**Anna’s Story of Hope and Help with Sonja Kampfer and Dr. Neil Shneider**

# **Transcript**

Stan

Hello and welcome to the n-Lorem podcast series that focuses exclusively on the needs of nano-rare patients and their families. I'm Stan Crooke. I'm the founder and chairman and CEO of the n-Lorem Foundation. Today we're privileged to have two very special guests, Dr. Neil Schneider, who is the Claire Tow associate professor of neurology at Columbia School of Medicine and Sonja Kampfer, who is a partner at Vectis Consultants, and her most important role, I suspect she would say, is she's also the mother of a wonderful 16-year-old daughter named Anna. Welcome to both of you. It's great to have you. So, Neil, I know that you did your undergraduate degree at Harvard and then an MD/PhD at Columbia. And then I think spent some time at the NIH and then came back home to New York. So, I guess you're a New York boy returned home, huh?

Neil

I am. I'm a chosen New Yorker, the best kind.

Stan

If you're a real New Yorker, it's tough to take you out of the city, right?

Neil

That's true.

Stan

Well, it's good to have you. So, I know all that Neil, but tell me how you got interested in motor disorders and in particular ALS and in those kinds of diseases which are so devastating to so many people.

Neil

Yeah, you know my interest in ALS was a little indirect. I did, as you said an MD/PhD and I did my graduate training in basic neuroscience, molecular neurobiology, and after my residency I returned to basic neuroscience and I was working with Tom Jessell, who's a developmental neurobiologist and working in the motor system, trying to understand how motor neurons are born and establish their identity, the specific identity. But I was a neurologist and I wanted to integrate my science, my research, with my clinical activities. And so, I walked across the street. I was at Columbia then again and met up with Bud Rowland who was a great figure in neurology and was an ALS specialist. I began to see ALS patients at Buds knee. And you know, if you understand anything about ALS, you understand that there's huge need, there's a great need of a population that is desperate for answers, and in the time until those answers come, clinicians like me need to take care of these patients and these families need to help walk them through the disease, you know, to try to do everything possible without real treatment and cure to lessen the burden on the patient and on their families and to maximize the length and the quality of their life. And it becomes a mission. You know, not one that's easy often, but one to which you know people like me become committed pretty quickly. And ALS becomes the enemy.

Stan

Yeah, it's pretty easy to understand how you could become committed to that. And all you have to do is meet one patient and it's pretty obvious. I don't know about you, but I've been amazed at how much has been learned about the central neurological system over the last 20-30 years. And of course, motor neurons are such fascinating cells because they can have these long projections called axons that are, you know, meter long and longer, it's hard to imagine a single cell with that kind of projection.

Neil

Absolutely, and motor neurons, they themselves are remarkable units. But they sit, you know, in this complex network of neurons and non-neuronal cells and they function in such a complicated system. And what we've learned, I think, over the last generation is that the dysfunction that leads to ALS is not just a dysfunction of the motor neuron, it's the entire system, that many elements of that system that are involved contributing to the dysfunction and ultimately the demise of the motor neuron. And as we begin to think about, you know how to treat this, how to prevent and treat ALS, we really have to think about all of the elements that are contributing to this disorder.

Stan

Yeah, and if you just think about what we're learning in the few patients that we've now been able to treat with ALS, which we'll come to in a little bit, it's pretty remarkable. And your wife Leah is curator at MoMA, is that right? Or a curator at MoMA?

Neil

She's a curator and she runs the research programs at the museum.

Stan

Yeah, that's pretty cool. So, you get to see the exhibits before they show up to the rest of us.

Neil

Well, hers anyway, I get spoiled. You get to see them before the crowds come. So, it's quite a privilege.

Stan

Yeah. Well, I'm going to hit you up next time I'm in New York.

Neil

You’re welcome.

Stan

And Sonja, I know that your husband is, did I pronounce that right?

Sonja

Yeah.

Stan

Well, good, that's the sum total of German I speak, but anyway it's just hard anyway, and I know he is head of an association of wine growers I suppose is what say. And you're a partner at Vectis as a business consultant, and so are you still able to conduct your business activities with all the issues that Anna is having?

Sonja

No, I gave up my job for the time being because there's so much to do around Anna and I feel that I have to be there for her. But it's not only a burden, it's also very rewarding to care for her and to see how, thanks to Neil and his colleagues, she's developing and is sort of escaping this really terrible disease, yeah.

Stan

One of the features of disease of all sorts, but especially these extraordinarily severe and rare diseases, is that they affect not just the person, they affect the family. And they're extraordinarily destructive, and families either come together or they split apart, it seems. I'm pleased to see that your family came together.

Sonja

For us this meant, first of all, not being together for Christmas in 2020. So, I spent Christmas and the New Year's Eve with Anna in New York. And her sister and my husband, they stayed in Germany also because of this Corona situation and really had a hard time and we had we had to find ways to still have a sort of normal family life.

Stan

So how old is Anna's sister?

Sonja

Anna's sister is 16, and Anna is 17 now.

Stan

On a sister is perfectly healthy and everything's alright with her.

Sonja

Yeah, yeah, yeah.

Stan

And that adds a burden to a young person that is a challenge for most young people to contend with, and the attention on the other child and all of the things that come into play I'm sure your families had to contend with a lot of that sort of thing, too. Why don't we move to the star of the podcast and that's Anna. Why don't you just tell us about Anna before, and then after she became sick.

Sonja

Well, Anna was born in 2004 in Hamburg and at the beginning, she was perfectly healthy. It was only at the age of three that some people in the kindergarten noticed that she was trembling from time to time, which was a bit strange, and we went to a neurologist for children. But he reassured us there's nothing wrong with her, it's good for her to do lots of sports, but well, we don't have to worry, and we didn't worry, and she developed like a healthy child, and she became very athletic, and she did well at school, everything was nice. We were just a normal family and at the age of 15 it started, that she was sort of having problems with her breathing, she was short of breath when she ran up the stairs at home, and that was the first sign, and then it moved on to her having problems speaking, and then she lost a lot of weight, she had problems eating, and well it developed really horrible, to the point that she really needed support for her ventilation, that she got a gastro tube because she was not able to swallow anymore. And yeah, we had horrible times. And what was also horrible was that we saw her suffering, getting weaker and weaker and no one had any idea. We went to see lots and lots and lots of doctors. No one had any idea what this could be. No one thought about ALS. Because ALS is not a disease of a 15/16-year-old person. Yeah, and it was then in, well, almost after a year that one specialist in Munich, Professor Mueller Felber, who had seen a lot of very rare diseases in children, neurological diseases, especially, who was the first to mention ALS, that it could be a very rare form of ALS and then we did Well, we did. genetic testing, and then the outcome was, yeah, it was ALS, and we were completely shocked.

Stan

She was short of breath initially. I imagine you got referred to some specialist of some sort. What sort of specialist was that person?

Sonja

The first person was a specialist on lungs and breathing. And they said, "ok there's some kind of obstacle, but we don't know what, we don't see anything." And then we had MRT's of her brain. One neurologist told us “Maybe it's a psychological problem. Yeah, maybe she has some, well, like teenager problem that is showing in such a rare form." Well, we went to see lots and lots of specialists. But as I said, no one thought about ALS except for this Professor Muller in Munich, yeah.

Stan

Yeah, it is a tragically very common story for these what we call nano-rare diseases, because physicians recognize patterns, and if you've never seen that pattern, it's hard to recognize. And your journey was, you know, typical in the process, but maybe a little better than many that we've dealt with in that you got an answer in a year or so, when it seems like the average time to diagnosis for most of our patients, somewhere around, if they live, five to eight years of what you go through. I understand how debilitating all that process is and regret that you had to do it. But at least you did get to an answer. So, Neil, why don't we why don't you walk us through what's wrong with Anna?

Neil

So, Anna has a very rare, nano-rare, case of ALS as Sonja suggested, ALS is not a disease of 15 and 16 year old people. It's an old person's disease, right? You're here in your forties, fifties, sixties.

Stan

Not old anymore for me, Neil.

Neil

No, no, no, for me either. But it is for Anna for sure. And so, people, as you said, don't recognize the patterns. 15/16-year-olds don't have ALS, so it doesn't get into the into the differential. And to make it more complicated, Anna has no family history of ALS. Annas mutation is what we call de novo, or spontaneous mutation. Neither Ubey or Sonja have this mutation. And so, it like other young people with this mutation, arose spontaneously for reasons we don't entirely understand, arose on its own in Anna's genome and it lay dormant. Not entirely dormant, she had symptoms, the tremors and maybe other issues that Sonja describes, you know, suggested were suggestions unrecognized that there was a problem. But it wasn't until she was 15 that this problem manifested itself as ALS, as motor neuron disease. And this is a mutation that is one of, if not the most aggressive, you know causes of ALS. Anna did relatively well. Perhaps because she had respiratory and bulbar symptoms, she became aware of the problem a year before diagnosis. I think other young people with this same mutation, like Jaycee and her sister, who had limb onset, they didn't figure this out until much later. They could compensate more for their problems in the way that you can't compensate for breathing and bulbar problems. And so Anna had a more of a of a pre-diagnostic phase, which was lucky, I guess, I mean not to say that she was lucky in any way here, but it gave time for her to, you know, to go through a diagnostic process to get a genetic diagnosis and, you know, she was lucky too, again in that she had, you know, extraordinary parents who were gonna leave no stone unturned for her. And upon the, you know, as soon as they have the genetic diagnosis, they began to reach out and made their way to me, I think in in pretty rapid order. And we had at that point treated a number of patients with the ASO that we called Jacifusen that was an ASO developed by Ionis, shared with us and made, this is pre-n-Lorem of course, But made this therapeutic available to us in a way that allowed us to treat Anna with an antisense molecule and antisense therapy. The goal of that therapy was to lower the levels of this toxic protein FUS in Anna's system, in her nervous system, and to sort of put the brakes on a process that had begun a year early. Her response has been, in my mind, remarkable. Young people with this mutation don't do well. They progress very rapidly as Anna began to do. And they usually reach some kind of a terminal point within a year, most 18 months of disease onset. And we met Anna in December of 2020 and we're 18 months almost since the initiation of her therapy and if you were to look at her now, I think you would say that she is doing well in a way that it's hard to explain based on the natural history of that disease.

Stan

So, Anna has a form of ALS called FUS ALS. The mutation is in this FUS gene and it's what's called a toxic gain of function mutation in that the protein that's being made is itself toxic to neurons and causes them to deteriorate, and at the time the decision about the FUS ALS effort at Ionis, of course I was chairman and CEO there, and so I'm well aware of what was going on. And you mentioned bulbar symptoms, you might just explain what kind of symptoms Bulbars are?

Neil

ALS is a disease that affects motor neurons. Motor neurons are the neurons that control muscular function. Those muscles include the muscles of our limbs, our arms and legs also include the bulbar muscles, those which control talking and chewing and swallowing. And ALS is ultimately a fatal disease, because those morons also control the muscles of respiration or breathing, the diaphragm and accessory muscles, of breathing and all of those things are compromised when the neurons, the motor neurons, degenerate. ALS in most cases, there's no known underlying genetic cause, but in about 10-15 percent of patients, we know that there is a mutation, a genetic mutation that underlies the problem that causes the disease. There are dozens of ALS associated genes, FUS is one of one of them, and a relatively rare cause of ALS, represents about maybe four percent of the genetic cases overall, but in the pediatric cases, juvenile pediatric cases like Annas, FUS mutations are more highly represented. It's a more common cause of this rare form of ALS, this nano-rare form of ALS, and so in this case FUS is our target. The ASO therapeutic is aiming at this one causal gene in this limited rare form of ALS.

Stan

And so, it is one of the big advantages that we have as genetic therapy that the nano-rare patient brings to us as they, almost all, not all, but almost all have a clearly defined mutation in a single gene that is the cause and many of the times that we can correct that. And Neil, I know that this all began with two identical twins. And one of whom had developed FUS ALS and died when she was 16, as I recall. And then the other, despite being an identical twin, didn't manifest her problems until somewhat later. Can you just briefly tell us about that family?

Neil

Right. So, Jaycee Hermpstead was my patient and Jacifusen is named in her honor. You know, this is a remarkable family that's been, you know, horribly affected by this disease. Alex, who said was 11-12 years old at onset, and she was kept alive on a ventilator for a number of years and ultimately succumbed to her disease at age 17, Annas age now. And Jaycee, her sister, lived without symptoms until she was 24 years old. And why there was a 12-year difference, you know, identical twins with the same mutation, de novo again, spontaneous mutation. Why it took an additional 12 years for Jaycee to become symptomatic is one of the great, you know, questions, big questions that we would love to understand. Because it speaks to the trigger events, right? It's not enough just to have the genetic mutation. There is a second event of some kind that triggers the onset of the of the disease. Why did Anna live for 15 years with this mutation and not have motor neuron disease? There's some second event. Some second hit if you will, that triggers the disease onset and we very much would like to understand what this is. We also don't care in the sense that whatever that event is, we would like to intervene before that event happens, right, in the future. If we can identify these mutations early and reduce people's risk of onset using the same kind of technologies, the same antisense therapeutics that we're using in the symptomatic affected individuals, we think we could maybe influence that onset event. So, Jaycee was the first, the therapeutic was developed with her in mind, her disease onset prompted our initial approach to Frank Bennett and Ionis about this as a potential therapeutic strategy for our patient. The first FDA program expanded access, investigational new drug. Protocol was written for Jaycee, and she was the first assuming all of the risks and potential problems associated with a therapeutic that had never before been given to a human being. So, Anna Benefited from Jaycees courage and sacrifice and a small number of other patients who were treated with Jacifusen before Anna. And it's been lovely, and Sonja has met Laurie, or spoken to Laurie, Jaycee and Alex's mom, and there's a community, you know, of people that gathered around this problem.

Stan

So, I'm gonna send you back to Anna. I suspect that the day that you were told you had ALS was the end of the world in the way you felt. And I'm sure that you heard there was no treatment. It was hopeless, right?

Sonja

From the doctors we heard there's no cure. Yeah, you can do therapies just to well, to make it easier, maybe to, well to have a bit more time, but there's no cure. You can't cure this disease. Yeah, it was my father-in-law, Anna's granddad who was a physician himself. He contacted a in a relative in in Newark, near New York. And yeah, this person, he well used his network to ask for anyone in the US who knows anything about this fast mutation. And so, we got into contact with Neil Shneider, and that was, for us the best, best, best thing that could have happened to us, yeah.

Stan

And you just described one of the really serious issues that we're trying to contend with nano-rare patients, is there is no path, there is no way to navigate. You were very fortunate, sadly most are not. And so, as a community, we have to come together and find ways to build better navigation systems for people and I think we're all committed to working on that. So, December, you spent Christmas in New York? Hardly a great way to spend Christmas if you're separated from your family. And at that stage, how sick was Anna?

Sonja

She could walk, still could walk, and we walked from the hotel to the first dose of Jacifusen together. And she was not able to really speak anymore. She had a gastro tube, so she was not able to eat anymore or to eat properly anymore. And well, she was quite weak, it was really exhausting for her. The flight to New York, and the treatment itself, was exhausting. She needed time to relax afterwards. Her biggest problem was breathing and not being able to eat or to speak or to swallow like these bulbar symptoms were quite elaborated already, yeah.

Stan

So, she had a feeding tube in and that was the only thing that was keeping her from just wasting away. And so, she was treated, I'm sure you had hope, but not expectations. What did you watch in Anna over the next little bit.

Sonja

I mean, over the next weeks, because we stayed in New York till the end of February, I noticed because I lived with her there that it sort of stabilized, I mean from May till December. Yeah, you could really watch her wearing off or getting weaker and weaker. And I had the impression with the first dose and the second dose two weeks later that she still lost some ground, but it was much, much slower than before. Yeah, and we could still do some sightseeing in New York. And she loves Central Park. And she could walk there and things like that. So, we really enjoyed our time in New York. We were missing the family, but well, we had to make the best of it.

Stan

You had hope.

Speaker 3

Stan

So, then she continued to get a little better and eventually she had another swallowing problem I think right? So, walk us through all that.

Sonja

Yeah, yeah, I mean when we came back, she sort of slightly lost more of the ability to walk. She got weaker walking, it was more, the distances became a bit shorter. And I remember in June last time we were in New York, she was not able to stand up and sit down on her own, but after June it got better. Then her ability to get up and sit down came back in July. She was able to walk upstairs slowly, but she was able to do that again. Before, in June and May, my husband had to carry her upstairs. There were signs of recovering. I mean, we had this hope, but this was really little miracles for us. But then, unfortunately, in August she got a lung infection. That was really horrible because her airways were blocked one night. She had to get reanimated, and you say that reanimated?

Stan

She had to be put on a ventilatory support, right?

Sonja

I mean, she was, like, 30 minutes without own circulation. Yeah, she had to be brought back to life. And then it took the doctor's two hours to really stabilize her again. And because of this infection, she was so weak that they put her in an artificial coma. And at the end of two weeks, the doctor said "we can't get her to breathe on her own again, she needs a tracheotomy. We had talked about that before, because what happened in between was that in July, we found the possibility, Professor Viba in St. Gallen in Switzerland that he could give the doses of Jacifusen to Anna in Switzerland because before in March, April, May, June 2021, we always traveled back for a week to New York, back and forth to get Jacifusen from Dr. Shneider and his team. But that was really exhausting for Anna, and we didn't have any possibility to get that in Germany. because there are a lot of regulations and very bureaucratic things against this treatment in August, then we well sort of had this crisis. She needed the tracheotomy, and we had talked about that with Professor Veba at the beginning of August. Just in case, and we were happy that we had done that. So, we were able to well to be sure that Anna wants that because she had told us she is convinced it's getting better and if a tracheotomy is necessary, she wants that to be done. So, she had that, and in the beginning, she needed ventilation 24 hours a day and in September we were really devastated. She couldn't move anymore because of this artificial coma and all the medication she had; she was completely paralyzed. She couldn't move her fingers. She couldn't move anything. She couldn't talk to us. Well, it was really horrible to see. We really had to guess what she was meaning when we were standing at her bed. But, in the end of September, slowly step by step, she got functions back. In the end of September, she was able to type on her iPhone, and then she was able to move more and more. Then in October she was able to get up, walk. And it became better, better and better. And at this point, she's able to do nine hours a day without any ventilation, a new record from last week. She's able to walk up to four/five kilometers. She is training to speak again, which is hard because her tongue is still paralyzed. We have a team of people here, people coming every day to work with her, therapists for breathing, and she's very ambitious. She's doing two hours of schoolwork every day today. So well, we really have more than hope now that she can get back into a state where she's able to lead a life on her own, yeah.

Stan

That's a wonderful story. And so, she had a swallowing problem that got her airway clogged, then probably aspirated, and had an aspiration. Pneumonia is what that's called, and I'm sure at that stage, Neil, you felt that despite all the progress that she had made, that it would be unlikely that you'd see any more progress out of Anna.

Neil

Yeah, the event that Sonja described was very serious. It was life threatening and we were worried. Typically, with our patients, when something like that happens it often is life ending. Anna has the advantage of being 17 years old and otherwise healthy and strong and was able to fight her way back. But our point here is that yes, she recovered from the acute insult, from the event that brought her to the hospital, but her motor system was able to recover, right? I mean, typically you would expect that her disease will continue to progress through that period, and that the disability associated with her hospitalization and illness would compound with the motor neuron disease, and that would really just spiral downward. But no, she was able to recover and in fact I think she is better now than she was before the event in August. And so that is just not what we would expect based on again the natural course, the natural history of the forms of ALS associated with this mutation, this particular mutation. Right, which is very stereotypical.

Stan

Well, it's a wonderful story punctuated by tragic events and deep sadness and loss. And you know, those are the stories of our patients. But it's a story of hope fulfilled, and a family that can look forward to a future that is, we hope, very different from the future that they had just a year or so ago, and I'm sure this Christmas was better than some other Christmases, and I'm hoping next Christmas will be even better for the family. I want to thank both of Neil and Sonja for this. But please especially thank Anna for her courage and stamina and for staying in there and putting up the good fights that she's had. It's wonderful sharing the story with you, and I'm sure you'll hear all kinds of appreciation from all our other listeners as well. Thanks so much.

Sonja

Anna is convinced that one day she will give her own interview to you, she's training for that.

Stan

Well, get her going. I look forward to doing it, we need the star on this show one of these days, okay?

Sonja

Okay.

Stan

Thanks so much everyone.

Speaker 3

n-Lorem is a nonprofit committed to discovering and providing personalized experimental treatments for free, for life to patients with genetic diseases that affect 1 to 30 patients worldwide, referred to by n-Lorem as nano-rare. Many of these patients progress and die without ever achieving a diagnosis. This is where n-Lorem comes in. They do the impossible by providing hope, and for those that they can help, free lifetime treatment. For more information about n-Lorem or today's episode visit n-Lorem.org. Any questions can be sent into podcast@nlorem.org. Search n-Lorem on Twitter, Instagram, YouTube, LinkedIn and Facebook to connect with us. Please rate and review the podcast on Apple, Spotify, or wherever you listen. This truly helps us climb the charts and allows others to find the show. This podcast is hosted by Dr. Stan Crooke. Our videographer is Jon Magnusson of Mighty One productions. Our producers are Jon Magnusson and Kira Dineen of DNA today. Thank you for listening.