CONVERSATIONS WITH MIKE MILKEN

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Director, National Center for Advancing Translational Sciences (NCATS)

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Mike Milken: Chris, thank you for joining me.

Christopher "Chris" Austin: It's good to be with you.

It was 25 years ago that we made the decision to put on The March. We brought a half a million people to Washington to finally get the efforts coordinated to double the National Institutes of Health budget and triple the National Cancer Institute's budget. But a number of years later we began to be concerned if the country was going to maintain its commitment to medical research. As we looked at the landscape, the first thing we did was decide to put on an Innovation Retreat: government agencies, policy makers, academic research centers, bioscience communities from around the world, philanthropists and a lot of entrepreneurs. We brought them all together to imagine a new organization that could accelerate medical science. As an outcome of that, work began on what is now call NCATS, the National Center for Advancing Translational Science. It was established by Congress with a funding commitment of more than a half billion dollars a year for a decade, and it culminated with our efforts and putting on the Celebration of Science in 2012.

This interview has been lightly edited for clarity and readability.

You have led NCATS from its inception. It's a critical organization, yet most of the people in the United States have never heard of it even though its role is so important. I'd like Chris, if you could first explain the difference to our listeners between basic science, translational science and clinical science, and then let's talk about why NCATS was needed and what its mission is.

Well, thank you Mike. I just want to thank you for your vision over the years. Your involvement has played a critical role in multiple stages of this evolution. Basic research, sometimes called fundamental research, is looking at how living systems work, when they work well and when they break. How do proteins and genes and cells and organs normally function? When they go wrong, when disease happens, why did they go wrong? That's absolutely critical for diagnosis and as a basis on which to intervene. But of course that knowledge itself, as many parents have told me, is not sufficient.

I had a mom characterize this once beautifully by saying, 'I love basic research and I love publications, but when my daughter gets sick I can't give her a publication.' On the clinical side, if you have an intervention, if you have a drug, a device or a behavioral intervention, a medical procedure – how does it work? Does it really work? Does it have the effectiveness and safety that you think, in what patients, and in what circumstances? But in the middle is the critical translation step, which is developing the intervention in the first place: developing the drug or the device or the behavioral intervention or the medical procedure, and showing that it's safe. That aspect, that critical connector of translation, is a very complicated process of going from a gene all the way to an intervention in the community. That's about a 20-step process that has currently about a 0.1% success rate and can take two to three decades.

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The critical thing about NCATS, and this gets to why it was formed, is to begin a new science. That is the science of translation – to understand the general scientific and operational principles by which this process happens. We will convert this from a mainly trial-and-error, mainly error, inefficient, ineffective process into a predictive science. That is what NCATS has brought to the field.

Obviously, as you know, accelerating science saves millions of lives. Let's take an example if you'd like of any particular disease or treatment and walk us through what happened at the basic, translational and then clinical phase.

I could use COVID-19 as an example because COVID-19 illustrates all of the translational roadblocks that characterize virtually every disease. The basic science of COVID was worked out in lightning speed, and it's a great example of how the public's investment in NIH over the last 50, 60 years has paid off, and from other countries around the world. The understanding of the virus sequence, its cellular receptors, how it gets into cells, what it does to cells, what it does to organs – all that was worked out very, very quickly. The problem then became, how does one intervene if you have a diagnosis? What patients want is not just a diagnosis, they want a treatment. In our case, we very rapidly took those discoveries out of the basic lab and developed a series of about 20 different, what are called assays, just a complicated word for a test. It's something that allows us to test thousands or hundreds of thousands of potential drugs across every potential Achilles heel this virus or its cellular receptors have to prevent them from functioning.

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We used not only very large compound chemical collections that we might be able to make new drugs out of it, but of course, like your own organization, we focused on so-called repurposing all the drugs that have been approved by regulatory agencies worldwide. We did an awful lot of screening looking for novel therapies. But it was important, particularly in this moment, to get that information shared as rapidly as possible. We've created an open-science browser where all that information is on our website so everyone can use it, everyone can contribute to it. That will give us additional potential treatments that can be tested in people.

On the clinical side, at the same time, we've very rapidly organized our trial innovation network to share information about how they were handling patients in real time in their academic health centers; the research they were doing; connecting people who wanted to do the same research to eliminate duplication and increase efficiency; and novel ways to get these studies done in a much more rapid, effective way. This is what the trial innovation network focuses on.

At the same time, we focused on more public health aspects where there are thousands, hundreds of thousands of patients going to hospitals all the time. But given our healthcare system and our electronic health record system, it's not always easy to figure out where those patients are, what their characteristics are, what drugs they might be on that might be helping them or hurting them. We very rapidly pivoted informatics, the so-called data effort that we had been working on for about three years, to tie all of these 60 centers around the country together. Cumulatively, they take care about 200 million people in this country; it's an absolutely unique national resource. We tie all those together in a common electronic health record system that will allow these centers to put all their data into a central place to be examined. That's something called the National COVID-19 Cohort Collaborative, or N3C, which just went live about two weeks ago that we're very excited about. We're really covering the waterfront from right after the basic research lab, taking that football and running it down the field to identify new drugs, moving those into clinical trials as rapidly as possible, and then looking at real-world evidence in hospitals, how patients are actually being treated.

If I had told you a generation ago that there was a virus and that the DNA of that virus would be posted for the whole world to see in a couple of weeks. Then 63 days later, there would be a vaccine that went into a human being. Moving from basic to translational to clinical in nine weeks, you would have said, 'Mike, that's absurd.'

Most of the vaccines that we all got we were kids are vaccines that are killed or inactivated in some way; people try to use proteins for those as well and still do. But Moderna [Therapeutics] had this crazy idea that maybe you could use the translator protein – that's literally what's called the translator molecule, the messenger RNA, which is used as the vaccine instead of the protein or the virus itself. It made perfect sense theoretically, but nobody thought it would work. But it appears to. The reason this is so critical is that using the mRNA [messenger RNA] is derived directly from the sequence of the virus. As soon as we knew the sequence of that virus, we were able, and Moderna was able, because you can make these molecules now in the lab, to actually make an mRNA molecule. And that became the vaccine. Then we just inject that.

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So how do we actually design a trial to demonstrate that it really does work? What do we have to measure the biomarkers? What do we have to measure to give the regulators

confidence that, if we're not going to wait for a protective response like you normally would have for a vaccine, what is going to give FDA the assuredness that they should approve this? How do you know who to give it to? Do you have to worry about immunocompromised people or not? And then the big deal, how do you make enough of the stuff? We've never had to deal with trying to make a billion doses of a vaccine from ground zero. This gets back to something that Mike, I know you like talking about, is that thinking about the means of production, the manufacturing, those kinds of technologies are translational technologies too.

We're able to do things much more rapidly in the early stages. But I'm afraid that for the most part, the later stages are still as slow as they normally have been. It's one thing if you look at the well-meaning debate currently going on: the debate among vaccinologists and public health people is that this is a unique-in-this-century public health challenge. Are we going to require the same level of evidence for a vaccine or a diagnostic for that matter, before it is approved? Could we potentially begin to use it at the same time we're still studying it? Normally we would never do that, but it's kind of translational innovation that this COVID crisis is making not only possible, but needed.

This particular vaccine, which is only one of more than 120 vaccines we are monitoring and only one of 10 that we already know have gone into human beings, is a potential game changer: the idea that I give you something and then your immune system effectively creates that vaccine for you. The United States government under BARDA [Biomedical Advanced Research and Development Authority] gave them a grant of $483 million to build manufacturing capacity to make the vaccine prior to knowing if it works.

As you have intimated, Chris, the stakes are so high that the cost of doing this, while large at almost a half a billion dollars, pales in comparison to what the economic and human costs are. We're well aware of what's occurred, with shutting down research laboratories or not treating others with other life-threatening diseases. How is NCATS dealing with your work on so many other life-threatening diseases while it's had to concentrate on COVID- 19?

This is something that concerns us greatly. I have begun to become concerned that the number of people who die as a result of the kinds of delays or absences of taking care of other diseases may end up rivaling or even exceeding the deaths we have directly from COVID. Our focus on COVID is appropriate and we're all doing it. I'm doing it too. But it's easy to forget that there are 7,000 other diseases which are not waiting and their progression for us to figure out COVID.

Cancers are not going to go into remission and take a time out while we deal with COVID. ALS patients are not going to stop progressing because we're dealing with

COVID. That research has, to a great degree, stopped. Those clinical trials have to a great degree, been suspended, at least in their recruitment of new patients. They're being seen if they're already in a trial on a bare bones level, but it's very clear that the screening for cancer has gone down about 30% in the last couple of months. We know cancer screening saves lives, so it stands to reason, if that screening goes down, it will cost us lives. Same thing with things like heart attacks and strokes. The number of heart attacks and strokes showing up in the emergency room has gone down, depending on where you look, 40 to 50%, apparently because people are afraid to go to the emergency room because they're afraid they're going to get COVID. But there is no reason to believe those heart attacks and strokes are not happening, they're just affecting people at home. And those people, if they die of an MI [myocardial infarction, or heart attack], they're not going to be listed as dying of COVID. But they really did.

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We at the NIH and I particularly am very concerned that we've seen the most in rare diseases. Mike, I know you know this, there are of the 7,000 or so diseases that affect the human family, 95% of which have no FDA treatment at all. That's a number that's just emblazoned into my brain – 95% of diseases which affect the human family have no FDA approved treatment at all. Of those, about 90% are rare diseases; less than 200,000 in the country and those are diseases that a lot of us have heard of. Cystic fibrosis, Huntington's disease, sickle cell anemia, et cetera. But there are many, many others and they tend to be rapidly progressive, disabling, and a cause of premature death often in children. We have heard a lot from that community saying, 'we can't get in to see our doctors, we can't get the treatments we need, we can't get our child diagnosed because nobody will see us.' One of the urgencies that we feel, and one of the reasons we're all beginning to work so heavily in diagnostics, is that we have got to open the research and medical system again to allow those patients who are getting sick and potentially dying out there, to get into the system. That kind of collateral damage, I think we're only going to really understand once a little bit more time passes.

Now I should say that for many diseases a two-month delay, it's probably not the end of the world. But I can tell you as someone who had a rare cancer melanoma a few years ago, if I had not had that diagnosis when I did, my oncologist estimated that two weeks later it would have been metastatic, given the pathology.

There is one other thing that I might say if you don't mind: we talked about collateral damage and that is very real, but I'm a big believer in collateral benefit. What do I mean by that? Mike, you and I spend a lot time trying to rally people to the need for *FasterCures*. For many people it's hard to get them to buy into that because they themselves or their family members are not acutely ill right then. Something that we come across over and over and over and over again, is that people who are disinterested in this translational problem, the week after they or their family member is diagnosed – they are all in. 'Why is the system so inefficient? Why is it so ineffective?"

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It doesn't have to be this way. Let's change, innovate on the process. Let's do everything from making drugs or vaccines to clinical trials and deployment in the community. That can all be innovated on to increase efficiency and effectiveness by 10- to 100-fold. I'm absolutely sure of that. But it's hard to get people who are not motivated because they themselves are not sick at that moment to realize that.

Here we have a singular moment when everyone realizes the need for faster cures and the limitations of the current system to deliver them. I would like to think that the message that *FasterCures* has been promulgating for all these years, and you have personally, and the tagline that NCATS uses, that 'it's our job is to get more treatments to more people more quickly,' is saying the same thing. This is a teachable moment. I'm so hoping we will not go back to the old [ways] and people will really stay on with this effort.

The other thing that I'm seeing which is very, very encouraging, is that in many of the behaviors that you and I have advocated for years – of teamwork, of data sharing, of connecting, of siloed experimentation to be able to separate the wheat from the chaff more quickly – we are seeing that on a scale I have never seen across NIH, across government agencies and with the pharmaceutical and biotech industry. I like to think, and I hope this isn't just my inveterate optimism speaking, but I'd like to think that all of those players will demonstrate to themselves how much more productive this is, and how gratifying it is to be that productive, and that that will serve as a return on investment for them. That will make them think twice before going back to the old siloed world, which you and I have been trying to change for the last many years.

Chris, I couldn't agree with you more. The level of cooperation which we've been pushing for 50 years, today is at a level unseen. It's the large employers that are allowing testing in their parking lots. It's the opening up for people to use things off patent without royalties. But there's something else you said. It's a way I have lived my own life over decades. When I speak to a person that's been first diagnosed with a potential life-threatening disease, when you talk to them, as you know Chris, it focuses your attention because nothing else matters at that point. I have made it my mission to make sure I talk to 10 people a week who either have been diagnosed for the first time with a life-threatening disease or have had a reoccurrence. When you do that, you are focusing at a very raw point in emotions. It's not that I was diagnosed a year ago and I've been on treatment, but right then and there it makes you focus on what should you do today and what you should do tomorrow. Chris, I do hope as you've stated, that this has been so devastating, not just medically but to people's way of life, that we will not go back and it will be one of the lessons learned from this experience. Thank you for joining us today and for your commitment to science.

Thank you, Mike. It's been wonderful being with you and I look forward to continuing on this journey we're on together.
