

Will Eiserman:

Welcome to Earworm. Dialogues on hearing health you can't stop thinking about. Earworm is brought to you by the National Center for Hearing Assessment and Management at Utah State University known as NCHAM. I'm Will Eiserman and I'm the Associate Director of NCHAM and I'm your host. Today, approximately 40% of early childhood hearing loss and deafness can be attributed to a virus known as cytomegalovirus, usually referred to as CMV. If a pregnant woman contracts CMV, it can be transmitted to the fetus in utero.

In fact, approximately one out of every 200 babies is born with CMV, of which 90% will present as asymptomatic and will very possibly go unidentified. Of those 90% with asymptomatic congenital CMV, it's estimated that between 10 to 15% will experience hearing loss, which may be present at birth or may develop later in life. In this episode of Earworm, we'll be talking about ways to mitigate the effects of CMV in the early childhood population, with a special focus on a new vaccine that is under investigation.

Our guest today is Dr. Lori Panther, who is the Vice President of Clinical Development Infectious Diseases at Moderna, where she leads the CMV Vaccine Development Program. Prior to joining Moderna, Dr. Panther was an assistant professor of medicine at Harvard Medical School and an infectious diseases specialist at Beth Israel Deaconess Medical Center in Boston. So welcome Dr. Panther.

Dr. Lori Panther:

First of all, thank you for having me on the podcast.

Will Eiserman:

So you work for Moderna. For many of us, the first we ever heard of Moderna was when it stepped into the national, if not worldwide, spotlight as one of the primary companies offering a COVID vaccine. So tell us a little bit about Moderna and what it is you all do.

Dr. Lori Panther:

Moderna is a biotech company that is really focused on filling the gaps in healthcare by tackling diseases that either do not have any mode of prevention or treatment or have modes of prevention or treatment that could be improved. And we do that all through one platform called mRNA technology. Prior to the coronavirus pandemic, we had quite a broad portfolio. Even before coronavirus we were working on and still continue to work on several vaccines that are still in development and have been trudging through development throughout the pandemic.

Certainly coronavirus changed the picture of the company and also the knowledge about mRNA technology, which was very exciting for us because a lot of our mission at Moderna is to educate the public through the technology, but also to educate the public that these diseases that are often really not paid very much attention to. So [inaudible 00:03:18] company's an incredible collection of incredibly smart, motivated people and it's just an amazing place to be working at.

Will Eiserman:

Well, we want to hear about mRNA technology, but first let's talk about one of the diseases that Moderna is investigating, which is cytomegalovirus, also known as CMV. What is CMV Dr Panther and why is it of particular concern for newborns?

Dr. Lori Panther:

Sure. Cytomegalovirus is a mouthful to be sure. So let's call it CMV and it's a virus that is in the herpes virus family. We think of herpes as a particular disease or infection. There are several viruses in this family called herpes viruses and CMV is one of them. CMV is complicated from A to Z. It's a complicated virus. It's complicated to develop a vaccine against and it causes a kind of complicated picture in infection in humans. The majority of us have been infected with CMV by the time we hit around 40 or 50 years old.

It's a virus that's acquired through contact with infected secretions, which sounds extremely yucky, but mainly the virus is present in saliva and urine. And so contact with those substances will often result in an infection of somebody who's never been exposed to the virus.

Will Eiserman:

So if so many of us have been infected by CMV, how is it that so few of us outside of the medical community know about or even ever heard of CMV?

Dr. Lori Panther:

If you and I were to get a CMV infection right now, we probably wouldn't notice it. Healthy people usually don't have symptoms, but caveat here is that when a mom who is pregnant or about to be pregnant is infected with CMV, she has a risk of passing on that virus to her unborn child. And when someone gets CMV infected, the virus is transiently in the bloodstream. So that's how the child gets infected through the placenta and then to the fetus. Most of the severe damage of CMV occurs in an infant who acquires that CMV infection through that route from mother to fetus.

Will Eiserman:

So CMV is a virus that easily floats around the general population without most people even realizing they're contracting it or spreading it. But it's when the pregnant individual who also may not be aware that she has contracted it, passes it on to the fetus in utero, that serious impacts can occur for the fetus.

Dr. Lori Panther:

The manifestations can be quite varied from no symptoms in the infant to severe symptoms right there in the labor and delivery room. To perhaps delay diagnosis of sensorineural hearing loss. The sensorineural hearing loss is the most common manifestation of CMV infection in a child. And the reason is that the CMV virus loves nerve cells and if CMV happens to be around during the development of the fetal ear and in hearing apparatus, then that definitely causes damage to the proper formation of the nerves that supply the cochlea.

Will Eiserman:

What is the incidence of CMV and some of the various outcomes of CMV?

Dr. Lori Panther:

Overall in the US, approximately one in every 200 live births are infants with congenital CMV infection. So that adds up to somewhere around 35-40,000 infants a year. The spectrum of what an infant with congenital CMV infection looks like in the delivery room or shortly after birth is quite wide. The most severe manifestations occur in about 10% of those congenitally infected infants and can range from microcephaly to manifestations of a systemic CMV infection. So the liver gets infected, which results in

jaundice, which results in abnormalities in the blood, like low platelet count, like high liver function tests.

CMV can infect the retina because retina are full of nerves as well. And so blindness can manifest again. Organ enlargement, liver enlargement, spleen enlargement, it's a systemic infection. And of those 10% of congenitally infected infants with those very severe manifestations, about 10% of those infants don't see their first birthday. The mortality rate is remarkable in those severely infected infants. And then there's the rest of the spectrum. So 85-90% of infants either have mild manifestations like a little rash or mild jaundice.

Will Eiserman:

So a small percentage of CMV infected infants can have pretty severe manifestations.

Dr. Lori Panther:

And majority of infants with congenital infection appear well in the labor and delivery room.

Will Eiserman:

And because they appear well, their CMV infection often goes undiagnosed.

Dr. Lori Panther:

Correct.

Will Eiserman:

So infants with symptomatic CMV can face a range of health challenges at birth, some of which can be quite serious. And among those challenges, one is being at risk for hearing loss with it either already present at birth or developing hearing loss later and even possibly progressing over time.

Dr. Lori Panther:

Correct.

Will Eiserman:

And so the risk of developing hearing loss is also present in that larger asymptomatic group of children who have congenital CMV, often without anyone realizing they have CMV. And that's no small deal because CMV is a significant contributor to early childhood hearing loss.

Dr. Lori Panther:

Yes, it's the most common non-genetic cause of hearing loss in children and estimated to be the cause of approximately a quarter of the world's neurosensory hearing loss burden.

Will Eiserman:

So sometimes children don't pass their newborn hearing screening.

Dr. Lori Panther:

Which prompts the doctor to test for CMV.

Will Eiserman:

And if the child tests positive for CMV, then they may be treated with antivirals which have increasing evidence of being able to minimize, if not maybe even reverse the effects of hearing loss on the auditory system.

Dr. Lori Panther:

Correct.

Will Eiserman:

A positive CMV diagnosis also provides the parents and doctor with important information suggesting the need to track the child's hearing status over time so that if the child's hearing changes, immediate steps can be taken.

Dr. Lori Panther:

Now otherwise in general, infants are not routinely tested for CMV when they're born. That's not a routine test that an infant is given. And so a lot of these kids fall through the cracks and go on to manifest their CMV infection as hearing loss and early childhood or later childhood, and it can be progressive.

Will Eiserman:

So a lot of kids with late onset hearing loss may not have the opportunity of having a timely diagnosis of their hearing loss because the CMV as a risk factor wasn't ever identified.

Dr. Lori Panther:

And so that opportunity for those kids who are going to be losing their hearing or diagnosed with a late onset hearing loss is lost because we didn't diagnose that CMV infection right after they were born.

Will Eiserman:

All of that really clarifies why identifying congenital CMV can be so important. But it sure would be nice if we could just prevent CMV in the first place, and that's where Moderna comes in.

Dr. Lori Panther:

The development of a vaccine against CMV infection has been underway at Moderna for around six and a half or seven years in the clinic and earlier than that in the laboratory. But like I said, CMV is a complicated virus.

Will Eiserman:

Dr. Panther take us into the so-called weeds.

Dr. Lori Panther:

Every virus has antigens, but CMV's antigens are called gB and pentamer and those antigens have a particular talent to allow that virus to enter a cell. And so the mRNA technology that we've leveraged to create a candidate vaccine, an experimental vaccine has been to encode those antigens so that we know

the genetic sequence of those antigens. And so the mRNA that was included in our particular CMV vaccine are mRNAs that encode the gB antigen in its full length and then the pentamer antigen.

And just as an aside, this antigen pentamer is called pentamer rein because it's not just one big protein. It's a protein that's made up of five little protein subunits. And so our vaccine includes those five mRNA sequences that encode those five pentamer subunits. And so what happens when we give the experimental vaccine to study participant is that those mRNAs go into the muscle just like every vaccine is as a shot in the arm. And those mRNA pieces are translated into their little subunit proteins and then within our cells just as if it were a truly real CMV infection.

But this is just a little chunk of CMV, those little five subunits self-assembled just like little magnets and create this pentamer antigen, this five subunit pentamer antigen, which physically looks like the actual CMV viral antigen. When we give ourselves the information or the recipe to make these proteins, our body does it in exactly the same way they would if it were a real viral infection. And so it's a natural conformity type of antigen that our immune system responds to, and we are in the process of investigating if it responds well enough that it actually prevents a real CMV infection. And that's what our development program is all about.

Will Eiserman:

So where are you in the development process?

Dr. Lori Panther:

At this point, we're in the phase three study, which a phase three study is essentially testing if the vaccine really works. A lot of the earlier phases of vaccine development are testing if it's safe first of all, and then if it's safe, then what dose is the best dose. And then the next phase is it safe and is it effective? And so we're at that third step at this point in time in our development program.

Will Eiserman:

What does that look like in terms of knowing if it's effective?

Dr. Lori Panther:

Is it effective in terms of does it prevent actual natural CMV infection? And luckily the way that we can easily detect that is that we can do a blood test before the vaccination and then after the vaccination and on into the couple of years. Periodically, we test these individuals who have gotten vaccinated. We are in the middle of a phase three trial, which essentially is a trial of approximately 7,000 women of childbearing age. So between the ages of 16 and 40, the trial is designed that these women are divided into essentially two groups.

One group gets placebo, one group gets active vaccine. And we can measure it through actually just a simple blood test throughout time, whether or not these women have acquired natural infection against CMV. And we have a lot of bells and whistles included into the study, but that's the basic bones of the study. It's a relatively simple question and size of the study has the biostatistical power to answer that question.

Will Eiserman:

Now, during the period when vaccines were being rolled out for the coronavirus, which also employed mRNA technology, there were some concerns about cardiac issues specifically associated with the mRNA vaccines. Is that concern being addressed in the current trial?

Dr. Lori Panther:

Yes, certainly. All of the trials that are currently ongoing are assessing for any occurrence of cardiac abnormalities. The exact causes of those reversible short-lived abnormalities in mRNA-based COVID vaccines is not fully teased out. There has been some suggestion that antigen focused that's particular to COVID. And I'd like to remind you at this point that individuals who are naturally infected with COVID-19 have much, much, much higher incidence of having the cardiac issues and severe cardiac issues from the actual viral infection than the very unusual event that happens after an mRNA-based COVID vaccine.

That said, as you might imagine, we are very closely following any safety issues at all, but particularly cardiac safety issues with all of our programs and have not found any cardiac signal in any of our other programs, but we're continuing to monitor.

Will Eiserman:

So I have to ask at a time when there are some fairly strong opinions in the general public and even voiced politically about vaccinations including a certain measure of vaccine hesitancy out there. How do you anticipate this being addressed if Moderna does in fact produce an effective vaccine for CMV?

Dr. Lori Panther:

Very good question. I think that we try to focus on education not only about the mRNA platform, but also very importantly about the effect or the burden on children that CMV causes. And it's not really a topic that people talk about over cocktails, CMV. We have a formidable group of individuals whose sole focus is to educate the public about CMV, especially educate women who are looking forward to having another child or starting a family. Approximately the same number of kids are born with CMV infection as the number of kids that are born with Down syndrome.

And if you were to ask your average person on the street, if they've heard of Down syndrome, there's a decent chance that they say yes, but there's practically no chance, a little chance that they would say, "Yes, I've heard of CMV infection." So we have a job to do and we're looking forward to this vaccine proving efficacy. We have worked extremely hard on designing the study to give us clean data and to tell us exactly what we want to know, assuming that we're going forward.

That's our next challenge, is to communicate the importance to the community that this really is sort of a hidden problem for families. And in many cases actually can be devastating to families and obviously devastating to the infected infant, but devastating to the family, every member of the family. And so it really does tug on all of our heartstrings when we talk to these families and hear their stories.

Will Eiserman:

Thank you so much, Dr. Panther for sharing the exciting work you're doing at Moderna that can potentially have a dramatic impact on the prevalence of the leading non-genetic cause of early childhood hearing loss cytomegalovirus. So we know with research and development of this type, you can't make predictions about when a vaccine will actually become available, but how can people follow your progress with this?

Dr. Lori Panther:

Watch the Moderna website, I would say.

Will Eiserman:

Which is modernatx.com.

Dr. Lori Panther:

This particular phase three trial will be able to give us the key, crucial information as to what comes next with this development program. It may give us enough information that we can actually file for licensure.

Will Eiserman:

And I'm sure that can be time-consuming in and of itself

Dr. Lori Panther:

For sure, but we're planning for success, and so we're hoping that we do meet that goal. We do meet that milestone. This is the trial that will essentially inform the direction of our next step.

Will Eiserman:

That was Dr. Lori Panther from Moderna. I'm Will Eiserman from the National Center for Hearing Assessment and Management at Utah State University. Check out earwormpodcast.org for other episodes of Earworm. Dialogues on hearing health you can't stop thinking about.

Singer:

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Will Eiserman:

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