Transcript of Cerebrum Podcast—A Novel Therapy for Huntington's Disease

Guest: **Albert La Spada**, M.D., Ph.D., is Professor of Neurology, Neurobiology, and Cell Biology at the Duke University School of Medicine, where he directs the Duke Center for Neurodegeneration & Neurotherapeutics. While a graduate student at the University of Pennsylvania School of Medicine, La Spada identified the cause of spinal and bulbar muscular atrophy as an expansion of a trinucleotide repeat in the androgen receptor gene. As the first disorder shown to be caused by an expanded repeat tract, this discovery of a novel type of genetic mutation led to the emergence of new field of study. La Spada's research remains focused on neurodegenerative disease, and he is seeking novel therapies to treat spinocerebellar ataxia type 7, spinal and bulbar muscular atrophy, Huntington 's disease, amyotrophic lateral sclerosis, and Parkinson's disease. He graduated *Summa Cum Laude* from the University of Pennsylvania with a Biology degree in 1986.

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. 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: Hello out there, and welcome to The *Cerebrum* Podcast. I'm Editor Bill Glovin, and today's guest on the phone with us is Albert La Spada, professor of Neurology, Neurobiology, and Cell Biology at the Duke University School of Medicine, where he directs the Duke Center for Neurodegeneration and Neurotherapeutics. He's also author of our most recent *Cerebrum* article, "A Novel Therapy for Huntington's Disease."

Bill Glovin: Welcome, Al, and thanks for joining us on the phone. This week you're in the middle of a hurricane. How did that affect the Duke campus?

Albert La Spada: Well, it did lead to a closure yesterday and today. But so far, things are fine. Just getting a little bit of rain. I think we're probably going to miss the brunt of it. But that remains to be seen.

Bill Glovin: That's great. Let's begin with how you got into this line of research.

Albert La Spada: Well, I was an MD-PhD student at the University of Pennsylvania and I was very interested in studying genetic disease. And I spoke to a number of faculty members who were working on different inherited disorders. And I was most taken by one particular individual whose name is Kurt Fischbeck. And he was and still is interested in inherited neurological disorders. So I chose him as my

mentor. And of the various projects available in the lab, I decided to work on a disorder known as X-linked spinal and bulbar muscular atrophy, also known as Kennedy's Disease.

It's an inherited neuromuscular disorder that affects only men and affected men become weak as young adults or middle-aged and often wheelchair-bound. And my project was to identify the gene that causes this disorder. And as someone who started to study inherited neurological disorders, I became really fascinated by them. And my work fortunately went very well with Kurt Fischbeck. And so I've continued in this field now for I guess it's nearly 30 years that I've been working in this area.

Bill Glovin: What distinguishes Huntington's Disease from let's say Muscular Dystrophy or ALS?

Albert La Spada: Well, Huntington's Disease is a neurological disorder and actually also has a psychiatric component as well. I think what distinguishes it from the disorders that you mentioned ... well, ALS is also known as Lou Gehrig's Disease, Amyotrophic Lateral Sclerosis, technically, can be inherited, but often it doesn't run in families. You don't see that in most cases. Muscular Dystrophy is often an inherited disorder like Huntington's Disease. So Huntington's Disease is a strictly inherited disorder. It is caused by a mutation in one of the two Huntington's Disease genes and so it's a dominant disorder. And so it can be passed from parent to child.

And the other thing that distinguishes it from other neurological disorders is that it has very specific symptomatology. Patients have difficulty with controlling their movements. So they have uncontrolled involuntary movements with flailing and jerking of their limbs. As I mentioned, there's sometimes a psychiatric component. So their behavior can change. And as the disease progresses they lose the ability to think. And so there's cognitive impairment. And, you know, that's much more I think devastating in terms of its rapidity compared to even a disorder like Alzheimer's Disease. And then patients, once they reach that point they usually need to go into a nursing care facility. And then they die from the disease usually within a few years or certainly a decade after.

So these are all bad disorders that you mentioned. And Huntington's Disease is certainly a devastating one. But it has some different features in terms of that it is an inherited disorder and it has certain symptomatology that's unique to it.

Bill Glovin: As you point out in your article there seems to be some commonality between Huntington's and Alzheimer's diagnosis. Can you explain?

Albert La Spada: Well, I think the point that I was trying to make is that really, in terms of therapy development, there's a debate going on in our field, the field of neurological diseases, and in particular neurodegeneration as to the stage at which we need

to offer therapy to patients to have the greatest impact on their disease—to have a chance of greatly slowing it or even stopping it in its tracks. And Alzheimer's Disease, as I'm sure your listeners will know, is a very common disorder. And it's quite a burden on our society because so many individuals are becoming affected with it. And then they become impaired and it's a great challenge for family members to care for them.

But in terms of the therapy issue, the question has come up, at what point can we still give therapy and have it have a positive impact on the course of the disease? And that's where Alzheimer's Disease and Huntington's Disease and related disorders all fall into the same category. When will a therapy be most effective? And how long can patients suffer from their disease and still be candidates for a meaningful therapeutic intervention?

So I think that's what I sort of trying to delve into in the article. I mean, the diagnosis of Huntington's Disease can be made by a blood test because it's a genetic disorder and we can look at the gene by isolating DNA from white blood cells. And we can tell someone whether or not they're going to get Huntington's Disease. We would only do that for individuals where the disease is running in their family. So we know the individuals who are at risk for Huntington's Disease. Alzheimer's can affect anyone.

So they're also ... You know, we're in the process, the field is, of developing a blood test. It's a little bit different than,... we wouldn't be looking at DNA. We would instead be looking at one of the offending proteins or fragment thereof called amyloid beta. And this is still very controversial, but work done over the last year by two different groups, one here in the United States and one in Japan, suggest that we may soon be at a point where we would have a blood test that we could offer to individuals in their 40's and 50's and that blood test would predict with high likelihood whether or not they will get Alzheimer's Disease in 10, 15, 20, 25 years in the future.

Bill Glovin: Whenever you Google Huntington's research or mention it to another neuroscientist, Nancy Wexler's name invariably pops up. Have you ever met Nancy? And can you explain her role in this line of research?

Albert La Spada: Yes. I met Nancy ... I'm trying to remember how long ago it was ... I want to say it was probably about 23 years ago I first met Nancy. And so I've worked with Nancy closely on a number of efforts. As you know, she directs the Hereditary Disease Foundation and has been very intimately involved in Huntington's Disease research for decades now. And I've had the pleasure of getting to know her quite well. I consider her a friend. And you know, I've served on the scientific advisory board for the Hereditary Disease Foundation that she directs. And I've been involved in a number of efforts in terms of reviewing grants to determine what research should be funded on Huntington's Disease through her organization. And I've spoken at conferences and symposia that her organization has organized.

So yes, I know Nancy quite well and I consider her to be a genuine inspiration for all of us who work on this disease because she's been so laser-focused on it for most of her career. And she cares deeply about patients and families who are afflicted by it. And that's really, I think very important to keep the focus on trying to help patients and family members. And that's always been her approach to this. And so yes, I've enjoyed knowing her and working with her for a long time now. And look forward to seeing her again hopefully this year to discuss the latest developments in Huntington's Disease therapy work, which right now is I think very exciting because it's so encouraging.

Bill Glovin: In the article, you discussed turning off genes. How is that done?

Albert La Spada: So as I mentioned there's a few technologies that have been developed over the last now I'd say more than two decades to specifically target genes to turn off their products. And as I mentioned and as many listeners will remember from their high school biology is that the gene is encoded in our DNA. But then what happens is a copy of the part of the gene that will give the instructions to the cell to make the protein is encoded on what's called a Messenger RNA or mRNA. And the protein translation machinery reads off the mRNA to make the protein. So this intermediate information carrier known as the Messenger RNA can be targeted for destruction using a number of technologies.

Technology that's being brought to bear on Huntington's Disease and other disorders right now is known as antisense oligonucleotides, or ASOs. And what is done is you make a small sequence of nucleotides that match the sequence of the gene's mRNA with the idea that if you introduce that into cells it will find that RNA and bind to it specifically and form what's called a heteroduplex, DNA bound to RNA. And then the cell has a certain enzyme RNAs, each one that will degrade the RNA that is bound by this oligonucleotide and destroy it. And then the protein will not be made. So in effect, the gene will be, you know, turned off.

So in reality, we don't turn it off completely, we really turn it down. So sort of like the volume goes way down. So it doesn't go off completely because we worry that might be too aggressive an approach. So we turn the expression way down and this is we believe an effective way to treat Huntington's Disease and perhaps a range of other related neurodegenerative disorders.

Bill Glovin: How far away are we in terms of testing this on human subjects?

Albert La Spada: So the testing is going on right now as we speak. And it's progressed quite rapidly. And so far successfully. And that's why when I said earlier it's an exciting time for therapy development in the Huntington's Disease field, I was thinking of this process, which is a complicated one. You know, what our Food and Drug Administration insists upon is that a specific testing process for new drugs be pursued where first you make sure the drug's safe. That's Phase One. That's been done.

And the ASO for Huntington's Disease was found to be safe. And then you go to what's called a Phase Two where you look for some sort of evidence that it's engaging with what's called its target. And work that just came out in December of last year showed that it appears that the Huntington Disease ASO is engaging with its target, the Huntington mRNA in reducing its levels in the fluid that bathes the brain, called the cerebrospinal fluid.

And so now what is being done is the final phase called Phase Three, where you do what's called a double-blinded study. And patients are enrolled and they either receive the drug therapy or they receive placebo. And doctors who are treating the patients don't know which agent the patient has received and they follow the patients. In this case it will be for a couple of years, at least two, to see if the disease is progressing or if it's not progressing as rapidly. Or if it's even been totally stalled out in terms of its progression to assess whether the therapy is effective.

So we've made it now to Phase Three with what appears to be a promising potential therapy for Huntington's Disease. So within the next couple of years we should know if we have a treatment that would be approved for this devastating disorder.

Bill Glovin: In terms of your own research, what are you working on now?

Albert La Spada: So in my lab we work on a variety of neurodegenerative disorders. Huntington's Disease is one of them. And we work on other related disorders that are caused by CAG/polyglutamine repeats, inherited disorders. As I mentioned earlier, the first disorder that I worked on, spinal and bulbar muscular atrophy, or Kennedy's Disease, when I was an MD-PhD student I discovered its cause as a repeat expansion in the androgen receptor gene. So we're developing therapies to target the mutant protein and we're considering the use of Antisense oligonucleotides as well as other drugs that specifically target the disease protein for destruction.

For Huntington's Disease, we've been very interested in the fact that Huntington's Disease pathogenesis involves a problem with energy production. And this work has been going on in our lab for 15 years and led us to identify a particular regulatory protein that's called a transcription factor, because it controls the expression of genes by binding to the promoters of genes in the DNA of cells. And that protein is called PPAR Delta.

And so we're developing what are called agonists that would activate PPAR Delta because we believe that there's a problem with PPAR Delta function in Huntington's Disease and therefore a problem with the production of energy and mitochondria, which are the powerhouses of the cell are not working properly. And this leads to a host of related pathologies. And we think this can be treated successfully by activating PPAR Delta with a drug agonist.

So that's work that we've been doing. And we continue to do that. And we also believe that that approach, if it works for Huntington's Disease, it can be applied to related disorders, including Parkinson's Disease, and we also believe even in Alzheimer's Disease. So, we're taking a variety of different approaches. In some cases we're using biological agents such as antisense oligonucleotides. We're doing that for spinal and bulbar muscular atrophy. We're also doing that for spinocerebellar ataxia type 7, which is a devastating predominantly inherited disorder where patients lose the ability to have proper coordinated movements and also go blind. It often affects young individuals, even teenagers. So we're working to develop an antisense oligonucleotide therapy for that disorder.

And we continue to study these pathways of energy production in the cell with the idea that if we can get that to work better it would be an effective treatment for neurological disorders. Because neurons are such energy hogs. And if there's any sort of disruption of the way they're making energy, it can cause disease or lead to more rapid progression of disease. So, we're doing a variety of different things. And hopefully some of these investigations will yield therapeutics that will end up in patients and hopefully be effective in treating their disease.

Bill Glovin: Is the funding levels appropriate for you to be attacking all of these things?

Albert La Spada: I'm very fortunate in that I have been well-funded by the National Institutes of Health. Certainly the money is tight in terms of the budgeting to do this type of research. It's very costly. And the budgets always get trimmed and we have to sort of sometimes feel like we have to try and cut corners a bit. But we find ways to keep the work going forward. But we rely upon the federal government primarily for our funding. And this has been fortunately a viable strategy for my research program for the last two decades.

We certainly rely on patient organizations such as the Hereditary Disease Foundation that Nancy Wexler leads and the Muscular Dystrophy Association as well. And so the patient organizations are great. Michael J. Fox Foundation for Parkinson's Disease. The ALS Association for Lou Gehrig's Disease. So these organizations also provide funding to us. And sometimes we partner with pharmaceutical companies, biotechnology companies who are interested in therapy development and they provide funding.

So we always have to sort of cobble together money from all these different sources. We sometimes are blessed by donors who give us money. Make a very timely philanthropic gifts to our research program. So that's how we do it. And through these various and diverse sources we've been able to put together a significant pot of funding to allow us to pursue a variety of different research projects in parallel. And right now, that's what we're doing. It's always a challenge. You worry about the future. But for now, we're doing okay.

Bill Glovin: One of the concerns especially when it comes to Alzheimer's and clinical trials is the idea that people who are involved need to be followed over long periods of

time. Is that also true for Huntington's? And is that one of the major obstacles in progress?

Albert La Spada: Well, there's no doubt that once you have candidate drugs that you want to evaluate in patients, that that type of research is very costly. And some of these disorders progress rather slowly, so you need to follow patients over a long period of time. When you have a candidate drug and you need to do clinical trials on human patients, this can be very costly. And in the case there are certain disorders such as ALS—Lou Gehrig's Disease—where the disease progresses rapidly and in a year or so, whether your therapy shows promise or not.

However, for disorders such as Huntington's Disease or Alzheimer's Disease, the disorder progresses much more slowly. So you need to follow patients on the order of at least two, three years or more to know with certainty whether a drug therapy is efficacious or not. And you also need to have enough patients enrolled in your study so that you have enough statistical power to detect an improvement.

And so you have to enroll sometimes dozens, if not hundreds of patients, to really know for sure. And so this type of clinical research to sort of test to see if a drug is effective, this type of clinical research can be very costly. Running into millions, tens of millions. Sometimes even hundreds of millions of dollars depending on the disorder that we're talking about. So it's definitely very challenging for certain neurodegenerative disorders that progress ... You know, they progress quickly enough that it really impairs people's lifestyles for sure. But just sometimes the progression is low enough that it plays out over years. And so you have to do study that are years in length with many patients and all the sophisticated testing and the repeated visits. That adds up to a very costly proposition.

Bill Glovin: Is there anything else that you think is important that I haven't asked you about? I haven't gotten into things in the article like repeat expansion and linkage analysis-

Albert La Spada: Sure.

Bill Glovin: Which are important. But people can go into the article to read about that. But is there something else in particular that you might want to add?

Albert La Spada: Well, this has been very comprehensive discussion that we've had, Bill, and I've enjoyed it. And delighted that I've had an opportunity to sit down with you and have this discussion. I think you've covered almost everything. The only point that I probably want to close on is to emphasize we're making great progress in terms of treating cardiovascular disease through surgical and medical approaches. Cancer, I guess, is the number one killer in the world and for certain cancers we still have a ways to go. But for others we've made great progress.

But as we have success with these disorders what we're left is the neurodegenerative disorders. And as our population ages ... And right now our population dynamics is such that we have many people entering the sixth, seventh, and eighth decades of life ... And we're going to be faced with an epidemic of individuals who are affected with Alzheimer's Disease, Parkinson's Disease, and also a significant number of individuals who get ALS-Lou Gehrig's Disease. Because they're living long enough to get all these diseases that perhaps 50 years ago they would not have developed. And we do not, as I speak to you today in 2018, we do not have a single what's called disease-modifying therapy, where we can give patients with these disorders a drug that affects the underlying disease process and slows it. Ideally we want something that stops it in its tracks.

And so our government has made a commitment to finding a treatment for Alzheimer's Disease and has pumped a lot of money into Alzheimer's Disease research. And this is really important and timely and a wonderful development. And people should thank their representatives in the federal government for doing this. But I also feel that Parkinson's Disease needs to be given the same degree of attention. And certainly ALS-Lou Gehrig's Disease is such a horrible and devastating disorder that it also deserves more funding support so we can come up with a therapy to treat it as well.

So we have great challenges. There are great opportunities because the research is moving forward. We have our work cut out for us and it's really a very pressing problem with the profound socio-economic implications. And so I just think people need to be aware of this and understand how they can make a difference by voicing their desire to policymakers that these are problems that deserve funding support. Because this is going to touch everyone's family in one way or another I think if we live long enough.

Bill Glovin: Well, I think that's a wonderful place to end on. It was just a great account of a very important brand of research. And I can't thank you enough, especially since you're in the middle of hurricane country.

You can find Al's article at dana.org. This podcast is brought to you by The Dana Foundation in New York City. Thanks for listening.