Natural Cancer Killers: How natural-killer white blood cells search and destroy

PLUS:
Identifying Cancer Before It's Cancer
CDK 4/6 Inhibitors: Stopping Cancer at Its Core
Dana-Farber’s 2018 Annual Report
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DEAR READERS

I’m always pleased, but not surprised, when I hear a Dana-Farber researcher say, “I couldn’t have done this work anywhere but here.” The remark is about more than the freedom to pursue interesting science or make use of the latest technology, but about what can be accomplished collectively.

Dana-Farber is exceptional in its ability to translate scientific advances into new approaches to treating, detecting, and preventing cancer. This is in part due to the array of tools available to our investigators to study the disease – whether it’s analyzing the genetic makeup of tumor cells, sorting different cell types within a tumor, or tracking the effectiveness of drugs in clinical trials. But it is also due to the range of expertise within our faculty. To an extent that’s rare in academic medicine, Dana-Farber researchers are apt to have colleagues – at the Institute or its partners – whose work intersects with their own in ways that help generate new therapies.

The power of these connections shouldn’t be minimized. Without them, science can become a tale of missed opportunities – of leads not followed because researchers lacked access to the technology or the fellow scientists who can help them explore the potential of a discovery. At Dana-Farber, we’ve created a unique continuum between the laboratories where discoveries are made and the clinics where they’re applied to treatment.

Several articles in this issue of Paths of Progress show this bench-to-bedside process in action. The cover story, for instance, traces a 30-year trail of research at Dana-Farber that has resulted in one of the most promising new classes of cancer drugs, known as CDK4/6 inhibitors. The story on our Chemical Biology Program is a second example, focusing on the development of small molecules to study and treat cancer.

If science is a matter of making connections – of recording observations and discovering patterns – scientific progress depends on making connections with other people. In many ways, collaboration is the story of science at Dana-Farber.

Laurie H. Glimcher, MD
President and CEO, Dana-Farber Cancer Institute

“Dana-Farber is exceptional in its ability to translate scientific advances into new approaches to treating, detecting, and preventing cancer.”
– Laurie H. Glimcher, MD
Melany Duval joined Dana-Farber in January 2019 as senior vice president, chief philanthropy officer, a role in which she will lead fundraising efforts for Dana-Farber and the Jimmy Fund.

Duval is a seasoned philanthropy executive with extensive experience in managing campaign planning and strategy. She previously served as vice president of development at Silicon Valley Community Foundation (SVCF), where she was a member of the leadership team for philanthropic activities. The largest community foundation in the world, SVCF raised more than $1.4 billion in 2017.

“The search committee and I were particularly impressed with Melany’s experience and leadership,” said Laurie H. Glimcher, MD, president and CEO of Dana-Farber. “She is a skilled and successful fundraiser and relationship-builder at the highest levels. As her experience demonstrates, Melany is an innovative strategist who produces results and we are delighted she is joining Dana-Farber.”

Prior to SVCF, Duval was the senior associate dean and associate vice president of Health Science Campus Development at the University of Southern California and provided leadership for the campaign to raise $1.5 billion for the USC Health Sciences Campus – the largest component of USC’s $6 billion fundraising campaign. She also worked for Children’s Hospital of Los Angeles in roles of increasing responsibility, where she helped successfully complete a $1 billion fundraising campaign – the largest in the institution’s history. She earned her bachelor’s degree in political science and business administration from Loyola Marymount University.

“I look forward to working together with Dr. Glimcher, the members of the board, the philanthropy team, and the Dana-Farber faculty and staff to amplify the philanthropic support that will sustain the mission of the Institute and create even greater impact for the patients and families served by Dana-Farber,” Duval said.

**Microbiome Research Team Wins Grand Challenge Funding**

A research team led by Dana-Farber’s Matthew Meyerson, MD, PhD, and Wendy Garrett, MD, PhD, also of the Harvard T.H. Chan School of Public Health, were announced by Cancer Research UK as winners of its Grand Challenge funding for a project that aims to discover how certain microbes inside the body lead to colorectal cancer and influence a patient’s response to treatment. The team will receive up to 20 million British pounds (approx. $25 million) over five years from the publicly funded research and awareness charity based in the United Kingdom.

**Jänne Earns Prestigious NCI Award**

Pasi Jänne, MD, PhD, director of Dana-Farber’s Lowe Center for Thoracic Oncology and director of the Belfer Center for Applied Cancer Science, was named a recipient of the prestigious Outstanding Investigator Award from the National Cancer Institute. The award recognizes researchers who have served as a principal investigator on an NCI grant for five years and demonstrated outstanding research. It provides up to $600,000 per year for seven years to investigators to work on projects of unusual potential. NCI developed the award to provide investigators with time to break new ground or extend previous discoveries to advance biomedical, behavioral, or clinical cancer research.
Finding New Drug Targets in Aggressive Cancers

Reporting in *Nature Cell Biology*, Dana-Farber researchers show that two hard-to-treat types of cancer—synovial sarcoma and malignant rhabdoid tumors—are dependent on a newly characterized “molecular machine” called ncBAF, which plays unique roles in regulating gene activity. The scientists showed that biologically and chemically disabling components of ncBAF—which is made up of several unique protein subunits—specifically impaired the proliferation of two types of cancer cell lines that share a common disruption.

“This is one of the first suggestions toward a route for therapeutic intervention in these cancers,” said Cigall Kadoch, PhD, the report’s senior author. “The findings identify new, cancer-specific targets which may be extendable to other cancer types.”

Dana-Farber Names New Chief Operating Officer

Dana-Farber this year named James Terwilliger executive vice president and chief operating officer (COO). He was chosen following an extensive national search to succeed former COO Dorothy Puhy, who retired in February after 25 years at Dana-Farber.

Terwilliger has a track record of leadership, strategic vision, and operational results at health-care institutions including Indiana University Health Methodist and University Hospitals, the University of Pittsburgh Medical Center, USC University Hospital, and UCLA Health System. Prior to Dana-Farber, he served as vice president of clinical services at Montefiore Medical Center, where he was responsible for faculty and community physician practices, including operations, revenue cycle, strategy, practice acquisitions, and program growth and development.

New Center Focuses on Young-Onset Colorectal Cancer

Dana-Farber this year launched the Young-Onset Colorectal Cancer Center, one of the first in the country dedicated to treating colon and rectal cancer in patients under the age of 50.

Colorectal cancer patients are considered “young-onset” if diagnosed before age 50. Since 1994, cases of young-onset colorectal cancer have increased by 51 percent, according to the National Cancer Institute. This rising incidence recently led the American Cancer Society to revise its colorectal screening guidelines to start at age 45 instead of 50.

“By 2030, colon cancer is estimated to rise 90 percent and rectal cancer to rise by a staggering 124 percent in young patients,” said Kimmie Ng, MD, MPH, director of the new center. “This highlights the urgency of trying to identify new ways to prevent, treat, and catch these cancers earlier at a curable stage.”

The new center will address unique issues faced by young patients, including therapies that affect fertility. And it will offer molecular testing to determine the best course of treatment for patients. All patients will have their tumors sequenced to identify their cancer’s specific genetic profile.

Kimmie Ng, MD, MPH
Putting the Spotlight on Lynch Syndrome

More than a million people in the U.S. carry a genetic mutation called Lynch syndrome that greatly increases their risk for developing a variety of cancers, but the majority of people living with the inherited condition don’t know they have it. Dana-Farber this year launched the nation’s first Lynch Syndrome Center dedicated to providing genetic counseling and testing to those at risk for the condition.

Lynch syndrome increases the lifetime risk of colorectal cancer by up to 80 percent and endometrial cancer by up to 60 percent – while significantly elevating the risk of ovarian, stomach, and other cancers. In the U.S., an estimated 1 in 300 people carry one of the five syndrome mutations, but most carriers are undiagnosed or diagnosed after they develop cancer.

“One of our big missions is to raise awareness,” said Sapna Syngal, MD, MPH, founder of the Lynch Syndrome Center. “We don’t want people walking around with an increased risk of cancer and not know.”

One of the indications that you may be at risk for Lynch syndrome is a family history of colorectal or uterine cancer. Learn more at dana-farber.org/lynchsyndrome.

Dana-Farber Helps Launch ‘Count Me In’ to Speed Research

Patient data can hold vital clues to new therapies or knowledge about which persons will best respond to treatment – but much of this information is never collected or made available for study, in part because many cancer patients receive treatment in small community hospitals and clinics where research is not a focus. To help address this issue for the benefit of both patients and researchers, Dana-Farber is helping steward a new nonprofit called Count Me In.

Count Me In allows cancer patients in the U.S. and Canada to share their medical information, experience, and tumor samples for genetic analysis. This information is rapidly processed, de-identified, and made available to all researchers worldwide. Dana-Farber is one of four leading organizations stewarding the nonprofit, which is supported by philanthropy and does not sell patient information. To learn more, visit www.JoinCountMeIn.org.

In the News

*Boston Magazine* named more than 115 physicians affiliated with Dana-Farber to its annual Top Doctors guide, published in January 2019. Drawn from a Castle Connolly Medical database, the list has hundreds of Boston-area physicians from many specialties.

Dana-Farber physician-researcher Geoffrey Shapiro, MD, PhD, has been awarded the Targeted Anticancer Therapies (TAT) 2019 Honorary Award for cancer drug development for his leadership in developmental therapeutics, particularly in solid tumors. The award acknowledges distinguished cancer drug development experts who have devoted a major part of their careers to the discovery and development of better anticancer medicines.

In December 2018, Dana-Farber oncologist Ann Partridge, MD, MPH, accepted the AACR Outstanding Investigator Award for Breast Cancer Research, supported by The Breast Cancer Research Foundation. The award recognizes a scientist whose novel and significant work has had or may have a far-reaching impact on the detection, diagnosis, treatment, or prevention of breast cancer.
What are some prominent advancements for lymphoma care?
In 2017, the FDA approved CAR T-cell therapy for patients with aggressive B cell non-Hodgkin lymphoma who have disease relapse after chemotherapy. In the clinical trial that led to its approval, 82% of these patients had a response, and 54% experienced a complete response. This therapy helps patients who previously had virtually no effective treatment options. There is also an increasing focus on quality of life. More clinical trials are measuring quality of life, helping us balance the impact of treatments on patient survival and well-being.

How can we help improve quality of life for lymphoma patients?
We need to listen to our patients and understand how their disease and treatment impact their lives physically and emotionally. In 2018, we started having a physician from Psychosocial Oncology and Palliative Care join us weekly during rounds for stem-cell transplant patients. The collaboration is helping us optimize symptom management and quality of life for patients.

How will treatment options for lymphoma continue to advance?
I believe immunotherapy and targeted therapy will further advance care options. Immunotherapy helps recruit the immune system to eliminate cancer, while targeted therapy attacks specific proteins that cancer cells need to survive. These therapies are exciting because of their activity in lymphoma. Moreover, targeted therapies are oftentimes better tolerated than chemotherapy because they work specifically on cancer cells; chemo does not distinguish between cancerous and healthy cells.

Is it important to talk about end-of-life care?
Yes. Despite improvements in lymphoma therapies, we still face situations where a patient’s disease stops responding to treatment, and they are left with limited treatment options — many of which are unlikely to be beneficial. Honest and empathetic conversations in these difficult situations allow us to understand our patients’ values and goals, enabling us to provide care that is aligned with their preferences. Instead of making assumptions about what our patients want, these conversations allow us to know their preferences.

How do you build a relationship with recently diagnosed patients?
Lymphoma is complicated. When I meet a new patient, I make sure we discuss their specific diagnosis. I go over what it means, how it is treated, what to expect, and answer any questions. I don’t want my patients to ever feel like they are left searching for answers. I also get to know them so I can tailor care specifically to them. I try to find ways to make the treatment journey less arduous. It is really rewarding to be able to form deep connections and support them.
When patients at Dana-Farber’s Longwood campus in Boston are treated with drugs known as CDK4/6 inhibitors, they’re about 30 years removed from the research that first revealed the promise of such drugs – and only about 30 yards from the laboratories where much of that research took place.

The story of CDK4/6 inhibitors – among the most broadly effective of all targeted therapies for cancer – was written to a large extent at Dana-Farber. It was Institute scientists who, in the late 1980s, helped identify the role of the cell proteins targeted by the drugs. It is Institute investigators who are leading a clinical trial of one such drug.
in almost 6,000 women around the world with a specific type of breast cancer. And it is Institute researchers who have shown in a group of highly influential studies over the past two years that the drugs may be even more powerful than originally suspected.

“CDK4/6 inhibitors have already been approved for patients with a particular type of breast cancer, in combination with hormone-blocking drugs – and if they perform well in clinical trials involving patients with other types of cancer, they have the potential to be one of the most widely used targeted therapies in our arsenal,” says Dana-Farber’s Peter Sicinski, MD, PhD, whose laboratory has been probing the drugs’ targets since the late 1990s. “Dana-Farber is one of the rare institutions with the expertise to carry research from the stage of investigating cells’ most basic machinery to converting that knowledge into potential drugs and then testing them in patients. CDK4/6 inhibitors exemplify the power of that approach.”

The best place to pick up the trail that led to the development of CDK4/6 inhibitors is with a quick description of the cell cycle – the series of events that take place as a cell prepares for, and then undertakes, division.

**Learning Division**

A typical human cell takes about 24 hours to divide, although the rate varies depending on what type of cell it is (a liver cell, for example, divides only once a year). The process involves a vast, interlocking choreography of dozens of proteins and other substances acting and interacting in response to a chorus of cues.

The cycle is a drama in four acts, or phases, including intermissions in which the cell conducts a series of quality-control checks to make sure all is in order before beginning the next phase. One of the best organisms for studying the process is yeast, because the phases are easily discernible as yeast cells form buds that become new cells. It was in yeast that researchers in the 1970s discovered proteins called cyclins, which help
Peter Sicinski, MD, leads a laboratory that has been probing the targets of CDK 4/6 inhibitors since the late 1990s.

push the cycle past the speed bump that separates one phase, called G1, in which cells grow in size, from the S phase, in which cells copy their DNA.

By the late 1980s, research into this aspect of cell division had become particularly intense. At the Dana-Farber laboratory of David Livingston, MD, scientists were working out the basic mechanics of the transition from G1 to the S phase – as were many other labs, including that of Ed Harlow, PhD, at Massachusetts General Hospital. The focus of much of their interest was a protein called pRb, also known as the retinoblastoma protein.

Livingston and his associates, including lab members James DeCaprio, MD, and William Kaelin, MD, discovered pRb to be a born obstructionist: Its job is to pause cell division at the end of the G1 phase so the cell can check itself for errors. As G1 proceeds, pRb is gradually induced to release its hold on cell division by a process called phosphorylation, in which compounds called phosphoryl groups are attached to pRb. The agent that affixes the phosphoryl groups is itself a stuck-together entity: a “D-type” cyclin paired with an enzyme called cyclin-dependent kinase 4 (CDK4) or its cousin CDK6. Matthew Meyerson, MD, PhD, a member of Harlow’s lab who would join Dana-Farber a few years later and is now the Institute’s director of Cancer Genomics, was the first to clone CDK6 so it could be studied by scientists, and showed it works in concert with a D-type cyclin.

It didn’t take researchers long to see the implications of these discoveries. Cancer is, at its core, a disease of runaway cell division. CDK4 and CDK6 (together known as CDK4/6) provide a necessary impetus for cell division: without them, phosphorylation of pRb won’t take place, and without that, cell division will freeze like a clock with a jammed pendulum.

As Livingston, now deputy director of the Dana-Farber/Harvard Cancer Center, says, “Under normal conditions, cells don’t divide until they get an ‘oomph’ from CDK4 and 6 to move out of G1 phase. Drugs capable of blocking these kinases could, in theory, help arrest the uncontrolled division of cancer cells.”

The rationale for pursuing such drugs became even stronger in the following years. Molecular studies revealed that one of the D-type cyclins, called cyclin D1, is overactive in many forms of cancer (actually, in most cancer
The cell cycle, illustrated here, is a four-part process by which cells duplicate their DNA and then divide into two daughter cells. CDK 4/6 inhibitors (retinoblastoma proteins, or RB) halt the cycle between the G1 and S phases, preventing cancer cells from dividing.

Such a drug would obviously be too toxic to take.”

Sicinski and his colleagues decided to test whether this view was valid. They engineered several strains of mice, each of which lacked a specific D-type cyclin, and found, contrary to prevailing dogma, that the animals developed normally. When skeptics argued that the animals’ remaining D-type cyclins had simply taken over the job of the missing one, Sicinski’s team created mice lacking all three D-type cyclins and found that they, too, developed normally in their early stages.

The case for CDK4/6 inhibitors was strengthened when Sicinski’s team showed that while cyclin D1 isn’t necessary for normal cell development, it is needed for the development of certain types of breast cancer. And lastly, they showed that in adult mice with breast cancer, shutting down cyclin D1 caused the tumors to stop growing. (These results might lead one to ask why researchers sought to develop drugs targeting CDK4 and 6, rather than cyclin D1. The reason, Sicinski explains, is that the chemical structures of CDK4 and 6 are easier to block with drug molecules. Since CDK4/6 and cyclin D1 work in tandem, blocking either of them would have an anti-cancer effect.)

Getting Specific

The work of Sicinski’s group and others convinced pharmaceutical firms to begin developing molecules that could throttle CDK4 or 6, or both. One potential drug, palbociclib, kept cancers in check in early clinical trials, but its manufacturer, Pfizer, was considering shelving it in favor of other agents.

“We thought the drug had potential, so with Pfizer’s support we launched a trial in patients with mantle cell lymphoma, a cancer in which the gene for cyclin D1 is rearranged and overexpressed,” says Geoffrey Shapiro, MD, PhD, director of Dana-Farber’s Early Drug Development Center. “We did an analysis, including PET scans that measure the cell cycle, in tumor samples from patients both before and during treatment and demonstrated the drug actually hit its target.”

The study, published in 2012 in the journal Blood, would prove to be the seminal paper in palbociclib’s journey from promising compound to approved drug. “We showed that pRb phosphorylation was reduced in tumor
cells that had been arrested in the G1 phase,” Shapiro remarks. “This resulted in responses and long-term benefit in nearly 30% of participants, including some who had previously been treated with multiple chemotherapies or a stem cell transplant.”

Research at UCLA spawned clinical trials of palbociclib in patients with metastatic, ER-positive, HER2-negative breast cancer, the most common breast cancer subtype, where the drug proved especially effective. Those trials and others led to FDA approval of palbociclib with hormone-blocking therapy and transformed the standard treatment for patients with this type of breast cancer. Shapiro also co-led the first studies of two other CDK4/6 inhibitors – abemaciclib and ribociclib – showing that they, too, hit their intended molecular targets. Both drugs have now received FDA approval for the same category of patients as palbociclib. Together, the three drugs have demonstrated that combining CDK4/6 inhibition with hormonal treatment is substantially superior to hormonal treatment alone.

Approval of the drugs to treat this form of breast cancer has galvanized researchers to explore whether CDK4/6 inhibitors can be effective at other stages of breast cancer treatment and in other types of cancer. Dozens of clinical trials of the drugs are currently underway in non-small cell lung cancer, mantle cell lymphoma, melanoma, glioblastoma, pancreatic cancer, colorectal cancer, and other malignancies.

When UCLA researchers reported their findings in breast cancer patients in 2012, Erica Mayer, MD, MPH, and Harold Burstein, MD, PhD, both from Dana-Farber’s Susan F. Smith Center for Women’s Cancers, were quick to perceive palbociclib’s potential. “We want to offer our patients medicines that are highly effective but also have minimal side effects,” Mayer remarks. “Work with palbociclib in metastatic breast cancer has highlighted its optimal balance of efficacy and tolerability, which has led to clinical trials of the drug in patients with earlier stages of
breast cancer.” She and Burstein launched a pilot study of palbociclib in a small group of these patients, finding it both safe and feasible to administer.

Today, Mayer is heading up one of the largest trials of palbociclib to date. Dubbed the “PALLAS” trial, it has enrolled almost 6,000 patients from 21 countries to evaluate whether the addition of palbociclib to standard hormonal therapy can lower the risk of recurrence in patients treated for earlier-stage ER-positive/HER2-negative breast cancer.

Susan F. Smith Center investigators are currently leading or participating in an array of trials involving CDK4/6 inhibitors. These include the “PELOPS” trial of palbociclib and hormonal therapy prior to breast cancer surgery, and the “PATINA” trial for patients with HER2-positive breast cancer led by Ott Metzger, MD.

Finding Serendipity
Palbociclib and its sister drugs were originally conceived as agents that could put cancer cells in a state of suspended animation—alive, but not dividing, and therefore less of a threat. Recent studies by Dana-Farber scientists suggest the drugs may be even better cancer-stoppers than anticipated.

In 2017, Peter Sicinski’s laboratory published a study suggesting that in tumors with high amounts of a certain protein complex, palbociclib not only prompts cancer cells to stop dividing but can also cause them to die. Within a few months, three groups of Dana-Farber scientists published papers showing that CDK4/6 inhibitors can spur the immune system to attack and kill cancer cells. When the drugs were coupled with immunotherapy agents, the anti-cancer effect can be even greater. These findings were the impetus for the “PACE” trial led by Erica Mayer, which is exploring the combination of palbociclib and immunotherapy in patients with metastatic breast cancer.

As CDK4/6 inhibitors have gained a place in standard therapy, Dana-Farber scientists are already working on ways to improve them. As part of his Metastatic Breast Cancer Project, Nikhil Wagle, MD, is collecting tissue from patients to understand why patients eventually become resistant to the drugs. Part of the answer, Wagle and Shapiro’s teams found in a recent study, is that breast cancer cells sometimes gain the ability to overproduce CDK6, countering the effect of the drugs. And chemical biologists Nathanael Gray, PhD, Baishan Jiang, PhD, and Eric Wang, PhD, recently demonstrated a way to selectively degrade and destroy CDK6, which may help researchers tease apart the separate roles of these two enzymes, reverse the process of resistance, and potentially develop more precise drugs.

“The thread that connects some of the earliest research in CDK4 and 6 to the latest work in CDK4/6 inhibitors runs directly through Dana-Farber,” Geoffrey Shapiro remarks. “The research that originally showed the potential of these drugs is today being complemented by work to make them more effective and extend their benefits to more patients.”

For a list of competing interest disclosures, see www.dana-farber.org/disclose.
Natural Killer Cells

How the immune system’s first wave of defense may play a newfound role in cancer care

BY ROBERT LEVY

As a resident at the University of Minnesota in the late 2000s, Rizwan Romee, MD, witnessed something that, though thoroughly grounded in science, seemed to mingle with the miraculous.

“There was a patient in her 60s with advanced acute myeloid leukemia who hadn’t responded to multiple courses of chemotherapy,” recalls Romee, now director of the Haploidentical Donor Transplant Program at Dana-Farber. “She had spots – skin lesions – covering most of her body. The attending physician suggested treating her with an infusion of natural killer [NK] cells donated by her son. What happened over the next 48 hours was pretty dramatic: The
spots almost completely disappeared, and she went into remission. I thought it was the coolest thing I’d ever seen.”

Although the improvement proved to be brief – the patient later died of her disease – Romee was captivated by what he had seen, and by what he sensed as the potential of NK cells as a therapy for cancer. The experience would permanently shape the course of his research.

NK cells are the shock troops of the immune system, the first wave of defenders against infection and disease. They’re called natural killers because they don’t require any special preparation or training to go on the attack. Like a well-organized strike force, they deploy quickly, do their job, and disperse.

As critical as their role is, their identity was, for many years, obscure. It wasn’t until the mid-1970s that researchers in Sweden discovered that NK cells were a distinct type of white blood cell, rather than a special subset of T cells or B cells, the only kinds of white blood cells known at the time. The late start means that research into NK cells is at a substantially earlier stage than research into T and B cells, which were discovered several decades ago. “In a way, we’re in a position of playing catch-up,” Romee says. “We’re still getting to know NK cells, their capabilities and limitations, and their prospects of being used in cancer treatment.”

So, whereas T cells have taken center stage in cancer immuno-therapy – as the focus of treatments that sharpen the immune system’s attack on cancer – NK cells are still mostly in the wings, but edging closer to the spotlight. In some respects, NK cells have the precise features one would look for in a cancer therapy. They demolish diseased cells with the ruthless cool of a battle bot, tearing holes in the membrane of target cells and injecting enzymes and other molecules that cause the cells to self-destruct. They also can eliminate cancer cells circulating in the body, helping to prevent metastasis.

Despite this proficiency, NK cells have a number of potential drawbacks as cancer-fighters. Unlike T cells, which multiply profusely in order to eliminate infected or diseased cells, NK cells decline to proliferate when infused into patients. This can put them at a sizable disadvantage. “In a patient with cancer, you’re dealing not with millions but

“We’re still getting to know natural killer cells, their capabilities and limitations, and their prospects of being used in cancer treatment.”

– Rizwan Romee, MD

Rizwan Romee, MD, leads research into NK cells’ potential as a cancer therapy.
to recognize a broader array of diseased cells than it could with either NK or T cells alone.”

For all their potential, NK cells carry several liabilities as potential workhorses of cancer therapies – namely, their lack of staying power and failure to proliferate when infused into a patient. Their prospects brightened considerably, however, as a result of a series of recent discoveries.

In the mid-2000s, researchers at Washington University found that exposing mouse NK cells to cytokines – immune-signaling substances – endowed them with memory-like properties. In 2012, Romee and his associates demonstrated the same effect in human NK cells. The enhanced cells, dubbed “memory-like NK cells,” behave much like T cells. “They gain memory function, they proliferate, and they persist longer within the body than standard NK cells,” says Romee. “This is the subject my career revolves around: How do we use these cells to our advantage?” Romee observes.

“My career revolves around the question of how to use natural killer cells to our advantage.”

– Rizwan Romee, MD

billions of cancer cells,” Romee remarks. “If you’re giving a patient a few million NK cells, they would need to divide thousands of times to tackle the tumor adequately, but for the most part, that doesn’t happen.”

A second shortcoming is the fleeting lifespan of NK cells. “T cells can live for a long time, but NK cells are thought to live for only a few days,” Romee notes, “so if you transfer them to a patient they’ll quickly be gone.”

The differences between T cells and NK cells reflect their very different roles in the immune system’s response to disease. NK cells are part of the innate immune system, which handles diseases and infections the body hasn’t encountered before. Because they don’t rely on a small subset of cells that “remember” previous infections and must proliferate in order to quell new infections, NK cells are ready to attack at a moment’s notice. (In this regard, NK cells’ refusal to proliferate is a major asset: They essentially sacrifice numbers for speed.) T cells, by contrast, are part of the adaptive immune system. They learn from experience. When they defeat an infectious agent, such as a specific type of bacteria or virus, they’re equipped to recognize and battle that agent whenever it returns to the body.

This isn’t to say that NK cells are indiscriminate defenders – that, like ill-trained watchdogs, they’ll attack any type of intruder. Instead, they take a more targeted approach, just as T cells do. T cells identify infected or cancerous cells based on bits of proteins contained in structures called MHC class I molecules on the surface of many diseased cells. NK cells target cells that don’t have MHC class I molecules but instead have tiny SOS flags – called stress ligands – on their surface.

Romee explains: “Infected or cancerous cells oftentimes have a certain group of molecules on their surface yelling for help, saying, basically, ‘We are infected, we are malignant, we have stress in our nucleus or genes.’ NK cells respond by becoming activated and killing the cells to prevent the infection or disease from spreading.”

The differing roles of NK cells and T cells reflect the hand of evolution. Malignant cells often try to avoid a T-cell attack by shedding their MHC class I molecules – the external signs that they are cancerous. This may provide a brief reprieve, but it ultimately lands them in a trap set by the immune system, for an absence of these complexes is precisely what spurs NK cells to go on the attack. “The unique capabilities of NK cells and T cells complement each other,” Romee says. “They make it possible for the immune system to recognize a broader array of diseased cells than it could with either NK or T cells alone.”

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Research into memory-like NK cells is at an early stage and much remains to be learned about their capabilities and limitations, but their promise is unmistakable. “This is the subject my career revolves around: How do we use these cells to our advantage?” Romee observes.
Natural killer (NK) cells are a distinct type of white blood cell, shown here attacking a cancer cell.

The recipe for making memory-like NK cells is fast and simple. NK cells – referred to as “regular” NK cells – are collected from the patient or a compatible donor and exposed to cytokines overnight, then infused the next day. “The idea is that most of these primary cells will become memory-like NK cells once they’re back in the patient,” Romee states. (Ideally, this could be accomplished without collecting NK cells outside the body, but scientists have yet to discover how to coax circulating NK cells safely to become memory-like. It’s a challenge they’re avidly pursuing.)

NK cells received one of their first tests as a cancer therapy in a small clinical trial led by Romee. The trial involved patients with advanced acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS, a bone marrow disorder that leads to a shortage of healthy blood cells) who hadn’t responded to at least three courses of chemotherapy. The goal was to see whether memory-like NK cells derived from patients’ family members could produce remissions.

The results were impressive by any standard. More than half the patients went into remission – “remarkable in patients with advanced disease who aren’t responding to chemotherapy,” Romee says. The infused cells lasted longer in patients than ordinary NK cells would, researchers found, and patients experienced hardly any negative side effects.

The trial, like all phase 1 trials, focused primarily on the treatment’s safety, and most of the patients eventually relapsed. Investigators theorize that patients’ own immune system eventually kills the donor NK cells, limiting the time they can be active within the body. For that reason, researchers see two futures for NK cell therapies: one, as a means of sending blood-related cancers into remission so patients can be eligible for a stem cell transplant; and, two, making memory-like NK cells from a close family member and combining them with a stem cell transplant from the same donor to increase the transplant’s chances of success.

At Dana-Farber, Romee has spearheaded the creation of an NK cell program that includes both laboratory and clinical research. He and his colleagues expect to open a trial in which patients who have relapsed after undergoing a transplant from a partially matched donor receive NK cells from the same donor in an effort to regain remission. A trial in the planning stages would use memory-like NK cells to eliminate tumor cells carrying specific genetic mutations, thereby making transplant more effective. In the lab, researchers are studying novel agents to make memory-like NK cells work even better.

“We’ve also started brainstorming about using NK cells for non-hematologic [blood-related] cancers,” Romee remarks. “We’re collaborating with Dana-Farber specialists in melanoma and head and neck cancers to develop NK-cell clinical trials for patients with advanced forms of those diseases.”

There are even efforts to create NK-cell versions of CAR T cells – the genetically engineered T cells that are programmed to attack specific types of cancer cells. “We’re still at a very early stage of NK cell research,” Romee says. “There’s a sense that we’ve only scratched the surface of their potential.”

For a list of competing interest disclosures, see www.dana-farber.org/disclose.
A cancer diagnosis can put a halt to many things, at least temporarily, in a person’s life. But the desire to return to what one loves – or set and achieve new goals – can prove a very strong medicine.

The individuals on these pages were all challenged by cancer. They refused to let it stop them from moving forward.

During aggressive breast cancer treatment, Anne Palmer, 55, trained for a half-marathon. Then, she returned to her childhood passion of skateboarding, competing in longboard competitions across the country.
Ben Tuval, 21, developed Hodgkin lymphoma as a college junior. He finished shooting his first short film two days after his last chemotherapy infusion, then completed editing between radiation treatments.
Less than a year old when his neuroblastoma treatment began, Landon Cato, 3, is now running, dribbling, and kicking his way through preschool. He also looks out for his new baby sister.
Sandi Schussel, 77, has always been active, so the grandmother wasn’t about to let a rare blood cancer known as angioimmunoblastic T-cell lymphoma (AITL) keep her off the ski slopes or her sailboat.
raging wildfire was once a mere spark or a patch of smoldering tinder – easily extinguished if caught in time.

So, too, most cancers are believed to originate as single mutant cells, proliferating to form premalignant lesions or conditions in the body that aren’t at that point dangerous, but may progress to become invasive, hard-to-treat tumors. The precancerous period may persist for years, and scientists are increasingly viewing this as a window of opportunity to slow, halt, or even reverse the development of cancer.

That’s the premise of a new focus in the field that some are calling “cancer interception.”

“Interception is the new frontier in cancer research,” says Phillip A. Sharp, PhD, chairperson of the StandUp2Cancer (SU2C) Scientific Advisory Committee and a Nobel Laureate and professor at the MIT Koch Institute for Integrative Cancer Research. “Essentially, we want to find cancer at its very earliest stages and stop it before it becomes a problem for the patient.”

This new focus has emerged in part, says Norman Sharpless, MD, former director of the National Cancer Institute (NCI), because efforts to prevent cancer in the entire population with some drug or supplement have been unsuccessful. Sharpless, who visited Dana-Farber in January and is now acting commissioner of the Food and Drug Administration, said, “The traditional idea that there’s a drug everybody should take to prevent cancer – that notion is dying a slow death. There have been trials of aspirin, vitamin E, vitamin D, selenium, retinoids – and most of them have failed. So, the new paradigm is identifying populations” that can be targeted with various interception strategies.

Interception – the term was first defined in a scientific paper in 2011 – is gaining traction in the field. The NCI’s Moonshot Initiative has funded research
“For a subset of cancers, at least, there does seem to be a precancerous or premetastatic state where there is a theoretical opportunity to change the course of the disease.”

– Matthew Yurgelun, MD

toward a “Pre-Cancer Atlas” to collect molecular and genomic profiles of premalignant conditions, and how they interact with their microenvironment. The goal is to discover measurable biological signals, or biomarkers, in premalignant conditions that can help predict which ones are likely to progress to invasive cancer and which ones probably won’t.

“It’s fair to say that for a subset of cancers, at least, there does seem to be a precancerous or premetastatic state where there is a theoretical opportunity to change the course of the disease,” says Matthew Yurgelun, MD, a physician in the Dana-Farber centers for Gastrointestinal Cancer and Cancer Genetics and Prevention.

In fact, some forms of cancer interception are already routine. Colonoscopy screening and removal of precancerous intestinal growths called polyps is estimated to reduce deaths from colorectal cancer by 50% in patients considered to be at higher-than-average risk for the disease. Other interception practices include removing precancerous skin growths before they develop into skin cancer or using Pap smears to detect abnormal cells on the surface of the cervix that can be eradicated before they become cancerous.

**Precision, Prevention, and Early Detection**

In a 2018 report published in *Cancer Discovery*, Yurgelun, Timothy Rebbeck, PhD, and Judy E. Garber, MD, of Dana-Farber made a case for what they call precision, prevention, and early detection, or PPED.

Rebbeck, associate director for equity and engagement at Dana-Farber/Harvard Cancer Center, explains that cancer prevention strategies can be thought of on three different levels. Policies aimed to reduce cigarette smoking or encourage HPV vaccination can reduce cancer risk in the general population; other strategies such as frequent screenings are targeted to specific high-risk groups, like heavy smokers or individuals with a family history of cancer. On the third level, says Rebbeck, “we can think about using molecular and biologically based mechanisms to achieve precision prevention.”

Cancer develops from a normal cell that undergoes genetic changes and spawns a clone of malignant cells. The goal of interception is to block that process at some point before it becomes harmful.
Along with population-based measures like smoking cessation, scientists are weighing molecular “precision prevention” strategies to reduce cancer risk for individuals, says Timothy Rebbeck, PhD.

For example, he says, we can design interventions for individuals who carry an inherited cancer risk mutation, such as Lynch syndrome or the BRCA breast and ovarian cancer mutations, or individuals who have been diagnosed with a precancerous lesion.

SU2C first publicized interception efforts in 2017, when it announced – along with the American Association for Cancer Research (AACR) – four interception Dream Teams aimed at two aggressive forms of cancer, pancreatic and lung.

The pancreatic cancer team includes several Dana-Farber investigators, including Yurgelun; Sapna Syngal, MD, MPH, director of research in Dana-Farber’s Center for Cancer Genetics and Prevention; Garber, director of the Center for Cancer Genetics and Prevention; Brian Wolpin, MD, MPH, director of the Gastrointestinal Cancer Center, and Jill Stopfer, MS, LGC, associate director for Genetic Counseling. The team’s goal is to find a way to intercept pancreatic cancer in high-risk patient groups.

In the first phase of the project, Syngal and her group are leading the GENERATE Study (GENetic Education Risk Assessment and TEsting), aimed to increase the use of genetic testing by families of pancreatic cancer patients who have a mutation in pancreatic cancer predisposition genes. Individuals who are found to carry such mutations will be offered enrollment in studies aimed at pancreatic cancer interception and early detection.

The current state of the art is periodic MRI-based imaging and endoscopic ultrasound to identify early pancreatic cancers or “worrysome” precancerous lesions that may be removed surgically, says Yurgelun. However, unlike snipping out precancerous intestinal polyps during a colonoscopy, surgery to remove precancerous lesions in the pancreas is a major, complex procedure with a significant risk of complications, so it is undertaken only if the lesions are considered at very high risk of progressing to pancreatic cancer, Yurgelun says. This highlights the need for more precise, less invasive methods of cancer interception. Along these lines, researchers in the SU2C project will try to develop and test a vaccine to block the progression of precancerous pancreatic lesions.

Preventing Progression

Another interception project got a start in April 2018, when SU2C announced a $10 million award to a Dream Team co-led by Dana-Farber oncologist Irene Ghobrial, MD, to improve the treatment of multiple myeloma, a cancer of white blood cells called plasma cells. Rebbeck is also a member of the team. Myeloma develops from the precursor conditions MGUS (monoclonal gammopathy of uncertain significance) or “smoldering” multiple
Currently, it is unclear whether someone with MGUS or SMM will progress to full-blown multiple myeloma. “We tell people with precursor conditions that we will ‘watch and wait’ until it turns into multiple myeloma, with multiple tumors that potentially can cause organ damage. We want to change that so that we can act before damage occurs,” says Ghobrial.

The team will follow those with precursor conditions and use the samples to search for biomarkers to help predict those with a high risk of progressing. By analyzing blood samples from about 50,000 people, the team aims to better understand the molecular and immune factors that lead to disease progression and establish effective interception strategies.

Ghobrial is also leading Dana-Farber’s new Center for the Prevention of Progression, a first-of-its-kind clinic where patients with blood cancer precursor conditions will be monitored, treated, and counseled. Researchers are leading several clinical trials of novel agents and immunotherapies for patients with MGUS or SMM to determine if they can help prevent disease progression.

Clinic specialists will also see individuals diagnosed with CHIP (clonal hematopoiesis of indeterminate potential), a new diagnosis recently characterized by Benjamin Ebert, MD, PhD, chair of Medical Oncology at Dana-Farber. People with CHIP – which is increasingly common at older ages – don’t have disease symptoms, but their blood harbors mutant clones that create an increased risk of developing leukemia and other blood cancers, as well as increased mortality from stem cell transplantation and from cardiovascular disease, for reasons still being investigated.

“The number of people with precursor conditions is growing, and it will continue to grow as the population ages,” says David Steensma, MD, clinical director of the new center. “It is clear that CHIP raises the risk of cardiovascular death as well increasing the risk of MDS and leukemia, and MGUS can lead not only to myeloma but also to a variety of renal, dermatological, and immunological conditions. There are now tools that may prevent complications that deserve testing.”

Focus on Lung Cancer

Because of the large burden of lung cancer and its high mortality, much effort has gone into early detection and treatment of the disease. Since 2013, based on studies carried out in the early 2000s, screening with low-dose CT scans has been recommended for adults ages 55 to 80 who have at least a 30-pack-per-year smoking history, and who currently
smoke or have quit within the past 15 years. However, this screening strategy has not been widely adopted thus far. One drawback is that the scans often detect lesions known as nodules that can’t clearly be determined to be benign or malignant. This can lead to repeat scans, biopsies, and even potentially unnecessary surgery. Researchers are intensively looking for biomarkers, which could be detected or measured noninvasively, as with a blood test, that could help point the way to more confident diagnosis and prevent overtreatment.

Identification of one such potential biomarker – which also might be a target for preventing precancerous growths or early lung cancers from progressing – was reported in January 2019 by a team at the University of California in Los Angeles. The biomarker is a protein called SGLT2, one of several proteins that transport glucose into cells. The researchers found that SGLT2 was specifically expressed in premalignant lung nodules and early stage tumors. The studies, which so far have been performed only in mice, also showed that treatment with a drug that blocked SGLT2 in models of lung cancer reduced tumor growth and modestly prolonged survival.

The findings “provide clues that could potentially help doctors sort out which lung nodules detected on CT scans are more likely to go on to be malignant lesions and which ones don’t need any further follow-up,” says Bruce Johnson, MD, Dana-Farber’s chief clinical research officer and a lung cancer specialist. However, he noted, the effects of blocking SGLT2 in the animal lung cancer models were not striking “and are still a long way from being applied to altering the growth of human lung cancers.”

With these and many other biomarker studies, and the funding of work toward a precancer atlas to increase understanding of how premalignant states progress to cancer, researchers hope to broaden the application of interception strategies and reduce the number of patients who go on to develop cancer.

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Matthew Yurgelen, MD, is involved with a study aimed at increasing the use of genetic testing as a means of early detection and interception in pancreatic cancer.
biomedicine always comes down to biochemistry – the exact chemical interplay between the dizzying number of molecules that drive health or disease. In every cancer research center, biochemists study these interactions, develop chemical tools, and collaborate with molecular biologists, genomicists, and other experts in biomedical science.

Within this vast field, chemical biologists focus primarily on designing and synthesizing small molecules for research and treatment. Back in 2006, Dana-Farber launched a bold experiment to accelerate this work: It hired three chemists with ambitious goals and gave them access to resources not usually found in academia.

One hope for the budding Chemical Biology program was that the chemists, in partnership with Dana-Farber physician-scientists, would be able to unlock some of the mysteries that drive cancer.

“A good chemical probe can do a lot for the basic biological understanding of a process, and it’s often very complementary to genetic tools,” explains Program Director Milka Kostic, PhD. “In genetic research, you usually remove the entire gene. With a chemical compound, you inhibit the activity of the protein, or remove the protein rather than the gene. So that offers you very complementary ways of asking about the function of a protein.”

The experiment proved a wild success. By 2015, the first three investigators had published more than 300 papers, filed more than 250 patents, formed eight...
startup firms, and, most importantly, made major contributions to the creation of six drugs in clinical trials. Two of the drugs, ceritinib and osimertinib, were approved by the Food and Drug Administration (FDA) in 2014 and 2015 for treating non-small cell lung cancer.

Today, the Institute’s Chemical Biology program hosts nine principal investigators and more than 100 researchers. Its headquarters, in state-of-the-art facilities at Dana-Farber’s Longwood campus, brings together Institute chemists, structural biologists, translational research experts, and other experts under one roof.

Investigators often take on challenges that most academic chemists might not. “We’re much more engineering-focused, working on the problems that are in front of us versus trying something new and then hoping that somebody cares about what we did,” says Nathanael Gray, PhD, one of the program’s first three members.

Another goal for the burgeoning Chemical Biology program was for investigators to connect the dots between basic academic research and drug development – since many promising findings in academic chemistry labs are reported in the literature without ever receiving serious attention from drug companies.

“Our unique ecosystem here lets us work on problems that are more difficult or are at an earlier stage of development,” Gray says. “We also work on rare cancers where the commercial case for development can’t be made at this point but the biological rationale for research is strong.”

Tiny stapled peptides (at left, in yellow) bind to alpha-helical peptides (red) to help them maintain their helical structure, bind tightly to their targets, and resist degradation in the body. This process may help doctors more effectively deliver drugs where needed.
Pursuing Peptides

One promising example of applying innovative chemistry to decipher cancer mechanisms and develop a new class of therapies is the “stapled peptide” technology. The potential utility of this approach in cancer research and drug development emerged from a collaboration between Gregory Verdine, PhD, of Harvard University, the late Stanley Korsmeyer, MD, of Dana-Farber, and then-postdoctoral fellow in Pediatric Hematology/Oncology Loren Walensky, MD, PhD.

As small subcomponents of proteins, peptides can often recapitulate key biological features of the original protein. The design of stapled peptides begins with natural peptides that have the shape of an “alpha-helix.”

Alpha-helical peptides have a distinctive structure that has evolved to bind tightly to specific protein targets. Peptide drugs shaped as alpha-helices, in theory, might target and disrupt protein interactions that drive cancer far more selectively and effectively than small-molecule compounds because the peptides are already evolutionarily honed to be a perfect match to the protein target, similar to a key fitting into a lock.

However, alpha-helical peptides removed from the context of the natural protein can lose their shape and biological function, and they can also get rapidly chewed up in the blood before reaching their intended targets.

Stapled peptides aim to solve these problems by chemically inserting struts into alpha-helical peptides, enabling them to maintain their helical structure, bind to their targets even more tightly, resist degradation in the body, and effectively enter cells and operate like a drug, says Walensky.

Walensky began working on the technology in the Korsmeyer lab in 2000. He opened his own lab in 2006 as one of the Chemical Biology program’s first members, and has steadfastly and meticulously advanced this research ever since.

Following up on discoveries from his lab and others, the startup biotechnology company Aileron Therapeutics has brought the first stapled-peptide drug into clinical trials for cancer. Aileron’s ALRN-6924 drug candidate is designed to unleash the p53 protein, one of the most prominent natural tumor suppressors, in cancers where the protein is intact but otherwise blocked from exerting its anti-tumor role. The drug is under study for treating a series of adult and pediatric cancers. In fact, ALRN-6924 is being tested in the very first clinical trial of its
Taking **Compounds** to the Clinic

Researchers in Dana-Farber’s Chemical Biology program made major contributions to the development of ceritinib and osimertinib, targeted therapies approved by the Food and Drug Administration for non-small-cell lung cancer. Here are some other drug candidates, also pioneered at least in part by program investigators, now in clinical trials.

- **Aileron Therapeutics ALRN-6924**, a stapled-peptide drug. In trials for acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), peripheral T-cell lymphoma, Ewing sarcoma, and other adult and pediatric cancers.
- **Medivir remetinostat**, which inhibits enzymes that wrap up DNA tightly in chromosomes. In trials for cutaneous T-cell lymphoma and basal cell carcinoma.
- **Novartis ABL 001**, which targets a different region of the BCR-ABL protein (which is mutated in chronic myelogenous leukemia, CML) than previous drugs. In a trial for CML.
- **Roche RO6870810**, which inhibits members of a family of proteins known as BET that are key players in cancer biology. In trials for AML, diffuse large B-cell lymphoma, multiple myeloma, MDS, ovarian cancer, triple-negative breast cancer, and various advanced solid tumors.
- **Syros Pharmaceuticals SY-1425**, designed to inhibit “super-enhancer” genes that can drive cancer cell growth. In a trial for AML and MDS.
- **Syros Pharmaceuticals SY-1365**, a first-in-class selective inhibitor of a protein known as CDK7 involved in two processes that drive cancer. In a trial for ovarian and breast cancers.

Other startup companies that exploit findings from the program are working on drugs that have yet to enter clinical trials. One firm is C4 Therapeutics, which is creating drug candidates that employ targeted protein degradation. Another is WntRx Pharmaceuticals, which generates stapled-peptide inhibitors of a protein thought to be implicated in brain, breast, colorectal, liver, lung, and ovarian cancers.

Sara Buhrlage, PhD, of the Chemical Biology program, leads a laboratory working to develop first-in-class drugs and bring them to use in patients.
“[This research] is a long and challenging path that requires laser focus and persistence, but if we can bring new drugs to patients as a result, then it is worth every minute.”

– Loren Walensky, MD, PhD

by Walensky and Aileron. Follow-up tests in cells and mice confirmed the therapeutic potential of their findings. Attending one of Stegmaier’s lab meetings, clinical researcher Steven DuBois, MD, heard about the results and immediately envisioned a clinical study, which opened in November 2018.

“This research exemplifies our mission to traverse the complete arc from chemical biology discovery to clinical translation,” says Walensky. “It is a long and challenging path that requires laser focus and persistence, but if we can bring new drugs to patients as a result, then it is worth every minute.

“Although ALRN-6924 is currently at the earliest stage of testing in the clinic, we are hopeful that stapled peptides could represent an entirely new treatment modality for relapsed pediatric cancers.”

**Breaking Problematic Proteins**

Another major effort is underway in “targeted protein degradation,” in which compounds are designed to destroy rather than inhibit proteins that are key targets in disease.

There is a curious history for this therapeutic approach. It begins in part with thalidomide, an oral drug first and forever notorious for causing tragic birth defects in thousands of babies. Years later, thalidomide and similar compounds quietly became mainstays for treating multiple myeloma, although it wasn’t well understood how these drugs work.

Eric Fischer, PhD, helped to solve this puzzle by establishing the crystal structure of thalidomide and how it binds to its molecular target. Related work in labs around the world eventually showed that thalidomide acts by degrading proteins that go wrong in multiple myeloma.

Protein degradation is a normal part of cell life; a small protein called ubiquitin acts as a tag that marks proteins for routine disposal. But in cancer cells, this routine disposal often fails. Better understanding of this process offers striking new possibilities for targeted therapies.

“It’s a conceptual change, a new treatment modality,” says Fischer, who joined Dana-Farber in 2015. “We can think more creatively about therapeutics, and go after targets within the cell that have been previously considered undruggable.”

“Essentially you’re tricking the cell into thinking specific proteins should be degraded when naturally they wouldn’t be degraded,” Gray explains. By doing that, the theory goes, you can effectively turn on the routine disposal process, allowing cancer cells to die.

A stapled peptide drug based on research by Loren Wallensky, MD, PhD, is currently undergoing clinical testing to treat a wide range of cancers.
Kimberly Stegmaier, MD (left), and Eric Fischer, PhD (right), lead research looking into new ways that cancers might be vulnerable to stapled-peptide strategies and other targeted therapies.

“This is opening up a huge new realm of potential molecular targets that we couldn’t touch before, either because we didn’t know what their function was or because they didn’t have a nook and cranny where a small molecule could bind,” he says.

In November 2018, Dana-Farber announced that Gray and Fischer will lead the new Center for Protein Degradation, a partnership with healthcare investment firm Deerfield Management. “Many labs at Dana-Farber and in the larger Longwood Medical Area want to collaborate with us to translate their findings into potential therapeutics,” Fischer says. “The Center for Protein Degradation will give us the resources to do this properly.”

“The primary purpose of the center is to invent the protein degrader technology of tomorrow, and then to deploy it,” Gray says. “We don’t actually know the best approaches for finding these molecules, because they defy a lot of the logic around conventional small molecule inhibitors, and so that makes discovering them and optimizing them quite different. We’re at the tip of the iceberg with this technology.”

Collaboration in Translation
Chemical biologists have established a dense web of research collaborations with other scientists at Dana-Farber and the greater biomedical research world, helping to push therapies toward the clinic.

Sara Buhrlage, PhD, for example, is researching “deubiquitylating enzymes” (DUBs), proteins that can remove the ubiquitin tags that mark a protein for degradation. By targeting these enzymes, one could in theory prevent the removal of the ubiquitin tags, thus allowing for normal protein degradation and cell death.

She gives one example of joint work that was, in fact, kicked off by the same genomic research from Kimberly Stegmaier’s lab that contributed to the clinical trial of the Aileron stapled-peptide drug for pediatric patients.

The genomic screening identified one DUB as a promising target for Ewing sarcoma, a pediatric solid tumor. However, scientists in the Stegmaier lab couldn’t confirm the result in cells with existing chemical probes.

But a compound from the Buhrlage lab that performed more cleanly clearly confirmed the genomic results. “That finding was added to Kim Stegmaier’s paper, and we’ve gone on to develop even better compounds for treating Ewing sarcoma with her,” Burhlage says.

“Dana-Farber is a wonderful place to work as a chemist and be able to do this translational research side by side with the world’s expert in whatever cancer you want to work on,” she adds. “We routinely talk to clinicians who just did their rounds, and we see patients when we go to the cafeteria. Even those of us who are working in early research stay focused on better treatment options for patients. It’s all about getting to an answer.”

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Meghara Walsh, BSN, RN

Meghara Walsh, BSN, RN, first knew she wanted to be an oncology nurse after a preceptorship program during her senior year at Saint Anselm College. “I had an amazing nurse preceptor who was a seasoned oncology nurse,” Walsh recalls. “I enjoyed watching her interact with patients and was amazed at how she was able to forge deep connections with her patients and their families. She helped people navigate through what was often one of the most terrifying times in their lives. The way she was able to make people feel better – both physically and emotionally – was inspiring. I could see the impact she was making; I knew I wanted my career to be in oncology.”

Walsh, who grew up in Foxborough, Mass., followed through on that goal. Today, she’s a clinical research nurse at Dana-Farber, moving to this role after five years as an inpatient nurse at Beth Israel Deaconess Medical Center on a bone marrow transplant and solid tumor unit. Ready for a change, she brought a long-held interest in research to her role at Dana-Farber.

Walsh also had a personal connection to oncology nursing: Her father was diagnosed with multiple myeloma 16 years ago, but unfortunately died two years later. She remembers him undergoing treatment. “Both my father and my mother would recount how it was the nurses who were able to help them get through multiple rounds of treatment,” she says. “My father was always proud that I wanted to be a nurse – especially an oncology nurse.”

At Dana-Farber, clinical research nurses like Walsh conduct research and provide care to patients who are undergoing clinical trials. As a member of both the research and clinical care teams, Walsh is a bridge between the two. Research nurses assist with protocol development, provide clinical care to patients receiving investigational treatment, and educate patients and their families.

“My father was always proud that I wanted to be a nurse – especially an oncology nurse.”

The role allows Walsh to engage in exciting research while maintaining a nursing practice. “The science is incredibly interesting,” she says. “And being part of finding new and better treatments for patients – and providing treatment opportunities for patients who may otherwise not have any – is exciting. Research nursing has allowed me to be part of the development and maintenance of clinical trials without losing out on patient interaction, which I really love.”

Meghara Walsh, BSN, RN
Cancer is really hard. I was diagnosed heading into seventh grade, which made fitting in difficult. Some kids can be really mean, but there were also so many people on my side. Even though I missed a lot of school that year, everyone pitched in to help me pass seventh grade; that helped so much.

Find your team. I had a really good support system with my family and friends. No matter how difficult things got they were there for me. They encouraged me and helped me feel like I could accomplish anything no matter how down I got.

It’s OK to be sad. Staying positive can be hard when you feel like your body is failing you.

Talk it out. Whether it’s a friend, family member, or therapist, it’s important to find someone who’s willing to listen and understands what you’re going through. I found the best way to get through the most difficult times was by talking to someone. There’s nothing wrong with going to therapy because it can make a difference.

Enjoy the little things. When I was first diagnosed my dad took me to the hairdresser to donate my long hair. Then I got it professionally done for the first time in my life before we went shopping for hats and bandanas. He helped make that part of the experience fun.

Your fight doesn’t end with treatment. Not only did it take me a long time to get my confidence back, but I dealt with survivor’s guilt into high school. It wasn’t until I opened up and talked to someone that I realized being alive is a good thing and you shouldn’t feel guilty about that. Know you’re here for a reason and you can make a difference.

Adjusting takes time. When you have cancer, it consumes every part of your life. It takes a while to relearn how to live your life without cancer.

Cancer made me who I am today. My cancer diagnosis made me grow up really fast, but I don’t think that was a bad thing. I have a lot of plans for my future that involve helping people, and I think that stemmed from having cancer and the support I received during that time.

Advocate for yourself. Nobody knows your body quite like you, so if something isn’t normal speak up; make sure someone hears your complaints. Originally, I was misdiagnosed, and it took multiple trips to different specialists to get it right. If I hadn’t stood up for myself, they might not have caught this as early as they did.

Hannah Levine
Paths of Progress

Dana-Farber Cancer Institute

Founded in 1947 by Sidney Farber, MD, Dana-Farber Cancer Institute (www.dana-farber.org) is world renowned for its unique blend of basic and clinical research and for using its discoveries to improve treatments for cancer and related diseases. Consistently ranked one of the top cancer centers in the country by U.S. News & World Report, Dana-Farber is a founding member of the Dana-Farber/Harvard Cancer Center, which is one of 49 nationally designated Comprehensive Cancer Centers. As a teaching affiliate of Harvard Medical School, Dana-Farber is also one of 19 federal Centers for AIDS Research in the United States. It has earned “Magnet” status for excellence in nursing and is a QOPI® Certified Practice.

Dana-Farber partners with Brigham and Women’s Hospital to deliver care for adults with cancer through Dana-Farber/Brigham and Women’s Cancer Center. It also has a long-standing alliance with Boston Children’s Hospital to care for pediatric cancer patients through Dana-Farber/Boston Children’s Cancer and Blood Disorders Center. These partnerships bring together the strengths of three world-class institutions, each of which provide an exceptional level of care for patients and their families.

The Jimmy Fund

The Jimmy Fund (www.JimmyFund.org) solely supports Dana-Farber, raising funds for adult and pediatric cancer care and research to improve the chances of survival for cancer patients around the world. It is the official charity of the Massachusetts Chiefs of Police Association, the Pan-Massachusetts Challenge, and the Variety Children’s Charity of New England. Since 1948, the generosity of millions of people has helped the Jimmy Fund save countless lives and reduce the burden of cancer for patients and families worldwide. Follow the Jimmy Fund on Facebook (www.facebook.com/thejimmyfund) and Twitter (@TheJimmyFund).

10% of all designated gifts supports our Faculty Research Fund to advance Dana-Farber’s research mission.

Three members of the dedicated team of nurses who care for patients at Dana-Farber Cancer Institute at St. Elizabeth’s Medical Center, in Brighton, Mass.

Dana-Farber shares patient stories which may include descriptions of actual medical results. Dana-Farber provides personalized care for each patient based on their unique needs; their experiences and results will vary.
A Message from Chief Financial Officer Michael Reney

Following a financially challenging 2017, the Institute returned to profitability in fiscal year 2018. Revenues grew in all areas and investments generated strong returns.

The Institute ended fiscal year 2018 with a consolidated operating income of $27.8 million, or a 1.6% operating margin. Non-operating revenue was positively affected by overall conditions in the investment markets, returning 10% for the fiscal year, as well as a gain resulting from the assignment of the Institute’s share of the rights to acquire the Medical Area Total Energy Plant to an unrelated entity, which resulted in an excess of revenues over expenses of $106.7 million.

Patient-care revenue increased by 18% across the Institute, including its main Longwood campus in Boston, its regional satellite centers, and its physician practice offices, continuing the trend of the last several years. Research revenues increased by 5% during fiscal year 2018, with growth coming from non-government foundations and clinical trial sponsors, as well as from the increased use of gifts. And, thanks to the generosity of our many donors, it was another outstanding year for fundraising, which saw a 3% increase in unrestricted giving.

Investments in research continued during 2018 as the Institute increased its footprint in the Longwood Center, a state-of-the-art laboratory facility that opened in January 2015. In addition to the purchased space, the Institute is also leasing two additional floors in the Longwood Center, thus reflecting its continued commitment to best-in-class scientific advancements.

Management, faculty, and staff throughout Dana-Farber – guided by the oversight of several committees of the Board of Trustees – worked diligently to achieve these results and return the Institute to profitability in fiscal year 2018. We are grateful to them and to the many donors and friends of Dana-Farber who continue to demonstrate their commitment to the organization with their valuable knowledge and vital ongoing support.
## Condensed Consolidated Balance Sheets

For the Fiscal Year Ended Sept. 30

(Dollars in thousands)

<table>
<thead>
<tr>
<th>Assets</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Assets</td>
<td>$479,274</td>
<td>$345,413</td>
</tr>
<tr>
<td>Investments</td>
<td>1,315,668</td>
<td>1,174,119</td>
</tr>
<tr>
<td>Debt Service Reserve and Construction Fund</td>
<td>12,868</td>
<td>12,762</td>
</tr>
<tr>
<td>Property, Plant, and Equipment, net</td>
<td>956,643</td>
<td>923,299</td>
</tr>
<tr>
<td>Contributions Receivable, less current</td>
<td>41,269</td>
<td>29,504</td>
</tr>
<tr>
<td>portion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Assets</td>
<td>55,581</td>
<td>48,997</td>
</tr>
<tr>
<td><strong>Total Assets</strong></td>
<td><strong>$2,861,303</strong></td>
<td><strong>$2,576,386</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liabilities and Net Assets</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Liabilities</td>
<td>$320,510</td>
<td>$286,944</td>
</tr>
<tr>
<td>Long-Term Debt and Other Liabilities</td>
<td>815,245</td>
<td>780,807</td>
</tr>
<tr>
<td><strong>Net Assets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrestricted</td>
<td>817,039</td>
<td>702,810</td>
</tr>
<tr>
<td>Temporarily Restricted</td>
<td>703,235</td>
<td>612,839</td>
</tr>
<tr>
<td>Permanently Restricted</td>
<td>205,274</td>
<td>192,986</td>
</tr>
<tr>
<td><strong>Subtotal Net Assets</strong></td>
<td>1,725,548</td>
<td>1,508,635</td>
</tr>
<tr>
<td><strong>Total Liabilities and Net Assets</strong></td>
<td><strong>$2,861,303</strong></td>
<td><strong>$2,576,386</strong></td>
</tr>
</tbody>
</table>

### Summary Statistical Information

(Unless otherwise noted, includes adult and pediatric patients)

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Treatments</td>
<td>176,630</td>
<td>165,792</td>
</tr>
<tr>
<td>Outpatient MD Visits</td>
<td>346,805</td>
<td>328,591</td>
</tr>
<tr>
<td>Number of Licensed Beds</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Adult Inpatient Discharges</td>
<td>1,304</td>
<td>1,044</td>
</tr>
</tbody>
</table>

*Subsidiaries include Dana-Farber Inc., Dana-Farber Cancer Care Network, and Dana-Farber Trust.*
For the Fiscal Year Ended Sept. 30  2018  2017
(Dollars in thousands)

<table>
<thead>
<tr>
<th>Revenues</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>$457,967</td>
<td>$434,228</td>
</tr>
<tr>
<td>Patient Service, net</td>
<td>1,166,614</td>
<td>990,809</td>
</tr>
<tr>
<td>Unrestricted Contributions and Bequests</td>
<td>77,711</td>
<td>75,227</td>
</tr>
<tr>
<td>Other Operating</td>
<td>31,094</td>
<td>24,671</td>
</tr>
<tr>
<td><strong>Total Revenues</strong></td>
<td><strong>$1,733,386</strong></td>
<td><strong>$1,524,935</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expenses</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Research</td>
<td>402,057</td>
<td>381,229</td>
</tr>
<tr>
<td>Direct Patient Care</td>
<td>825,246</td>
<td>717,139</td>
</tr>
<tr>
<td>Indirect</td>
<td>478,226</td>
<td>463,401</td>
</tr>
<tr>
<td><strong>Total Operating Expenses</strong></td>
<td><strong>$1,705,529</strong></td>
<td><strong>$1,561,769</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operating (Loss) Income</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investment Return, net</td>
<td>47,250</td>
<td>46,916</td>
</tr>
<tr>
<td>Gain on Sale</td>
<td>23,802</td>
<td>46,916</td>
</tr>
<tr>
<td><strong>Interest Rate Swap Agreement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net interest received/(paid)</td>
<td>(3,973)</td>
<td>(4,830)</td>
</tr>
<tr>
<td>Change in fair value</td>
<td>11,797</td>
<td>15,997</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excess of Revenues Over Expenses</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>7,496</td>
<td>13,276</td>
</tr>
<tr>
<td>Increase in Temporarily Restricted Net Assets</td>
<td>90,396</td>
<td>72,522</td>
</tr>
<tr>
<td>Increase in Permanently Restricted Net Assets</td>
<td>12,288</td>
<td>8,015</td>
</tr>
<tr>
<td><strong>Increase in Net Assets</strong></td>
<td><strong>216,913</strong></td>
<td><strong>115,062</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Net Assets at Beginning of Year</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,508,635</td>
<td>1,393,573</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Net Assets at End of Year</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$1,725,548</td>
<td>$1,508,635</td>
</tr>
</tbody>
</table>

The preceding selected consolidated financial data as of Sept. 30, 2018, and 2017 (except for the summary statistical data) have been derived from the consolidated financial statements of Dana-Farber Cancer Institute Inc., Dana-Farber Inc., Dana-Farber Cancer Care Network, and Dana-Farber Trust. These have been audited by independent auditors KPMG, LLP (in 2018) and Ernst & Young, LLP (in 2017).

In FY 2018, the Institute raised $280 million in new gifts and new pledges through its Division of Philanthropy and the Jimmy Fund, and through the Friends of Dana-Farber Cancer Institute. For accounting purposes, the financial charts reflect new gifts and new pledges calculated at present value, excluding commitments the Institute could not record due to conditionality.
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Assistant Treasurer

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Richard S. Boskey, Esq.
Assistant Secretary

Sharon Herrick, Esq.
Assistant Secretary

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Tracey L. McCain, Esq.

Compensation Committee
Joshua Bekenstein

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Joshua Bekenstein

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Peter Palandjian

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John J. O’Connor

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Mary Ann Tocio

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Christopher J. Hadley

Committee on Quality Improvement and Risk Management
Steven P. Koppel
Robert J. Sachs, Esq.

Medical Staff Appointments Committee
Bradley A. Lucas

Trustee Science Committee
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Lawrence Lucchino

Gift Planning Committee
Barbara L. Sadowsky
James P. Sadowsky

Trustee Annual Fund Committee
Marian Heard
Jennifer Perini

The governance listings in this annual report are current as of Jan. 1, 2019.
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Samuel. Redstone
Sumner M. Redstone
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James P. Sadowsky
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H. Terrence Samway
Rebecca Sanders
Eric D. Schlager
Judith P. Schlager
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Thomas Sellers
Laura Sen
Paul J. Severino
Jean S. Sharf
Richard A. Smith
Ruth F. Snider
J(erry M. Socol
Gloria H. Spivak
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Esta Stecher
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Ronald S. Sullivan Jr.
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Beth F. Terrana
David T. Ting
Mary Ann Tocio
Delores Barr Weaver
J. Wayne Weaver
T. Conrad Wetterau
Lori Whelan
Gregory A. White
Frederica M. Williams
Jane Brock-Wilson
Winnie W. Wong, PhD
Carl Yastrzemski
Krishna Yeshwant, MD
Mortimer B. Zuckerman

The governance listings in this annual report are current as of Jan. 1, 2019.

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2 Trustee
3 Distinguished Trustee
4 Honorary Trustee
* Member, Executive Committee
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President and Chief Executive Officer

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Senior Vice President; General Counsel; and Chief Governance Officer

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Chief Medical Officer

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Senior Vice President, Experimental Therapeutics

Lisa R. Diller, MD  
Chief Medical Officer, Dana-Farber/Boston Children's Cancer and Blood Disorders Center

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Senior Vice President, Chief Philanthropy Officer

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Chief Nursing Officer and Senior Vice President, Patient Care Services

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Chief Research Strategy Officer and Chair, Executive Committee for Research

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Senior Vice President, Human Resources

Bruce E. Johnson, MD  
Chief Clinical Research Officer

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Senior Vice President, Chief Financial Officer, and Assistant Treasurer

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Chief Scientific Officer

Steven R. Singer, MPA  
Senior Vice President, Communications

Robert J. Soiffer, MD  
Chair, Executive Committee for Clinical Programs

Lesley Solomon, MBA  
Senior Vice President and Chief Innovation Officer

Mary-Ellen Taplin, MD  
Chair, Executive Committee for Clinical Research

James Terwilliger, MPH  
Executive Vice President and Chief Operating Officer

Eric P. Winer, MD  
Chief Clinical Strategy Officer and Senior Vice President, Medical Affairs

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Chair, Pediatric Oncology

Jon Aster, MD  
Interim Chair, Oncologic Pathology

Benjamin Ebert, MD, PhD  
Chair, Medical Oncology

Daphne A. Haas-Kogan, MD  
Chair, Radiation Oncology

Rafael A. Irizarry, PhD  
Chair, Data Sciences

Moritz F. Kircher, MD, PhD  
Chair, Imaging and Radiology

Rosalind Segal, MD, PhD  
Co-Chair, Cancer Biology

Thomas Roberts, PhD  
Co-Chair, Cancer Biology

James A. Tulsky, MD  
Chair, Psychooncology and Palliative Care

Kai W. Wucherpfennig, MD, PhD  
Chair, Cancer Immunology and Virology

The governance listings on this page are current as of Jan. 1, 2019.
A patient in one of the procedure rooms in the Jimmy Fund Clinic at Dana-Farber/Boston Children’s Cancer and Blood Disorders Center.