Transcript of Cerebrum Podcast— Spinal Muscular Atrophy: Huge Steps

Guest: **Lee L. Rubin**, Ph.D., is a professor of stem cell and regenerative biology at Harvard University and director of therapeutic medicine at the Harvard Stem Cell Institute. Rubin received his Ph.D. in neuroscience from the Rockefeller University and completed postdoctoral fellowships in pharmacology from Harvard Medical School and in neurobiology from Stanford University School of Medicine. Since then, his work has been mostly in translational neuroscience, both in academic and industrial settings. Work from his lab has led to the discovery of approved treatments for multiple sclerosis and for cancer. Rubin's group currently focuses on studying neurodegenerative and neuropsychiatric diseases, including various aspects of spinal muscular atrophy.

Host**: Bill Glovin** serves as editor of *Cerebrum* and as executive editor of the Dana Foundation. He was formerly senior editor of *Rutgers Magazine*, managing editor of *New Jersey Success*, editor of *New Jersey Business magazine*, and a staff writer at *The Record* newspaper in Hackensack, NJ. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: What does it mean when muscles atrophy? How is this tied to the brain? Are we making any progress in fighting this dreaded disease? Hi, I'm Bill Glovin, and welcome to the *Cerebrum* Podcast. To find the answers to some of these questions, we have Lee Rubin on the phone with us. Lee is co-author of our *Cerebrum* article, "Spinal Muscular Atrophy: Huge Steps," which can be found at dana.org. Lee is a professor of stem cell and regenerative biology at Harvard and director of the therapeutic medicine at the Harvard Stem Cell Institute. Work from his lab has led to the discovery of approved treatments for multiple sclerosis and for cancer. Rubin's group currently focuses on studying neurodegenerative and neuropsychiatric diseases, including various aspects of spinal muscular atrophy.

Welcome, Lee. Let us start with a plug for your website, which is at hscrb.harvard.edu. When you go to the homepage, there is a photo of 20 people. That is quite a crew to manage.

Lee Rubin: That is correct, and we do a lot of different things in the lab. As you said, we work on a few different diseases of the nervous system, both degenerative kinds of diseases and psychiatric kinds of diseases. We also have recently started an interesting project on aging. Aging is a major contributor to many of the diseases of the nervous system, although not to the one that we are going to be talking about today.

Bill Glovin: Do you have any trouble attracting students to your lab?

Lee Rubin: Well, Harvard is a very good institution and it is generally very attractive for students and post docs. Sometimes we require, in my lab for what we do, some very, very specialized skills which are more commonly found in pharmaceutical companies. So, sometimes for some of those more specialized things, it becomes a little bit trickier to find the right people.

Bill Glovin: I notice in the photo of the 20 people there is quite a few women. Do you find that there are more women in this field than before?

Lee Rubin: Well, I do not know about more in the field, but my lab has a majority share of women. And it was not for a particular reason, I would say we got a lot of excellent women applicants and, luckily, they decided to come here. So, definitely compared to, let us say, when I was a student many, many years ago, there are many more women who are graduate students, and post docs, and beyond in the sciences and that's been really wonderful for the lab. We have, as you can see from the picture, a fairly diverse lab overall.

Bill Glovin: Yeah, that's great.

I also noticed in reading your bio on your website that, before you came to Harvard, you previously were chief scientific officer for a biotechnology company. Why did you make the transition?

Lee Rubin: It is a funny story of some sorts. When I was working in industry on a particular pathway that is very important in embryonic development, called the “Hedgehog Pathway,” we knew when I was still an industry that that pathway was hyper activated in cancer. And we were looking for inhibitors of that pathway to use in cancer. And, as you mentioned when you introduced me, actually one of them developed with Genentech is now approved for treating certain kinds of cancer.

At the very same time we also identified some drug like molecules that turn on the pathway. And those molecules turned out to be extremely useful for making neurons from stem cells. And, as a neurobiologist, I had never had access to neurons before, but suddenly a method became available to make billions of neurons and I really was motivated to use those neurons to study diseases like spinal muscular atrophy. However, that had never been tried before in industry. So, I went back to academia to see if I could, even though I was working still on diseases, try a new method to study disease. So, that is how I ended up here.

Bill Glovin: Wow, that is really interesting.

Again, I want to thank you so much for writing the article. The title has the phrase huge steps in it, but before we get to that, maybe you can tell the listeners what it means to have muscles atrophy.

Lee Rubin: Yeah, so everybody knows that muscle strength is very important. And the muscles we are talking about here are, skeletal muscles or the muscles that move you, so the ones that are important when you play sports, and lift weights, and just walk around and breathe, as opposed to let's say your heart muscle, which is a different kind of muscle. So, because everybody knows that the breathing muscles and the movement muscles are very important, everybody could also appreciate that if those muscles become dysfunctional, they start to deteriorate and atrophy, as you called it. It's very disadvantageous.

It's something that happens normally when people get very old, they lose muscle strength. Everybody knows that. But unfortunately, there are also various diseases, muscular dystrophy is one of them and the other one is spinal muscular atrophy, in which for several different reasons your muscles begin to malfunction, including the muscles that are important for breathing, and walking, and lifting your head up, and so on.

Bill Glovin: There seems to be quite a few different diseases that fall under the muscular atrophy umbrella. Can you tell us the difference between them?

Lee Rubin: The difference between them at the large level is what causes the different diseases. That is actually quite different from disease to disease. For instance, the cause of muscular dystrophy is a mutation in a muscle gene. The cause of spinal muscular atrophy is a mutation in a gene which is expressed not only in muscle, but also in the neurons, the cells, and the spinal cord that connect to muscle and are necessary to initiate movement. And that gene happens to also be expressed in all other cells in your body. So, the cause is different in the different kinds of diseases. And, actually, the particular muscles that are affected can be different in the different diseases.

For instance, ALS, Lou Gehrig's disease, another disease most people have heard of, is a disease that also affects breathing and skeletal muscle. The cause of that is different and the muscles that are affected, again, in ALS, are different from the muscles that are affected in SMA. So, as a big picture, of the cause is different in all of the different diseases, and at the smaller level of detail, exactly the muscles that are affected are different. But all of them are very, very serious diseases.

Bill Glovin: By the way, SMA is the acronym for spinal muscular atrophy. Is it a disease someone inherits?

Lee Rubin: Yes. It's a purely genetic disease, unlike many other diseases. For instance, Lou Gehrig's disease, ALS, is primarily non-genetic, which is to say, “it does not run in families.” To get SMA, to be a child with SMA, each one of your parents would have had to have an SMA disease gene. And, if a child inherits two SMA what I'm going to call “disease genes,” then that child will have a form of SMA.

Bill Glovin: Is it age related?

Lee Rubin: This particular disease, unlike most diseases of the nervous system, is quite early onset. So, it is more a childhood onset disease. Again, by comparison to Lou Gehrig's disease, which is an adult or late adult onset disease. So, it is the childhood motor neuron disease.

Bill Glovin: How widespread of a problem is it?

Lee Rubin: Well, it is very interesting and probably not known to most people is, about 2 percent of people in the world, which is to say roughly six or more million people in the U.S., carry one disease gene. They don't get spinal muscular atrophy because they have one non-disease gene that is sufficient to keep them apparently quite functional. However, the chances in the population are about one in five thousand or so births of children with spinal muscular atrophy of one form or another. That could be a severe form or it could be a milder form, but it is actually quite, quite frequent.

Bill Glovin: What are the symptoms?

Lee Rubin: The symptoms vary a little bit with the severity of the disease, but most of the obvious symptoms are motor symptoms or muscles symptoms, which is to say in the severe kids, they do not move well, some of them cannot even lift their heads. And for those severe kids, those symptoms are detected quite early. For some of the milder forms of the disease, children may be able to lift up their heads and progress a little bit further in their muscle development but may end up spending later life in a wheelchair. So, it can vary a little bit, but it all relates to the degree of movement capacity.

Bill Glovin: In your article, you talk a lot about proteins. And we know proteins from, let's say, tau, and encephalopathy, or amyloid from Alzheimer's. Are proteins in the brain something that spurs problems?

Lee Rubin: Well, many diseases of the nervous system, so they all involve genes and they all involve proteins. Many diseases of the nervous system, like the ones you're talking about, let us say Alzheimer's disease, involve proteins, which can even be normal proteins, and they are processed, mishandled in the sow so that, in the case of Alzheimer's disease, you build up aggregates or plaques of those proteins or tangles of those proteins which make neurons dysfunctional.

In spinal muscular atrophy, it is a little bit different than, let us say Alzheimer's disease, because again, spinal muscular atrophy involves a gene and a protein. But, in this case, what happens is, when you have a disease gene you actually end up with much less of the functional protein that you need. And that protein plays a very important role in the function of cells. So, in Alzheimer's disease, the disease is caused by an aggregation or accumulation of protein. And in spinal muscular atrophy, it's actually caused by the loss of a protein.

Bill Glovin: Very interesting.

Your article talks about new drugs that have shown great promise in treating SMA, how were those drugs developed and by who?

Lee Rubin: So, first of all, the disease, even though it is not particularly rare, was completely under studied until a little bit more than ten years ago when the Spinal Muscular Atrophy Foundation came into existence and really spurred a lot of the research and actually funded a lot of the research in this field. And luckily, Kelly Howell, who is a coauthor on our article, actually works at the Spinal Muscular Atrophy Foundation.

And the interesting thing about this whole body of work is, even though everybody knows the genetics of the disease, everybody knows the name of the gene that causes spinal muscular atrophy, everybody knows roughly speaking what the protein that that gene codes for does, nobody really knows why motor neurons die or muscle fails to function when the protein decreases in amount. All people knew, at the time, was more of the protein makes the disease less severe. So, it was a very unusual group of projects because normally you try to understand what the gene is doing, and that's still to this day not completely clear. So, everybody focused on the more is better aspect of this.

And it was really a combination of work done in academic labs and then, interestingly, in several biotech, and then pharmaceutical companies that all together led to, not only the fact that there is an approved drug right now, but there are two other drugs in late stage clinical testing, and also a viral gene therapy drug, also in late stage clinical testing. That all arose from efforts made of different kinds to find ways of increasing the amount of functional SMN, survival of motor neuron protein. Survival of motor neuron is the protein that is coded for by the gene that causes spinal muscular atrophy.

Bill Glovin: The article on the front page of the *Science Times* yesterday, I don't know if you saw it, talked about the two dozen clinical trials that are going on for muscular dystrophy. But the focus of the article was how restrictive these clinical trials are. Why is that?

Lee Rubin: Well, I think, and I did not read the article extremely thoroughly, but I did look at it. I think it is for a combination of reasons. I think everybody probably accepts that there's a reason to do a clinical trial in the sense that you want to make sure something is safe and effective before it becomes freely available to people. So, when you do a clinical trial, and of course it is always true that companies, well, almost always true that companies are running clinical trials because they're the ones that are trying to develop the treatment. They have to come up with criteria to enroll patients in the trial. And then, the FDA, as everybody is aware, has to approve the criteria.

So, the FDA is very mindful that they don't want to cause any harm to anybody. So typically, the clinical trials are very well defined to try to give a drug a good chance of succeeding, but to absolutely make sure it's safe. And therefore, it ends up being quite, in a way, exclusionary because only a certain number of

patients can be treated. They can only be treated in a certain way, at a certain dose, in a certain order. So, even though it might not make sense to people, parents with kids who are ill, and it's a very distressing situation, and everybody wonders why their child can't get enrolled, I think in large part it's actually for quite legitimate and understandable reasons that, unfortunately, in the longer run, will be the right thing to have done to do things diligently and make sure the data are collected in an appropriate way. But it is a situation which is definitely sad for many people who cannot get treated or whose kids can't get treated.

And for rare diseases there is an additional factor that is involved, which is to say there are not necessarily for the rare diseases enough patients with the disease to be enrolled in many, many clinical trials. So, it is a very complicated process, I would say. And it is completely understandable that people who are either ill or have a child who is ill would be distressed by the system as it is now. But, while understandable, I think there is some rationale for designing clinical trials the way they are currently designed.

Bill Glovin: The article also mentioned that the technology is moving so quickly that some people are kind of holding off and waiting for something better to come along.

Lee Rubin: Yes.

Bill Glovin: So, that is kind of an intriguing aspect of it.

Lee Rubin: Yeah. And there is another thing because some of the trials don't want to enroll people who have had another treatment before. And so, there is a kind of, in a way, a rationale for wanting to hold out until the best one becomes available. And then, of course everybody is wondering, should I just go for what is available now and try that? Or should I wait longer for something that may come about at some time in the future that may be better? And that is a very tough kind of decision matrix.

Bill Glovin: Two strategies that the article mentioned were exon skipping and gene therapy. Do they apply to SMA?

Lee Rubin: Yeah, so they are both applicable to SMA. So, I did not go into detail, but in spinal muscular atrophy, the disease gene is a form of the gene in which the gene, instead of coding for an RNA of a particular size, it codes for an RNA which is smaller. And that RNA leads to the production of a protein which is smaller than it should be, and it is not functional. Actually, what happens is that protein is rapidly degraded in cells. So, there is not enough of it to stay around to be functional. The exon skipping drug corrects that genetic defect and allows for more what's so-called full-length messenger RNA and, therefore, more full-length functional protein. So, it's a kind of a way of tricking the cell so that it can take a disease gene and make it seem like a normal gene.

The gene therapy gives you a copy of the normal gene. And so, it makes you more kind of like the carrier of the disease, that is to say more normal, because it's just directly giving you a non-disease gene that the kids do not have, but each of their parents does have one copy of the gene. So, we would move them in the direction of being normal just by directly replacing the disease gene.

Bill Glovin: For the drugs that have been developed, are they affordable?

Lee Rubin: Well, there is one drug that's approved at the moment and it's quite expensive. I think the current pricing is something like, it's a drug that is given by injection into the spinal cord directly. And so, the price includes the surgical procedure and so on. But the price is high, it's about seven hundred and fifty thousand dollars for the first year. And I believe it's half that in at least the second year and maybe subsequent years. So, it is definitely a very expensive drug. I believe it's covered by health insurance, at least in some places for sure. But it is expensive.

There are three other new possibilities. I mean, there are two drugs, regular drugs, that do not need to be injected into the spinal cord that are in late stage clinical testing now. One is being developed by Roche, one is being developed by Novartis. They're not yet approved. People are optimistic. I don't know that anybody has released information on what the pricing would be if they get approved.

And then, there's the gene therapy treatment that you were mentioning, which was originally developed by a company called AveXis, which was then acquired by Novartis. And that also is in late stage clinical testing. I think that also has not been priced out yet, but I believe that people are imagining that it might be quite expensive, maybe like the numbers I mentioned before.

Now, that is an interesting thing because, potentially, that treatment could last a very long time. And, if it does last a long time, it is essentially saving a lot on health care costs and everything else. So, to me, I am not a healthcare economist or anything like that, but to me it's the total cost of the drug and care. And, if this drug happens to be expensive, this treatment happens be expensive, but it saves hugely. Number one, prolongs kids lives and make them function better. And number two, actually reduces the overall amount of money that needs to be spent on these kids to keep them as healthy as they can be. To me, I think that should be taken into account. But, again, I am sure these things will be negotiated.

Bill Glovin: So, the title of your article, “Spinal Muscular Atrophy: Huge Steps,” in ten years could it be, “Spinal Muscular Atrophy: a Cure?”

Lee Rubin: Well, that will be interesting to see. I mean, I think that the currently approved treatment, Spinraza, developed by Ionis, which is a company in California and in partnership with Biogen, is basically given in the spinal cord, it only really

directly corrects features of the disease which are related to what is dysfunctional about spinal cord cells.

We also mentioned in the article that there is reason to think that there are other tissues like muscle itself that is directly affected in the disease. And it may be the case that other kinds of treatments will be required. For the other treatments, which are given systemically, so they could potentially improve multiple tissues, I think whether or not they will work to cure the disease, if I could say that, or simply make it milder or make it almost as if it doesn't exist, I think that remains to be seen.

The gene therapy vector I think some people are definitely optimistic about it, because that may have the possibility, if given early enough, and if that vector has access to all of the cells that it needs to get into, and if the effect really does last, that may be more in the direction of something like a cure. But it is too early to know, I would say.

Bill Glovin: In your view, is there enough funding for research in this area?

Lee Rubin: I think that in general in the area of neurodegenerative disease research or childhood disease research, I think there is a significant amount of funding for Alzheimer's disease, which of course there is a major problem where there are maybe 20,000 or 30,000 children who are surviving with spinal muscular atrophy at the moment, there are about five and a half million people in the US with Alzheimer's. And so, that funding is completely understandable.

I think, however, for a number of the other diseases, even terrible diseases like SMA, ALS, the amount of funding is probably inadequate. And I think one thing that, if you read the science section in the *New York Times* every week, you will see is that it is not always what happens when you gain knowledge and when you do research. It is not always predictable what the outcome will be. I mean that in the positive sense that, in studying spinal muscular atrophy, perhaps we will learn something that will help contribute to a cure for ALS, just as an example. And that is always, when people campaign for support for basic research, it is really because it is knowledge generation in very important areas that are very applicable to human health that we all are very enthusiastic about feeling that that's money well spent.

Bill Glovin: As someone on the front lines, is there anything the public can do to help gain more funding or in any other way?

Lee Rubin: Well, until recently, Congress has actually been quite supportive of the NIH, which is the major funder of research in the United States. And hopefully, their support will hold up, even in the current budget year. Obviously, if people really believe in the value of basic research and they can see that basic research directly affects their lives or the lives of their children, any communication with their congressional representatives is always a positive for us. And, of course,

for those people who have the ability to donate philanthropically, that money is also extremely valuable to people doing research. So, I would definitely encourage people to think carefully about that.

Bill Glovin: Well, I think that's a great explanation of the disease and some of the policy issues around it. Thank you again so much for the article and for taking the time to do the podcast. Again, “Spinal Muscular Atrophy: Huge Steps,” can be found at dana.org and you can find all our Cerebrum Podcasts at dana.org/multimedia/podcasts. Thank you for listening and have a great day.