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A breakthrough in genetic engineering is set to transform biology and medicine, reports **Colin Barras**

# RIGHT ON TARGET

SEQUENCING genomes has become easy. Understanding them remains incredibly hard. While the trickle of sequence information has turned into a raging torrent, our knowledge isn't keeping up. We still have very little understanding of what, if anything, all our DNA does.

This is not a problem that can be solved by computers. Ultimately, there is only one way to be sure what a particular bit of DNA does – you have to alter it in real, living cells to see what happens. But genetic engineering is very difficult and expensive.

At least, it used to be. Last month, two groups announced that they had performed a mind-boggling feat. They targeted and disabled nearly every one of our genes in cells growing in a dish. They didn't knock out all the genes in each cell at once, of course, but one gene at a time. That is, they individually modified a staggering 20,000 genes. "It's truly remarkable," says Eric Lander, director of the Broad Institute of MIT and Harvard, who led one of the studies. "This is transformative."

To put it into perspective, in 2007 an international project was launched to target and "knock out" each of the 20,000 genes a mouse possesses. It took the collective effort of numerous labs around the world more than five years to complete, and it cost $100 million. Now two small teams have each done something similar in a fraction of the time and cost. The secret: a simple and powerful new way of editing genomes. The term breakthrough is overused, but this undoubtedly is one. "It's a game-changer," says Feng Zhang, also at the Broad Institute, who led the other study.

The technique, unveiled just a year ago, is generating tremendous excitement as its potential becomes clear. It is already starting to accelerate the pace of research – Lander and Zhang used it to find out which genes help cancer cells resist a drug, for instance. In years to come, it is likely to be used in gene therapy, and to create a new generation of genetically engineered organisms with extensive but precise changes to their genomes. And if we ever do decide to genetically modify people, this is the tool to do it with.

While genetic engineers have done some amazing things, their first tools were very crude. They bombarded cells with extra DNA – sometimes literally – in the hope that it might occasionally get added to a cell's genome. But there was no way to control where in the genome it went, and if added DNA ends up in the wrong place it can cause havoc. Also, this approach does not allow for any tinkering with existing genes, which is the key to finding out what they and their variants do.

So in the past couple of decades the focus has switched to genome editing. To visualise how it works, imagine the genome as a collection of cookbooks written on long scrolls of paper and cared for by blind librarians. The librarians try to repair any damage but because they can't read they are easily tricked.

If you cut a scroll in two in the middle of a recipe, the librarians will join the pieces together again but in the process they often wreck the recipe. In other words, you can disable, or "knock out", a gene by cutting it.

What's more, if you add an extra piece of paper and then cut a scroll in two, the librarians will often assume the piece was cut from the scroll and add it in where the cut was made. In this way, segments of DNA can be added exactly where you want.

So the secret of genome editing is to cut DNA at just the right spot, and let the cell's DNA repair mechanisms do the rest for you. In practice, this means finding a molecule that, if added to a cell, will bind to a specific DNA sequence and cut the DNA at that point. There are natural proteins that do exactly this, but the chances of finding an existing protein that happens to target the one site in the entire genome that you are interested in are vanishingly small.

Instead, artificial proteins that bind to a specific DNA sequence have to be designed, made and tested for each edit you want to make. That can and is being done in many research labs around the world. Indeed, this kind of gene editing could soon be used in gene therapies to treat everything from sickle cell anaemia to HIV. Yet although there are now various tricks for speeding up the process of creating a designer DNA-binding protein, it is still far from easy. It can still take months or years of work to do yourself, or cost tens of thousands of dollars to have it done for you. To complicate matters further, much of the underlying technology has been patented.

Now, though, there is an alternative that is much faster, cheaper and – so far – freely available to all. The story of how it came ›