NEIL WEBB

DRUG DEVELOPMENT

# Releasing the brakes

*Tumours can put a brake on the immune system, but new therapies work by removing these brakes. Now, researchers have to figure out how to use them most effectively.*

BY KAREN WEINTRAUB

First it was one melanoma patient, a woman named Sharon, who should have died but didn't. Then, several more outlived their prognoses — not just surviving but seeing their tumours shrink dramatically or even disappear. As the successes accumulated, in both individual patients and larger clinical trials, oncologist Antoni Ribas slowly began to accept that the immune treatments he was giving to his cancer patients were making a profound difference. Initially only about one in ten patients improved, but that fraction increased as he and his colleagues tested newer versions of the therapy. Ribas, a tumour immunology researcher, now has dozens of patients, like Sharon, whom he had expected to succumb cancer years ago. His patient load at the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles (UCLA) used to stay about the same from one year to the next, with new melanoma patients roughly equaling the number who didn't make it. Now, the number of patients is growing.

The drugs he uses are known as immune checkpoint blockades and they are designed to circumvent one of the insidious ways in which cancer staves off an immune response. The immune system has a number of checkpoints — mechanisms that help to prevent it from getting out of control and attacking the body's own cells. The checkpoints act much like the brakes on a car: even if the immune system is trying to prompt its T cells into action, the checkpoints suppress the activation. Tumours can turn on these checkpoints and prevent a T-cell attack, but immune checkpoint blockades take the brakes off the T cells, freeing them to fight the malignancy.

When other researchers saw the results of clinical trials of checkpoint blockades in melanoma, they dismissed them as too narrow to be of much use in other cancers. Melanoma was different, they said, and has a known immune component. Then, in 2012, everything changed. In one study, a checkpoint blockade caused a measurable improvement in 31% of renal cancer patients, and in 18% of patients with lung cancer, which kills more people every year than colon, breast and pancreatic cancers combined[1]. Researchers and drug companies realized that these blockades, also called checkpoint inhibitors, might be as effective in patients with any type of solid tumour as they were in those with melanoma. Jedd D. Wolchok, a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York City, says the lung

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cancer findings were "a pivot point for the entire field," changing immunotherapy from a niche, experimental approach into something that could eventually be considered a conventional cancer treatment. In 2013, larger studies confirmed the lung cancer results as well as showing similar benefits in patients with prostate, breast, kidney, colon and other cancers.

The findings have been so tantalizing that researchers started asking a simple question: if one checkpoint blockade drug could do so much for a small proportion of patients, could a cocktail of several such drugs — or a combination of checkpoint blockades with chemotherapy, genetic treatments and other types of immune therapies — help more of them? "It's not realistic to think of immunotherapies only as single agents," says Lawrence Fong, a cancer immunologist and haematological oncologist at the University of California, San Francisco. "Combinations will probably be needed to realize the full potential of cancer immunotherapy."

## SURPRISING HUMAN STUDIES

For more than half a century, scientists have been trying to turn the body's immune system against cancer. But decades of failures have revealed that tumours have the ability to evade, tamp down and overwhelm the normal immune response. Most modern immune therapies try to get the immune system to recognize and attack tumour cells (see 'Honing that killer instinct, page S13). One such treatment, the vaccine sipuleucel-T (marketed as Provenge by Dendreon Corporation in Seattle), was approved by the US Food and Drug Administration in 2010 for use in prostate cancer — a move that generated a lot of excitement. But the drug has proven disappointing, with benefits limited to a small percentage of patients; Dendreon is now reported to be for sale.

The problem, researchers have slowly been realizing, is that stepping on the immune system's gas pedal isn't enough: it is also necessary to release its brakes — and that's where immune checkpoint blockades come in. Eighteen years ago, James Allison, now an immunologist at the MD Anderson Cancer Center in Houston, Texas, figured out how to do just that. Allison, then at University of California, Berkeley, noticed that one checkpoint protein, called CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4), seemed to prevent T cells from attacking tumours. So he blocked CTLA-4 activity in mouse models of various cancers (including melanoma) and, to his surprise, some of the mice experienced complete remission.

In 2011, the US FDA approved the anti-CTLA4 drug ipilimumab (developed by Bristol-Myers Squibb and marketed as Yervoy), which was based on Allison's research and eventually saved the lives of some of Ribas's patients. Allison says the reality has been even better than he expected. Mouse studies suggested that ipilimumab wouldn't work well by itself and would need to be combined with other drugs to show any significant effect. But the first patients responded to ipilimumab even better than the mice had.

CTLA-4 isn't the only checkpoint being targeted by researchers and drug developers. Early trials suggest that drugs that block a different checkpoint, called PD-1, are even more effective and have fewer side effects than ipilimumab[2]. In recent studies, checkpoint blockades produced improvements in between 20% and 65% of patients, depending on the drug, dosage and type of cancer. In one long-term study of ipilimumab in patients with advanced melanoma, 22% of the 1,861 patients survived for three years, and 17% for seven years or longer (with median survival nearly a year); historically, average survival was six to nine months[3]. Early research suggests that ipilimumab may be even more effective when combined with other drugs.

In further evidence for the value of drug combinations, ipilimumab and nivolumab (another Bristol-Myers Squibb drug, which targets PD-1) appear to complement each other. In one study published in early 2013, 53% of patients with melanoma who took the highest safe doses of both drugs showed reductions in tumour size of 80% or more[4]. But not everyone fared well. Nearly one-fifth of the subjects involved in the study suffered severe, though treatable, side effects, including pancreas and liver dysfunction, itchy skin, lung inflammation, and uveitis (inflammation of the eye).

*"Checkpoint blockades take the brakes off the T cells, freeing them to fight the malignancy"*

Drug companies consider these side effects manageable, and remain enthusiastic about checkpoint blockades. Merck, for instance, is testing its PD-1 blockade, MK-3475 (also called lambrolizumab), in seven clinical trials that are expected to enroll more than 3,000 patients with bladder, colorectal, head and neck, melanoma, non-small cell lung and triple-negative breast cancer (so-called because it doesn't express three of the most common genes). Although most of that research is being done using MK-3475 alone, "we are especially interested in combinations with other immunomodulatory agents," says Eric Rubin, vice-president of oncology clinical research at Merck, which is based in Whitehouse Station, New Jersey. The company is testing MK-3475 in combination with several chemotherapy drugs, including carboplatin, cisplatin and pemetrexed.

Bristol-Myers Squibb is also pursuing combinations of checkpoint blockades with other therapeutic approaches. One combination the company is testing pairs ipilimumab with the cancer vaccine sipuleucel-T. Tests in mice suggest that this mix should work well, says Glenn Dranoff, an oncologist at Harvard's Dana-Farber Cancer Center who helped to develop the vaccine. And, following a successful phase I trial[4], Bristol-Myers Squibb is pursuing phase II and III trials of ipilimumab combined with nivolumab in patients with melanoma. But they're also hedging their bets. "We have to be prepared for the possibility that this is not the optimal combination," says Nils Lonberg, senior vice-president of biologics discovery at Bristol-Myers Squibb.

Lonberg points to the fact that, among other combinations, Bristol-Myers Squibb is testing a drug called lirilumab together with ipilimumab and with nivolumab, in separate phase I trials involving patients with various types of cancer. Lirilumab, a human monoclonal antibody, promotes activation of a different part of the immune system — the natural killer cells — to attack the tumour. The goal is to fight the disease with both arms of the immune system simultaneously — the innate, nonspecific natural killer cells and adaptive T cells, which are finely adapted to respond to new insults. "There is the possibility of synergy between overcoming blocks to the innate anticancer response and overcoming blockade of the adaptive immune response to cancer," he said. "We're looking very closely to see whether or not that occurs."

## HUNTING FOR THE BEST MIX

Ultimately, the right treatment combination is going to depend on many factors — the type of cancer a patient has, as well as their genetics, age, race and gender. Figuring out which combinations will work best for which patients is going take years of trial-and-error experimentation, and is likely to be risky for both drug companies and cancer patients. For instance, some chemotherapies could end up suppressing the immune system instead of supporting it, warns Keith Flaherty, an oncologist at Massachusetts General Hospital and Harvard Medical School in Boston who specialises in melanoma. "There's the concern that immunotherapy and chemotherapy would in fact be antagonistic," he says. But Flaherty is optimistic about the potential intersection of checkpoint blockades with therapies that target the specific gene mutations that are found in various tumours — such as the *BRAF* mutation that is common in melanoma patients. "If you want a drug that specifically counters some of the mechanisms by which tumours escape immune surveillance, targeted therapies are the place to look."

Flaherty criticizes the haphazard nature of much of today's immunotherapy research. Some pharmaceutical companies, he says, are trying combinations without understanding the biology behind them. "That's pretty unscientific." In addition to putting cancer patients

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**Cancer patient Stew Scannell receives intravenous Lambrolizumab during a clinical trial at UCLA.**

at risk, such a scattershot approach is more likely than rationally designed approaches to fail, which could pull down the whole immunotherapy field.

Flaherty also has an even more basic concern: with so few biomarkers available to identify which patients are most likely to respond to checkpoint blockades and other immune treatments, is it even possible to study combination therapies? "I worry that we don't have a scientific and rational way to develop combination immunotherapy," he said. "That doesn't mean I don't think it should be pursued, but a steady focus needs to remain on the mechanism of interaction between different classes of therapies."

Researchers are also pushing for a better understanding of why the successes of immune blockades are so uneven. Why don't all patients respond to them in the same way? "That's a very important question to answer," says Rafi Ahmed, an immunologist and director of the Vaccine Center at the Emory University School of Medicine in Atlanta, Georgia. "It might give us insights into combination therapies and also perhaps allow us to target additional approaches."

If biomarkers can be identified, they could help scientists and clinicians to pair the appropriate immune therapy or combination with the right patient. Early research, for instance, suggests that people whose tumours express the molecule PD-L1 are more likely to respond to PD-1 blockade treatments than those whose tumours don't express PD-L1, says Suzanne Topalian, director of the melanoma programme at Johns Hopkins University's Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland. The association between protein expression and drug effect is logical, given that the presence of PD-L1 suggests that these patients have active blockades of precisely the kind that these drugs target.

Despite their checkered successes, checkpoint blockades are proving exciting enough, and generating enough promising data, that in April 2013, the FDA labelled Merck's MK-3475 a "breakthrough therapy" in recognition of the dramatic clinical effect seen in a phase I melanoma trial. Designation as a breakthrough therapy is meant to speed up the development and review of a candidate drug that shows promise for treating a life-threatening disease. The FDA is working with investigators and pharmaceutical companies to accelerate the development of these drugs, Topalian says.

***"Patients treated with immune therapies could potentially gain a lifetime of protection."***

## SHIFTING PERSPECTIVES

For decades, scientists have focused on cancer genetics and on designing treatments that counteract specific mutations. But now they need to broaden their focus, says Ira Mellman, vice-president of research oncology at Genentech, a member of the Roche Group that is based in San Francisco, California. Checkpoint blockades and other immune therapies don't work on the same genetic model of cancer that has dominated research and treatment for more than forty years. "We now know that genes are not the whole story, because we have all sorts of drugs targeted to oncogenes and people don't get cured," Mellman says. The success of checkpoint blockades is slowly driving researchers away from the genetic view of cancer — and without this necessary shift in perspective, Mellman says, progress will stall and immune therapies won't reach their potential.

Doctors must also adapt their clinical strategies so that they can effectively use checkpoint blockades and other immune-based approaches. Patients treated with immune therapies often show different patterns of response from those treated with standard drugs, Topalian and others say. With chemotherapy and genetic approaches, success is typically measured by a decrease in tumour size, and if a patient is going to improve it usually happens relatively quickly. With immune therapies, however, it's not unusual for it to take several months before the cancer begins to visibly recede. Sometimes, tumours can even get larger at first as T cells and other immune cells flood to the site. "Physicians using these drugs really need to be well-educated about response patterns," Topalian says. "With these drugs, the response may not occur until later on, and then you have to make a decision about whether to continue treating the patient."

Right now, it's unclear how long patients will need to be on immune-blockade treatments. Ribas is using MK-3475 for many of his patients, and is giving them infusions every two to three weeks. He plans to keep each patient on the drug for two years and then pause the infusions to track how the patients respond. "There's not enough data to say when we can stop or whether we need to continue," he says. Ideally, a patient's immune system would eventually be able to take over and eliminate the cancer, or at least keep it in check indefinitely.

Topalian notes that patients treated with immune therapies could potentially gain a lifetime of protection, similar to the buffer against certain diseases offered by childhood vaccines. "We hope that the same thing is happening in cancer," she says. "We hope that we are re-educating the immune system and that, even if it doesn't completely destroy every last cancer cell, it can keep it in check for a very long time." ■

**Karen Weintraub** *is a science writer based in Cambridge, Massachusetts.*

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