THE KILLER WITHIN

The immune system can be a powerful weapon against cancer — but researchers are still grappling with how to control it.

BY HEIDI LEDFORD

The first tumour was a small melanoma on the left side of attorney Mark Gorman's neck. Doctors removed it, and assured him that the cancer was gone.

But eight years later, in 1998, a physician felt Gorman's abdomen during a routine physical examination, arched an eyebrow, and asked if he had become a heavy drinker. The melanoma had spread to Gorman's liver, seeding an inoperable beast of a tumour that wrapped around the inferior vena cava carrying blood to his heart.

People with advanced melanoma typically live for just six to ten months after diagnosis. But Gorman, then 49, had little patience for the doctors advising him to get his affairs in order. When his sister told him about a drug called interleukin-2 (IL-2) that was being used together with chemotherapy against melanoma at a hospital in Colorado, he travelled from his home in Silver Spring, Maryland, to give it a try.

IL-2 is a protein produced by white blood cells called T cells during an immune response. Taking high doses of it sends T cells into overdrive, making them more likely to recognize and attack cancer cells. Gorman was treated, and remains cancer-free 15 years later. "Some doctors say my immune system is really smart," he says. "I just know I'm lucky."

The drug that saved Gorman's life was the first treatment approved by the US Food and Drug Administration (FDA) to fire up the immune system's response to cancer — a technique known as immunotherapy. After that 1992 approval, researchers and pharmaceutical companies spent years trying to develop new immunotherapies that could produce success stories like Gorman's. But those attempts failed to live up to their promise in the clinic, leading to decades of frustration.

Now the tide seems to be turning. Clinical-trial successes in the past five years suggest that a new generation of approaches has potential against several forms of cancer that resist conventional treatments. Some analysts predict that in the next ten years, immunotherapies will be used for 60% of people with advanced cancer, and will comprise a US$35-billion market. "It is kind of crazy," says Cary Pfeffer, chief executive of Jounce Therapeutics, a company specializing in cancer immunotherapy in Cambridge, Massachusetts. "This field has become so crowded. It's frenzied."

But the sobering experience with earlier drugs has made many researchers and clinicians cautious. Despite its potential for miracles, IL-2 produces complete remission in only around 6% of people with melanoma. The treatment kills as many as 2% of recipients. Researchers are now racing to find ways to boost the number of patients who respond to immunotherapy and to reduce the dangerous side effects. "The good news — and the bad news — is that the immune system is incredibly powerful," says Robert Tepper, chief medical officer at Jounce.

CHECKMATE

Cancer immunotherapy was born in 1891, when a New York surgeon named William Coley began injecting bacteria into patients' tumours in the hope of triggering an immune response to the infection that would also attack the tumour. Physicians before him had noted mysterious and rare cancer remissions following infections, and Coley was eager to harness that therapeutic power.

It would not be so simple. Tumours wield many defences against the immune system's most powerful cancer-fighting weapon: T cells that hunt out and eliminate problem cells. Cancer cells disguise themselves and make it difficult for T cells to find them. Tumours also fend off immune attack by expressing proteins that suppress T cells in the surrounding environment.

For decades, researchers chased the possibility of a vaccine that would alert the immune system to cancer cells. But those efforts have largely failed: the only FDA-approved therapeutic cancer vaccine is a complicated and costly therapy for prostate cancer. Whether it provides a significant benefit to patients is a matter of debate.

The field turned a corner in 2011, when the FDA approved a new kind of immunotherapeutic drug. Yervoy (ipilimumab) binds to and blocks a 'checkpoint' protein called CTLA-4, which normally acts as a brake on the immune system by preventing T-cell activation. Checkpoint proteins keep the cells in check so that they do not attack normal tissue. When Yervoy releases the brake, T cells are free to destroy tumours.

Like IL-2, Yervoy can bring long-lasting responses. Some participants in the original trials have been in remission for 13 years, says James Allison, a cancer immunologist at the University of Texas MD Anderson Cancer Center in Houston. But those clinical cures occur in just a small fraction — about 8% — of patients. And although Yervoy can rouse T cells to battle against

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cancer, sometimes the cells attack healthy tissue, too. Of the 540 people who took Yervoy in the largest trial, up to 15% experienced serious side effects and seven died of immune-related events. Some oncologists prefer to steer clear of the drug, says Suzanne Topalian, a melanoma researcher at Johns Hopkins University School of Medicine in Baltimore, Maryland.

Still, the promising aspects of Yervoy established the potential of checkpoint inhibitors — drugs that block checkpoint proteins — and that has prompted researchers to look at other potential target proteins. By the time Yervoy was approved, some investigators had begun to focus on PD-1, a checkpoint protein that some cancers use to deactivate the phalanx of T cells that surrounds the tumour.

Because PD-1 interacts directly with cancer cells, unlike CTLA-4, its inhibitors have the potential to be more potent and less toxic. Early clinical trials suggest that this is the case. A leading PD-1 inhibitor — nivolumab, made by New York's Bristol-Myers Squibb — shrinks tumours in 28% of people with advanced melanoma. The FDA is expected to issue a decision on whether to approve it by early 2015, if not sooner.

Hopes are high that, although there are some side effects, the new drugs will be less toxic than Yervoy. Some people notice no problems at all. "Many patients say, 'Doc, are you even giving me anything?'" says Antoni Ribas, a melanoma specialist at the University of California, Los Angeles, who has participated in trials of PD-1 inhibitors. "Then the tumours start disappearing, and they know."

Researchers want to push immunotherapies even further. "We wish response rates were higher than what we currently have," says Michael Postow, an oncologist and cancer researcher at Memorial Sloan Kettering Cancer Center in New York. Inhibitors of other checkpoint proteins are trickling into clinical testing and clinicians may one day match patients with the inhibitors most likely to act on the proteins expressed by their own cancer cells.

For other patients, the challenge may be in attracting T cells to the tumour in the first place. PD-1 inhibitors do not accomplish this — they simply remove the shackles from T cells already amassed at the tumour's edge, says Daniel Chen, head of immunotherapy development at Genentech in South San Francisco, California, a subsidiary of the Swiss pharmaceutical giant Roche. "Some patients just seem to have no existing immune response to start with," he adds. "So then we need to add something that will generate that response."

BETTER TOGETHER

The key to attracting T cells is to create an 'inflamed' tumour using combinations of therapies, says Postow. Yervoy and PD-1 inhibitors are already in clinical trials with each other and a range of other treatments intended to alert T cells to the cancer. Radiation, for example, breaks open cancer cells and releases antigens, molecules that can trigger immune responses. In another approach, researchers alert a patient's immune system with experimental cancer vaccines containing proteins that are overexpressed by tumour cells. "The future is clearly combination therapy," says Anthony Marucci, chief executive of Celldex Therapeutics in Hampton, New Jersey.

Eventually, checkpoint inhibitors could also be combined with a form of immunotherapy called adoptive T-cell transfer. This is a personalized treatment in which physicians isolate T cells from patients and select those that react to cancer. They then multiply the T cells and stimulate them with molecules such as IL-2 before injecting them back into the bloodstream. Trials of this method led by tumour immunologist Steven Rosenberg at the National Cancer Institute in Bethesda, Maryland, have shrunk

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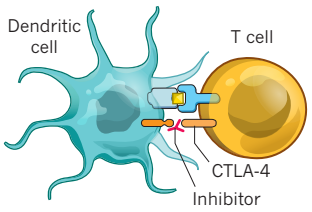
IMMUNE BOOST

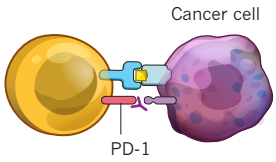
Several methods are showing promise in helping immune sentinels called T cells to attack cancer.

CHECKPOINT INHIBITOR DRUGS

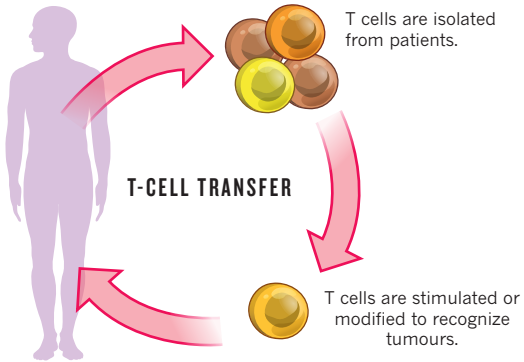
'Checkpoint' proteins block T-cell activity. Inhibitor drugs can release the brakes on T cells at different stages.



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.



The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.



tumours in more than half of people with advanced melanoma receiving the treatment, with 20% experiencing complete remission.

A newer form of T-cell transfer promises to broaden its reach to other cancers, by engineering extracted T cells to express an artificial tumour-targeting receptor called a chimaeric antigen receptor (see 'Immune boost'). A trial using T cells engineered to target B cells wiped out cancer in 14 of 16 people with acute leukaemia (M. L. Davila *et al. Sci. Transl. Med.* **6,** 224ra25; 2014).

But technical challenges have limited the spread of T-cell transfer therapies. Only a handful of academic medical centres have performed the procedure so far. "After our initial results, we were besieged with melanoma patients," says Rosenberg. "We couldn't possibly treat all the patients sent to us."

Since those early days, researchers have simplified and standardized protocols. That, plus the remarkable results in leukaemia, has lured industry investors. Novartis, based in Basel, Switzerland, has bought a facility in New Jersey to process T cells extracted from patients around the United States. The facility will be key to the company's plans to expand its clinical trials to more sites this year. Smaller firms are following suit. In early 2015, Kite Pharmaceuticals in Santa Monica, California, hopes to launch a multicentre trial of adoptive T-cell transfer in a form of lymphoma that kills around 37% of patients within five years of diagnosis.

THE TRUE TARGET

Another big challenge for adoptive T-cell transfer is to broaden its reach by finding new molecular targets that will guide T cells to specific tumour types while sparing healthy cells. The approach works well in leukaemia and other cancers that affect B cells, another class of white blood cell, because researchers can engineer T cells to target a protein called CD19, which is found only on B cells. Although the treatment wipes out healthy B cells in addition to the cancerous ones, patients can tolerate that side effect relatively easily. But finding a similar target for solid tumours, which are less uniform than liquid tumours, has been difficult. "It's a major limiting step," says Ribas. "We're all excited about CD19, but it's not clear what the next target will be."

Researchers are mining growing databases of gene expression to find the best candidates. But firing up immune responses to specific proteins can be dangerous: a few years ago, four patients died in trials of T cells engineered to attack cells expressing a protein called MAGE-A3. This protein is expressed only in embryos and in some cancer cells in adults, so it seemed an ideal target. But researchers later learned that the T cells attacked similar proteins present in the heart and brain. "These T cells are professional killers," says Arie Belldegrun, chief executive at Kite. "If their target is expressed even in minute quantities on normal cells, these super killers are going to find those cells and destroy them."

In response to the deaths, ImmunoCore, an immunotherapy company based in Abingdon, UK, developed new bioinformatic methods to search for signs that any possible T-cell target could be expressed in normal tissue. The company also began to do its initial safety testing in three-dimensional cell cultures that better reflected the cells' natural environment. This approach has led to a collection of more than 20 potential targets for various cancers. Michel Sadelain, a cancer geneticist at Memorial Sloan Kettering, hopes to engineer T cells that target two proteins, both of which would have to be expressed on a cell for the T cells to destroy it. The idea, he says, is that the chance that a healthy cell will have both targets on its surface will be slim.

Finding more targets could help immunotherapy to reach more types of cancer. So far, researchers have focused on melanoma and kidney cancer because they responded best to immunotherapies in early trials, and are thought to be particularly visible to the immune system.

Rosenberg says he is working on 11 clinical trials testing adoptive T-cell therapies against a variety of cancers, including a particularly lethal and rare form called mesothelioma. The door to much wider applications for cancer immunotherapies opened in 2012, when results showed that the checkpoint inhibitor nivolumab shrank tumours in 18% of people with certain types of advanced lung cancer (S. L. Topalian *et al. N. Engl. J. Med.* **366,** 2443–2454; 2012). Because lung cancer is one of the world's most prevalent forms of cancer, the results raised hopes that immunotherapy could make a sizeable dent in cancer deaths. "This was a cancer that we thought was not immunogenic," says Ribas, who notes that both Yervoy and IL-2 failed to shrink lung-cancer tumours. "We thought immunotherapy wouldn't have a chance."

Some cancers, including liver cancer, may still pose a challenge to immunotherapy approaches, says Lisa Butterfield, a cancer researcher at the University of Pittsburgh in Pennsylvania. The liver processes pathogens and antigens in the blood, and the immune system is carefully controlled there to avoid prompting reactions that would target an individual's normal cells. Breast, colorectal, pancreatic and ovarian cancers are also particularly adept at suppressing immune cells. Combination therapies may provide a way around these limitations, she says.

Combination therapies may also be the salvation of the cancer-vaccine concept. Although the vaccines tested thus far have fared poorly, they may work synergistically with other immunotherapies, says Willem Overwijk, a cancer researcher at MD Anderson.

After so many years of disappointing results, the growing excitement over immunotherapy has surprised many cancer researchers and families touched by the disease. Since his own remarkable recovery, Gorman has mourned again and again as friends he made at melanoma support groups succumbed. Then, a few years ago, he had a new experience: a close friend was given Yervoy, and went into full remission.

As for his own melanoma, Gorman goes for scans to look for new tumours every two years. In February, he noted that it might be time to schedule his next set of scans. But he wasn't sure — he had stopped fearing his cancer's return years ago. "I'm a cool cucumber now," he says. "My immune system has it under control." ■

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