
# Episode 39: Behind the Scenes: A Look at the Science and Research for New Treatments

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**Mindy Henderson:** Welcome to the Quest Podcast, proudly presented by the Muscular Dystrophy Association as part of the Quest family of content. I'm your host, Mindy Henderson. Together we are here to bring thoughtful conversation to the neuromuscular disease community and beyond about issues affecting those with neuromuscular disease and other disabilities and those who love them. We are here for you to educate and inform, to demystify, to inspire and to entertain. We are here shining a light on all that makes you, you. Whether you are one of us, love someone who is, or are on another journey altogether, thanks for joining now. Let's get started.

Well, today I have two guests with me who I'm very excited to speak with. We're going to delve into the topic of the science and research it takes to create treatments and therapies for neuromuscular disease and a bit about the State of the Union of that science and research. And the best part is, we're going to break it down so that people like me who are not scientists will understand. So let me introduce our guests to you.

First, we have Dr. Jeffrey Chamberlain. Dr. Chamberlain is a geneticist with expertise in the muscular dystrophies and is currently a professor of neurology, medicine, and biochemistry at the University of Washington School of Medicine, director of the Wellstone Muscular Dystrophy Specialized Research Center, and the McCaw Endowed Chair in Muscular Dystrophy. He is also president of the American Society for Gene and Cell Therapy. Research in the Chamberlain Lab focuses on understanding the molecular basis of and developing treatments for the muscular dystrophies with a focus on gene therapy. Several of his vector

designs are being tested in human clinical trials for Duchenne muscular dystrophy.

And our second guest is Dr. Sharon Hesterlee. Sharon is one of my favorite people at the Muscular Dystrophy Association and is going to co-facilitate this conversation along with me. She is incredibly impressive herself with a PhD in neuroscience from the University of Arizona as MBA's chief research officer and over 20 years of experience in neuromuscular research in both the nonprofit and industry spaces where she has served variously as head of research, project lead and CEO. She's been involved in numerous efforts to remove barriers to therapy development for rare disease and foster interactions between patient advocacy groups and industry. Thank you both so much for being here with me.

**Dr. Sharon Hesterlee:** Thank you.

**Dr. Jeffrey Chamberlain:** My pleasure to be here.

**Mindy Henderson:** I'm exhausted after reading both of your introductions. Clearly, there's a lot to talk about. So I'm going to jump right in for my first question for you, Dr. Chamberlain. First of all, would you mind telling us just how you got into the field of neuromuscular research specifically?

**Dr. Jeffrey Chamberlain:** Well, it was a slow process. I think I always had it in the back of my mind about the Muscular Dystrophy Association and what they were trying to do, primarily from growing up watching the MDA Labor Day Telethon for many years. But when I got into graduate school, I was initially interested in developmental biology and ended up in a laboratory run by Steve Hauschka that was interested in how muscle develops during human fetal and embryonic development. We were working on that for a number of years and I just became more and more interested in muscle biology and decided I wanted to do something a little more applicable to human health and got an offer to go work with Tom Caskey in Houston to start studying Duchenne Muscular Dystrophy. And that led to everything else after that.

**Mindy Henderson:** Fantastic. So I had the pleasure of hearing you speak recently at MDA's Annual Clinical and Scientific Conference as you were presented with the MDA Legacy Award. Congratulations by the way, very well deserved. Your career progression and body of work, even to my unscientific ears, are incredibly impressive. We have a lot of individuals listening, I think, who like me live with a neuromuscular disease but are not scientists. You gave a really amazing overview of your 30- or 35-year career, I think it was, during your speech at conference and it was so impressive. Can you break your work and your accomplishments down for us into layman's terms, if at all possible? I'm sure that's a big ask.

**Dr. Jeffrey Chamberlain:** Well, I can try. I guess I think of my career as falling into three general phases, my graduate schoolwork, my postdoctoral training, and then life as a faculty member running my own laboratory. And usually in our field, those are very

distinct phases of one's career and often you're encouraged to jump from one field to another and leave behind what you did in the past. In my case, all three of my phases have tied together fairly well, which is not something I set out to do initially. It was just somewhat coincidental and fortuitous that it worked that way. But in graduate school, I mentioned earlier I was studying developmental biology of muscle. The approach I took to that was to try to clone a gene that was only active in muscle cells and try to figure out why that was. What were the on-off switches? Why was it an active gene in muscle and not in liver? Things like that.

And then I thought I was leaving that behind for the rest of my career. But years later, as I started getting more interested in gene therapy, we realized that a critical part of gene therapy was having good and strong on-off switches to make sure that when you tried to deliver genes to muscle, that they were active only in muscle and not in other tissues. So that was kind of a fortuitous occurrence of mine.

After I left the developmental biology areas of my research, I started learning about genetics and becoming interested in human diseases and diagnostics and things like that and started applying that to muscular dystrophy. However, the laboratory I was in as a postdoc, which was at Baylor College of Medicine in Houston, was one of the first labs that started focusing on gene therapy. They were mainly interested in blood disorders. The muscle wasn't a big focus of the lab at that time, but a lot of that rubbed off on me, I guess. And I started learning about gene therapy even though I wasn't yet working on that.

I started working on a mouse model for muscular dystrophy, which turned out to be a good model for Duchenne muscular dystrophy. So when I went to set up my own laboratory, I kind of combined all of that and decided to actually see if we could explore gene therapy for Duchenne muscular dystrophy. And at the time, gene therapy was not a popular topic. A lot of people were very vocal in saying it would never work and it was kind of a silly area of research to go into. I got a lot of negative feedback early in my career with people telling me, "Why don't you do something important and leave this stupid gene therapy stuff behind?" And I'm glad I didn't.

We actually became one of the early advocates trying to argue that gene therapy was potentially a good way to try to treat the muscular dystrophies. And my lab, after the first couple of years of trying to set it up, it became heavily focused on gene therapy. And we took advantage of this mouse that had been identified as a possible candidate for Duchenne. We identified the gene. I mean, the gene had already been identified by Lou Kunkel, but we started working with the mouse gene and developing various tools and techniques that we could use to try to figure out a way to put genes back in the muscle. And that led just in sequential step year after year to getting closer and closer to finding out how to do that.

The real challenges we had were, how do you deliver a gene into all of the muscles of the body? There's an enormous amount of muscle in the human body. How can you do that safely? And also, what exactly do you want to deliver? Because the gene that causes Duchenne muscular dystrophy is unusual in that it's an enormous gene. It's by far the largest gene that's ever been found in nature. So it's very difficult to work with. It's so large, much less to try to find a way to deliver it back into the human body. So there were a lot of challenges we faced along the way. We certainly never ran out of questions to answer or problems to solve. We're getting closer. We're finally have some things that look like they're showing tremendous promise, but we're not done yet so we're going to keep plugging away at that.

**Mindy Henderson:** Incredible. Well, I think I speak for a lot of people when I say that we are glad that you didn't listen to those early naysayers. So big congratulations on that. I'm curious how you manage to continue moving forward on such uncharted territory when there are people along the way who maybe don't believe in the science or what you're doing?

**Dr. Jeffrey Chamberlain:** Well, you never know quite how you're going to react to these things. And everybody reacts a little differently. It is certainly something I discussed with the people that have trained under me over many years. Some get discouraged easily, some do not. And in general, the approach is you have to believe in what you're doing. I guess I'm fortunate in that I've always had a fair amount of confidence in my ability to analyze situations and try to figure out what the best path forward might be. So when people gave me negative feedback, I just kind of passed it off and said, "Well, that's your opinion. That doesn't line up with my opinion. I'm going to stick with my opinion and you can go do what you want to do. So that's fine."

The other thing is research is a huge area. There are so many human health problems out there. There's so many basic biological questions that remain unanswered that we'd like to find out about. So there's a tremendous number of things one can do. From my point of view, settling into something that I thought was interesting and important, it was kind of good enough for me and I figured, "Look, I'm going to do what I can do. And if it doesn't pan out, if we don't get to the goal that I want to get at, so be it. At least we're going to make a contribution along the way and hopefully I'll be able to train some good young people to move along and take it to the next level." So I've never worried that much about what other people say. I mean, sometimes it can be a little irritating, but it hasn't led me to change my goals in any way.

**Mindy Henderson:** You said a good example for a lot of us. And again, we thank you for your tenacity and for staying the course. I'm sure it's hard to pick one, but what has been your proudest accomplishment in your career to date?

**Dr. Jeffrey Chamberlain:** Well, it's difficult to say. At a general level, my proudest accomplishment are the people that have come through my laboratory that I've helped to train. I've had a tremendous amount of just incredible folks work with me over the years.

They're the ones that do a lot of the basic work and really advance the field and allow my lab to have the success that it's had. So I enjoy working with people, training them. And seeing them succeed is a very proud event for me.

More scientifically, the fact that I was one of the early people to advocate for gene therapy to see it come to the point where we have clinical trials ongoing for gene therapy and just in the past year we had the first gene therapy product approved by the FDA, which is now available by prescription, was a tremendously exciting event in the culmination to more than 30 years worth of work in my laboratory. So collectively, I think that's probably the thing that I'm most proud about.

**Mindy Henderson:** Fantastic. And Sharon, I'm going to pivot over to you for just a second. Can you talk a little bit about Dr. Chamberlain and how MBA has worked with Dr. Chamberlain over the years?

**Dr. Sharon Hesterlee:** Yeah, sure. So if I recall correctly, our very first gene therapy grant actually went to Dr. Chamberlain in the '90s, I believe. And since that time, he's been a regular grantee over the years. So we are very proud that we've been able to support his work many different ways for a long time. But he's also helped us. So Jeff was on our research advisory committee that reviewed grants, and that was usually... It's a lot of grants and a lot of work. So he did that for many years, which we very much appreciate. He's also been on the MDA Labor Day Telethon multiple times, met with Jerry Lewis, and continues to participate in different fundraisers for the organization. I know there's a major golf tournament every year in Seattle now. So on a lot of many different levels and probably some things I don't know about as well. But yeah, no, he's participated very actively with us over the years.

**Mindy Henderson:** That's fantastic. And another question for you, Sharon. We're going to be talking, I think, a lot about Duchenne muscular dystrophy. We've already heard about it a couple of times as part of this conversation. Can you talk a little bit more for us about Duchenne and what it is and what causes it?

**Dr. Sharon Hesterlee:** Yeah. So Duchenne is a severe childhood form of muscular dystrophy. It affects boys because it's due to defects on the dystrophin gene and that's carried on the X chromosome. So women, girls have two copies of the X chromosome. Men only have one. So if the defect is on their one X chromosome, they'll get the disease. And that's why you see it in boys. Typically, it causes muscle wasting and weakness. They're often diagnosed around age four or five when boys aren't keeping up with their peers, sometimes they can't alternate feet on stairs. A lot of them are never able to jump to get both feet off the ground at the same time. Eventually, they're flagged by someone either at school or at home, and they get the diagnosis of Duchenne muscular dystrophy. And after that, they continue to lose muscle strength and get weaker. Many of them stop walking around the age of nine or 10, although with a lot of new treatments, they're walking longer.

And eventually, the respiratory muscles are affected. All of the skeletal muscles involved in movement, but also the respiratory muscles and the heart are affected. And that's really the severe problem. This is still a fatal disease unfortunately, although men are living longer or they're into young adulthood, sometimes into their 30s, but severely impacted by the disease, which eventually either causes heart failure or respiratory failure.

**Mindy Henderson:** Yeah. And correct me if I'm wrong, but I think that that's thanks largely to the medical care. Certainly, that's available to people living with Duchenne today. And also the therapies that have come onto the market. Dr. Chamberlain, do you mind talking about the current therapies? You mentioned gene therapy that was approved recently, but there are a few of them that have been approved today, and maybe what's working well and where there are still gaps.

**Dr. Jeffrey Chamberlain:** We're at an unprecedented time in the development of therapies for the muscular dystrophies. When I first started working in this area more than 30 years ago, there was very little available for the patients. And there's been an increasing number of drugs come online. It's very exciting. As Sharon mentioned, it's leading to an increase in lifespan. It's making life easier for some patients. And we're slowly getting there.

The last five years in particular have seen approval of a new generation of different drugs. There's a couple of different things kind of in the gene therapy space. The first thing to come online were these antisense oligonucleotides that have primarily been pushed by Sarepta, but a couple of other companies are coming out with some new ones now, that are designed to not really a hardcore gene therapy, but they're designed to sort of tweak the genes that are defective in different muscular dystrophies and allow a little more of the missing protein to be produced. That was an exciting development.

In hindsight, I don't think those therapies are working as well as we had hoped. It is an improvement, it is better than where we were before, but we need to go beyond that. The gene therapies are starting to come online now. Direct gene therapy where you're bringing in a new copy of the missing gene is something that ultimately I think is going to be a lot more effective. It is already looking more effective than some of the other strategies, but it's still not quite where we want to be. So both of those methods need improvement. As I mentioned earlier, there's been a lot of advances and breakthroughs, but we're still not quite there yet. But we're learning as we go along. We're having drugs that are more and more potent, more and more effective, and we're slowly increasing our ability to treat these diseases. But we need to keep moving.

And the other things that have come along the line are other drugs that are slowing down the progression of the disease and improving the quality of life, allowing these kids to get out and do more things, go to college and things of that nature. It's the things as simple as a steroid hormones like Prednisone, some of the newer generation ones that are now coming online, like Bromadiolone, things of that nature. We have a lot of improvements in

respiratory care and cardiac function that years ago people never really thought about applying some conventional medical approaches to patients with muscular dystrophy, but those can have a big impact also. So there's a lot of different options out there where we still don't have a cure or something that I would argue is a lifelong treatment that is going to allow everybody to really have a long and happy life. So we need to build on what we have out there, learn what's working, what isn't, and take that to the next generation.

**Dr. Sharon Hesterlee:** I can build on that question, Jeff. Maybe you could talk a little bit. There've been so much progress, but as you mentioned, we're not quite there yet. Why is muscular dystrophy and Duchenne in particular so challenging?

**Dr. Jeffrey Chamberlain:** Well, the muscular dystrophies are challenging for several reasons. One is that the target muscles, we need to go in there and get drugs or genes or cells, whatever type of therapy you're looking at, back into all of the muscles of the body. The estimates are, that about 40% of the human body is muscle. So it's an enormous target area. Some of the earliest gene therapies that have worked quite well are designed to work in blood cells, and that's comparatively simple. You can isolate a couple of blood stem cells, put a gene into them and inject that back into the body, and those cells will repopulate the entire blood system in muscle. It's not nearly that simple. We have an enormous target we need to be able to target our drugs against.

The other thing is that muscular dystrophy is also a disease where many, many things go wrong and the muscle start breaking down that leads to a reaction by the immune system. You get a lot of inflammation going on. You have fat cells coming in. You have other non-muscle cells invading the muscle that lay down connective tissue and things like that that are just not good for overall health of muscle. So there's many different biological processes happening simultaneously. And you need to not only combat all of those, but in some cases, fight off some of these other processes that are thwarting your main efforts to develop gene therapy.

So for example, one of the reasons that the gene therapy hasn't been more effective than it is, is because of the immune system. In order to deliver so many genes to get to all of the muscles in the body, that's quite an onslaught into the human body. And the immune system often recognizes this as a foreign invasion and the immune system just kicks up and tries to fight it off. So we're not only trying to deliver new genes to improve the health of the muscle, but we're trying to keep the body from rejecting that very same therapy. So there's a lot of different features that come into play. It's one of the things that makes it complicated from a researcher's point of view, is that no one person has the expertise to figure all of that out. And so research in this area has to be collaborative. We're constantly talking to other laboratories trying to get advice from other individuals. And you need to have many people approaching the development of therapies from a variety of different areas of expertise and background in order to bring it all together.

**Mindy Henderson:** So interesting to listen to you talk about all of this. Dr. Chamberlain, with the magnitude of the problems that you are trying to solve and the nature of research, what keeps you going and how do you continue to move forward in, what I'm sure happens, those moments of frustrations when maybe a theory doesn't pan out or you have a discouraging moment in your work?

**Dr. Jeffrey Chamberlain:** Well, there's a couple of things. From the positive side, I enjoy what I'm doing. Even back when I was a little kid, I liked science. I enjoyed learning about things. I liked reading science fiction in my spare time. In some ways, what I'm doing as a job is it's like I'm getting paid to work in the science fiction field, only we're trying to take it from the area of fiction to the area of reality. But it's interesting work to me. I enjoy doing it. Not only my own work, but all my colleagues around me. We go to a lot of lectures and teach classes in a wide variety of areas of science and just absorbing all that information and helping to contribute to it is something I enjoy doing and I find exciting.

So that's one of the motivations, is it sure makes it a lot easier to come to work when you enjoy what you're doing. It's one of those things, there's a lot of common cliches about that, but sometimes it surprises me that people pay me to do what I'm doing because it's something I might do anyway even if I didn't have a job.

On a more practical basis, the fact that you're doing something that can have an impact on human health is incredibly motivating. As I mentioned, I enjoy science. At one time, believe it or not, I thought of going into a career in particle physics, trying to understand how is the atom made up and what are those different particles doing. But I eventually came to the conclusion that while that was kind of fun to me, sustaining that level of interest for the rest of my life might be a little more difficult to do. And having something that was a little more relevant to human health that I could relate to my friends and neighbors and family members about what I was doing and why it was important, that became important also. I liked the idea of contributing to society and not just doing something for myself. What we're doing in the lab I feel can have a big impact not only on the muscular dystrophy, but potentially on other diseases. And that's probably motivating.

And specifically though, the patients. One of the things that I've tremendously enjoyed about my relationship with the Muscular Dystrophy Association over the years is they bring together all these different communities. We have the researchers, we have the clinicians, and most importantly, we have the families and the patients. I've had tremendous opportunities to meet with probably thousands of family members and patients over the years, talk to them about their experiences, what they need, what the problems are in their life, where they see the future moving. And that's tremendously motivating, and I try to impress that on the people in my laboratory.

We always welcome families and patients to come visit our laboratory and do a little tour. Not only do I enjoy doing that, but it has a huge impact on the

students in my laboratory and the scientists that work with me because so many people go into science because they enjoy it, because it's an intellectual challenge. But when you're confronted by meeting and realizing how many thousands, if not millions of people are out there waiting on progress and watching and listening to what's coming out of your laboratory, suddenly it goes from, "Well, this is kind of cool" to, "Maybe I should start working a little harder and really make some progress." And so that's motivating.

There are ups and downs all the time. But the downs, everybody goes through moments of where things aren't going well in their life. You just got to work through that and focus on the positive, focus on the potential of what you're trying to do. And keeping in touch with the families really helps us get through a lot of that and is the biggest motivation of all.

**Mindy Henderson:** Well, and that's a perfect segue because Brooke Eby, who lives with ALS, was our keynote speaker at conference, and she talked a lot about the urgency of the work that scientists like you do. I understand that it can be motivating from one point of view, but there's got to also be an emotional impact of that urgency. How do you balance the two?

**Dr. Jeffrey Chamberlain:** Well, you just do the best you can. As I mentioned, everybody has their highs and lows. Often, when I do meet with a family or an individual that's maybe not doing very well with their disease, it can be devastating. It's extremely sad and impactful and sometimes I think to myself, "Well, we haven't done enough. We're letting these people down. What's the point? Should I just give up?" But you can't let yourself sink too low into that. I'm always preaching to people that remain positive to look at the good things. I'm one of those "the cup is half full" kind of guys. You just got to kind of fight through it and remember that you're doing the best you can. Life isn't perfect, but hopefully we can do things to make it better. And so like I say, I try to use it as a motivator and try not to dwell too much on some of the sad realities. So sometimes it's an exercise in self-delusion, if you will, that it is going to be okay, it's going to work out, but we just need to keep working hard and get there.

**Mindy Henderson:** I like that attitude.

**Dr. Sharon Hesterlee:** Yeah. Well, so thinking about the glass half full approach, maybe you can talk to us a little bit about what you think is exciting right now in gene therapy. So can you talk a little bit about in other areas, what is exciting from a research standpoint in Duchenne right now?

**Dr. Jeffrey Chamberlain:** Well, there's a lot of exciting things. I mean, it goes back aways. One of the real challenges that frankly I thought was going to be one of the hardest things to overcome was this concept of so much of the human body being muscle tissue and how can you possibly engineer a drug that can target so much, so many of the cells in the body? I mean, there are billions and billions of muscle cells in the body.

So we actually made a discovery in my laboratory almost 20 years ago now, where we found a particular delivery vehicle known as adeno-associated viral vectors or AAV that we could actually harness to deliver genes to muscle. And to me, that was just enormous that we now we know we can deliver genes to muscle, so we just got to figure out how to do it safely, effectively, when's the best time to do it, things of that nature. And since then, we're of course, as always happens, we're discovering that AAV is not the perfect delivery vehicle. It is the best thing we have, but there are tremendous advances now in how to modify these AAV delivery vehicles to overcome some of the safety issues that have been seen in the clinic with them.

The other thing is that there's a lot of work going on now in trying to find alternative delivery vehicles. That's something that I always push my lab, is you don't want to get too comfortable with what you're doing. You always need to look for alternatives and things that may work better, may not work better, but you've got to keep an open mind. You can't get to set in your ways and say, "I'm going to make this work and I'm not going to do anything else until it works." You've got to look at these alternatives.

The other thing is that one of the things that we've seen in going... It's always a lot easier to treat a disease in an animal model than in the clinic. And in going into clinical trials, we've learned a lot of things that weren't apparent in some of the animal studies. That's opening up new avenues of research. I mentioned the immune system. The immune system is one of the biggest hurdles to gene therapy. So much work is going on in the muscular dystrophy space and in many other diseases that's allowing us to get a better handle on that and find ways to overcome the issues that are arising, and that's going to be really important.

The other thing that excites me is that even the non-gene therapy angles. You need to take a broad approach to this disease. We were talking earlier about all the different things that go wrong in muscular dystrophy. We're learning now that gene therapy can halt a lot of those processes, doesn't necessarily reverse some of the pre-existing damage. There's a lot of advances in drugs that bulk up muscle make it stronger, that they block the immune system, that reverse some of the other cell types that invade muscle and kind of get in the way. And ultimately, what we're going to have I think when we really have tremendously effective therapies for all these diseases is they're going to be combinatorial approaches with multiple different types of drugs. I think gene therapy is going to have a major role to play in that, but it's not going to work all by itself. We need these other drugs coming in to combat other aspects of the disease reversing and things like that.

And that leads to maybe one of the most exciting discoveries over the last five years or so has been paved by two labs in particular. Many others, but Michael Rudnicki up in Canada and Lou Kunkel in Boston have been pushing this idea that despite all our focus on muscle cells themselves, there's a tremendous role to be played by muscle stem cells, the cells that ultimately create all the muscle

in the body. And that there's actually some defects in these muscle stem cells that we didn't appreciate until recently.

There's some new drugs coming online and scientific studies trying to understand why those cells aren't working well. There's some exciting data, some of which was just presented last week at the MDA Scientific and Clinical Conference, suggesting that if you could improve the health of these muscle stem cells, that that in itself can make a huge impact on the quality of life in these patients. So just a couple of the examples of things that are moving this field forward right now.

**Mindy Henderson:** So interesting. It makes me want to go work in a lab.

**Dr. Jeffrey Chamberlain:** Well, we need all the help we can get.

**Mindy Henderson:** I don't think you'd actually want that, but I would love to come be a fly on the wall. Again, just because gene therapy is such a topic of conversation right now, can you talk a little bit more, again for the non-scientists in the room, about how Gene the works and what can be expected as a result of receiving the gene therapies that are on the market today?

**Dr. Jeffrey Chamberlain:** I mean, gene therapy is kind of a general term that actually encompasses a couple of different classes of drugs. The concept of gene therapy was really put forward back in 1975, quite a long time ago, where people realized that a lot of diseases that are out there have an inherited component. Some obviously like muscular dystrophy, if you inherit a defective gene, you're going to get this disease. But many other diseases like heart disease and cancer are influenced by your genetic makeup, the background of genes you have. So the whole idea of gene therapy is to either restore the function of a defective gene or to augment the genes you have in order to help combat some of the problems that arise in genetic disorders where there's not a single gene that's involved.

In terms of what we've been hearing about in the muscular dystrophy space the last couple of years, the main type of gene therapy that's moving forward is what we sometimes call gene replacement therapy. And that's probably the simplest type of gene therapy where let's say you have an individual that's born with a defective copy of a single gene. Everybody, every human has somewhere between 20,000 and 30,000 genes, but often a mutation in just one of those genes can lead to a very devastating disease as you grow up.

So the simplest concept of gene therapy is to take a normal copy of this defective gene and put it back into the cells where it normally works. And so in other words, you're replacing the defective gene. You don't have to get rid of the mutant gene, you just need to bring in a working copy of that gene. And so again, so that's called gene replacement therapy. And that's what we're trying to do with Duchenne muscular dystrophy and many of the other muscular dystrophies, is identify a normal copy of the gene, figure out how to get it back

into muscles. And then it should take over for the defective gene, and in the best case, restore normal muscle function.

Now, it turns out it's a little more complicated than that. One of the things we're finding out is that yes, you can get a new gene back in the muscle, it can take over for the defective gene and start leading to more normal muscle function, but you don't necessarily clear out all the damage that's already been there. I mean, you can think about a simple scenario of a highway and you have an earthquake and that highway's damaged. Well, often what happens is there's a lot of infrastructure for miles around that's also damaged. So gene therapy in a way is coming in and putting up a new highway, but you're not necessarily replacing the water lines or the electricity and all those other things that have gone down at the same time. So those are the things that we need to figure out how to deal with now to really improve muscle health.

One approach to that is to apply gene therapy as early as possible. We've seen that in the spinal muscular atrophy field where that's a disease that you need to treat really early. There's been remarkable progress in that disease, but we're still seeing that the older the patient is when you treat them, typically the therapy is not as effective as if you were able to apply it at an even younger age. So you not only need to figure out how to get the gene therapy in there, but you need to ask, "Are we just stopping the disease? Are we slowing it down? Are we reversing it?" And if not, what else we do to overcome some of these other issues that we're having to deal with?

Now, there are other types of gene therapy. Some of the other muscular dystrophies are more complicated. They're what we call dominantly inherited. And in those cases, your defective gene is actually doing things that it's not supposed to. And in that case, you can't simply deliver a new gene. You've also got to shut down the defective gene and make sure that it stops wreaking havoc, if you will, in the muscle cells. And so that's a different type of therapy. Rather than replacing the gene, you're delivering tools that will try to shut down the defective gene and hopefully that'll lead to a restoration of health. And then you can also bring in stem cell therapies and combinations of gene therapies and stem cells. You can use small molecules that can tweak how active a gene is or in which cell types it's produced. So it is turning into a field of its own. It used to be gene therapy we used to think of as sort of a subset of genetics. Now it's turning into its entire own discipline, but one that is absolutely dependent on all these other areas of study too.

**Mindy Henderson:** Wow. Wow. So the gene therapy for Duchenne muscular dystrophy that is available today, that's a one-time treatment, is that correct?

**Dr. Jeffrey Chamberlain:** At the moment, it's a one-time treatment. Hopefully, it's not going to always be that way. I mean, well, depending on how you look at it, I mean, it's nice to have a one-shot treatment. But one of the issues we're dealing with is it's not a complete cure. It's having an impact. It can slow down progression of the disease. And in some cases, it seems to be stabilizing the kids. They get this gene

therapy. But I think one of the things we're realizing is that we want to build upon where we're at now and potentially improve the gene delivery vehicle itself to be able to give patients something that's going to be more potent down the road.

One of the issues though is that currently the way gene therapy is applied, it's limited to a one-shot treatment because you're not able to do it a second time. And the reason for that is that having to deliver the massive quantities of these genes that it takes to get into muscle essentially vaccinates the patient against your delivery vehicle. So it becomes very difficult to give them a second dose. And I think the current gene therapies would work even better than they are now if we could give multiple doses. But that's not the end of the story. That's just another challenge creating another area of research to tweak the system and make it work better. There's a lot of labs right now that are working very hard to try to find ways to overcome this vaccination type barrier so that we can give multiple doses of these drugs. I think that's going to happen. It'll happen in the semi-near future, and that's going to have a big impact on the disease.

The other thing that's happening is that we're coming up with new generations of gene therapy vehicles and we're finding ones that are more potent, that are longer lasting and things of that nature. And as an example of that, one of the things that we're working on in my laboratory is to find a way to deliver a much larger and more potent versions of the dystrophin gene. One of the limitations with Duchenne muscular dystrophy and dystrophin that we talked about earlier is the gene is so large it's not been possible to deliver it in a single piece. We have to kind of chop it up and deliver smaller versions of that gene. We think we have a way now to deliver possibly even the entire gene to muscles over the body. We're not quite there yet, but it is an exciting development and it's something that has become a major focus in my lab to try to push this and make this the next generation of gene therapies.

**Mindy Henderson:** That is exciting. Now, Sharon, I know that MDA, you mentioned earlier how long MDA has been supporting this kind of research. Can you talk a little bit more about that and what MDA is doing to help within the area of gene therapy?

**Dr. Sharon Hesterlee:** It's interesting. When I was listening to Jeff talk about the challenges he had at the beginning of his career when people were saying, this will never work, MDA had some of the same headwinds early on when we were funding gene therapy. The field suffered a really tragic setback in the late '90s when there was a death of a young man in a trial, and a lot of things just kind of shut down for a while. There were young new companies built around this technology that went out of business. I think we just believed it and we believed it was going to work. And sometimes it takes a long time for technologies to work.

So we just sort of quietly kept funding it in Jeff's lab and other labs in this space. We ultimately funded the first gene therapy trial for any form of muscular dystrophy, it was actually in limb girdle muscular dystrophy, and then the first trial for Duchenne muscular dystrophy, which was an intramuscular injection at

the time just to see if we could get the gene in. And I know, Jeff, you were on the committee that helped advise around that project. And all told, I think we spent about little over $125 million just trying to build the field, trying to understand all these different pieces of the therapy. So it's pretty gratifying now to see these therapies start to be approved drugs.

**Mindy Henderson:** Absolutely. And as someone who is living with spinal muscular atrophy myself, I always, my entire life, it was the research that was going on that always gave me and my family hope. So what you do is so important to so many.

I have one question left for each of you. Sharon, let's start with you. I think we all know that research and drug development don't move as quickly as it's clearly very complicated. And so it doesn't move as quickly as the community of individuals living with these conditions would always hope. However, it is an exciting time in neuromuscular medicine, and I feel like we're gaining momentum. What would you say to people listening as MDA's Chief Research officer about why people living with these conditions should feel hopeful?

**Dr. Sharon Hesterlee:** MDA is fast approaching its 75th birthday, which means the organization has been around for a very long time with a single focus of developing treatments and therapies for neuromuscular disease. I think for a while, the progress, there was huge progress that was happening, but it was sort of below the surface. It wasn't highly visible. I think that was frustrating for many years for many people, but it didn't mean that things weren't happening. So there's over a billion dollars total that has been invested in research and it's building this whole field of neuromuscular disease research. It's doing things like advocating for the MD Care Act, which increased the NIH funding of neuromuscular disease research. The Department of Defense is now funding neuromuscular disease research.

And so all of these things have come together, and what we've seen in the last 10 years is over 20 drugs approved in the neuromuscular disease space. And that's a sudden leap from having very little to having quite a few. I think what we're seeing is we've sort of hit a critical mass of our understanding across all of those years of research are really starting to pay off and really bear fruit. So that would be my message to people out there, is we're starting to see the benefits of all that research that's sort of been maybe not as obvious to people for so many years.

**Mindy Henderson:** Yeah, it feels like the floodgates have been open, doesn't it?

**Dr. Jeffrey Chamberlain:** Yeah.

**Mindy Henderson:** So Dr. Chamberlain, as someone with boots on the ground, doing the work to help create these therapies for, again, anyone in our community who may be listening whether it's someone living with one of these conditions, a caregiver,

family, friends, what final thoughts would you like to share about the future of therapies and treatments for neuromuscular disease?

**Dr. Jeffrey Chamberlain:** Well, I am more optimistic now than I've ever been in my life about the potential to treat the muscular dystrophies. Frank to be, honest with you, when I first started working on this, I was not convinced that there would be an effective drug developed in my lifetime. I am so happy that I was wrong and that the field has moved along much faster than I thought it would. We're not quite there yet, but as Sharon mentioned, we're making tremendous progress. It's accelerating. And even the things that aren't perfect, there are great ideas out there that people put forward on what to do to make them better. This field is going to continue accelerating and we're going to have a major impact on many different types of muscular dystrophy over the coming years.

The key to that is we need to keep the research dollars flowing, which is always a challenge. I hate to say with the politics in Washington, DC, the federal funding for research has stagnated over the last 20 years. It's not keeping up with inflation. But thank goodness we have organizations like MDA that are able to fill that gap, come in and identify the highest priority areas, put money into it when they need to, and they move quickly. NIH, the federal government, is a big bureaucracy. It takes over a year from an idea to actually being able to start a project. MDA can step in a hurry and jumpstart a project. It's not just giving money, it's giving support and motivation and connecting you with patients and doing everything you need in a holistic way to develop the next therapies. And that's what we need. I'm so fortunate to have been affiliated with this organization for so many years.

**Mindy Henderson:** That's so great. Well, I wish that we had two more hours to talk. This is so interesting, and I've really enjoyed our conversation. I can't thank you enough. I know that you are incredibly busy, both you Dr. Chamberlain, and you, Sharon. So thank you so much for taking the time to talk with me today.

**Dr. Jeffrey Chamberlain:** Well, thank you for everything you do also.

**Dr. Sharon Hesterlee:** Thank you.

**Mindy Henderson:** Thank you for listening. For more information about the guests you heard from today, go check them out at mda.org/podcast. And to learn more about the Muscular Dystrophy Association, the services we provide, how you can get involved, and to subscribe to Quest magazine or to Quest Newsletter, please go to mda.org/quest. If you enjoyed this episode, we'd be grateful if you'd leave a review, go ahead and hit that subscribe button so we can keep bringing you great content. And maybe share it with a friend or two. Thanks everyone. Until next time, go be the light we all need in this world.