

REFINITIV STREETEVENETS

EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc Science & Technology Day

EVENT DATE/TIME: MAY 17, 2022 / 1:00PM GMT

CORPORATE PARTICIPANTS

Jean Sung

Lavina Talukdar Moderna, Inc. - Senior VP & Head of IR

Melissa J. Moore Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

Phil White Moderna, Inc. - VP of CMC Lifecycle Management

Stephane Bancel Moderna, Inc. - CEO & Director

Stephen Hoge Moderna, Inc. - President

CONFERENCE CALL PARTICIPANTS

Edward Andrew Tenthoff Piper Sandler & Co., Research Division - MD & Senior Research Analyst

Hartaj Singh Oppenheimer & Co. Inc., Research Division - Research Analyst

Michael Jonathan Yee Jefferies LLC, Research Division - Equity Analyst

Simon P. Baker Redburn (Europe) Limited, Research Division - Head of Pharmaceutical Research

Husain Attarwala

PRESENTATION

Stephane Bancel - Moderna, Inc. - CEO & Director

Well, good morning, everybody. Good afternoon, if you are live. Thank you so much for joining us. We are so happy to see you in person. So thank you for making the trip, some of you from far away, some of you from New York or other places in the U.S., to be with us today. It is our first live meeting since the pandemic started. The last one was in 2019, in R&D day in New York.

If it's okay with you, I would like to thank and congratulate the Moderna team for the amazing work that has happened. If you think about it, it has been 10 years of really hard work to make the science work, so we could be ready for this moment. And as you can imagine, it has been a crazy 2 years over the last 2 years. So please join me, thank all of the scientists.

So as you know, I'll be making forward-looking statements. There are a lot of risk involved in investing in Moderna. You can look at those in our SEC documents or on our website.

So we believe mRNA is a unique opportunity to change medicine forever. As you all know, we are very excited and have been for 10 years about this concept that mRNA is an information molecule, which has really never existed in pharmaceuticals, from 150 ECLs, small molecule, recombinants doing wonderful things for patients. But the power of information medicine has never really happened before.

And because it has never already happened before, as you know, we always believe that the best years of mRNAs were ahead of us, that it was going to be an S curve like every technology that mankind has touched, and that belief has not changed. And I think what the team will show you today, I hope, is how we keep learning and we keep getting stronger about the technology behind mRNA in medicines.

And the other piece, which we are very excited about, is that we have incredible tailwind because if you look at what's happening in the labs around the world, every day, there's an exponential increase in mechanistic understanding of disease. And that gets us very excited because as we push and increase our knowledge of the platform and of mRNA, we can do more and more things for patients as we have more and more understanding of how the human body works and how disease work.

And so if you think about what we're trying to do as a company, is we're trying to really maximize our impact on patients. And we believe this goes by building a platform so that we can scale and learn very quickly around products and by obsessing about how fast we can expand the platform in terms of its application for patients.

So if you think about the expansion of a platform in terms of new clinical application, of course, the first thing is the ability to deliver mRNA to new cell type. And as you see today, there are some very interesting new science we're going to share with you around that angle. Being able to get the mRNA in more and more cell types, so we can do interesting medicines.

The other angle for us is to make better mRNAs. As you know, for those of you that have followed the company for many years, there's so many possibilities of how do you design an mRNA molecule to have a specific pharmaceutical effect. And then, of course, which we don't talk a lot about for obvious know-how reasons and trade secrets, is manufacturing. Manufacturing is really important, both how you manufacture the mRNA, how you put it into a lipid and other things that goes around it, a lot of insights right there.

And as you know, and I want to go back to it in detail, what is incredible about this technology, it has so many levels of freedom. When you have a small molecule and it doesn't work, you're kind of stuck. But with mRNA, what is really remarkable is that at the mRNA molecule level, you have so many choices you can make. We only put here 3 that we've talked about in the previous years, but there are many, many more that the team can make for every medicine.

Same thing for the delivery system, very big design space that the team is always exploring, trying to understand better how we can expand what we can do. And then manufacturing. It's, of course, a gross overstatement to just show just one decision for mRNA and lipid. We have dozens of decisions that the team has to make for every molecule as we learn about the platform.

So it's really incredible because you can learn about how to make a better medicine and explore a lot of space versus having been stuck with molecule that either it works or it doesn't work in human.

So if you think about this time in the company history, it's kind of really unique. We have this opportunity to really lead this emerging field of mRNA. First, and we believe it's really important, that's what we do. We are an mRNA company. So unlike other companies that do small molecule, large molecule, cell therapy and all of those things at the same time, all of our team thinks about, dreams about, sometimes as nightmares about, is mRNA. So we have a very, very strong focus on mRNA technologies with a capital T.

The other piece that we're very excited about, which is very different from 5 years or 10 years ago, is we have the scientific scale. Today, if you look at the science team on the platform and the science team in technical development, process development, all the engineers and scientists we have working on how to make mRNA and to integrate all those pieces together, we have more than 700 people that give us incredible scale because it is not easy to make mRNA work.

The other piece that I feel very proud about is the culture that has been built over the years by Stephen and Juan in those organizations in terms of cross-functional culture. I do not believe that you can do this technology and optimize it for patient in the best ways if you run the company in silos like a lot of time as the larger companies are run. Here, the culture is really how do you work together to optimize the system, the drug in the vial. And that's a very important feature of a company.

The other piece is how we've invested over the years and continue to invest heavily on digital to be a digital company, so that our scientists have access to data.

And now we're starting with our team of data science to layer a layer of AI into the access to that data so that we can learn faster from what we are learning in the labs or in the bioreactors.

And then, of course, we have a lot of capital that we want, of course, to invest to keep building the platform.

So I think those 5 elements really position Moderna in a really unique way in this exciting, emerging field of mRNA. As you know, we've always believed we are going through a S curve and that our best days are ahead of us. And I hope you'll get a good sense of that. As you see the team, you'll see a lot of progress, also a lot of ideas, a lot of excitement about what's coming next.

And as you saw when we roll out our mindset in the fall, learning is really critical side of Moderna culture. We have this quote that comes from Stephen that he has used for many, many years since we started the company. We don't have to be the smartest and that's really what we believe, but we have to learn the fastest. And I think it's this humility and this ambition for patients, this humility and the science that really is part of the secret sauce of the company, and I'm so thankful for the team and how we run the science at Moderna.

So we have seen this slide many time. I'm just using it as a framework for what we're going to talk about today. We're going to start by walking you through some very exciting new data on the delivery [to plan]. And some of you might have missed it recently in the Q1 earning call of partner, Vertex, announced that the GLP tox study for this program was successful and that they are on track to be in the clinic in the second half of the year.

So I'm going to spend time on this piece, the expansion of the platform into more clinical application through the lung. And then what we're going to show you a few vignettes of scientific work on how we have invented so much in vaccine, but also harvest so much more to inventing vaccine. We really believe that there's still a lot of opportunities and white space for us to make better vaccines and that's what the team is going to spend the day with you, through the morning.

So what I'm going to do now, I'm going to hand over to Melissa. She'll introduce you the team and the plan of the day. And then at the end, Stephen will come and close and we'll take Q&A with the team. So Melissa, it's all yours.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

Thank you, Stephane. Wow, it's great to be back in person. It was -- as Stephane said, it was 2019 was the last time that we had this in person. So really glad to be looking out at friendly faces instead of speaking to a screen and not knowing whether anybody is listening or not.

So I'm Melissa Moore, and I'm the Chief Scientific Officer now of Scientific Affairs. But I've been at Moderna since 2016 and until recently was running the entire platform research team.

Now one of the things that I wanted to say and also thank Stephen and Stephane, who are back there in the back, for when they recruited me to come out of academics and give up my academic tenure and give up my Hughes position, they promised me that Moderna was obsessing over science and would invest heavily over science and would continue to do so. Now I came to the company at a time when we were about 300 people. And that promise has been completely not only held, but also much -- done much bigger than I had ever imagined.

And so now our science and technology ecosystem consists, as Stephane said, of over 700 people in our discovery and platform science teams and then our technical development teams. And then we have another 200 people who are engaged in -- they are the so-called -- what I call the app developers for developing the applications for our platform technology, so the therapeutics. Now the therapeutic area of research is what you hear about on Vaccines Day and on R&D Day. But today, which used to be called Science Day, but this year, we're expanding that, so it's now Science & Technology Day, to really give an acknowledgment to the fact that we do both fundamental science and a lot of it, but also a lot of engineering and technology buildup. And so we -- that's why we've renamed it as Science & Technology Day.

Now in previous Science days, what we have done is there's no way that with this many people working hard, and really hard and they're very dedicated, that we can possibly give you an overview of everything that we do. And as Stephane said, a lot of what we do, of course, we're not going to talk about it in public because it's our secret sauce. So what we try to do every year at this day is to give you a peek into things that -- an early view on things that were either -- have recently patented and our patents have published or we're going to soon be publishing or new technologies that we expect to go into new medicines.

And so oftentimes, what we do, and I would just want to show you, is in a lot of these Science Days, so this is one of the vignettes from 2020 and '21 Science Days, we talked about engineering T7 RNA polymerase not to make double-stranded RNA. That's now in press at Nature Biotechnology. We also, a couple of years ago, talked about a novel amino lipid that enabled us to make a new LNP formulation. That has now been published and is in -- and starting to go into clinical trials.

We also, last year, talked about how we obsessed over tracking the variants of COVID as they were emerging so that we could test whether our current vaccine was working against them. And we have a number of publications related to that. And then we've also recently published the impact of size on vaccine -- of lipid nanoparticle size on vaccine performance. And so a lot of the things that you're going to see here today are things -- as I said, you're getting an early view into things that we are going to be publishing in the near future.

And that is one of the things about Moderna. We are a deep science company. We not only obsess over learning, but we want to then take those learnings and communicate those to the world so that it's very clear that we do also peer-reviewed research that supports all of our patent filings.

Now what are we going to talk about today? So first of all, today, we're announcing our new inhalable pulmonary LNP. Secondly, we will be talking about our -- how we achieved a better understanding of our -- the pathways leading to mRNA activation during and that was affecting vaccine stability. And this particular vignette will tell you why our vaccine was very -- much more stable at the outset than competitors.

We also -- I'm going to tell a story about biodistribution and safety of our IM vaccines because we often get questions about when the mRNA is injected, where is it going? We're going to show you that today.

And then lastly, we're going to talk about the use of mathematical modeling to help us predict vaccine immunogenicity and reactogenicity.

So for this first part -- oh, before that, I want to tell you a little bit more about Moderna's mRNA delivery systems. So as Stephane said, we are a fully integrated company. And that's really one of the reasons for our success so far, is that the people working on RNA, the people working on the delivery, the people working on scale up in manufacturing are all under one roof with no CDAs between them so they can easily interact with one another.

And so if a problem arises with, say, Phil White over there, when he's trying to scale something up that we've invented at the research level and it's not working, then we rapidly talk together and swarm on to problems and fix them quite quickly. And that is really different from many other companies in the space where one company is an RNA company, one company is a delivery company, one company is a manufacturing company. And so that's a real strength of Moderna.

Now this has been -- that's enabled us over the last several years to have an incredible number of programs in development. We now have, as it says at the bottom of the slide here, 46 programs, including 31 vaccines in development. This is just an unprecedented number of new therapeutics coming out of a company at this stage.

Now for this -- all of these different potential medicines, of course, we need different routes of administration. And so we -- for each of these routes of administration, they -- we use different delivery vehicles because we need -- we're not only using the route administration to get into certain tissues, but also we need our delivery vehicles to be picked up by the particular cell types that we want.

And of course, our preferred delivery vehicle at this point is lipid nanoparticles, which just to remind you, contain the -- our mRNA and ionizable lipid that has -- binds to the RNA via charge-charge interactions, a phospholipid and a sterile that form a beautiful lipid bilayer around the outside of the lipid nanoparticles. And then the PEG lipid and the polyethylene glycol lipid is there to prevent the lipid nanoparticles from fusing when they're in the vial because these are soft materials. And so they're basically big fat balls. If you left them to their own devices in the vial, they would start fusing with each other and getting bigger and bigger. And so the polyethylene glycol keeps them apart. Now that cryo-EM image there in the lower left-hand corner is Spikevax. So you can see what beautiful particles these things make.

Now in order to -- as I said, we don't just have 1 lipid nanoparticle that we use for all applications. In fact, we have many different lipid nanoparticle formulations, as I will show you in a moment. But we engineer the -- we spend -- a lot of those folks who are in the early research and technical development space, they spend their time trying to figure out how to engineer our lipid nanoparticles for different applications.

And there's a lot of different levers that we can play with. So not only can we play with changing the molecules that are interacting with our RNA and their chemical makeup, and so we have a bunch of organic chemists and they make lots and lots of molecules, we can also change the composition. So what the -- how much of each one we're mixing, and we can change the process by which we're mixing them. Do we put them all together at one time? Or do we put in a couple first and then add some others? And then this gives us different lipid nanoparticles that have different surfaces. And it's those surfaces on the -- outside of lipid nanoparticle that dictate what proteins bind to the lipid nanoparticles once they get into the body, so the so-called opsins, and then also what cells like to take up those particular nanoparticles.

Now we also have to -- there's a real sort of Goldilocks zone here because we also have to think about chemical and physical stability in the vial. We have to think about does it -- is it getting to the right cell types. Once it is in, what has gotten to those cells, does -- is it able to get into the cells, be efficiently taken up? Is it able to release the RNA efficiently? Last year, I talked about a problem called sticky lipids and that we found a lipid nanoparticle that seemed to get into the cells really well, but it wouldn't let go of the RNA. And so we had to engineer around that. In fact, that's part of what Jean is going to talk about today. That was our pulmonary LNP.

Then we need to make sure that once the RNA is out of lipid nanoparticle, it is well translated. And so all of those individual steps, we obsess over. And we have developed assays and techniques to measure each one of those steps so that we can then optimize each of those steps.

So in doing so, and we have here -- we're showing our virtuous cycle of engineering. We have synthesized over 2,000 novel delivery components to date. So those would be 2,000 unique molecules that we have looked at for making better lipid nanoparticles. And we've tested over 10,000 different composition and process variants to date and that continues. So we will keep doing that.

So that has resulted in 4 different lipid nanoparticles that are now in the clinic. You're very familiar with our prophylactic vaccine and cancer vaccine, lipid nanoparticle for IM delivery. That's what we -- that's the SM-102 lipid nanoparticle. We now have 2 different lipid nanoparticles for systemic delivery, one that we're using for the MMA and PA program, one that we're using for the GSD1a program. And we also use a different lipid nanoparticle for our intratumoral immuno-oncology products. And what I've listed here are a lot of the papers that we've published describing the components of these lipid nanoparticles and their discovery.

But what I -- what we're really excited about to tell you today is the culmination of a collaboration that started in 2016 with Vertex. And they were very interested in treating the 10% of patients who they cannot currently treat with their small molecule drugs because these patients don't even make CFTR at all. And so we've been quiet about this for 6 years now. It was a hard slog. It was a difficult delivery problem. But we obsessed and we kept at it, and we would not give up. And we worked very hard with Vertex to finally arrive at this point where we're able to tell you about the work that we did at Moderna to enable now Vertex to soon be filing an IND. And so we now have a fifth LNP, which is our inhaled pulmonary LNP.

So with that, I am going to turn over the podium to Jean Sung, who is the Senior Director of Respiratory Delivery and Drug Product Development. And Jean was really, I would say, the key player in driving the -- our ability to bring this pulmonary LNP over the finish line. And so here she is to tell you about it. Jean?

Jean Sung

Thank you, Melissa. I'm Jean. I've been at Moderna for a little over 5 years and really have the honor of leading the efforts from discovery and now bringing this program forward into development. I'm representing the efforts of an incredibly large team that was relentless in solving this delivery challenge as well as collaborative and cross-functional. It was really important to be able to develop tools as well as understanding of the cells in the in vivo systems and the delivery challenges.

But it wasn't only the Moderna scientists, as Melissa mentioned. It was really important that we have a very strong collaboration with Vertex in solving this problem. And it has been inspiring in terms of their dedication to having a solution to the patients that they have not been able to

treat with their small molecules. So we have both an mRNA program to deliver CFTR mRNA as well as moving into the gene editing space with these delivery vehicles. So I'll tell you a little bit of the story today about how we were able to solve this problem.

The applications for an inhalable LNP expand beyond CF as well. This ranges from a number of different rare diseases to infectious diseases. And each of these may have different cell types even within the lung that we want to achieve delivery to. There are a number of challenges in how we deliver to the lung that are a little bit different than our other routes of administration.

So first, we have to get this vehicle into the lung, and that requires a device. You can use a nebulizer for liquid delivery that creates droplets. These droplets are similar to a humidifier that you have in your home that creates a fine mist. But the sophistication of the devices requires manipulation of both the droplet size as well as the LNPs that are contained within that droplet.

So as you can imagine, the aerosolization in the process of creating these droplets can impact the retention of activity of these LNPs once they're delivered into the lung. And the size of these droplets impacts where it's delivered into the lung for certain indications. Like cystic fibrosis, you want to be in the conducting airway, which is your upper airway, and you might want larger droplet sizes. If we have other diseases where we want to get into the alveolar range, you need to have smaller droplet sizes. So you need to think about not only the delivery vehicle, but how you deliver it into the person.

Once it gets into the lung, there are a number of other challenges here. If you think about it, the lung is your first defense mechanism to what you breathe in every day and is built to then protect you from what you breathe in. There are a number of different cell types here, so depending on the disease as well, what type of cell you get into, how many cells you get into can all impact how efficacious you are as a therapeutic.

There is also a layer of mucus that's on your lung surface that moves by mucociliary clearance to remove anything that you're breathing in. And that, as you can imagine, if you're trying to get into those cells, provides a barrier and a delivery challenge to get through that and to access the cells themselves.

So once you get to the cells, you have to get inside of them. And that surface is really important in terms of how it interacts with the cell and is able to get in, but you also need to be able to get out of the endosome once you're into the cell and release the mRNA to allow for protein translation. So we'll walk through a little bit of the tools that we use to look at the cellular level as well as delivery to the lung through the story.

So some of the key questions, and if we start from the delivery to the cell, we kind of work backwards because the largest challenge here was delivery to the cells. So can we efficiently deliver mRNA using our LNPs to target specific pulmonary cells. For CF, we were looking at the epithelial cells of the bronchial region in particular.

Next, as they delivered mRNA express protein, once you get it in, does it actually release the sticky lipids that Melissa was talking about and can we get translation into the protein that we want. The next, can we aerosolize them? Can we use a certain device to get into the body and maintain the functionality of those LNPs? And then finally, once you have something that looks like it works, can you actually bring that forward? The scale of material that's needed for something like a CF therapeutic, which is a daily delivery, can be a large scale. So can we scale that up? Is it stable? And can we move that forward into further development?

So we do go through the cycle that Melissa mentioned in terms of discovery, design, making these LNPs. The process in terms of how they're put together is really important in terms of getting functionality and then testing them in different systems. So we'll show you some of the in vivo data as well as in vitro data that we generated through this process.

So first, we started by using LNPs that were within our existing LNP library and this included some of those LNPs as shown for different routes of administration and delivered them to mice through intratracheal installation, which is essentially just directly delivering the liquid into the lung. You can see that we saw a range of performance here in terms of imaging results, and that was really exciting to see in terms of some things worked really well and some things didn't. But as we looked, and this was through whole body imaging of the animals, but as we looked a little bit more closely into the lungs of the animals, you can see that this is in the same order as was shown in the previous slide, but that a lot of them look very similar.

So as we delve a little bit deeper into what's happening, just seeing a lung light up, as exciting as that may be when we first saw it, doesn't always tell the entirety of the story. And really, as we dug in even deeper, we saw that this really was not all of the story. So when we switched to looking at a different reporter here, the GFP reporter, where we could look a little more closely and say, where was the mRNA once we get it into the lung and where is the protein being expressed.

As I said, for something like certain indications, we want to get into the endothelial cells. So that's shown in kind of the open white space on the right is the airway and the cells lining that space are where we want to have expression. So many, many of the LNPs that we saw prior to this had absolutely no expression in that space. So even though it was promising to see these things lighting up, there was really nothing and that was a little disheartening. But we did see that some of those LNPs did have expression, but it was localized to alveolar macrophages. So again, for our purpose, this was not so interesting, but for certain disease indications, you may want to target the macrophages. So there's always something that these different areas could be used for in terms of different indications.

So we continue to screen and go through that process of designing LNPs and the chemistry as well as the way that we put them together and started to see a little bit of expression. So this was 2 examples of many LNPs where we start to see in the red circles a little bit of protein expression. But you can see that there's a lot of kind of background noise here. There's this blushing where it's a little bit brown throughout the airway/so it was difficult to tell how much expression are we getting, where exactly was it.

But this tiny bit of hope was what led us to really dive in deeper, understand what the problem was and figure out how we could put together LNPs to solve this. But we really needed tools to enable us to understand that better and to allow us to have a higher throughput way in terms of screening these LNPs.

So the -- what we really wanted to look at then more deeply was we're along the way. Right now, we're just looking at if we get protein on the other end. But where is the delivery limitations here. So you have the LNPs to get into the cell. It has to escape the endosome. It has to be able to be translated into protein, and then that protein has to get to the right place and express.

So we have tools to look at all of the different steps along this way that are quantitative as well as qualitative. One of the first steps here was for lung delivery to have a higher throughput system. And this is where a human bronchial epithelial cell system is an incredibly useful tool. This takes lungs and dissociates it into progenitor cells that are then put in a dish and are grown at an air liquid interface. So this system really recapitulates what you see in the lung. You have the different cell types. These cells create mucus and have the different barriers that you would encounter in the lung. This is -- enables a higher throughput way then of being able to look at the delivery challenges that we see in an animal and in a human.

The next step was to have a better reporter. As mentioned, in the mouse studies, we see a lot of this blushing and background noise in our imaging. So we took a concept of nascent peptide imaging and optimize the mRNA that we use for this purpose. So here is where you have a system where you can really detect a nascent peptide and it localizes into the nucleus of the cell, so that you can get a much stronger signal within that cell.

This tool also has a number of other applications that will give us a more advanced understanding of the delivery that I'll walk through in a little bit. But as you can see from these images, which is the same delivery vehicle delivered using either a GFP mRNA or this NPI-Luc mRNA, that is a much cleaner signal. You can see a very strong localized signal within the nucleus of the cells. We could also apply this within that HBU system to look for protein expression, not only in terms of the percent of expressing cells, but also how much protein we got in the cells as well as applying a fluorescent dye label to the LNPs themselves. So we take a dye and incorporate within a particle and can then count how much of the LNP has actually gotten into the cell. So how many cells have uptake and how much is taken up into those cells.

The other piece of the NPI-Luc mRNA is that we can use it to look even deeper into what's happening within the cell. We can use it to count the number of mRNA that have made it into the cytoplasm of the cell and also assess their translational activity. So you can label the mRNA, label the nascent peptide that is being translated. See if those are co-localized together to count how many of the mRNA are actually translating. Look at how many proteins are within the cell and then also how many are within the nucleus. So this really allowed us a deeper insight into where our delivery challenges were.

So when we translated this into the HBU cell system as well as the mouse system, you can see on the left an indication of uptake into the cells. So in the mouse that's looking at the mRNA and then the HBE, that's let fluorescent uptake. And we were getting into a large number of cells, 60% plus of cells with uptake. But if you look at the image on the right, which is a representation of the protein expression in those cells, in the mouse, you can see a little bit of those cells within the epithelium and then the HBE, about 1% of those cells were expressing. So these tools really allowed us a more quantitative way to say, well, we're getting into a lot of cells, but we're not actually expressing in all of them.

So what's going on here? What can we do to solve this, not really knowing what else is going on. So when we looked even more deeply using one of those tools with the NPI-Luc, we could see that for this specific delivery vehicle, that a large number of those of the mRNA were in the cytoplasm. So they had gotten into the cell and out of the endosome and were in the cytoplasm and able to be accessed. However, they weren't actually translating. So they were there, but they couldn't actually be used. And this is where that sticky lipid story comes in.

So how do we solve this problem in terms of mRNA that's there? We've solved this difficult delivery challenge. But now we need to be able to use these LNPs to actually get protein. So we went through this process of now how can we think about how we put together the particles and use the different components to separate out these different needs of getting into the cell and then translation.

And we use the HBU system here to have a much higher throughput. So in the mouse studies that were shown, we were looking at tens of particles. And now in the HBE, we were able to look at hundreds of particles. This is a representation of some of the higher throughput screening that was done in the HBE where we started really at the baseline of that original LNP, and were able to, as we iterated through the process, that cyclic design process, get us up to 10- to 20-fold over that original LNP.

So we took ourselves from this level, high level of uptake and a small amount of protein expression and were really able to develop this pulmonary LNP, where we have a lot of protein expression as well as maintain that amount of uptake into the cells.

So the next part of this is then applying the aerosol delivery as well as further advancing our tools in terms of how we look at the quantification in the mouse or in the in vivo systems. And here's where we applied AI learning to really automate the system.

First, we can take auto sampling to bring the different slides in and get a larger number of samples taken from the different lungs and then apply AI detection to teach the system in terms of what we're looking at. It was previously a very manual process where somebody would go in and say, here's the epithelial layer, and we want to look at that and count the number of cells. Here, we are able to teach, through the neural network, the system how to see that itself and to translate that into an algorithm that can then go in and identify the cell types of interest and how many cells were expressing versus the number of epithelial cells. So this really gave us a number -- a quantitative number in, in vivo systems on the number of cells. And this can allow us then to look at tens of thousands of cells within a given lung.

So we applied this to a rat aerosol delivery study and saw these beautiful images of a high level of protein expression really throughout the airway and localize to the airway epithelium in the rat. The dots in green as well as the brown on the bottom are showing the positive expression in the epithelium. And we're also interested, of course, in the nonhuman primate system and the delivery challenges there. And we saw the same level of expression. So this is not always the case for -- as we move up in species, so this was really nice to see that we were able to maintain and even increase the level of expression throughout the lung and also in that lung epithelium again.

So the next part of this then is that question around development and scalability. So we have shown that we can develop this product at a larger scale. The materials that were used in those early mouse studies were in the milligram range. And we have now been able to scale up to hundreds of grams of material to support these studies. Through that, it's not always the case that the expression and the activity of the particles will be retained. And we've been able to show that, even an increase in performance of those particles as we scale up across this 10,000-fold scale increase.

The next piece of this is around stability and can we store and use it for the patient. So we've shown that these LNPs can be stored for up to a year at our -- a minus 7-degree C storage conditions.

And finally, for the aerosol delivery piece, can you put it into a device and can it actually make it into the lungs? And for this part, the size, the aerodynamic size of that droplet is what matters. So it's not just the LNPs that we care about, but the droplet that they're contained within. And

we looked across a range of different devices to see if they worked and can optimize the kind of droplet size for different indications. So the smaller sizes for delivery to the deep airway and the larger sizes for more into the conducting airway.

So really, in summary, we've developed this new LNP specific to the inhalation area. It has efficient delivery to the epithelium and also has been enabled by aerosol delivery. We were able to do this by using in-house systems and assays that we developed to have higher throughput specific to this route of administration, but also tools that could be applied more broadly and allowed rational LNP design to look at really what the problem was in the different steps of the process and solve for those.

This LNP that we've designed does have high levels of protein expression that are localized to the airway epithelium. And we've also shown through our studies that they're well tolerated in rats as well as NHPs. And that this LNP is suitable for development and can be scaled up, is stable and is able to be delivered by an aerosol.

So in culmination, as mentioned, we are very excited that our program will be moving forward with Vertex, and they're bringing it into the clinic and looking at an IND in the second half of this year.

So that was the story. And next, I'd like to introduce you to Phil White, who will be telling you about improving that vaccine stability.

Phil White - Moderna, Inc. - VP of CMC Lifecycle Management

Good morning, everybody. It's a pleasure to be here today with you to speak to you about some of the aspects of applying that fundamental learning of our platform to development and scale-up of our products. So I sit in the chemistry, manufacturing and controls organization, and I've been at Moderna for almost 7 years now. And so I've seen firsthand how that fundamental understanding and how that deep obsession with learning has led to better products, more scalable products and what you've just seen as part of our response to the global pandemic.

So again, just reiterating that we've been investing very heavily for over 10 years. I've seen this firsthand both through research and development. And that fundamental only really did help us with the COVID vaccine scale-up and stability. And I will talk a little bit about a couple of mechanisms that we identified that we were able to control and fundamentally then get us a much more consistent product.

So right now, we sit here with an industry-leading knowledge of this type of product, of the mRNA LNP product, and that has led to significant consistency and control of our products. So I just wanted to go back a little bit to start off with here and do a little bit of a history lesson on our vaccine platform and to really give you the route into how we identified one mechanism of inactivation of our product. And this was identified, first off, in the personalized cancer vaccine program, which has a -- back in 2017. And this product, as you know, is, as the name suggests, personalized to individual subjects.

But the important aspect of this from a chemistry, manufacturing and controls perspective was the way that we chose to store the product and formulate the product. And for the PCV program, originally, we started off with a drug product that was stored at refrigerated temperatures, 5 C, 2 to 8, but in a simple phosphate buffered system.

And this was really for ease of storage and administration, given that we were dosing for 9 cycles over a course of about 6 months to aid maximum flexibility in the clinic. But we had an interesting observation, and this observation is shown here. Specifically, that the method that we used to look at mRNA content, how much mRNA is actually in the vial, which we used here with something called anion exchange chromatography, we saw an apparent drop in the mRNA content when we stored these products at 5 C. And this was somewhat confusing for us because this method is not intended to be what we call stability indicating.

This method just looks at total mRNA. And you'll see why that is because the diagram here shows that the method requires us to break the LNPs apart with a detergent into their mRNA and constituent lipid parts. We capture those -- the mRNA molecules on an anion exchange column. And then we elute them off into a single peak and we quantitate that so we know how much mRNA is a product. So that method really shouldn't see any differences as we store the product.

So we ended up with a quandary. And we saw this numerous times on numerous batches because, of course, we were generating a lot of product here for a lot of different products for different subjects. So we asked ourselves a question: what, based on our understanding of the platform, that fundamental understanding of the platform and with the tools that are available to us, could really be causing these observations that I just presented to you.

As a parallel activity as well, I have to introduce that we are also developing a new purity method for looking at the mRNA itself and seeing how that degrades. So I have to note that, that we use something called reverse phase HPLC. Those of you who have some background in analytical chemistry will know that this is a methodology that's well established and has been used for a number of years for smaller RNA and nucleic acids, but hadn't previously been applied to longer molecules, to mRNA molecules.

But in this technique, we use a HPLC column, which is able to separate the mRNA molecules according to both their size but also their charge, understand the mRNA molecules have various different charged groups on them, which we can use as a handle to separate the molecule at and get more information about the product.

And typically, what we expect to see is shown here in the graph on the bottom right-hand side. We expect to see a front area peak on an HPLC trace where we see degraded mRNA molecules, and that's how we can see how much -- how pure the product is. And then a significant main peak, which represents the full length intact mRNA molecule, that's the mRNA molecule that we are very interested in.

But we didn't see that when we extracted mRNA from lipid nanoparticles. This diagram shows an HPLC trace of mRNA that was not formulated into lipid nanoparticles. That's the blue trace. And you'll see that actually does demonstrate that expected profile. But the mRNA that was extracted from the lipid nanoparticles showed the significant late-eluting peak.

Interestingly, when we looked at the UV spectrum, this is an indication of what that actually is. It had very similar properties to the main peak area, which showed to us that it was largely comprised of mRNA. When we isolated that peak and reinjected it in the same methodology, in the same reverse phase HPLC method, we saw the same profile, and this was very indicative to us that this just wasn't simply an analytical issue. We know we can isolate the peak, reinject it and get the same results. We also applied a number of other parameters to really dig in to see whether this was fundamentally the method, and it wasn't.

So I'm going to introduce some other analytical techniques here that have been used historically, and we have also applied to characterization of mRNA that's been extracted from lipid nanoparticles. Firstly, capillary electrophoresis, this is a methodology where we introduce mRNA into a small glass capillary with a matrix and apply a current, a charge across the capillary. And in this separation methodology, we can separate out molecules according to their size and their charge. And that's important, again, because if you imagine, if mRNA is degraded, if it's cleaved, if it's broken down, we will see a larger predominance of smaller mRNA molecules in there.

Also another technique that's been applied historically is size exclusion chromatography. And in this methodology, we put the mRNA molecules down on an HPLC column and larger molecules on this particular matrix are not able to interact with the pores of the column and move through very quickly.

Smaller molecules can interact and elute more slowly. So again, both of these techniques also show us something about the size of the mRNA molecule and how intact it is.

The reason I'm introducing these techniques to you is that we apply these to that late-eluting peak to see if we could learn something more about what it actually was. So again, you'll see on the left here, this is the same HPLC -- reversed-phase HPLC chromatography with a late-eluting peak. And that late-eluting peak was subjected to CE or capillary electrophoresis. And interestingly, whether we isolated mRNA from the lipid nanoparticle, whether we introduced it -- we analyzed it from the main peak area or just from a mix of both, we didn't see any of this profile that we saw in the reverse phase HPLC analytical methodology.

And again, that methodology of size exclusion chromatography that I introduced similarly was completely blind to this impurity. I didn't see it. It didn't show any differences when we identified it, when we injected it and when we did combinations of the main peak and non formulated mRNA.

Worryingly, for us, though at this stage, we did some time core studies, and we showed that, that main peak, that additional material which we haven't characterized at the time grew over time. There was more of it. And that also was exacerbated by increased storage temperature. So if you store the product for longer at a higher temperature, you get a rapid increase in this additional peak on the HPLC analysis that we had previously seen.

Even more worrying than that for us, we noted as we identified and isolated that late-eluting peak that it essentially did not express the intended protein. And in my world, in chemistry manufacturing controls, this talks to me about a very important critical quality attribute of our product.

We have something in there that we hadn't seen before, and we have something in there that we know is not expressing the intended protein. So very, very concerning. So we threw the analytical toolkit that we had at Moderna at the time at the characterization of this late-eluting peak to try and find out what it was. And as is the case in many scientific investigations, the majority of the techniques that we applied didn't really give us a smoking gun. When we digested the mRNA down to its consistent nucleotides, we saw a very similar chromatographic profiles. And when we added some other standard analytical techniques, FTIR spectroscopy, digestion and oligo mapping, nuclear magnetic resonance and a whole host of other techniques, they all looked consistent when we isolated the main peak and the late-eluting peak.

So you can understand, we asked ourselves another question. What is this thing? What is the late-eluting peak and where is it coming from? It was only when we started to really dig into using a mass spec analysis that we started to see differences between the main peak and the late-eluting peak.

And notably, these were very low level changes that we had seen. There wasn't a high abundance, even though we've seen like a high peak change, but there wasn't a high abundance here of these changes. And what I'm showing here is that as we digested the mRNA away from both the main peak, as I said, and the late-eluting peak, we noticed that there were additional masses associated with the nucleobases. So the nitrogenous bases of the mRNA were being modified in some way. But again, at a low level, if you look at the mass spec trace, you'll see that the main bases are called out and they look consistent. But there's this low level of impurities and peaks that we see, which, as we looked at corresponded to modification of those nucleobases.

So that then led us down at least to have a handle of what potentially might be going on. So we knew from the previous analysis that these additional masses could be related to something coming from the lipid nanoparticle system itself. And of course, the previous observations where we had seen main peak versus -- or it's where we had looked at non-formulated and formulated mRNA that we could see differences there.

So we started a series of studies, which we call binary studies, where we add combinations of the lipids together with the mRNA and then look at the amount of that late-eluting peak that's generated to see where the culprit was. And I think it's very clear to see from this figure here that wherever our ionizable lipid, our SM-102 lipid in this instance was present within these binaries, we saw quite a high level of this late-eluting peak formed where there was no ionizable lipid. As you see in the figures, the second 3 bars here, there was little to no late-eluting peak in the sample.

So we look -- started to look at ways that lipids themselves can potentially degrade or can interact with mRNA molecules. And we looked at various different standard mechanisms of degradation and different reactive groups that could be causing us a problem. And I'm jumping really very much to the point here that we identified very early on that aldehydes, as a very reactive moiety or a very reactive functional group have the potential to interact with mRNA.

We of course, looked at many others and looked at similar studies that I'm going to show you here. But really, we keyed in on aldehydes very early as a potential functional group, as a potential reactive group being derived from the lipids that could be causing this observation. And in fact, this actually was proven out to be the case. We did a series of well-designed studies based on fundamental science, and we really saw the following, which was that, first of all, when we took the lipid and particularly when we took an oxidized form of that lipid and did these binary studies, we saw a higher amount of that late-eluting peak. And again, this is important because we know that if we store our lipids for a period of time, if we store them in oxygen or air, there is a propensity there for those lipids to degrade through an oxidative degradation mechanism to form something called the N-oxide or the lipid oxide. But when we look at that oxidized form of the lipid, we saw a higher amount of the adduct.

When we make things worse, when we perform that in an acidic buffer, which again talks to this mechanism of formation of this aldehyde group and did the precipitation again, we saw even further and more profound generation of that late-eluting peak. And then bringing that all together when we generated some synthetic aldehydes to probe the system, see if that was really going on, we, in fact, saw exactly the same chromatography. We saw the same -- we saw the same profiles that we've seen before, which led us to this mechanism, to elucidating this mechanism. So what we see is when we generate and manufacture our ionizable lipid, which is important, as Melissa introduced earlier on, in terms of delivery and activity of the product. When we generate that, there is a possibility for that to become oxidized just as part of normal storage, as part of manufacturing, that an oxide molecule, that oxidized lipid can then undergo subsequent degradation through a hydrolytic mechanism to form an aldehyde and the aldehyde group, as you see here, is the culprit. This is just going into this into a little bit more detail. That's the culprit that really interacts with the nucleobases and forms what we term an adduct. This is a covalent linkage between the component coming from the lipid and the mRNA molecule.

So it was this -- we asked ourselves another question. Is this specific to that particular molecule? We know that a lot of these in ionizable lipids have similar structures. And certainly, at Moderna, as again, as Melissa introduced earlier on, we have screened many hundreds of different compounds. And here is just a smattering of some analysis of those different compounds that were in development at the time. And again, you can see these late-eluting peaks, so this was consistent across our platform for molecules that have this structure. And indeed, we can say that this is a -- this proposed adduct formation, this mechanism. It's likely to be widely applicable to all RNA LNP products. And you'll see here our competitor product from Pfizer out in the market, suspects has similar properties.

So why is that a problem? I talked a bit a moment ago about lack of expression. And clearly, that's a problem. But exactly how is this thing stopping expression. So you'll all be aware that the mRNA is a large complex molecule that falls in a very in a very specific way based on the sequence of the mRNA itself. But there are many single stranded regions, meaning that those are available to participate in this reaction that we just saw and have a lipid component essentially stuck onto an mRNA molecule. And where that causes us problems from a biology perspective is that as that mRNA molecule is interacting with the cellular machinery, with the ribosome in this case, as the ribosome is moving along the mRNA and expressing the protein. If it meets something like we see here, if it meets a component of a lipid somewhere along its molecule, that will then stop, the ribosome will essentially choke on that mRNA molecule, and we won't -- and that won't be able to produce the intended protein. So a significant quality problem for us from a vaccine perspective and from a platform perspective.

So in my world, in chemistry manufacturing controls, we have used that fundamental understanding, but also we invest deeply in our understanding of our processes, of our manufacturing approaches and our analytical tools. And we have this triumvirate of opportunities to be able to control our products. So first of all, we control the raw material. We have manufacturing controls in place through the origination of the synthetic scheme, how we make the lipids, the control of those oxidation mechanisms and our purification processes, which are all proprietary to us to make sure that we start off with high-quality lipids in our process. Allied to that, we have deep and detailed analytical understanding and state-of-the-art techniques to be able to understand degradants and impurities both in the lipids, our mRNA and in our final drug product. And combined with specifications and limits, we can make sure we have a consistent manufacturing process.

And then finally, on the drug product side and the final vial, the drug in the vial, we have manufacturing controls around that, and we also have an opportunity to optimize the formulation, what's actually in there. What buffer is in that product to see if we can prevent this. And through these, as we demonstrated through the pandemic, we have -- we're able to improve the shelf life of the product, to maintain a higher storage temperature, better activity and a very consistent manufacture.

I will just talk a little bit about one specific control we have in place around our product, and this is based on this historical knowledge and learning going back all the way back to 2017 around the original product, is that we know that these aldehydes are present and now we have characterized them. And so we opted to include within the formulation, a molecule that could essentially serve as a sink to the aldehydes. So as they're being generated, can they be mopped up? Can they be prevented from interacting with the mRNA molecule and maintain stability? So we used a well-known buffer known as Tris, and this is in our commercial product. And this does exactly what I said a moment ago. This serves as I think, as a sponge, so when these aldehydes are formed, the Tris forms an adduct with the aldehyde as opposed to the aldehyde forming an adduct with the mRNA molecule. And you can see very clearly that when we store our product in 100 millimolar Tris at 5C compared to the original PBS formulation, we have a much more stable product, we have much less adduct and that material is obviously going to be much more active. And

we can see direct evidence from that. If we take synthetic aldehydes again, if we incubate them with Tris, we can see the Tris and aldehydes adduct-forming, so we know this is a mechanism.

So just looking back to the original observation, if you remember, I wanted to just to double down on this to ask whether that original observation we've seen, did the adduct formation and this mechanism that I just outlined for you, did that explain that original observation? And again, if you remember, the methodology that we used as anion exchange chromatography, where we put these extracted mRNA molecules down an anion exchange column. And we then look at the quantitation from that column. And indeed, the methodology is sensitive to these adducts. What you're seeing here is an HPLC trace on anion exchange methodology, where we have a control mRNA, the main peak that we've seen before and then the reinjected late-eluting peak. And the late-eluting peak has a very aberrant chromatographic profile. It has an additional peak and -- sorry, additional shoulder and it elutes more later off the column itself. And this is indicative of the fact that, that molecule is more hydrophobic, it's interacting with the anion exchange column and is not giving us a good recovery in the methodology, which explains the original observation.

So just for a few moments here before we go to break, I just want to add in another component. We know that, that mechanism that I just outlined is very important in determining shelf life of our products, but what other factors determine our shelf life for our product? And for this, I'd just like to give you an orientation here on the mRNA molecule, which I'm sure many of you have seen many times here. But I think, I would just like to say that, of course, in order for an mRNA molecule to be expressing the protein that we intend or the peptide that we intend, these structural elements need to be present. There needs to be a 5 prime cap. There needs to be 5 prime and 3 prime untranslated regions, which are regulatory, the coding region and then a polyadenylated tail. All of these components enable the mRNA to interact with the ribosome and to express the protein.

But mRNA itself is inherently unstable, and this is just due to the chemistry of the mRNA molecule. And what we see, if we just store mRNA at elevated temperatures for a period of time, we will see strand scission. We will see the mRNA molecule starting to break into chunks. And this is driven just again, fundamentally by the way, that the backbone of the molecule is put together, together with the nucleobases. So you'll see here a mechanism that we're outlining called transesterification. And really what happens is the hydroxyl group on the nitrogenous base here, which I can probably point to, loses its hydrogen at deprotonates, and that then leads to a very reactive side group here, an oxygen group, which actually has -- which is deprotonated and is very reactive. And what can actually happen is that, that oxygen moiety then interacts with the phosphate group on the backbone through this transesterification reaction forming an intermediate, which then cleaves the backbone. And this just happens inherently for mRNA that -- this is well known and this happens over time. And of course, through that mechanism, we see over time we see degradation of the product, and we also see a reduction in expression from that product. And that is essentially what drives a lot of the shelf life for our product. So what we can say is that we know that as we have these cleavage events, these transesterifications -- these strand scission events, we see degradation of the mRNA molecule, and we see a net reduction in the amount of protein that's expressed and then, of course, that impacts the efficacy of the product.

And this is a well-defined process. It's well understood, and we can simulate exactly the degradation rates for our products. So we know because that's a stochastic event, it happens randomly across the mRNA molecule. And it's also chemically driven that it will increase, that breakage event will increase as a function of temperature, and you see this very clearly here that when stored at minus 20 C, our product, our mRNA products are pretty stable for our platform. When we increased the storage to 5 C that chemical reaction occurs more quickly, and we see a higher rate of degradation and breakage of those strands.

And then even more obviously, when we take this up to a 25-degree storage temperature to essentially room temperature, we see a very rapid degradation in mRNA molecule -- of the molecule through this mechanism. And you'll note here that the scales are in hours on that final graph, showing that's a very rapid degradation.

But also the length of the mRNA molecule has an important part to play here in determining the overall degradation rate and ultimately, the shelf life of the product. So these are some rates of degradation for our mRNAs in the Moderna platform. And you'll see clearly that as the mRNA length increases, the rate of degradation also increases because the probability of getting a strand cleavage somewhere on that molecule increases also. And this is unfortunately where everybody, ourselves included, had a challenge when responding to the coronavirus because the spike protein, which we drive the hematological response to, is a particularly large protein. And it, of course, has a particularly large mRNA associated with it, which means that our shelf life is reduced as a function of that. And the reason why our product is still at minus 20 and many others are at ultra-low temperatures because of this mechanism.

So just before we get a break, I will just point you in the direction particularly around that lipid adduct mechanism. This is -- this has been published in Nature Communications. For those of you who want to see more information and more specific details on that mechanism. I'll point you in the direction of that publication.

So in conclusion, our deep knowledge of the platform through all these fundamental investments that you've been hearing about really led us to some of these key observations. And our broad analyst call takeaway, which I think I've shown you some examples of here and our state-of-the-art methods, they uncovered this critical quality attribute, which had never been reported before, and a lot of the state-of-the-art techniques were completely blind to it. So a critical quality attribute that had never been seen before and methods were blind to.

We know that the formation of this adduct it's in universal impurity in lipid nanoparticles that have a ionizable lipid in them, which contains a tertiary amine. And by extension, it's an important component of driving our shelf life in addition to strand scission, which I've just outlined to you, which is the degradation of the product. So we are in a fantastic position as an organization to have a very well-characterized platform. We have leading industry-leading knowledge. And we also have very detailed manufacturing and pharmaceutical controls and that gives us a very robust and consistent product. And it's a privilege to be in the manufacturing and scale of organization and be able to leverage all of that knowledge, that platform, those analytical tools, all of that know-how to get our sales that are much more consistent, but more scalable commercial product and have these fantastic partnerships that we have with the platform and the rest of the organization. And we continue to invest. We're continuing to do this.

Every day, we look in this select level of depth in our both commercial products and our manufacturing processes to make sure we have a much more robust product. So that gets us to the natural breaking point here. I think we're going to take a break for 10 minutes. So thanks very much for listening in.

[Break]

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

All right. Well, welcome back. I hope you've got your coffee and your heads on straight again after all that chemistry. I know that was a lot, but I thought Phil did an amazing job of taking -- walking us through his world of analytical chemistry. And that was just a really crucial finding for us in terms of being able to make a stable vaccine product.

Now in the second half of today's presentation, we're going to have 2 stories, one of which I will tell and then Husain Attarwala will come and talk about his mathematical modeling in our quest to be able to figure out what is the best dose for our vaccines.

But first, I want to talk a bit about the biodistribution and safety of our IM vaccine LNPs. And why do I want to talk about this? We -- now that we have a commercial product and of course, our vaccine has been in millions of arms, we're often getting questions, have been people worried about where does the mRNA go? And will it get into my DNA? And how long is the protein expressed? And will it affect the fertility of my daughters? And we wanted to present publicly a lot -- some of our preclinical biodistribution and pharmacokinetics data that we had filed with the FDA to show people that we know where it goes and it's -- it doesn't go any -- very far at all.

But I will start with by talking about just -- and I've put this up here before, we've told the story before. We published in 2019 the preclinical formulation that has SM-102, our INI proprietary ionizable lipid in it. And we had -- in this publication, we had specifically been looking for a delivery vehicle that was optimized for prophylactic vaccines. And so for prophylactic vaccines, what you want is, obviously, you need to maintain protein expression, you need to maintain immunogenicity.

But in particular, it has to be very well tolerated. And that's what our vaccine, our delivery vehicle does. And it actually has this -- this high degree of tolerability actually allows us to dose a little higher than our competitors. And so that also was something that is -- it was crucial to our success for their vaccine.

But we often get, as I said, many common questions, where does the mRNA go after IM administration? what tissues, what cell types? How long does it last? Where is the protein expressed? What tissues and cell types? And then are there any concerns relative to fertility and pregnancy?

So let's start looking at some of these questions. So in order to answer that first question about where does the RNA go, we do many preclinical studies of biodistribution. And we can do these studies where we inject into the muscle. And then at different time points after injection, take out various tissues from the preclinical species, from the rat in this case. We then homogenize those tissues, make a lysate and then we can measure the -- how much mRNA is in each of those tissues using an assay called the b-DNA assay. Now this assay is a -- directly detects the messenger RNA. And I'm not going to go through it in detail. But basically, what it is, it's a sandwich-based assay where you're capturing the mRNA on a surface with complementary probes. And then you have other probes that bind to the RNA via base pairing and have additional molecules on them that either can cause chemiluminescence in this case, and this is what we use for the for quantitative measuring. A little bit later, I'll show you a different version of this where we use a fluorescent indicator instead of a chemiluminescent indicator.

But this is the -- some analysis of when we used a vaccine that had 6 different mRNAs in it. So we were measuring 6 different mRNAs at once. And what I'm showing you here is the mean tissue of mRNA concentration, the mean of those 6 different mRNAs. And what you can see on this graph is that the main place where the mRNA is localized is at the site of injection. And very rapidly over the course of 24 hours, it goes away. So it's hardly detectable at the site of injection after 24 hours by 48 hours, barely detectable.

With different kinetics, it then goes to -- it can be detected in the draining lymph node. And so you can see because the 2-hour and the 8-hour time point are very similar in the draining lymph node, that's different from the tissue because the RNA is now going to the draining lymph node. But again, after 48 hours, it's all but gone. After 5 days, it's practically undetectable. All of the other tissues that we looked at either had very extremely low levels of RNA, not really over the limit of quantitation. So the RNA really is at the site of injection and in the draining lymph nodes.

Now let's take a look -- so that told you the RNA actually in that tissue, but it doesn't tell you what cell types in that tissue are taking up the RNA and expressing the protein. So in order to explain that, I need to give you a little skeletal muscle anatomy lesson. So you're -- and you're laughing because you know I'm a professor, so I can't resist giving you a little lesson, right? So your muscle -- here's something that you're showing your muscle fibers. What's important here is in between the muscle fibers that have the actinomycin in them is the interstitial space. And in that interstitial space. And that interstitial space is filled with lymph and -- or interstitial fluid, which ultimately becomes lymph. And in the interstitial space, there are a lot of resident immune cells. So there are resident macrophages and monocytes, some neutrophils, but they're all sitting in-between the muscle fibers, okay? So we are able to assess exactly what cell types are taking up the RNA and expressing the protein using 2 techniques. One is RNAScope. So it's that same technique I was showing you before, except now these have a fluorescent or other ways of detecting the RNA, so the other probes or we can use immunohistochemistry to detect the encoded protein. So what this shows you, and it's very clear here, it's a common misperception that it's the muscle fibers that are expressing the protein. The muscle fibers do not take up the RNA and they do not detect -- they did not express the protein.

The muscle fibers are the big white things that are -- the big white circles. Where the RNA is and where the protein is expressed is in the connective tissue in-between the muscle fibers. Now if we do a time course, what we can see is that using this technique, the mRNA is undetectable at the injection site after 3 days. So it really goes away, it's not lingering. Similarly, the protein is undetectable at the injection site after 3 days. So the protein is no longer being expressed there. So where is it going? Well, of course, what's important are the draining lymph nodes. And so here's a picture of a draining lymph node where we can -- after injection, and we can detect both the mRNA and the protein. And what you can see is that both the mRNA and the protein are really kind of around the edges of the lymph node.

Now so the question then arises, well, what cell types are expressing or taking up the RNA and expressing the protein? So the cell types that are really important for generating an immune response are antigen-presenting cells. And they -- their job is to capture and present foreign antigens to help develop an adaptive immune response. And there are a number of different cell types that are called -- that are professional antigen presenting cells, monocytes, macrophages, dendritic cells and B cells to some extent. But the one that you really want to get into are the subcapsular-sinus macrophages because they're the ones that are in the right place in the lymph node to make those interactions with the T cells and the B cells to trigger an adaptive immune response. So this is a fluorescent image showing expression of the protein that was in this particular vaccine as well as staining for those sub capsular macrophages. And what you can see is there's very good overlap between those 2 stains. So they're the predominant cell type that's picking it up.

But we can do even better than that. We can take the lymph node and dissociate it and then run it through flow cytometry to where we can identify the actual cell types that are expressing the protein. And what you can see here is that -- and here, we're looking at -- we use an mRNA expressing green fluorescent protein. But what you can see is predominantly, again, it's the macrophages, the dendritic cells and monocytes, all of which are antigen-presenting cells that are expressing the protein with very low levels in the B and C cells in the lymph nodes. The other thing that you can see on here is that if we take a non-draining lymph node, so a lymph node from the other side of the animal, we don't see anything. So it really is just in the draining lymph nodes.

So that answers those first 3 questions. The last question is, are there any concerns relative to fertility and pregnancy? So again, we've done significant preclinical testing. And here, what -- this is data from a repeat dose toxicity study in rats, and we're using a messenger RNA -- excuse me, a vaccine that contains 6 different mRNAs at a clinically relevant dose. And when we did this study, what we were interested in is at the end of the study, what did we have in terms of clinical pathology or tissue histopathology? And what we found is that, yes, there were some transient injection site reactions, which we've all experienced when we got the vaccines, right? But they typically went away, and they were typical of IM vaccines. We observed no histopathological effects observed in the reproductive organs or importantly, in heart or cardiac tissue. And so we do not believe that this myocarditis or reaction to the heart tissue is a function of our platform.

Now in terms of fertility and development, we did also this type of study where we took rats, female rats. We dosed them twice with vaccine prior to them getting pregnant. We dosed them twice again while they were pregnant, and then followed them -- allowed them to give birth and then follow the pups after birth. We saw -- so these rats got a lot of vaccine. We saw absolutely no effect on mating performance, fertility or pregnancy or development of the pups. We did see transient effects at the injection sites, as you would expect. And the other thing is that we saw were that the antibodies, when we did the antibody titers, even though the pups themselves were not injected, the antibodies were transferred from the dams to the pups. And so that says that the moms are giving passive protection to their offspring if they've been vaccinated.

And so the -- this is basically a summary of what we have observed, both in the preclinical studies and in the clinical studies, that we see antibodies and T cell responses are present in pregnant and lactating persons following vaccination. They're generally well -- the vaccinations are generally well tolerated, and there's no difference in adverse pregnancy or neonatal outcomes dependent on whether you've been vaccinated or not vaccinated. And so the CDC clearly recommends a vaccination for all people who may become pregnant or our breast feeding.

So I just wanted to present this. I know there wasn't a lot of data there, but I wanted to present this particular story to just really show the data, so that people can feel confident that we both know where the protein is going and that there is no risk for pregnancy in particular.

So in summary, after IM administration of our vaccine, the mRNA is found almost exclusively at the injection site and the draining lymph nodes. It's more than 95% gone after 48 hours. It occurred -- the protein expression occurs in the immune cells of the muscle interstitial space and the draining lymph nodes, and there are no adverse consequences for pregnancy or fertility. Okay. That's that story.

Now for our final story of the day, we want to talk about our use of modeling and simulation to guide dose selection for our vaccines. Now to start out this, I'm going to just introduce a couple of concepts to you. So the concepts are pharmacometrics, pharmacokinetics and pharmacodynamics. And I -- frankly, I'm not a specialist in this area, so I always get these things confused, so I just thought I'd put them out there for you. So pharmacometrics is a science of interpreting and describing pharmacology in a quantitative fashion. Pharmacokinetics or PK is a mathematical understanding of how a drug is absorbed, distributed, metabolized or eliminated and its metabolites. And then pharmacodynamics is a study of the pharmacological response to a different drug concentration.

Now why am I bringing this up? So it's true in all of science that if you really understand something, how it works, you should be able to describe it with a mathematical model. If the mathematical model fits your data accurately, then you know, okay, I have achieved full understanding of my system. If you make a model and it doesn't fit the actual data, then you know something is missing and you've got to go back and refine your model. So one of the things that pharmacokinetics and pharmacodynamic modeling have been widely used across the industry to predict the doses in therapeutics. So using preclinical data from animals, we want to predict the doses in therapeutics. And we did this, and we showed this before for our Chikungunya monoclonal antibody. This was when we last met in person, I think, in September of 2019 at R&D Day. And we had developed based on our preclinical models or preclinical data, we had predicted the response, so the amount of antibody that would be made from our Chikungunya mRNA in people across different doses.

And then we actually -- this was before we got the data, and then we actually got the data and wow, it fit pretty well. So our model, we are able to model the performance of our mRNA medicines that are encoding a protein, again, not a vaccine, but a protein that's secreted into the blood. So what we wanted to know is, could we take this -- use the same kind of modeling to predict the performance of our vaccines? And in particular, to predict the -- to help us set the doses that we should be giving in clinical trials, especially for different age groups in our vaccines.

And so I'm now going to hand us over to the expert, who is Husain Attarwala, and he is the Senior Director of Pharmacometrics in clinical pharmacology. And he's going to tell you how he has adapted PK/PD modeling to be able to predict what doses we should use in our vaccines. Husain?

Husain Attarwala

Thank you, Melissa. It is a pleasure to be here in front of you today and present this work that has been ongoing since quite some time at Moderna.

So I'm Husain Attarwala, I'm Senior Director of Clinical Pharmacology and Pharmacometrics here. So as Melissa mentioned, that we have used these models for our therapeutics where we predict PK/PD in humans and use them for dose selection in the clinic. Now we wanted to apply this approach for dose selection in vaccines.

So after vaccine dose, you can see that we have stimulation of immune response, which is after a dose we stimulate that response and then there is some dynamics. So how the immune response persists over time. So we want to describe that using our model and this modeling, we call as immunostimulatory, hemodynamic modeling.

Now looking at the typical time course of our model. With vaccines, we know that they stimulate the response. And how do we predict, how do we model them mathematically? So with any pharmacometric model, we first go in and see what is the underlying mechanism. So we want to understand how is the underlying biology underpinning those mechanisms. I want to understand those, and we add our drug. So what is a vaccine doing? How is our drug behaving? And what are those -- yes. Yes, I have some pollen allergy, which is causing this voice. Yes. Yes. So what does this model look like behind the scenes, yes?

So here, the mechanism underpinning these processes is shown here on the right-hand side of the slide. So this is a simplified conceptual schematic underlying the generation of neutralizing antibody titer response following vaccination. And following the first dose, we can see that naive B cells are activated to produce antigen-specific antibody secreting plasma cells. After some of these cells get converted into memory B cells and the plasma cells, which are formed after first vaccination produce antibody titer response. And that is what we see after the first dose.

Upon administration of second dose, we can see that not only the naive B cells which are there, we have memory B cells that get activated upon second vaccination. And there, we see a boost in response. So this is the mechanism where -- how the antibody titer response is produced. And there are a number of breaks and clearances that go in this process. So how do we model them mathematically?

So here, behind the scenes, this model looks -- that there are a bunch of ordinal differential equations that go into building this model. And -- now I will give you a lesson on differential equations. But I'm not Melissa.

So I will spare you the pain of going into details of these equations. So the model, when we build it, it had -- we started off with a few differential equations to see if we can describe in a very simplistic manner. But as we went into model building, we ended up having 10 differential equations and 17 parameters that we had in the model.

So now why, why do you build this model? And how do we use it? So there are key questions that we want to help address with this modeling, is what vaccine dose should be used in clinical studies? And how do we select doses for different age groups? And to walk you through how actually we use this in our programs. I will go through 2 specific examples that is IS/ID modeling for our CMV vaccine, where we use this modeling approach to select Phase III dose. And then IS/ID modeling for our mRNA-1273 vaccine where we use this modeling to predict what is the dose for a pediatric population.

So we began this modeling exercise in 2019 when we had our initial Phase I clinical data from our CMV program. So as a reminder, CMV vaccine has 6 mRNAs in it, 5 encode for pentamer and 1 encode for gB. So neutralizing antibodies against the pentamer neutralize -- prevent CMV from infecting [BTU] cells and neutralizing antibodies against the gB prevents CMV to infect fibroblasts. And this was the data available at time of model development.

As you can see, over time, we collect antibody titers. And as the dose is given, the arrows indicate the dose. After the first dose, we see generation of some titers. And then once we use a frequent dose, you see an increase in [dose titers]. And then after third dose, you see how those titer flows are maintained and how they persist over time. So the mechanism of immune stimulation and immune dynamics. We had similar data for our gB antigen where we had this data over time.

So we went through a number of different models, as I said before, and fit different types of parameters and equations. And finally, we ended up with a model that describes the data pretty well. So here, on the plot, you can see that dots are the observed data. And the blue line is the fitted mean and the shaded area describes the interindividual variability of response. So the model describes the variability data well, and we did a similar exercise for our gB antigen where the neutralizing antibody titers against the gB antigen were fitted to the model and that also then described the data well. So once we have this model built and the model is qualified using a number of numerical and predictive diagnostics, then we can use this model to simulate clinical trials. So let's say, if we pick this node, this regimen, what it will look like. So we can like do a number of scenarios that -- what the responses are going to look like using this model.

So the key question at that time was what should be our dose for our Phase III clinical study? So here -- so then we used this module to simulate a dose response across a range of doses. And this model allows to then create a dose response curve, which is continuous. So instead of having a few dose levels that were evaluating the clinical study, we can have doses that were -- that were not valued. So like 75-microgram dose, what is that going to do? 125, what is that going to look like? So we can have all of those different scenarios that we can simulate.

So from here, what doses do we pick? So if we look at a dose of 50 micrograms. So here, responses against the epithelial cell at this stage, we are aware about the benchmark of natural infection. So here, the dotted line, horizontal dotted line is the GMT benchmark of natural infection. And if you look at our model prediction for the epithelial cells, they are way above those reductions.

And for GMT, for fibroblast cell infection, we are barely about that benchmark are meeting the GMT, but there's some portion of operation that is not. So now if you go to a higher dose, which is 250 micrograms, then we can maximize the immune response. But when we think about dose selection, the goal of dose selection is to get a dose that maximizes immunogenicity, but also is very safe or reduces the risk of adverse events.

So how do we do that? So we look at totality of clinical data. So there is a lot of observed data, clinical safety data that is there. But from a modeling standpoint, we model those adverse reactions using an approach called logistic regression, which is very typical.

So given a dose in an individual, there could be events, adverse reactions or there maybe not. And once we have the clinical data across few doses, we can derive what is the probability of having such a new one.

So once we have the probability more done for having any adverse event, we can use that model to derive a risk score. So given totality of data and different types of adverse reactions, what is the composite risk of having certain adverse events active in a certain dose, which is shown here on this slide where the composite risk score gives us the total -- overall probability of having a certain event where 0 is minimal risk and 1 is maximum risk.

Now if we look at our doses at 250-microgram, the dose of 250, there is a slightly higher risk of adverse events. And if we go back to our dose of 100 to -- then the risk of having adverse events is very minimal. And this was all supported by observed data as well. What this modeling approach helps us is to view this on a continuous x scale where we can visualize composite risks of having such events.

So after going through our modeling for immunogenicity and our adverse events, we then landed on a dose of 100 micrograms. And as you can see, that 100-microgram dose maximizes the immune response against both antigens and also has a very good safety profile. And this was selected as our Phase III dose.

So now that was our Phase III dose selection approach. We started with CMV building these models. Now these models we then use for modeling our COVID-19 vaccine. So here for COVID-19, the use case we are going to go through is selection of pediatric dose.

So the model was developed using pool data across different clinical studies. So we had -- for COVID, we had a lot of data. We had data from Phase II studies in adults, adolescents and pediatrics, which were greater than 6 years of age, older children, and our Phase III study in adults.

So we used the CMV IS/ID model to develop this model for COVID-19 then we evaluated age and dose as covariant on this model. So what is the impact of age? What is the impact of dose on the neutralizing antibody titer response? And then once the model was predicted and qualified, we used it to simulate what will be the predicted antibody titer response in the pediatric population.

So our goal for this was to predict which dose level in young children and infants would yield antibody titers that are similar to young adults. And for this, we had a predefined non-inferiority criteria or a reference to match. So the reference that we had to match was immunogenicity in young adults, which is 18 to 25 age group.

So we had decided this distribution from our Phase III trial. And the goal was to predict what those is in different age groups would yield these same titers. So we used our model to simulate a number of different doses in different age groups and evaluated which dose is going to give us a response that is similar to young adults.

So if -- and there are like set statistical criteria which are predefined and accepted by regulators that we look into. So what is the geometric mean ratio, that we take ratio of geometric means and see how it matches against that criteria.

So we did that exercise, and this was our model prediction. So this is what we predicted back in August in 2021 before we had the data. And as you can see here, that our dose of 25 micrograms in the young children and infants was predicted to meet the non-inferiority criteria in here -- yes. Then we got the actual clinical data. So I am very happy and very excited to let you know and show here that what we predicted using our model turned out to be what we observed as well. So our observed clinical data matched very well with what we predicted.

So what this approach has led us to help is it really makes us forward-looking and have a predictive tool that we can use to build such models and then use our clinical data to derive certain inferences, yes.

So in summary, modeling and simulation helps to drive data-driven decision-making for clinical dose selection. And this is one of the themes at Moderna, which is we obsess about learning. We really want to learn as much as we can from the data that we have. We've built predictability analytics, the AI icon that you saw. This is the AI in action here, which helped us to get to -- those that we met that criteria.

And then we adapt it [in here]. In this exercise, we adapted the traditional BKB modeling approach for therapeutics to develop IS/ID models for vaccines. The IS/ID models can be used to successfully predict neutralizing antibody responses across various doses. Our IS/ID model can also predict a priority immunogenic responses in various age groups. And we have demonstrated utility of these models for our Phase III dose selection for a CMV vaccine and successfully used it for predicting our pediatric doses.

So why is this important? So we are a vaccine company. We have a lot of different upcoming programs. And having all of those programs in clinical development and having a tool developed to predict such doses is going to help us. So having this analytical engine and modeling engine built will help us drive our different programs for them.

So with this, I thank you all for your time. And I would like to now hand it over to Stephen Hoge, who will take questions and concluding remarks.

Stephen Hoge - Moderna, Inc. - President

Thank you so much, Husain. Thank you, Husain, and thank you to all of our speakers. I have just a few concluding remarks, and then I'll be inviting Melissa and Stephane to come up and join me for some Q&A, which is probably the fun part of this for all of us.

I do want to take a note. It is so exciting to be back in person. We're happy that many of you are joining us remotely, but it is fun to see people in a room. It is -- there are faces here that I recognize from over 9 years ago when we first met and some new faces as well that we've met just recently. If there's anything, though, that I hope you leave today with, whether you were here 9 years ago or whether this is your first event, is that, as a company, Moderna has been committed to the basic science investments that we do in our platform from the beginning.

Melissa said it best, I think, when she said we're kind of science geeks. We actually really love this stuff, which is why we spend so much time on it. We go deep on it even in ways sometimes that maybe aren't as obvious to everyone as to why we care so deeply about things like modeling or distribution or maybe some of the delivery technology space. But it is who we are and I hope those of you who've known us for years are reassured that it's still part of our fabric, that we're committed to this sort of investment and what we want to do. And those that are just getting to know the company in this way, although we're famous maybe for a vaccine, the core of how we got there was through investments like this. And although this is our fifth Science Day, those of you who've known us for much longer than that know that we've been this way really from the beginning, for over a decade.

So what I'd like to do is briefly summarize some of what we've covered today, but the most important thing to leave you with is we're still investing in this platform. This is an image from, I think, from around the time of our IPO actually, sort of 2018, but actually some of the stuff we've been talking about before with all of you. And we've been saying from the beginning that the company is really based on 3 big pillars.

Everything we're going to do in medicine, and we hope we change medicine forever, not just for the COVID vaccine, but everything we're going to do in medicine is really about building on these 3 foundational basic science and technology areas: mRNA across chemistry, which we used to speak a lot about, now sequence and targeting elements; delivery, a lot of talk about LNPs back before LNPs maybe were in vogue; and then all of the things we've invested in terms of manufacturing technology across some of those. And actually, we tried to provide a little bit of a representation of all of this here today, including as Melissa said, bringing in some of that manufacturing technology that really allowed us to move forward.

We were, as a company, 3 years ago -- or 2 years ago, my gosh, time -- in 2020, we were the only people that had ever advanced an mRNA LNP vaccine in the clinical trials, as many of you know. We've had 9 different vaccines against 9 different viruses. We've produced those clinical results. We've had success. But 2 years ago today, we were the only company that had ever done one. And many people probably didn't think that a company of 600, 700 people with only that foundation and working on a novel technology like mRNA and LNP was going to have the impact that we've ultimately been blessed to have over the last 2 years, advancing our vaccine, obviously seeing phenomenal clinical trial results, scaling up the manufacturing and delivering a billion doses, and we're still going.

It is only because of the preceding decade of investment, those 9 prior experiences, that we're able to do that. And what we want to reassure all of you with today or at least give you a sense of is we're not done. This field may be new, but we are not new to it. And our approach is we are going to continue to invest in the basic science and technology. We'll provide updates for those who have appetite for going deep in the basic science. We'll always be happy to show you the raw material that motivates us. But those investments in technology and science we think will continue to shape this scale. We do not think this field is anywhere near maturity.

So 4 things we covered today. We tried to divide it into, as Stephane said upfront, some stuff that's on the very cutting-edge of where we think the technology will be applied and some things that are about the technologies we're using it today.

So first, an expansion of our platform. Jean presented where we are in developing a new LNP for getting into the bronchial epithelium of cystic fibrosis patients. Now you already know the punchline, which is Vertex has announced and obviously we've announced as well, that, that program will be going into the clinic, that we've completed its preclinical development, it's GLP toxicology studies. And we're encouraged by those results, and we'll expect to be filing and moving into the clinic in the second half of this year.

That is a transformational medicine. And it was no small feat over the last 6 years of engineering. Everything about getting into those specific cells in the lung was not supposed to happen. We had to solve problem after problem, and I assure you Jean presented it in far too easy a way for what it felt like in a time, day after day, year after year, 6 years of work. But it is so exciting to see what that persistence and investment in basic science can produce, and that is something we're excited about. So that is the leading edge of where we're going, and we'll keep moving, but encouraged as that go into humans this year.

But we also have a lot going on in vaccines and so we thought it may be worthwhile showing the breadth of how we continue to invest in that technology, including in vaccines, even though maybe half the world has interacted now with an mRNA LNP vaccine that we're proud to have pioneered. The first is showing how we've actually solved questions about stability. And actually things we didn't even know that we need to solve, but that we worked on in 2018, 2019, 2020 before there even was an mRNA and LNP vaccine. And this is why we had that stability, that refrigerant stability as well as frozen stability in place for the pandemic, years of investment and ultimately solving a problem before you even knew you had it, but one that we were working on.

We also talked about how we understand the safety of our platform and allows us to move so quickly into so many other programs, including as we announced just recently that we're now in 4 Phase IIIs, right? We've got a flu Phase III that we're starting imminently, a RSV Phase III, we're in a CMV Phase III, and then obviously people are pretty familiar with COVID. But the pace with which we can do that is because we truly do understand how this technology performs from a safety and pharmacology perspective.

And then Husain's presentation, talking about how we use that then to predict dose. If you're going to go fast, you need to be able to predict that dose. And we're actually encouraged that we're able to do that increasingly well and as recently has been evidenced by our ability to predict that pediatric dose and those pediatric filings that have just happened for that last unprotected population against COVID. We're really proud of those results and that progress.

But this is just the tip of the iceberg. It by no means represent the totality of the science we're doing. And as you all know who've been with us for years, we'll keep coming back and trying to show you the ways in which we're committed to this basic science, but in fact, this is really just a small smattering of the things that we're doing across our platform, across manufacturing and across the company to continue to explore the space.

We do believe this is just the beginning. And although we're excited to see it, moves as dramatic as it going into cystic fibrosis patients we hope this year, we actually believe the greatest things are still ahead of us, not just this year but in a decade ahead.

So with that, I will invite Stephane and Melissa to come join us -- join me up here for some Q&A. I think we're going to be standing, which is great. And we'll start with questions in the room. For anybody who has them, I believe that Lavina will help coordinate these questions with the mic. And then after we get through some questions in the room, we'll invite questions from anybody watching on the webcast, and again, Lavina will help moderate us for that. So I'll turn it over to Lavina. So it's Mike.

QUESTIONS AND ANSWERS

Michael Jonathan Yee - Jefferies LLC, Research Division - Equity Analyst

Michael Yee from Jefferies. Two-part question on the pulmonary delivery, which you spent a lot of time talking about. One is obviously just thinking about proof of concept and what you would need to show in a Phase I. I mean, I guess you said it would be in the clinic later this year, either in healthies or in CF patients, what you would need to see to prove that out that it's working and getting delivered there?

And then secondly, one would think that would unlock value in terms of the platform for other diseases. You listed a bunch of them there. Any of those you can close? And a lot of those are different problems to solve. One is delivering a protein, others are totally different. So maybe just comment about how that would unlock.

Stephen Hoge - Moderna, Inc. - President

Right. Great question. Thank you for that. So the question -- I assume people can hear the questions online?

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Not very well.

Stephen Hoge - Moderna, Inc. - President

Not very well. Okay. So a question about cystic fibrosis, both in terms of what are we going to be looking for in that Phase I, and then the second part of that question was around the rest of our pipeline or what does that unlock from a modality perspective more broadly.

So first, I will defer to our partner at Vertex to do some more description of what they will do in that clinical trial, but as you expect, we will be going into patients. You want to go demonstrate the benefit where it is needed in those patients in many rare diseases, and CF is no different. Now part of that is because the benefits that you will look for, functional measures you can imagine like FEV1 that you'll want to look at, those will be measures that you really want to see that benefit -- only be able to see that benefit in the context of disease. And so we will defer to them to disclose more about what endpoints they'll be specifically looking for, but we are keen to see that program move forward and move forward in patients.

And this is one of those situations where Vertex is uniquely capable of helping us accelerate that development. There is no company better identified with their impact in cystic fibrosis. And what I will say, they share with us, based on that patient population, it is really such a dramatic need right now for the roughly 5,000 people who make no CF protein, who cannot take any of the correctors because there's now been this big gap in terms of the benefit provided by current medicines versus this. And what we're hopeful for is that we can, with them, help address that gap, bring those 5,000 patients back up to a more normal standard of life, which is so essential.

So excited for that. We do hope that this will move into patients. We do hope, as Vertex has announced, that it will move very quickly this year, subject to regulatory, of course. And we'll be looking for functional measures of improvement as you would imagine.

The second question about where we go from different diseases. We have been so focused, and you know this for us, on our pioneer indication, we call it the central indication. We just want to go solve that problem. And there's something incredibly unique about bronchial epithelial cells. These are, in some ways, the hardest cells in the lung to get into. And the technology that Jean presented allows us to get in there and express high levels of protein, and we do think we'll have a, hopefully, corrective effect in cystic fibrosis.

There are not that many diseases of the broncho-epithelial cell, but there are others, and we presented some of them. And of course, as we see, let's hope for proof of concept very quickly in CF patients, we will then look to those other diseases.

But what Jean alluded to in the earlier part of the presentation is the delivery system that we pulled together actually taught us a lot about how to get other places in the lung. It could be deep in the lung, like where we are with pulmonary macrophages, alveolar macrophages and their diseases down there across a range of populations. And we've begun the discovery work inside of Moderna on both of those, both things in the broncho-epithelial nodes, in the deeper lung, but there is also an opportunity to get to generally the respiratory epithelium, right? And so although unrelated to nasal vaccination or other things like that, there are opportunities in the upper airway that we could be doing as well.

So we're looking broadly at those applications. And I think where you will see us move first with the technology after seeing that proof of concept with Vertex is more in the rare diseases, as I was describing, and then eventually thinking more broadly about other applications, inflammatory, immuno-oncology and infectious disease where it could be used.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Next question from Simon Baker.

Simon P. Baker - Redburn (Europe) Limited, Research Division - Head of Pharmaceutical Research

Simon Baker from Redburn. Two, if I may. Firstly, a broader question on lipid nanoparticles. We saw some fascinating data about the importance of the LNP in expression. And I just wonder if you could kind of position the importance of the nanoparticle optimization versus codon optimization in terms of boosting translation.

And related to that, there was some interesting work, I think, back in April out of UPenn looking at single component LNPs using these (inaudible) [instruments]. Just interested to get your perspectives on that.

And then on the Vertex cystic fibrosis product, could you just talk about the IP situation around that? If I remember rightly, Shire was working in that area about 7 or 8 years ago. Just wondering if there are any constraints on freedom to operate there.

Stephen Hoge - Moderna, Inc. - President

So 4 very good questions. I will take the last couple if you would take the first 2.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

Yes. I think that -- I had a little bit of a hard time hearing, but I think that you were asking, for LNPs, what is the relationship between optimizing the mRNA versus optimizing the delivery vehicle? Is that right?

Stephen Hoge - Moderna, Inc. - President

Relative importance.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

What's the relative importance? I mean the simple answer is they're both important, right? The -- but we -- the thing about optimizing the coding sequence and the codon optimization and the mRNA, that can be applied independent of the tissue and cell type that you're trying to get into. Although we have been learning some really interesting things, and maybe we'll talk at another Science and Technology Day about the different mRNA decay pathways and how they differ in different cell types, that's not widely appreciated yet. And so the design of our mRNAs, increasingly we're trying to design them specifically for the cell type that we want them expressed in.

But the -- also, the importance of the delivery vehicle, and I talked to this last year in Science Day, where not only do you need to design the delivery vehicle to be taken up by the cell types of interest, but it's got to let go of the RNA efficiently. Many of you will know that in the siRNA field, with the lipid nanoparticles that deliver siRNA, they're only getting about 1% of the siRNA out of the lysosomes and into the cytoplasm. And that actually is a good thing on their -- for their drugs because that gives them this long duration of effect because they're able to synthesize the siRNAs that are completely impervious to degradation by either chemical processes or the degradation machinery.

We can't do that with mRNA because we can't really mess with the 2 prime hydroxyls too much because the ribosome uses those to make sure that it's putting in the right amino acid. And so we need to get that mRNA out of the endosomes and released quickly. And we've previously shown that we're getting, with our delivery vehicles specifically formulated for mRNA and designed for mRNA, that we're getting between 10% and 30% of our mRNA out of the endosomes and into the cytoplasm, which is incredibly high number. And that's very efficient, but we also need to make sure that the mRNA is fully released from the lipids and is accessible to the translation machinery. And so they're both -- designing the LNPs and optimizing the mRNA, they're both crucial.

Stephen Hoge - Moderna, Inc. - President

Right. But if you joined the first Science Day, or maybe you were and apologies if you were, we would have been talking intensely about mRNA, nucleotide substitution, the chemistry there and the codon optimization algorithms to make that work. It's now sort of -- the fields move to a point where they accept where we were, which is that 1-methylpseudouridine, we think, is the ideal way to replace one of those bases. And then the codon optimization rules have been worked out.

So it's -- as Melissa said, it is both. We did them in sequence. A lot of the early work in the company was mRNA, nucleotides and a lot of the middle term work has been around LNPs. And now we're about co-optimizing them against each other for different deliveries, but we think they build on each other.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

If I could add one just thing to that. I mean we understand so well now and we've put so much energy into learning how to design mRNAs that give very good protein expression that when we -- the COVID -- the SARS-CoV-2 virus came up, we designed that RNA. We only designed one mRNA. It's the one that ended up in site vax, so that's how good we are. It's amazing. It still gives me shivers whenever I think about it.

We did make backup RNAs. Nothing was better. But literally, we understand the design principles for mRNA that well. So that's why we're now really starting to more focus on these Science and Technology Days on the LNPs because we really understand those design [senses.]

Stephen Hoge - Moderna, Inc. - President

So the last couple of questions, Simon, I'll maybe do the last one first. Just in terms of CFTR and where that program is going, we're incredibly excited by it. There had been prior work by -- I think you mentioned Shire, I think you have (inaudible) and then [the subsequent acquired.]

There's -- without specifically commenting on the IP situation, which I don't have the depth on specifically, it's important whenever -- from an IP perspective though, that something has to work. And I would just note that in the case of that technology and approach, there was a question about whether they were, in the bronchial epithelial cells, whether they were or not.

Ultimately, that program was abandoned. And so we did not follow, from an LNP perspective, that technology route. We obviously were aware of that work. We considered it carefully. We did not think it was going to achieve what we needed to in terms of getting to the broncho-epithelial cells. We chose a very different route for the work that Jean presented today.

And ultimately, we think that's now answering the questions, including in the broncho-epithelial, human broncho-epithelial cell models as well as in primates that we wanted to answer. So from a practical perspective, I'm not sure that it's relevant IP, but I can't speak to the specifics of it.

The -- on the single component, I'm actually not as familiar with that work. And so did you say it was a single component lipid system? And so those have been around for quite some time. Lipoplex, cationic stuff that you shake and bake with RNA is actually something that's been broadly used for transfection with DNA and RNA for decades, right? And there are lots of other sort of substitutes for them.

One of the challenges with our single component systems gets to the pharmaceutical properties. And one of the reasons why we like the 4-component system we currently use is that the aminolipid is incredibly important, but without the helper lipid and without that peg lipid to really stabilize that particle, particularly on storage over long term and prevent these lipid balls from sticking together and growing and then ultimately your drug doesn't really work, we actually have never really found a single-component system that can do all 4 or 5 things well. And there's really no problem with the 4-component systems themselves. And so while we look at that space, we do think the pharmaceutical properties of the presentations we're using are superior.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

So if I can just add one little thing to that. So the other thing about the lipid nanoparticles, they have this beautiful lipid bio-layer around the outside, right? So the mRNA is fully encapsulated within the lipid nanoparticle.

With lipoplexes, what happens is that the mRNA might be covered mostly with that lipid, but it can stick an elbow out. And if it sticks an elbow out, then there's a digestive enzyme that's going to clip it and then you're going to kill your RNA. So the RNA is not -- even though you can deliver some fraction of it, it's not going to be nearly as efficient and it's not going to survive the digestive enzymes that are in the biological fluids.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

We will take our next question from Ted.

Edward Andrew Tenthoff - Piper Sandler & Co., Research Division - MD & Senior Research Analyst

Thank you everyone. And I always start by just thanking you all for all of your hard work to really change our lives in such a profound way over the last 2 years.

So really intrigued by the pulmonary delivery. Particularly, I'm kind of thinking back to large molecules. So firstly, and maybe this is for Jean, but trying to understand better the mechanism or the complications of the LNP actually crossing or penetrating the mucus and whether there is some kind of detrimental effect to that.

And then also thinking all the way back to the experience from the inhaled insulin days (inaudible) with some of the (inaudible) from the RSV programs and even more recently, an ENaC clinical hold for an oligonucleotide. What's the potential for long-term talks of this mechanism of taking up macro molecules through the epithelial layer?

Stephen Hoge - Moderna, Inc. - President

Great questions. So I'll try and answer them, but obviously invite Melissa to fill in anything on this.

The -- so first on the barriers, your question about whether the mucosal barrier, particularly mucus, is a barrier. Look, both in the lungs, you have both a layer of mucus and the cells, the ciliated action cells that are trying to prevent things from getting in, and both represented real challenges for delivery of LNPs with mRNA in them. We actually think that they had not previously been solved based on even some of the benchmarking work we had done.

The mucus is probably the most obvious physical barrier. If you can get the LNP to the surface of the cell through that mucus, it's got a good chance of being internalized.

Now we had a lot of other work to do to make sure that when that got internalized, that we could get the RNA out. But one of the balancing acts was the types of technology that Jean was presenting that allowed us to get through that mucus also had a problem, which is they were -- we call them sticky, but they would hold -- they would get through the mucus to the [circular] cell, but they hold that RNA a little too tight, right? And that ultimately was the story that was presented today, part of that story today.

And so we had a balancing act. How do we make sure that we had a feature to that nanoparticle that allows it to get through that mucus based on features that -- we obviously filed patents on them. We're not publicly disclosing yet, but we will get into some of that basic science over time. But changing the components of the nanoparticles that we could do that and then make sure that those didn't become a liability inside the cell, which is the first or second versions of what we were doing, generations, we're working our way through them.

We did end up solving both. We did end up seeing that work in the human broncho-epithelial cell explants -- that were not explants, but the systems that Jean was describing. And that's why we have a high degree of confidence this is going to translate well in a human context. Obviously, also encouraged by the primate dosing, the repeated primate dose.

Now on your question of safety. The only way to really answer that question until you get into humans is you got to run a repeat dose, a large, many repeat dose tox study in a couple of species. And generally, we find primates to be very predictive in our experience. Obviously, you do 2 species.

That was the data that was announced by Vertex and by us in our, respectively, quarterly calls. I think I'm asked to stick to the script, which was those were positive studies and we're encouraged, and we see no reason we're not moving forward in terms of filing. But we would have -- as you could see from those histology studies that we were doing over the course of the last couple of years, we have been looking very closely at that.

And if we had seen in any of our non-GLP work that there was a signal from a safety perspective -- and again, we've been repeat dosing, in many cases daily, in those non-GLP studies for extended periods of time. If we've seen anything of concern there, we would have stopped and addressed it. And so both in the non-GLP studies, of which there are many that we've done, and in the GLP studies, we think we've addressed that.

Now at the end of the day, we've got to go run the clinical study and confirm that primates are predicting what we see in humans. And that will happen, as we said earlier, hopefully, this year.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

We'll take our next question from Hartaj Singh.

Hartaj Singh - Oppenheimer & Co. Inc., Research Division - Research Analyst

Hartaj Singh with Oppenheimer. My second Science Day. Great updates, I always learn a lot. So thank you very much.

Just 3 specific questions. One is, I remember in March, April of 2020 when you were talking about the COVID-19 vaccine, you're thinking of a lyophilized potential version because it would make distribution easier, especially in parts of the world where cold chain storage is not as good. So just your thoughts there.

Also, what methodologies are you working on to get the storage temperature of your vaccines down below that -- the negative and more in line with the cold chain storage in different parts of the world?

And then lastly, you've given your vaccine now at hundreds of millions of people all over the world. Any idea about, just for example, auto-antibodies against the LNP or the mRNA, like the (inaudible) vectors tend to have sometimes? So just thoughts there on that.

Stephen Hoge - Moderna, Inc. - President

Yes. Great questions, all. I will maybe take a stab and then ask Stephane if you want to talk on the manufacturing questions and then I can take the third question last.

So first, in terms of where we were in March, April, talking about lyophilization, I think when we were starting in that path of March or April of 2020, which -- gosh, that seems forever ago even though it's 2 years -- lyophilization was an option for us. We have a Phase III program right now. Our CMV vaccine is lyophilized. So we've been doing this. We're actually comfortable with it.

Lyophilization, though, is maybe okay if you're making tens of millions of doses, but if you're going to make 1 billion, it's going to become a -- there's going to become a physical limitation to how much you can do.

And as we -- ultimately, we're one of the more successful vaccines. We're proud of that. And there was a lot of demand for the product. It just didn't make sense to do a small batch of lyophilization as opposed to putting out large volumes of vaccines we did frozen.

Anything you'd changed about that?

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes. No, just very that -- we actually, even before March, it was almost end of January, I remember we would be talking to Ron and Stephen, and he was clear because of the CMV work, we could have done lyo, which would have been easier, but there are 2 things that we were solving against.

One was there's not enough lyo capacity in the world to get to 1 billion dose. So like, there was no way we could do it because that capacity does not exist. And of course, you don't have time to build it in the pandemic.

And the other piece that was weighting very heavily on our shoulders was the yield. As you know, every time we have a manufacturing process, you keep adding steps, you take your yield down. And so if we think about a loss of, I don't know, 5%, 8%, 10% on the yield, if you make 800 million doses, you're talking maybe 40 million, 80 million doses will never get into arms.

And so because of those 2 limitations, we looked at each other and said it makes no sense. If we can get a vaccine that works for them and the only problem for the world is to buy freezers, it's going to be okay. And so it was a very quick decision that we made with the team to say that lyo, which would have been preferred because it will be easier, it's just not a option in the pandemic setting. But if you look at all the other vaccine that Stephen and team are developing like CMV, BV and so on or (inaudible) and so on, we're going to use lyo, yes.

Stephen Hoge - Moderna, Inc. - President

And then on the question of -- Hartaj, I'm sorry, can you just remind me the third question? It was...

Hartaj Singh - Oppenheimer & Co. Inc., Research Division - Research Analyst

The antibodies generate, for example, against vector (inaudible).

Stephen Hoge - Moderna, Inc. - President

Yes. Thank you. So the short answer is it's not something you systematically look for in the vaccines and the deployment of it.

So the best place to look at it is actually the place where we've given the most doses in clinical trials. We didn't see anything of concern in any of our clinical work with COVID, but more specifically and I think even more deeply, we have looked obviously closely in our cancer vaccine context where we've given well over sort of 19 doses and some 10 to 20 doses in that trial, often in the background of checkpoint inhibitors, which will also potentiate some of those responses. And we have not seen a systematic area of concern there.

And I think we announced just a couple of weeks ago that the other place where we're doing a lot of dosing and obviously closely following safety is in our rare disease context where we're giving very, very high doses to young children. In some cases, folks on that study, the propionic acidemia study, have received a year's worth of dosing. And obviously, if we saw something that was of a concern in terms of an immune response to the LNP that would be impacting that pharmacology or safety, we obviously would report that.

So fingers crossed. In those more intensive places where we've looked both in cancer and in our rare disease context to date, we haven't seen any concerns there. Obviously, we haven't seen concerns in the vaccines, the COVID vaccine, but that is a less intensive place to look anyway because you're really only giving 2 doses.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Great. So I will take some questions from the webcast. The first one is on the theme of the obsession over learning and the use of AI. It sounded like this AI was helpful to unlock the inhalable LNP program in terms of characterizing protein expression in epithelial cells. What other ways do you foresee AI to help in clinical development?

Stephen Hoge - Moderna, Inc. - President

So I'll start. We -- where machines are fantastic because where you can train them -- or AI or machine learning depending the -- but you can train them on really robust data sets and then have them attack those data sets in a way that ultimately a human never quite could. And I think what we heard in the question, but what we were able to do in the pulmonary delivery space is we were able to massively increase our ability to characterize what cells we're getting the delivery system into by using an AI-trained or a machine learning-trained algorithm.

We do something very similar to that everywhere in our system that we have large data sets. And so it's not only in LNP delivery to the lung that we've done that. We've done that in other delivery work where there's data sets like histology that we need to look at, but where there's data sets like those cryo-EM pictures, those -- and they look like the gray and black pictures that Melissa puts out there where you'd say, well, those look like a bunch of golf balls, but they're in black and white or in sepia. The reality is there's a tremendous amount of information in those pictures about how those LNPs are formed and we do use machine learning to try and characterize that and understand it and then relate that to the performance of those LNPs, but also curate it, let humans look at that and say whether they agree with some of those characterizations.

Now in the clinical data space where we will be using machine learning, we already use it extensively in the CMC and technology space, right? So as we make materials, I think you can imagine, particularly as you get to 1 billion doses, you start to get to that kind of data set and you can use AI to help inform and identify issues that we see in CMC and look across the data and try and learn or spot trends that we haven't yet seen. And that's the most immediate place that we use it in clinical research.

As we do early clinical research in smaller numbers of patients, particularly in rare diseases and some of that stuff, we look -- you tend to look more intensely. And so there's less data for a machine to train on. But as we move to later stages where we are in currently in some of our large-scale vaccine studies and where I expect we'll be going with latent vaccines, there is an opportunity to start to look at, more broadly, at ways that we might predict response to the vaccines or protection using machine learning. And so those are places that we'll be looking in the near term.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

I was kind of smiling when you asked that question because -- and then maybe Stephane wants to talk to this, we have such a focus on digital and AI. And we have -- we make everybody take, as a company, take classes about where can we -- what is AI and where can you apply it to whatever it is that you do. And so it's truly pervasive across the company.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Thank you for that. Our second question comes from Tyler Van Buren from Cowen for Melissa's section. Melissa, you discussed where mRNA goes and how long it sticks around for. But how long does the LNP stick around? And where does it go?

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

So yes, we do have data about the components of the LNP, right? So we can do bio-analytical measurements of the different -- like our proprietary lipid. Obviously, we can't do cholesterol or those other things.

But the -- by following the lipids, that's not telling you that that's an intact lipid nanoparticle. So our best measure of having an intact lipid nanoparticle is following the RNA. And so yes, those data are available and are out there, but they're not telling us about the intact LP.

Stephen Hoge - Moderna, Inc. - President

Right. So when we do track things like -- Melissa has pointed about cholesterol, we got lots of cholesterol in our body. So since that's a large portion of the LNP, it doesn't really matter. You're never going to figure out which ones -- where that went.

But the aminolipid, which is the novel chemical, you can't follow the degradation. It's on a similar time trajectory. It's cleared relatively quickly within days. It is on a similar bio-distribution. It is largely in the [draining on products] and you will find almost trace amounts anywhere systemically in preclinical species, but again, disappearing quickly. We don't think that's, the chemistry itself, as we've previously presented in Science Days, is engineered to fall apart quickly. And so that's not surprising if it clears quickly. But as Melissa said, we don't think what you're seeing is outside of -- the lymphatic is actually intact LNPs. It's just the final degradation of the components.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Great. A question coming from Salveen Richter of Goldman Sachs. How are you ensuring IP protection around LNPs?

Stephen Hoge - Moderna, Inc. - President

Well, there's -- IP, first and foremost, we focus on patents. And as folks would know, we pioneered this space. In many cases, our filings from 9 years, 10 years ago have really shaped the space, including our first work in vaccines. And so just looking in vaccines, our first demonstration that an mRNA and LNP could make a very special vaccine was in 2013, 2014. There's 7 or 8 years of work where we were the only ones who really believed in that.

And I think at a -- the last number I remember, there's something almost on the order of 300 issued patents that cover the underlying technology across a range of geographies. In fact, the technology that Phil presented today, how you stabilize and prevent adduct formation based on the formulation you present, that's actually something we patented, issued patent in the United States and issuing very -- many have already issued in Europe actually as well so broadly. And so we're very aggressive when we make these sorts of discoveries as you've seen today and making sure we file those patents, prosecute them aggressively and get them issued. And that is one of the best ways we protect ourselves.

Now there's unique circumstances in a pandemic. And we're quite proud of the fact that during the pandemic, we were adamant from the beginning, even before we had data, saying we were not going to enforce our patents to prevent vaccines for being available. But in the future, one of the ways that we protect ourselves, that the world wants to protect because the world wants investment in innovation is that we will obviously enforce patents where we think they are valid and others are infringing.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Thank you, Stephen. Our last question is coming from Gena Wang of Barclays and she asks a 2-part question. Can you please provide an understanding mechanistically on how LNP modification can improve active mRNA translation? Wouldn't LNP be gone by the time mRNA escapes the endosome?

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

So the mRNA is not going to be stable in the endosome unless it is still in an LNP because there are digestive enzymes, both in the endosome and the lysosome. So we believe that the LNP -- that the surface of the LNP fuses with the membrane of the endosome to release the mRNA.

So the secret sauce for how we enable the ability of the LNP to retain it's, for example, ability to get through the mucus, and as Stephen said, get into the cells versus letting go of the RNA, that's just not something that we're ready to talk about. But what we demonstrated here is that we can do it, right? So I'm sorry.

Stephen Hoge - Moderna, Inc. - President

The efficiency of that, I think you've mentioned we're now 30% plus.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

Yes.

Stephen Hoge - Moderna, Inc. - President

We view that as an opportunity to improve, but 30% is maybe 30x higher than where we started.

Melissa J. Moore - Moderna, Inc. - Chief Scientific Officer & Member of Scientific Advisory Board

Yes, that is very good. Yes.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Perfect. Thank you. There is one additional question in the room. Please introduce yourself and ask your question.

Unidentified Participant

[Ali Dolgen], science journalist. So in the presentation about the CF program, you focused on the LNP and your ability to get these -- the therapeutic mRNA to the cells that you want to get it to, but I'm -- this is sort of about the CF program, but also about therapeutics in general. I think you guys have very successfully shown that mRNA is this kind of hit-and-run technology that you can get treatment of acute diseases in the heart, you can get vaccination -- prophylactic vaccination against infectious diseases. Others have shown you can use it to encode gene editing components for, again, kind of a quick hit kind of thing. But as far as I can tell, it's still an unproven technology for anything where you need repeat administration, chronic administration to get long-term protein replacement.

And so I'm curious why -- where you see success in the CF program and everything else that's still in the clinic, like some of the rare diseases you mentioned where previous programs, whether it was the Chikungunya antibody or the Fabry disease or any of the other programs that you guys have since abandoned, where those ones failed, why you see success in these chronic diseases now?

Stephen Hoge - Moderna, Inc. - President

Great question. So I think the premise is fair, which is we have not yet proven in humans. We have shown in primates and disease models chronic dosing and being able to keep those animals alive, but we're still looking for the first clinical trial example where we'll really state it and showing that we've been able to dose-regulate.

The short answer is that, which is, as we've shown in rodents or now in primates, repeat dosing is our objective. The regimen for that dosing will really depend upon the disease and how long that protein sticks around. So in our propionic acidemia program where we've been dosing for a

year in some patients, that's every 2 or 3 weeks. Again, different cohorts. And what we'll be looking for is a demonstration that that's sufficient, putting the enzyme inside the cells, inside the mitochondria inside those cells will be sufficient to provide, let's say, 2 to 3 weeks of protection.

That's not too dissimilar to a lot of other rare diseases. A lot of the Genzyme or Shire portfolio from back in the day, enzyme replacement therapies were given every 2 to 3 weeks. And this won't be any different, right? And we think that mRNA will create that protein over a couple of days, but none sustain itself over a couple of weeks. And that means you'll create it for a couple of days and then you'll follow the pharmacology.

We're looking forward to that propionic acidemia data. That will be the first time demonstrating it. That might be, when it comes out, the first time of us demonstrating that in humans, but we have shown that in the preclinical species.

Now your question specifically around cystic fibrosis, it will be something similar. We do not know today what the dosing frequency will need to be in a CF patient to maintain the right level of the CFTR protein on the surface of those cells. It could be that you need to do it, I don't know, best case scenario once a month or every -- a couple of times a month or it could be that you need to do it more frequently. Maybe it's daily as a nebulization treatment to put it there.

It will depend a lot upon that disease, and when we get into those patients, how stable is the protein in their lungs once it's put there. So we don't know. That will have -- something we'll have to demonstrate over time. Clinical data will ultimately answer this question.

Lavina Talukdar - Moderna, Inc. - Senior VP & Head of IR

Great. That concludes our Q&A section. I'll hand it over to Stephane for quick concluding remarks.

Stephane Bancel - Moderna, Inc. - CEO & Director

Great. Well, thank you so much for coming, for attending the webcast today. As you can see, we are very excited about where the technology is going. And we really believe there's so many opportunities to impact patients over the next years. They get us very excited. And I'm very thankful for the team who keep pushing hard everyday to push and treat the boundaries of science for the benefit of patients. So thank you very much. Have a great day. Thank you.

DISCLAIMER

Refinitiv reserves the right to make changes to documents, content, or other information on this web site without obligation to notify any person of such changes.

In the conference calls upon which Event Transcripts are based, companies may make projections or other forward-looking statements regarding a variety of items. Such forward-looking statements are based upon current expectations and involve risks and uncertainties. Actual results may differ materially from those stated in any forward-looking statement based on a number of important factors and risks, which are more specifically identified in the companies' most recent SEC filings. Although the companies may indicate and believe that the assumptions underlying the forward-looking statements are reasonable, any of the assumptions could prove inaccurate or incorrect and, therefore, there can be no assurance that the results contemplated in the forward-looking statements will be realized.

THE INFORMATION CONTAINED IN EVENT TRANSCRIPTS IS A TEXTUAL REPRESENTATION OF THE APPLICABLE COMPANY'S CONFERENCE CALL AND WHILE EFFORTS ARE MADE TO PROVIDE AN ACCURATE TRANSCRIPTION, THERE MAY BE MATERIAL ERRORS, OMISSIONS, OR INACCURACIES IN THE REPORTING OF THE SUBSTANCE OF THE CONFERENCE CALLS. IN NO WAY DOES REFINITIV OR THE APPLICABLE COMPANY ASSUME ANY RESPONSIBILITY FOR ANY INVESTMENT OR OTHER DECISIONS MADE BASED UPON THE INFORMATION PROVIDED ON THIS WEB SITE OR IN ANY EVENT TRANSCRIPT. USERS ARE ADVISED TO REVIEW THE APPLICABLE COMPANY'S CONFERENCE CALL ITSELF AND THE APPLICABLE COMPANY'S SEC FILINGS BEFORE MAKING ANY INVESTMENT OR OTHER DECISIONS.

©2022, Refinitiv. All Rights Reserved.