BENOÎT HELLER/TRANSGENE

The cancer vaccine TG4010, shown here being manufactured by Transgene, extended lung cancer survival time in a phase II trial.

IMMUNOTHERAPY

Chemical tricks

Lung cancer uses cunning mechanisms to evade the immune system. Can new antibody therapies outwit the disease?

BY BIANCA NOGRADY

The immune system has evolved over millions of years to protect the human body against microbes, pathogens and parasites. Which makes it all the more puzzling to immunologists as to why, when it comes to helping the body defend itself against cancer, immunotherapy treatments designed to enhance the immune system have so far failed to make even the slightest dent in halting the spread of the disease.

So when medical oncologist Naiyer Rizvi became involved with the phase I trial of a tumour antibody a few years ago, he was prepared for failure. In fact, there was a certain glum expectation in the lung-cancer community that this trial would go the way of so many other attempts to fight cancer by enlisting the body's own immune system.

One of the first trial patients Rizvi saw at Memorial Sloan Kettering Cancer Centre in New York City had a large adrenal tumour that was causing him so much pain he was rushed to hospital for emergency treatment soon after he got his first dose of the trial treatment, the immunotherapeutic agent nivolumab that was under development by Bristol-Myers Squibb based in New York City. In May 2014, Rizvi saw the same patient again. It was one year since completion of a two-year course of therapy with nivolumab and the man's tumours were still shrinking. "When you've got these dramatic unexpected responses," Rizvi says, "you kind of rethink the direction of your career."

He's not the only one feeling this way: a wave of optimism is sweeping through the lung-cancer field. Data from trials of different immunotherapies raise the promise of new agents with response rates and survival advantages that outweigh anything else on offer, adding months and even years to life expectancy.

CHECKPOINT CHECKMATE

There is a long, sad history of immune system approaches to cancer therapy going awry. Early attempts to develop drugs that would help immune cells fight tumours failed dismally in clinical trials. Vaccines would generate the desired immune response, and there would be high levels of immune cells primed to attack the malignancy. Yet for reasons that researchers could not understand, there appeared to be no effect on tumours: they weren't shrinking.

For Lieping Chen, an immunologist at Yale University in New Haven, Connecticut, it was the frustration of having so little to offer his oncology patients that drove him into the field of cancer immunology. That was more than two decades ago, when the first steps were being taken to discover how molecules on the surface of tumour cells might affect the body's immune response. Chen set out to find specific molecules that would stimulate an immune response against tumours or inhibit whatever was blocking that response.

Chen's first big success came in the late 1990s, when his team discovered and cloned the gene coding for a protein that keeps the body's immune response in check — a fundamental function because if the immune system enters overdrive, the result would be chronic and damaging inflammation[1]. Not long after Chen's discovery, a separate group figured out the mechanism by which this protein kept the immune system from over-responding. The key was in its interaction with T cells (white blood cells that are a key component of the immune system). Specifically, Chen's protein interfered with a receptor on the surface of T cells called PD-1. By binding to this receptor, the protein triggered the death of the T cell, suppressing immune activity[2].

Further research showed that the T cells are involved in their own demise (see 'Immune assistance'). When T cells arrive at their target, they release a molecule called interferon-γ to boost their cell-killing ability. The tumour takes advantage of this mechanism — interferon-γ causes tumours to go into overdrive in their production of Chen's protein, now known as PD-L1. And when the PD-L1 protein binds to the PD-1 receptor on T cells it makes the T cells commit suicide.

The finding shed light on one of the main mechanisms that allowed tumours to neutralize T cells. "You can have a very good response in the blood and in the lymphatic organs, but they shut down in the tumour cell," says Chen, speaking about the immune system.

The goal, then, is to disrupt this pathway and therefore unleash the immune system to attack the tumour. A class of drugs called checkpoint inhibitors do this by one of two means. The first approach is to introduce a molecule that binds to the T cell's PD-1 receptor and therefore prevent the tumour protein PD-L1 from doing so. As a result, T cells can resume their normal function and destroy the tumour.

Nivolumab, which Rizvi used so effectively at Memorial Sloan Kettering, is an antibody that does just that. Other researchers have also seen its impressive results. Julie Brahmer, an oncologist at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland, has seen nivolumab move from phase I through to phase III trials. She says that at least two of her patients, both treated with nivolumab for two years, are still alive a year and a half after their treatment finished. Her patients had advanced, metastatic lung cancer and had already undergone treatment with chemotherapy and radiation, so the odds were stacked against them. "Both of these patients should no longer be around if you look at the statistics around lung cancer," says Brahmer.

The other way to interfere with this pathway is not to bother with binding to the receptor, but instead block the tumour's PD-L1 protein directly. That's what medical oncologist Jean-Charles Soria is doing. A phase I trial designed to test the safety and clinical activity of an antibody that blocks PD-L1 found that around 25% of patients with non-small-cell lung cancer (most lung cancers are of this type) responded to the drug. Soria, who heads drug development at the Gustave Roussy Cancer Center in Paris (and who reported the results of the ongoing study at the 2014 American Society of Clinical Oncology meeting) notes that this response rate is better than the 3% rate generally seen in patients who are receiving their third course of chemotherapy after earlier treatments have failed.

Although the response rates are similar for drugs that bind to the T cell's PD-1 receptor and those that block the tumour's PD-L1 protein, there may be a slight safety advantage in targeting PD-L1. The phase I nivolumab study reported a 3% incidence of drug-related pneumonitis[3] — inflammation of the lung tissue — but this side effect has so far been less severe or absent with the PD-L1 inhibitors.

Both experimental therapies seem to benefit smokers more than never-smokers. Soria reported the results of a phase I trial of the PD-L1 inhibitor at the 2013 European Cancer Congress (see go.nature.com/b3z1wr); the study indicated that 26% of smokers responded to the drug, but only 10% of never-smokers responded. Researchers speculate that this is probably due to the greater number of mutations present in smokers' tumours, an abundance that would probably present the newly awakened immune response with a far greater array of tumour antigens to respond to.

Despite the positive results from tests of both varieties of checkpoint inhibitors, Brahmer says that researchers are keeping their optimism in check. "Long-term disease control is probably the most realistic expectation of these antibodies," she says, likening the outlook to that of treatment for a chronic condition such as hypertension.

GLIMMER OF HOPE

The main purpose of checkpoint inhibitors is to undo the local blockade of the immune response and allow the immune system to resume normal function and attack the tumour, but they might also breathe life into vaccine therapies against lung cancer.

Philippe Archinard is chief executive of drug-development company Transgene, of Illkirch-Graffenstaden, France, which is preparing for phase III trials of its therapeutic lung-cancer vaccine, TG4010. He believes the two approaches are complementary. "Boosting the immune system is one way to address the issue," he says. But to achieve the greatest benefits, "you would need to increase the immune response and create it when it's not present".

The TG4010 vaccine uses a viral vector (a tool used to transport genetic material into a cell) that has been engineered to manufacture a variant of a tumour glycoprotein called MUC1. When MUC1 is injected into the body, the aim is to stimulate the immune system to respond to and attack cells that contain it. The MUC1 antigen is widely expressed on the surface of non-cancerous epithelial cells. But many tumours overexpress an abnormal version of it, which is why it is such a potent target for immunotherapy. A phase II trial of TG4010, used in conjunction with standard chemotherapy in patients with advanced non-small-cell lung cancer, showed that patients given the vaccine as well as chemotherapy survived a median of 17.1 months compared to 11.3 months for patients on chemotherapy alone.

TG4010 is not the only vaccine targeting MUC1. Pharmaceutical firm Merck Serono, based in Darmstadt, Germany, under a license agreement with Oncothyreon of Seattle, Washington, is developing a vaccine called tecemotide. In a 2013 phase III trial, tecemotide's survival benefits did not quite reach statistical significance[4]. However, an analysis of a subgroup of patients showed that those who were undergoing both chemotherapy and radiation treatment concurrently survived for around ten months longer than patients given the placebo vaccine. The lead researcher on the tecemotide trial, Charles Butts, says that as more data accrue from the trial, they point to a continued survival advantage — there's an almost 10% improvement in three-year survival compared with placebo, says Butts, an oncologist at the University of Alberta, Edmonton, and at the Cross Cancer Institute in the same city.

After 20 years of treating lung cancer, and 20 years of dashed hopes in lung-cancer immunotherapy, Butts says there is finally a glimmer of hope in both vaccines and non-vaccine immunotherapies, such as the PD-1 and PD-L1 inhibitors. "The fact that these checkpoint inhibitors are showing such responses — and durable responses — is quite amazing," he says.

If the past decades of failure have taught the industry anything, it is that early trial success rarely leads to a breakthrough drug. Phase III trial data from the checkpoint inhibitors and the vaccines are eagerly awaited — and researchers are waiting anxiously to see if these treatments can deliver the results that lung-cancer patients and their doctors are so desperately hoping for. ■

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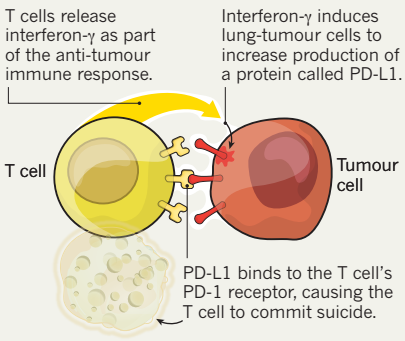
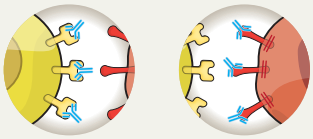
IMMUNE ASSISTANCE

New drugs help to outwit lung tumours.

Tumours suppress the immune response by hijacking an immunological pathway and inducing T cells to self-destruct.



Drugs called checkpoint inhibitors can deceive the tumour. The inhibitors work in one of two ways:



1. By binding to the T cell's PD-1 receptors to prevent the tumour protein PD-L1 from triggering cell death.

2. By inhibiting production of the tumour protein PD-L1, enabling the tumour-fighting T cells to survive.

SOURCE: D. M. PARDOLL *NATURE REV. CANCER* **12,** 252–264 (2012).