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FOR TOMORROW

Quarterly review
N°5 — 2022

Inside the mind of a Nobel Prize laureate...

Conversations for tomorrow

DR. JENNIFER DOUDNA

Nobel Prize laureate and Professor of Biomedical Science, University of California, Berkeley

EVOLUTION 2.0

Dr. Jennifer A. Doudna is the Li Ka Shing Chancellor's Chair and a Professor in the Departments of Chemistry and of Molecular and Cell Biology at the University of California, Berkeley. Her groundbreaking development of CRISPR-Cas9 as a genome-engineering technology, with collaborator Emmanuelle Charpentier, earned the two the 2020 Nobel Prize in Chemistry and forever changed the course of human and agricultural genomics research. Dr. Doudna is an investigator with the Howard Hughes Medical Institute, senior investigator at Gladstone Institutes, and the President of the Innovative Genomics Institute. She co-founded and serves on the advisory panel of several companies that use CRISPR technology in unique ways.

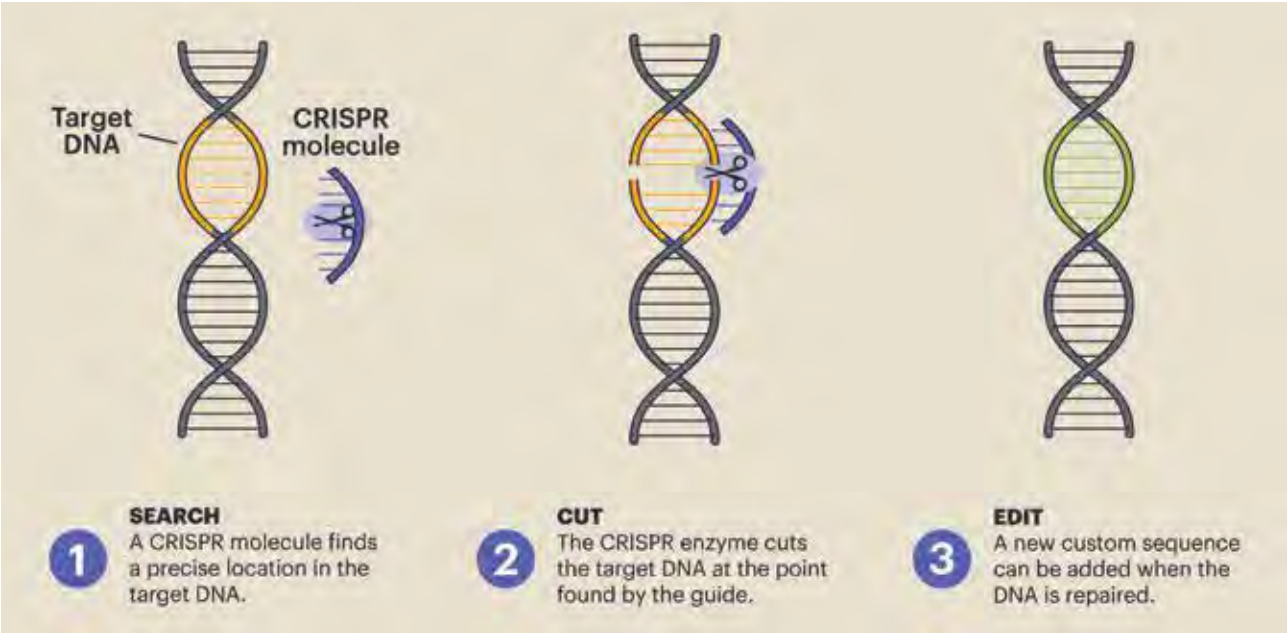
UNDERSTANDING CRISPR AND ITS APPLICATIONS

What is CRISPR-CAS9?

— The CRISPR-Cas system, sometimes referred to as "CRISPR" for short, is a technology for editing DNA. It is made of a guide RNA and a Cas protein. The guide RNA leads the Cas protein to a particular DNA sequence. The Cas protein then acts as molecular scissors, cutting the DNA. When DNA is cut, cells initiate a repair process that can change or "edit" the DNA sequence. CRISPR can remove, add, or change DNA "letters." In 2012, I published a research paper together with Dr. Emmanuelle Charpentier that laid out the inner workings of this technology. At that time, it did not attract much attention. Only in retrospect did it become clear to people who weren't specialists what an important moment that was.

"CRISPR is a technology for editing DNA."

Figure 1: How Does CRISPR Genome Editing Work?



Source: Innovative Genomics Institute

GENE EDITING [CAN BE USED] TO OPTIMIZE PHOTOSYNTHESIS IN CROP PLANTS FOR INCREASED FOOD YIELD AND ENHANCED CARBON CAPTURE.

What real-world examples are we seeing of CRISPR-CAS9 having an impact?

— There are now half a dozen clinical trials of CRISPR therapies for sickle cell disease underway already. I recently spoke to Victoria Gray (the first sickle cell patient in the U.S. to be treated with CRISPR) to hear about her life before and after the therapy. I'll just never forget that moment. For a scientist to see the real-world impact of work they were involved in, there's just nothing like it . To see that real-world impact within 10 years of that original publication? That's just mind-blowing to me.

Can you help us understand how CRISPR-CAS9 helps fix sickle cell disease?

— It's referred to as sickle cell disease because when you look under a microscope, the cells have a classic sickled shape, and people with sickle cell disease make a form of the protein called hemoglobin that carries oxygen in the blood that is prone to aggregation, prone to sticking together and forming aggregates that lead to these sickled shape of the cells. To treat sickle cell disease at its source, what's done is to remove what are called

blood stem cells from an affected individual. These come out of the bone marrow. And they are cells that have the potential to develop into new red blood cells. And to ensure that they don't have the sickle cell trait, CRISPR can be used to either change the DNA of the affected gene, or they can actually suppress the effects of the sickle cell gene mutation. And that's what's done. So CRISPR is used to make those changes in blood stem cells, and then the edited cells are infused back into the patient where they can repopulate the bone marrow and effectively replace the red blood cells with corrected cells. And if this works well and is proven safe, then it is a great solution to genetic diseases that have hitherto been transferred from generation to generation.

CRISPR FOR A BETTER WORLD

How can CRISPR-CAS9 be used for helping cut down carbon emissions?

— At the Innovative Genomics Institute (IGI) that I founded, we are working on using genome engineering to help agriculture adapt to a changing climate . While we have viable solutions for reducing greenhouse gas emissions for many sectors, agriculture stands out as a glaring exception, and it accounts for nearly a quarter of all global emissions. Plants and microbes can be part of the solution, versus part of the problem, and genome engineering can help make this scale to meet the size of the challenge. We currently have a variety of ongoing projects in this area:

- Using CRISPR genetic screens and gene editing to optimize photosynthesis in crop plants for increased food yield and enhanced carbon capture.
- Gene stacking in rice to reduce pesticides and fertilizers. We are also using gene editing to develop drought-tolerant plants.
- Investigating the effect of rice root system architecture on microbes that could reduce methane emissions.
- Genomic and chemical analysis of the soil microbiome of rice paddies, with the ultimate aim of optimizing more long-term carbon storage in the soil and reducing greenhouse gas emissions.

Together, these projects aim to realize a vision of a net-zero farm that maintains food security with reduced input from farmers and greenhouse gas emissions, and use farming to capture and store more carbon from the atmosphere.

How can gene editing be used to help reduce poverty and malnutrition?

— One in four people globally, and rising, are unable to afford a healthy diet. COVID-19 has exacerbated this trend by disrupting food production and distribution, driving up by 20 percent the number of people threatened by hunger in 2020. The pandemic is unfolding amidst an environmental and climate crisis which is undermining food production and our ability to nourish the world. The IGI recently partnered with CGIAR, the world's largest publicly-funded agricultural research partnership, to harness the power of science to help millions of people overcome poverty, hunger, and malnutrition. The IGI is testing technologies with great potential to benefit people in the countries where CGIAR is active, such as a way of removing the cyanide found in cassava[1] and fighting diseases in economically important crops like wheat, rice, and bananas. We are using technologies such as gene editing to accelerate the development of more disease-resistant, water-efficient varieties that can improve food production and nutrition in areas that are especially vulnerable to climate change.

1 **A staple upon which nearly a billion people depend.**

"There are now half a dozen clinical trials of CRISPR therapies for sickle cell disease underway already."

THE ETHICS OF GENE EDITING

What do you think is the future of biology and CRISPR?

— There's a lot of evidence that we're entering an era in biology in which we have increasingly, at our fingertips, a collection of tools that allow manipulation of biological systems in controllable ways. Those capabilities will advance, the kind of things that have only been dreamt of in biological systems to a point where we can actually achieve them. Imagine that someone gets a diagnosis for a condition. They could have gone to a company like 23andMe or Color Genomics, and they have their DNA sequenced. And the result comes back that they have susceptibility to Alzheimer's disease in the future. Today, that kind of information is not directly actionable. Whereas imagine in the future, it's possible to use a technology like CRISPR to change those genetics so that that person no longer has that susceptibility. That would be extraordinary if we get to that point. Will we get there in 30 years? I don't know, but I think it's entirely possible that we will.

"Imagine in the future, it's possible to use a technology like CRISPR to change those genetics so that that person no longer has that susceptibility [to Alzheimer] "

What worries you most about the transformative impact of CRISPR?

— It is important to remember that what we're talking about here is effectively changing evolution. It's changing us at our core and going back to the instruction manual that makes us who we are and making changes there. When we talk about it in the context of a disease like sickle cell disease that is so debilitating, it certainly seems like this might be something that some families might want to consider eventually, especially if the technology is vetted carefully and shown to be safe. But the broader issue really is equity, access to technologies. Who decides about something like that, something as profound as that? Who pays for it? Who has access to it? I think it gets complicated quickly. In a most extreme case, you could imagine that someday, couples, go to an in vitro fertilization clinic, and they receive a menu? And they can decide what types of traits they want for their children. This raises a number of ethical questions that we have to carefully consider. And this is why I and my colleagues have called for a global pause in any clinical application of the CRISPR technology in human embryos, to give us time to really consider all of the various implications of doing so.

So, is there any solution? How can we prevent this worst-case scenario?

"A global pause in any clinical application of the CRISPR technology in human embryos gives us time to really consider all of the various implications of doing so."

— By 2016, the US Government had designated gene editing as a potential weapon of mass destruction . The same year, the Defense Advanced Research Project Agency (DARPA), set up a program called Safe Genes which had a goal of building tools to counter bioterrorism threats including weapons that employ CRISPR itself. That solution lies in what's called as anti-CRISPR molecules that nullify the effects of CRISPR. My team and I are investigating the development of novel, safe gene editing tools for use as antiviral agents in animal models, targeting the Zika and Ebola viruses. As part of the DARPA project, we are also aiming to identify anti-CRISPR proteins capable of inhibiting unwanted genome-editing activity, while developing novel strategies for delivery of genome editors and inhibitors.

THE BROADER ISSUE REALLY IS EQUITY, ACCESS TO TECHNOLOGIES [SUCH AS CRISPR]. WHO DECIDES ABOUT SOMETHING LIKE THAT, SOMETHING AS PROFOUND AS THAT? WHO PAYS FOR IT? WHO HAS ACCESS TO IT?

WOMEN IN SCIENCE

You and Emmanuelle Charpentier are among the very few women recipients of the Nobel Prize. What are your views on women in science?

— It's important for young girls and women to be able to see themselves as a scientist. When I was growing up, it was a woman scientist researching cancer who redefined my image of a scientist and inspired me to pursue my passion for chemistry, despite being discouraged from it by many others. We need to celebrate the contributions of women researchers, mathematicians, and engineers to encourage more women to pursue careers in science by underscoring the fact that science is a field where women can thrive and where we belong.

You work with supporting women in science. Can you elaborate on that?

— A recent Harvard Business Review study found that female founders in biotechnology only received 2.3% of venture capital funding in 2020 . I've found being an entrepreneur in the biotech world incredibly exciting and rewarding. But too few women have the opportunity to become entrepreneurs, even though a lot of the needed innovation today is coming from women researchers. If women have the dream of founding a company based on their research, the barriers that stand in their way need to be removed. At the IGI we recently announced the launch of the Women in Enterprising Science Program. The objective is to support aspiring entrepreneurs seeking to translate genomics research into impactful solutions to real-world challenges and advance the representation of women founders in biotechnology.

Is there anything that you wish the general public understood better about the science that you've developed?

— I think it's important to understand that technologies like CRISPR, more often than not, come out of fundamental curiosity-driven science. So, it really is important to support that kind of work, in concert with people that are taking those discoveries and applying them. Something like this doesn't just get created. It has to be uncovered by a more stochastic process of fundamental science.

> **"Technologies like CRISPR [...] come out of fundamental curiosity-driven science."**

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"Female founders in biotechnology only received 2.3% of venture capital funding in 2020."