**Shifting Mindsets to Expedite Rare Treatments with Emil Kakkis**

# **Transcript**

Narrator

This episode of the Patient Empowerment Program is brought to you by Ultragenyx. Ultragenyx is on a mission to transform the lives of people living with rare and ultra-rare diseases and is a proud partner of the n-Lorem Foundation. With multiple approved therapies in the deep pipeline of potential treatments in development, Ultragenyx is going beyond every day for the rare disease community. Learn more about how Ultragenyx is leading the future of rare disease medicine at ultragenyx.com. That's ultragenyx.com.

Stan

Hello and welcome to the n-Lorem podcast series, a series that focuses exclusively on patients now referred to as having nano-rare mutations. I'm Stan Crooke and I'm the founder, Chairman and CEO of n-Lorem. n-Lorem is a nonprofit foundation that I initiated in January of 2020. Our mission at n-Lorem is to take advantage of the technology we created at Ionis Pharmaceuticals, antisense technology, or ASO technology to discover, develop and provide experimental ASO treatments. To nano-rare patients, and to do that for free for life. Our special guest today is Emil Kakkis. Emil is chairman and CEO of Ultragenyx, one of the important companies that are involved in multiple new medicines for rare diseases. Emil, welcome. Thank you so much for joining us.

Emil

Thank you for having me, Stan. Happy to be here.

Stan

Yes, it's great. And so, I assume since you went to Pomona and then UCLA and never seem to leave, that you're a California boy?

Emil

Yeah, born and raised in California and my parents were Greek. They immigrated to the US, and they loved Southern California weather. And that's where we started there, and I circulated around that valley for school and ultimately left when I came to join BioMarin in 1999.

Stan

So, as I understand it, your family is full of physicians of all sorts. So, I guess you sort of were, to the manner, born as a physician scientist.

Emil

Yes, my father is a neurologist. My uncle was a nephrologist, and they had a lot of their closest friends were physicians. So, a lot of the families and people coming over were all physicians. Me and two of my siblings are physicians, and two of us married physicians, so medicine became a core of kind of our life and living. And it became a way of life and a way of thinking, in terms of caring for patients and taking care of them. And really an old school approach, which is the all-in type of care of physicians where you do whatever you have to do and however late it takes you to get it done right.

Stan

Yeah, as physicians always used to do and still should do, right?

Emil

Right.

Stan

And so, after you finished undergrad, you then went to UCLA and you did a joint MD/PhD program, I think, right?

Emil

Yes, that's the Medical Scientist Training Program. They had just opened that program at UCLA in 1982. And I was lucky enough to get a slot because it was hard to get slots at that time. And the great thing about that is it provided tuition and fees and also gave you a stipend, which was great because otherwise seven years of medical school would be pretty darn expensive and a lot of debt.

Stan

It still is. And were you always interested in pediatrics, or when did you become interested in neurology, pediatric neurology and all that?

Emil

Well, I didn't go to it immediately. I became interested in genetic diseases because of all the things that were going on at that time during my PhD years in the middle there in the 80s. Every week a nature genetics journal came out with new genes being cloned, a new dysmorphology syndrome being figured out, the biology being nerved, and it was a really exciting time for genetics. That led my natural thinking about medical genetics as specialty, which naturally was usually preceded by a pediatrics. So, that was the direction I took to take advantage of the new discoveries and medical genetics.

Stan

So you entered medicine, you became interested in pediatrics, then genetics, and then that led you to rare diseases. Is that sort of the progression of it?

Emil

Well, with medical genetics, you're always getting rare diseases pretty commonly, and as an academic physician, I was thinking of medical genetics, cases and situations as natural experiments. If people have mutations and problems, and while we manage their problems, we're also learning about the diseases in these natural experiments. At the same time, when I started my fellowship as a medical genetics fellow, I was looking around for a project, a research project. And at that time, Dr. Neufeld had just cloned the gene for MPS I, and it was just the fortuitous timing. The cloning had just occurred. I needed a fellowship project, and she was willing to take me on as a fellow, and that put me into studying MPS I. I didn't know anyone with the disease, nor did I know particularly much about it at all, and I had to get a crash course learning about MPS and lysosomal diseases, and meeting patients. And it was a great starting point, but I had no idea that I'd be spending the next 30 years working in that area.

Stan

Yeah, well, life is always a surprise, isn't it? And so, after you finished your residency and fellowship, then you joined the faculty at UCLA. So, you sort of stayed homegrown for a long while, huh?

Emil

Yes, well, I took advantage of opportunities. I actually did a fast-track pediatric residence. So, I only had two years of residency, and then I went right into fellowship. And sometimes this happens in the university system, Stan. A faculty slot opened up at Harbor, and they said I could do my first year of faculty concurrently with my third year of fellowship. And so, I said, why would I say no to that? I said yes. So, they need to fill the slot because if they don't fill it, someone might take it away. So, I just got lucky, and I got started a year earlier as a faculty member. And my wife was a resident. And so, we had already established some routes in the area.

Stan

Sounds like it managed to condense a little bit of time for you, which is always important when you're thinking about all the time that is invested in just getting ready to do some work. Did you discover a drug for MPS while you were at UCLA?

Emil

Well, I wouldn't say I discovered it. I helped develop one. Dr. Neufeld cloned the gene, and my first day of fellowship with her, she said to me, "I think you should work on enzyme replacement therapy for MPS I." It was a lysosomal disease, missing an enzyme called hyaluronidase, and she thought we had never been able to make this enzyme in appropriate quantities with the right marker. Let's do that now. I was most interested in doing gene therapies, and gene therapy was just starting with French Anderson, and retroviral packaging, and I thought that was the sexiest science going on. And she crushed my spirit right at that first meeting and said no, you should do enzyme therapy. And I said alright, I'll do enzyme therapy. Now, the reason this is an important part of the story, Stan, is that we all get excited about things. But sometimes, our excitement is not well placed. And the retroviral stuff never really went very far. In the end, she put me on enzyme replacement, and it had one distinct advantage over sexy science. That is that enzyme replacement actually worked. And therefore, the ability to change and treat someone, make them better, Stan, overtakes all the sexiness of science, and fancy journal publishing, and all the world you could think of, disappear as important when you've actually been able to treat some patients and help them.

Stan

Couldn't agree with you more. I often talk about the fact that when people get excited about new drug discovery technologies, they forget time failures and dollars, and the fact that the vast majority of times you start out and it doesn't work, and gene therapy now is, what, 40 years in and $50 billion in or something like that, and still a lot left to be done, and we'll get to that in just a little bit, Emil. And so, that sort of takes you to the rare disease enzyme replacement. Is that why you ended up then going to BioMarin in 1998 or 99?

Emil

Yeah, I joined them officially in 98, but moved to the Bay Area In 1999. I stayed down south for one more year, but the transition to industry was a big change for me. I had planned to be an academic physician all my life, right? R01 grants, do all kinds of studies, become a member of the National Academy. You know, get the accolades of your peers, and do great science. But when I treated patients and saw them get better and realized how important that was to me and how important it was to have the adequate financial capability to do it, I realized if I really want to make a difference in rare diseases, I'd be far better at going inside a company and advocating for them inside the company. And the reason that was important, Stan, at those times, and we're talking about 1998, at that time, rare disease was like, Genzyme was like the only one. There were a few people taking generic products through. But there weren't people really doing rare disease focused, even when I joined BioMarin. I was told by other executives that there would never be another rare disease developed at BioMarin after the MPS one. I was told that, but I thought if I move inside the company, I can advocate for those diseases. And I did step by step, one by one as we added product after product. They always succeeded, Stan, and all the other stuff failed. And BioMarin became a rare disease company because seven out of seven succeeded and all the other ones didn't.

Stan

Like a lot of the rare disease companies, even Genzyme didn't start as a rare disease company. They staggered their way into it. And you're 100% right. The value of a drug is an incredible amount of leverage for good. And more than you can do as a single practitioner or as a single scientist for sure. And I think too few people realize how much value is created out of the leverage of a good medicine. So, then you went to BioMarin, and you had success with a number of products. And the diseases are different, but the solution was the same which is enzyme replacement for MDS and for phenylketonuria and even Batten's disease if I recall correctly. Is that right?

Emil

Several lysosomal diseases, MPS I, MPS 6, MPS 4a, and CLN2 or late infantile Batten's. Also worked on KUVAN and Peg PAL for PKU, and then in addition Vosoritide, which is the new drug for achondroplasia.

Stan

Now, now, achondroplasia wasn't a replacement therapy, was it?

Emil

No, achondroplasia was a very novel strategy where an academic physician, Bill Wilcox came up with a strategy on how to treat a mutant receptor by using a hormone that had equal opposite downstream signaling effect. It was like one hormone to counterbalance the abnormal receptor, which I thought was the coolest idea. I had no idea how to treat achondroplasia, and I told people, "We should try this," and people said, "No one's done it before," I said, "Yeah. But there's no other way to treat that disease, so why not take the shot?" And honestly, in a few months, we came up with a version of their hormone that was stable just got approved, Stan. It's a hormone to treat achondroplasia. I think that's a disease people thought would never get treated.

Stan

I agree with you, and you know I think it brings us to a general message, and that is everything is a set of pathways, and as we understand the pathways, it opens up opportunities that were not obvious and in the case of achondroplasia, an opportunity that was very far afield from what you had done before, right?

Emil

Yes, but we learned a lot about taking risks for really important results. And in this case, it wouldn't take long to figure out if you could do it and if you could, what a great result that was. So, it's been a guiding principle, all the work we've done since then is, don't fear taking a small risk to figure out if something will work, but if it will, and have a huge impact, it's worth it. And I was very happy to see Vosoritide approved, and really getting utilized, like a lot of families are using it. So, I think it's a great testament to the importance of the work.

Stan

And that's wonderful. And just to make sure everybody understands, achondroplasia is a former dwarfism. And so, it's a lot of short stature people, but it isn't just stature, it's also a bunch of other problems that they have, and to be able to do something about that is a great achievement. And then so tell me about why you founded Ultragenyx and left your cushy job at BioMarin for an even riskier opportunity.

Emil

Well, BioMarin had grown and evolved. And there's a point, 11 years in, with three approvals, that it began to be a different company from the one I joined. And I felt like there was time to do some other things. I left actually to start a foundation. The foundation was to focus on regulatory policy around rare diseases, and we worked for a number of years on what I called the cure the process campaign. And that foundation in the EveryLife foundation for rare diseases still operates. And I'm on the board. But after about a year of doing that and getting it going, I came up with the thought of starting another company. I hadn't thought about it Stan, but I realized there were so many parents coming to me trying to get help to treat their kids, as you know from your experience with n-Lorem, that I felt like I couldn't not do more treatments. So, I founded Ultragenyx to focus on ultra-rare genetic disorders. And we started off with very simple small molecules and simple proteins. And ultimately the idea was to build a company treating each disease with the right mode. And we've added over time gene therapy and other things, but it's about doing a company that was built about rare diseases from the beginning with the right philosophical view of taking care of people before approval, after approval, and assuring that whatever we develop becomes accessible to patients that need it. And that's a higher-level responsibility in how we operate as a company.

Narrator

We hope you're enjoying the n-Lorem Patient Empowerment Program podcast. We at n-Lorem want to provide support to our podcast listeners the best way that we can. There's no better way for us to do that than to ask you directly. Do you have questions you want to ask Stan Crooke? Stan will be taking questions directly from you and other podcast listeners and dedicating an entire episode towards answering your questions, AMA style. If you're a nano-rare disease patient, family member, friend, physician, rare disease advocate, or you just enjoy the podcast, we want to hear questions from you. Please don't be shy. All questions are important and may end up helping other listeners. So don't miss a great opportunity to get your questions answered by the Patient Empowerment Program host, CEO of n-Lorem and the father of antisense technology himself, Dr. Stan Crooke. To submit a question for the upcoming Q&A episode, e-mail podcast@nlorem.org that's podcast at nlorem.org with the subject line podcast question. If you wish to be identified, mention your name and e-mail, if not, we'll keep your submission anonymous. We can't wait to hear from you. Now back to the episode.

Stan

So, that brings us to EveryLife, which is an interesting foundation. And you know, I'm familiar with it because some of the publications, for example, the publication that describes the economic impact of rare diseases and so on in the US. And it, to my mind, is first and foremost a foundation that engages in relevant scholarship on these diseases. And obviously you and others have participated in the revolution in treating rare diseases, which I'm interested in. The way I look at it, the patient voice was the key event here and it really began with AIDS and then the recognition that the patient voice matters and getting that in front of the FDA and other companies and so on. Is that your view of the history of it or do you have a different perspective?

Emil

I think the patient voice piece is very important and the rehabilitation of the patient’s role because the patients had been reduced to being emotional and non-rational people somehow, and no one bothered to actually ask them, and that harmed drug development. And I think now we're much more working with rare disease patients as partners in the process, continuing to evolve and improve that model. But I think it's the regulators also that are starting to connect and realize that they are an important contributor to the whole process. Because I think the other piece though, is on the regulation and the law that the FDA applies, and their guidance as an approach are an important part of what the foundation was working on. A lot of this is maybe technical about the details of how accelerated approval is evaluated, or how biomarkers are qualified, or study designs and other technical pieces. So, at the foundation we did a little bit of that work to trying to move the ball forward on the quality of the development strategies and the regulation. Building the patient’s voice was just part of that bigger picture of improving the quality of drug development. And it involved a lot of workshops, a lot of investigational reports, and analysis as you were talking about, and to some extent discussing in Capitol Hill what are the needs of rare disease patients, and having the patients come to the hill during rare disease week, where hundreds of patient advocates come together, and we send them out on the hill to talk to their congressman on the very same day. Give them the kind of bulk that a common disease has, but with all the individual rare disease patients gathered together as one team.

Stan

Yeah, I think of course, I've been in the industry long enough to remember way before you, and there was no patient voice, and I think the industry has benefited tremendously, and the FDA has benefited tremendously by integrating the perspective of the patient, and obviously you've spent a lot of time thinking about clinical trials, and what endpoints ought to be, and how we should go at that. But I think we'll leave that for another conversation because that does get pretty technical, and if you were to pick one thing that EveryLife did that you're really proud of, what would it be?

Emil

I think it's gathering together the rare disease community truly during rare disease week, where we actually bring hundreds of people together from all different segments, and help all of them actually find a common vision and a common voice. I think that's what has been most important because they then don't feel alone, they feel empowered and rejuvenated. And I think it propagates across the country. So I think it's bringing the whole community together that has been really important, and in that, enabling and empowering them to actually take action on behalf of their disease area.

Stan

You know, that's very much what this podcast series is about for the even less, even more poorly served, or non-served. And n of 1 people literally don't have anyone to talk to. And again, I think that's a matter of providing a forum, a place to be heard. But also, a place to be taught, because certainly my experience is that parents and patients are doing remarkable things with no training. What could they do if they had some training? And I know you've thought a lot about that too. And at Ultragenyx you have what you call a boot camp, which I spoke at this year. But why don't you tell our folks about what that is, and how that's working.

Emil

Well, one of the philosophies underpinning Ultragenyx as a rare disease company was that we would use our knowledge to help everyone around us do work on their disease. The idea that we won't work on every disease, but we can help others be successful. That involved a lot of individual one-on-one consulting and with time one of our employees felt that we could be even more effective by grouping together some people and creating a boot camp. A several days in person, a place where a small group of selected family foundations or small nonprofits could come with their drug development questions and get trained and insight from experts in the field and build camaraderie among themselves as well as make relationships with others that would help advance the development of treatments for their care. And the boot camp follows up with some consulting and help that we do pro bono for families. And we think it's the kind of camaraderie and shared ecosystem to solve rare diseases. It's an important part of being a rare disease company.

Stan

How do you measure the value that you create out of boot camp?

Emil

Well, I measure it because of the number of families that have actually developed a drug and their kid. One of the early ones who has a kid, and she got her kid treated, and it was such a great thing to see. And you of course are familiar with, you know, the other n of one cases that are out there. Most recently Terry Pirovolakis developed a gene therapy for his SPG50 affected child, and got him treated, and sends me pictures of that. So, I measure it in another, disease after disease, actually getting a treatment to a few patients. And that is, you know, it's priceless in terms of what it means for your career to know that you've helped make that happen.

Stan

Yeah, I've had the privilege of putting a lot of drugs on the market and having that experience. And of course, n-Lorem; I describe it as much more like practicing medicine for me. It's one patient at a time. It's that intimacy that you don't get when you're developing drugs commercially. And of course, your pipeline has small molecules, it has enzyme replacements, it has antibodies, it has genes, it has antisense. Early on, I talked with you, and all the gene therapy companies about whether gene therapy was ready to sort of be industrialized to take on the nano-rare patient. And I think most everybody concluded that no, not yet for a variety of reasons. What do you think needs to happen for gene therapy to get to the place where it can be applied as antisense technology is today?

Emil

I think the biggest challenge is manufacturing, scale and cost. That is where I think it's challenged now, because we're talking about single dosing, it does help, but it's very hard to develop a manufacturing process that may take tens of millions of dollars, and have only one kid get treated right? And while there can be ways to leverage and simplify, the truth is it hasn't really dramatically altered the cost structure of getting there. I think that is the biggest, number one issue. More and more, though, there are people focused on intrathecal CNS strategies for gene therapy, like Terry did for his son with SPG50, where they're just plugging and playing another vector in an Av9 and are able to get a few million dollars put together to do the manufacturing. And so, there may be some improvements if you can narrow what you're doing, and if you're using a particular intrathecal strategy, the amount of vector you need is less, so manufacturing, that's the biggest issue. And I think getting to high quality, lower cost manufacturing would have the biggest impact.

Stan

Yeah, I think there's still a lot to be learned too. And where we have nearly zero cell turnover in the central nervous system, that's not the case of the rest of the organs. And so, I think when you move out of the brain, it becomes even more challenging. But obviously at n-Lorem we are anxious to see gene therapy progress to the place where it can help because we can't fix null mutations. So, let's move on then to n-Lorem. First of all, I want our listeners to know that you and Ultragenyx have been incredibly supportive, and we appreciate that. Of course, you yourself and Ultragenyx, you have plenty of places to put your money. That's never the issue. What is it about n-Lorem that convinced you that investing in n-Lorem made some sense?

Emil

Definitely a large number of ultra-rares are so rare that the traditional drug development path is just not going to be plausible. And I've worked on some very rare ones. But when you have a few dozen or less, there's just no way to get the traction with the company to invest. And therefore, then you start looking at strategies in which you can customize the development of a treatment, and do it at scale appropriate for that, and get it done and I think the use of antisense oligonucleotides and the n-Lorem approach is that you can custom create therapies that would actually address very small population. And unlike, let's say, making an enzyme, or biologic, you can kind of plug and play the sequence in this chemistry. You don't have to create a whole huge manufacturing system to produce it. So, the ability to plug and play the sequencing chemistries means that you can make small lot drugs and make that work in a time frame, and the cost structure that I think is plausible for approaching some of the rarest of the diseases.

Stan

Yeah, we're doing it. I mean, we've already proven it can be done, and now the next step is to prove that it's sustainable as a charitable endeavor. And with support from you and many others in the industry, I think we're well on our way to doing that. So, I want to thank you very much for participating. Is there a question I should have asked you that I didn't?

Emil

Well, I guess the biggest question right now is what can we do to help rare disease get treated. And I am working on one thing Stan, I'm working on us improving the ability to accept primary disease activity biomarkers, that's a type of biomarker that really reflects the underlying disease as clinical endpoints to get approval, that we need to change the paradigm of drug development and a lot of these ultra rare-diseases, if you wait for clinical endpoints, it takes so long, there's so much variation, and many diseases will have irreversible symptoms by the time you treat, that you'll never get to the end. And we as a country have to get smarter about using the primary cause of disease as a true measure of disease and understand that we can develop drugs better than you can any other way, just like HIV, drugs and viral loads. Stan, can you imagine developing a quadrivalent combination, highly active retroviral therapy using clinical endpoints, impossible. It's time to enter the 21st century and use the proper disease activity biomarkers as the true measures of disease and transform our drug development system into a really effective, efficient system. And that means getting past our limitations and our angst about biomarkers and starting to realize we need a precision medicine equivalent for the measurement of disease and that's my big question.

Stan

And as you know, I strongly agree.

Stan

I think you call it the tyranny of statistics. And you know it, it goes well beyond rare diseases. The bigger problems are in the large diseases where you have to treat a massive number of people, each of whom probably has a different disease that just got categorized like diabetes or whatnot, and I think there's a great deal of work to be done there. And I think the lessons that will be learned from n-Lorem and ultra-rare and rare diseases eventually will be applied. I would assume that you also strongly agree that among the things we all have to work toward is adoption of genomic sequencing as a standard part of newborn screening.

Emil

Or at least symptomatic patient evaluation at minimum right somewhere.

Stan

You know, it's happening in other countries, and you know, the cost is coming down. And if you think about what cost you would save by getting to these patients, actually understanding what the prevalence of nano-rare and other kinds of mutations is and getting to them before they've progressed to the place that they're almost impossible to treat. So, I think what's encouraged me in doing n-Lorem is the tremendous momentum behind this and in the regulatory community in the office of science, technology, the president, and throughout the industry. So, we all recognize that there's a desperate need here, and that the only way we're going to get it done is band together and work together. So again, thank you very much for the opportunity to interview you and all your support in the past, and I'm sure we'll have opportunities to work together again in the future. So, with that, thank you Emil and thanks everyone for joining us and look forward to the next podcast that's coming up real soon.

Emil

Thanks for having me.

Narrator

This episode of the Patient Empowerment Program is brought to you by Ultragenyx. Ultragenyx is on a mission to transform the lives of people living with rare and ultra-rare diseases and is a proud partner of the n-Lorem Foundation with multiple approved therapies in a deep pipeline of potential development. Ultragenyx is going beyond everyday for the rare disease community. Learn more about how Ultragenyx is leading the future of rare disease medicine at ultragenyx.com, that's ultragenyx.com. 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 nlorem.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.