CRISPR genome editing and immunotherapy – the early adopter

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Credit: Cancer Research UK

It's been a couple of years since the genome editing tool CRISPR first hit the headlines. And talk of its potential to cure all manner of diseases, create superhumans and bring dinosaurs back from the dead has followed.

But among that speculation, one area of medicine has been quick to pick

up the technology and is now leading the way in early clinical trials.

In this second post in our series taking a closer look at CRISPR, we explore its potential for new developments in cancer immunotherapy.

Immunotherapy can take a range of forms. Some experimental approaches use viruses that kill cancer cells and alert the immune system to attack. Others involve giving patients drugs that release the 'brakes' on immune cells to target cancer. And some use specially engineered immune cells that when injected into a patient have the potential to hunt out and kill cancer cells.The aim of immunotherapy treatments is to alert the body's immune system to cancer, so that it's better equipped to recognise and fight the disease.

In each of these cases, scientists need to be able to understand and fine-tune the body's complex immune system. And some are turning to CRISPR for help.

> CRISPR gene editing is a hot topic. What could it mean for cancer research? And is it worth the hype? Find out more: https://t.co/GiZi3ccOXo pic.twitter.com/85B5780sx3
>
> — Cancer Research UK (@CR_UK) April 11, 2017

Dr Martin Pule, a clinical senior lecturer in haematology at UCL, says that genome editing techniques such as CRISPR have quickly become part of the tool-kit for researchers like him.

"In the past, many of the technical problems around introducing new genes into cells were worked out, but we didn't have an easy way of efficiently and precisely disrupting existing genes," he says. "New genome editing technologies changed all that."

By using CRISPR, scientists are able to tweak specific genes in viruses or the body's own immune cells, and so make them behave differently.

Researchers have been able to do this before using similar techniques, but the excitement around CRISPR is that this can be done much quicker, cheaper and more precisely than ever before.

Out of the lab, into the patient

Genome editing techniques have been used in people to treat cancer and other diseases before.

There was lots of excitement when news broke in 2015 of a 1 year old girl with acute lymphoblastic leukaemia (ALL) being treated with a similar editing technique known as TALENs, after all other treatments had failed.

She received a transplant of cancer-fighting immune T cells from a donor, which had been tweaked in the lab to give them 2 new characteristics.

Normally, the donated cells would see their new environment as foreign and attack the patient's healthy cells, but genes that control this process were turned off. The T cells would also be susceptible to attack from the anti-cancer drugs that the baby was receiving, and so modifications were made to protect them.

She responded well to the treatment, and another infant received a similar therapy.

Following in the footsteps of its cousin TALENs, CRISPR itself has moved on from the lab to clinical trials. Late last year, a Chinese group became the first to use CRISPR-edited cells in humans.

The team took immune cells from a patient with an aggressive lung cancer and edited them in the lab. This editing deactivates a gene that allows tumours to put the 'brakes' on these immune cells, preventing them from attacking cancer cells.

By switching off the gene, which produces a molecule on the cells' surface called PD-1, the full force of the body's immune system is released, helping it clear the tumour. Drugs that target PD-1 are among the much-lauded immunotherapy treatments already showing promise in advanced melanoma and lung cancers. So there's a lot of hope that CRISPR may provide another step forward here too.

10 patients will be involved in the early-stage Chinese trial, and it will look at whether the treatment is safe, rather than testing effectiveness.

The scientists are also hoping to start clinical trials using CRISPR to treat bladder, prostate and kidney cancers. It's also positive news that both blood cancers and solid tumours appear to be responding to various immunotherapy approaches, as different challenges are faced in treating these diseases.

Kickstart the CAR

One clever immunotherapy trick fuses together 2 components of the immune system with different jobs.

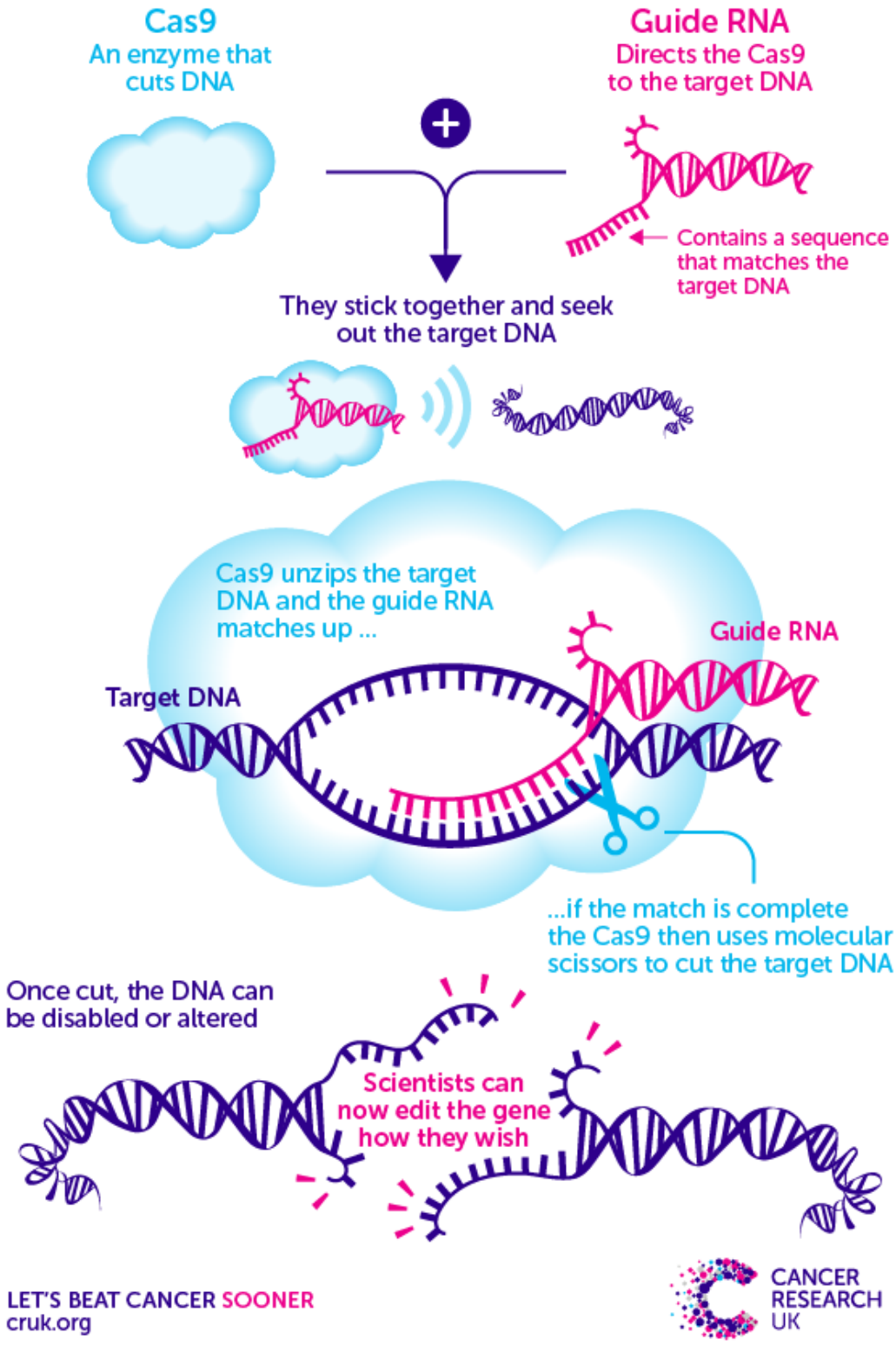
Chimeric antigen receptor (CAR) T cells are a mix of an antibody molecule, which can home in on a specific target on tumour cells, fused to a T cell that provides the knock-out blow to the cancer cell.

We've blogged before about how these engineered cells work, and small trials in 2011 caused lots of excitement. But one of the latest updates is that using CRISPR instead of older genome editing techniques might

supercharge these CAR T-cells even further.

EDITING GENES WITH CRISPR

CRISPR is a tool used by scientists to precisely edit genes inside cells. It's comprised of two parts...



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Credit: Cancer Research UK

The older technology is less precise and can result in the genes mistakenly being inserted at random locations in the cell's DNA. The knock-on effect is that the engineered cells' might be less effective or unintended side-effects could be introduced.

But a US-based group found that CRISPR improved the precision with which the modified gene was inserted into T cells. Their research suggests that the cells were then more potent in their fight against leukaemia in mice because they had more stamina. The researchers are now hoping to test these findings in people.

"Cancer cells are relentless in their attempt to evade treatment, so we need CAR T cells that can match and outlast them," Dr Michel Sadelain, the researcher leading the study at Memorial Sloan Kettering Cancer Center, said at the time.

It's findings like these that will hopefully make engineered immune cell treatments better and kinder in the future, though they aren't yet the Holy Grail.

"In one kind of leukaemia called B-ALL, almost 100% of children who received engineered T cells responded, despite having a disease which had become resistant to all standard treatments," says Pule.

This suggests that, in some circumstances, there may not be an upper limit on who may respond to these treatments. But achieving this in other cancers will take further fine-tuning. In other diseases, such as another

kind of blood cancer called DLBCL, the response rates are more like 60%.`

"This reflects the fact that a good CAR T cell product is hard to make, or that there are factors inside the tumour making the T cells less effective," Pule adds.

Lots of the progress using CAR T cells has so far been in blood cancers rather than solid tumours, which have even tougher conditions.

Because CRISPR allows scientists to do lots of small-scale tinkering, this is a rapidly developing field and researchers are trying to find solutions.

"Right now a lot of people are asking why there's this response gap between DLBCL and B-ALL. Can we edit something in the CAR T cell, or put something extra in which will increase the response rates?"

One reason might be that the tumour lives in a hostile environment that stops the engineered T-cells' ability to attack the cancer cells. One way around this is to delete the molecules on T cells that coordinate the stop messages from the microenvironment.

"This strategy looks like it might be quite effective and could increase the number of patients who respond," says Pule.

The other side of immunotherapy

Some of the research that's taken place since CRISPR burst onto the scene has also raised more questions than answers. The immune system is a powerful and complicated machine, and we don't yet understand how to control it.

Not all of these treatments have been as successful as hoped. As well as

varying response rates, they can also cause serious side effects, including, in rare cases, death.

There have been recent reports of patients with bladder cancer whose tumours increased in size after immunotherapy treatment, although this has caused some debate among researchers. Side effects including extreme fever or organ damage have also been well documented in clinical trials.

In the US, a total of 5 patients died following treatment with an experimental CAR T cell therapy for ALL. The clinical trial was paused after 3 people died, and then stopped after 2 more deaths.

While this is very rare, it's clear that as well as working to make treatments more effective in more people, researchers also need to look at how they can reduce side effects.

Similar problems were seen in the past in the early days of treatments such as combination chemotherapy, before they were refined.

Pule points to how scientists are already using genome editing to increase safety. For example, in many cases, it isn't possible to engineer a patient's own T cells and so cells from a donor are needed.

But this raises some challenges.

"The donor T cells might attack the recipient causing graft-versus-host disease," says Pule. Graft-versus-host disease is a condition where the donor cells see their new environment as foreign and attack it. "If we remove a specific molecule in the donor T cells using gene-editing technology, we can reduce the chance of this happening."

This is how the two infants with ALL were treated.

Where next?

Like many new technologies, CRISPR was greeted with excited fanfare in some parts, and a more cautious realism is now settling in.

It's clear that CRISPR opens up so many doors for immunotherapy and lets researchers go further, more easily than ever before. But as the technology is understood better, its limitations and challenges also come into focus.

The third part of our CRISPR series will take a look at what the future might hold for CRISPR and cancer research.

Provided by Cancer Research UK

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