CONVERSATIONS WITH MIKE MILKEN

Jennifer Doudna

Biochemist, University of California, Berkeley; Founder, Innovative Genomics Institute (IGI); Co-inventor of CRISPR technology; Nobel Laureate (2020)

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Mike Milken: So Jennifer, it's been about four months since our last podcast. A lot has happened. Congratulations on winning the 2020 Nobel Prize in Chemistry. You were awakened from a sound sleep by a reporter at 2:53am, learning for the first time you had won the Nobel prize. You pointed out, I think, this prize refutes the idea that women will not be recognized for their work. It makes a strong statement that women can do science, women can do chemistry, and that great science is recognized and honored. So Jennifer, congratulations. We couldn't be more happy for you, your work, but even more important what your work's going to do – to improve life on earth.

My first question, has anything changed since then phone call at 2:53 in the morning?

Jennifer Doudna: Well, I'd like to start by thanking you Michael, for inviting me. It's a real pleasure to be here. I would say yes and no, in the sense that my science carries on as it has been, and that's what I really am passionate about. But what's changed is the attention to the science. I think the opportunities right now to really serve as an ambassador to science and point out the importance of recognizing fundamental discoveries and the value in investing in fundamental research. That's been really exciting. And also, just

This interview has been lightly edited for clarity and readability.

having the opportunity to connect with a lot of people that I'd lost touch with. People from my elementary school have reached out. The House of Representatives in Hawaii sent me a letter signed by every single member, and I feel a lot of pride coming from my home state. So that's really been very exciting for me personally.

We can now genetically change human beings. Some people said it was kind of spell check for a genetics: when we have one of the little letters wrong, we can change it. But for our listeners, before we really get into the opportunities that your discoveries bring, I'd like you to talk a little bit about what is CRISPR?

I love the spell check for genetics analogy. That's great. I hadn't heard that before. I think it's a pretty good one because CRISPR is a technology for editing the code of life. We've had for a while the ability to synthesize molecules of DNA; we've also had the ability over the last few decades increasingly to read the code; we can sequence DNA. We have the sequence of the entire human genome now that's been available for the last two decades. And what hasn't been possible up until now is an easy way to manipulate the code, allow scientists to make a change to an individual gene or to a set of genes; to understand, first of all, how they work, but also really importantly make changes that correct disease causing mutations. That's what CRISPR now enables.

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Well, the promise is just so unbelievable when you think about it. I'd like to really focus today's talk on the Innovative Genomic Institute at UC Berkeley, which you founded in 2014. And in the wake of this pandemic, how can CRISPR help us regain health? How can the IGI help scale up testing globally to regain our health and our feeling of safety?

It's a great question. And I think it speaks to the heart of the purpose of the Innovative Genomics Institute, which is to make genome editing and all of the associated technologies available and affordable to people globally to address healthcare issues that we know this technology will be able to address. I'm excited to have an institute established now at the University of California, Berkeley, and in partnership with the University of California San Francisco, that allows us to bring together scientists who have the right expertise to take fundamental discoveries, which is where CRISPR came from, and apply them in the clinic. And we're also doing a lot of work in agriculture to address climate change. Those are really our two big focal points.

In terms of how we use this as a way to feel safe again, I'll give you a very specific example. So, when it became clear early in 2020 that there was a pandemic emerging, the IGI was able to institute a clinical testing lab in three weeks. We got a pop-up lab going, and we've published how to do that, so we put the blueprint out there for others that wanted to do as we have done.

And since then, we've now tested well over 100,000 clinical samples for COVID-19 diagnosis, and we've been able to partner with a number of community healthcare groups to provide the testing importantly, to people that would otherwise have had no access. So, this means people living in homeless encampments, nursing homes, and many frontline workers. We routinely now test our police, our fire support personnel, California Energy Commission, the people keeping the lights on around the state of California. One of the really interesting things about CRISPR is that it's also a great technology for diagnosing viral infection. We know this will be a useful technology for diagnosing other viral infections in the future, influenza, and even getting ready for other pandemics if they should emerge in the coming years.

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Two of the early vaccines are the Moderna vaccine and the Pfizer that use mRNA technology, a new technology for vaccines. And when we look at AstraZeneca or J&J, we're seeing more of a vector technology, a more traditional type vaccine technology being developed. In terms of regaining this feeling of health with these two new technologies, what role can CRISPR play in that area?

Diagnosis goes hand in hand with vaccination and of course, with therapies as well. What CRISPR is doing is providing for rapid turnaround testing at a lower cost and higher throughput than we've had with other technologies. We'll see that happening in various testing labs, certainly around the U.S.

Time will tell how durable those, those RNA-based vaccines are. If they really induce a long lasting immune response remains to be seen, but certainly I think one of the things that from a scientific point of view is very exciting that I think everybody needs to appreciate, is that those RNA vaccines, first of all, they were incredibly fast, right? It's extraordinary to think that a year ago we didn't even know about this virus, and now we have two different RNA-based vaccines that look highly effective in these early studies because of fundamental research that was done years ago in an academic setting and then later in companies to develop RNA as a delivery vehicle. It's very effective in inducing an immune response, so my hope is it'll be possible in the future to use this as a more general approach that will allow vaccines to be developed much faster than they

have been in the past. And maybe to also do other things where RNA delivery will be effective as well.

Every human life is priceless, but when we make economic arguments – more than 50% of all economic growth has come from advances in public health and medical research for the last two centuries –what role can the IGI play in this feeling of maintaining health of the general population?

The IGI is about science for the public good. In addition to supporting first-rate science that addresses real world challenges, we're also all about making sure that we're doing always with an eye towards affordability, accessibility, and availability to people globally. The IGI really seeks to play an important role educationally with outreach, making sure that it's clear why we do what we do, welcoming people to come and visit us. We have a visitor's day every year where we welcome people of all ages to come in and talk to us, find out who we are, what we're doing and give us feedback. We loved hearing people's reactions to our work and to engaging with us in whatever way would be helpful to them.

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Philanthropy today makes about 3% of what goes on on research and biosciences and life sciences, between for-profit companies and governments. Part of the reason I've asked you to join me is just to reemphasize for individuals how important the investment is in organizations like the IGI, to give you the flexibility and the public funding here for the Institute. When we analyzed our own philanthropy over three to four decades of our foundations, the highest rate of return we can measure on changes in society has been to fund science, particularly life sciences. When we talk about bioscience, we're not just talking about a person's health, we're talking about the environment, we're talking about agriculture, air, water, and ultimately energy. How can someone interact with the IGI and see your work that's going on?

Well, first of all, we invite everyone to visit our website, www.innovativegenomics.org. And if you go there, you'll see that we have a very nice introduction to our work and our mission. Another is our Ask a Scientist Forum. Many people have questions, whether it's what is CRISPR, or how is CRISPR going to affect me? What do I do if I know somebody that has a genetic disease that could benefit from CRISPR? Where do I go? How do I get information? Those are all the kinds of questions that can be addressed by our panel of scientists who will respond very quickly in real time to those kinds of queries.

And then thirdly, for many people who are giving presentations, whether they are high-school teachers or students, we have a lot of various types of media available for people if they want to use slide decks that we put together that explain CRISPR. We've got some really cool videos that explain fundamentally about the technology, but also importantly about how it's being deployed and all of the associated factors that go into decisions about using genome editing as a solution to healthcare or agricultural challenges. So these are the kinds of things that everyone can get access to through our website and through our Ask a Scientist program.

We've regained confidence in our health system. Now let's focus on improving. We understand sickle cell or cystic fibrosis that we've identified a particular gene, and maybe we can "correct" that gene. A woman is diagnosed with triple negative, the genes that would make her likely more likely to get an aggressive form of breast cancer. We know there's certain mutations, for example, in prostate cancer that are found in 73 other forms of cancer, and found often colon cancer, breast cancer, ovarian in higher percentages than you would find in prostate cancer. If we could change the genes that accelerate and increase the probability of us getting life-threatening diseases, even from birth, it would be a totally different world for us to live in. What can we do to help you accelerate that day?

One of the things that I see as a really exciting opportunity is the ability to proactively act on genetic information as you just indicated. Imagine a day when each of us has access to our own genetic information and we know what are some of our genetic susceptibilities might be. Instead of having to just hope for the best, we actually have technology based on CRISPR that allows us to make changes to our genetic makeup in the right tissue types where they can have a proactive, protective kind of effect.

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And I guess the example that is I think very real in a way in terms of real opportunity is a way to protect against cardiovascular disease. The idea that one could use genome editing to give all of us a protective gene that is known to, in a few lucky people that inherit this naturally, have a protection against high cholesterol. And they also have very few incidences of cardiovascular disease over the course of their lifetime. Imagine that you could distribute that protective gene through the population. That'd be huge if we could do something like that.

Then you can start to imagine how that sort of proactive genome editing could be used in other diseases as well, or to protect against the examples that you gave with cancer and being able to use genome editing to correct a disease-susceptibility gene in the tissue. Now, I think that's still a ways off; I don't want people to come away from this

conversation thinking that we're a year away from being able to correct BRCA1 mutations in people that would give them protection against breast cancer, for example. But I do think that in the coming decades, it will become increasingly possible to not only predict these kinds of genetic susceptibilities, but also to deploy CRISPR.

What we really need to do right now, Michael, is we do need to figure out how to deploy CRISPR in clinical settings, patients in C2, meaning in their body without having to take cells out to do the editing in the lab and then put them back, there's still some fundamental research that needs to get done; we need to figure out what I call the challenge of delivery. I'm very optimistic about this, but it's going to take investment and it's going to take recruiting some of the best minds and young talent into the field. Together, I don't think there's anything that we can't achieve if we focus on this.

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When we felt we needed to figure out how to accelerate innovations, in 2011 we put on an event and we brought about 80 to 90 people from varied backgrounds to Lake Tahoe to sit down for three or four days. One of the things that grew out of it was NCATS, the National Center for Advancing Translational Science, that became a new center at the NIH that the U.S. government agreed to fund for $500 million to $600 million a year for 10 years. Chris Austin was the first head of the center and still is today.

We felt the disease-specific foundation where you had a group of people very focused on a specific disease, and FasterCures is interacting with almost 190 to 200 and helped launch many of them with the idea that a group of people that are focused on a particular disease could help accrue patients faster to clinical trials, focus on the issue and target money. So I think the question is, there's a lot of people listening to this podcast. Is there something that they could do so it'll be five years instead of 10, it'll be 10 instead of 15? What can they do as it relates to new standards of clinical care? Is there something that would be helpful besides just financial support? What could shorten this timeframe, as you look out?

It kind of gives me chills when you say that, because it's so, so exciting to think about that day coming, and how can we get there faster? You put your finger on the fact that we obviously need resources, but it goes beyond money. I love what you said about NCATS and the ability to pull people together. I do think that's one of the really powerful things that the IGI is doing, is creating a community of scientists who are working together. And here's the thing you might not have expected, that there would be obvious value in having plant biologists working right next door to people that are doing T-cell therapies.

But we've found that those scientists have an extraordinary opportunity, in a way, when they are rubbing elbows to exchange ideas. We've had some really interesting technical advances come out of those kinds of collaborations that have led to better ways to deliver genome editing molecules into different kinds of cells, whether it's in plant cells or T cells or other types of human cells.

I think that's something that I really want people to understand; IGI is breaking down traditional academic silos. And the other thing is that financial support is critical. We welcome opportunities for philanthropic support at IGI, but also for various kinds of partnerships. We have a number of company partnerships right now that are really useful for advancing the science quickly.

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I'll come back to the example of facing the COVID-19 pandemic, and the way the IGI was able to quickly put up a clinical laboratory at Berkeley where we don't have a medical school. Why were we able to do that? Honestly, it was because we had the staff and the infrastructure at the IGI to quickly work with state regulators, federal regulators, with our university president's office – all of those groups had to be involved to get this to work. Having this Institute is truly enabling, and having it embedded within a world-class university is just extraordinary. I welcome all of the folks listening to learn more about us, reach out. We'd love to have your partnership, whether it's financial or scientific or otherwise to move forward on all of these goals that I think we share.

I do hope that we can find a way to accelerate your work from decades to a decade. Thank you for joining us today, and we wish you all the best. Congratulations, and I couldn't be more excited about the future of the IGI.

Thank you so much, Michael. It's great to chat with you.