., and with the International Rescue Committee in a refugee camp
on the Cambodian-Thai border—experiences that helped shape his commit-
tment to service. And when he was a resident at New York Hospital-Memorial
Sloan-Kettering Cancer Center, the chair of medicine was legendary physi-
cian-scientist Ralph Nachman, MD, who, says Dmitrovsky, “has been an in-
fuential person in my entire career.”

“it’s a real privilege to work as a physician-scientist,” Dmitrovsky de-
clares. “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 gains 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 that, 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
would link drugs to fish: acid to target them to the folate receptor on cancer cells. It was interesting, but it was also so simple.” The hypothesis were straightforward, she recalls. “It was just too mechanical. It got really boring.”

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. “I didn’t really know any immunology. So I took an immunology course.” And, suddenly, the light shone on what she already knew, but didn’t realize it:

“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.”

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, and melanoma was 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. Turk “had no question—that’s exactly where I wanted to be.”

Education

John Carroll University ’95 (BS in chemistry); Purdue University ’01 (PhD in biochemistry)

Training

Memorial Sloan-Kettering Cancer Center (fellowship in immunology)

First job

“My first real job was telemarketing—magazine sales. I did it for a summer, a short summer. I was horrible at it. I got fired. Well, I told them I was leaving and they fired me at the same time.”

“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 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 dismal stretches of failed experiments will pale in comparison to the joy of a single new finding.”

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 we don’t know that,” asserts Turk. “I think that’s a false argument. People say that because there are spontaneous regressions of 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.
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 bed-ridden, 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 directly. 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 those 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, 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. 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.
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 of how to look at cancers of nonessential organs.”

In a difficult set of experiments, Turk says, another graduate student, Katelyn Byrne, showed that in mice which exhibit an autoimmune response—evidenced by destruction of the melanocytes—there is a good immune response against cancerous skin cells or breast cells, for example, “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 immune response,” because the liver is an essential organ. By contrast, explains Turk, in experiments with her laboratory, she realized that the control of that “dimmer switch” didn’t need to be so finely calibrated in the organism’s existence. “So she realized that the control of that ‘dimmer switch’ didn’t need to be quite so finely calibrated in cancerous of nonessential organs.”

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William Black, MD: “A call to order”

W illiam 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.

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 as more. The big uncertainty is ... understand- ing how effective our interventions, our treatments, are — as well as if, and when, they should be used.

He examined to test and refine his ideas on the subject while serving for four years on the faculty at the University of Virginia, than for three years at the Na- tional Institutes of Health, where he conducted health outcome 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, an- other 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 ex- tremely careful researcher who really raises some funda- mental questions,” Welch says. “He expresses some of the more interesting and important ideas in medicine.”

Finding that they shared an interest in understand- ing the benefits of screening and in studying health outcomes, Black and Welch began a long and productive collaboration. Their work includes a concept now summarized 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. 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. For example, 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 dev- estating side effects. As a result, almost everyone with a positive finding on a screening test gets treated. As a result, almost everyone with a positive finding on a screening test gets treated. But that approach misses a soft-potting-styling, 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 summariz- ing their thoughts on overdiagnosis in cancer. Overdiagnoses, they write, “are the diagnosis of a ‘cancer’ that would otherwise not go on to cause symptoms or death.” Because 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 dev- estating side effects. As a result, almost everyone with a positive finding on a screening test gets treated. But that approach misses a soft-potting-styling, 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.

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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 finding that Black says is truly significant. “Even though the participants with a positive CT scan received an invasive procedure—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 who got 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 observed that this showed that it is possible to do large-scale 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.”

“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.”
The members of 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, clinical 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.

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 Tusher 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.

Members of the Research Programs: “Science for society”
Cancer Control Research Program

Anna Adachi-Mejia, PhD • Member since 1997
Assistant Professor of Pediatrics
Professor of Community and Family Medicine
Performs statistical analysis of longitudinal data, epidemiologic risk modeling, and population assessment of media exposures.

Ethan M. Berke, MD • Member since 2010
Professor of Community and Family Medicine
Professor of Anesthesiology
Professor of Medicine
Performs statistical analysis of longitudinal data, epidemiologic risk modeling, and population assessment of media exposures.

Ardis L. Olson, MD • Member since 1997
Professor of Community and Family Medicine
Professor of Anesthesiology
Professor of Medicine
Studies colorectal cancer screening and prevention, effectiveness research in general.

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Anna Adachi-Mejia, PhD • Member since 1997
Assistant Professor of Pediatrics
Professor of Community and Family Medicine
Performs statistical analysis of longitudinal data, epidemiologic risk modeling, and population assessment of media exposures.
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 T. Danil, MD, MPH • Member since 2005
Assistant Professor of Pediatrics
Studies the adoption of cancer risk behavior during adolescence, the measurement of secondhand-smoke exposure, and smoking cessation for parents.

Anna N. A. Tosteson, ScD • Member since 1993
Assistant Professor of Pediatrics
Studies breast cancer, diagnostic reproducibility, prognostic markers, and quantitative biophysiological correlates to validate breast imaging.

Lisa Schwartz, MD, MS, and Steven Woloshin, MD, MS

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 care and conducts proof-of-concept clinical trials.

Diane Gilbert-Diamond, DDS • 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 Community and Family Medicine
Professor of Medicine
Director of Clinical Research, Department of Obstetrics and Gynecology
Studies women's use of preconception nutrition, and the effect of oxidative stress on implantation and early pregnancy loss.

Brook C. Christiansen, PhD • Member since 2011
Assistant Professor of Community and Family Medicine
Assistant Professor of Pharmacology and Toxicology
Uses molecular biology, genomics, bioinformatics, and quantitative methods to study determinants of human epigenome and its effect on disease risk and survival data, and measurement error.

Zhigang Li, PhD • Member since 2011
Assistant Professor of Community and Family Medicine
Assistant Professor of Pharmacology and Toxicology
Works on the development and application of statistical methods for high-dimensional data (e.g., microarrays, SNP arrays, proteomics).

Jiang Gui, PhD • Member since 2007
Director of Clinical Research, Department of Obstetrics and Gynecology
Use epidemiologic methods to study determinants of the human epigenome and its effect on disease risk and outcome; develops translational biomarkers.

Margaret R. Karagas, PhD • Member since 1996
Professor of Genetics
Professor of Community and Family Medicine
Professor of Medicine
Codirector, Cancer Epidemiology and Chemoprevention Research Program
Studies vitamin A derivatives (retinoids) in cancer prevention and molecular epidemiology of endometrial, ovarian, and prostate cancers.

Jennifer A. Doherty, PhD • Member since 2012
Codirector, Cancer Control Research Program
Serves in bench-to-bedside (translational) research.

Ethan Dmitrovsky, MD • Member since 1998
Director, Institute for Quantitative Biomedical Sciences
Applies studies in human genetics, bioinformatics, and the analysis of complex biomolecular data to theoretical aspects of cancer science.

Christopher L. Amos, PhD • Member since 2006
Professor of Cancer Epidemiology and Cancer Center
Professor of Community and Family Medicine
Professor of Medicine
Uses molecular biology, genomics, bioinformatics, and quantitative methods to study determinants of human epigenome and its effect on disease risk and outcome; develops translational biomarkers.

Ying Qi, PhD • Member since 2008
Assistant Professor of Pharmacology and Toxicology
Develops statistical methods and studies genetic and molecular toxicology and genetic and molecular epidemiology of endometrial, ovarian, and prostate cancers.

Angeline S. Andrew, PhD • Member since 2002
Assistant Professor of Community and Family Medicine
Studies breast cancer, diagnostic reproducibility, prognostic markers, and quantitative biophysiological correlates to validate breast imaging.

Erik M. Jacobs, MD, PhD • Member since 1996
Professor of Community and Family Medicine
Professor of Medicine
Professor of Epidemiology
Focusing on informed choice in health care and oncologic plastic surgery (e.g., breast reconstruction).

H. Gilbert Welch, MD, MPH • Member since 1993
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.

JON GILBERT FOX

Jiang Gui, PhD • Member since 2007
Director of Clinical Research, Department of Obstetrics and Gynecology
Use epidemiologic methods to study determinants of the human epigenome and its effect on disease risk and outcome; develops translational biomarkers.

Carmen J. Murat, PhD • Member since 2011
Assistant Professor of Pharmacology and Toxicology
Specializes in longitudinal and clustered data analysis, survival analysis, joint modeling of longitudinal and time-to-event, and measurement error.

Jason H. Moore, PhD • Member since 2004
Professor of Genetics
Professor of Community and Family Medicine
Professor of Medicine
Director of Institute for Quantitative Biomedical Sciences
Associate Professor of Biostatistics, Norris Cotton Cancer Center
Director, Bioinformatics Shared Resource
Applies studies in human genetics, bioinformatics, and the analysis of complex biomolecular data to theoretical aspects of cancer science.
Judy R. Rees, BS, BC, MHI, 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 drug resistance, cancer epidemiology, infectious disease epidemiology, childhood controlled trial methodology, and vitamin D
Douglas J. Robertson, MD, MPH • Member from 2001
Associate Professor of Medicine
Associate Professor of Pharmacology
Conducts research involving environmental and occupational medicine
Barjor Gimi, PhD • Member since 2011
Research Assistant Professor of Radiology
Focuses on experimental cancer therapeutics (e.g., photodynamic, hyperthermia), animal models, pathology, and imaging.

Richard Rothstein, MD
Cancer Imaging and Radiobiology

Research Program

Ian Baker, DPhil • Member since 2005
Memorial/MD Anderson Cancer Center
Senior Associate Director for Scientific Affairs, Thayer School of Engineering
Focuses on advanced engineering methods—mechanical behavior, phase transformations, EM, x-ray tomography, and diffraction—to cancer research.

Ian Baker, DPhil • Member since 2002
Research Assistant Professor of Community and Family Medicine
Academic Director, Thayer School of Engineering
Conducts research involving gastrointestinal and neurological pathology (e.g., neuroepithelial, neuropathology, neuroimaging, and neuropathology).

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

Michael B. Sparn, MD • Member since 1996
Grady C. Coch, PhD, MSc, Foundation Professor of Pharmacology and Toxicology
Focuses on cancer chemoprevention—phytochemicals and outrosides as anti-inflammatory, antioxidants, anticarcinogenic agents.

Linda J. Titus, PhD • Member since 1996
Professor of Community and Family Medicine
Professor of Pediatrics
Conducts research involving environmental and occupational medicine.

Lesley A. Jarvis, MD, PhD • Member since 2011
Research Associate Professor of Radiology
Professor of Engineering
Conducts research involving radiological imaging and image-guided oncological surgery.

Brian W. Pogue, PhD • Member since 1997
Professor of Engineering
Adjunct Professor of Surgery
Professor of Physics and Astronomy
School of Engineering
Codirector, Cancer Imaging and Radiobiology Research Program
Focuses on biomedical applications and its integration with focused ultrasound surgery applications.

Lesley A. Jarvis, MD, PhD • Member since 2011
Research Associate Professor of Radiology
Professor of Engineering
Codirector, Cancer Imaging and Radiobiology Research Program
Focuses on biomedical applications and its integration with focused ultrasound surgery applications.

Ryan J. Halter, PhD • Member since 2010
Research Assistant Professor of Engineering
Associate Director, Research and Development Center for Medical Imaging (RDCMI)
Studies free radical biology, oxygen metabolism in solid tumors, and cancer therapeutics, including imaging, hyperthermia, and targeted therapy.

Pat M. Mowry, PhD • Member since 2002
Professor of Engineering
Conducts research on the development of genitourinary and urologic pathology (e.g., nephropathy, genitourinary, and urologic diseases).
Constance Brinckerhoff, PhD • Member since 1996
Professor of Biochemistry
Investigates transcriptional mechanisms and distal regulatory elements regulating c-myc expression and other genes relevant to cancer.

Michael D. Cole, PhD • Member since 2003
Professor of Genetics
Studies the control of cell cycle progression, the behavior of tumor cells.

James B. Moseley, PhD • Member since 2010
Professor of Pathology
Investigates endocrine, neuroendocrine, bone, pulmonary, and surgical pathology.

Vincent A. Memoli, MD • Member since 2007
Professor of Surgery
Novel animal models of human brain tumors.

Steven N. Fiering, PhD • Member since 1996
Associate Professor of Genetics
Studies pathways regulating hematopoietic stem cell development and maintenance, leukemia, and the epigenetic regulation of both.

Amy S. Gladfelter, PhD • Member since 2006
Associate Professor of Biochemistry
Studies the structural basis and the mechanism of action of different peptide hormones.

Mark A. Israel, MD • Member since 2001
Chair, Department of Pathology
Examines the transport of messenger RNA from the nucleus to the cytoplasm and its impact on normal and abnormal cell biology.

Duane A. Compton, PhD • Member since 1996
Professor of Pharmacology
Conducts research involving brain tumors, epileptic disorders, migraines, and trigeminal neuralgia.

Dale F. Mierke, PhD • Member since 2011
Professor of Pathology
Investigates the transport of messenger RNA from the nucleus to the cytoplasm and its impact on normal and abnormal cell biology.

Yashi F. Ahmed, MD, PhD • Member since 2002
Conducts research involving the genetic control of human tumors.

Andrew G. Wallace Professor of Pharmacology and Toxicology
Ethan Dmitrovsky, MD • Member since 2002
American Cancer Society Professor
Analyzes chromosomal instability and aneuploidy in other genes relevant to cancer.

Andrew G. Wallace Professor of Medicine
Investigates molecular toxicology—host genetic consequences of APC loss.

Amy S. Gladfelter, PhD • Member since 2006
Associate Professor of Biochemistry
Studies dynamic changes in global chromosome structure and nuclear architecture and their impact on cell division and gene expression.

Angeline S. Andrew, PhD • Member since 2002
Assistant Professor of Genetics
Investigates transcriptional mechanisms and distal regulatory elements regulating c-myc expression and other genes relevant to cancer.

Constance Brinckerhoff, PhD
Professor of Biochemistry
Examines the transport of messenger RNA from the nucleus to the cytoplasm and its impact on normal and abnormal cell biology.

Ethan Dmitrovsky, MD
Senior Associate Dean for Research, Geisel School of Medicine
Directs, Transgenics and Genetic Constructs Shared Resource

Scott A. Gerber, PhD • Member since 2006
American Cancer Society Professor
Conducts research involving brain tumors, epileptic disorders, migraines, and trigeminal neuralgia.

Duane Compton, PhD
Director, Transgenics and Genetic Constructs Shared Resource

Scott A. Gerber, PhD
Director, Proteomics Shared Resource

James DiRenzo, PhD • Member since 2001
Associate Professor of Pharmacology and Toxicology
Conducts research involving the genetic control of human tumors.

Scott Gerber, PhD
Director, Cancer Mechanisms Research Program
Assistant Professor of Pharmacology and Toxicology

Mark A. Israel, MD
Chair, Department of Pathology
Conducts research involving the genetic control of human tumors.

Friday afternoon began with the plenary session of the Cancer Mechanisms Research Program, which was followed by the Cancer Imaging and Radiobiology Research Program. These sessions highlighted recent advances in the field of cancer research, including the development of new diagnostic and therapeutic approaches.
Mary Ja Mulgann-Kathan, PhD • Member since 2002
Associate Professor of Surgery
Investigates angiogenesis in mouse models of atherosclerosis and the function of PDL-1 proteins as anti-angiogenic agents.

Laurence C. Myer, PhD • Member since 2000
Associate Professor of Biochemistry
Designs tools to reveal the basic mechanisms that facilitate positive/negative cytokine gene regulation at the molecular level.

C. Herko Rhodes, MD, PhD • Member since 2007
Professor of Radiology
Conducts research that involves the molecular biology of plasmin, the molecular pathogenesis of neuro-psychiatric disorders, and neuropathology.

Richard M. Saito, PhD, Member since 2005
Associate Professor of Genetics
Conducts research that involves the regulation of gene expression during cell division and the identification and mechanisms underlying telomerase subunits.

Immunology and Cancer Immunotheraphy Research Program

Richard J. Barlow, MD, Member since 1996
Associate Professor of Surgery
Chief, Section of General Surgery
Conducts research involving hematology and bone marrow transplantation, including autologous grafts in transplantation, and cancer vaccines.

Brent L. Berwin, PhD • Member since 2004
Associate Professor of Microbiology and Immunology
Studies the hormone and cytokine regulation of macrophage function.

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 telomerase subunits.

Immunology and Cancer Immunotheraphy Research Program

Randolph J. Noelle, PhD • Member since 1996
Professor of Microbiology and Immunology
Associate Director for Clinical Research, Norris Cotton Cancer Center
Focuses on cancer immunotherapy, especially as it relates to melanoma and renal-cell carcinoma.

Mark W. Mullins, PhD • Member since 2011
Assistant Professor of Microbiology and Immunology
Focuses on regulatory T cell biology, B cell memory/plasma cell development, immune tolerance in transplantation, and autoimmunity.

Lawrence J. Smith, PhD • Member since 1992
Research Assistant Professor of Microbiology and Immunology
Studies biomarkers for multiple sclerosis to predict responder status and to predict disease progression.

James D. Gorham, MD, PhD • Member since 1999
Professor of Medicine
Focuses on novel cellular therapies applied across the field of medicine and evidence-based approaches to the use of apheresis.

Edward J. Usherwood, PhD • Member since 2002
Associate Professor of Physiology and Neurobiology
Studies tumor immunology, T cell memory to tumors, the role of autoimmunity, and the immunology of molecularly targeted cancer therapies.

Charles L. Sontag, 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 immune immunity and NK cells.

Jacqueline Y. Smith, PhD • Member since 1992
Research Assistant Professor of Microbiology and Immunology
Studies the immune responses to viral infections and how the immune receptors, how they function in tumor models, and innate immunity and NK cells.

Edward J. Usherwood, PhD • Member since 2002
Assistant 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.

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Codirector, Immunology and Cancer Immunotherapy Research Program
Investigates new cancer immunotherapies based on immune receptors, how they function in tumor models, and immune immunity and NK cells.

James D. Gorham, MD, PhD • Member since 1999
Professor of Medicine
Focuses on novel cellular therapies applied across the field of medicine and evidence-based approaches to the use of apheresis.
Develops novel cancer chemotherapeutic strategies that target cell cycle checkpoint regulators and the process of apoptosis.

Burton G. Eisenberg, MD • Member since 1995
Professor of Surgery
Studies the molecular basis of cancer initiation, growth, and metastasis.

Elinor B. Krusin, PhD • Member since 1997
Professor of Pharmacology and Toxicology
Investigates the translational application of novel drug targets regulating pathways for breast cancer therapy.

William G. North, PhD • Member since 1983
Professor of Pathology and Laboratory Medicine
Studies how cancer cells acquire and evade programmed cell death to acquire chemoresistance.

J. Marc Pipas, MD • Member since 2007
Associate Professor of Medicine
Focuses on genetic screens for drug discovery.

Gustav E. Lienhard, PhD • Member since 1997
Assistant Professor of Pharmacology and Toxicology
Researches small molecules that target proteins in cancer and as drug targets for cancer; uses chemical genomics for drug discovery.

Oscar M. Cohn ’34 Professor of Pharmacology and Toxicology
Michael J. Spinella, PhD • Member since 1998
Associate Professor of Pharmacology and Toxicology
Studies cell-cycle checkpoints in the etiology of cancer and as drug targets for cancer; uses chemical genomics for drug discovery.

Gary N. Schwartz, MD • Member since 2001
Associate Professor of Medicine
Investigates pharmacodynamic and pharmacokinetic drug discovery.

Manabu Kurokawa, PhD • Member since 2012
Associate Professor of Pharmacology and Toxicology
Studies the molecular dissection of cancer initiation, growth, and metastasis.

Christopher H. Lowrey, MD • Member since 1996
Professor of Medicine
Conducts research involving sarcoma, breast, and gastrointestinal malignancies.

Burton L. Eisenberg, MD • Member since 1995
Professor of Surgery
Studies the molecular basis of cancer initiation, growth, and metastasis.

Manabu Kurokawa, PhD • Member since 2012
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William B. Krusin, MD • Member since 1997
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Investigates novel cancer chemotherapeutic strategies that target cell cycle checkpoint regulators and the process of apoptosis.

Elinor B. Krusin, PhD • Member since 1997
Professor of Pharmacology and Toxicology
Investigates the translational application of novel drug targets regulating pathways for breast cancer therapy.

Todd W. Wieler, PhD • Member since 2012
Assistant Professor of Pharmacology and Toxicology
Investigates the translational application of novel drug targets regulating pathways for breast cancer therapy.

J. Marc Pipas, MD • Member since 2007
Associate Professor of Medicine
Focuses on genetic screens for drug discovery.

Michael J. Spinella, PhD • Member since 1998
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Studies cell-cycle checkpoints in the etiology of cancer and as drug targets for cancer; uses chemical genomics for drug discovery.

Gary N. Schwartz, MD • Member since 2001
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Investigates pharmacodynamic and pharmacokinetic drug discovery.

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Associate Professor of Pharmacology and Toxicology
Studies the molecular basis of cancer initiation, growth, and metastasis.

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Conducts research involving sarcoma, breast, and gastrointestinal malignancies.
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 improve 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
603-655-9000 • 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.