Talks at GS
Samarth Kulkarni, CEO, CRISPR Therapeutics
Amit Sinha, Moderator
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Sam Kulkarni: We're going to think of medicine very differently 50 years from now because we're not going to be popping pills. We're going to do one-time procedures to change your genome, and hopefully you're preventing disease or completely curing yourself of disease.

Amit Sinha: Good afternoon, everybody. I'm delighted to welcome Dr. Sam Kulkarni, chief executive officer of CRISPR Therapeutics. Sam has a long history and expertise in strategy and operations in biotech across a range of cutting-edge therapeutic technologies. He joined CRISPR Therapeutics as chief business officer in the early stages of the company. And prior to that, co-led the biotech practice at McKinsey.

Sam is at the forefront of an industry that's moving so fast it sometimes feels like science fiction. We are thrilled to have you here with us today, Sam. Welcome.

Sam Kulkarni: Thank you.

Amit Sinha: I want to start with the technology behind CRISPR, which more and more people have become aware of over the last several years. It was discovered by Dr. Doudna both and Dr. Charpentier, your founder of CRISPR Therapeutics. Talk a little bit about how it was discovered because I think it offers a unique insight into how some of the most important discoveries are made.

My understanding is that they weren't looking for a gene-editing technology. They were actually studying how bacteria defend themselves against viruses. So can you talk a little bit about how CRISPR was discovered and how it's become adopted for its current use?

Sam Kulkarni: Happy to. It's actually one of the most fascinating stories. There were two parallel efforts ongoing. Dr. Charpentier, our founder at CRISPR Therapeutics, was actually a microbiologist who was looking at strep throat, or the strep pyogenes, which is the bacteria that causes strep throat. And she was looking at mechanisms by which strep throat, or the strep pyogenes, defends itself against phages.

Meanwhile, there was a separate effort ongoing at these yogurt companies. You know, all these advanced yogurts that have probiotics, they have bacterial cultures in them. And they would create large vats of yogurt that would go bad because the bacteria got attacked by viruses. And they were trying to figure out what's going on there.

And it turned out that bacteria are not as dumb as we

thought they were. Some of these vats where the bacteria would survive, right? And what was going on is that, you know, like we're attacked by bacteria, viruses attack bacteria themselves. But some of them survive. And what they do is they take a little snippet out of the viral genome, put it in an accordion-like region in their own genome -- which that's why the name CRISPR, stands for regularly interspaced repeats. And the next time they get attacked by the bacteria, they use molecular scissors to cut the viruses and activate them and protect themselves.

So it turns out, like, bacteria, which we think are dumb organisms, are actually very intelligent and have an advanced immune system of their own. And that's how Charpentier started looking at it and said how do we then take this immune system that's in bacteria and use it in the human genome? Can we port it to cut -- use the same molecular scissors to cut DNA in a directed fashion in the human genome?

And just like that, that became this amazing tool that we'll talk about that has amazing applications across medicine, food, you name it.

Amit Sinha: It's fascinating. There's been a lot of news recently about CRISPR, all of the diseases that it can be potentially used for. You mentioned the term "molecular scissors." Talk a little bit more about how CRISPR technology works and how it works in the context of gene editing and potential treatment for diseases.

Sam Kulkarni: Yeah, you know, our bodies have about 3 billion base pairs of code in it. That forms the basis of life. How do we know -- how does our body, starting with one cell, know how to make eyes and ears and all these different organs? And it's all encoded in our genome. And a lot of the diseases that we know are all have molecular bases. You know, it starts with the gene. There's a central dogma of life. You have the code in the DNA, which is translated into mRNA, the same mRNA that we took vaccine shots of, that become protein, and they do all the work in the body, right?

And for the last several years, we've all been trying to treat diseases at the symptom level, by treating proteins or what are the associated molecules. Here, we can go to the molecular basis of disease and say this gene is missing; hence, this disease. So let's go correct that gene. Or here

is a gene that's over expressed for whatever reason. Let's delete that gene, and all of a sudden you fix the disease. So it provides a whole new way of thinking about medicine, and that's why there's so much excitement about CRISPR in biomolecular research or biomedical research because you can now think about tens of diseases, if not hundreds, that can all have a potentially curative therapy that acts on the basis or the fundamental aspect of the disease, that's the DNA.

Amit Sinha: And so this is where the idea of a potential one-and-done, a lifetime cure comes from with this technology.

Sam Kulkarni: Absolutely.

Amit Sinha: When you think about the potential of CRISPR and you think about the last 50 years of innovation in biomedicine, biotechnology, how would you contextualize the importance of this technology that you and your company are working on?

Sam Kulkarni: Yeah, I'm happy to do that. You know, and I was starting to look at 50 years, and I'm a bit of a

history buff and I started going back further. And I also was trying to learn a little bit about Goldman Sachs.

So it turns out Goldman Sachs was founded in 1869. That was the same time that the father of human genetics, Gregor Mendel, was doing his famous pea experiment. Gregor Mendel was an abbot in a church. And in his spare time, what he was trying to figure out is, if I just breed these different pea shoots or different types of pea plants, what comes out? And he's very puzzled because he would take these yellow and green pea shoot producing plants, and every time they mated them, you would always get yellow peas. And he was, like, what's going on here?

But then several generations later, all of a sudden, green peas would pop up. And so he did this massive experiment of 28,000 pea shoots, and that became the basis for genetics, of inheritance, how genes are coming down. And that was in the 1860s. But it took a while for us to figure all this out. You know, even by the turn of the century. And again, I was looking at Goldman Sachs. The big IPO that Goldman did in 1906 with Sears and Roebuck, at that time was the first time we realized that there's something called gene in our body.

The term “gene” was termed based on a variation of what Charles Darwin had coined a term called “pangene” when he was doing his voyage around the seas. And so the term “gene” was produced, which said here's a code. But there was a lot of -- we talk about fake news. There was a lot of fake news back then.

People said, oh, you know, the mother doesn't matter. It's just the father's genes that go in. And that's how the child inherits the father's genes. There were other theories around eugenics that were happening at the same time. But all this understanding of the genome took a while.

About a hundred years ago, we learned that genes in its current form, and we started understanding the basis of what genes are made of. You know, the double helix, the chemical composition. And only about 20 years ago did we learn how to read the entire genome. And that's when we came up with the 3 billion base pairs or so in the human genome.

But CRISPR has a profound place in that timeline, which is, for the first time now, we know how to write genes,

right? So we've known how to read genes now. And everybody assumed after the 2002-2003 time frame when the human genome was encoded that we were going to have hundreds of drugs come into the market, we were going to figure out every disease. It didn't happen, right? The first of genomics were delayed.

And that's because we don't know what to do with it. We have the information that tells us that these diseases are caused by these genes, but what are we going to do with it? And now with CRISPR, we can fundamentally rewrite the genome. Now, we're not at the -- we're not quite at the place where we can just take a Word document and edit the genome entirely, right? But we can go take parts of the genome and change the code to the extent that we can alter the disease.

And that provides us possibilities that's going to reimagine medicine, in my view. We're going to think of medicine very differently 50 years from now because we're not going to be popping pills. We're going to do one-time procedures to change your genome, and hopefully you're preventing disease or completely curing yourself of disease. And that's the promise of CRISPR, which we're trying to exploit and

advance today.

Amit Sinha: So we've talked about the potential of the technology. I want to spend a couple of minutes just on some of the risks that come with this approach. And so you've talked about CRISPR as a pair of molecular scissors, can cut DNA, can edit DNA. Some of the risks of this technology include off-target editing, maybe creating double-stranded breaks which may, over time, increase a patient's risk for cancer. How have you and other people working in the field worked to address or mitigate some of these risks to create safer medicines for patients?

Sam Kulkarni: Yeah, absolutely. I think, you know, for us, at CRISPR Therapeutics, patient safety is number one. Absolutely. No questions asked. At the beginning of all technologies, there's always these risks that are portrayed because you don't fully understand the technology. What you're doing here is let's say you're trying to find a place in the genome that you're trying to edit, okay? And it's guided by an RNA. An RNA is also base pairs. You know, and there's four different bases in DNA, four different bases in RNA. That goes to the site where you want to make the edit or the change. And then you bring the effector

molecule to make the change, right?

But the way I explain this is this is like a 20-letter passcode. You know, if you have a 5-letter passcode, odds are it's easier to hack or easier to figure out or easier to have off-target effects. But if you have a 20-letter sequence, there's a trillion combinations. The odds that you're going after a particular 20-letter sequence that happens somewhere else in the genome is very low.

Now, it does happen once in a while. You know, sometimes there's 19 common bases, and the 20th is different but that's enough to cause an off-target edit. But we've done this robust analysis, almost in an industrialized fashion, to say let's just take 1,000 guides or 10,000 guides, characterize every one of them, and make sure there's no off-target edit. And the only change you're making in the genome is the one you want to make. Because obviously everyone's worried about what if you change something else? You're trying to change a cardiovascular risk factor, and all of a sudden you're changing your metabolic factor or something like that. You know, you don't want that.

And I think with this industrialized approach, it's going to

be very reliable. And the FDA are getting very comfortable with it. You know, they're the ultimate gold standard to say what's safe, what's not safe, and what's the risk-benefit profile. And so early days of CRISPR, I think the -- you know, if I had come here for a talk five years ago, the talk would be about who owns the IP, what are all the risks, is there going to be germ-line editing and all that? Now it's completely shifting and people are saying how many medicines are we going to have in the next five years?

And so that dialogue has shifted. And I think companies have done their part to risk mitigate the safety issues as well.

Amit Sinha: This idea of editing a patient's genome to address disease, maybe over time prevent disease, the fact that that's permanent may mean that you've got to think about developing the technology and the drug differently than a lot of the medicines that we're all used to saying and that some of us take today. Talk about just some of those differences because of the nature of the technology. What are they? And how have you navigated them as you've been developing the programs for CRISPR Therapeutics?

Sam Kulkarni: Absolutely. I think some of the things we're doing, for instance, in our trial for sickle cell [UNINTEL] and we'll talk about that, we have a 15-year follow-up. You know, once we change the genome or the bone marrow of the patient, we follow them for 15 years. Now, it obviously costs a lot more money and everything else, but that's our job. I think that's our -- almost our obligation to do that, to make sure it's safe. That over the period of that time, there's no unwanted effects, for instance, right?

The trials are also different. You know, in a case we're using a depression drug or something else, right, you have to study this in thousands of patients because the objective measures are not there. You're relying on people saying how they feel, so you have to do randomized control trials, double-blinded trials to say what is the effect really.

But here, you know there's a person who has major pain crisis or has an inability to eat fructose or digest fructose or any of the other metabolic diseases. You're giving them a medicine to fix the genome, and all of a sudden they're normal, right? So there's a black-and-white effect in these patients, so you don't need large trials. But at the same

time, we do need to follow these patients longitudinally for a very long time to make sure there's safety and there's no unwanted effects.

Amit Sinha: Okay, that makes sense. Right now, you're focused on genetic diseases and cancer cell therapy. When you think about where this technology is most likely to have an impact in medicine, maybe outside of those places, what else comes to mind?

Sam Kulkarni: Yeah, I think when the technology was first elucidated, the immediate reaction was this is perfect for rare diseases, right? There's 600 odd -- actually, there's more than that now. We're discovering new rare diseases all the time as we sequence people, as more people do IVF and everything else. You know, for these 600 rare diseases, here's how you just fix the gene. That's the cure, and that's the model, right? That was the first four years of CRISPR. These pharma companies thinking this is a rare disease kind of play.

But today, you know, I think the biggest impact of CRISPR is going to come in a lot of the common diseases. Look at the biggest causes of mortality. You know, heart disease,

cancer, diabetes. And CRISPR has a role. And we have programs in all three of these diseases. One, to prevent heart disease. Two, to make artificial pancreas that prevent diabetes if your pancreas fail. And cancer, where we're unleashing immune cells, engineered immune cells, to go fight the cancers as opposed to toxic medicines that oftentimes come from chemical industries.

And so I think CRISPR is going to have a profound impact in common diseases as well. And that'll extend to almost every disease that we know.

Amit Sinha: And what about if you go away from medicine? Because CRISPR has got applications in a bunch of different areas. How do you think about those applications? And where do you think we'll see CRISPR pop up as something that gets adopted outside of potential medicines?

Sam Kulkarni: There's so much activity right now with CRISPR and plants and food. I just saw this video of non-browning potatoes and non-browning mushrooms and food you can store for a very long time that don't go bad because you CRISPR-ed it. Interestingly, in Europe, that's still a

GMO. In the US, it's not considered GMO. GMO is something where you're irradiating plants and doing a forced natural selection. Here, it's a much more deterministic way.

In fact, somebody had hosted a dinner that was all CRISPR edited food for the dinner. And you're seeing a lot of work by companies like DuPont and Pioneer. But what's interesting to me there is not just the jazz factor of it, but actually it could have a major impact on sustainability. Foundations like the Gates Foundation are doing work to say how do we keep food -- how do we treat this hunger issue around the world? Part of that is food storage. And how can we have food that doesn't go bad easily?

And the other one that's real interesting I came across is in Lyme disease. There's a very controversial sort of effort ongoing right now to sterilize mosquitoes or bugs that would spread malaria or Lyme disease or whatever else. And the way you do it is by using CRISPR you can sterilize the mosquitoes and release these sterile mosquitoes into the population. They did this in Brazil. And that then, when they mate with all of the other mosquitoes, end up sterilizing the population. And they get rid of all of the

species in that population. And that's one way to control malaria in parts of Brazil where there's huge swathes of malaria.

So those are all applications. Again, there's a lot of questions behind what should be and what shouldn't be used. But I would say for every medical application, there's ten non-medical applications where people are starting to use CRISPR.

Amit Sinha: It's fascinating when you think about the breadth and depth of impact of this technology. It'll literally touch our day-to-day lives in ways that we probably won't even think about. We'll just go buy an apple, and it'll be a non-browning apple and maybe it'll be CRISPR-ed.

I want to turn back a little bit to CRISPR Therapeutics and some of the programs that you're working on. You've got a major program in the works for a couple of blood disorders -- sickle cell anemia and beta thalassemia. What's fascinating to me is, as I looked at these programs, is you're not necessarily editing the specific mutation that causes the disease, but instead you're creating an edit that

brings about a second mutation, a compensatory mutation, and it's actually something that is observed in nature. And so you're kind of taking a playbook from nature in terms of creating this potential permanent cure for disease. So talk a little bit about that journey, how you figured out that this could be an interesting strategy, and how you've prosecuted it.

Sam Kulkarni: Yeah, there's a book coming out on this approach for sickle cell and thalassemia, and it's quite fascinating. In the '80s and '90s, people were doing these studies around sickle cell. Why do we have so much sickle cell in the United States, for instance, or in parts of Africa?

It turned out that, if you had a sickle trait, you were protected against malaria. You had bouts of malaria in Africa which would wipe out entire villages except those that who had a sickle trait. And so then people with sickle trait, when they married or intermarried or whatever else, you had people with sickle cell disease, both their genes have the defect.

So thalassemia is a disease where the hemoglobin is deficient that carries oxygen. Sickle cell is a disease where

the hemoglobin is defective and polymerizes in a cell and causes the cells to form a sickle shape that doesn't flow in the blood right.

Then we did all this population genetics, and people like Francis Collins [sp?] of the NIH found populations or families in Saudi Arabia, Syria, Greece, where they had the genetics of sickle cell, they had a fault hemoglobin gene, but they were completely normal. And they're wondering what's going on here? And it turns out that we're all born with an altered form of hemoglobin called fetal hemoglobin.

So when the fetus is in the womb, it has a form of hemoglobin that latches onto oxygen stronger than the mother's hemoglobin. So you get the oxygen transport. You know, you pull the oxygen from the mother to the fetus. And once we're born, in about six months, our body has a natural switch to turn off the fetal hemoglobin and it's replaced by adult hemoglobin. The evolutionary theory is, when the wild animals were chasing you, you needed something that releases oxygen faster. So you have adult hemoglobin that releases hemoglobin faster.

But you could simply just turn back on -- and these

families that had these normal phenotypes, they had a naturally occurring mutation that turned back the fetal hemoglobin, which made up for the deficiency or defectiveness of the adult hemoglobin.

So we said why don't we just recapitulate that using CRISPR? So instead of this canonical way of saying let's go fix the gene that causes sickle cell disease and thalassemia, we said let's just look at all these families and create what happened to families.

By the way, while we were doing all that research, it was pretty fascinating that you can literally trace history through the incidence of thalassemia and sickle cell. Thalassemia is called thalassemia because it's named after the Greek goddess of the sea, Thalassa. And because people in Greece by the waters had this mutation somehow, and they couldn't get up the hills. And so they were not very great for the army back in the day, but a lot of them were part of the Greek armies of Alexander the Great. And you can trace war history based on the incidence of thalassemia.

In fact, there's a little conundrum of where did Alexander's

army stop in India at the end? And no one knew because there are lots of different stories. But if you look at the thalassemia population in this particular village, you know that's where they stopped.

Amit Sinha: That's so fascinating. Let's talk a little bit about just gene editing and ex vivo versus in vivo, which is really editing cells outside of the body and then putting them back in versus doing it internal to the patient. You've started with ex vivo, and that's kind of where you started with your initial programs. You're now taking on in vivo. Tell us about just the incremental hurdles, the risks, why is it so much harder? How have you kind of worked to make it more viable?

Sam Kulkarni: Yeah. So I think ex vivo, as you were saying, is you're doing editing outside the body. So we'd take, for instance bone marrow cells from a sickle patient, edit them, and put the bone marrow cells back in, right? So we can control what we're doing in our manufacturing facility. The cells we're editing, characterizing it robustly, etc.

In vivo means we're taking the CRISPR cast line [?]

medicine in a lipid nanoparticle or a virus and injecting it into the arteries or veins. And they go to the organ of interest and do the edit, right? So it's an order of magnitude harder because, one, you don't want it to go all over the body. You don't want it to go to the gonads. You want it to go to the liver if you were doing liver gene editing. You want it to go to the lungs if you're doing lung gene editing. So you have to direct it to a particular organ of interest.

You need to be able to deliver it in the right way. These nanoparticles are basically soapy bubbles. One billionth of a meter, okay? That's how small they are. And inside that is the CRISPR cast line machinery. And you want it to go to the cells, go inside the cells, go into the nucleus, and then make the edit, and then disappear. So it's a lot you're asking this machinery to do. But remarkably -- again, I was talking about the technology cycle and how fast it's going -- we've been able to do it. The first few sets of data in humans show that you can edit the liver to 80-90% efficiency right now with one injection. And that opens up a whole new slate of possibilities. There's so many diseases related to the liver. And you can take one dose one time, and you're done.

And so we're doing a lot of work on in vivo gene editing because, in the future, that'll be a more efficient or facile way of editing organs or cells versus taking the cells out and doing it externally.

Amit Sinha: Okay, great. I'm going to shift gears a little bit and talk about the biotech environment. We're kind of entering a third year of correction in the markets. The biotech markets hit their all-time highs in early 2021. And so here we are in 2023. Talk a little bit about how the current environment's impacted the company, what changes you've had to make, how you've been navigating the current correction.

Sam Kulkarni: Yeah, happy to do that. You know, you're more qualified to talk about all of that than I am, and we've had many a conversation about the ups and downs of the biotech market. But for me, fundamentally, two things are important. One is the ability to underwrite risk has changed a lot. We raised $3.5 billion at CRISPR. If I had said that 20 years ago, I want to raise $3.5 billion for this notional technology, that I want to develop a drug, and who knows if it's going to work or not? They would

have laughed you out of the room.

But now, people are very technical who are able to underwrite that risk, and we can do that now. It's gone from a cottage industry to a somewhat -- it's still a bit of a cottage industry but slightly more mature industry.

And the second thing is all the technologies are converging. I was working in lab on delivering [UNINTEL] nucleotides 20 years ago. But I didn't have advanced viruses. I didn't have advanced mRNA technology. I didn't have advanced lipid nanoparticles like we do with the COVID vaccines now back then. So it was very hard to do. And so as the technologies coverage, more possibilities emerged.

So we truly are going to have the Roaring '20s of biotech. What happened I think from a market standpoint is people got really excited. There were, like, 700 companies formed, many of them sub-scale without the same technology promise that something like CRISPR has. And whole thing became inefficient. Half the $200 billion that's going into biotech every here is inefficient. It's going towards managing these companies as opposed to true clinical trials and technology advancement.

And as the technology -- you know, as we mature as an industry, I think that problem will go away. For us at CRISPR, we have a very strong balance sheet, and we can continue aggressively investing while others are slowing down.

Amit Sinha: Makes sense. I'm going to shift gears now and talk a little bit about your career and just kind of your personal trajectory into your current seat as CEO of CRISPR Therapeutics. Let's start with just how did you get into healthcare?

Sam Kulkarni: Yeah, serendipity. So, you know, I grew up in India in a relatively small town, and I had never traveled out of the country. My ticket to success was to get into one of the IOTs. It was called the Indian Institute of Technology. There were only five of them at the time. And 2 million people applied and 2,000 got in.

And I applied. I got in. And at 17 years old, you're asked to make a choice of your career. You don't have the flexibility that you do in the US of saying I'm going to go try out different majors, different courses, and then pick what

my major is going to be. You have to pick. That's what you get.

And while everybody was going into computer science or at the time I know mechanical engineering was a big thing, I said you know what? Let me try this new thing. It's biotech. I don't know what it is. It was a complete chance I took at the time. And then I got fascinated. I was, like, this is -- you know, there's so much we don't understand about life and so much we don't understand about biology. And I got more and more fascinated. And I said I want to be a professor and study this for life.

And that was my incentive to come to the US was to become a professor. And then when I came here and did my research, I found that there was a bit of a glass ceiling. You know, if you're trying to make an impact as a professor, it's not that easy, and you needed to learn a little bit about the business end of things. And that's when I joined McKinsey and worked with a number of biotech companies.

And then obviously the choice I made to come to CRISPR was one where 30 or 40 different biotech companies had

tried to hire me before, and I kept saying no. But CRISPR was a no-brainer decision. The biggest thing that can come in biotech in the last 40 years, I need to be part of it.

Amit Sinha: What would you say is the hardest thing about your job?

Sam Kulkarni: I love my job. I like most aspects of my job. It's just great going into work every day and being part of making medicines.

The one thing that is hard for most biotechs and for me as well and managing failures. In a world where 80% of what you do fail, you have to keep the team -- one, you have to create an environment where you're celebrating the failure. What did we learn from that failure?

We had a drug for multiple myeloma that didn't do as well as we'd hoped for compared to the competition. We said what did we learn from that? What can we do with the next iteration of that program that's going to allow us to be better? Not just better than what we had before but the best in class? And then managing that team to make sure they're motivated to keep persisting. And that's what it's

going to take to get a drug eventually. It's never a straight line. There's always ups and downs. But managing failure but managing morale and motivation through that is something that's always challenging, but again it's part of my job.

Amit Sinha: Thank you, Sam, for spending time with us.