Taking Aim with Neoantigens
Finding New Targets for Anti-Tumor Vaccines

PLUS:
The Future of Immunotherapy
Can Cellular Therapy Crack Cancer’s Defenses?
The 2016 Dana-Farber Annual Report
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Dear Readers,

If Paths of Progress existed 125 years ago, its pages likely would have been filled with articles about a revolutionary idea in the treatment of cancer: that the body’s immune system can be a potent weapon against tumors. An American surgeon named William B. Coley, MD, noticed that cancer sometimes went into remission in patients who developed a type of bacterial infection of the skin. He reasoned that in fighting the infection, the immune system launched an ancillary attack on cancer. His thinking seemed to be vindicated when he injected mixtures of live, inactivated bacteria – called Coley’s toxins – into patients and saw some of the cancers go into remission.

The concept of immune system-based treatment, or immunotherapy, for cancer never disappeared, of course. In the 1970s, for example, it scored some notable successes with the development of monoclonal antibodies – immune system proteins designed to zero in on and destroy cancer cells – and, more recently, the creation of vaccines to prevent and treat some forms of cancer. But for the most part, Coley’s work didn’t spark the kind of rapid treatment advances that his findings seemed to herald.

One of the reasons for this – in addition to the risks of infecting patients with bacteria – was that doctors and scientists didn’t know enough about the immune system to understand how Coley’s toxins worked. In the absence of this knowledge, surgery, radiation therapy, and, later, chemotherapy came to be the three pillars of cancer treatment.

Today, thanks to the perseverance of generations of scientists, immunotherapy can finally claim its place as that fourth pillar. As you’ll read in this issue, treatments that impel the immune system to a more vigorous, sustained, and precise attack on cancer are producing remissions, many of them long-lasting, in many patients in clinical trials. At the center of much of this work, both in developing new immunotherapy approaches and testing them in patients, are Dana-Farber scientists and physicians.

As an immunologist myself, I’m excited by these advances, and impressed at how rapidly they’re coming. Impressive as the gains have been so far, we know there’s much more work to do: to better understand the intricacies of the immune system and to develop combinations of therapies that maximize the effectiveness of immunotherapies. It may have taken more than a century to get to this point, but the promise of this approach is greater than ever.

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

“Today, thanks to the perseverance of generations of scientists, immunotherapy can finally claim its place as the fourth pillar of cancer treatment.”

— Laurie H. Glimcher, MD
Kaelin Wins Prestigious Lasker Award

Dana-Farber’s William G. Kaelin Jr., MD, professor in the department of medicine and Harvard Medical School, won the 2016 Lasker Award for Basic Medical Research by the Albert and Mary Lasker Foundation. Kaelin, along with his colleagues Peter Ratcliffe (University of Oxford/ Francis Crick Institute), and Gregg Semenza (Johns Hopkins University School of Medicine), was cited for the discovery of a tumor-suppressor gene called \(VHL\) which provides key insights into the body’s response to changes in oxygen levels. He discovered that \(VHL\) helps control the levels of a protein known as HIF, which ratchets up or down the response to low oxygen, such as the production of red blood cells and new blood vessels. His subsequent discovery of a molecular switch that renders HIF oxygen-sensitive was critical to understanding how cells react to variations in oxygen level.

“The work of this year’s honorees epitomizes the power and impact of dedication to rigorous and innovative medical research,” said Claire Pomeroy, president of the Lasker Foundation. “These outstanding advances have illuminated fundamental aspects of life, developed a cure for a deadly disease, and raised public engagement with science.”

The Lasker Awards carry an honorarium of $250,000 for each category and are among the most respected prizes in medicine. In all, 87 Lasker laureates have received the Nobel Prize, including 41 in the last three decades.
Anderson Assumes Leadership Role at ASH

Kenneth C. Anderson, MD, director of the Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics at Dana-Farber, is now serving as president of the American Society of Hematology (ASH) for a year-long term through December 2017.

During his more than 30 years of involvement in ASH, Anderson has served in a variety of volunteer roles, including executive editor of Hematology (ASH Education Program). As ASH president-elect in 2016, Anderson served as the society’s representative to the National Cancer Moonshot, and he continues to lead efforts towards developing a system for sharing multiple myeloma and ultimately other hematologic cancer data among the world’s top research centers.

As the organization’s new president, Anderson says he is interested in identifying new opportunities to attract and groom the next generation of hematologists through mentorship opportunities with experts in the field.

Study Suggests Need for More Colorectal Cancer Genetic Testing

A study of more than 1,000 colorectal cancer patients at Dana-Farber revealed a surprisingly high proportion of them—about 10 percent—carry inherited genetic mutations thought to increase the susceptibility to gastrointestinal and other cancers. The study results, published in the Journal of Clinical Oncology, support an expanded role for genetic testing of inherited risk for colorectal cancer, with the aim of finding more people in whom the disease might be prevented or caught earlier.

Physicians have long known that about 3 percent of colorectal cancer patients who have a genetic condition known as Lynch syndrome are at high risk for the disease. “But data from our study say we should be at a much lower threshold for genetic testing in colorectal cancer patients, because we’re missing another 7 percent of people with hereditary risk,” says Dana-Farber’s Matthew Yurgelun, MD, lead author the study.

“It’s time for colorectal patients to have the same awareness about genetic testing that exists for other cancers,” says Sapna Syngal, MD, MPH, corresponding author on the paper and director of research in the Center for Cancer Genetics and Prevention, part of Dana-Farber’s Division of Population Sciences. “Every patient with colorectal cancer should raise the idea of genetic testing with their physician, and every physician should raise that idea with their patients, because it has implications not only for patients, but also for their family members.”

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To get the latest news and information delivered to you, subscribe to our Insight blog at www.dana-farber.org/subscribe.
Linde Family Foundation Gift Supports Chemical Biology and ALL Research

Building on its earlier philanthropic contributions to Dana-Farber, the Linde Family Foundation made a new exceptional gift to support the Institute’s research in chemical biology and pediatric acute lymphoblastic leukemia (ALL). The gift will enable the Institute to recruit new scientists to the Linde Family Program in Cancer Chemical Biology, as well as establish the Linde Family ALL Program Core Endowment to bring together key resources for ALL research.

“We have seen great progress being made over the years in these areas and are proud to continue to support Dana-Farber’s efforts,” says Institute Trustee Karen Linde Packman, who is also a trustee of the Linde Family Foundation.

The Linde Family Program in Cancer Chemical Biology was established in 2008 as part of an earlier gift to Dana-Farber by the Linde Family. Using the combined power of structural biology and medicinal chemistry, Linde Family Program investigators partner with disease-focused investigators to gain a better understanding of genetic mutations, identify why certain mutations promote cancer, and engineer drugs to block or counteract those mutations. The new gift will enable the Linde Family Program to expand its team of chemists and biologists and broaden its investigations.

Long-time supporters of the Institute’s ALL Program, the family devoted a portion of the new gift to create an endowment that will help maintain and expand the infrastructure on which current and future ALL research depends. That infrastructure includes three core facilities that provide access to patient samples across 17 member institutions; statistical design and analysis for laboratory, clinical and population-level studies; and specimen storage and molecular assessment for future research.

“We hope that through our gift to enhance and sustain two important cancer programs, cancer patients and families nationally and internationally will benefit from Dana-Farber’s cutting-edge research and discovery,” says foundation Chair Joyce Linde.

Boston magazine named 51 physicians and surgeons affiliated with Dana-Farber to its annual Top Doctors guide. Drawing from a Castle Connolly Medical database, the list consists of more than 600 Boston-area physicians from 60 medical specialties.

Dana-Farber researcher Stephanie K. Dougan, PhD, was one of five early-career cancer scientists chosen as a 2016 Pew-Stewart scholar by the Pew Charitable Trusts and the Alexander and Margaret Stewart Trust. The prestigious award selects scientists nationwide for their dedication to pursuing innovative leads aimed at finding a cure for cancer. Each awardee receives four years of flexible funding.

Myles Brown, MD, director of Dana-Farber’s Center for Functional Cancer Epigenetics, was elected to the National Academy of Sciences, joining 84 new members and 21 foreign associates from 14 countries elected to the academy in recognition of distinguished and continuing achievements in original research.
AROUND THE INSTITUTE

Advances May Aid Pediatric Brain Tumor Treatment

A recent study by investigators at Dana-Farber/Boston Children’s Cancer and Blood Disorders Center suggests that precision medicine, in which diagnosis and treatments are keyed to the genetic susceptibilities of individual cancers, has advanced to the point where it can now impact the care of a majority of children with brain tumors.

In the largest clinical study to date of genetic abnormalities in pediatric brain tumors, researchers performed clinical testing on more than 200 tumor samples and found that a majority had genetic irregularities that could influence how the disease is diagnosed and/or treated with approved drugs or agents in clinical trials. The findings, reported in the journal Neuro-Oncology, demonstrate that the results of testing pediatric brain tumor tissue for genetic abnormalities can help guide patients’ treatment. The study authors say the need for new approaches to treating brain cancer in children is urgent.

“Although there has been a great deal of progress over the past 30 years in improving survival rates for children with cancer, advances in pediatric brain cancer haven’t been as dramatic,” says co-lead author Pratiti Bandopadhayay, MBBS, PhD, of Dana-Farber/Boston Children’s.

To learn more about the study and how it may aid treatment options, search for “pediatric precision medicine” at www.dana-farber.org.

‘Bridge Project’ Research Surge with $20 Million Gift

A new challenge gift of $20 million has been received by the six-year-old Bridge Project, expanding its support for innovative cancer therapy research. Its work is performed by teams composed of collaborating researchers from Dana-Farber/Harvard Cancer Center (DF/HCC) and the Koch Institute for Integrative Cancer Research at MIT. New DF/HCC-MIT teams compete each year for Bridge Project grants.

Thanks to the gift from the Virginia-based Commonwealth Foundation for Cancer Research, an esteemed philanthropic institution supported by philanthropists Bill and Alice Goodwin, the project will now be able to fund additional applicants who propose to test entirely novel approaches and hypotheses to understanding and treating cancer. The number of grants given each year is expected to at least double.

In addition to the new funding, DF/HCC and MIT will raise matching funds resulting in a combined $40 million expansion of the project, its largest ever.

“This gift enables the Bridge Project to fund larger numbers of collaborative projects of extraordinary quality,” says David Livingston, MD, deputy director of DF/HCC and a Dana-Farber cancer scientist and oncologist.

The collaborative project aims to combine MIT’s strengths in basic cancer research and bioengineering with the basic cancer science, clinical cancer research, and clinical cancer care of DF/HCC.

First envisioned by Art Gelb, a Dana-Farber Trustee and MIT Corporation member who also provided its first capital gift, the Bridge Project has so far funded 37 teams who are pursuing advances across a wide variety of cancer types that represent areas of the greatest clinical need. The work of these teams has led to multiple publications in the highest-profile journals, the filing of 160 patent applications, the formation of new companies, and the initiation of clinical trials. In 2012, the Commonwealth Foundation for Cancer Research also provided $4.5 million in Bridge Project support.

www.dana-farber.org 5
Gift from Robert and Renée Belfer Drives Innovation at Dana-Farber

A $10 million gift in 2015 from Robert and Renée Belfer is accelerating drug development at Dana-Farber.

A $10 million gift from Dana-Farber Trustee Robert Belfer and his wife, Renée, is driving essential campus expansion and revitalization projects at Dana-Farber, helping foster collaboration and innovation among the Institute’s scientists, and paving the way for developing next-generation cancer treatments.

The gift helped spur the relocation of Dana-Farber’s Robert and Renée Belfer Center for Applied Cancer Science to the Longwood Center, which opened in 2015 at the corner of Brookline and Longwood avenues. The Belfer Center, a major driver of industry partnerships and drug development at Dana-Farber, now occupies several floors of modern research space in that building, alongside renowned scientists from Dana-Farber’s Chemistry program, Blais Proteomics Center, and Biostatistics and Computational Biology programs. Working closely under the same roof, these scientists strive to accelerate the pace of novel drug discovery at Dana-Farber and deliver new treatments to cancer patients faster.

“The move into Longwood Center positions the Belfer Center to further build alliances with big pharma to engineer revolutionary therapies to treat cancer,” Robert Belfer says. “Cancer has had a devastating effect on my family. I can think of no better way to honor the memories of my loved ones than by continuing to support this fine institution.”

The Belfers pledged an additional $10 million to Dana-Farber if the Institute reaches certain milestones in commercial revenue over the next 10 years and invests this income in its research efforts. This challenge encourages Dana-Farber to continue to forge additional partnerships with drug development and biotechnology companies in the decade ahead.

Robert and Renée Belfer have a long history of support for Dana-Farber and the Jimmy Fund, beginning in 1996. In 1999, the Belfers established the Belfer Genomics Center with a $5 million gift. In 2006, they made a $10 million gift to the Institute, establishing the Robert and Renée Belfer Center for Applied Cancer Science to convert insights gleaned from cancer genomics and biology research into effective new drugs. This transformative $10 million gift brings the Belfer family’s total giving to Dana-Farber to more than $25 million.

A closer look at a few of the thousands of words associated with cancer medicine and research.

**adjuvant therapy:** Additional treatment given after primary cancer treatment to lower the risk that cancer will return. Examples include chemotherapy, hormone therapy, and radiation therapy, among others.

**antigen:** Any substance the body encounters that provokes an immune response. Antigens include bacteria, viruses, chemicals, and other foreign substances. Cancer cells also have antigens that can cause an immune response.

**MUC-1:** A protein found on certain epithelial cells that line surfaces of the body. Patients with breast, ovarian, lung, or prostate cancers may have elevated levels of MUC-1 in their blood. Measuring the amount of MUC-1 in the blood may help doctors judge how well cancer treatment is working.
How do you view the promise of immunotherapy?

I’m very optimistic because there are so many ways of enhancing the body’s immune response against tumors. Very different approaches are already benefiting patients. For example, already we have checkpoint inhibitor drugs, vaccines, CAR T cells, oncolytic viruses, and there will be others. We’re also thinking about how we can combine immunotherapy with established modalities like targeted therapies and radiation.

How does cancer prevent attack by the immune system?

Cancer cells take advantage of the natural checks and balances in the immune system. It’s a very powerful system and it needs to be adequately controlled. When the immune response against an invader winds down, populations of inhibitory immune cells become more prominent to limit damage to normal tissue. A tumor can send chemical messengers to recruit some of these inhibitory cells to suppress an immune response against the cancer.

What is the biggest question in immunology today?

Resistance. Why do some patients not show any response to immunotherapy, and why do some initially respond and then relapse? This is the key problem. There is a wealth of biology on resistance in the data we obtain from our patients. We need to examine these data to figure out what the key molecules and pathways are. Our hope is that once we understand how they cause resistance, we can do something about it.

How is Dana-Farber responding to immunotherapy successes?

We’re going to expand cancer immunology and immunotherapy at every level – the clinical side, the basic research side, the translational research side. Over the next several years, immunotherapy will become mainstream in cancer. We’re already seeing that many more people are getting interested in cancer immunology – including non-immunologists. There’s an infusion of talent into this field.

Are scientists collaborating to tackle these challenges?

Yes. There is a major initiative called the Cancer Immune Atlas at Dana-Farber and the Broad Institute of MIT and Harvard. It involves teams of immunologists and computational biologists. The goal is to figure out what types of immune cells are in different tumors; what key genes are turned on or off in those cells, and which could be therapeutic targets.
If the human immune system was a powerful racing car, you could say that scientists in the past few years have gained unprecedented control over how to make it accelerate, and what causes it to slow or stop. This knowledge has spawned new immunotherapy drugs that are delivering dramatic benefits to some patients with advanced cancers.

“Checkpoint blockers are transformational,” asserts Laurie H. Glimcher, MD, president and CEO of Dana-Farber and a prominent immunologist, referring to drugs that disable the brakes that cancer cells use to fend off an attack on them by immune system T cells.

“The idea that you can take someone who has stage 4 metastatic cancer and halt the cancer – and manage it more like a chronic disease…it’s remarkable,” Glimcher says.

“However,” she adds, “it’s just the tip of the iceberg.” Beyond the impressive but limited successes of recent immunotherapy advances lies the potential to bring the strategy to more patients and more kinds of cancer.

The iceberg’s tip also represents current knowledge of the powerful immune system’s intricate and complex set of controls. Much of what will be needed to shape and steer the immune attack against cancers remains to be discovered.

“There’s so much we don’t understand,” Glimcher says. “Our task is to figure out the answer to at least two questions. First, why do only some patients with tumors that can respond to immunotherapy – like melanoma, lung, bladder and kidney – not respond to immunotherapy? Why is it only 20 or 30 or 40 percent? Why don’t all of them respond?

“And second, why do some cancers not respond at all, like pancreatic, prostate, ovarian, and breast cancer, glioblastoma, and colon cancer other than patients with Lynch syndrome?”

Despite those unanswered questions, the science behind immunotherapy is far more advanced than it was even a decade ago. For nearly 100 years, since the idea first emerged, efforts to harness the immune defenses as a cancer treatment met with many failures and limited success – even though the immune system, which evolved mainly to combat infectious viruses and bacteria, is capable of eliminating body cells that have become cancerous. Many strategies focused on stimulating the immune response with vaccines or removing T cells from a patient, “educating” them in the laboratory, and returning them to the body to seek out and destroy cancer cells. But except in a few instances, these measures didn’t spark an effective immune reaction.

It took what Glimcher calls an “Aha!” insight to jump-start the field of cancer immunotherapy. That realization was that the best way to activate the immune system was not by stepping on the gas pedal – but by removing the brakes. Scientists learned that cancer cells evade the immune forces by activating molecular “checkpoints” that both conceal the identity of the cancer cells and switch off the immune response. These natural checkpoints are crucial to health – without them, people would be much more vulnerable to misguided attacks on normal tissue, as in autoimmune diseases like lupus. The role of one of those checkpoints on cancer cells, PDL-1, was identified by Dana-Farber’s Gordon Freeman, PhD, who in 2000 discovered that it partnered with another molecule on T cells, PD-1, to stave off attack by immune T cells. Another checkpoint, CTLA-4, also switches off the immune response.

“The T cells can get exhausted, and go into a state where the tumor is masked from the immune system’s attack.”
While many other checkpoint blockers are in company pipelines or clinical trials, researchers are exploiting the power of the immune system in other ways. One approach that has gotten a lot of attention because of some early dramatic successes is CAR T cells. (See related story on page 16.) The patient’s T cells are removed and genetically modified in the laboratory to produce special receptors on their surface that recognize a specific protein on tumor cells. Then billions of the CAR T cells are infused into the patient to seek out and destroy the cancer. In some patients with very advanced blood cancers this strategy has had remarkable success, but it also can produce severe side effects that need to be closely managed.

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Cancer vaccines continue to intrigue immunologists. Even though there are effective vaccines against the human papilloma virus (HPV), which causes cervical cancer and some head and neck, and anal cancers, only a minority of people at risk have undergone vaccination, Glimcher says. “It’s really a crime,” she says. “No women should die of cervical cancer.” She says she believes effective vaccines for non-viral cancers are possible, but the field is still in its infancy. Such vaccines would provoke the immune system to react against proteins displayed on the surface of cancer cells.

“Ultimately,” says Glimcher, “I think the answer is going to be combination therapy, just as it was for HIV/AIDS. The key to turning HIV from a lethal disease to a chronic disease was realizing you have to attack it with several drugs at the same time. It’s going to be trying to figure out which drugs work in which patients, precision immuno-oncology both for the tumor and the immune system.”

The potential of immuno-oncology is just beginning to be realized. Uncovering more of the iceberg will take both a much more detailed understanding of how the immune response is controlled and the tools or treatments to manipulate it for clinical benefit. “I can’t think of a place that’s better equipped than Dana-Farber to take this on. We have fantastic researchers who work closely with clinicians. And we can actually generate drugs here – we can take a basic discovery in the lab, do a proof of principle assay in animals, identify tool compounds, and then our chemists can turn that into a drug that could go into humans. Very few institutions have this capability.”

Learn more about Dana-Farber breakthroughs. Visit www.discovercarebelieve.org.
In Check

The next success of immunotherapy may lie in an attack on cancer from many fronts.

BY SAUL WISNIA
As a pediatric dentist, Jay Schwab had a clear-cut enemy: dental disease in children and adolescents, and the apprehensions they faced in the dental environment. Cavities could neither hide from his drill nor fool his X-ray machine, and plaque could easily be scraped away. Generations of patients went away smiling and in good dental health.

As a patient, however, Schwab faced a far more cunning adversary: cancer. He had lost his three younger siblings to the disease, and, at 76, knew he was lucky to have survived his own bout with melanoma in the 1960s. After a long day at work, he would pull out his old pathology reports, think of his wife and kids at home, and remind himself that things could be much worse.

This seemed the case when Schwab received a second and more serious melanoma diagnosis in 2016. But a lot has changed in the decades since his first time with cancer, and he is undergoing treatment at Dana-Farber with profound optimism – due, at least in part, to recent breakthroughs in immunotherapy. Schwab is among a growing number of patients benefiting from remarkable advances in the field, which centers on harnessing the power of the immune system to fight cancer.
This revolution capitalizes on our immune system’s natural function – recognizing foreign cells and attacking them. But cancer cells often find their way by this surveillance. One way is through the use of natural proteins called immune “checkpoints” that act as brakes to prevent an immune system attack.

Now, led in large part by researchers at Dana-Farber, scientists have learned how cancerous cells work their deception. Partnering with colleagues around the world, they are developing checkpoint inhibitors, drugs that take off the brakes and let the immune system do its job. Some tumors that once proved stubbornly resistant to chemotherapy and other treatments are being thwarted quickly and dramatically, a breakthrough that is offering some patients their best chance yet of beating even the most challenging cancers like melanoma and lung cancer.

“What’s exciting to me about immunotherapy drugs and checkpoint inhibitors is not only their underlying efficacy, which is very impressive, but the fact that they work through a mechanism that’s completely different from our other treatments by mobilizing a patient’s own immune system,” says Barrett Rollins, MD, PhD, chief scientific officer at Dana-Farber. “That tells us that there is this wonderful new pathway for us to exploit – basically a whole new way to treat cancer.”

Checkpoints inhibitors have been approved for use in six types of cancer, and are currently being evaluated in hundreds of clinical trials in more than 30 cancer types – with more than 80 of those trials at Dana-Farber. But challenges remain. Only 20 to 25 percent of patients benefit from checkpoint inhibitors, and some encounter serious side effects. Researchers are working to develop new strategies – including combining checkpoint inhibitors with other immunological drugs, vaccines, radiation therapy, and traditional chemotherapy agents – to find the best approach for each patient’s cancer.

Catching Wolves

The emergence of checkpoint inhibitors represents the fulfillment of long-held hopes. For more than a century, researchers sought to harness the body’s own cell-fighting abilities as a means of killing cancer. They knew that the immune system could stop infections and malignancies in their tracks before they could damage healthy tissue, but they didn’t know all the intricacies of the process – or why cancer could often resist it.

In the 1990s, scientists learned more about the role of T cells, the foreign body watch dogs – and attack dogs – of the immune system. It is T cells that scramble to shut down invading cells. Initially, researchers couldn’t figure out how cancer cells were avoiding the T cells’ attack. (For more on T cells and how cancer fools them, see “Catch Me If You Can,” page 16.)

Then, in 2000, Dana-Farber scientist Gordon Freeman, PhD, and his colleagues discovered the protein PD-L1 – and they had their answer. Freeman’s team found that PD-L1 can cover the surface of healthy cells like a coat, and it is this coat that binds molecules on incoming T cells known as T-cell co-receptors (PD-1). The co-receptors serve as both brakes and hall passes, telling T cells that an immune response is not needed and giving the healthy cells free reign of the body.

The challenge is that some cancerous cells are also coated in PD-L1, making them essentially wolves in sheep’s clothing. By fooling T-cell co-receptors into thinking they are healthy, these malignant cells can avoid an immune response just like their healthy counterparts – and allow cancer into the body. Blocking PD-L1 (or its related binding molecule, PD-L2), Freeman’s team concluded, could “turn off the brakes” and allow the immune system to kill off the cancerous cells.

“There is this wonderful new pathway for us to exploit – basically a whole new way to treat cancer.”

– Barrett Rollins, MD, PhD
Pharmaceutical companies went to work developing drug agents to block PD-1, PD-L1, or PD-L2 and give the immune response the help it needed. And as these first immune checkpoint inhibitors became available, Dana-Farber physician-scientists began administering them to patients with a variety of cancer types for whom standard chemotherapy or other treatments had failed.

In one trial of the PD-1 blocker nivolumab, 87 percent of Hodgkin lymphoma patients who had not responded to chemotherapy or a stem cell transplant experienced a full or partial remission – and the majority were still doing well 18 months later. Hodgkin lymphomas have a genetic basis for enhanced PD-1 signaling, the likely reason for the very high response rate to PD-1 blockade.

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Study leaders Margaret Shipp, MD, and Philippe Armand, MD, PhD, of Dana-Farber published their findings in the *New England Journal of Medicine*, and in 2015 the U.S. Food and Drug Administration (FDA) gave nivolumab its Breakthrough Drug Designation for use in Hodgkin lymphoma patients. By the start of 2017 nivolumab had been FDA-approved for use on individuals with Hodgkin lymphoma, melanoma, non-small cell lung cancer, bladder cancer, kidney cancer, and squamous cell cancer of the head and neck.

“The Hodgkin lymphoma findings are a variation on the precision medicine theme,” says Shipp. “Instead of finding genetic alterations in tumors and attacking the tumors directly with precision drugs, here we’re targeting alterations in tumor cells that shield them from attack by immune cells.”

Ipilimumab, a drug targeting another checkpoint protein, CTLA-4, has shown promise for patients like Jay Schwab with advanced melanoma. Stephen Hodi, MD, of Dana-Farber led a phase 3 clinical trial testing ipilimumab in patients whose melanoma had not responded to other treatment. Just as in the PD-1 studies, the results were dramatic.

Patients who received the CTLA-4 blocker ipilimumab lived significantly longer, on average, than those who did not, marking the first time survival rates for metastatic melanoma had ever gone up through treatment. Some patients even appeared to be cured, and by 2011 ipilimumab had received FDA approval as a metastatic melanoma therapy. More than 2,000 metastatic melanoma patients have since received it at Dana-Farber and elsewhere, and about 20 percent have benefited from it. Of these individuals, the majority are alive today.

“We are seeing miraculously rising survival rates,”

Treatment with checkpoint inhibitors offers Jay Schwab, shown here with his oncologist Elizabeth Buchbinder, MD, a chance for more time with his family.
says Elizabeth Buchbinder, MD, Schwab’s primary oncologist at Dana-Farber. “Before checkpoint inhibitors, melanoma was unfortunately a very aggressive cancer that did not respond well to any treatment. Now many patients are years out from their checkpoint inhibitor treatment and doing great. In many of them, their disease is shrinking.”

**Putting It All Together**

The challenge now is to build on that progress. As researchers continue learning more about which immunological approaches work best, and in which cancers, they are treating patients with combination therapies in which checkpoint inhibitors are given with other treatment such as chemotherapy, vaccines, or radiation therapy.

“One area of investigation that Dana-Farber scientists like Stephen Hodi are studying is why certain people don’t respond well to checkpoint blockades,” says Bruce Johnson, MD, chief clinical research officer at Dana-Farber. “Some may need a way to stimulate their T cells, while others require inflammatory cytokines that are suppressing their immune response removed. We need to sort out what we understand about these tumors to know which drugs might work in concert with a checkpoint inhibitor.”

Sometimes, Johnson explains, cancer cells may have two different checkpoints that are keeping an immune system attack at bay; in these cases, two checkpoint inhibitors may be an effective treatment option. Other studies – forming in fact, an almost new field of their own – involve removing, modifying, and reinserting a patient’s T cells to make them better able to detect and destroy cancer cells.

The list of cancers targeted successfully by checkpoint inhibitors continues to grow, as does the number of patients receiving them. Elaine Shusterman is one example. A patient of Johnson’s, Shusterman was diagnosed with non-small cell lung cancer in June 2016. In addition to being treated with nivolumab, a PD-1 inhibitor approved by the FDA in 2015, she is also receiving a CTLA-4 inhibitor to stimulate her T cells.

“I know my lung cancer is not totally curable, but thanks to this treatment we’re hoping to make it a chronic disease,” says Shusterman, 66, who after starting on an immunotherapy trial in August 2016 spent that October hiking to the bottom of the Grand Canyon. “There has been significant shrinkage in pretty much all of the spots on my lung, and I had a lump on my neck that appears to be completely gone. I feel great.”

While Johnson calls immunotherapy and checkpoint inhibitors “the biggest thing to happen to lung cancer in more than a decade,” he knows mysteries remain. It’s not clear, for instance, why many patients do not respond to the treatment. The side effects also differ; Shusterman didn’t lose her hair or suffer from nausea, but the powerful immune response carried out by T cells can sometimes affect healthy tissue and organs. This can cause problems ranging from skin rashes to more serious issues like pneumonitis (inflammation of the lungs), colitis, hepatitis, and pancreatitis.

Dana-Farber’s Center for Immuno-Oncology, directed by Hodi, is looking into such issues and is involved in nearly 100 clinical trials using checkpoint inhibitors.
The Next Gleevec?

If scientists can build on the early success of checkpoint inhibitors to gain an even greater understanding of how the body’s immune system fights back against cancer, the findings could prove as significant a research breakthrough as another agent that Dana-Farber played a major role in helping develop and bring to the world: Gleevec (imatinib).

Considered the gold standard of 21st-century cancer therapies, Gleevec was first used in clinical trials during the 1990s on patients with chronic myelogenous leukemia (CML), and achieved striking success when approved for CML treatment in 2001. At the time, just one in three patients with the disease lived five years from the point of diagnosis. Within a decade, the five-year survival rate had more than doubled. Today, 90 percent of patients consistently taking Gleevec reach this benchmark.

Along the way, Gleevec was approved for use on other hematologic malignancies. At Dana-Farber, physician-scientists led by George Demetri, MD, found that Gleevec could shrink and even eliminate tumors in some patients with a rare and otherwise incurable digestive-tract cancer called gastrointestinal stromal tumor (GIST).

“Gleevec was a proof of principle that if you could understand mutations in cancer and make a drug that counters the effects of those mutations, you could get strong responses, and its success led to two decades of expanding work based on that principle,” says Dana-Farber Chief Scientific Officer Barrett Rollins, MD, PhD. “Checkpoint inhibitors are similar. They are a proof of principle that if you educate a patient’s immune system correctly, it can fight the cancer. Now, we need to exploit that in the same way we exploited targeted therapy with Gleevec.”

Inhibitors and other immunotherapy treatments including vaccines. Physician-scientists believe that combination therapy approaches using PD-1 inhibitors as the “backbone” of treatment will be a key to improving the accuracy and success of immunotherapy.

“One important reason why PD-1 inhibitors do not work in many patients is that the immune cells that promote the attack against the cancer have not reached the tumors in sufficient numbers,” says Patrick Ott, MD, PhD, clinical director of the Center for Immuno-Oncology. “One of the approaches to tackle this problem is adding a cancer vaccine, which has the ability to increase the numbers of these cells and to potentially drive them into the tumor.”

This approach has already shown some success in melanoma patients. Adding a drug called TVEC, which has cancer vaccine properties in addition to its tumor-killing effect, has shown to substantially increase the clinical activity of ipilimumab and is currently in clinical trials in combination with PD-1 inhibitors. Another mechanism that can suppress an immune response against cancer is an enzyme called IDO; using small molecules of it in combination with PD-1 inhibitors has shown early promise (as evident by higher response rates in melanoma and lung cancer) – leading to several clinical trials in different cancers.

“We have a new strategy to attack all cancers. The success of immunotherapy has opened the door and also unleashed a flood of creativity and discovery,” says Gordon Freeman. “We know ways we can do better and are bringing those to patients. In 10 years, we hope that 60 percent of patients will be benefitting from immunotherapy.”

In the meantime, Freeman and others will be learning from patients like Schwab and Shusterman, each of them a pioneer in this powerful new era in cancer research and care.

Learn more about Dana-Farber breakthroughs. Visit www.discovercarebelieve.org.
In the high-stakes contest of hide-and-seek between cancer cells and the human immune system, the advantage doesn’t always lie with the body’s defenders. A new approach to treatment, known as CAR T-cell therapy, may shift that balance of power.

Cancer cells conceal themselves from the immune system not by barricading themselves in an impenetrable shell, but by the biological equivalent of hiding in plain sight. Their strategy is to make themselves inconspicuous by blending in, as far as possible, with their normal neighbors. They accomplish this by displaying proteins, known as antigens, on their surface, that are similar to those on the well-behaved cells nearby.
This uniformity can mislead the body’s T cells, the patrol officers and duty inspectors of the immune system. T cells conduct their interrogations of the body’s cells with specialized protein hooks called receptors. The receptors interlock with different types of antigens: if the antigen is normal, the cell is left alone; if it signifies a cancerous or infected cell, the cell is destroyed. The trouble is that T cells may not carry receptors for certain cancer-associated antigens and therefore don’t recognize the cells as cancerous. Such T cells are in the position of a colorblind detective searching for a criminal known to be wearing a red scarf.

In the late 1980s, an Israeli chemist named Zelig Eshhar saw the potential for a powerful new form of cancer therapy. At first glance, his approach seems almost too contrived and ungainly to work. What if it were possible, Eshhar wondered, to equip T cells with a receptor for a specific antigen found on certain types of cancer cells? In theory, the newly accessorized T cells would recognize the cancer cells, snag them with the receptor, and initiate their destruction. The concocted cells were dubbed chimeric antigen receptor (CAR) T cells. (“Chimeric” derives from “chimera,” a Greek mythological monster with a lion’s head, goat’s body, and serpent’s tale. Like the chimera of old, the CARs on T cells are composites of elements not found together in nature.)

To build a CAR, researchers glean materials from the immune system. The “hook,” or receptor, is an antibody that homes in on diseased cells such as cancer cells. Other components include a protein that puts the T cell in killing mode, and one that keeps it in that mode. “CAR T cells are, in a real sense, a ‘living drug,’ a treatment created by enhancing a patient’s own immune system cells,” says Sarah Nikiforow, MD, PhD, a physician in Dana-Farber’s Adult Stem Cell Transplantation Program and assistant medical director of the Institute’s Connell and O’Reilly Families Cell Manipulation Core Facility, which makes CAR T cells. “When they’re infused in a patient, they reproduce dramatically and instigate a ferocious attack on tumor cells. They’re one form, maybe the most high-profile form, of a new generation of engineered cell therapies, in which cells are altered to generate a more potent immune response to cancer.”

Clinical trials of the latest generation of CARs began in earnest in 2015, primarily in patients with B cell malignancies such as acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Even in a field as replete with breathtaking results as cancer immunotherapy has been in recent years, the results of these trials have stood out – for physicians, patients, and researchers alike.

Example: A phase 1 trial of CAR T cells in patients with relapsed B-cell ALL that hadn’t responded to other therapies. Traditionally, further treatment would control the disease in only about 10-20 percent of such patients. In this trial, 82 percent of the participants had a complete remission.
response – tumor cells were no longer detectable in their blood, bone marrow, or in body scans. The CARs were fast: the median time that it took to produce a complete response was three weeks. Some patients experienced such a response within eight days.

Another example: In two trials involving patients with NHL who had relapsed after undergoing stem cell transplants, 82 and 97 percent of the participants, respectively, had a clinical response to CAR T-cell therapy, meaning at least some decrease in tumor burden. The historical response rate for patients in this situation is about 26 percent.

It’s too early to know how lasting these remissions will be. Cancer cells are notorious camouflage artists; they may find ways to shed the antigens that CARs recognize, rendering themselves invisible to the immune system. To date, however, CAR therapies are showing strong signs of durability.

From the earliest reports of the success of CAR T-cell therapies, Dana-Farber investigators have sought to make them available to Institute patients in clinical trials. “As an academic community, we could see how promising these therapies would be,” Nikiforow says. “It was clear that the early-stage trials opened by several research centers in 2015 would quickly expand to include other institutions. We wanted to be able to offer these cutting-edge therapies to our patients.”

Today, Dana-Farber and its clinical partners, Boston Children’s Hospital and Brigham and Women’s Hospital, have joined in eight trials of CAR T-cell therapy, including one trial for pediatric patients. The trials are open to patients with certain types of ALL, NHL, acute myelogenous leukemia, or multiple myeloma, who have relapsed after previous treatment – often, several previous treatments. More than 30 patients have participated in them so far.

In two trials, 82 and 97 percent of the participants, respectively, had a clinical response to CAR T-cell therapy.

Making a Better T Cell

CAR T-cell therapy begins with the collection of thousands of a patient’s T cells. From a needle in the patient’s arm, blood flows through a tube to an apheresis machine that separates out immune system cells and returns the rest to the other arm. The collected cells are then sent to a lab, such as the Connell and O’Reilly Families Cell Manipulation Core Facility or a commercial facility, where they’re expanded and engineered to express the new receptor. The engineering involves a deft bit of gene therapy: a virus carrying a particular trio of genes is allowed to infect the cells. The virus, essentially a molecular delivery van incapable of replicating, releases the genes, which are then sewn into the cells’ genome. Ensnconed in the cells’ basic operating system, the genes direct the assembly of the three-part CAR to the cells’ surface.

The process of engineering and growing sufficient quantities of CAR T cells can take a few weeks. In the meantime, patients may receive chemotherapy for their cancer. When the CARs are ready, they’re reinfused into patients in a process similar to a blood transfusion.

Caron Jacobson, MD, is involved in clinical trials of CAR T-cell therapies for patients with a type of lymphoma.
A single CAR T cell can annihilate 100,000 cancer cells.

The biggest challenge for patients, and for those charged with their care, comes after the infusion. Effective CAR T cells typically multiply profusely and besiege cancer cells throughout the body. A single CAR T cell can annihilate 100,000 cancer cells. And CAR T cells don’t work alone—they initiate a massive release of proteins called cytokines, which whistle to other elements of the immune system to come join the attack. The resulting onslaught can trigger an inflammatory condition known as cytokine-release syndrome—more evocatively dubbed a cytokine storm—an array of complications that includes dangerously high fevers, extreme fatigue, difficulty breathing, and a sharp drop in blood pressure. The condition tends to be particularly severe in patients with extensive cancers.

“Cytokine release syndrome tends to arise within one to five days of infusion,” says Dana-Farber’s Caron Jacobson, MD, who is leading the Institute’s participation in several clinical trials of CAR T-cell therapy for patients with treatment-resistant large B-cell lymphomas. “We have medications that in most cases can treat these symptoms effectively. They usually abate in about five days.”

In a set of trials involving patients with lymphoma, the ebbing of the cytokine storm has often been a prelude to a second wave of complications that affect the nervous system. “These patients have often experienced memory loss and difficulty understanding language and speaking,” Jacobson relates, noting that this period can be particularly difficult on patients’ families. The cognitive problems have so far proved impervious to drug treatment, but tend to last just a few days, although they sometimes last for weeks. “At the time of infusion, patients are generally admitted to the hospital for a minimum of seven days, and remain hospitalized until the symptoms abate, which usually takes about two weeks,” Jacobson says.

Because of the potential for complications, the severity and breadth of those complications, and the fact that they aren’t always predictable and may arise after hospital discharge, caring for patients receiving CAR
T-cell therapy poses enormous logistical, communication, and coordination challenges for caregivers. At Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC) and the Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, clinicians have built an extensive infrastructure to ensure the therapy is delivered safely.

“CAR T cells and other engineered cellular therapies are some of the highest potential benefit/highest potential risk treatments that we have for cancer,” Nikiforow states. “We’ve brought together clinicians and staff from an array of areas – physicians, nurses, the pharmacy department, information technology, and others – to create a system that’s efficient and provides for a rapid response when complications arise. It has involved educating physicians about cellular therapies and cell-collection processes, establishing direct lines of communication between caregivers and the principal investigators of CAR T trials, and developing guidelines and pathways for treating specific complications. We consult regularly with the leaders of CAR T-cell therapy trials at other institutions to share information, including details of any new complications and how to respond to them.”

Reassured by these arrangements, patients have been undaunted about enrolling in clinical trials of CAR T-cell therapies, and unfazed by the science fiction-sounding process of retrofitting T cells with genes intended to make them better cancer fighters. In part, this is because patients eligible for the trials have few remaining treatment alternatives, and because they’ve educated themselves about the promise and risks of CAR T-cell therapy.

“Patients eligible for these trials have advanced disease that has relapsed after previous treatment, often several previous treatments,” says Dana-Farber’s Daniel Deangelo, MD, PhD, who is leading the Institute’s involvement in two trials of CAR T cells for a form of B-cell leukemia. “They’re excited by the results they’ve read about, particularly in pediatric patients, and are eager to participate in a trial. We’re glad to be able to provide options where there otherwise might be none.”

Although the initial clinical trials of CAR T-cell therapies involved B-cell cancers, other engineered T-cell trials are rapidly opening for patients with certain kinds of solid tumors, including sarcomas. The challenge is to identify antigens unique to specific types of tumor cells, then to construct CARs or other T-cell receptors that target them. “Basically, any antigen that we can generate an antibody to, we can also make a CAR T cell against,” Nikiforow says. “There are many years of trials to come.”

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Immune system targets called neoantigens on cancer cells are fueling a new breed of anti-tumor vaccines.
It’s a compelling idea that has attracted scientists for decades: rather than poison tumors with chemicals and radiation, use a biologic agent – a vaccine – to rally the body’s formidable immune defenders to kill cancer cells and shrink tumors.

Yet, even as other forms of immunotherapy are showing promise against some cancers, efforts to make an effective and safe cancer treatment vaccine have struggled.

Treatment vaccines differ from preventative vaccines, such as the human papilloma virus (HPV) vaccine, which prevents cancers caused by certain strains of HPV. A treatment or therapeutic cancer vaccine, by contrast, is designed to stimulate a patient’s immune system to attack cancer cells. Only one such vaccine – Provenge, for advanced prostate cancer – is approved for wide use. Much of the time, despite researchers’ best schemes, vaccines have failed to land much of a blow against cancer.

But rather rapidly, a series of molecular discoveries, together with increasingly powerful DNA sequencing methods and predictive computer algorithms have brought a promising new vaccine concept based on “neoantigens” to the table – and, just recently, to the clinic.

**The Neoantigen Approach**

Neoantigen vaccines are highly personalized therapies. An antigen is any substance the body encounters that provokes an immune response. “Neo” antigens are molecules newly minted by mutations that occur randomly as cancer cells divide and grow. Neoantigens are unique to each patient and his or her cancer, and – critically important – can be recognized by the immune system as foreign. The neoantigens from a patient’s tumor are used to make a customized vaccine that stimulates the immune system to react against cancer cells that carry the selected neoantigens.

“It’s a new thrust – neoantigens are reinvigorating the vaccine field,” says Catherine Wu, MD, a Dana-Farber physician-scientist who has discovered unique mutated neoantigens in leukemia and is a leader in neoantigen vaccine development.

Scientists have long tried to create cancer vaccines
Cancer Immunology and Virology. “I think this is going to be important.”

Neoantigen vaccines are in very early human testing and haven’t yet been shown to benefit patients. They have, however, been shown to control cancer in animals. There is also indirect evidence for the power of neoantigens in humans. Some studies have found that patients treated with checkpoint inhibitors (among the most promising new class of immunotherapy drugs; see related story on page 10) have better outcomes if their tumors contain greater numbers of neoantigens. This suggests that the patients’ immune systems are reacting more strongly to the tumor because of neoantigens on the cancer cells’ surface, and scientists see this as an indication of how a neoantigen vaccine would cause a more potent immune response.

Even at this early stage, Wu and her colleagues are confident they are onto something transformative.

At left: Patrick Ott, MD, PhD, and Catherine Wu, MD, developed the NeoVax vaccine now in clinical testing.

that contain a distinctive antigen – some molecule or part of the cancer cell which would spur an immune response against the tumor, while leaving normal organs and tissues in the body unscathed. The problem is, while the immune system can recognize antigens on cancer cells, these antigens tend to be similar to those on normal cells. As a result, the immune system fails to respond with enough power to subdue tumor growth. Cancer cells are also adept at hiding their identifying antigens.

“Finding a good antigen for a cancer vaccine has been difficult because most are ‘self-antigens’ – they induce tolerance by the immune system,” explains Patrick Ott, MD, PhD, clinical director of the Center for Immune Oncology at Dana-Farber. Tolerance refers to the lack of an immune reaction against an antigen perceived as harmless.

Neoantigens are unique not only to the cancer but also to the individual patient; they are antigens that the immune system has never encountered. As a result, the body’s defenses should have zero tolerance for a cell bearing a neoantigen.

Wu and Ott, working with collaborators at the Broad Institute of MIT and Harvard, have developed a personalized neoantigen-based vaccine called NeoVax. NeoVax is in early trials at Dana-Farber in patients with advanced melanoma, glioblastoma brain tumors, and kidney cancer. The scientists say the vaccine, which is injected under the skin, appears to trigger strong immune activity in some patients, with no safety problems.

“What’s exciting about neoantigen vaccines is that the T-cell responses to these peptides tend to be highly tumor specific,” says Kai Wucherpfennig, MD, PhD, chair of Dana-Farber’s department of Cancer Immunology and Virology. “I think this is going to be important.”

Neoantigen vaccines are in very early human testing and haven’t yet been shown to benefit patients. They have, however, been shown to control cancer in animals. There is also indirect evidence for the power of neoantigens in humans. Some studies have found that patients treated with checkpoint inhibitors (among the most promising new class of immunotherapy drugs; see related story on page 10) have better outcomes if their tumors contain greater numbers of neoantigens. This suggests that the patients’ immune systems are reacting more strongly to the tumor because of neoantigens on the cancer cells’ surface, and scientists see this as an indication of how a neoantigen vaccine would cause a more potent immune response.

Even at this early stage, Wu and her colleagues are confident they are onto something transformative.

Unique neoantigens from a patient’s tumor are used to make a vaccine specific to that person.
Scientists say checkpoint blockade drugs could make vaccines more effective, and vice versa.

David Reardon, MD, is testing the NeoVax vaccine in patients with glioblastoma brain tumors.

In a 2013 paper published in Cancer Immunology Research, she and her co-authors wrote: “We are entering a new era of cancer immunotherapy in which a sophisticated vaccine loaded with patient-specific neoantigens is poised to generate a powerful yet precisely targeted antitumor immune response.”

Any success that neoantigen vaccines may have, they will owe in part to rapidly developing DNA sequencing technology and computational bioinformatics.

It’s been known for many years that new mutations occur as cancer cells evolve – mutations that didn’t necessarily cause the tumor or drive its behavior, but occur only in the cancer cells and not in healthy cells. Only in the past few years, with powerful whole-exome sequencing technology, has it become feasible to rapidly search through the protein-coding parts of a patient’s normal genome and the tumor’s genome in order to identify all the mutations that have occurred.

To make a neoantigen vaccine, scientists first sequence the patient’s tumor exome DNA and compare it to the DNA of the patient’s normal
The neoantigen concept has spurred a wave of investment and startup companies.

One enthusiast is Sean Parker, the Silicon Valley entrepreneur and founder of the Parker Institute for Cancer Immunotherapy. In December, the Institute announced a collaboration for neoantigen vaccine research that includes Dana-Farber, the Broad Institute of MIT and Harvard, Cambridge-based Neon Therapeutics and a number of academic research centers and companies. The collaboration will enable different research groups to compare methods for predicting which neoantigens (based on their DNA sequence) will be most potent in a vaccine.

NeoVax isn’t the only advance in vaccine research being developed by Dana-Farber investigators.

In a highly encouraging recent study, Dana-Farber’s Donald Kufe, MD, and collaborators at Beth Israel Deaconess Medical Center (BIDMC) showed that a personalized cancer treatment vaccine was highly effective in preventing relapses in older patients with acute myeloid leukemia (AML) who were in remission following chemotherapy.

Kufe, who discovered MUC1, an important cancer-related protein, spent years making a cancer treatment vaccine against it, as well as neoantigens. His team fused cancer cells from patients with dendritic cells (key immune cells that process antigens and alert the immune system to attack them) from the same patient to form a hybrid hunter-killer product. They then used that product as a vaccine to stimulate the immune system to attack the patient’s cancer cells.

“The development of this personalized vaccine was based on the premise that effective treatment of established cancers would require the induction of immunity against multiple antigens, including neoantigens, specifically expressed by the patient’s own cancer cells,” says Kufe. Support from the Barbara and James Sadowsky Family made the development of this vaccine possible.

In a trial based at Dana-Farber and BIDMC, the personalized vaccine markedly improved outcomes in AML patients who were in remission but at risk for relapsing. The researchers said it generated a broad and durable immune response against MUC1 and other cancer-related antigens without significant side effects.

As a result of these findings, a multicenter national trial for patients with AML has been initiated with support from the National Cancer Institute. In addition, this personalized vaccine is being evaluated in an ongoing multicenter national trial for patients with multiple myeloma (MM), based on evidence of immune responses against MUC1 and other MM-related antigens, and clinical activity.
Next generation sequencing of tumor DNA and normal DNA identifies mutations that generate “neoantigens” found only in cancer cells.

Mutations in tumor DNA

Vaccine contains multiple neoantigens plus immune stimulant

Vaccine steers immune T cells to target neoantigens in tumor

Neoadtigen vaccines contain small proteins present only on cancer cells that stimulate the immune system to attack the tumor with T cells. Because neoantigens aren’t present on normal cells, they make an ideal target for cancer treatment vaccines.

Testing the Strategy

In the ongoing clinical trials, the neoantigen approach is showing encouraging activity and safety profiles.

In one Dana-Farber study, the NeoVax vaccine is being given to six patients with melanoma who have had their tumors removed surgically. The study is examining the safety of the vaccine and whether the vaccine is triggering an immune response among T cells called CD4 and CD8. Says Wu: “Based on our computer predictions, we generated vaccines directed against antigens on the tumors, and all four of the patients with stage III disease have remained in remission.”

The two patients with stage IV disease who had recurrences were treated with pembrolizumab, an immune checkpoint-blocking drug, and went into complete remission, says Wu. In addition, patients treated with the combination of vaccine and pembrolizumab had persistent and broadened neoantigen-specific responses. “This is very exciting, because
A clinical trial of patients with advanced melanoma at Dana-Farber/Brigham and Women's Cancer Center is the first to evaluate an implantable vaccine device placed within their bodies to promote an immune response against tumors.

The thin, fingernail-sized round wafers are made of synthetic polymer materials and are implanted under the skin. Each vaccine wafer contains fragments of the patient’s cancer cells, which act as an antigen to incite an immune response, along with GM-CSF and CpG, immunity-stimulating compounds.

The vaccine chips are implanted near lymph nodes, part of the immune system, and are designed to attract dendritic cells into the chips. Dendritic cells capture foreign antigens and present them to T cells, which then seek and attack cells bearing those antigens. The goal is to generate a force of activated dendritic cells that will “prime” T cells to destroy cancer throughout the body.

The patients receiving the chips are being treated as part of a clinical trial headed by F. Stephen Hodi, MD, director of the Center for Immuno-Oncology and the Melanoma Center at Dana-Farber. Each patient has four vaccine chips prepared and implanted one at a time. Over time they are absorbed into the body.

Hodi says no safety concerns have arisen. “The patients get a local reaction and we are measuring immune changes in the blood and tumor sites that suggest immune activation” by the dendritic cells, he says.

The vaccine chip concept was originated by bioengineer David Mooney, PhD, at the Wyss Institute for Biologically Inspired Engineering, and the vaccine wafers are manufactured at Dana-Farber’s Connell and O’Reilly Families Cell Manipulation Core Facility.
WHY I WORK HERE

Justin Sanders, MD, MSc

By JESSICA CASSIDY

Justin Sanders’ path to Dana-Farber’s Psychosocial Oncology and Palliative Care department has meandered across the world. He grew up in Utah, studied art history in Pennsylvania, medicine in Vermont, and, as a Fulbright scholar, medical anthropology in London before working as a family doctor in the Bronx and then a hospitalist in rural New England. His interest in palliative care, however, is rooted in one pivotal moment.

“My closest friend died of ovarian cancer at 21,” says Sanders. “I held her hand as she took her last breath. It was a formative experience because I realized I could be present in those difficult moments, and that healing could take place even when a cure wasn’t possible.”

Sanders also learned that many doctors aren’t prepared to discuss what matters most to patients as they approach end of life. “That was the case for my friend,” he explains. “She and her parents did not have an opportunity to prepare for a case in which the cure they were hoping for didn’t come.”

In 2014, Sanders joined the Serious Illness Care Program at Ariadne Labs. Led by Susan Block, MD, the group developed an approach to improving serious illness care by helping clinicians communicate better with seriously ill patients and their families. Its centerpiece is the Serious Illness Conversation Guide, designed to document and spark meaningful conversations between doctors and seriously ill patients.

Sanders says there’s data showing that good communication leads to better outcomes for patients.

For the past two years, Sanders has focused on understanding how the conversation guide can improve the care of people in underserved communities – specifically African-Americans, who can suffer disproportionately at the end of life due to disparities in health care across their lifespans. “Working in medically underserved areas opened my eyes to the profound consequences of these disparities, as well as opportunities to improve care through good communication,” he explains.

His mission, he says, it to make medical care for seriously ill patients a vehicle for social justice and to adapt interventions that have the potential to address disparities in care for the most vulnerable patients.

“Dana-Farber is one of only a handful of institutions across the country supporting this work,” Sanders says. “I’ve seen how communication can transform the experience of seriously ill patients and their family, how it can help them get the best care, and prepare in case things don’t go as we hope. The care and treatment we provide here are among the most sophisticated in the world, and there are some things only good communication can do.”

Justin Sanders, MD, MSc
Larry Lucchino
President/CEO Emeritus, Boston Red Sox
Chair of the Jimmy Fund
Two-time cancer survivor

As told to
SAUL WISNIA

WHAT I KNOW

Life is too hard to be lived alone. Count on your friends and your family. This support system will make a difference, and if you work at it, and are fortunate, the line between friend and family will become indistinct.

Deliberate aggressively and imaginatively. If you want to win, you need to think outside the box.

Treat yourself when you can. After my stem cell transplant at Dana-Farber, my first trip outside my room in isolation was down the street to watch a ballgame at Fenway Park.

If you are a cancer survivor, return the favor. I believe all survivors have an obligation to give back with our time, our consideration, our thoughtfulness, and our interest by supporting cancer treatment, awareness, and research.

A rich life is a balanced life. Embrace change and widen your gaze. If you have blinders on, take them off. The world is open and full of opportunity.

Cancer made me a better person. It gave me an ability to focus and prioritize in a new way, and to treat other people with a heightened level of consideration, respect, and humility.

In cancer, as in baseball, a championship team is built with stars, depth, character, and personality. Every person involved in your care is essential to your ultimate goal.

One person can have a catalytic effect on a community, a nation, a compelling cause, or a nagging injustice. Be confident that if you fight long and hard enough, you too can make a difference.

Life is not about warming yourself by the fire – life is about building the fire. Help some people along the way. Find a cause you care about, and involve yourself in it. It’s like the old proverb: “If you want happiness for an hour, take a nap. If you want happiness for a lifetime, help somebody.”

“IF YOU ARE A CANCER SURVIVOR, RETURN THE FAVOR. I BELIEVE ALL SURVIVORS HAVE AN OBLIGATION TO GIVE BACK.”

Larry Lucchino
A fire truck pulls into the truck bay and idles for a minute or two as a firefighter attaches tubing to filter the exhaust out of the station. The firefighter’s face may be close to the exhaust for 30 seconds while the tubing is attached. It’s a routine task, one that’s performed by the same firefighter as many as 30 times a day as a crew responds to calls.

While many studies have focused on whether firefighters’ regular exposure to toxic compounds when fighting fires increases their cancer risk, Dana-Farber scientists are partnering with the Boston Fire Department in a novel exposure assessment of cancer risk factors – like diesel exhaust – at firefighters’ second home: the fire station.

“We are looking at chronic low level exposures in the fire station,” says Emily Sparer, ScD, a postdoctoral fellow working on the pilot study with Glorian Sorensen, PhD, director of the Center for Community Based Research in the Division of Population Sciences at Dana-Farber and the Harvard T.H. Chan School of Public Health.

“We will be looking at occupational exposures and combining those with other potential factors in firefighters’ daily routines,” says Sorensen. The effort is part of work funded by a federal grant to the Harvard Center for Work, Health, and Well-Being, of which Sorensen is the principal investigator, with additional funds for the pilot study provided by the Chan School’s Occupational Safety and Health Education and Research Center.

Sparer and Sorensen began working with the Boston Fire Department in 2015 after Deputy Fire Chief Greg Mackin contacted Dana-Farber expressing concern that local firefighters are being diagnosed with, and dying from, cancer at higher than normal rates.

Studies have found significantly elevated rates of some types of cancers in firefighters, particularly multiple myeloma, non-Hodgkin lymphoma, prostate cancer, and gastrointestinal and lung cancers.

After meeting with representatives of the Boston Fire Department and Firefighters’ Union Local 718, Sparer set out to study exposures in the firehouse. For example, she notes that because of the building design, which can date back to the 1800s in some Boston fire stations, the kitchen may be next to the truck bay. This may allow diesel exhaust from trucks to flow into the kitchen and potentially degrade air quality.

Sparer and Sorensen, who are working on a number of initiatives with the fire department, may study other risk factors, including behavioral ones such as sleep and diet during a firefighter’s 24-hour shift. The team is working on data analysis from the project and plan to use results to inform a future study on cancer prevention among firefighters.
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 45 nationally designated Comprehensive Cancer Centers. As a teaching affiliate of Harvard Medical School, Dana-Farber is also one of 20 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. Bringing together the strengths of three world-class institutions, these partnerships provide an exceptional level of care for cancer 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.

Participants in the annual Boston Marathon® Jimmy Fund Walk presented by Hyundai.

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Additional Photography Getty Images, John Deputy

If you have any comments or would like to be removed from the mailing list, please contact:
Michael Buller, Editor
Dana-Farber Cancer Institute
450 Brookline Ave., OS301
Boston, MA 02215
617-632-4090
pathsofprogress@dfci.harvard.edu
A Message from Chief Financial Officer Michael Reney

Fiscal year 2016 was a strong year financially, as Dana-Farber continued to record positive operating results, grow revenues in all key areas, and generate solid investment returns.

The Institute ended fiscal year 2016 with a consolidated surplus from operations of $29.7 million, or a 2.1 percent operating margin. Non-operating revenue was positively affected by overall conditions in the investment markets, returning 8.4 percent for the fiscal year, which resulted in an excess of revenues over expenses of $36.8 million.

Patient-care revenue increased by 20 percent across the Institute, including the main Longwood campus in Boston, our regional satellite centers, and our physician practice offices, continuing the trend of the last several years. Research revenues increased by 8 percent during fiscal year 2016 with growth coming from federal, commercial, and clinical trial sponsors, as well as in the increased use of gifts. And, thanks to the ongoing support of our donors, it was another outstanding year for fundraising, which saw a 6 percent increase in unrestricted giving.

Our investments in research continued during 2016 as the Institute exercised an option under its lease to acquire condominium space currently occupied in the Longwood Center, a state-of-the-art laboratory facility that opened in January 2015. The purchase is expected to take place during the summer of 2017. In addition to the purchased space, the Institute also committed to leasing another floor in the Longwood Center, thus reflecting our continued commitment to best-in-class scientific advancements.

Management, faculty, and staff throughout Dana-Farber – guided by the oversight of several committees of our Board of Trustees – worked diligently to achieve these results. We are grateful to them and also to the many donors and friends of Dana-Farber, who continue to demonstrate their commitment to the organization with their valuable knowledge and generous contributions. We are proud of all these efforts and thankful for this strong and ongoing support.
### Condensed Consolidated Balance Sheets

**For the Fiscal Year Ended Sept. 30**

*(Dollars in thousands)*

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Assets</td>
<td>$588,321</td>
<td>$230,235</td>
</tr>
<tr>
<td>Investments</td>
<td>1,034,466</td>
<td>950,994</td>
</tr>
<tr>
<td>Debt Service Reserve and Construction Fund</td>
<td>12,703</td>
<td>12,666</td>
</tr>
<tr>
<td>Property, Plant, and Equipment, net</td>
<td>923,299</td>
<td>748,560</td>
</tr>
<tr>
<td>Contributions Receivable, less current portion</td>
<td>28,824</td>
<td>40,469</td>
</tr>
<tr>
<td>Other Assets</td>
<td>48,262</td>
<td>21,305</td>
</tr>
<tr>
<td><strong>Total Assets</strong></td>
<td><strong>$2,635,875</strong></td>
<td><strong>$2,004,229</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liabilities and Net Assets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Liabilities</td>
<td>$264,419</td>
<td>$262,055</td>
</tr>
<tr>
<td>Long-Term Debt and Other Liabilities</td>
<td>977,883</td>
<td>437,715</td>
</tr>
<tr>
<td><strong>Net Assets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrestricted</td>
<td>668,285</td>
<td>612,732</td>
</tr>
<tr>
<td>Temporarily Restricted</td>
<td>540,317</td>
<td>516,907</td>
</tr>
<tr>
<td>Permanently Restricted</td>
<td>184,971</td>
<td>174,820</td>
</tr>
<tr>
<td><strong>Subtotal Net Assets</strong></td>
<td><strong>1,393,573</strong></td>
<td><strong>1,304,459</strong></td>
</tr>
<tr>
<td><strong>Total Liabilities and Net Assets</strong></td>
<td><strong>$2,635,875</strong></td>
<td><strong>$2,004,229</strong></td>
</tr>
</tbody>
</table>

### Summary Statistical Information

*(unless otherwise noted, includes adult and pediatric patients)*

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Treatments</td>
<td>157,533</td>
<td>149,413</td>
</tr>
<tr>
<td>Outpatient MD Visits</td>
<td>321,900</td>
<td>309,750</td>
</tr>
<tr>
<td>Number of Licensed Beds (as of year-end)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Adult Inpatient Discharges</td>
<td>1,270</td>
<td>1,258</td>
</tr>
<tr>
<td>Clinical Trials (open to patients at Dana-Farber, including therapeutic and nontherapeutic trials)</td>
<td>921</td>
<td>752</td>
</tr>
</tbody>
</table>

---

*Subsidiaries include Dana-Farber Inc., Dana-Farber Cancer Care Network, and Dana-Farber Trust.*
### Condensed Consolidated Statements of Operations and Changes in Net Assets

For the Fiscal Year Ended Sept. 30 2016 2015  
(Dollars in thousands)

#### Revenues
- Research $386,793 $357,625
- Patient Service, net 925,328 773,222
- Unrestricted Contributions and Bequests 73,276 69,398
- Other Operating 21,130 20,941

Total Revenues $1,406,527 $1,221,186

#### Expenses
- Direct Research 337,901 310,721
- Direct Patient Care 624,564 512,950
- Indirect 414,340 375,516

Total Operating Expenses $1,376,805 $1,199,187

#### Operating Income
- Operating Income 29,722 21,999

#### Investment Return, net 26,280 (7,345)

#### Interest Rate Swap Agreement
- Net interest received/(paid) (5,354) (5,593)
- Change in fair value (13,836) (11,238)
- Other — (248)

#### Excess/(Deficit) of Revenues Over Expenses
- Excess/(Deficit) of Revenues Over Expenses 36,812 (2,425)
- Other 18,741 8,294
- Increase/(Decrease) in Temporarily Restricted Net Assets 23,410 (21,163)
- Increase in Permanently Restricted Net Assets 10,151 7,603

Increase/(Decrease) in Net Assets 89,114 (21,163)

Net Assets at Beginning of Year 1,304,459 1,312,150

Net Assets at End of Year $1,393,573 $1,304,459

**The preceding selected consolidated financial data as of Sept. 30, 2016, and 2015 (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 Ernst & Young, LLP, independent auditors.**

**In FY 2016, the Institute raised $228 million in new gifts and new pledges through its Division of Development 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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The governance listings in this annual report are current as of Jan. 1, 2017.
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J. Wayne Weaver3
T. Conrad Wetterauer3
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Jane Brock-Wilson1
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Mortimer B. Zuckerman4

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3 Distinguished Trustee
4 Honorary Trustee
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Stephen E. Sallan, MD  
Chief of Staff Emeritus

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Chief of Imaging

Eric P. Winer, MD  
Chief Strategy Officer

*The governance listings on this page are current as of Jan. 1, 2017.*
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Suzanne Chapman

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Cristina S. Peters*, Co-Vice President of Patient Services
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Lori Whelan, Vice President of Fundraising

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Trudi Feinstein
Anita Fink
Seth Andrea McCoy
Lucy Santos

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Program Director
Dawn Belizaire

Art Program Administrator
Elaine L. Tinetti
* Past President
** Deceased

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Edward F. Rover

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Winnie W. Wong, PhD

Visiting Committee for Hematologic Oncology
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Jennifer Perini

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Alison Poorvu Jaffe
T. Conrad Wetterau

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William M. Gillen
Susan M. Poduska

Visiting Committee for the Susan F. Smith Center for Women’s Cancers
Jane P. Jamieson

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Laurie H. Glimcher, MD
President and Chief Executive Officer
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Treasurer and Vice Chairman
Neal J. Curtin, Esq.
Secretary
Richard S. Boskey, Esq.
Assistant Secretary
Kathleen Harkey
Assistant Secretary

Trustees
Joshua Bekenstein
Laurie H. Glimcher, MD
Brian J. Knez
Robert Stansky

Dana-Farber Inc. manages the investments of Dana-Farber Cancer Institute Inc.

The governance listings in this annual report are current as of Jan. 1, 2017.
A young patient shares a smile with her health care provider during an appointment at Dana-Farber/Boston Children’s Cancer and Blood Disorders Center.