

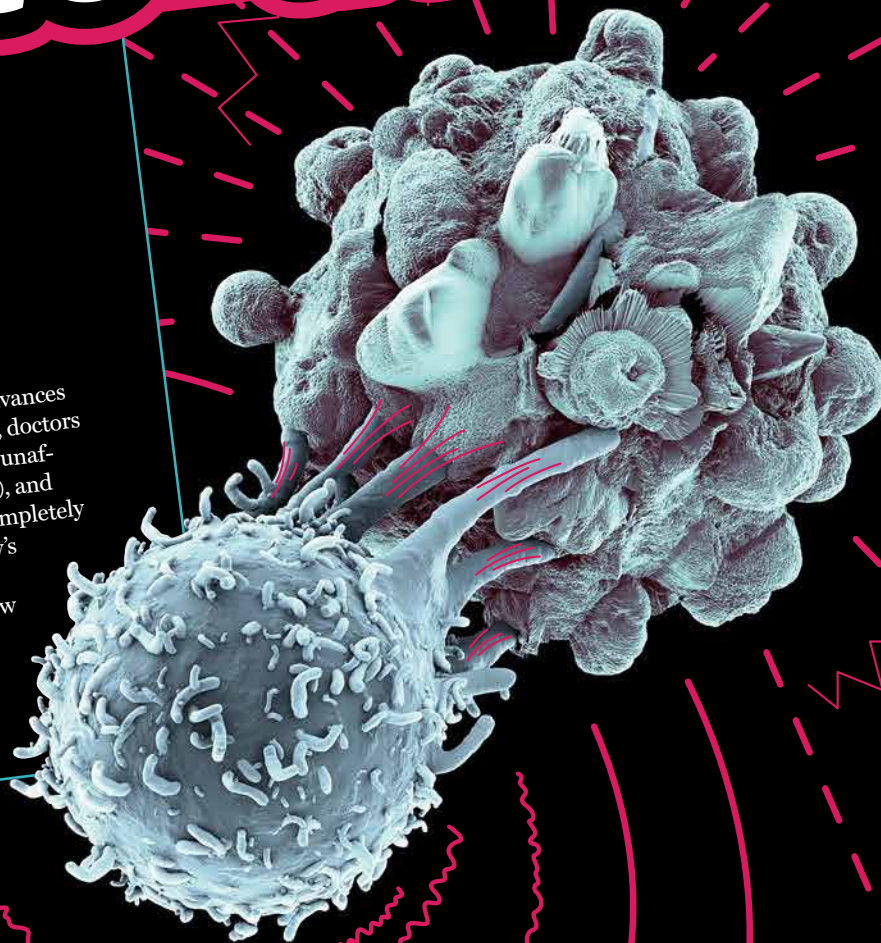
What you need to know about...

Immuno therapy

A Remarkable Cancer Breakthrough

BY AMY PATUREL

Immunotherapy is one of the most important advances in cancer treatment in decades. For a long time, doctors have relied on three types of treatment, known unaffectionately as slash (surgery), burn (radiation), and poison (chemotherapy). Immunotherapy is completely different. It works by harnessing the power of the body's own immune system, helping immune cells seek out and destroy cancer cells more effectively. With this new approach, cancer can potentially be attacked in a way that doesn't just extend lives for months or years but actually eradicates the disease.



The War Begins
A killer T cell (bottom), one of the immune system's soldiers, attacks a cancer cell.



Drug Delivery
Immunotherapy drugs are given intravenously, like most traditional chemotherapy.

“The reason immunotherapy is so promising is because we’re not treating the cancer or tumor cells—we’re treating the immune system,” says Padmanee Sharma, a professor of genitourinary medical oncology and immunology at MD Anderson Cancer Center in Houston. “Once we get the immune system working correctly, it shouldn’t matter which type of tumor we’re targeting. This really represents a paradigm shift in cancer research and treatment, resulting in unprecedented responses in melanoma and lung and kidney cancers,” Sharma says.

Researchers are hopeful that eventually all forms of cancer will succumb to this new treatment. More than 1,500 cancer immunotherapy drugs are currently in the research and development pipeline, according to the Parker Institute for Cancer Immunotherapy.

We asked top experts to answer some of the most common questions about this breakthrough.

1 What is immunotherapy?

It’s been part of the medical arsenal for decades, mainly in the form of vaccines that spark the body to produce antibodies to prevent infectious disease. The new immunotherapy treatments are drugs that have been specifically developed to help strengthen the body’s defense system against cancer.

Doctors have long wondered why the immune system doesn’t fight off cancer as effectively as it does other diseases. “We knew the immune system should be able to fight cancer, but it wasn’t

generating a strong enough response to kill off the disease,” says Nora Disis, a professor of medicine at the University of Washington.

In the 1980s, scientists figured out one of the problems: Cancer cells sometimes contain many of the same molecules as normal cells, without enough abnormal molecules for the immune system to recognize them as dangerous. Armed with this new knowledge, scientists began the search for substances that would help the body identify the rogue cells and destroy them.

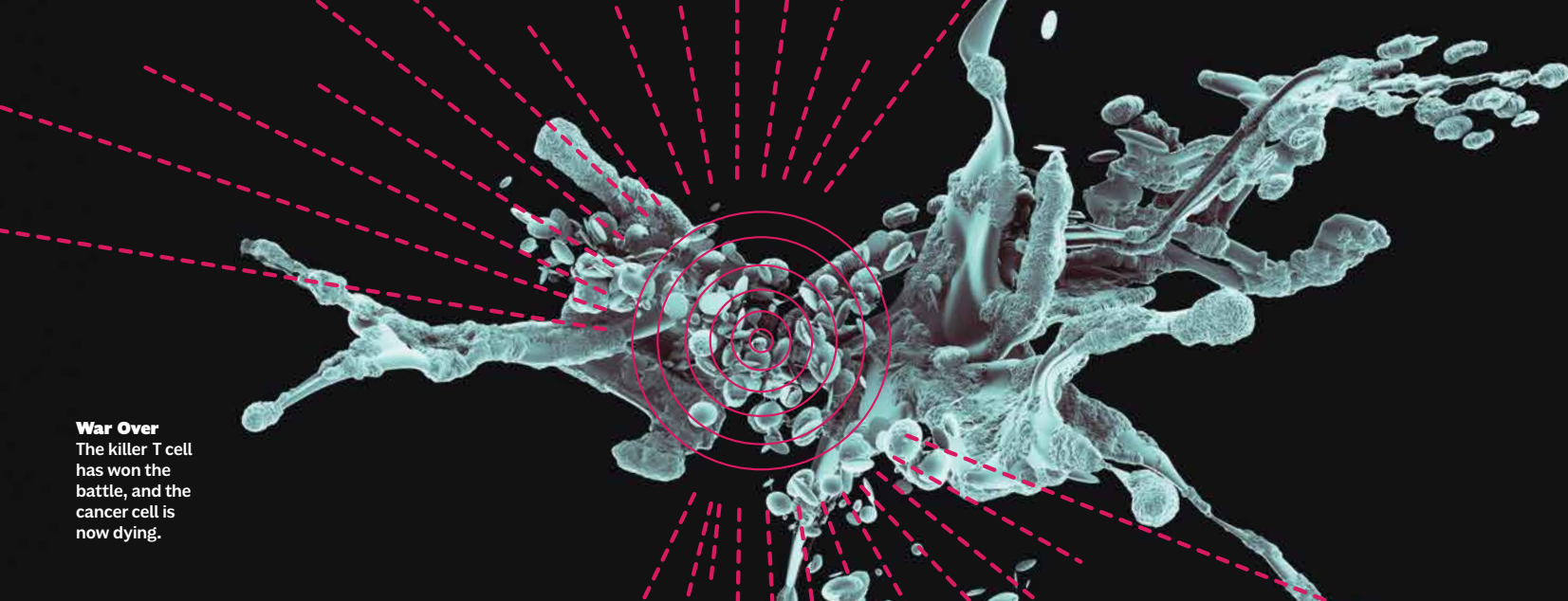
2 How do immunotherapy drugs work?

The immune system features an intricate network of on-off switches that free immune cells to fight disease when and where necessary but keep them in check otherwise so they don’t spin out of control and damage the body’s healthy organs and tissues. Today, the most widely used immunotherapy drugs, called checkpoint inhibitors, release the brakes and allow the immune system’s fighter T cells to attack cancer.

The strategy seems to be working. For example, long-term follow-up of nearly 5,000 patients with metastatic melanoma, a deadly form of cancer with a median survival rate of 11 months, shows that 20% of those who took a checkpoint drug called ipilimumab (Yervoy) survived for 3 years; some lived 5 to 10 years or longer.

To date, the FDA has approved four checkpoint inhibitors—ipilimumab, nivolumab (Opdivo), pembrolizumab

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War Over
The killer T cell has won the battle, and the cancer cell is now dying.

(Keytruda), and atezolizumab (Tecentriq)—as cancer therapy. All are given intravenously, like most cancer chemotherapy drugs.

3 What are the advantages of immunotherapy?

Many cancer treatments, including radiation and chemotherapy, weaken the immune system. In addition to obliterating cancer cells, they damage the body's infection-detecting white blood cells. "With immunotherapy, there's less risk of infection because those white blood cells remain intact," explains Matthew Davids, an attending physician at Dana-Farber Cancer Institute and Harvard Medical School.

Even cancer cells that are resistant to chemotherapy are responding to immunotherapy drugs, both in the short and long term. Once the drugs have

enabled the body's T cells to recognize and respond to tumor cells, the T cells are programmed to keep working until the tumor is eradicated. "Those targeted T cells remain in your system indefinitely," says Disis. "So if the cancer ever comes back, your immune system will kick in and kill it even before you realize you're having a recurrence."

4 What are the side effects of immunotherapy?

Most side effects that accompany immunotherapy are considered mild to moderate, but about 20% of patients have reactions that are dangerous or even life-threatening.

"When we release the brakes with checkpoint inhibitors, we're allowing the immune system to fight cancer," explains Sharma. "However, the resulting inflammation can damage the skin,

lungs, intestines, joints, and virtually any bodily system."

Adds Disis: "If patients know what to watch for and see their physician when those symptoms set in, we can stop the reaction and combat the symptoms."

5 Which cancers are responding to immunotherapy?

So far, the FDA has approved checkpoint inhibitors for advanced melanoma, Hodgkin's lymphoma, and a small subset of solid tumors, including cancers of the lung, kidney, and bladder. Another type of immunotherapy called chimeric antigen receptor (CAR) T-cell therapy (more on this later) is still under investigation. It's not an FDA-approved treatment yet, but patients with blood cancers like leukemia and lymphoma are responding remarkably well to these novel agents.

6 Why doesn't immunotherapy work for everyone?

Right now, checkpoint inhibitor drugs work for only 20 to 30% of patients, and researchers aren't entirely sure why. "We know that tumors with a lot of mutations, such as most melanomas and cancers of the lung and bladder, appear almost like mini-viruses, making them easier for the immune system to detect and fight," says Disis. So researchers are trying to figure out how to boost tumor-specific immunity so the drugs will work better.

Scientists are also paying attention to something called the tumor microenvironment, which is the area immediately around the tumor. "Some tumors have built a wall, preventing the immune system's T cells from getting in, so we have to find ways to break down the wall before the immune system can

ILLUSTRATION BY CONEYL JAY/GETTY IMAGES

attack the cancer,” says Sharma. “Once we learn more about what the hurdles are, we can devise the strategies to overcome them.”

7 Are there patients whose immune systems don't recognize cancer as a threat and therefore can't benefit from immunotherapy?

For a checkpoint blockade to work effectively, the immune system has to have already produced fighter T cells against the tumor. Some cancers don't generate any response from T cells, but scientists across the country are finding ways to work around this obstacle by genetically engineering a patient's own immune cells to spot and kill cancer. In CAR T-cell therapy, scientists harvest the T cells from a patient's blood and genetically engineer them to target specific proteins in the patient's tumor. They grow several billion of these modified cells in the lab and then reinfuse them into the patient, hoping the billions of extra immune cells will be able to overwhelm the tumor.

So far, this approach has been used only against leukemia and lymphoma, with dramatic responses. In early trials in patients with advanced acute lymphoblastic leukemia, many of the cancers disappeared entirely. “CAR T cells are sometimes called ‘serial killers’ because they persist in the body for a long time and protect against recurrence,” says Davids. “The trouble is, you need to genetically engineer CAR T cells for each patient, which is very labor intensive—and expensive.”

8 Can immunotherapy also be used to prevent cancer?

Yes. There are now vaccines that target viruses that can trigger cancer, including hepatitis B (the leading cause of liver cancer) and human papillomavirus, a type of virus that causes 99.7% of cervical cancers. “If you're vaccinated against the virus, you don't get infected, so your chance of getting cancer is dramatically reduced,” says Brian Czerniecki, chair of the department of breast oncology at Moffitt Cancer Center in Tampa. Since it became available in 2006, the HPV vaccine has helped reduce the prevalence of cervical cancer by 64% in females ages 14 to 19 and by 34% in those 20 to 24 years old, according to a study published in the journal *Pediatrics*.

9 How much does immunotherapy cost?

Immunotherapy is a complicated technology that has already required significant time—and billions of dollars—to investigate. In other words, it's extremely expensive. Pharmaceutical companies are understandably trying to recoup their research and development investment. Ipilimumab, the FDA-approved checkpoint inhibitor drug for melanoma, for example, costs roughly \$120,000 for four doses over 3 months. But if immunotherapy actually cures cancer, it may turn out that it's far less expensive than rounds of chemotherapy and radiation that have to be repeated at each recurrence. “Some of the drugs that are currently

on the market to treat chronic blood cancers, for example, cost \$100,000 per year, but you might need treatment for a decade or more,” says Davids. “So even though the upfront costs of immunotherapy are high, they may represent a savings over other cancer drugs because of the potential for a cure.”

Insurers cover the FDA-approved immunotherapy treatments, but copayments may be high. Unapproved immunotherapy agents, CAR T-cell therapy, and combinations that are under investigation are available only to patients participating in clinical trials. “In those cases, the agency or company funding the study covers the cost,” says Disis.

10 What's the future of immunotherapy?

In addition to treating cancer, immunotherapy is being looked at as a cure for other diseases. For cancer, the aim is to take off the immune brakes and get the system revved up. But if you make the brakes stronger instead, you may be able to halt autoimmune conditions—in which the immune system attacks the body itself, rather than an invader—such as lupus and rheumatoid arthritis. “Once we can understand how to focus immunotherapy in specific ways, I can see

lots of different ways it can be used,” says Sharma.

In the fight against cancer, experts agree that the future of immunotherapy involves stringing together treatments—such as CAR T-cell therapy, cancer vaccines, immune checkpoint inhibitors, and other techniques—to produce even greater effects. “Most people still think of cancer as a death sentence, but there is hope. With immunotherapy, we're making significant headway, and we now have patients whom we consider cured,” says Sharma. “That's remarkable progress.” ■



More on the Way
There are more than 1,500 new immunotherapy drugs currently in the pipeline.

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