CLOSING IN ON CANCER

A new type of drug is shattering cancer's grip on the immune system, with astonishing results. ***Andy Coghlan*** *reports*

WHEN Vicky Brown was diagnosed with advanced malignant melanoma in 2013, she was in shock. Even with the best treatments available at the time, most people with her diagnosis lived for about six months.

Then her fate took a turn for the better. Through the Melanoma UK charity, Brown was referred to take part in a trial of an experimental treatment at the Royal Marsden Hospital in London. Over several weeks, she received three intravenous infusions. After the second, the lumps she had felt in her throat and breast had vanished. "I was thrilled," says Brown, who is still alive almost three years after her initial diagnosis. "The consultant says he'd never seen a result like that so quickly."

Brown's results may be extraordinary, but they aren't unique. Other people who have taken part in similar trials are still alive a decade later, despite starting out with similarly bleak prognoses. Optimistic headlines and column inches have been dedicated to these new drugs, not least since former US president Jimmy Carter announced that they were responsible for clearing potentially lethal melanoma from his brain.

This new generation of anticancer drugs – called checkpoint inhibitors – is having such a profound impact that some scientists are pitching it as a turning point in cancer treatment. "Melanoma and lung cancer used to be death sentences, but they're not any more," says Gordon Freeman at the Dana-Farber Cancer Institute in Boston. "It's a revolution, and it's only the start."

The story of these treatments began in the 1960s when Tasuku Honjo, a Japanese trainee doctor, learned of the death of a close classmate from gastric cancer. "My dream became to cure cancer," he says.

The dream began to materialise in 1992 when, as an immunologist at the University of Kyoto, he was studying how and why T-cells – immune cells that recognise and attack invaders and abnormal cells – sometimes self-destruct. He discovered a protein produced on the surface of some T-cells and suspected it was involved in this process. So he called it "Programmed cell death-1", or PD-1.

To find out what PD-1 does, Honjo disabled the gene that makes the protein in mice. He found that they developed autoimmune disease, including mild arthritis, heart degeneration and joint disease.

This suggests that PD-1 helps to prevent the immune system running out of control. "The immune system needs brakes and accelerators, and PD-1 was clearly a brake," Honjo says. So he started to wonder whether the immune system could be unleashed against cancer by blocking PD-1 with a drug.

The idea that drugs might boost the immune system's ability to fight cancer – so-called immunotherapy – has been the subject of intense research for decades. Ideally, our immune system would do this on its own. But one of the reasons that cancer is so good at thriving and spreading in the body is its ability to quieten the immune system. For this reason, most conventional treatments use brute force, zapping tumour cells with drugs or radiation.

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Jimmy Carter's brain cancer was successfully treated with the new drugs

Such treatments work to a varying degree, but they are unspecific, damaging healthy cells alongside the tumours. They are also unable to keep up with cancer as it evolves in response to their onslaught.

Better would be to find a way to loosen the grip that cancer cells have over the immune system, reawakening it to do the job it is intended for. Attempts have included a range of vaccines and immune-stimulators, but none has worked consistently well.

Then, about six years ago, came sensational results from a trial of a drug called ipilimumab, or "ipi" for short, which had unprecedented effects against melanoma, the most lethal type of skin cancer. Some 45 per cent of people were still alive a year after the trial ended, and 24 per cent were alive after a further year – around four times better than standard chemotherapies.

More strikingly, there was a subset of people who seemed to be almost completely rid of their cancer. "Around 20 per cent of the patients survived longer than three years," says Jedd Wolchok of the Memorial Sloan-Kettering Cancer Center in New York City, one of the main clinicians involved in testing the drug. "Some are still alive 10 or 11 years later." Once people have reached three years survival, they seem to go on without the cancer coming back, says Wolchok.

But although ipi was approved for treating melanoma in the US in 2011, it brought with it a toxicity that many people taking it found intolerable. Side effects included lung inflammation and hepatitis. Some died.

The problem is that ipi lifts a master immune brake, sending the whole immune system into overdrive, exposing healthy as well as cancerous cells to the blitzkrieg – a similar problem to that seen with standard chemotherapy. What was needed was a ›

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TIMELINE

March 2011 Ipilimumab (brand name Yervoy, made by Bristol-Meyers Squibb) approved by the US Food and Drug Administration (FDA) for advanced melanoma, but it has severe side effects

July 2014 Japan approves nivolumab (brand name Opdivo, made by Bristol-Meyers Squibb) for treating melanoma that has spread to other organs, making it the first PD-1 inhibitor to receive regulatory approval

September 2014 Pembrolizumab (brand name Keytruda made by Merck) approved in the US for treating melanoma

October 2014 Pembrolizumab approved by the FDA to treat non-small cell lung cancer in people who had not responded to other treatments, after it was shown to shrink lung tumours in 41 per cent of patients

December 2014 Nivolumab approved in the US for melanoma after it was shown to shrink tumours in a third of patients

March 2015 Nivolumab gets approval from the FDA to treat advanced non-small cell lung cancer, after trials showing that 42 per cent of people survived for at least a year, twice the survival rate of those taking the standard treatment drug, docetaxel

June 2015 European Commission approves nivolumab for lung cancer

October 2015 Nivolumab approved by the FDA for kidney cancer after a trial showed that, on average, people on the drug survived for more than two years – five months longer than those on rival treatment everolimus

January 2016 The UK's National Institute for Health and Care Excellence recommends that nivolumab should be available to people with melanoma being treated by the UK National Health Service

February 2016 Atezolizumab (made by Genentech and Roche) is undergoing clinical trials for melanoma, breast cancer, non-small cell lung cancer, renal cell carcinoma and bladder cancer. It could be the first important drug for bladder cancer, because it has been shown to shrink tumours in 27 per cent of recipients

much more targeted approach.

That's where Honjo comes in. As PD-1 is a "receptor" molecule produced only on immune cells, his team reasoned there must be something that binds to it and switches it – and the brake – on.

Honjo sent samples of PD-1 over to Freeman, who, along with his colleagues, tested it against different proteins produced by human cells, to see if it would bind to anything. They found it attracted a molecule now known as PD-L1 (programmed death ligand-1).

Crucially, they also discovered that cancerous cells often produce PD-L1. "The first ones we found were on ovarian and breast cancer cells," says Freeman. "Then, we found it on lots of other cancer cells, and realised it seemed to be produced to engage PD-1 and turn on the immune brake. That was the 'aha' moment."

"The immune system machine-guns the tumour rather than taking one shot"

What Freeman, Honjo and their teams had discovered is that PD-L1 on the surface of cancer cells forms a truce-like handshake with PD-1. This calls off the immune attack, allowing the cancer to proliferate unchallenged (see diagram, opposite).

So could blocking PD-1 stymie cancer? To test the idea, Honjo tried growing human tumours in mice engineered to lack PD-1. Sure enough, he found that the tumours wouldn't grow.

The next step was to make antibodies against PD-1, to see if they would protect against cancer by "releasing the brake". They did, although not as well as knocking the gene out completely. But it was enough to show that it was possible to give the immune system the desired boost.

And yet the findings scarcely excited any interest, drowned out by the success of ipi. "I tried to convince the pharmaceutical industry, but with enormous difficulty," Honjo says.

That changed with the realisation that the side effects of ipi often outweigh the benefits. Finally, the pharmaceutical industry turned its attention to the PD-1 system, which is much more targeted to the interaction between the immune system and tumour cells.

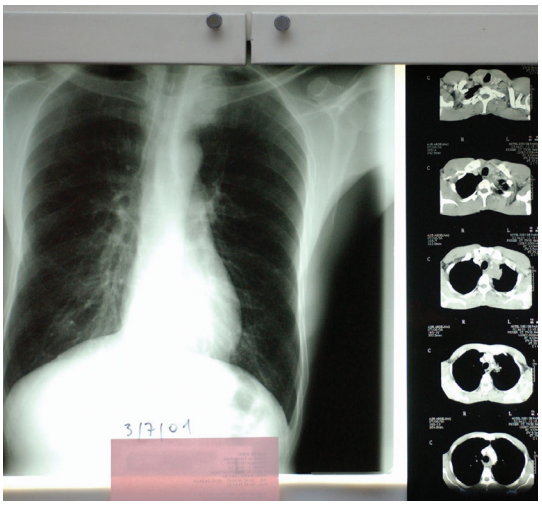
The drugs now setting the cancer world alight are called PD-1 inhibitors. The two blazing the trail are nivolumab, or "nivo", and pembrolizumab, or "pembro", the drug used to treat Jimmy Carter.

These focus the immune attack on cancer cells rather than on healthy tissue, which means they are more effective and milder than ipi. "They have remarkably few side effects," says James Larkin, a consultant medical oncologist at the Royal Marsden, who has been treating people with melanoma or kidney cancer – including Brown – with nivo, pembro and ipi. "But overall, the biggest boost from the new drugs is that there's a 30 to 40 per cent chance the effects will be durable, for years, not months," he says.

In trials so far, nivo and pembro have routinely outperformed both ipi and the best existing chemo- and radiotherapy treatments, often triggering double the rate of tumour shrinkage and patient survival with far milder side effects. In July 2014, nivo received regulatory approval, in Japan, for treating melanoma that had spread. Pembro and nivo shortly followed suit in the US (see Timeline, left). They are also showing promise against the most common form of lung cancer, which kills more than 4000 people a day worldwide.

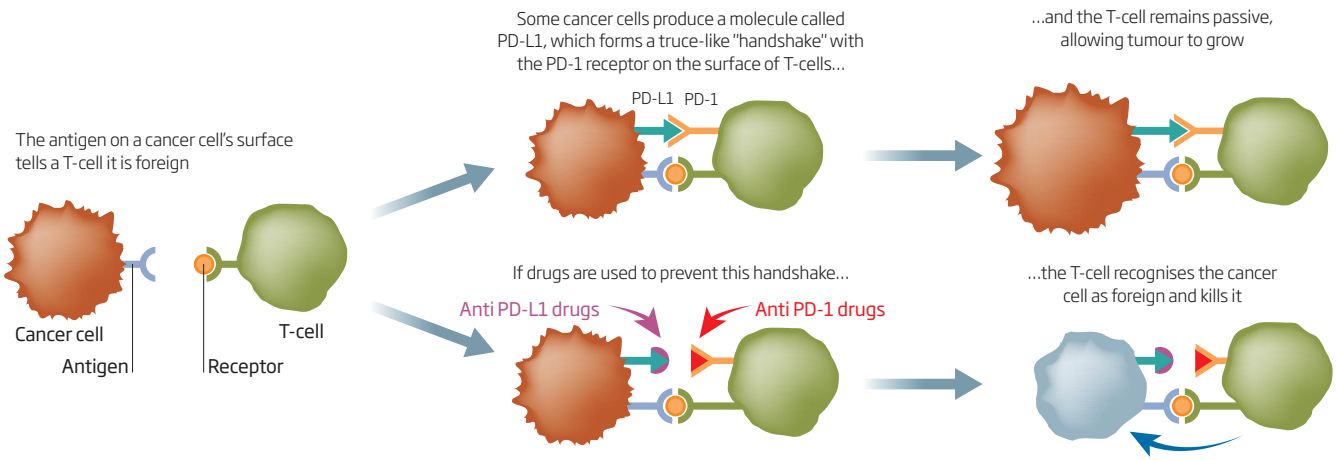
One reason the drugs are proving so successful is that remobilising the immune system allows it to continuously evolve to keep the tumour in check, limiting the ability of the cancer to escape detection and destruction even if it develops hundreds of mutations. "The immune system doesn't see one target on the tumour, it sees 10, or 50 maybe, so it machine-guns the tumour, rather than taking a single pot-shot," says Freeman. "It's a lot harder to evade a machine gun."

And while nivo and pembro both disrupt the "handshake" by blocking PD-1, a second wave of drugs is under development that blocks the other partner, the PD-L1 molecule



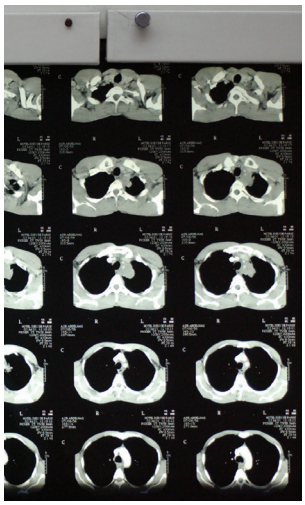
Keeping tumours in check

A new class of drugs can boost the immune response to cancer cells



on the cancer cells. The most successful so far is Atezolizumab, developed by Genentech and Roche. It has recently shown potential for treating lung cancer, extending the lifespan of patients by almost 8 months more, on average, than docetaxel, the best currently available drug.

There is a significant downside: these drugs only work for some of the people who receive them. "In lung cancer, two or three out of 10 have very significant responses, or their disease is stable for a long time," says Julie Brahmer of Johns Hopkins University of Medicine in Baltimore, Maryland, and co-leader of some of the PD-1 inhibitor trials. "But the majority of lung cancer patients are not responding, and that's where the work is now."



PATRICK ALLARD/REA

Some people with lung cancer are responding particularly well to the new drugs

Another big question is why the drugs don't seem to be as effective for some of the major cancer types including prostate, colon and breast cancers. One possibility is that the more mutations a cancer has, the better, because it gives the immune system more "abnormal" molecular targets to aim at. This could explain why melanoma, lung and kidney cancers are seeing the most compelling results. Through exposure to mutation-causing ultraviolet rays, cigarette smoke and toxins, they are likely to have more mutations than tumours in tissues that are better insulated from the environment.

One way to broaden the drugs' reach could be to use them together. The most dramatic results so far have been seen with the combination of nivo and ipi in treating melanoma. Almost 60 per cent of people showed a response, with their tumours shrinking by more than 30 per cent, compared with 44 per cent in those taking nivo alone and 19 per cent for ipi alone. In 12 per cent of people taking the combination – 36 people in all – tumours vanished completely. The preliminary results also showed that 80 per cent of those given the combination were still alive two years after treatment.

It was a trial of this combination that Brown had taken part in, and which cleared her tumours. She didn't know it at the time, but she happened to receive the combination.

Even so, her story is a reminder that even if these combinations work better, they aren't guaranteed to work perfectly every time. Two years after her first combined treatment, Brown was told that new lumps had appeared in her lungs. Shortly after, she became one of the first people in the world to have a repeat treatment. That was last September, and just two weeks ago, she received the welcome news that her cancer is stable. "I feel very lucky. I've been given a second chance," she says.

An even better approach could be to combine the new drugs with other kinds of cancer therapies, such as radiotherapy or anticancer vaccines, something many pharmaceutical companies are now trying.

That's because many conventional treatments act like sledgehammers, smashing apart their target cells, says Dan Chen, head of cancer at Genentech. By creating more cellular debris, they could open up the way for PD-1 inhibitors to work better, exposing the remobilised immune system to targets that would otherwise be locked away in tumours.

Nobody has all the answers yet, but there is a feeling that cancer treatment has turned a significant corner. "We're at the point where we've discovered the cancer equivalent of penicillin," says Chen. Although penicillin itself couldn't cure all infections, it gave rise to a whole generation of antibiotics that changed medicine forever, consigning most previously fatal infections to history.

If this really is cancer's penicillin moment, we might see some types of cancer consigned to a similar fate. Other people are similarly optimistic. "I hesitate to say the 'C word'," says Brahmer, "but potentially it will offer the chance of cures. It's a very exciting time." ■

Andy Coghlan is a reporter for *New Scientist*.
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