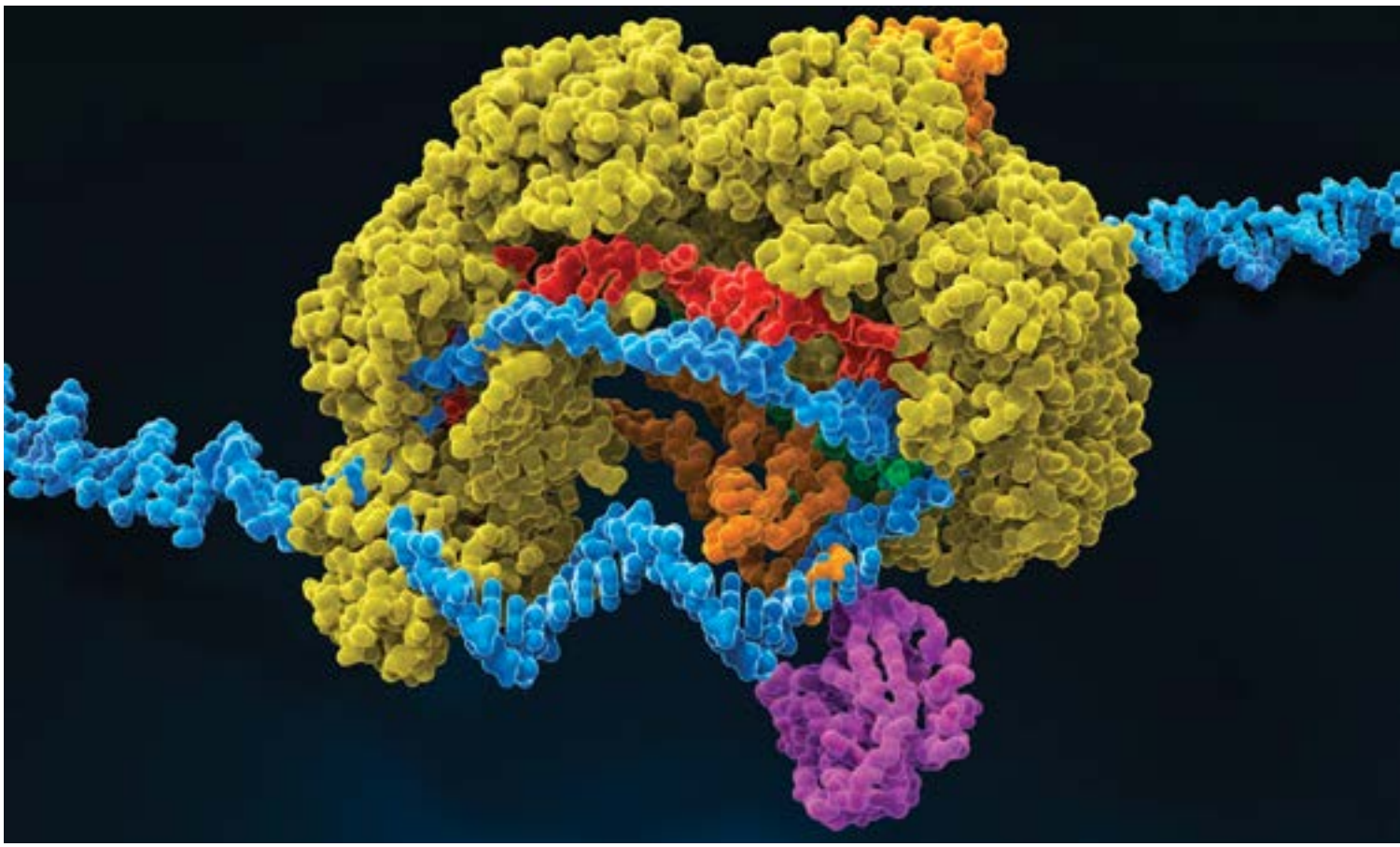
MOLECULAR SCISSORS



Jennifer Doudna is behind a pioneering gene editing technique, potential applications of which range from curing genetic diseases, to improving crops. She discusses the practical and ethical issues.

The prospect of gene editing, or the process of changing and manipulating the DNA of a living organism, has been looming from the moment in 1953 when the double-helix pattern was discovered and described.

Small incremental steps towards making the technology a reality were replaced with a giant leap in 2012, when the teams headed by Jennifer Doudna, Professor of Chemistry and Molecular and Cell Biology at the University of California, Berkeley, and Emmanual Charpentier, then Professor at the Laboratory for Molecular Infection Medicine in Sweden, perfected the gene-editing technique called CRISPR-Cas9.

CRISPR is the acronym for "clustered regularly interspaced short palindromic repeats", and Cas9 is the CRISPR associated protein 9, which is an RNA-based enzyme used to make specific cuts to the DNA. Cas9 was developed in the wake of the discovery that certain bacteria in the immune system could fend off invaders by slicing up their DNA.

"CRISPR harnesses a naturally

occurring defence process that bacteria use to fight viral infection," says Jennifer Doudna. "Like a pair of molecular 'scissors', CRISPR enables researchers to make precise changes to the DNA of virtually any organism. We can do this because Cas9 can be programmed with a short piece of RNA. The sequence of DNA that gets cut can be easily changed by changing this short piece of RNA. The technology may allow us to cure genetic diseases, enhance drug development, reprogramme immune cells to fight cancer, improve transplant organs, and produce even more nutritious crops."

So the advantage of CRISPR-Cas9 is that it's a relatively simple, clean and precise method for editing genes. But this accessibility and comparative ease of use also presents a problem, as was shown last year when a Chinese scientist – Dr He Jiankui – said that he had injected two embryos with CRISPR technology in a bid to make them HIV resistant. Condemnation was swift and united, with one of the key voices belonging to Doudna. Through her work in developing the technique, she has become deeply aware of its potential for transforming health and society, and highly concerned for its ethical application.

In the light of recent developments, what are her thoughts on the ethics of editing genes? "CRISPR-Cas9 is entering legitimate clinical trials that could lead to cures for sickle cell disease and blindness in individuals, and 2019 will likely see an acceleration of this amazing progress," she says. "Though we should be mindful not to over-regulate, the global community needs to work together to ensure that advances come as safely and quickly as possible while respecting ethical boundaries.

"Nearly all of the current efforts to use CRISPR-Cas9 in humans involve somatic cell editing: changes to DNA that affect just an individual and are not heritable. But a major issue has been if, how and when to use CRISPR for germline editing: changes to DNA in embryos, sperm or eggs that are then passed down to other generations. In the US, the 1995 Dickey-Wicker Amendment prohibits human germline editing, and the National Institutes of Health are forbidden to fund any such research. The practice is banned in many, but not all, countries. At this stage, I support the plans of WHO and the National Academies to recommend strict regulation that preclude use until scientific and technical questions are addressed, and until ethical and societal matters are resolved. But open discussion and transparency around this important topic should be encouraged."

In the meantime, what should researchers be doing? "They must stick to sensible boundaries and avoid unintended consequences," says Doudna. "To have a reasonable discussion, we must focus on asking how do we ensure the safety of embryo editing, what diseases or genetic conditions should we allow to be edited out of our germline, how will access to this technology impact society, and how do we engage in active and informed public discourse? Right now, germline editing does not pass even the simplest of those tests – safety – so researchers should not be editing embryos for implantation."

What do we know about the risks and other possible side-effects? "Like any experimental technology, we are learning about unforeseen issues and trying to solve them through continued research efforts. Rigorous pre-clinical testing in cells and animal models is key to uncovering any unpredicted issues before moving to human patients. The issues that we have seen so far are surmountable, and do not detract from the power and potential of the technology."

It's that power and potential of gene editing that has so many people excited. Beyond the vast scope of healthcare applications, the technology is also being used in other sectors, such as agriculture, and might even revolutionise construction, where it's suggested it could pave the way to self-repairing building materials. More immediately, what does Doudna think gene editing will achieve in the next decade or so?

"Human applications particularly interest me, since CRISPR technology can take drug discovery and development to a higher level. Within the next 10 years we could see therapies for blood diseases, such as sickle cell disease and various eye diseases. In cancer, scientists are attempting to harness CRISPR to edit a patient's T cells so that they can target a particular type of tumour.

"For non-human applications, researchers are applying CRISPR to engineer pest- and disease-resistant and anti-browning crops, protect trees from bark beetles, and explore the possibilities of 'gene drives' to control mosquito populations and reduce their ability to spread Zika virus and malaria." BMS

JENNIFER DOUDNA

- ✔ Degree in chemistry from Pomona College, California, 1985.
- ✔ Worked at Harvard University under Nobel Prize-winning biochemist Jack Szostak.
- ✔ Completed a PhD in 1989, carried out postdoctoral studies at the University of Colorado.
- ✔ Joined the faculty at Yale University in 1994.
- ✔ Became Professor of Biochemistry and Molecular Biology at UC Berkeley in 2002.
- ✔ Her many honours include the Kavli Prize, the Breakthrough Prize in Life Sciences, the Heineken Prize, the BBVA Foundation Frontiers of Knowledge Award, and the Japan Prize. She is also a foreign member of the Royal Society.

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