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CONVERSATIONS WITH MIKE MILKEN

Tal Zaks

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Mike Milken: Tal, thank you for joining me today.

Tal Zaks: Mike, it's great to be with you. Thanks for having me on the show.

We were introduced to each other many years ago by a mutual friend. I was impressed with your work then, and over a period of time you were eventually elevated to be in charge of the oncology program at Sanofi. But I'd like to go back earlier. Tal, both you and I had a love of mathematics, an affinity for mathematics, as young students growing up. What was it like growing up in your family?

My father was the president of the Israeli mathematical society for a number of years, so growing up I always had that very strong math background. My mother is your typical "do everything for the kids," very socially outgoing, empathetic person. My fascination with medicine and patient care actually started in the army. I think it stems back to that military experience. There was always this fascination with how to combine the right side and the left side in the sense of understanding the quantitative nature, caring about mathematics, but then making

> ***"The Chinese published the sequence on January 11. … On January 13, we started to manufacture our vaccine."***

This interview has been lightly edited for clarity and readability.

sure that my medical training was actually almost the opposite. I think that home life – of such a depth, but two very different worlds between mom and dad – in a way set me up for how I think today and how I act in this translation of science to medicine.

So we have many touch points in our life. One of them was you coming to the United States to work in Steve Rosenberg's lab at the National Cancer Institute. Many, many years ago, Steve was the very first of our young investigators – the enormous talent and opportunity we saw in Steve, and the desire to keep him in research. What was it like, and why did you eventually leave the NCI?

For me to have that opportunity to come to the NCI – it's the mecca of research in the field of tumor immunology. And I have to tell you, Steve himself is – I have not met anybody else like him in my life. The way that he has been able to embody his vision of what tumor immunology could be, not just in his science, not just in his caring for patients, but in one facet that is not often as recognized just because of our culture – in his mentorship and ability to train probably three generations by now of people who are steeped in that potential. I don't think anybody in our modern era has come close to that leadership and ability to foster the same passion in trainees.

You asked me why I left and I think the flip side of the story for me was I wanted to get back and complete my clinical training. I wanted to get back to the part of seeing patients.

You eventually moved to the private sector. First Sanofi, then Moderna. Take us through your decision to go to the private sector and then the decision to go to Moderna coming from a very large pharmaceutical company.

So, let me start with going to the private sector because that was the one that was probably the least obvious to my wife. In fact, I think for a while she was even disappointed in me. Here I was, I have just spent 18 years in training and being a physician and doing research and all of it steeped in academia. Why was I going to the private sector, to industry?

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If you actually open up a drug label – you know, those little white pieces of paper that we often throw away that are in the carton of the vial before we inject the medicine – those drug labels don't say this drug was made at the National Institutes of Health. They don't say they were made

by the U.S. government. They actually say they were made by private industry. So if you care about translating science into medicine, you want to understand how to make medicine. Well, then it behooves you to go to the place where medicine is made. I calculated that I would be between one and three logs more effective in industry than I would be had I stayed in academia.

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And the flip side of that was, okay, you have to learn how to work in a team. It's not all about you. Well, I kind of started my career figuring out how to work in a team. So that sort of made it obvious. You know, when I was a pediatric intensive care unit nurse, the first time I remember we did a procedure across a patient's bed. The physician who later became my mentor put his hand on mine and stopped me from cleaning up, forced me to look up at him, took a moment and said, *Thank you. I think that went really well.* I can tell you that "thank you" is still ringing in my ears 35 years later. It's the concept of working in a team where different people bring what they have to the table to make the magic happen that I actually enjoy so much in the private sector, and I think it's what makes the private sector so effective at being able to develop these medicines and translate science.

Now coming back to Moderna. When I joined Moderna there were elements that I found just completely irresistible. And again, why would somebody who's a tumor immunologist and running one of the large pharma groups to develop drugs in their domain – why would I leave all that and go to a small company that was preclinical at the time? We didn't have a pipeline, we didn't have anything in the clinic. And again, my wife kind of looks at me and says, are you sure you know what you're doing here? And the answer for me was as follows.

First, the company's mission has been always to translate the potential of mRNA into medicines and vaccines. And the company had always seen that potential as actually building a completely new class of medicines. And with that, it opens a world of opportunities that have not been opened before. You can make a completely different kind of drug and a completely different kind of vaccine with it. And with that you can go after targets that traditional medicine has found really hard to target. You can go after targets that are inside the cell and not just outside the cell floating in the blood. You can go after a combination of targets. So when you have five proteins that have to come together and to form a function, we can actually put five different mRNAs together in a vial, and it works. That intellectual challenge forced me to think about drug development orthogonally different. It was no longer about how do I take this drug and make it into a

cancer medicine. It was suddenly, if I could get this to work, what kind of medicines and vaccines could we make? For somebody who's come to define their passion as translating science into medicine, this was a completely new and much more profound way of taking on that challenge. If we would be successful, it would have implications and impacts far beyond what I could envision at the time. But the allure was there.

The second element was speed. So one of the most frustrating things about translating science into medicine is that science has been moving at phenomenal speed and speed that is ever-accelerating, and yet medicine – if you think about clinical trials and the need to demonstrate that something that you think has potential actually does have that potential – clinical research hasn't really kept up. And so that connecting space has become really challenging. Here was a technology that it was conceivable because it's all synthetic biology – it all happens in water; you can condense it; you can make it faster; it's all based on enzymatic processes. It was conceivable that you can go in months from an idea on a whiteboard to a new drug that you're testing in man as opposed to years. Now that was a potential when I joined five years ago. We have since actually turned that aspect into a reality time and again.

"We make the messenger RNA that encodes just for that little snippet of the virus. … That's our vaccine. … It teaches the immune system now to recognize the rest of the virus."

When *FasterCures* was formed, the concept was what you've just said: Science is moving forward and the speed is accelerating, but the challenge was other parts of the equation – infrastructure, legislation, approvals – were like the tracks. So you had science as a train – and trains might be able to travel at 200 miles an hour – but they're traveling on tracks, and those tracks don't allow them to move forward at that speed. I want to talk a little bit about what you've done that allows science to accelerate. You spoke about mRNA and the uniqueness of being able to do this. I'd like you, if you would, to spend a couple of minutes talking about this technology that allowed you and Moderna, in 63 days, from having the molecular makeup of the virus to putting in a human being.

All of our cells have the same DNA in them. That's our nucleic acids. That's our genes. But different cells have different functions, right? A skin cell is different than a cell in my eye. And what makes different cells unique, they all have the same genes, but it's different parts of those genes that get translated into proteins. And it's the proteins that every cell makes that makes that cell unique.

The way that we translate our genes into proteins is through an intermediary. Think of a carbon copy. It's a temporary copy of a part of our genes that tells that cell to go make that kind of protein. And that temporary copy is the messenger. That's called the

messenger RNA. Because every protein that's made is made via a messenger RNA that tells the protein-making machinery what protein to make, if we could introduce our own sequence into that equation, if we could put our own messenger RNA, we could actually coax a cell to make a protein that is not necessarily in its genes, that it didn't know it was supposed to make. And that's the fundamental biological concept of messenger RNA.

So what do we do when we make an mRNA vaccine? We don't teach the body to recognize a virus by giving the whole virus or making bits of the virus. We basically just take the information, the genetic code of the virus, and we go and we make the messenger RNA that encodes just for that little snippet of the virus, and that's what we give the human body. That's our vaccine. That's what we inject into the muscle. Once it goes into the body, it goes into some cells and it actually then teaches those cells; those cells go off and make that protein. Once the cells make the protein, that protein is displayed to the immune system, and it teaches the immune system now to recognize the rest of the virus. So that is the fundamental biology of all of our drugs and all of our vaccines.

"This investment of the U.S. government, while substantial, recall that proportionally it comes on top of billions of dollars that the private sector has already invested in Moderna. Had it not done so the government wouldn't have this opportunity to invest and we wouldn't be sitting here talking about the potential to have a vaccine available for the broader public in the coming months."

The reason that we can go so fast as you mentioned is because we're starting from information. The Chinese published the sequence on January 11 of SARS-CoV-2. On January 13, we had all the information. We had decided this is going to be the sequence of the vaccine. On January 13, we started to manufacture our vaccine.

Where our technology can move very fast is, first, we start from digital information. Second, our process is such that we can move in weeks and months and not years. That's a tenfold improvement. And finally, we have the ability to do combinations in a way that traditional medicine struggles to do. Traditional chemistry really has a hard time doing it. I'll give you one example. We've got one vaccine against two viruses together and we basically combine the two in one vial and the cells make the two different proteins at the same time.

You mentioned the point about *FasterCures*, and I applaud you on that. I'm going to use your train analogy because it's something that I've been reflecting on – thinking of what does it actually take to be successful if you want to move faster? A number of years ago, my wife and daughter and I went to Japan and we took one of these bullet trains from Tokyo to Kyoto, and I've never been on a bullet train before. Now when you get on a train and you look out the window, you have an expectation for what the landscape is

going to look like. And so you focus naturally at a certain distance where you kind of watch the buildings in the landscape go by. Well, when you're on a bullet train, it moves so fast that if that's your focus, everything's a blur. The only way to really get a sense for the ride is to look far out. If you focus on Mount Fuji, which you can see halfway through, then you get a sense of the journey and you understand where you're going. But if you try to focus on the usual distance as you would in a normal train ride, it's a blur. And I think people like you and others who've had the vision to put the focus point further out and understand what it takes, I think have allowed the rest of us then to come with our own version of a bullet train and have those train tracks be ready for us. Without that vision that is appropriately far out, you can't really change the pace and the understanding of the landscape as it evolves around you.

Tal, the world is hoping for the Moderna vaccine to be approved for COVID-19. My personal interaction with the company has focused on how to accelerate. And obviously the breakthrough was the United States government, through BARDA, realized that the effects of this COVID-19 crisis are so devastating that we can't wait to see if it works and then make it, we need to make it and then hope it works. And if it doesn't, the cost to make it as very small relative to that. What has to happen over the next few months as we look out to September, October of maybe widespread deployment of the Moderna vaccine?

So Mike, first of all let me say I think we are, in this country, in a uniquely fortunate space by having the professional government agencies and their ethos of civil service, and I truly salute them. We were discussing with Tony Fauci last October the potential, the theoretical benefit, of using an mRNA technology for a pandemic threat. And we were talking to his team – John Mascola, Barney Graham – about what should be a demonstration virus where we could leverage what we thought was a very rapid potential with technology. And unfortunately here we are, three or four months later, and we actually have an acute need to demonstrate that.

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I expect we'll translate into a very thoughtful and expedient look at the clinical data as it emerges so that we pick the right time and the right amount of data that allows us to responsibly immunize the people who need it the most. And so, as I look at the months ahead, I'm not thinking of this as a black-and-white "when will the vaccine be approved?" I'm actually thinking about this as gradations of approval so that as the earliest data come in and substantiate our expectation for benefit, even if we haven't proven it yet, we're already starting to immunize those who

are at greatest risk. And over time, as our confidence and the data mature and grow, we will appropriately be vaccinating broader and broader segments of the population. The last piece I'll say on that front is, in this fight, where we are today – this is May of 2020 – there's a lot of other companies and a lot of other approaches that are trying to generate vaccines. I wish them all success, and we all need to be successful here. I have only two competitors in this race: the virus and the clock.

The public read that the Biomedical Advanced Research Development Authority (BARDA) announces a $483 million partnership with Moderna.

That grant allows us to do two things. The first is to scale up manufacturing. We so far have demonstrated time and again that we can effectively immunize people. But we're a young company and we've yet to scale to manufacture to be able to deliver the millions of doses that would be required. And so that investment has to happen ahead of time and at risk, in parallel to the clinical development. Otherwise we'll never get there in time for the many people who are going to need it.

The second thing this grant does is it allows us to run the clinical trials to demonstrate the potential and the benefit/risk profile of this vaccine. So that grant for us is very enabling. Again, we are a relatively young company. We have not yet brought anything to market. If you look at companies that have a profit and loss, as my CFO told me years ago, I'm the guy who's responsible for the loss – I spend the money. And I say that tongue-in-cheek, but this is an investment in our future at this stage. And without that level of investment, we're not going to get there.

If you step back and take that wider view of the company, my sense is that this investment of the U.S. government, while substantial, recall that proportionally it comes on top of billions of dollars that the private sector has already invested in Moderna. Had it not done so the government wouldn't have this opportunity to invest and we wouldn't be sitting here talking about the potential to have a vaccine available for the broader public in the coming months.

Our mutual friend – Mark Simon, who brought us together – we did a study in the late 1990s where we looked at Merck's market cap, and its valuation was larger than all the biotech companies combined. But the biotech companies combined were spending 3x, 4x, 5x as much money on research and development as Merck. And then a number of years later we see that just one of those biotech companies became more valuable than Merck. So this investment that you describe as the *loss* is really the future and the importance of investing in the future. What Moderna has done that you've talked about exciting you was a whole new way where your body makes the medicine to treat the diseases from that standpoint. Are there risks in moving too fast that we should consider here or has your technology eliminated a lot of those risks?

So look, Mike, I'm a chief medical officer. The number one thing that keeps me up at night is always patient safety and subject and participants safety. So this is a young technology and we don't know what we don't know. So I don't think we've eliminated the risk. I think by virtue of having tested this in 1,500 subjects across 10 or 11 different clinical trials to date, we have a pretty good emerging understanding of the risk and so far it looks like what you would expect from a typical adjuvanted vaccine, but this is still a relatively small database in the grand scheme of things, and we need more safety experience.

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That being said, what is the benefit that you anticipate, what is the risk that it entails to people who take the vaccine or the drug, and is the benefit worth the risk? I think in that context, if you look at the unmet need today that COVID-19 disease poses to our society, then if a vaccine could come in and change that, ameliorate some of that, prevent some of that, then the benefit would be larger than probably what we've seen in our lifetime for a palpable benefit from a vaccine. And this is not to dis all the other important vaccines that people get and without which our pediatric mortality, infant mortality rates, and overall survival wouldn't be so good. We take them for granted these days. But that unmet need today is so palpable that I think that benefit, that magnitude of benefit, is really significant. So whatever risk we have – and there are risks and there's always risks of unknowns – has to be taken in context of that benefit.

Tal, do you believe we'll be able to use this technology to bring individual treatments to individual mutations or even to deal with genetic problems that can be corrected?

The world of potential applications is quite large. If you look at genetic diseases, I actually think that is going to be the next frontier where we demonstrate the utility of this technology. We were on the verge of dosing our first pediatric patient with a rare disease when COVID hit. Obviously things have slowed down a little bit right now out there in the world of clinical research. But if you think about the potential to teach cells in the human body how to make a protein, an obvious place to go is to a genetic disease where a kid is born missing an enzyme. And for some of these rare genetic diseases that we've been working on now for a number of years, the only standard of care for these children is really a liver transplant. We believe that it should be possible to just give them the missing information via the infusion of a messenger RNA that encodes for that. And

if we can get the technology right, it will go into their cells and actually make a protein. In fact, on a different application last year, we've already proven the principle that that is doable. So I anticipate that you will see many applications in the coming years based on this technology that have nothing to do with vaccines and everything to do with genetic medicines and rare diseases that are a function of hereditary mutations that we're going to be able to correct using messenger RNA.

Tal, thank you for joining me today. And we look forward to what you and your colleagues at Moderna will be capable of doing to hopefully bring COVID-19 to an end, but also to deal with other life-threatening diseases in the future. All the best to you and your family.

Mike, thank you so much for having me on today. It's been a true honor and a pleasure, and I deeply appreciate your leadership and the leadership of the Milken Institute in everything we've talked about today. Thank you.
