

'It's a wonderful technique that enables us to do great things.'

Carefully cutting into genes

John van der Oost, professor of microbiology at Wageningen University & Research, is one of the founders of CRISPR-Cas. This revolutionary technique allows scientists to remove, add or modify genes with high precision. In 2018 Van der Oost received a Spinoza Prize worth 2.5 million euros for his work.

Text: NWO, Nienke Beintema Image: NWO, Rafaël Philippen

CRISPR-Cas is the new buzzword in the life sciences these days. What does it actually mean?

'CRISPR-Cas is a molecular system that enables you to cut DNA in specific places. As a result, you can essentially alter every gene in every organism. This method of "genome editing" is much easier, more precise and more efficient than other kinds of genetic modification. It's truly revolutionary.'

What role did you play in its discovery?

'CRISPR was discovered about ten years ago as a system in the DNA of bacteria. It concerns DNA in which small sequences of genetic code are continuously repeated. In 2005 foreign researchers discovered that there are fragments in that DNA that are identical to pieces of virus DNA. That's why they thought it was probably an unknown kind of immune system, which bacteria use to protect themselves against viruses. In other words, it's a system that recognises an incoming virus in order to subsequently render it harmless. I found this so exciting that I decided to use part of the money from my Vici grant to discover how the CRISPR system works. We were one of the first groups worldwide to start working on this, so the timing was fantastic.'

And what was the result?

'We were able to show that it did indeed concern an immune system. We introduced it into bacteria that didn't have it themselves, and the CRISPR design enabled us to make the bacteria resistant to a specific virus. We called this a "flu shot" for bacteria. And we showed for the first time that CRISPR-Cas is suitable for general genome editing.'

So how does that work?

'CRISPR-DNA, which contains pieces of virus DNA, is like a database of intruders. A kind of archive with fingerprints. In order to use this information, that DNA has to be transcribed into RNA, a process that we know from regular protein synthesis in every living cell. In this case, CRISPR-RNA is made that acts as a guide to lead DNA-cutting enzymes such as Cas to the right place in the virus DNA. Cas will only bind to that DNA and then cut it if there is a match.'

What can that be used for?

'As soon as an enzyme cuts the DNA of a certain cell, repair proteins attempt to mend the break. In many cases, these kinds of breaks are easily repaired, but there are often small errors that inactivate that gene. But what's even more exciting is that you can also insert a completely new piece of DNA where the cut took place. From another organism, or DNA that you made yourself.'

Does this always happen in practice?

'This is being used extensively in biotechnology to give microorganisms and plants certain desired properties. Companies are using the CRISPR technique on bacteria and fungi to improve the production of biofuels, for example. It works extremely well in plants too. In the United States, for example, there are apples on the market that no longer turn brown once they've been cut open.

'There are also many examples of successful genome editing of human cells. For example, you can silence genes in an extremely targeted way to study what their precise function is. A next step would be to make people better, but that's still a long way off for most genetic diseases. People frequently send me e-mails asking: when can you cure my disease? But of course you could never alter all cells in an organ or tissue with CRISPR. With the current technology the most you can hope for is to renew some of the cells at an extremely local level.'

Which diseases would this benefit?

'Haemophilia, for example, in which your liver is unable to effectively generate a certain blood clotting factor. If you were able to locally renew liver cells, then the liver would be able to generate that factor. Or you can alter white blood cells, which are part of our immune system, in such a way that they can attack specific cancer cells in a much more targeted way. These are great examples. But I'm afraid that for now CRISPR-Cas can only help us with a few genetic diseases. That's what I try to explain to people: that they shouldn't have unrealistic expectations.'

If you correct a genetic defect in an extremely young embryo, can it grow into a healthy person?

'Yes, theoretically that should be possible. But we're still very far away from that stage. And in addition to technical challenges, all kinds of major ethical issues come into play as well.'

Don't they always come into play, as soon as it concerns genetic modification?

'Yes, it still has a nasty aftertaste. But essentially it's no different than what's happening in nature. If there was no exchange of DNA, then we would still be bacteria crawling through the mud. What we're doing is actually nothing new. We're just doing it much faster than how it happens in nature. And plant breeders have been using another trick for years: they treat the DNA of plants with radioactive radiation, which results in mutations, and ultimately new varieties. And that is perceived as being something "natural". But that's like shooting a gun without taking aim because many other changes occur as well. Yet these plants end up at the greengrocers in no time. CRISPR enables us to change specific genes now, seamlessly and efficiently.'

What are the most promising applications?

'You can make crops resistant to drought, disease or salt, for example. Or you can significantly increase your yield. With the world population constantly on the rise that could become extremely important. You can have microorganisms make certain medicines, or biofuels or bioplastics. In short, there are countless possibilities. Of course we have to closely monitor that the end products are safe and healthy. But in my opinion this discussion has started to spiral out of control. CRISPR allows us to make extremely precise changes to DNA. It's a wonderful technique that enables us to do many great things.'

Are people insufficiently aware of this?

'Yes, I think we made mistakes in that respect, especially in the past. I think that as scientists we should have explained the story of genetic modification better decades ago. People are saying: "I don't want that on my plate". Take the apple that won't turn brown. That's the result of a fairly simple mutation. It was achieved by CRISPR-Cas, but you could have done it with radioactive radiation, or by waiting until the mutation occurred on its own volition.

'I think that the most important thing is to emphasise the huge challenges we're facing, from global food security to climate change and the depletion of fossil fuels. We have to give better explanations of all the possibilities, but also what the dilemmas are.'

What's the situation with regulations?

'The rules still stem from a time when there was much less knowledge and far fewer technical possibilities. We have to talk about that more at the European level. If we don't tackle this now, it will have serious economic consequences. Legislation in the US has already been eased: there modification is allowed as long as the end product cannot be distinguished from what could happen in nature itself. At the Royal Netherlands Academy of Arts and Sciences we drafted a message in 2016 in which we urgently asked for legislation to be adapted. I think we have a good case for why that's necessary.'

Rumours are going around that the CRISPR-Cas work deserves a Nobel Prize... but there's a lot of haggling about who should get it.

'Yes, that's right. In a column in *NRC Handelsblad*, Piet Borst predicted that that Nobel Prize would go to the people who are working on the most spectacular human applications. And so not to the microbiologists who laid the foundation for that. He thought that was a pity. I thanked him for his column at the time. But I try not to occupy myself with that anymore. I think the Spinoza Prize is much better. Everything's fine this way.'

What are you going to do with the 2.5 million euros?

'As far as bacterial immune systems are concerned, we only have the tip of the iceberg in our sights at the moment. There are a huge number of fundamental questions that still need answering. At Wageningen we have identified a few systems that are comparable to CRISPR-Cas, but which can do slightly different things. I would like to further investigate these systems. And make improvements, by creating synthetic variations. Perhaps there still are more natural variations. And so we dream on, that's the beauty of our profession.'

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