Form & Function

By Laura Stephenson Carter

Combating cancer has always been a complex enterprise, requiring the efforts of clinicians and researchers from across many disciplines. Now, the work of Dartmouth's Cancer Center is truly coming together, in new space designed to enhance multidisciplinary collaboration.

First it was an idea. Then it was a "little kiosk." Now it's a spectacular multistory, glass-fronted building. Dartmouth's Norris Cotton Cancer Center has come a long way since the late 1960s.

That was when Frank Lane, M.D., then the director of radiation therapy at Mary Hitchcock Memorial Hospital, concluded that New Hampshire's cancer-treatment facilities were inadequate. The state's death rate from cancer was among the highest in the country, even though its incidence of cancer wasn't above the national average. So Lane set out on a crusade to build a cancer center. Thanks to U.S. Senator Norris Cotton—who represented New Hampshire in Washington, D.C., from 1954 to 1975—$3 million in federal monies were allocated for the purpose.

By 1972, the first phase of the facility opened—two underground stories housing a 45-million-volt Betatron for radiation therapy, as well as space for clinical oncology, nuclear medicine, radiobiology, and radiation physics research. Lane was named director of the center, which itself was named for Senator Cotton. But the building's physical presence was underwhelming. Its only visible, aboveground manifestation was—as O. Ross McIntyre, M.D., who succeeded Lane as director, describes it—"a little kiosk in the middle of the parking lot" for Mary Hitchcock Memorial Hospital.

Then in 1973, Congress allocated another $4 million for an addition—two aboveground stories that were completed in 1977. By 1975, McIntyre had taken over as director, and he led the Cancer Center for the next 17 years.

Early on, there was a realization 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," explains McIntyre. "I became a proponent of the view that . . . interdisciplinary programs make more progress than single-disciplinary programs if you are talking about human medicine."

McIntyre's success in nurturing a collaborative spirit and in recruiting well-funded investigators brought the Cancer Center to national recognition. Under his leadership, in 1990, Norris Cotton became one of the first cancer centers in the country to be designated by the National Cancer Institute (NCI) as a comprehensive cancer center.

Laura Carter is the associate editor of Dartmouth Medicine.

When the Cancer Center opened in 1972, it consisted of two underground levels and the "little kiosk" visible on the left.

By 1977, the two aboveground stories depicted in the foreground of this photo had been added to the Cancer Center.

In 1995, the center's clinical operations moved into the Rubin Building, above, on DHMC's Lebanon campus. And a few months ago, cancer researchers joined clinicians in a four-story addition—whose dramatic facade is pictured on the facing page and its insides in the inset and on the following pages.

Although Dartmouth's new space is even more open than the labs at the Whitehead Institute, Speck says that "we tried to reach a little bit of a balance. A truly open lab . . . I think has kind of a warehouse-like look to it. What we were hoping to do was create 'neighborhoods' that weren't so large that they would be daunting."

Edward Bresnick, Ph.D, chair of DMS's Department of Pharmacology and Toxicology, took over as director in 1992 and research funding continued to grow faster than the national average. In 1994, upon Bresnick's departure to become vice chancellor for research at the University of Massachusetts Medical Center, he was succeeded by epidemiologist E. Robert Greenberg, M.D., a longtime member of the DMS faculty.

The challenge Greenberg faced was to reunite the Cancer Center's clinical facilities with the rest of DHMC. In 1991, DHMC had moved from Hanover to Lebanon, to a complex designed by the Boston-based architectural firm Shepley Bulfinch Richardson and Abbot. The Cancer Center had been left 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-story 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 contained the radiation oncology and hematology-oncology services, related laboratories and offices, a conference room, and a 165-seat auditorium.

But although the Norris Cotton Cancer Center 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 in the Borwell Research Building on DHMC's Lebanon campus, but many were still back on DMS's Hanover campus.

So when Mark Israel, M.D., a pediatrician and cancer researcher from UC-San Francisco, succeeded Greenberg as the Cancer Center's director in 2001, he wanted to bring all the cancer researchers together in one building. Planning was already under way for an addition to the Rubin Building, and Israel moved quickly to ensure that, as he explains it, the "physical lab space . . . would enhance the opportunities for interdisciplinary interactions and collaborations."

Designing the addition was itself a collaboration between the Shepley Bulfinch architects and members of the Cancer Center, including Israel. Together they figured out how to create communal spaces where people would be likely to run into one another—like they do at the post office or the supermarket—and strike up conversations. The idea is that these informal interactions can spark ideas that can turn into fruitful research endeavors. That meant opening up the walls between the labs and turning the research space into "neighborhoods."

ALL: FLYING SQUIRREL GRAPHICS

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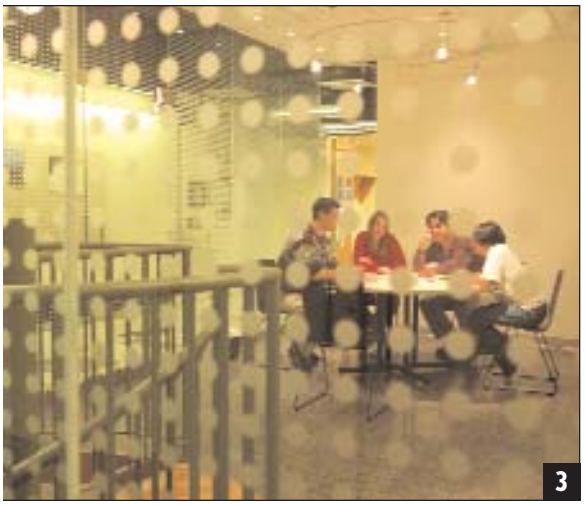
Nancy Speck, Ph.D., who cochaired the planning committee, has a clear recollection of the first presentation made by the architects. They "showed us some of the classic landmarks in scientific buildings," she says, including the Salk Institute and the Whitehead Institute at MIT. "I had actually worked in the Whitehead," she adds. "It was an open design, and as a postdoc working there I found it a fabulous environment. So I had some feeling myself for what an open environment was like, because I had worked in one and liked it very much."

Although Dartmouth's new space is even more open than the labs at the Whitehead Institute, Speck says that "we tried to reach a little bit of a balance. A truly open lab—where you have all the offices on one end and just rows of benches as far as you can see—I think has kind of a warehouse-like look to it. What we were hoping to do was create 'neighborhoods' that weren't so large that they would be daunting."

Malcolm Kent, the Shepley Bulfinch architect who oversaw the Norris Cotton addition, agreed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1 *Nancy Speck, left, cochair of the planning committee that oversaw the design of the addition, confers here with Mark Israel, the Cancer Center's director, after the move into the new space. Its common areas were designed to foster interactions, such as* **2** *daily afternoon tea in the atrium,* **3** *get-togethers in the glass-walled break rooms, and chance meetings* **4** *along the balconies that ring the atrium or* **5** *on the atrium's lowest level. The new space features practical details such as* **6** *easily moveable shelves and* **7** *adjustable lab benches, plus aesthetic touches such as* **8** *sun-dappled stairwells and* **9** *windows in every lab. And to facilitate impromptu brainstorming sessions, there are* **10** *whiteboards in handy locations throughout the lab areas; here, Alan Eastman works at the board while Bethany Salerni, Ray Perez, and Giovana Alonso look on.*

The labs ring the perimeter of the 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. Whiteboards are placed strategically throughout the lab areas to encourage impromptu brainstorming sessions. And the centerpiece of the addition is a dramatic three-story atrium intended to serve as a crossroads.

that early open labs elsewhere were too warehouse-like. So he modified the design for Dartmouth so the space would feel intimate but not cloistered.

The $40-million addition went up rather than out. Consisting of four new stories, it nearly doubled the building's size, to 200,000 square feet. The project also includes extensive renovation of the clinical areas on the three original floors—work that was still ongoing at press time. The top new floor contains offices for Cancer Center administrators and epidemiology researchers. The lowest new floor contains more administrative space and offices for clinicians. And in between are two floors with the new "laboratories without walls."

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In recent years, architects have been designing research buildings as beautiful as theaters, museums, and hotels. This is for very practical reasons—the goal is that people will love to go to work in such buildings and that interdisciplinary collaborations will flourish in a place where people enjoy mingling.

Atrium-style buildings are inspired, in part, by the 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 architect Malcolm Kent. "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 addition is off to a good start. Although it's been occupied for just a few months, people are already mingling in the atrium over daily afternoon tea, meeting there to take a break from the lab environment, and using the conference rooms located just off the soaring space. There have even been a couple of large receptions

Optimal space for science

The comments below by researchers regarding the benefits of open-space scientific labs like those in Dartmouth's Cancer Center addition were excerpted from interviews conducted by Dartmouth Medicine *Associate Editor Laura Carter.*

Charles Brenner, Ph.D.

Brenner, codirector of the Cancer Mechanisms Research Program, uses genetics, protein biochemistry, and x-ray crystallography to dissect the cellular functions of enzymes that play a role in cancer.

The room where I did my graduate work had six benches and six individuals from six different laboratories, so there was a lot of cross-pollination.

Medicine is such a complicated problem. I might identify a molecular target for genotype-specific treatment of a particular type of tumor, and work on the enzymology of that molecule and potentially obtain some lead compounds to inhibit a particular enzyme. But if I don't consider the cellular, organ, and physiological effects of inhibiting that target in a living animal, in a living cancer patient, then ultimately that drug would fail at some point before it gets to the clinic. The benefit of having researchers in the Cancer Mechanisms Program, the Immunology Program, the Molecular Therapeutics Program, and other programs in this building is that we talk to each other about our research interests and we try to consider in advance the rate-limiting steps to improve cancer care.

Randolph Noelle, Ph.D.

Codirector of the Immunology and Cancer Immunotherapy Research Program, Noelle does research on CD40 cell-signaling.

I see tremendous advantages to the open labs. The architectural design and engineering is superb. It's bright, it's cheery, it's lively. That has a very significant impact on doing science. Science is a chore if you're in unattractive surroundings. Everything you can do to improve your environment is very worthwhile.

And I don't see any disadvantages. The disadvantage I had perceived is not one. Each lab has its own personality. We have a rather chaotic, loud, obnoxious personality as a lab, and I thought the open space would dampen individualism. It doesn't. It's so well-engineered that one group can express their personalities without interfering with other groups.

We are already talking about brain tumor

models with Mark Israel. My postdocs talk to his postdocs about applying our immunology expertise to his brain tumor expertise. That wouldn't have happened as quickly if our people weren't talking to one another. It's not just me. Actually, I'm probably the least important. It's our people—our postdocs and graduate students—talking to one another. It's sitting in the coffee room. It's people getting to know one another—having casual contact—that leads to really important scientific relationships.

Michael Cole, Ph.D.

Cole, a member of the Cancer Mechanisms Research Program, studies genetic events leading to cell proliferation and cancer. Among his collaborators is geneticist Steven Fiering, Ph.D.

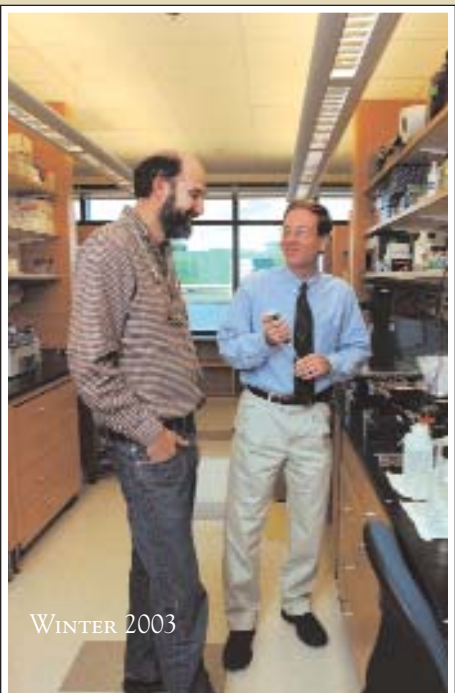
The person I've had more contact with so far is Steve Fiering, who is a mouse geneticist mainly. I'm interested in chromosomes in gene regulation, in oncogenesis. Steve has been working for a long time on bigger questions of chromatin structure and how long-range interactions can control gene regulation. That's exactly the kind of thing that I've been working on for a long time. We all put in our dibs for who we wanted to be next to, and he ended up being the one who was a good pairing.

Christopher Lowrey, M.D.

Codirector of the Cancer Mechanisms Research Program, Lowrey studies how cancer subverts normal cell growth and behavior.

I just happened to bump into Steve Fiering in the hall, and we started talking about a project that we're doing together. We're studying how genes get turned on and off in blood cells. We're working on a brand new system that no one else is using, so we have to work out some things from the ground level. For the first time, our offices are right next to each other, our labs are right next to each other. Even in the week that we've been together it's made a difference already.

BOTH: FLYING SQUIRREL GRAPHICS



Kenneth Meehan, M.D.

Meehan, director of the Bone Marrow Transplant Program and a member of the Immunology and Cancer Immunotherapy Research Program, works on Interleukin-2 therapy for myeloma.

I like the open-air atmosphere. It lends itself to creativity. We are finding that there's a lot of molecular similarity between tumors—that you might be able to use the same drug to treat different tumors based on cell mechanisms. In an environment like this, hopefully a lot of clinicians will be in tune to opening up their horizons and saying, "Let's not use just the old standard chemotherapy, let's try some of these new drugs and see if they work, based on molecular mechanisms."

William Kinlaw III, M.D.

A member of the Cancer Mechanisms Research Program, Kinlaw does research on a protein called S14.

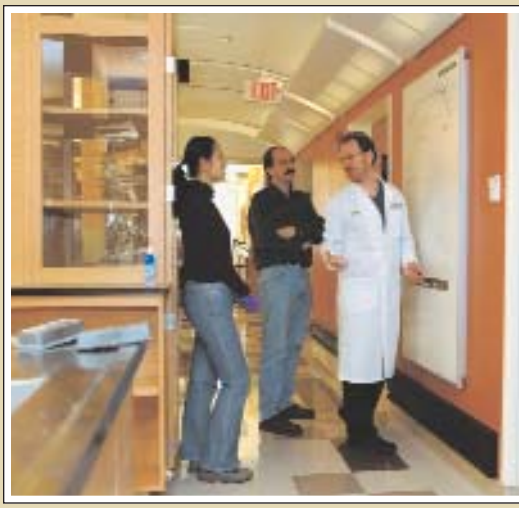
I really liked the group that was in my immediate vicinity up in Borwell. But over the years, my research changed so that slowly I morphed into somebody who had very little in common in terms of research with the folks that I was in the midst of.

Everybody is showing a really good heart with this move. For people who are used to having their own little bailiwick, their own lab space, it's a change to be sharing everything. It raises some obvious possibilities for friction and territorialism. But I haven't seen any of that—not any—which surprised me. I was even worried that I might start showing it, especially with sharing my tissue culture. But this obviously seems a more efficient way to do things. It seems like it's really going to offer a lot more possibilities for informal interactions that are productive.

E. Robert Greenberg, M.D.

A member of the Epidemiology and Chemoprevention Research Program, Greenberg is also former director of the Cancer Center. He works on the national cancer registry program of the Centers for Disease Control.

You don't want people going off into their offices like turtles. When you have nice open spaces, people will take the opportunity to sit down and discuss ideas. It adds to the interconnectedness, and the Cancer Center is an organization that requires interconnectedness—it's at the heart of what the center is. Form follows function, if you will.



Above: Charles Brenner, right; Pawel Bieganowski, center; and Huan Liu, left, strategize at a whiteboard. Below: Steve Fiering, left, and Chris Lowrey, right, now have adjacent labs.

Tim Ahles, Ph.D.

A member of the Cancer Control Research Program, Ahles studies the cognitive effects of chemotherapy and works on improving palliative care and the care of chronic illnesses.

When we were back in Hanover, basic science people were in labs that were in different buildings; paths did not cross that often. I think by moving out here, and with the new Cancer Center space, people are brought into closer proximity. It's become much easier to collaborate.

Alan Eastman, Ph.D.

Eastman is codirector of the Molecular Therapeutics Research Program. He studies novel molecular targets and collaborates with oncologist Raymond Perez, M.D., on developing new drug strategies to treat cancer.

Ray Perez and I are actually going to integrate our research meetings. We're going to be sharing a tremendous amount of equipment and an office complex as well. The work that we do is completely different on a scientific basis. I'm doing preclinical development, looking for novel molecular targets—strategies for therapies. But that's meaningless if I can't put them into a patient.

I see the new space as facilitating far more interaction with everybody. You talk to people you meet in the corridor. You talk to people you meet at the coffeepot. Science is

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"To cure a disease," explains immunologist Randolph Noelle, Ph.D., "one has to apply many different types of science." The new building is aimed at "bringing those disciplines in juxtaposition to one another. And getting people to talk to one another. You know, everybody's busy. Unless you happen to walk past somebody with a cup of coffee in the middle of the day, you don't talk to them."

held in the atrium. Other communal areas in the building are serving as gathering places, too.

But is it clear that beautiful research buildings really create an environment where more creative science gets done? Though there's a lot of anecdotal evidence, there's very little scientific data to back up such claims—so far. A new organization called the Academy of Neuroscience for Architecture has just started to measure the psychological effects of architectural design. And some architectural firms have tried to evaluate how well their designs live up to expectations. Shepley Bulfinch, for instance, compared atrium-style science buildings they designed about 10 years ago to ones completed more recently and published their findings in *R&D (Research and Development)* magazine. According to the article, teachers, researchers, and students have been impressed with how well the atrium spaces help to foster serendipitous social and professional interactions.

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"Immunology will not cure cancer," Noelle points out, "and genetics will not cure cancer, and structural biology will not cure cancer. But all of them together may. And that's what the building is about." (See page 4 for a description of Noelle's latest research finding.)

Although the expanded Cancer Center is now a hub for cancer-related research, there is still some work going on at DMS's Hanover campus, as well as in DHMC's Borwell Building. But Israel hopes to one day build what he calls an "integrator"—a multistory glass lobby to connect the Cancer Center directly to Borwell. And he'll continue recruiting bright minds to work within the beautiful space—laying, as he puts it, "a broader foundation of physician-scientists and physician-investigators who can help with the process of translating Dartmouth science into impacting on the health of people."

That impact is hard to quantify: the way cancer data is collected has changed so much over the years that it's impossible to accurately compare current figures to the ones from the 1960s that motivated Frank Lane. But from his vision, to a "little kiosk," to an NCI-designated comprehensive cancer center housed in architectural splendor is quite an impact by any measure. ■

Changes in cancer care

By John Milne

Milne, a freelance writer in Concord, N.H., is a former Cancer Center patient; he received a stem-cell transplant for lymphoma in 1998 —which he wrote a feature about for our Summer 2001 issue.

Actor John Wayne once defined cancer the way one of his movie characters might refer to an adversary. "I licked 'The Big C,'" rasped Wayne in the 1960s. The remark made cancer "a thing you could shoot down, like a cattle rustler," wrote Wayne's biographer, Garry Wills.

There's a reason "The Big C" entered the American dialect; it resonated with the concept of cancer as a life-or-death struggle. Patients "battled" their disease. Those who came through treatment were "survivors." Behind the saber-rattling metaphors was a stark reality: Medical treatments for invasive cancer can be uncomfortable, painful, and, to a degree, risky. Radiation, surgery, and high-dose chemotherapy change the body as they save the patient's life. Their aftereffects can even lead to new diseases, some of them life-threatening.

In the 21st century, the metaphor may need to change from war to containment. After decades of research, drugs are being developed that manipulate the actual chemistry of the cell. For a few cancers, this new biochemistry can reduce a malignant tumor to an inert mass. Other cancers can be controlled with a few pills a day. Cancer is on the way to becoming a chronic disease—like diabetes.

"This is a very exciting time for cancer medicine," says Burton Eisenberg, M.D., the new deputy director of Dartmouth's Norris Cotton Cancer Center. "Finally, a black box is opening, telling us a lot more about the genetic foundations of cancer and increasing the number of new compounds that will fight cancer at the molecular level."

Eisenberg's office is on the top floor of the new addition to the Cancer Center—an expansion that is part of this transformation in cancer treatment. Previous discoveries in cancer biochemistry came largely from basic-science and private-sector laboratories. Eisenberg believes the new breakthroughs will take place in integrated cancer centers such as Dartmouth's, where laboratory discoveries can take a more direct path to patients. At the same time, practi-

cal feedback obtained in the clinics can easily inform and guide the researchers' scientific efforts. "This will permit better communication between the people who work with the test tubes and the people who conduct that actual practice," he says. "In the past, doctors didn't know how to talk to scientists and vice versa."

The Cancer Center's expansion also dovetails with a recent decision by the National Cancer Institute. The NCI has assigned a top priority to research "into the genetic, molecular, and cellular basis of cancer" and to making new drugs and therapies more quickly available to patients. The U.S., says NCI Director Andrew von Eschenbach, M.D., stands "at that defining moment in history when a surge of new technologies and the fruits of many years of investigation will yield, over the next two decades, unimagined leaps forward in our understanding of cancer and our ability to control and eliminate it."

During the second half of the 20th century, cancer treatments were broadsword-crude but increasingly effective. Surgery removed cancerous tissue—or sometimes the entire organ containing that tissue. Radiation killed cancer cells—though its beams often passed through and damaged other organs, too. Chemotherapy showed remarkable success at destroying fast-growing cancer cells—as well as other fast-growing cells in the body; that's why chemo patients lose their hair and get mouth ulcers.

But what happens to patients after treatment ends? There hasn't been enough data to draw firm conclusions but, according to the NCI, "what is clear is that most of our current treatments, although benefiting the patient overall, will produce some measure of adversity." In August, the Institute of Medicine issued a report noting that aftereffects of treatments for various childhood cancers include heart problems, learning disabilities, osteoporosis, kidney damage, and infertility. Patients have paid a price for survival.

One such price is an effect known as "chemo brain." A team of Dartmouth researchers headed by Tim Ahles, Ph.D., and Andrew Saykin, Psy.D., has discovered much of what's known about this phenomenon—a post-chemo decline in the capacity for tasks requiring concentration or the ability to change focus quickly. Even when such factors as depression and age are taken into account, roughly one in four recipients of chemotherapy reports frustrating mental declines. "We're convinced there are long-term cognitive differences," Ahles says, even though the affected population is "a subgroup and . . . probably a minority." A likely explanation, revealed by new imaging methods, is startling, says Saykin: "Chemotherapy can influence brain structure."

Concern about these aftereffects is emerging because only now are there enough long-term survivors—almost 10 million, according to the American Cancer Society—to count and study. "We were so busy trying to cure their problems," Eisenberg says, "that we didn't take into account what life would be like after their cure."

Just as the weaknesses in the old strategies were becoming apparent, some new cancer drugs started showing promise. In 2003 alone, the number of approved drugs designed to attack cancer at its genetic and molecular roots rose from two to more than half a dozen. These drugs stop the uncontrolled cellular growth that characterizes a tumor by introducing proteins into the cell itself. One may countermand a too-prolific protein. Another may prevent a rogue protein from entering a cell, like putting a dummy key in a car's ignition so the real key can't be used to start the engine.

The most successful of these new drugs, imatinib mesylate (better known by the brand name Gleevec), works like a dummy key in a rare cancer of the gastrointestinal tract called GIST, or gastrointestinal stromal tumor. GIST resists chemotherapy and radiation, and surgical removal of the stomach or small intestine is usually ineffective. A protein called KIT may be the culprit. From its location on the surface of the cell, KIT turns on and off as it signals a cell that it is time to reproduce; GIST, however, makes KIT signal the cell to multiply without end. Eisenberg, who participated in clinical trials of Gleevec before coming to Dartmouth, explains that the drug creates a protein that blocks KIT from entering a receptor on the cell surface. "It stops the proliferation of the signal to make the cell abnormal," he says.

Above: Murray Korc, left, chair of medicine, moved his lab into the new Cancer Center. Below: William Kinlaw, left, and a pair of colleagues.

Gleevec appears to be effective against chronic myeloid leukemia (CML), too. The drug does have some side effects. They're not trivial, Eisenberg says, but are far milder than the pain, nausea, and aftereffects of powerful chemotherapies. Doctors also anticipate less physical weakness, which increases the risk of infection. Furthermore, administration is easy—Gleevec can be taken as a pill. "The concept of cancer as a chronic disease is becoming realistic," Eisenberg says, "because we finally understand how a cell is growing and changing."

But, cautions NCI official Anthony Murgo, M.D., "we're not ready to discard the traditional approaches" of chemotherapy, radiation, and surgery. "Although we'd like to mitigate the side effects, the benefits still outweigh the risks." Gleevec and the other newfangled compounds have been successful with cancers such as GIST and CML because each has a single cellular Achilles' heel. Many cancer cells, Murgo says, require that two or more proteins be neutralized.

But the conceptual shift is already so sig-

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BOTH: FLYING SQUIRREL GRAPHICS