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Undergraduate

The Function and Future of CRISPR Gene Editing

Interview with Dr. Jennifer Doudna



BY LIANE ALBARGHOUSHI, EMILY MATCHAM, KAITLYN WANG, ANANYA KRISHNAPURA, AND ELETTRA PREOSTI

Dr. Jennifer Doudna is a professor in the Departments of Chemistry and Molecular and Cell Biology at the University of California, Berkeley. She is also the Li Ka Shing Chancellor's Chair in Biomedical and Health Sciences and a Howard Hughes Medical Institute Investigator. Dr. Doudna is currently the president of the Innovative Genomics Institute (IGI), an organization focused on applying genome engineering to global problems. In October 2020, Dr. Doudna was awarded the Nobel Prize in Chemistry alongside her colleague, Dr. Emmanuelle Charpentier, for their development of CRISPR-Cas9, a powerful gene editing tool. In this interview, we discuss the implications of CRISPR technologies for society, as well as how to ensure equitable access to gene editing therapies in the future.

BSJ: You have recently collaborated with researchers at UC Berkeley and the Gladstone Institutes to develop a CRISPR-based COVID-19 diagnostic test that uses mobile phones to detect SARS-CoV-2 within half an hour. Could such examples of the versatility of CRISPR technology change the way society perceives scientific discoveries?

JD: I certainly hope so. This past year has demonstrated in real time the value of science and technology in the context of understanding how to detect and fight back against viruses. When a technology like CRISPR is used to address ongoing real-world issues, like detecting the COVID-19 virus, it elicits greater public appreciation for the value of the science that led to the technology.

BSJ: Since 2012, research has uncovered the potential of several other Cas proteins aside from Cas9. How are these proteins functionally different from one another, and what is their significance in the context of CRISPR?

JD: What is really interesting about CRISPR is that it is highly variable in nature. Naturally, CRISPR is a part of the immune system in bacteria, and there are many different versions of it. This is likely because viruses are evolving all of the time, so for the bacterial immune system to be effective against viruses, it also has to evolve. CRISPR works as an immune system by cutting up foreign DNA and RNA. Each CRISPR system has its own molecular scissors in the form of a Cas gene. What makes these Cas genes so interesting biologically (and technologically) is that when we look into the details of how they work, they are each a little bit different. For example, the Cas9 protein, the first type of CRISPR-Cas we studied with our collaborator, Emmanuel Charpentier, turned out to be a very robust tool for changing DNA in cells. Another type of Cas protein called Cas12 can also act as a programmable system in bacteria and as a technology for genome editing. However, Cas12 has an additional biochemical activity that allows it to work as a diagnostic. When Cas12 detects the presence of DNA, it can then trigger a fluorescent marker, which is something that Cas9 does not do. It is really interesting to see how that difference in behavior at a molecular level dictates how these proteins can be used for different technologies. Cas9 is a great genome editor, but it is not a great diagnostic, while Cas12 is an okay genome editor, but it is a great diagnostic.

BSJ: You have previously said that there is a growing disparity in biomedical research between diagnostics and therapeutics. Can you briefly describe what you mean by this disparity? What needs to be done to propel further research or studies centering on therapeutic applications of genome editing?

JD: One thing that comes to mind is thinking about whether people are able to access these technologies. As exciting as CRISPR is, as a technology, it is only going to be impactful if people can access it, afford it, and benefit from it. That has really been the focus and goal of my work over the last few years at the Innovative Genomics Institute. In the case of diagnostics, it would be great if CRISPR could be used as either a point-of-care test or an at-home test for virus detection. With enough research, I think that this could be possible. However, it will be harder to achieve affordability and accessibility for therapeutic applications of genome editing since there are several steps that need to happen in order to make sure the technology is safe and functional. Understandably, all of those steps would add up to a significant cost of treatment. However, by paying closer attention to the steps in that process, we can start to reduce the financial burden.

BSJ: It is essential for bioethicists, scientists, clinicians, and regulators to work together to ensure safe, effective and affordable outcomes. Given that many of these stakeholders have disagreements about genome editing, what possible additional steps

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need to be taken to ensure efficient collaboration moving forward?

JD: Collaboration is critical in science and is responsible for much of the progress that is made. As smart as any one scientist might be, nobody has all of the ideas. From my experience, it has been great—and certainly more fun—to work collaboratively with other people on projects. That being said, how do we make sure that technologies move forward in a responsible way such that other stakeholders benefit from, and are not harmed by, the technology? How do we make sure that they are engaged and informed and that their points of view are taken into account? These are hard questions to answer since there are a lot of potential stakeholders. We need to ensure that we are reaching out to people and working in an open, transparent environment. The way that I have been approaching this is to start by engaging with people who are interested in CRISPR—some of whom may be stakeholders who agree with us and some of whom may be looking at this issue with a different point of view. I still remember a conference we had sometime in the last five years that focused on agricultural uses of CRISPR and genome editing. In addition to scientists and bioethicists, we also had people attend who were very anti-GMO and believed that one should not manipulate the genome of any animals or plants. It was a fascinating meeting. The good thing about it was that although people did not share the same viewpoints, they were willing to listen and discuss. I think that is

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Figure 1: Illustration of Cas9. After the single-stranded guide RNA in the CRISPR-Cas9 complex recognizes the target DNA sequence downstream of a short protospacer adjacent motif (PAM), the Cas9 nuclease proceeds to cleave the target DNA.

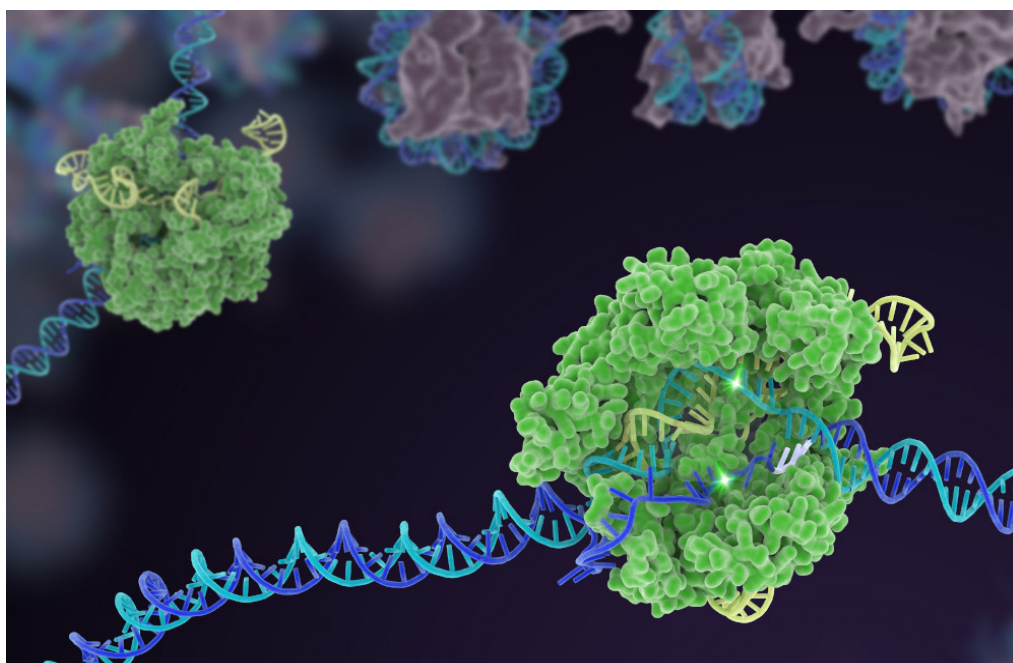




Figure 2: Image of COVID-19 Testing Lab Robot at the Innovative Genomics Institute (IGI).

where progress starts. Even if individuals have different perspectives on something, we can make progress if they are willing to discuss their differences. The goal is to create that open community and environment where people feel comfortable discussing their ideas, even if they are not in agreement.

BSJ: What technical or general advice do you have for undergraduate researchers to be more innovative and imaginative with science?

JD: In my experience, a lot of the most creative ideas actually come from people like yourselves who are new to an area of science. They come to the field unbiased by other ways of thinking and ask key questions. I have had college students come to the lab and ask the most probing questions that make us step back and consider, “Why am I doing this?” They make us stop and think. For all of you who are going into science, be willing to ask these questions—you might actually be cutting right to the heart of something that is really, really important to discuss. Secondly, follow your passions. I think if you are really curious about something, that curiosity will often drive innovation and creativity; that certainly was true for me. When I began my work on CRISPR, it was a field that had just started off with a handful of scientists, and they were not working in fancy labs and publishing papers in fancy journals. They were just microbiologists who noticed an interesting

“I think if you are really curious about something, that curiosity will often drive innovation and creativity.”

phenomenon in bacteria fighting back against viruses and wondered how it worked.

This interview, which consists of one conversation, has been edited for brevity and clarity.

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