CONVERSATIONS WITH MIKE MILKEN

Francis Collins

Director, National Institutes of Health

December 23, 2020

Mike Milken: Francis, thank you for joining us today.

Francis Collins: Hey Mike, it's great to be part of this conversation with you. We've been doing stuff like this for quite a few years haven't we?

This is our fourth decade together. Francis, as we think about what's occurred this year, I'd like to break our conversation today really into three parts: the past, the present and the future. Let's start today with what happened over the previous decades that allowed us to move as quickly, to create things such as RNA vaccines, to move clinical trials, for you to reach a level with industry, academics, government agencies of collaboration, both internally in the U.S. and around the world that really has never been achieved before in the life sciences, except maybe during those efforts on the Human Genome Project, which you led. Talk about the key elements that were in place that allowed us to move as quickly as we've had over the last eight to 10 months.

Mike, that's a great place to start. And I do think it's really important when we are talking about advances in science such as we have seen happen in this remarkable year, to recognize that they were built upon a foundation, and that foundation has to be invested in over the long-term if you're going to expect to have this kind of responsiveness. A couple of the things that you mentioned on the larger scale, certainly the genome project was a new effort in life science to bring together scientists from across the world, 2,400

This interview has been lightly edited for clarity and readability.

of them working together, not worrying too much about who got the credit, coming up with very stringent rules about what had to be the quality of the data and the data released. And everybody kind of got into that, and that changed the approach, at least for genomics, and increasingly for other things.

On top of that, we learned a lot about nucleic acids. The opportunity to be able to not just read DNA and RNA, but synthesize it, emerged as part of that. And if you look at how we got to these mRNA vaccines that Pfizer and Moderna have generated, it is built upon 25 years of deep investigation of whether in fact, mRNA might be useful as a vaccine by basically putting the instructions for a protein into muscle cells instead of the protein itself. And there was a big breakthrough that had to be made so that that RNA could be stable, it wouldn't break down, and it wouldn't cause an inflammatory reaction and years of hard work.

> **"It has been a year of terrible tragedy. And yet it's also been a year of heroism: the first responders, the healthcare providers. But I also think there are heroes in the research community, in the business community, figuring out how to band together to try to help those who are helpless and need that assistance."**

And much of it, I have to say actually done at NIH at our Vaccine Research Center, got us to this point where then as we've all heard, in just a few days after learning the sequence of SARS-CoV-2, that first vaccine was designed and got into individuals in a Phase One trial 65 days later. People marvel at that, but marvel at the way in which all of those things had to be done over the course of many years to make it possible and to have this kind of collaboration possible, building in fact, out of the genome project experience and other things where we've figured out how industry and academia and government can work together in ways that previously weren't really tried, and which are turning out to be really empowering and successful.

When I think back at the 1970s, 1980s, 1990s, it was 1995 when we had the first ever National Cancer Summit. We got eventually to The March in 1998, which really culminated the work of thousands of people, where we doubled the NIH budget and President Clinton signed it into law, tripled the National Cancer Institute budget, increased funding for the FDA, CDC and others. And the efforts that we had in 2011 how to innovate and accelerate medical research that led to NCATS [National Center for Advancing Translational Science]. But as you and I began talking in February, I had mentioned to you, this time was different. Capital was going to be made available. The government understood the issues. And what did this increase funding allow you to do?

Looking at where we were in the early part of 2020, it was clear to me as the NIH

director, that we had resources in terms of scientific capability. We had talent. We had

technologies. But if we were really going to tackle this worst pandemic in 100 years, we're going to need to bring all of the skilled-set folks together around the same table and see what we could do and how we could do it faster than it'd ever been done before.

At that point, things were a little scattershot for a while. Everybody had ideas, but there wasn't a real sense of prioritization. It wasn't clear how clinical trials could be sped up to test out vaccines and therapeutics.

So with some calls that I made to leaders in industry who I've gotten to know over the last seven or eight years as we have done various things together in something called the Accelerating Medicines Partnership, it was pretty clear there was an appetite in industry as well to kind of break the mold here. Let's all get together, not worry about who's going to get the credit, try to keep too many lawyers from getting involved and building too many documents that are going to take us too long and slow us down. And out of that was formed what's called ACTIV – the Accelerating COVID-19 Therapeutic Interventions and Vaccines, which in the space of just two weeks went from an idea to becoming a reality involving about 100 people who dropped everything and worked 24/7 to see what could be done to advance the science that we needed to tackle COVID-19.

"Congress gave NIH $1.5 billion and said, 'go do something about diagnostics.' Four days later, NIH essentially set up a program to perform the role that you would normally see done by a venture-capital organization setting up an opportunity for those small businesses or academic labs that had come up with some really cool new ideas. The ones that look most promising got put into what was called a Shark Tank."

About half those people came from industry, half from academia or government, including FDA as a critical partner; also CDC, the Veteran's Administration, BARDA [Biomedical Advanced Research and Development Authority], multiple institutes at NIH and 22 different industries represented at a very high level; an executive committee that I co-chaired with Paul Stoffels of Johnson & Johnson, trying to steer this effort.

The results have been nothing short of dramatic and historic in the space of just a few months. That group, under the ACTIV umbrella, has written master protocols, which is where these vaccines are now being able to go forward because you don't have to reinvent that every time you start a new trial. They figured out how to organize clinical trial networks so that they could be quickly shovel-ready and ready to go when there's a trial that needs to happen. They took what was more than 600 different therapeutic ideas, and Mike, your effort at *FasterCures* was part of trying to compile that inventory, and then figured out how to prioritize them because you can't do all of those at once. And out of

that has come such things as remdesivir and therapeutic monoclonal antibodies that look as if they provide benefit if you get somebody early in the course of illness.

All of that happening in a dramatically rapid timetable by people who I must say have demonstrated their commitment by working day and night to make things happen that normally would take many, many years. It happened in two weeks. When people say, 'well, you just can't do things that quickly,' we now can say 'yeah you can' in many instances if you really have to; it's amazing what you can do.

Our discussions over the years, Francis have really focused on collaboration. The response from the industry was significant, shutting down production to open up manufacturing facilities for new products that might work here. Let's talk about your efforts to advance diagnostics quicker.

> "It's really important when we are talking about advances in science such as we have seen happen in this remarkable year, to recognize that they were built upon a foundation, and that foundation has to be invested in over the long-term if you're going to expect to have this kind of responsiveness."

Let me explain what RADx is, because this is another really dramatically new approach that NIH has not previously invested in.

RADx is Rapid Acceleration of Diagnostics. We all recognize that if we're going to get an end to COVID-19, we need vaccines and therapeutics, but we also need the opportunity to do diagnostic testing cheaply, rapidly, point of care, even at home. And yet as this particular pandemic began to spread across the country, most of the testing was being done in large-scale laboratories with turnaround times of at least a day or two. And it was not the point-of-care option that you would really most want to see.

On April 25th, the Congress gave NIH, as part of one of their supplements, $1.5 billion and said, 'go do something about diagnostics.' Four days later, NIH essentially set up a program to perform the role that you would normally see done by a venture-capital organization, setting up an opportunity for those small businesses or academic labs that had come up with some really cool new ideas about how to detect the presence of this virus.

And they came in, hundreds of them, as applicants. The ones that look most promising got put into what was called a Shark Tank with business experts, engineering experts, technology experts, to see whether their particular platform had promise. If it did it moved to the next phase for validation, and then to the phase after that, where it got significant funding to scale up and to begin to actually contribute testing in the real world.

We now have 22 of these technologies that have come all the way through that innovation funnel and collectively are adding about two million tests a day, much of that being point of care. And we're about to investigate in a larger-scale way how to make this work for home testing. This is pretty dizzying when you consider this started in April and here we are in December, but it is basically the kind of thing that we can do now with some authorities we got in the 21st Century Cures Act something called Other Transaction Authority [OTA], that make it possible to do things this fast, kind of like DARPA [Defense Advanced Research Projects Agency] does. It is basically borrowing the DARPA model for NIH.

> **"When people say, 'well, you just can't do things that quickly,' we now can say 'yeah you can' in many instances if you really have to; it's amazing what you can do."**

Learning from this, I think there are other applications like this that we could apply. And certainly since this isn't the last pandemic or the last need for diagnostic testing, I'm hoping that this particular kind of innovation funnel can live on even after we get through this crisis.

So I think Francis, if we could create a permanent structure at the NIH with its leadership, how would that work going forward in the future to address worldwide challenges in the terms of health?

Clearly it would be beneficial to have an ongoing structure to try to be prepared to do the scanning for the next pandemic, to be able to identify small molecules that might work as antivirals. We screened all approved FDA drugs or any drug that's ever been approved by any country to see if any of them had activity against SARS-CoV-2, and we got a couple that seemed promising. Remdesivir is certainly one of those. But for the most part, there wasn't time to do the full soup to nuts screening of large-scale libraries to identify promising compounds.

And that is something that we really wished we had had, and need to have the next time. So one thing – and industry is also pretty excited about this – that we need to do is to come up with a strategy to have that kind of capacity and already begin to look, for instance, for polymerase inhibitors or protease inhibitors that would have broad applicability against all coronaviruses, because we probably haven't seen the last one of those. We could do that together. We could do that in an anticipatory way if we had an active partnership to drive that with appropriate oversight and resources. We can learn from this experience that it doesn't have to be just a crisis. We can do this in a more preventive way as we imagine what we might need coming a few years from now.

We have a model Frances that we've put forth probably since the 1950s, and that was after Sputnik went up, the creation of DARPA, and the idea that we would not be behind in science again and be prepared. It still exists today. And one of the lessons from DARPA over the last 60 years now has been the ability to fail and try again. If we're going to demand 100% success, we're never going to be pushing "out the envelope." When you went over the last eight to 10 months, I remember that every day someone called us at FasterCures with a new idea for testing. I only can imagine how many you saw, because we passed them on to you to deal with. With government structures, can we get the NIH to have something like DARPA inside of it?

I think we did that with this RADx initiative. We've done it in a few other places before this, using this Other Transaction Authority for such things as a gene-therapy approach to sickle cell disease, for instance. But we haven't quite done it this way, where we effectively stepped into the role of being a venture-capital organization and had that very robust innovation funnel. We had 700 applications for RADx; 100 of them made it into the Shark Tank. But as you heard, only 22 got out the other side. There was a lot of failure here.

> "It was pretty clear there was an appetite in industry to break the mold. Let's all get together, not worry about who's going to get the credit, try to keep too many lawyers from getting involved and building too many documents that are going to take us too long and slow us down. And out of that was formed what's called ACTIV – the Accelerating COVID-19 Therapeutic Interventions and Vaccines."

I think though, the applicants who didn't get all the way through learned, and some of them are coming back now trying again because they've fixed some of their problems. So it's not just a destructive process. It's also constructive.

We could do this in other spaces as well having had this experience. Again, I think the Congress has expressed some confidence in us by giving us these authorities. And let me say the Congress in the course of the last five or six years has been wonderfully supportive of NIH, basically counting on us to rise to the occasion for cancer, for Alzheimer's disease, for diabetes, for rare diseases, for common diseases, by this slow steady increase in our support that you could kind of count on taking risks and not be fearful. We can't do these innovative things if we don't have that confidence that the resources are going to be there and they're not going to be suddenly in this rollercoaster mode of up and down, which is so harmful to science.

I want to move if I could Francis to an area that you and I really worked, on the birth of,

and that's NCATS. If you remember the bipartisan effort, Speaker Pelosi, Majority

Leader in the Senate Harry Reid. At the time, the majority leader in the House, Eric Cantor, Senator Inouye and so many others were with us on that effort. What role has NCATS played – the National Center for Advancing Translational Science – in accelerating our work here on COVID-19?

It's been absolutely fundamental. NCATS, being the first new component at NIH in a long time, established for scientific reasons, they had a lot to do with our efforts to try to make sure we had optimized the screening of all existing libraries to see if there might be compounds there that would be active against SARS-CoV-2. They set up probably the boldest effort that I've ever seen to get everybody to contribute their clinical data so that we could learn from what's happening with patients who are affected with COVID-19, something called N3C.

> "Congress gave NIH $1.5 billion and said, 'go do something about diagnostics.' Four days later, NIH essentially set up a program to perform the role that you would normally see done by a venture-capital organization setting up an opportunity for those small businesses or academic labs that had come up with some really cool new ideas. The ones that look most promising got put into what was called a Shark Tank."

And they've because they also run the network of some 60 clinical and translational science institutions across the country, they've been a major player in our clinical trials, including right now running one on immune-modulators called ACTIV-1, which we hope will give us some additional insights into how to help the people who are the sickest with COVID-19 in the ICU in a cytokine storm that needs to be somehow settled down. So yeah, they're everywhere you look when it comes to what we've been doing to respond to COVID-19.

We have seen over 50 years in our various foundations, the highest rate of return we've had has been supporting people early in their career. And earlier in their career is generally in the early thirties. They've been going for PhDs, MDs, fellowships, internships. residencies. Talk to us a few minutes about how this could help us in the future, Francis.

Mike, I'm glad you're bringing it up. This is a personal passion for both you and me, and we are pushing as much as we can right now to try to be sure that those early-stage investigators who are feeling the pinch right now with all the things that COVID-19 has done to the enterprise. We want them to feel reassured that there's a career path, and boy do we need them right now with all the things that are possible.

One of the things I did was to set up a program that allowed talented doctoral students to go directly to faculty positions without having to pass through what might be a three-, four- or five-year post-doc. Postdocs are good. We need postdocs, but not everybody is well-suited to that. And sometimes we slow people down. And so now there's a program to skip that if you're one of those people that is already independent-minded and ready to go, and that has funded some amazing science over the course of the last few years.

The other thing we did was we looked across the entire NIH portfolio and we said, you know, we can only fund about one out of every five or one out of every six grants. But when it comes to an early-stage investigator, those are the people we most want to prioritize. Now let's fund at least 25% of those, and let's make that the case across all of the institutes. So if you're an early-stage investigator, you haven't previously had a grant, your chances of getting funded with a good proposal went up substantially a few years ago as a result of this.

"We can only fund about one out of every five or one out of every six grants. But when it comes to an early-stage investigator, those are the people we most want to prioritize. In 2015, we funded 600 of those first timers. This past year we funded over 1,300. We've more than doubled that, and I'd like to keep that number climbing."

In 2015, we funded 600 of those first timers. This past year we funded over 1,300. We've more than doubled that, and I'd like to keep that number climbing. Again, it helps that Congress has been able to keep our trajectory as far as resources going up at about inflation plus a few percent. But that is our most important resource. We talk about technologies and we talk about equipment and buildings and universities and all of that, but it's the people, and particularly those early-stage investigators that are our future. They have to be at the top of our list.

You and I spent countless hours early this year talking about what happens if something works, but we don't have the ability to manufacture it at scale. And as we know, many people, and with the support of BARDA, started building and working on things before we knew that they would work. And I think the humanity showed of the life-science community, both nonprofit and for-profit, with the risks they were willing to take. Talk to us a little bit about this challenge.

Well, it's another important lesson from this year that we've been through. I think it is pretty remarkable to see what was accomplished in that space. But we weren't quite ready for it. I want to give a big shout out to the U.S. Secretary of Health and Human Services Alex Azar about Operation Warp Speed and how that came to pass. And to

Moncef Slaoui, who stepped in to lead that, because this was a big part of what was

needed to try to figure out not just how to do the trials, but how to build a manufacturing capacity. We could still going forward have a plan that was better prepared to shift capacity from one facility to the next if it was needed. That required a lot of diplomacy and hard work. And maybe if it would be a little bit more seamlessly put together in advance, that would be a good thing.

But this won't be the last time where we need to go in a big hurry to make a lot of a drug or a vaccine, or maybe have a diagnostic platform. I've got to tell you, I can't believe that when I came to NIH, I thought I was going to work primarily on scientific issues. I can't tell you how much I've spent on my time today worrying about where the swabs are going to come from. Or all of the home tests that we are trying to do for for SARS-CoV-2 because we have a manufacturing problem with swabs. That's the kind of thing that you didn't expect, but it has to be part of the solution.

"When I came to NIH, I thought I was going to work primarily on scientific issues. I can't tell you how much I've spent on my time today worrying about where the swabs are going to come from. Or all of the home tests. That's the kind of thing that you didn't expect, but it has to be part of the solution."

So Francis in closing, people choose to go in life science like yourself for a number of reasons. And I think their true humanity has been shown this year. I know you're a religious person Francis. How have you seen those that you've interacted with in the life sciences this year? Has it given you more faith in humanity even than you had before? I'd love to close on how you feel about what's occurred over the last eight to 10 months.

Well that's a good place for us to finish this conversation. It has been a year of terrible tragedy, lives lost; now losing more than a life, every minute to this terrible virus. And all kinds of lives that have been terribly affected by grief for a lost loved one or economic distress that nobody really saw coming at this magnitude. And yet it's also been a year of heroism. And we all think, and should think, of those who are on the front lines, the first responders, the healthcare providers, putting themselves at risk to try to help those who are suffering.

But I also think there are heroes that have risen to this challenge in the research community, in the business community; basically willing to put aside what might be otherwise more-prominent issues about personal credit, and basically said, 'this is it. This is up to all of us.'

You want to see an example of humanity, figuring out how to band together to try to help those who are helpless and need that assistance. You can look at the biomedical research community in 2020 and you'd feel pretty good about it. For me, I never dreamed, as somebody who started out in physics and then got into life science because I thought it

might be a chance to help people, that I'd be called upon in quite this way. But it is a privilege indeed to be able to be in this position. Exhausting yes, but a privilege.

And to be able to see now a light began to appear at the end of this long tunnel, with science having risen to the occasion and brought forward solutions that we almost dared not hope for. And yet here they are in vaccines, with therapeutics that are coming quickly, with diagnostic testing – all those things that we need to get past this. And I can say with competence, we are going to get past this. And then I pray, let us not forget the lessons we've learned. Let us not slip back into complacency. Let's keep in mind that we are a vulnerable blue planet, and that it's up to all of us to anticipate the things that we might need that science could bring to bear on the next problem and not wait until it's a crisis.

Francis, I treasure our friendship, our partnership, and I look forward to when we might be able to address the next challenges with a little more relaxation than emergency. Thank you for what you've done and thank you for a commitment. And I sleep a little better at night knowing that you're the director of the NIH. Thank you, Francis.

Thank you my friend, Mike; it's great to have a chance to talk with you. I only wish we could be in the same room; maybe next year we'll do that.
