How can CRISPR genome editing shape the future of cancer research?

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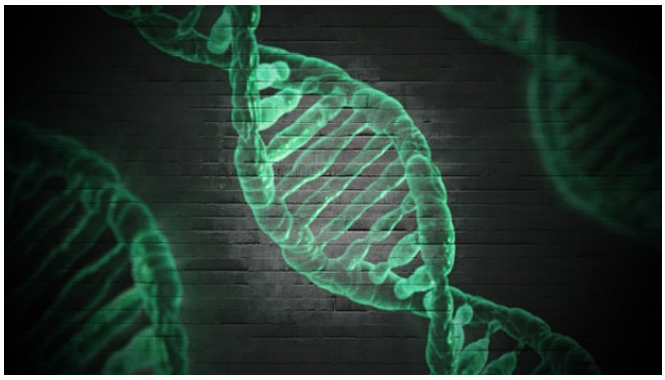

Credit: Cancer Research UK

The genome editing technology CRISPR is causing plenty of excitement in cancer research.

CRISPR allows scientists to precisely tweak genes faster than ever before, and at a fraction of the cost of older techniques. These tweaks can be used to answer questions in the lab, but there's also excitement, and trepidation, over the potential use of the tech to treat diseases.

This excitement has been coupled with hype around the potential return of dinosaurs, or a slippery slope towards designer babies.

But more realistically, CRISPR is progressing early lab research that will help answer questions previously out of reach.

One giant leap

Excitement has led to speculation about CRISPR being used to edit diseases out of people.

In theory this means editing either a fully formed human, or editing an embryo, egg or sperm cells.

The first is particularly difficult – CRISPR is fine for manipulating cells in a Petri dish in the lab, but falls short as a method to alter each of the trillions of cells that make up the human body.

The second approach, which homes in on fewer, more specialised cells, is more plausible and therefore of greater potential impact. In this case, changes could be made to a single cell that then repeatedly divides, meaning the changes should be passed on to every resulting cell.

But there are ethical questions around editing cells integral to early development and some people are strongly opposed.

The truth, however, is that this sort of approach would likely only be possible for a subset of cancers.

That's because cancers are more often tied to the accumulation of lots of DNA errors (mutations) inside cells, rather than a single, correctable fault. And for every cancer-causing mutation there are plenty of harmless others.

Pinning down which is which and dealing with the culprits isn't always feasible. Only a fraction of cancers are tied to inherited gene faults. And these so-called 'germline mutations' increase the chance of cancer developing, rather than making it a certainty.

"The precision of CRISPR technology means that if a patient does have a germline mutation that predisposes them to cancer, there is the possibility that in the future the technology could target and correct that fault," says Dr. Irene Chong, a clinician scientist at The Institute of Cancer Research, London, and a consultant clinical oncologist at The Royal Marsden NHS Foundation Trust.

While she's doubtful that this approach is anywhere near being tested, she sees the potential to one

day treat and help patients who have a strong family history of cancer.

"That would be the ultimate hope – prevention rather than cure," says Chong.

This same challenge is being faced by scientists working on other genetic diseases – only a minority can be pinned down to a single genetic cause.

But the early murmurs of progress are beginning to be heard. Scientists have edited embryos in the lab to remove a gene that causes some heart disease, and to make them resistant to HIV infection. And in the UK, scientists are editing human embryos to understand early development, rather than directly cure disease.

In all of these cases the embryos were destroyed before they were 14 days old, and were never intended to be implanted into a woman.

That would be a huge ethical and technical leap that's illegal in the UK and many countries, and so it's unlikely to happen here anytime soon. Before those steps could even be considered, a massive amount of work needs to be done to prove that the changes made to embryos would be both safe, effective. But most of all, it would need to be proven that the approach was better than those already available to tackle certain inherited conditions.

So what can CRISPR do for cancer?

Lots of small steps for people in lab coats

Our genes are made from DNA. This, with the help of another molecule called RNA, is the blueprint for making proteins. Proteins are the workers of the cell, carrying out a huge range of important jobs.

"So far, we target proteins with drugs or medicines, and RNA with small molecular scissors called siRNAs," says Professor Olaf Heidenreich, a Cancer Research UK-funded expert in childhood leukaemia at Newcastle University. "CRISPR lets us directly target DNA to change its sequence and information."

This is important because cancer progresses as DNA faults accumulate in different genes. These faults change how proteins work, helping cells become hardier, grow out of control or invade other tissues.

"Working out which are the key genes in each of these processes, and how their mutation drives cancer, is critical for understanding cancer and developing better drugs," says Professor Simak Ali, a breast cancer expert at our Imperial College London centre.

CRISPR is such a powerful technique because it lets scientists do this by precisely manipulating individual genes – they can delete them from cancer cells in the lab and ask basic questions about what those genes do.

"Deleting and replacing genes in human cancer cells in the lab used to be extremely laborious and there was very little success," says Ali. But CRISPR makes it possible to do quickly and simply, bringing results much sooner.

Scientists can now replace the normal form of a gene with faulty, cancer-causing versions. They can then assess the impact of these faults, see how the mutant molecules work, and design treatments against them.

Combining new technology for a bigger boost

The best way to study cancer is in patients, but this isn't always possible with early stage technology. So scientists hunt for increasingly ingenious ways to make sure that their lab work is as close as possible to the real thing.

Organoids are groups of cells grown as 3-D structures, designed to be more representative of conditions in the body than cells grown like a flat piece of turf in a dish.

Scientists in the Netherlands have used CRISPR to targeted two genes that fix mistakes in DNA, and that are often missing in cancer cells.

By deleting them from bowel organoids the researchers are trying to mimic what happens in bowel cancer and watch how it progresses –

something that's impossible in patients.

"With the help of CRISPR/Cas9 in organoids, we can perfectly mimic this mutation accumulation seen in patients," Dr. Jarno Drost, joint lead researcher on the study from The Hubrecht Institute, told Drug Target Review.

So by combining two cutting edge techniques it's possible to get a much clearer picture of what goes wrong in cancer.

And while we know many of the genes that play an important role in how a cancer cell grows, divides or spreads, CRISPR is finding others.

"This can identify genes that allow cancer cells to become resistant to cancer drugs, and also help us decide which drugs to give to which patients," says Ali.

Heidenreich's work involves using CRISPR to find out which genes childhood leukaemias need to become resistant to treatments.

"Adding another medicine targeting those indispensable genes may lead to a very powerful combination, which efficiently eliminate cancer cells without causing so many side effects," he says.

Double trouble

In sniffing out new genes to target, researchers have uncovered pairs of genes that have intertwined roles within cells. If a cancer cell carries a particular faulty gene, the cell may rely on another to keep growing.

Kicking away this cellular crutch with a drug can therefore kill the cancer cell.

This idea, called synthetic lethality, is already being used to treat some patients. The ovarian cancer drug olaparib (Lynparza) works against cancer cells that carry a faulty BRCA gene and are therefore reliant on another molecule called PARP, which olaparib switches off.

It's not the easiest idea to test in the lab, so it's likely there are other genetic alliances out there that could be targeted with drugs. CRISPR's speed means that thousands of potential combinations can now be rapidly tried out, with the best ones being tested further.

By switching off different pairs of 73 genes across two types of lab-grown cancer cell and one type of healthy cell, US researchers found 152 partnerships that might be suitable targets for treatments.

But most of these pairs were important in only one of the three cell lines suggesting that, as expected, different genes will need to be targeted in different cancers.

CRISPR 2.0

CRISPR itself is an improved version of genome editing techniques that have been around for a few years. And more souped-up versions have been quick to arrive.

CRISPR sometimes edits genes that it isn't supposed to, so it's hoped that newer versions will increase accuracy. And its molecular components are too big to work in viruses used in gene therapy, for example, so smaller machinery needs to be developed.

By making adjustments to the molecules that form the CRISPR machinery, scientists can get their version to work better or do a slightly different job.

But it's not all plain sailing – one study reporting a better alternative had to be retracted after publication in a scientific journal because the findings couldn't be repeated. It's a reminder of the caution and double-checking that's required of science before talk of treating diseases can happen.

So, as ever, research is steadily progressing bit by bit, rather than in astronomical bounds.

CRISPR isn't the final word or a miracle cure, but it lets us explore new areas that weren't accessible even a few years ago. Science continuously pushes boundaries and some of these areas need open discussion. CRISPR's power means better

treatments could follow sooner than ever before, but with this comes renewed responsibility.

Provided by Cancer Research UK