Infectious optimism

Harnessing viruses to kill tumours may help us beat cancer – and spur our immune systems to join the fight, finds **Michael Le Page**

TEN years ago, Randy Russell found out that a small mole on his shin was skin cancer. He got it removed, but then he found another, and more after that. Each time he had the tumour cut out. "After 10 or 11 surgeries, I got aggravated because it was beginning to bankrupt the family and it wasn't working," he says.

Ultimately, he was told it was the end of the road. "They said, 'You've got maybe six, seven months to live. Just go home and die.'" Then, as Russell was leaving the hospital to return to his home in Rock Spring, Georgia, one of the doctors shouted down the hall after him: "Try Vanderbilt!"

A few weeks later, Russell was having an experimental drug injected into his tumours at Vanderbilt University Medical Center in nearby Nashville, Tennessee. Each time he went back, the tumours were half the size. "It was just amazing," he says. "Finally, the doctors said, 'Look, there's nothing more we can do for you. It's just gone.'"

That experimental drug, called T-VEC, was actually a live virus that researchers had tinkered with to make sure it was safe for Russell's healthy cells, but deadly to his cancer. It is the first ever virus to be approved for treating cancers, and many more are now being tested. These anticancer viruses could give us a powerful new way to kill tumours, not only because they target tumour cells directly, but because they spur our immune systems to do so too. That could make them particularly potent when combined with other immune therapies already transforming cancer treatment.

Usually, viruses cause us harm, from the minor miseries of the common cold to the devastation of Ebola. But they can have an upside (See "Hijacking the hijackers", page 46). This was first reported in cancer in 1904, when a doctor described a dramatic drop in cancerous cells in the blood of a person with leukaemia after a bout of flu. After that, there were many other reports of cases where people with cancer saw improvements in their condition after coincidentally getting infected with a virus.

It was thought that this effect was due to the viruses being more likely to infect and kill cancer cells than normal cells. "They love cells that have found a way to avoid the immune system," says Charlotte Casebourne of Theolytics, a UK company developing viruses for treating cancers. And they also love rapidly dividing cells, like you get in many cancers.

When a virus gets inside a cell, it makes lots of copies of itself and then breaks the host cell apart to release all these new viruses, which go on to infect other cells. "One virus enters the cancer cell and out come 10,000 viruses," says Gunnel Halldén of the Barts Cancer Institute in London. The idea that viruses thrive in tumours was then confirmed in several human trials starting in the 1950s. In one, for instance, 30 women with cervical cancer saw their tumours temporarily shrink after they were infected with an adenovirus, the kind that causes colds.

These pioneering trials often produced positive results, but they never led anywhere, partly because of safety fears. Then, in the 1990s, biologists began to figure out how to engineer viruses that can kill cancer cells without harming healthy ones, which led to much more interest in this approach.

The first to be tested in people was Onyx-015, an adenovirus with some genes deleted so it can replicate only in cells in which a key anticancer gene called *p53* is inactive, as in most cancers. It proved safe and made some tumours shrink.

These early trials also revealed something crucial: that viruses kill cancers not just by directly infecting tumour cells and bursting them apart, but also by stimulating immune attack. Tumours hide from the immune system in several ways, taking cover behind a shield of normal cells, say, or exploiting signals our healthy cells use to tell the immune system not to attack.

A virus can stimulate such a strong immune response that it overcomes the "don't attack me" signals. And when viruses burst cells open, that releases a lot of debris, some of which is specific to the tumour. "You're showering off lots of bits of cancer," says Hardev Pandha at the University of Surrey in the UK. That debris effectively unmasks the cancer to the immune system and helps it learn to target it.

"A person with leukaemia had a dramatic drop in cancerous cells in the blood after a bout of flu"

This immune response to cancers triggered by viruses may be just as important as the direct killing effect, if not more. "A virus can't be guaranteed to get into every bit of a cancer," says Pandha.

This is why T-VEC was designed from the start to boost the immune response as well as to kill cancer cells. First, the team took a herpes simplex virus – the kind that causes cold sores – and removed a gene that helps the virus overcome cellular defences. These defences get turned off in most cancers, so the result is a herpes virus that can replicate in a wide variety of cancers but not in healthy cells. ›

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HIJACKING THE HIJACKERS

Viruses are one of humankind's greatest enemies, but they can also be harnessed to prevent and cure diseases. The first vaccines were simply less harmful strains of deadly viruses, such as the cowpox virus used to protect against smallpox. Modern genetically engineered vaccines are far more sophisticated.

For instance, the vaccine being used in the ongoing Ebola outbreak in central Africa uses a different kind of virus in which the gene coding for the outer protein coat has been replaced with the Ebola version. This makes it look like Ebola to the immune system, and it is proving to be highly effective.

Viruses have also been used since 1990 to deliver gene therapies to treat rare genetic disorders. For instance, some children have to live in plastic "bubbles" because mutations in a key immune system gene prevent them fighting infections. Adding a normal copy of the gene to cells can often cure the disease – and adding genes to cells is what viruses excel at.

Viruses replicate by injecting their DNA into cells and making those cells produce lots more copies of them. For gene therapy, the viral DNA is replaced with whatever doctors want to deliver to cells. These "viral vectors" aren't infectious as they can't replicate themselves.

The researchers also deleted a couple of genes that help the virus infect skin and nerve cells. Most importantly, they added genes for a protein called GM-CSF that boosts the immune system response to the debris of shattered cancer cells.

After a clinical trial showed that T-VEC shrank tumours in a third of people with melanomas that can't be surgically removed, it was approved in 2015 by the US Food and Drug Administration and the European Medicines Agency for this use. In that trial, for 16 per cent of people the tumours vanished. David Ollila at the University of North Carolina has just analysed T-VEC outcomes at three centres in the US. "People wanted to know, 'Hey, in the real world is this drug working as well as it is supposed to?'" says Ollila.

His team found that it wiped out the tumours in 39 per cent of people treated. That success reflects the fact that doctors now know which patients are most likely to benefit, says Ollila.

T-VEC also has minimal side effects, meaning people can go straight back home after injections. "I hear all these horror stories about people with their chemo, and their radiation, and their sickness and all. My treatments were a blast," says Russell. "It was like a road trip. There were zero side effects, none at all. I went to work the next day."

"One company is generating thousands of mutant viruses – evolving viruses to be better at killing cancers"

Upping the potency

Biologists have no shortage of ideas for making viruses provoke an even stronger immune response, so the next generation of viral treatments should be even more effective. In the first instance, combining viruses with the immunotherapies already revolutionising cancer treatments (See "Immune boost", right) could produce much better results than either alone.

For example, new drugs that block the "don't attack me" signals that cancer cells exploit have also been producing excellent results for many cancers. But these drugs, called checkpoint inhibitors, don't work for everyone. They really only make a difference if your immune system initially recognised and went after the cancer before the tumour developed the "don't attack" signal. "There needs to be a pre-existing response to a tumour, which the brakes can then be taken off," says Robert Coffin, a member of the team that developed T-VEC. "In most patients, there just isn't a response."

Lots of teams around the world are trying to understand why, and to find ways to provoke this immune response in the first place. One strategy is to use personalised cancer vaccines. To create these, one approach is to extract tumour cells, break them open – like viruses do – and then mix the debris with immune cells also extracted from the person being treated. This trains the cells to recognise the cancer before they are injected back into the patient. "That's very complicated, and takes time," says Coffin, who now runs Replimune, a UK firm that is developing anticancer viruses.

Using off-the-shelf viruses to do the same thing inside the body is faster and cheaper – and could be even more potent when combined with immunotherapy drugs. In people with melanoma, a trial that combined T-VEC with the immunotherapy drug ipilimumab found the treatment was twice as effective as giving the drug alone. Several similar trials are under way.

Meanwhile, researchers are trying to engineer viruses that are even more effective at triggering this immune response. To create one called RP1, Coffin and his team at Replimune began by screening 200 strains of herpes to find the one that was best at killing cancers. Then they armed it to the hilt: adding a gene that makes cells fuse together before dying and the *GM-CSF* gene that boosts the immune response to debris of shattered cancer cells. This souped-up virus is already in human trials and is being tested both alone and alongside other drugs right from the start.

Entering trials is, of course, no guarantee of success. So far, T-VEC remains the only virus to get approval. Several others have failed. In August, for instance, a major international trial of a virus therapy called Pexa-Vec was halted by regulators after it failed to show any benefit in people with advanced liver cancer.

There are several reasons for these failures. Trials like the Pexa-Vec one have involved notoriously hard-to-treat cancers. "My heart always sinks when a new virus is made and the first thing they go for is refractory brain cancer," says Pandha, whose team has just reported good initial results for bladder cancer using another modified virus. "It must be the hardest of all to treat."

He thinks researchers should go after easier targets and get viruses established as a standard way of treating cancers before taking on such tough challenges.

Another issue is that researchers worried about safety have chosen "wimpy" viruses, says Coffin. And Casebourne thinks they are playing it too safe by sticking to what they know. Instead of making a handful of changes to an existing virus, her company, called Theolytics, is generating thousands of mutant viruses and picking the ones that work best. In other words, it is evolving viruses to be better at killing cancers.

Yuman Fong at the City of Hope cancer centre in California has used a similar approach. His team created a promising virus called CF33 by generating hundreds of different vaccinia viruses – the virus type used for smallpox vaccines – and testing which ones killed 60 different kinds of human cancer cells growing in a dish. Those found to be safe in animal tests were then winnowed down based on how strong an immune response they provoked. Clinical trials will start next year.

There are many other promising developments. Halldén recently found that a virus she had created killed the connective tissue cells that surround and protect pancreatic cancers, for instance. "This is one of the reasons why it is so difficult to treat pancreatic cancer," she says. Kerry Fisher and his team at the University of Oxford have added a gene to a virus that leads to the destruction of this shield of normal cells around some tumours.

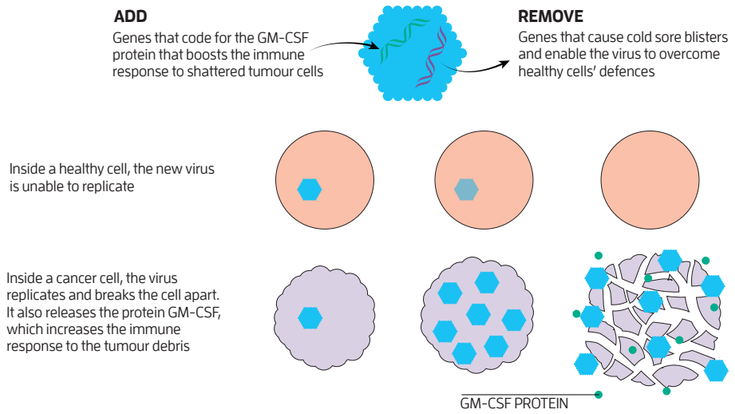
Meanwhile, Amin Hajitou at Imperial College London is doing things completely differently to most other groups, by using a virus that normally only attacks bacteria and that can't replicate in humans. His team modified the virus so that it injects DNA coding for toxic proteins into cancer cells. Human trials are due to start this year.

As well as developing better, more potent anticancer viruses, many researchers are also trying to create strains that can be injected directly into the bloodstream and reach cancers anywhere in the body, rather than having to be injected directly into a tumour.

There is no shortage of ideas for new ways to supercharge viruses, and many big drug companies have started to pay close attention. It is too early to tell whether viruses will become a common treatment for all kinds of cancers. But for some people they have already been lifesaving. Like Russell, dozens of the first people treated with T-VEC have remained cancer-free for five years or more, long enough for doctors to call it a cure. "It's the beginning of the possibilities," says Coffin. ▮

Killing cancer by going viral

Altered viruses allow us to target cancer – and spur the immune system to action too. One example is T-VEC, an engineered herpes simplex virus



IMMUNE BOOST

In 1891, New York doctor William Coley began injecting inoperable cancers with various bacteria, in the hope that a resulting infection might cause the tumours to shrink. His idea sometimes worked; occasionally tumours even disappeared entirely.

In 1909, German doctor Paul Ehrlich proposed that the immune system kills off most cancers long before we detect them, and that only cancers that evade this immune surveillance become a problem.

We know now that Ehrlich was right, and that Coley's treatments worked by stimulating the immune system to attack cancers that had previously been evading immune surveillance. However, it took until the early 2000s to establish this. For many decades, doctors instead focused on killing cancers directly, using surgery, drugs and radiation.

Now, a wide variety of immunotherapies are being developed, and many have proved highly effective. Some drugs stimulate the immune system generally. Others, known as checkpoint inhibitors, block the "don't attack me" signals many tumours use to evade detection.

Another approach is to take immune cells from the body, program them to attack cancer cells and put them back. One way of doing this, known as CAR-T, works very well against blood cancers such as leukaemia, but not solid tumours so far.

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