The Economic Club of New York

117th Year
749th Meeting

Dr. Jennifer Doudna
Founder, Innovative Genomics Institute
Nobel Laureate in Chemistry
Co-Founder of CRISPR

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Moderator: Richard P. Lifton, Ph.D.
President, The Rockefeller University

Introduction

President Barbara Van Allen

Good afternoon and welcome to the 749th meeting of The Economic Club of New York. I'm Barbara Van Allen, President and CEO of the Club. Recognized as the premier nonpartisan forum in the nation, The Economic Club of New York stands as the leading platform for discussions on economic, social, and political matters. For more than a century, the Club has hosted over 1,000 prominent guest speakers contributing to our tradition of excellence which continues up to today.

As we celebrate the U.N. Women's Week, today's event will be a compelling conversation into the realm of leadership, innovation, and inspiration. And we're pleased to have you join us.

It's my honor to welcome Dr. Jennifer Doudna. Jennifer's groundbreaking work and unparalleled contribution to science and technology make her a beacon of inspiration for aspiring women leaders globally. She is the Li Ka Shing Chancellor's Chair and a Professor in the Department of Chemistry and Molecular and Cell Biology at the University of California , Berkeley.

Her groundbreaking development of CRISPR-Cas9 as a genome-engineering

engineering technology with collaborator Emmanuelle Charpentier earned the 2020 Nobel Prize in Chemistry and forever changed the course of human and agriculture genomics research. In addition to her scientific achievements, Jennifer is a leader in public discussion of the ethical implications of genome editing for human biology and societies and advocates for thoughtful approaches to the development of policies around the safe use of CRISPR technology.

She's an investigator with the Howard Hughes Medical Institute, Senior Investigator at Gladstone Institutes and the founder of the Innovative Genomics Institute. She co-founded and serves on the advisory panel of several companies that use CRISPR technology in unique ways. She's a member of various prestigious academies, both national and international. She's been honored with significant awards, including the Breakthrough Prize in Life Sciences, the Japan Prize, and the Kavli Prize. *Time* recognized her as one of the Most Influential People in 2015 and Runner-Up for Person of the Year in 2016.

The format today will be a conversation, and we're honored to have President of the Rockefeller University, Dr. Richard Lifton, as our moderator. We're going to end promptly at 12:45, and as a reminder, this conversation is on the record, and we do have media on the line. In addition, we'll be using the chat box for the conversation, and you can enter questions directly into the chat box for their consideration time permitting.

Without further ado, I'm pleased to pass this time over to you, Rick. Thank you.

Conversation with Dr. Jennifer Doudna

DR. RICHARD LIFTON: Thank you very much, Barbara, and I'm delighted to be with everyone today. And it's thrilling to have the opportunity to spend time today with Jennifer. Jennifer has had a remarkable career in science and its application to therapeutics. So, Jennifer, perhaps we can start, I'd love to have you tell the audience a little bit about your upbringing and what brought you to a career in science.

DR. JENNIFER DOUDNA: Hi Rick, and hi everybody. It's really a pleasure to be here. I grew up in a small town on the island of Hawaii. I grew up in a rainy place, not the glamorous vision you might have of the sunny beach in Honolulu – but in a town called Hilo. My parents were academics, but not in science. And I grew up in a family of, I like to say teachers and preachers.

So I had to make my way in science on my own. And I was fortunate to have a number of teachers along the way who were very influential for me and motivating. And also I thank my father because he was the person who actually turned me on to molecular biology. Back when I was in, probably before high school, read *The Double Helix*, that he gave me, a book by Jim Watson, that described the discovery of the structure of the

genetic material, DNA. And that's really how I got started on my path towards becoming a biochemist.

DR. RICHARD LIFTON: So from there, you left Hilo and came to the mainland for college. And did you immediately pursue a career following that inspiration in molecular biology?

DR. JENNIFER DOUDNA: I did. I wanted to be a chemist of life. I wanted to study the chemistry of living systems. And I didn't exactly know what that would be or exactly what I would study, but I found the idea of understanding the chemistry of life to be fascinating. So I pursued a degree in biochemistry as an undergraduate in California. And then I made my way east. I was a graduate student in Boston where I worked on actually looking at how molecular biology can explain or help us understand the origin of life – kind of one of the biggest mysteries that we can imagine in biology. And then I made my way to Colorado and eventually to the faculty of Yale where actually you and I met, Rick.

DR. RICHARD LIFTON: So you had a remarkable career both as a graduate student with Jack Szostak and as a post doc with Tom Cech. I note that both of them were Nobel Prize winners, and we can discuss cause and effect, but the work that you did with each of them certainly was incredibly important to their careers. And then you

landed at Yale. And what were your pursuits while you were on the faculty there?

DR. JENNIFER DOUDNA: Well, first I thought, I was shocked that Yale would hire me. It was a place I was hoping I could possibly go and when they actually made the offer, I thought, wow, did they really make the offer to me or was that a mistake? But I did go there. And the reason was that at the time I was pursuing the structures, molecular shapes and structures of RNA molecules to try to understand how they could explain, again, really understanding the most fundamental chemistry of life, namely the replication of genetic material.

And so I went there to work on molecular structures of molecules of RNA. And I had an incredible experience. I loved my time there and was able to do some very exciting work. But I did find myself attracted to the University of California so I moved there in the early 2000s.

DR. RICHARD LIFTON: So your background in RNA biochemistry as a graduate student, then as fellow and then as a faculty member at Yale really put you in good stead when opportunities came along with surprising new technologies and opportunities. So obviously I'm referring to CRISPR-Cas9 and the opportunities in genome editing. So it's a fascinating story in its own right, and I'd love to hear your thoughts on the origins of CRISPR-Cas9 and its biology and how you were attracted

into working in this area.

DR. JENNIFER DOUDNA: Well, Rick, I think the story of CRISPR is kind of a poster child for how scientific discovery often works. And it really goes hand in hand with curiosity-driven science as well as an eye towards how discoveries can be applied to help us do new research. And so in our case, when I moved to the University of California, Berkeley in the early 2000s I met a colleague, Jill Banfield, who was in a completely different field from me.

But she had made a remarkable discovery that just a few other people on the planet knew about at the time, which is that bacteria have, in their genome they have a signature of an adaptive immune system, meaning a way they can detect viruses that infect bacterial cells and fight back. And furthermore, she thought that there was a likelihood that this bacterial immune system involved molecules of RNA, which were the types of molecules that I was deep in the weeds studying at the time. And so she reached out and told me about this and asked me if I would like to work with her to investigate whether this was, in fact, true. It was a hypothesis, you know, did bacteria have an RNA-guided adaptive immune system?

And so we started to study this and this was actually a system that came to be called CRISPR. And so we began investigating how it worked. And what was remarkable is

that very quickly it became clear that not only do bacteria have an adaptive immune system, they have many. And they are highly variable in the way that they operate and the chemistry they use to detect and destroy foreign DNA. And by studying that process and eventually collaborating with Dr. Emmanuelle Charpentier, who is one of our closest collaborators over the years, we figured out how it worked. And not only that, how it could be harnessed to make targeted changes in the DNA of any organism.

DR. RICHARD LIFTON: So when you started out, it wasn't clear how CRISPR-Cas9 was operating. And I think many people thought it would likely be working on RNA the way some of the other bacterial immune systems operated. And then it became recognized that it's actually attacking DNA rather than RNA. And that obviously was a real game changer because suddenly you could see how you could not only make transient use of it, you might be able to make permanent modifications in DNA. And the key question was, or one of the key questions was could you reduce this to something that you could make work in not just bacteria but in other cell types. And you really made the key contribution in showing what the minimal system would be. I'd love to have you tell everyone about how you came to this.

DR. JENNIFER DOUDNA: Well, I think what makes CRISPR so interesting, both as a biological phenomenon and as a technology is that it's a seek-and-destroy sort of mechanism in biology that could be harnessed for a different purpose as a technology.

And to describe that, I guess I would start by saying that it's a programmable system. So it's a way that bacteria can learn about the genetic material of viruses that infect them. And not only that, to store a genetic vaccination card in their DNA that allows them to essentially remember what viruses have infected them in the past, and not only remember them but also find them and cut them up if they should show up again.

And that was what was so exciting and so interesting. It was to discover that this system is truly programmable and that cells are using it to, in real time, acquire immunity to viruses. And this is happening in bacteria. And so by understanding and really digging into the chemistry of that and understanding the molecular basis for that process, we recognized and "we" here is the "royal we" – it's myself and Emmanuelle, but as well as our lab members who were studying this process – we recognized that it could be utilized as a tool to change the DNA sequence in a new kind of cell.

DR. RICHARD LIFTON: So in 2012, you published this remarkable paper in which you took biochemically purified components of the CRISPR system and in a test tube demonstrated that these enzymes could do the cutting of foreign DNA that was targeted by a specific RNA molecule for the first time. And that really proved that we understood what the elements were, and you showed that it, in fact, could be programmed with any desired piece of RNA. That must have been an amazing experience.

DR. JENNIFER DOUDNA: It was really exciting. I mean, you and I both know, Rick, this is what we live for in science, right? It's those aha moments, and they don't come along every day. But when they do, it's very, very exciting because you feel like you're understanding something about our planet and life on our planet for the very first time. And that was the case for us with this work on CRISPR, was not only the fascinating biological pathway that we were studying, but also the recognition that we could now with our knowledge use that to harness it as a powerful tool to manipulate DNA in any kind of cell.

DR. RICHARD LIFTON: So tell us about the course of your own thinking and applications as well as the rest of the field, because this obviously very rapidly was a tidal wave that overtook all of molecular biology and now it's starting to find its way, not just theoretically toward the clinic, but with FDA-approved drugs.

DR. JENNIFER DOUDNA: Yes, it's amazing. While you were asking the question, I was actually thinking about a dinner I had with my neighbor right around that time in those, you know, early days. It was actually before we had published that paper in 2012, but when we knew about how the CRISPR system was working.

And my neighbor is a computer scientist. He's not a biologist. But he was over for dinner with his kids and our kids were playing and we were chatting. And he said, so, what's

going on in the lab? And I said, oh, my gosh, Bob, I have to tell you about this unbelievable thing we're doing that's just blowing my mind, it's so interesting. And he got it immediately because he's a programmer. And so he said, oh, you mean you can program this thing to go into a cell and look up a particular DNA sequence and trigger a change? And I said, that's right. And he said, wow, that is going to be absolutely huge. And he was right. He was right. So it was the kind of discovery that immediately, I think, everybody who heard about it or understood it could understand the implications.

And so what's happened over the last now, more than a decade since that work was originally published, is that many labs globally have adopted the CRISPR technology for all kinds of fascinating applications, not only to make fundamental discoveries about genetics, but also to, as you just said, to manipulate DNA sequences even in patients, in humans that have a genetic disorder where a targeted change to their DNA can be curative.

And so back in December of 2023, so just a couple of months ago, we saw approval from the Food and Drug Administration here in the United States as well as in the United Kingdom of the first CRISPR therapeutic. It's for patients that suffer from sickle cell disease, a very well-characterized genetic disorder in humans that is a great initial target for CRISPR because it's a single very well-characterized mutation in people that causes this terrible and really devastating disease. And with CRISPR now we have an

opportunity with a one-and-done cure that effectively creates a change in the DNA that can prevent patients from ever suffering from sickle cell symptoms again is what it looks like.

DR. RICHARD LIFTON: So the example of sickle cell anemia is a fabulous example of bringing this novel technology of CRISPR gene editing to a disease that was one of the first molecularly understood human diseases. Sickle cell anemia is a disease in which copies of the beta-globin gene are mutated to a form that now sickles causes the red blood cells in the body to sickle at low oxygen concentrations causing these vaso-occlusive crises where blood can't get through blood vessels and causes terrible pain in patients who suffer from this disease. And it historically has resulted in severe outcomes and death at young ages. And so the prospect of being able to treat this disease is really fascinating. Do you want to talk about the way that it's actually been attacked using CRISPR?

DR. JENNIFER DOUDNA: Yes, it's a very interesting situation because, as you just said, it's a devastating disorder, very well-characterized. It affects people primarily of African descent although there's also a large population with this disease in South America, which is very interesting. So there's some fascinating genetics going on there. And, you know, at least in some of these patient populations, these are populations that haven't been very well treated in the past by the medical community. So I'm really proud

that CRISPR is coming to bear on a disease that affects them right now and can have a very positive outcome.

That being said, it's difficult to get access to the therapy because it's treated, the way the CRISPR molecules are put into these patients is in a process that involves taking blood stem cells – these are cells that can give rise to mature adult red blood cells – taking those from the patient, doing the genome editing in the lab, and then reintroducing the edited cells back into the patient through what is effectively a bone marrow transplant. So it involves multiple weeks in the hospital and it's very expensive and it's very invasive of course. And so many patients that could benefit from this aren't going to be able to do so because of the cost and the process that's involved.

So I think we have a really interesting opportunity right now to change the way that this therapy is being delivered. And that's one of the reasons I founded the Innovative Genomics Institute, which is on my banner here, because we really want to focus on the ways that we're going to be able to bring this kind of therapy, and not only for sickle, but in other diseases as well, to a point where it's much, much more widely available for people to access it.

DR. RICHARD LIFTON: So one of the barriers in this case is, as you said, to date the only practical way to administer this is to take bone marrow cells out of the body and

treat them outside the body and then replace them after ablating the person's ability to make their own blood cells with their unmodified DNA. And that obviously is very challenging both for the patients and for the medical community to do bone marrow transplants and so that's not a terribly scalable method. So one of the big questions with CRISPR going forward is which diseases are likely to be most amenable? And what can we do to make it deliverable to the tissues and cell types that we want it to go to?

DR. JENNIFER DOUDNA: Well, I think initially we're going to see continued opportunities in blood because it is a tissue type that is more easily accessed, at least with the strategy that you just outlined – ex vivo – meaning in the lab. And there are a number of well-characterized genetic diseases that affect the blood, so there could be a benefit there for patients. That being said, I think clearly we need a different strategy for delivering CRISPR molecules therapeutically in the future. And so I think we and, of course, many people now appreciate that probably the biggest bottleneck right now to genome editing is the delivery of these molecules, how we can actually get them into the right cells in a patient, ideally in the body, without having to pull cells out and then try to put them back in.

And so our institute and of course others are currently working hard on different strategies for that kind of delivery where you could have ideally a targeted delivery vehicle that would take your editors right to the cells that need editing, not bother any of

the other cells, and ensure that the kind of editing that's therapeutically beneficial is what happens then in those cells. So that's, I think, really the forefront of where the field is right now.

DR. RICHARD LIFTON: And how is that going? Are there interesting ideas about how to target? What do you see as the progress both in your own institute and elsewhere, both in academia and in companies that are interested in this idea?

DR. JENNIFER DOUDNA: Yes, and thanks for bringing up companies because, of course, companies play a huge role here too. And we may want to say a little more about this too, Rick, but I think one of the things I think about a lot right now is, you know, what are the things that are appropriate to do academically and really make more sense to do in a nonprofit or academic setting – and our institute is a nonprofit organization of the University of California for example – versus what's appropriate to do in a commercial outfit.

And I think with this delivery challenge, we need both. We need both kinds of efforts. Academically, we're focused on what, you know, kind of asking the fundamental questions about what are the biology of certain cell types that might make those cells amenable to delivery of CRISPR using different strategies.

And very broadly speaking, what kinds of strategies are people using? Well, they're either using viruses to do delivery, viruses that can get into particular kinds of cells, or they're using non-viral strategies that involve typically more general access to lots of different kinds of cells, but trying to use various efforts to strategically direct those kinds of delivery vehicles into certain cell types, especially in the liver is where we're seeing that kind of work going on right now.

And so, for example, there's a Phase 3 clinical trial underway at a company right now that is targeting the liver to cure a genetic disease of the liver. And right now it's in Phase 3 meaning that it's gotten pretty far along showing that it's quite safe and is effective in patients, and they're now at the stage of trying to just adjust the dose. And so I expect that kind of thing, you know, we're probably going to see at least applications for FDA approval within the next couple of years for that type of strategy.

DR. RICHARD LIFTON: So the CRISPR revolution has really sparked, not just broad use of CRISPR technology on its own but has also spurred the search for other systems that can do gene editing with different wrinkles that might have advantages under particular circumstances. Tell us about some of those and your interest in pursuing them.

DR. JENNIFER DOUDNA: Well, I think it's fascinating. Yes, you're right. I think there's

been a huge, especially academic effort to discover other ways that, you know, bacteria fight viruses, thinking that that may be another avenue to look for new tools, which it certainly could be. And I think what's every interesting right now is that, you know, the molecular mechanism of CRISPR, which uses RNA to pry apart DNA and allow an enzyme like those involved in CRISPR pathways to get access to DNA, it's just a very powerful mechanism.

And so a lot of the technologies that have come along certainly so far for making manipulations to DNA sequences rely on that fundamental chemistry of CRISPR. And that's true for things like if people have heard of base editors, you know, that's one strategy. And then there are strategies that involve other kinds of changes to CRISPR molecules that can allow integration of short DNA sequences to correct a disease-causing mutation. So I think these are very interesting, very exciting technologies. They're still under development in my opinion. So I think they're still, you know, being kind of validated as approaches that could work clinically.

And then a little bit further out, there are ideas that are coming along just really very quickly right now about other ways to insert DNA sequences in a precise fashion into cells. And that could allow, it could be very important. It could allow much larger changes to be made to DNA. So, for example, we could imagine correcting an entire gene. So all the patients that might suffer from a mutation in a particular gene, there

may be hundreds of different types of mutations that would all be found in that gene, but we could correct all of them if we had a way to precisely just replace that gene sequence with a correct one. So these are very interesting and very important, but it's early days still. Not possible yet.

DR. RICHARD LIFTON: So one of the potential downsides that has been raised about CRISPR-Cas is this element that you mentioned of it cutting both strands of DNA, which sets off the cells' alarm system because there shouldn't be free ends of DNA sitting in a cell. And the patchwork to put them back together can sometimes introduce other errors such as long deletions of DNA sequence. Your thoughts about how this has evolved with CRISPR-Cas therapeutics and how base editors might get around this? But also this gets to the question of safety with CRISPR-Cas. So I'm interested in your thoughts on this.

DR. JENNIFER DOUDNA: Right. Well, first of all, there's been a huge effort, mostly in academic labs, although I'm sure companies are doing this too, but academics are publishing their work, over the last, more than a decade to figure out exactly how precise is CRISPR, how good is it at finding the right sequence? And, you know, how often does it make a change at an undesired position? Or like you just said, how often does DNA repair that is part of the genome editing process involve changes to DNA that would be potentially very harmful, like losing a piece of a chromosome or something like

that?

And the short answer is that, yes, those kinds of changes are detectable but they've often been detected in cells that are not clinically relevant. And also they've been, you know, they've been shown to arise when you have a very high concentration of the CRISPR molecules present in cells, which is, you know, often what you need to do if you're studying this process. But in a clinical setting, I think what's very interesting is that so far, and this is like, for example, if you look at the data that went into the FDA for approval for this first CRISPR therapy, it was actually very hard to find off-target editing in those patients' cells. And furthermore, when it did occur it seemed that those cells had a disadvantage in the patient, and they ended up getting probably mostly eliminated in the body because it was hard to detect them later in the patients.

And so, you know, time will tell, of course, and it's very important with clinical use that we be incredibly careful about this kind of potential for off-target or undesired editing to occur. But I think I'm cautiously optimistic right now that we're learning enough about how to work with CRISPR in a clinical setting that we can really protect against those kinds of undesired changes to DNA. That being said, I do want to comment on base editing since you brought it up because I think it's a very interesting alternative to cutting both strands of DNA.

So DNA is a double helix and when you cut both strands, it's like cutting a rope. You know, now you've got two broken ends and they have to be found and repaired. And the idea with base editing is let's not do that. Let's just make a targeted chemical change to one DNA base meaning one letter in the DNA, in A, G, C, or T. Let's change it to something else to make a corrective change to a gene. It's a very exciting, very interesting use of CRISPR. I think that it has a lot of clinical potential. I think that we're still at a stage where it's clear from, if you look, you know, in the weeds at the data from these kinds of studies that there are still off-target base edits that happen. And so we just still are at an early stage of understanding well enough how to use base editing, that it could be safe to use in humans.

DR. RICHARD LIFTON: As you know, there have been, a clinical trial for editing PCSK9 base editor in vivo in the liver that has done remarkably well in clinical trial. I've been impressed with all of these trials, both base editors and the CRISPR-Cas efforts in sickle cell anemia at the relatively high efficiency with which the edits have been made in the targeted cells. In the case of sickle cell anemia, about 80% of the targeted alleles, the specific strands of DNA, have the desired edit. And in the PCSK9 trial in the liver, about the same, up to the same level. Which means that these are incredibly efficient at getting into cells and finding the right targets and making the desired edits. In many ways it all exceeds expectations in my view.

DR. JENNIFER DOUDNA: It's really extraordinary, isn't it? And I think one of the reasons for that – if I may speculate for a moment – is that it does come from an immune system. And so if you are a bacterial cell and you're relying on your immune system to protect you from a viral infection, that protection better be good because those viruses replicate very fast in bacterial cells, and they blow them up essentially. And so I think there's really strong evolutionary and selective pressure for these enzymes to be extremely good and efficient at what they do. And they are. And I think that works to the advantage of the CRISPR technology in the sense that these enzymes are just very effective at finding target sequences, cutting them, and then allowing the cell to make a change.

DR. RICHARD LIFTON: Which gets to a further potential application that has been perhaps more controversial, which has been contemplating germ line genome editing. What are your thoughts about potential risks, ethical considerations on germ line editing?

DR. JENNIFER DOUDNA: Yes, well, let's start with what is that, and what's the difference between germ line editing and what we've been talking about with, say sickle cell disease? And with sickle, that's a situation, as is being contemplated for lots of other kinds of disorders, where one can make gene edits in cells of an individual. And those cells then will affect that individual but they don't affect their eggs or sperm so

they don't get passed on to future generations.

But germ line editing is different. That means making targeted changes in eggs or sperm or embryos such that those genetic changes can be passed to future generations. And it was clear, you know, again very early on in the development of CRISPR technology that there didn't seem to be any technical reason why that couldn't happen or couldn't be done.

And so we started back in 2015 actually, when the Innovative Genomics Institute was in its very early days, that was one of the first things we did as an institute, was to call a meeting of stakeholders in the field and start talking about what are we going to do about the potential for this technology to be used in the germ line? Should it ever be used in a germ line? And how do we start that conversation? And fortunately, the national academies in multiple countries have stepped up and have now made this kind of a thing and so we have an annual international conference now that happens to discuss this kind of application of CRISPR.

In the meantime, however, there was, in 2018, an announcement from a scientist who said that he had actually done that kind of germ line editing in humans, giving rise to the birth of two kids that had modified DNA that is in the germ line, meaning it can be passed to future generations. And I think that, you know, the details of that when it

came out were really quite shocking. And I think many people internationally felt that that was an inappropriate use of CRISPR, at least at that time.

Now, do I think it should never be used in the germ line? That's not what I currently think. I feel that there may be reasons that one would want to mitigate disease or remove a disease-causing gene from a family, let's say that has a terrible genetic affliction. But it will certainly take more work to understand how to use CRISPR safely in that type of an application before we're ready to do so.

DR. RICHARD LIFTON: So CRISPR not only had immediate applications using the native CRISPR-Cas system but also suggested to scientists other ways to modify CRISPR that could, interesting biology could be prosecuted. Do you want to comment on some of those?

DR. JENNIFER DOUDNA: Well, we already spoke about base editing, so that's one. And then there are other ways to use CRISPR enzymes for more precision applications. Another that's termed primed editing where you can insert DNA sequences in a targeted way using the CRISPR molecule to actually initiate that process at a particular place in the DNA of a cell.

But beyond that, and you may be referring to applications that include diagnostics, so

being able to detect sequences and report on them. So this was something that had started before Covid, but actually during the Covid pandemic was really accelerated, both in companies and academic groups that started to say, great, could we take this detection system of CRISPR and apply it to detecting and diagnosing the presence of a virus, like the virus that causes Covid-19? And so that work is still ongoing, again mostly in companies right now but I think there are some academic groups using it as well.

And interesting there to note that, and you mentioned this a little bit earlier, but a lot of the CRISPR systems that we know about biologically target DNA, but there are some natural ones that also target molecules of RNA, which are often the genetic material of viruses, including the virus that causes Covid-19. So the great thing about CRISPR as a diagnostic tool is that we can easily apply it to detect either DNA or RNA and it could, in principle, be faster than some of the technologies that are used today to do that.

DR. RICHARD LIFTON: So beyond that, in the academic setting CRISPR has been modified to alter gene expression. Do you want to comment on those technologies, which you might be a part of?

DR. JENNIFER DOUDNA: Yes, of course. Yes, that's great. That's a great one to talk about a little bit. Yes, because one of the things that CRISPR is great at doing is parking itself on DNA. And so it turns out that by changing the CRISPR molecules we can turn

them into great DNA binders, meaning that they sit at a place in DNA. They don't actually make a chemical change to the DNA, but they prevent other molecules from getting access to, say, a gene.

And so that means that, or they can either prevent access or they can actually accelerate it. And so that means that it's possible to use modified forms of CRISPR to either increase or decrease the production of proteins that are being made in a cell and to do it, not randomly, but in a targeted fashion. So that you're right, Rick, that's a really interesting direction and could have very exciting clinical use as well in the future. And there are a number of teams, both academically and commercially, that are pursuing that right now.

DR. RICHARD LIFTON: So, Jennifer, you commented earlier about what should best be done in academia and best be done in companies, and you've seen both sides of that coin. So I'm interested in, and I'm sure the audience is interested in hearing your thoughts on, first, the importance of academic research as part of the ecosystem, and second, how that handoff is or should be working to make sure that the fruits of federally-funded research are seen in the public.

DR. JENNIFER DOUDNA: Well, we could ask ourselves what's the point of academic research? And believe me, I have people that ask me that. You know, if you have a

great idea, that should immediately just be a company, shouldn't it? And what I say to that is that, well, yeah, but the thing is that we often don't know which ideas are good. And we don't know what we don't know.

And so the reason that we do academic research, or at least one important reason beyond educating students, which is, of course, a very important reason, but we also want to have opportunities to pursue ideas that may or may not have any commercial value but they have incredible value in terms of understanding fundamental biology. And so a lot of the research that goes on in universities is being carried out by very smart, young students or post-graduate students, post-docs who are pursuing ideas that they think are interesting because they are passionate about discovering an answer. And if those ideas end up having commercial value, that's great, but that's not the purpose of doing that work.

And that's the type of research that's typically funded by taxpayer dollars. And it really has, if we look back at the history of that type of research, at least in our fields, Rick, and kind of across biology, I would say that it's really that type of research that has led to some of the major breakthroughs that have then opened the door to all kinds of clinical developments that would have never been possible without those early initial discoveries.

That being said, companies play a hugely important role in taking ideas that clearly have some value and could have real world applications to solve problems that are unsolved right now and build teams and finance them so that they can run fast and hard after those goals and get them to a point where they're actually benefitting people. So I really think of it as kind of an ecosystem. We really need both. We need great academic research going on, and we need to fund it appropriately, but we also need to pave the path towards allowing those that want to, to take their discoveries and turn them into companies or license their discoveries to companies when that makes sense.

DR. RICHARD LIFTON: So you've been a serial entrepreneur in developing some of these companies, and I greatly admire your ability to go between academia and the company environment. I think it exemplifies an important idea that having a great discovery and throwing it over the transom and hoping that other people figure out how to use it right may not be as easy as it seems. How do you find your own experience in going back and forth in this fashion?

DR. JENNIFER DOUDNA: Well, I feel like I'm always on a trajectory of learning, which is great. I enjoy that. When I started with our CRISPR research, I had never been involved with companies really. I mean, I guess I'd done a little bit of advising for pharmaceutical companies, but I really had never been involved at all in the world of start-up companies and venture capital teams and that sort of thing. And that changed

with CRISPR because it was just clear from the beginning that this was going to be an entire toolbox of very interesting molecules that could be valuable for all kinds of uses as we've been discussing.

And so ever since then I've been really excited to mostly, you know, help people who are coming out of my lab, trainees in my lab who clearly have an eye towards becoming entrepreneurs, either starting companies or joining companies, who want to do that, and helping them to do it. And it's really been fun. And I love the team building part of it, but I also love the science that sometimes is primarily possible in the context of a company. And it's been really fun to see these teams start to take off. And I just particularly enjoy enabling younger scientists who want to go in that direction to help them make that possible.

DR. RICHARD LIFTON: Perhaps as a last question, Jennifer, if you think about how rapid the progress of technology has been over the last 10, 20 years, if you project 10, 20 years into the future, where do you think this field will go?

DR. JENNIFER DOUDNA: It's mind-blowing, isn't it? I think we're going to see a future where not only can we treat rare disease, like we discussed in this conversation, like sickle cell disease, but potentially we can also prevent disease. I mean, wouldn't it be extraordinary if someday it's possible for people that have a genetic susceptibility to,

say, cancer, or even cardiovascular disease, where you could offer them an opportunity to edit cells in their body that would then be preventive of that kind of disease? I think that's not completely out of the question at all. And, in fact, as you know, there already are groups pursuing that kind of idea. So over the next 10 to 20 years, I think it's very possible we could get there.

DR. RICHARD LIFTON: Thank you. Barbara, I'll turn it back to you.

PRESIDENT BARBARA VAN ALLEN: Well, Jennifer, Rick, thank you. What a great conversation, and actually very inspiring and hopeful, and it's refreshing, frankly. So thank you both for joining us today.

We have many more great speakers ahead on the Club's spring calendar. March 12th, we're back with a luncheon. We'll be hosting David Ricks, the CEO of Eli Lilly. That will be followed on the 27th of March by Chris Waller, who is a Member of the Board of Governors of the Federal Reserve. On April 2nd, we have Jeremy Siegel, from Wharton, will be joining us, and he'll be in a conversation with John Williams. On April 4th, we have the Chairwoman of the Federal Communications Commission, Jessica Rosenworcel joining us. And then on April 11th, Susan Collins, who is the fairly new President and CEO of the Boston Fed. On April 16th, we have Francois Villeroy de Galhau, and he's the Governor of the Bank of France. April 23rd, we still have tickets

available, it's filling up though, Jamie Dimon of J.P. Morgan. And to end the month, April 30, Jared Bernstein, the former Chief Economist and Economic Policy Adviser to the President. And all these events are listed on the website. Please be sure to review these dates and add them to your calendar.

And, of course, as always, we'd like to take a moment to recognize those of our 372 members of the Centennial Society joining us today as their contributions continue to be, represent the financial backbone of support for the Club and all of our programming. So thank you all for attending today. Have a great week. And we look forward to seeing everyone again soon. And again, thank you to Jennifer and Rick. Just a wonderful conversation.