CONVERSATIONS WITH MIKE MILKEN

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Mike Milken: you for joining me today.

Jennifer Doudna: Thanks for inviting me, Mike.

I thought I'd start with just a quote here – "one of the most monumental discoveries in biology" – from one of the world's leading newspapers about your work on CRISPR. That was a very powerful statement and obviously is going to change the world. But I'd like to step back and how a young girl from a small city on the big Island of Hawaii, Hilo, and this American dream that you've led Jennifer and the role model you're going to play, not only for women who might want to go into science but anyone that wants to go into science.

"We really think about how genome editing will impact human health in the future and curing genetic diseases, and also how it will impact our planet as we grapple with climate change."

Hilo 1971. That's when I moved there with my family, I grew up in a

This interview has been lightly edited for clarity and readability.

wonderful environment of the Big Island learning about how evolution had shaped all of the plants and animals that ended up there. And honestly, Mike, I think that actually was one of the reasons I wanted to go into science. I just was fascinated by the incredible variety of life that you could find in that environment and wondered how it came to be. So it was a very special place to be growing up. At the same time, I have to say that it had challenges. When people think of Hawaii, they think of beautiful beaches maybe, and you know, sipping mai tais or something. For me though, as a white girl or a howlie, early in the seventies I was not always the most popular person. And there was a lot of discrimination that I had to deal with. And I do think that for me, one of my respites actually from that was to retreat into the library. In those days, we didn't have the internet.

"A lot of bacteria have an adaptive immune system that allows them to, in real time, respond to viruses that infect bacterial cells. This system called CRISPR. It's increasingly apparent that our microbial populations in our bodies have a huge effect on our health, everything from cancer to dementia and everything else."

I was trying to understand where I was living and what was happening around me and, books were my solace . The other thing was that I found I loved doing puzzles and this came from my dad. He was a literature professor, but he loved doing crypto quotes. He loved solving all kinds of puzzles. He really encouraged my interest in mathematics, and so I think that that combination really made me think, 'gee, this would be a lot of fun to do in the future.'

Eventually you decided to come to the mainland and to go to Pomona, one of the five Claremont colleges. What was that experience like for you?

Big culture shock. I was only 17 when I left home to go to college. It was a big change quite honestly. That being said, the science that I learned at Pomona really set me up for what I did later. I met incredible people there and and I really came into my own in a way, in terms of my love of learning and taking that passion in a new direction. Nobody in my family was a scientist. So in many ways when I got to college, I really felt like I was forging my own path for the first time.

So most people don't realize that the Claremont colleges really, there are five schools that make them up: Pomona, one of the leading liberal arts schools in the world, where you went; Harvey Mudd, which I think last time I checked in terms of test scores of students coming in, heavy math, science, computer science, had the second-highest test scores of entering freshmen; a woman's college, Scripp's; Claremont McKenna; [and Pitzer College]. But you had five parts of that world that you can interact with.

One of the really interesting things about being in that Claremont college environment was that each of the colleges that you just mentioned had its own personality and yet they were all adjacent to each other. So at some level you felt like you were part of one big uber college in a way, and yet each school had its own its own culture. For somebody like me coming from a small town and going into a new area of learning that I didn't have anybody in my family to kind of lean on about it, it was quite a nice place to do that because it felt safe in a way.

So a young girl, who's about to make one of the greatest discoveries in the history in biology and life sciences, then ventures out from California and begins the journey that takes her to Harvard and Harvard Medical School, University of Colorado, Yale, and eventually to Berkeley. Along that journey, how important were mentors in that process?

"Our work on that system – CRISPR – led to a fundamental understanding that allowed us to propose the system as a technology for genome editing, which means being able to rewrite the DNA sequences in any cell – human plant animal or bacterial – to allow cells to reprogram genes in a precise fashion."

I've just really encountered wonderful, supportive people at every step in my career, which has been amazing. I never imagined that my life or my career would go in the direction that it did. I just followed my passion really. I kept asking myself, 'I really liked doing science. How can I do more of it?' But that being said, you just indicated I did encounter incredible mentors. At Pomona, I had a wonderful professor of biochemistry who went by Sharon Penesanko in those days; she's now her changed her name. She was very tough in a way, but she was also very supportive, and I think that's a great combination. She pushed us as students to do our best, and she also really encouraged us to trust ourselves. That's something that I needed to learn. And then when I got to graduate school. I was the most shocked of anybody that I got accepted to Harvard. I sort of put it in an application on a lark and when they let me in, I thought they must have called the wrong person. When I got to Boston to get another bit of a culture shock, but quickly found a good cohort of people there who were like-minded in our interests and our passions.

I ended up working with a fantastic scientist there, Jack Szostak, who was widely reputed to be kind of a young genius. I thought his ideas were really exciting; he was very passionate about this work. Then when I left Harvard, I went to Boulder, Colorado, as you mentioned, and there I worked with Thomas Cech, another just extraordinary scientist; very different style than I had my mentor in graduate school, but equally brilliant. And, he also pushed us to do our best and be rigorous scientists. At the end of that training period, I realized that I loved working in the laboratory with other people and especially with students. So I decided to pursue that work in an academic position that I was fortunate to get at Yale. I moved back to the East Coast and that's where I launched my initial independent work.

You flourished at Yale, but eventually decided to go to Berkeley. So many people told me you went because it was halfway back to Hilo. I told them no, as a graduate of University of California, Berkeley, they had the most known Nobel Prize winners in the sciences. What brought you to Berkeley and how nurturing an environment was that for yourself?

I had been a faculty member at Yale for eight years at the time and Yale had treated me very well. I had been tenured. They gave me a Henry Ford II professorship, which was again really extraordinary for me; kind of shocking. I guess what happened for me was really two things. One was realizing that my initial scientific interests were broadening out and that, although Yale had been a fabulous place for me to get started, that I felt that there opportunities I wanted to pursue scientifically that were open to me at a very large, diverse public university like Berkeley that were just not as apparent at Yale. And secondly, as you said, it also was halfway back to Hilo; that did not escape my notice. I found that it's a place that has incredible natural beauty, it's situated right across the San Francisco Bay from one of the world's greatest cities, and it felt like a gateway to the Pacific and the South Pacific and to Asia. That made me frankly, feel more connected to my roots in Hawaii. So for many reasons, it just felt like the right thing to do.

“We are creating a community of scientists that are doing two things: not only extending this extraordinary science and thinking about how to apply genome editing in ways that will have real impact on humanity, but also doing it with an eye towards social responsibility. How do we make sure that a very powerful tool is used in a transparent and appropriate fashion?”

I just want to repeat Jennifer, your discoveries will change the world for every human being. I have spent four to five decades working in medical research and trying to accelerate it, and our studies, particularly in the microbiome that we can maybe change the way your genes are expressed. But in many ways, all of our research and all of our work is going to over time change dramatically by your discovery. The idea that we can edit our genes, the idea that those that are about to be born with diseases such as cerebral palsy or cystic fibrosis, things that are dramatically going to affect the quality of someone's life, that they can be “edited out.” A generation from now how we look at disease or serious disease or inherited diseases will totally change. So, you've returned

to Berkeley, and a few years later you publish your work. Tell us about what led up to the publishing of your work.

One of the most interesting things about doing science as I do is that you never know what is going to come next, and that makes it a lot of fun. It's kind of an adventure. That was certainly true for the work that we did on a system called CRISPR, which is an acronym [clustered regularly interspaced short palindromic repeats] that represents a bacterial immune system. It's literally a way that bacteria fight viral infection. For many people listening, this sounds like a very obscure area of biology and you're right. It was a very obscure area when we started to investigate it back in the mid-2000s.

The reason I got into it and got interested in it was through a colleague at Berkeley. This is the thing that's so great about being at a university like this is that we're surrounded by creative, innovative people who are working on all sorts of interesting problems or projects that I would otherwise have never had any knowledge of. And in the case of CRISPR, it came to my attention because of a colleague, Jillian Banfield, who had established a fabulous research program studying bacteria in the environment. These are important for everything from industrial processes to winemaking to making various kinds of food products like cheese and yogurt, and also to understanding human health.

As you said, Mike, it's increasingly apparent that our microbial populations in our bodies have a huge effect on our health, everything from cancer to dementia and everything else. Jillian Banfield is one of the world's experts in studying these microbes. She had uncovered a fascinating example of something that scientists at the time had no knowledge of, which was basically evidence that a lot of bacteria have an adaptive immune system that allows them to, in real time, respond to viruses that infect bacterial cells. And this system called CRISPR, at that time around 2005 was just a hypothesis. It was just an idea based on some observations in a handful of labs around the world, but nobody at the time had actually done any experiments to test this idea that a bacterial immune system could really function as an adaptive system. And that's where I got involved.

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So I started working on it after Jill had called it to my attention. And you might wonder why did I do that? Well, I've had a very long-standing interest in the evolutionary basis for life, and more specifically in understanding how various organisms are able to control their genes, how they control the genetics that allow them to adapt to their environments.

We can learn a lot about ourselves by studying how other organisms interact with the environment. So we started to investigate CRISPR, and that eventually led to a remarkable international collaboration with another scientist, Emmanuelle Charpentier, to study a specific protein known as CRISPR-Cas9, and figure out how it works to protect bacteria from viruses. Our work on that system led to a fundamental understanding that allowed us to propose the system as a technology for genome editing, which means being able to rewrite the DNA sequences in any cell – human plant animal or bacterial – to allow cells to reprogram genes in a precise fashion. And that's really what CRISPR is. It's a tool that allows scientists to in a precise fashion change the genes that make up an organism or a cell, and allow that those genes to be manipulated and changed in ways that will have extraordinary impacts on agriculture as well as biomedicine and various kinds of manufacturing in the future.

"CRISPR proteins are quite useful for detection of viruses. They can report on the presence of a virus in real time and with a visual signal in a way that I think could be a very powerful diagnostic tool in the near future. Having an emergency like [Covid-19], if there is a silver lining, it's that I think it does catalyze and focus everybody's attention to get work done quickly that might've otherwise motored along, but maybe not as quickly as it is now."

More than 90 percent of all the genes in the human being are not human, they're bacteria. And so when you think of your body, the work that we've spent four or five decades working on, if we could change from bad bacteria "good," we might be able to change the outcome without being able to change your genes. Now, when we talk about CRISPR-Cas9, I remember when I was trying to explain this to our oldest grandchild, I described it as just imagine that you're going through your paper and you notice that you have a few letters that are wrong. CRISPR-Cas9 allows you to potentially to correct those letters, those mutant letters that have jumped into your story. This has the potential, as you've pointed out, not only to potentially change an individual who might have a life-threatening disease, but also to correct it in agriculture and other things; to improve the quality of everything. Eventually you form the Innovative Genomics Institute, IGI, in 2014. Can you talk to us about what led to the formation of this institute?

We published a paper in 2012 that described the biochemical activity of CRISPR-Cas9 and how it could be used for genome editing. And at the time that I published that paper, and I still remember this moment like it was yesterday, submitting that manuscript to a scientific journal, and almost feeling like I was firing the starting gun at a race. Because I knew that people would read this paper, and if the work is interesting and they think it can be useful in their own work, they quickly get on it. And that's exactly what happened. So quickly, the CRISPR-Cas9 technology was adopted by other laboratories who started using it for all kinds of human genome editing. Someone was quickly able to make changes to zebra fish; so fish embryos that showed that you could manipulate the genes in a whole organism. Sometime later in 2013, I went to my dean at Berkeley and I basically walked him quickly through the data and he got it immediately. And he said, this is extraordinary; what should we do? And I said the world is changing and biology is changing – this technology is going to be truly transformative. I can't really tell yet all the directions it's going, but I really want to be building on this technology here at Berkeley and making sure that we are creating a community of scientists that are doing two things: not only extending this extraordinary science and thinking about how to apply genome editing in ways that will have real impact on humanity, but also doing it with an eye towards social responsibility. How do we make sure that a very powerful tool is used in a transparent and appropriate fashion? That's a tall order. So the Innovative Genomics Institute, from the very beginning, and by the way it was founded with my colleague, Jonathan Weissman at UC San Francisco. So we from the very beginning conceived this as a joint campus institute that would really allow scientists to use genome editing and develop the next generations of genome editing, but always doing it with an eye towards social responsibility.

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How can one learn more about the Innovative Genomics Institute if one wanted to learn and potential applications and interact? Because I know you have more than 100 researchers, scientists involved with the Institute today. What is the best way to engage?

We are a nonprofit organization that exists within the University of California. We work within the university, but that being said, we also have established quite an incredible team of people who are focused on the goals of genome editing and social responsibility. We really think about how genome editing will impact human health in the future and curing genetic diseases and also how it will impact our planet, as we grapple with climate change. And so we have projects that are in both of those areas. Largely those projects are supported by philanthropy, so we are incredibly grateful to our donors who have given money to support the work that we do. And for folks that are listening, I would love to invite you to learn more about the Innovative Genomics Institute, and you can go to innovativegenomics.org is our website. If you go there to the home page, you will see that there are a lot of stories about the work that we are doing right now. We have a lot of work that is COVID-19 related, as you can imagine. We run a clinical testing laboratory in the East Bay that is testing for free people that otherwise would not have access to coronavirus testing. And we're also working with our campus to help bring students back safely through regular testing as they re-occupy dormitories and that sort of thing. Beyond that, we have been continuing to work on ways that genome editing is going to impact people in the future. And I firmly believe that we need to make a concerted effort to make sure that this technology as it develops is available to everybody that needs it and can benefit from it.

Let's take biomedicine as an example. When you have a technology that comes along that is offers extraordinary promise, as you can imagine companies get going and people are looking for ways to commercialize technologies, which is entirely appropriate and makes sense when you have to invest a lot of money to develop therapeutics. But on the flip side, as a scientist and a citizen, I really want to make sure that the work that gets done on this technology also has an eye towards making sure that it becomes affordable and accessible as soon as possible. So that's really where we focus at our nonprofit. We're not looking to make money from CRISPR-Cas9. We're looking to make sure that as the technology unfolds, the work is happening in a way that will be as impactful as possible on people around the world.

"The CRISPR-Cas9 technology was adopted by other laboratories that started using it for all kinds of human genome editing. Someone was quickly able to make changes to zebra fish; so fish embryos that showed that you could manipulate the genes in a whole organism. This technology is going to be truly transformative"

So we launched the "Healthy Human, Healthy Planet" effort a number of years ago at the Milken Institute, with the idea that maybe half of the effect on environmental change comes from the food chain, whether it's wasted food, whether it's growing animals for people to eat, and that you can improve the health of individuals plus change the environment at the same time. Your discoveries, Jennifer and the Innovative Genomics Institutes efforts are far, far wider and reaching today. Could you talk about some of the practical applications that you see?

I think many people are familiar with the fact that when a baby is born every now and then there is a change in the DNA that is hard to predict, but leads to a genetic disease. Some examples are sickle cell disease, cystic fibrosis, Huntington's disease and muscular dystrophy. It would be really great if we had a way to not just diagnose those types of diseases as we do today, or give palliative care, but to actually be able to treat or cure the disease at its fundamental cause, which is the sequence of DNA that leads to that disorder.

With CRISPR, that's exactly what this technology in principle will allow. And I'm really excited that on sickle cell disease, the technology has already been shown to work. Some people may have the announcements a few months back about Victoria Gray who received a CRISPR treatment for her sickle cell disease, and she is now more than a year out from that having that treatment and is effectively cured of her disease, which is just extraordinary. It's incredibly inspiring to see her life changed in such a positive way with this technology. And it goes back to the issue of how do we make that now available to everyone that would want this. This is still going to require a lot of research and development, for sure, but also I think really paying attention to how that work is done in ways that will make the technology affordable and available to people, especially around the world.

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Another great example is treating a neurodegenerative disease such as Parkinson's disease or Huntington's disease, and maybe at some point even things like ALS or Alzheimer's disease. This is not going to happen overnight. This is not going to happen even in the next couple of years, for sure. But I think that many of us working in the field can see the opportunities for treating neurodegenerative disease using CRISPR technology. I think most of us know people that are affected by these types of diseases, and to have for the first time a technology that could in principle offer a cure is really very motivating.

My mother-in-law got breast cancer and we began funding breast cancer research in 1972. And over the years as we interacted with numerous and built numerous cancer organizations, what struck me is how many women would have mastectomies because they discovered that they had certain genes that made them highly susceptible to getting breast cancer. This, over the next we generation, might eliminate those fears by correcting or changing those genes. But it's a complicated issue and you want to make sure it's safe. When you develop a new technology, there was a fear as to what it would bring. Are people going to use it to make their children taller, smarter, impervious to pain, all these other potential applications that you discover. I know you are first focused on responsible development of this technology. How have you interacted with these fears that people around the world have had?

I think we think about it in a couple of ways. One is there's a very clear need to be communicating and articulating what the technology is. Maybe not going too deeply into the weeds, but just helping people understand what it does and what it can enable, where it is today, and where it's headed in the future. So that's certainly an important goal of the IGI. And of course, the University of California in general needs to be involved in very clear education for people so they understand what's happening with this technology and all of the associated things that come along with it. Being embedded at a great public university like Berkeley allows us to do our work, not only with the world's best scientists and working with the collaborators at UCSF, at Stanford, and of course all around the world for projects that we're doing and also with companies, but we also have on our campus some of the best people who think about sociology, history, economics and the law. So these have all been groups of people on our campus who have already gotten involved with work that we're doing, and we hope to engage even more going forward.

So that's really one thing that we try to catalyze at IGI. The other approach that we're taking to making sure that as much as possible we're encouraging responsible use of genome-editing technology, is to be working with the international community on projects that will encourage that kind of transparency and openness about about research. Over the last five years, we've been involved in a large number of meetings, some of them convened at the IGI itself, some of them convened around the United States or the world. We've worked with the National Academy of Sciences in our country and other countries to put on a couple of international summits; the next one will be held next year in the United Kingdom. And also increasingly with international organizations, including the World Health Organization, the United Nations and other groups that are keenly interested in technology developments as they impact either human health or our planet, our environment. I think that is also very important work that we do to make sure that we're integrated and that we're really leading a lot of those conversations.

As you think about all the innovations that occur, if not COVID-19, how can you protect us with your technology from the next virus that might come along? What have we learned and how could we use this technology and the enormous breadth of the Innovative Genomics Institute and the talent you have associated with us to accelerate our work, either in COVID or on the next potential pandemic that comes down the line?

As you well know at the Milken Institute, it starts with an incredible team of people who are nimble and able to quickly pivot to address things that come up. In our case at the Innovative Genomics Institute, I think we were very fortunate that we had a great team in place. When the pandemic was emerging in the early part of this year here in the U.S., we realized that we needed to pivot our attention at least in the immediate term to addressing this health emergency. And we decided that the most immediate thing that we could do is actually get a testing lab going. And at the same time, we also began supporting researchers in the Bay Area who were willing to quickly turn their expertise and their teams to working on projects related to COVID-19, whether they're developing new therapies, looking into interesting alternative strategies for vaccine delivery, or coming up with new diagnostics and on the diagnostics front.

This is where I think CRISPR genome editing technology has taken an interesting twist because it turns out that based on research that we did a few years ago and has now been done in Boston and elsewhere. We know that some types of CRISPR systems, CRISPR proteins, are quite useful for detection of viruses. And in fact, that's what they naturally do in bacteria. And not only that, they operate by a molecular mechanism that allows them to release a signal when they find their targets. So they can report on the presence of a virus in real time and with a visual signal in a way that I think could be a very powerful diagnostic tool in the near future. So the Innovative Genomics Institute as well as a number of other academic and company partners are now advancing CRISPR technology as a diagnostic.

"Nobody in my family was a scientist. So in many ways when I got to college, I really felt like I was forging my own path for the first time. I met incredible people there and and I really came into my own in a way, in terms of my love of learning and taking that passion in a new direction."

I certainly hope it impacts the current pandemic, but importantly, it's also a technology that can be deployed for detecting other kinds of viruses or other coronaviruses or anything else that has a unique sequence of DNA or RNA, that genetic material that CRISPR can find and report on. So that's really, really exciting. And I think having an emergency like this, if there is a silver lining, it's that I think it does catalyze and focus everybody's attention to get work done quickly that might've otherwise motored along, but maybe not as quickly as it is now.

You've laid down a new technology that over the decades will dramatically change how we treat people, how we focus on environment. Take us out 20 years here – how has the world changed?

I certainly think that we will see genome editing woven into everything that is going on on the research front, certainly in biology. I can imagine that it's only going to get exponentially faster and better than it is today. We're going to see our agricultural products affected by this; I should just mention that the question about genetically modified organisms always comes up, and the thing to appreciate is that first of all, everything we consume and grow agriculturally is effectively genetically modified because plant breeders have been introducing random changes to DNA and then selecting desired traits for a millennia. So there's lots of random genetic changes that come along with those desired traits. And with CRISPR, we now have a technology that gets around that need to introduce random changes because, in principle, it allows plant breeders to put into plants traits that are desirable and make changes to genes that impact those traits but not affect the rest of the genes in the plant. And so that has extraordinary potential. It means that in the future 20 years out, I suspect that a lot of the plants that we'll be using will be modified in ways that will allow them to be drought-resistant or resistant to pests that may be coming up more and more with climate change, but also things like making plants more nutritious, making them less toxic. These are all projects that are underway today and I think that in 20 years will be absolutely apparent to many people around the world.

Beyond that, I think that we're likely to see increasing use of CRISPR in the clinic. There are multiple clinical trials underway today that are targeted towards single-genetic, mono-genetic diseases like sickle cell disease, but I think increasingly we'll see an expansion of that whole set of applications to other types of diseases. And you mentioned cancer. What's really interesting is that CRISPR could actually be a very important technology that pairs with the whole area of cancer immunotherapy, which involves harnessing the patient's own immune system to go after cancer. I think that we'll see increasingly that CRISPR will be used to help program those immune cells to be capable of targeting other types of tumors that are currently possible.

Well Jennifer, your journey is a story of really advancing the American Dream. The curiosity of a young girl that ultimately is going to change the world for the better for all of us. You play as a mentor for so many people around the world as to the opportunities that are available. I want to thank you for joining me today. I wish you the best, and I wish I could spend more time in Berkeley with you.

Thank you, Mike. It's been great. And thanks for all the wonderful work that you and your institute are doing as well.
