**Coming Together for the Nano-rare Patient with John Maraganore**

# **Transcript**

Narrator

This podcast is proudly sponsored by Alnylam Pharmaceuticals. Since 2002, Alnylam has worked to pioneer RNAi therapeutics, an innovative new class of medicines that silence genes that cause disease, and in doing so, help people live longer, healthier lives.

Stan

I'm Stan Crooke. Welcome to the n-Lorem podcast series. Today, I'm honored to welcome Dr. John Maraganore as our guest. For most of our audience, John needs no introduction. John is one of the best known and most widely admired CEOs in the history of biotechnology. And though John and I were on occasion directly competitive, I count myself as one who admires John immensely. Until late last year, John was the founder and CEO of Alnylam. As CEO, he led the conversion of siRNAs from fascinating cell biology to a powerful platform for drug discovery. In addition to all the business successes he had, he has made important contributions to the science, and he's also been very broadly involved in the senior leadership of our industry and served as a mentor to many. John grew up in Chicago and completed his undergraduate studies and PhD at the University of Chicago in 1986 and immediately entered the industry for being a scientist at Silent Genetics and then moving on to Biogen, where once again he demonstrated his capabilities and advanced steadily. And then on to Millennium and again the same pattern that's typical of somebody who's so talented, and left Millennium as Vice President of Market and Business Development, and in 2002 he became the founding CEO of Alnylam, and the rest as they say, is history. Today, John serves on a number of boards of directors, is involved in several investment funds, and continues to play an important role in the industry and continues to serve as a mentor to many in the industry. John has been a colleague, he's also been a very tough competitor and a friend for a good many years, so it's a real pleasure to welcome John Maraganore today. John, it's good to see you.

John

It's great to see you, Stan. And thanks for all those kind words. You are an amazing colleague and friend and also a fierce competitor.

Stan

Yeah, yeah, we'll try not to dwell on that too much here, John. So, you know, John, I know your biographical history well, but what I realized as I was getting ready for this that I really don't know much about your background. I know your parents were Greek. What sort of family do you come from?

John

Well, you know, my father was a physician, and my mother was a nurse. She stopped being a nurse when we were born so she can raise the kids. But they were immigrants that came to Chicago from Greece and brought us up in a typical, you know, Greek American household. And you know, we ate well, of course. And, you know, we were motivated by my father mostly. And my mother too, you know, keep trying harder and harder and working harder. But, you know, my father drove my passion for science and medicine. And my mother, I credit her with giving me the gift of optimism. Which has been pretty helpful as a CEO for sure.

Stan

In biotechnology, when you're pioneering an entirely new technology, if you're not optimistic, you don't even try, right?

John

You got it. You got it, very key.

Stan

So I'm interested in when you realized that you were interested in not just basic research, but research applied to bringing therapeutics to patients.

John

Yeah, I mean, I always loved science, Stan. I was the typical nerd who had the chemistry set, the biology set and did all that stuff. And it was my passion for sure. And when I went to the University of Chicago, I entered a research lab in my sophomore year and started working on, you know, after school hours and on the weekends and basically doing basic research on structure function of proteins and enzymology. And I just loved it. I just enjoyed being in a laboratory and doing things. It always occurred to me when you were doing science that, you know, you're doing something that nobody else in the world is really doing, and you're finding something out in your work that could illuminate a whole, you know, level of understanding scientifically. So, I just enjoyed that completely. But you know, in 1986, when I got my PhD, I went to the Upjohn Company, and I went there because my thesis advisor was recruited to the Upjohn Company to basically become one of the early scientists. And I did a postdoc at Upjohn, which really illuminated for me the power of the biotechnology and pharmaceutical industry working together, you know, in a team like manner to basically identify, you know, potential therapies or cures. And it really became my calling at that point in time to stay in the industry and to be driven by what the industry can do.

Stan

 It is an enormously complex and joyous experience that too few people get to experience, right?

John

Right. Absolutely right.

Stan

So, I know that you grew at both Biogen and Millennium, and they are two companies that, at least from the outside, seem very different to me. How would you describe your experience in those two places and what were the big take-home things that put you ready for being so successful at Alnylam?

John

They were two very, very different companies. Of course, Biogen is one of those early pioneers in the biotechnology industry, one of the admired, still independent, you know, biotechs, and I went there in in 1987, and went there as a bench scientist and began doing some early work, initially in the HIV field, when HIV was just getting up and starting. I also discovered a drug at Biogen that ultimately made it to the market, Bivalirudin, which is a anticoagulant direct trauma inhibitor. And at Biogen I learned about, I really learned about drug discovery. Because I took this invention, I was the program leader, I led the multidisciplinary team all the way into phase three clinical development, and then in 1994 we decided to stop the development of that program when the phase three trial ended up with mixed results and it was a a very important learning experience for me. The drug ended up getting approved in the hands of another company, but for me to actually lead that program and do the drug development was really one of the funnest things I've ever done to this day. I then transitioned at Biogen into the business side and became the head of business development at Biogen for the last three years that I stayed at Biogen. And at Biogen, Stan, you may remember, Jim Vincent. I really benefited from that person, you know, may he rest in peace. But Jim was a notorious leader in the industry because of his stubbornness and his thick headedness. But he did teach me about the critical nature of just having a very high bar for everything you do, and the management skills I learned from Jim to this day, I think were really very helpful. But then I went to Millennium in 1997 and worked for a great visionary leader, Mark Levin, one of the biggest thinking leaders I've ever met and worked for, very colorful individual as you know. And Millennium was a company that was driven off of a big vision, a big idea. And I learned the benefits and the challenges of working in a company under that type of roof, but it really was a fantastic experience. Of course, we were focused on the genome and solving the genome and helping make drugs out of genomic research.

Stan

Well, it's fascinating experience and very different from mine of course. I suppose that you would probably agree that for the last 20 years, you've been a dream merchant, that what you did was conceive the dream, and sell the potential of that dream, and then convert that to, you know, the daylight, the reality of actually doing it. Talk to me a bit about how that felt.

John

Yeah. Well, I mean I made the decision in 2002 to leave Millennium to go start Alnylam as the founding CEO. And you know Stan at the time, I have to say I was very happy at Millennium. I would often get phone calls to go be a CEO, but I was really very happy in Millennium. I loved work with Mark Levin, he was a tremendous leader and a friend. But I became convinced, as the recruiters and people like Phil Sharp and other people were trying to persuade me to go to Alnylam, I became convinced that if we're able to understand how to make drugs out of these small interfering RNAs, that I could actually be involved in helping create a whole new class of medicines. And of course, at the same time I was looking at the scientific progress that was being done at Ionis, and ultimately Alnylam stood on the shoulders of Ionis to be able to advance the medicines that we did. But you know, there was a foundation there of reason to believe in developing very high impact medicines. And so, I had to take the plunge. I remember I was just getting married the same year I talked to my fiancé. I said, "Look, I think this is gonna be the right thing to do," you know? Obviously, she was very happy with me doing the transition along with getting married the same very year. In fact, my offer letter for the job was sent to my honeymoon suite in Mauritius. And I was pleased to accept it, but I really believed that with Alnylam's technology and what the founders had put together, that we could really create a whole new drug class. And I really believe that joining the company at that time would be, you know, a remarkable endeavor, and it turned out to be the case.

Stan

And of course, you focused meaningfully on rare diseases. Your pipeline of course is much larger than just rare diseases. What drove you into the rare disease space, John?

John

Well, it's driven by the patient, Stan. First and foremost, I mean the disease burden for people living with a rare disease is enormous and at the same time there is incredible genetic data that really shines a light on how science can solve the problem. And so when you have this situation, patient with a rare disease combined with the genetic understanding of how you can treat it, and then you have a technology that can be applied to it, there's nothing else you can do then go down that path, and it's a guiding light that's a clear direction of travel that you really have to take on and we're really proud we brought three rare disease medicines to the market and we have others in registration right now, and in late stage development. But the impact that we've been able to have in some of these rare diseases is really, you know, to me one of the greatest thrills and joys of the Alnylam story for sure.

Stan

Yeah, it is a powerful way to do work and to feel good about the work you do, and people appreciate it outside the industry. I'm sure you would agree.

John

Totally agree. Totally agree.

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@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

Well, I remember sitting in my office in Carlsbad and you and Barry Greene showing up looking for a license as I recall. And at that time, there were a lot of other siRNA would be companies, and we were entertaining proposals from all of them. And then I met you and Barry and I said, "I don't know whether siRNA's ever going to be a drug, but if it's going to be a drug, it will be with these guys." And so, we ended up doing that license. And then from there, of course, we collaborated on a large number of things including co-founding and co-funding Regulus, a MicroRNA company. So, we had a long positive experience even though we were seen in the rest of the world as direct competitors in terms of the technology space. But you know, I do think that working together helped us both achieve the ends that we sought to do. Would you say that too?

John

Absolutely Stan. I mean the deal that we did back in 2004 and I'll never forget, flying over to Carlsbad and visiting with you and Lynne and putting that arrangement together was frankly one of the smartest things that we ever did at Alnylam because it created, and I think also for Ionis, it created this I like to call it, you know, Pax Alago, like the Pax Romano that occurred, but this sense of peace between these two technology competitors, but frankly two technology pioneers, and it also created this remarkable synergy between the companies that allowed us to do some really good science together. We had very frequent engagements with each other. As you know, we started the company together as you mentioned. We also found ways in which we could avoid, you know, competition with each other on specific programs, which was smart and a clever thing to do. But it really was an important arrangement for sure. For us to have tried to find a way around the remarkable, you know, accomplishments that Ionis had done from an intellectual property standpoint would have cost us years and hundreds of millions of dollars to do it. So, it made, from a business standpoint, it made a lot of sense. And then at the same time, I think Ionis had a partner in the RNAi space that they can count on and benefit from. I mean, Ionis benefited economically from our success as well, which is really terrific. So, it was a good arrangement, and it was one that I'm really proud of at the end of the day.

Stan

As am I. And so, we did all kinds of great stuff together, and then we had a couple of drugs that were directly competitive. And we discovered that we're both really competitive. And we had a falling out. And you know, each of us has his own perspective about that. But we didn't talk to each other for a few years. And as I thought about the patients that we're trying to serve at n-Lorem, I realized that I need all the help I could get, and you could be an incredibly helpful person for these patients. And it made no sense to hang on to whatever bitterness I felt. But I was very, very worried when I wrote that e-mail to you asking you if you'd like to talk and you were immediately gracious. So, I knew how I felt from my end. What about you?

John

I'll tell you, Stan, I never ever stop admiring you. And you know that. And I also was watching the n-Lorem story from afar, from the East Coast, and really thought it was powerful, you know, in the Talmud there's a phrase: Whoever saves a single life saves the whole world. And it's a phrase that really comes to mind when I think about what you did in this new effort with n-Lorem, because the power of treating just a single patient with the disease, with the technology that can address it, is just awe inspiring. And so, I was seeing all this and I was excited about what you were doing. So, when you reached out, I was so happy to respond and get back to you. And listen, when we had this competitive period of two to three years together you know, we ultimately got back together. To me, it reminded me of a big brother and a younger brother. They get into a fight, but they still come together at the end because they're family. And I really felt the same way as we've now been working together on n-Lorem.

Stan

Well, I think we did come together around the family, and the family is the nano-rare patient. And in the end, it's vital to these patients that the two of us participate in this because we're the people who created this opportunity. And so, it was certainly, I'm embarrassed that I waited as long as I did. And you've been just extraordinarily helpful already. And so why don't we spend some time now talking about n-Lorem, and the patients, and the model that we're proceeding with, which is a nonprofit model, and how you see all that potentially unfolding.

John

Well, listen, I think starting with the power of the technology, the antisense technology, and maybe other technologies that come into it in the future, but being able to selectively design a medicine for a patient or small very small group of patients with a very discreet genetic defect is incredibly powerful. Being able to deliver that, achieve a desired therapeutic effect, do it safely, and then on top of it, have the regulatory framework, the framework from the FDA that enables all that, that's not trivial. You know, the FDA obviously had to think a lot about how does it enable the advancement of these type of medicines for patients. So, one aspect of it to me is the technology which is really impressive and the regulatory framework for the technology. The other aspect of it is really the patient, and the ability of giving hope to a patient with a nano-rare disease and a family that surrounds that patient as well. And then frankly, the generations of other patients with nano-rare diseases who can see what we can do one patient at a time. It is a very powerful thing, and it really does go back to that Talmudic quotation that I gave a moment ago about how you can really save a world by virtue of saving just one life.

Stan

And for me, it's very much like returning to the practice of medicine, which I still miss, because it is that intimate experience of one patient, one family, one hope at a time. And of course, I'm looking forward to your involvement, and getting you more involved with some of the patients and families and so on. And we've both been trail blazers. We've both taken an opportunity that was a blank piece of paper and wrote a textbook, and we both then took steps that meant we were always in uncharted territory and the name that Jefferson gave to the Lewis and Clark expedition has always been something I admire a lot and he called it the Corps of Discovery. And I think of n-Lorem, Alnylam, and Ionis as corps of discovery focused on the inner landscape of health and disease and helping patients. And so, it's a great tourist value to these patients to be able to have you on the team and helping us do the things we need to do. And I firmly believe that the next technology that will be ready to take on this task and industrialize this task so that we have quality at every step, and scale will be siRNA and so it also made sense, from my point of view, that we would bring the two people together who knew those technologies better than anyone else so that when the technology makes one more step or two, then our patients could benefit from that. And obviously, even though you've retired from Alnylam, this collaboration extends to Alnylam now. There is no better organization to discover an siRNA, and develop it than Alnylam. And you know, I don't know exactly when that's going to happen, but it will happen. That's the next thing.

John

Yeah, it will happen. It will happen. And Stan, I couldn't agree with you more in terms of how you see it all coming together. And I also, to your point about being on the frontiers as a discovery, you know, doing it together with a colleague, a brother, an older brother or younger brother, whatever the case might be, it is just that much more powerful at the end. And I think that we can bring ASO and siRNA technologies together, help this amazingly important cause, and help first and foremost these patients with these nano-rare diseases.

Stan

I welcome you to all that, and I guess the final comment that I'll make and leave it open for you to sort of finish is I believe we made great progress at n-Lorem. But what we have left in front of us is an enormous task. And one of the biggest questions that we must answer: Is a nonprofit model like we're developing sustainable? And as you thought about n-Lorem, how did you think about solving that, and proving indeed that it is sustainable, industrializable, and scalable?

John

Well, I think it is sustainable, Stan. And I think you're beginning to prove that it is. One of the ways that you create sustainability is by creating relationships with other companies, whether it's the Alnylams of the world, but also the clinical trial networks of the world, and other stakeholders in the system that work with patient groups that obviously have a vested interest in advancing medicines for nano-rare diseases. So, these are all the different communities that together, we can create. And then with the generosity of philanthropy and others that could contribute, we can do this in a nonprofit manner and ultimately deliver cures for patients that otherwise have no hope.

Stan

They really have no hope. They are hopeless, and you're right, hope is a powerful, powerful thing to lose and an important thing to recover, not just for the patient, but for the family. So, it's been a great pleasure chatting with you. I wanna end then giving you the floor. Anything that you would like to say to the community that's interested in what we're doing, the nano-rare patients?

John

Well, I would just say this: I hope that people take a look at what's already been done with n-Lorem, but then also think about the power of n-Lorem going forward. I have no doubt that as people get to understand the stories of patients that have been impacted already by n-Lorem, and then the framework that's been put together to help patients going forward, they will truly understand the impact and potential power of this approach. And so, I really encourage everybody out there to take a really close look. This is a remarkable effort here to help a patient community in a high impact way. That is what we are all about as a biotechnology industry. That's what we're all about as scientists, and physicians, and it's something which of course, you know, Stan, you have done a brilliant job in leading thus far. And I'm happy to be on the boat with you this time and look forward to many years of working together.

Stan

I do too, and I think it is showing the true heart of our industry, and I know we share that passion, that heartfelt passion to see people who are suffering be better. Thanks so much John, for joining us and it's been a great privilege to know you all these years and to get to know you a little better in this conversation as well.

John

Terrific. Great Stan, thank you so much.

Narrator

This podcast is proudly sponsored by Alnylam Pharmaceuticals. Since 2002, Alnylam has worked to pioneer RNAi therapeutics, an innovative new class of medicines that silence genes that cause disease, and in doing so, help people live longer, healthier lives. n-Lorem is a nonprofit committed to discovering and providing personalized, experimental treatments for free, for life to patients with genetic diseases that affect one 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.