# **Fostering Collaboration to Fight ALS with Manish Raisinghani**

# **Transcript**

Narrator

Target ALS Foundation is a nonprofit whose mission is to accelerate ALS research into successful clinical trials. Since 2013, the foundation has built an innovative ecosystem for biomedical research that has catalyzed ALS drug discovery through collaborations. Target ALS envisions a world where everyone with ALS lives.

Stan

Hello everyone, I'm Stan Crooke. I'm the host of the n-Lorem podcast series. Welcome, everybody. Today we have a special guest joining us, Manish Raisinghani, who tells me that I pronounce his name better than most of the people in India. So, I'm already a giant step forward. Manish, welcome.

Manish

Thank you, Stan. It's a pleasure to be with you.

Stan

And Manish, maybe we can just start with a little of your background because it is fascinating. Did you grow up in Mumbai or elsewhere in India?

Manish

I did. I was born in India, born in Calcutta in India, but I lived most of my growing up years in northern India, in a city called Kanpur, which is really famous for this Indian Institute of Technology, which is an engineering institute. So, my father was a faculty member there. And so, I grew up there, but yet I moved to Bombay for my medical schooling. And after that, I came to the US for my graduate work.

Stan

In India do a residency after you go to medical school? Is that the way that works there?

Manish

Yes, so we follow the British system, which is we do what is called MBBS, which is a five-and-a-half-year undergraduate followed by residency, yes.

Stan

What was your focus in your residency?

Manish

I was doing anesthesiology in residency.

Stan

Lots of good pharmacology in anesthesiology, right?

Manish

Very true. It always fascinated me, the fact that one could use chemicals and alter the consciousness, and a person could almost go away and come back. It's absolutely fascinating.

Stan

Yeah. And it's amazing how far it's come over the last 20-30 years, really. And then what motivated you to come to the US?

Manish

Well, after a while, I think I was asking more whys than I could answer with through medicine. And so, I felt compelled to sort of pursue that path and see if I can get answers to more of the whys that were there. And that's why I came here, pursued actually a graduate degree in pharmacology, continuing that trend of fascination with that topic.

Stan

And that was in Illinois, is that right?

Manish

Right. That was in Illinois. Yes, Southern Illinois, yes.

Stan

And then at some point you end up at Columbia I think, right?

Manish

So, I initially, after my postdoc, I joined a biotech company. I was running drug discovery platforms there and did a short stint in marketing. But then, at some point, I felt that I needed to do something that was helping other people. And so that sort of led me to look for positions. And there was this position at Columbia University for a new, what was a program back then, which was a precursor to Target ALS, and that intrigued me, the profile, and that's what made me join that program, which was based out of Columbia University that after a couple of years spun out as this independent nonprofit, which is known as Target ALS today.

Stan

And so, the original Target ALS was basically a research initiative to better understand the mutations and non-mutational characteristics of ALS, is that the idea?

Manish

Indeed, in fact the name itself Target ALS was really rooted in the idea that there was a real dearth of therapeutic targets based on a solid biological rationale. So, we needed to expand that pipeline of therapeutic targets, hence the name Target. And at that time, in around 2013, we felt that was a dire need. And so we did initially focus on identifying and discovering new genes and therapeutic targets, biological mechanisms which could be modulated for therapeutic benefits, and it was a program based out of Columbia University, and the objective was that the funding was not for Columbia University, but Columbia University was allowing us to leverage their administrative structure to implement the program, and it was to the credit of Columbia University that they allowed us the flexibility to do that.

Stan

And how did Target ALS come to be? It was funded directly, not through an NIH grant, but some other type of funding, right?

Manish

So, I mean the story of Target ALS really starts with our founder, Dan Doctoroff. After his father and uncle passed away from ALS, he decided he needed to do something about this disease, and he's the one, along with Bloomberg Philanthropies, and then David Rubenstein came together as founding members, and they founded Target ALS, which, as I said, was a program out of Columbia University. And then subsequently we recognized that the program needed to have a certain level of nimbleness for a disease where there are no treatments and the clock is always ticking, so to speak. And it was unfair to burden a university system to move as fast as we needed it to move, and so that's when we decided that it was best that we were an independent entity and became an independent 501(c)(3) nonprofit. And that's how we have been since then.

Stan

You know, it's 10 years since that began, a good time to take stock, I suppose. I imagine that's something you're doing, but to a person who has only a peripheral involvement in ALS, but a meaningful involvement, it feels to me like the last 10 years have been years of extraordinary progress in better understanding the genetics of ALS, and all of the various contributors to ALS. Do you see it that way as well?

Manish

Indeed. And in fact, you make a great point. Like if one looks at the decade preceding, let's say, 2013, as you know SOD1 was the first gene which was identified cause familial forms of ALS. And as we all know, there is a clinical trial ongoing targeting SOD1 right now, and that's an extraordinary span of time for a target to be identified and a trial to start. If one looks at the last 10 years, the progress has been exponential, as you well know, Stan. There are always multiple factors, one of them being this expansion of the therapeutic toolbox with the technologies like ASO which n-Lorem is so masterfully applying to nano-rare disease forms, but also this real exponential increase in the fundamental understanding of the genetics and biology of the disease, and ALS in some ways has been at the forefront of the cutting edge of neurodegenerative research. And so, what we have seen is work funded through Target ALS, where there were these ideas which did not exist, be identified, observed, they are observations made in the lab, and within a span of five to seven years, transform into an ongoing clinical trial, and I think that speaks to the real growth in the understanding of the biology of the disease. But we like to think also because of the existence of the kind of ecosystems Target ALS has created, where investigators and the ideas they have the opportunity to accelerate using the funding mechanisms and the different tools and resources we provide access to sort of fast track towards clinical trials and be really rooted in a strong biological rationale at the same time, which as you well know, that's the only way we'll increase the chances of success in clinical trials.

Stan

Yeah, I think the word that you use is a really apt word, which is accelerate and the pace at which knowledge has been gained over the last 10 years as a product of all the investments that took place over decades and created genomics and all the other basic tools that we have. But the translation of those basic science advances to medicines in development is a very different kind of process. And you folks have played a critical role in that, with SOD1 one being the first and Tofersen actually now being at the FDA, with an NDA filed by our partner Biogen, which we're very excited about. So, how did you guys go about actually making this work?

Manish

So early on, when we looked at the ALS research landscape in 2013, we wanted to see what, there was a lot of funding in ALS, but what were the barriers that were really hindering progress towards clinical trials? And what we found was there were real silos within the research community. So, if you look within the academic research community, there was not as much collaboration, but also there was complete siloing between the academic and pharma biotech industry and as we all know, they are the experts in creating drugs, in the end, the academic community is really good at making discoveries, and we needed to combine and leverage the expertise of these two constituencies and incentivize them to work together. That was one of the key factors. And so, what we decided was we needed to create an ecosystem that incentivize these two research constituencies to work together, but also in a way, democratize ALS research so that anyone within an outside ALS research community with an idea on the disease could work on it. And so, we needed to provide access to critical research tools and resources which they needed, and they could partner with a complementary partner who had the expertise that was needed to move the idea forward. And so, what we did was we started to engage the pharma biotech companies, and in parallel really venture capital firms and engage them in any formulation and implementation of any new initiative that we launched. And that brought with it their sense of investment in the process. And then, when we had these funding opportunities, they knew we were this neutral arbiter who is only looking to identify and support the best ideas. And the other key thing we did, and I give all the credit to our founder, Dan Doctoroff, and he recognized this, and said, "We will not ask for any ownership of the data or intellectual property that is generated from the work that we fund or provide support through these tools and resources we provide access to." And I think that really one, lowered the barriers to enter into ALS research, but also accelerated it, because suddenly we were not adding a wrinkle along the way that we needed a piece of the pie if there was success. And I think the results speak for themselves in that way that we have had six clinical trials come out of our ecosystem. We've funded now over 50 collaborative projects and more than half of them have had a pharma biotech industry partner and over 60% of them have an ongoing drug discovery program come out of the research we have supported. So, there's real movement because for all these different elements that we put into place.

Stan

And it's such a remarkable model. And would you say that others are paying attention to what you guys have done and emulating it because there's no reason this couldn't be a portable solution to lots of diseases like ALS, right?

Manish

Very true. And before I answer that, I do want to point out that we also practice what we preach, so it's not like we incentivize and ask the community to collaborate with each other. We collaborate with other foundations, and we are very proud of it, so we have multiple partnerships across the board with organizations working on ALS, but also related neurodegenerative diseases like FTD and Alzheimer's disease for example. But yes, to answer your question, it's been really gratifying to see that sometimes when a there is a thought to launch a new foundation on a different disease, we have been approached to ask about the approach, the model that we have pursued and see how they can adapt it. Or sometimes organizations that have ongoing efforts have reached out to us to understand better how we have implemented this model, which has attracted so much engagement from across the research constituency and apply elements of that in their own model.

Stan

You know, of course, many of the folks that we deal with at n-Lorem, in the nano-rare community are engaged in trying to find solutions and forming their own institutions, their own nonprofits, and sometimes for-profit organizations as well. Have you thought about actually writing up the model and presenting it in more wholesome detail for people who might take advantage of it?

Manish

Yes, I think more recently, as we have grown, there's been this recognition, and it's a realization that sort of behooves us to share the lessons we have learned along the way with the wider research community, and we feel a special kinship to the constituencies that are working on what are classified as orphan diseases, as ALS is as well, because the challenges are unique in these types of disease spaces. But certainly, these lessons are scalable and are applicable to more common disorders as well. And recently we have had conversations where someone was interested in working on Alzheimer's disease, for example, and wanted to emulate this particular model that we have pursued, and there are elements that are certainly applicable in those disorders as well. So yes, to answer your question, we are, and that is an ongoing effort, and we hope to be able to share that with the wider communities soon.

Stan

I think it will be very valuable. So, focusing on ALS now, how many different genes and mutations is the community aware of that are associated with ALS now as of this year?

Manish

So, experts generally comment that there about 31 different genes that have been associated with ALS, and that number may very well grow as the efforts continue to identify new genetic mutations. And one of the things that will be helpful in that regard is to create bigger data sets, and not only create, but create access to these big data sets so investigators worldwide can go in and analyze these and identify new mutations, and further the science as we know it right now, and those are some of the areas that we are working on diligently to see how we can help the community move the needle on those efforts.

Stan

Are you moving beyond just genomics and trying to understand how the interplay of genomics, epigenomics, and the other kinds of omics yield these changes in pathways that result in a common end product, which is ALS?

Manish

Yes. And in fact, one of the major areas of focus for us has been this natural history study that we have ongoing. And the whole purpose of that was to create a very comprehensive integrated resource of bio samples and omics data sets that could be made accessible to the worldwide research community. And they can then go in and query this to answer the kind of questions that they have, and to understand the biology in a more fundamental manner. And this was in response to an overwhelming ask from the research community. So, in 2019 we did this, we asked the community, we spoke to over 100 members of the research constituency from Pharma, biotech, venture capital, academia, nonprofits, and they overwhelmingly set that Target ALS must do something about access to human bio samples and longitudinal samples. And so, we launched this natural history study where we collect biofluid samples longitudinally from individuals who have ALS, and healthy controls. And this is an incredible contribution from individuals who are facing the disease. And the idea is we'll have whole genome sequencing data sets, but we'll also create additional omics like whole unbiased proteomics, lipidomics, metabolomics from these. We are going to measure some biomarkers in the, right now neurofilaments is certainly one that we are going to measure, and the idea is to have all of these data sets in one place, along with the De-identified clinical and demographic information. And as you can see, the more comprehensive this data set is, the more impactful it becomes. So that's where we are headed right now.

Stan

That's wonderful to hear, because it's certainly one of the main lessons that I've learned over the last three years. There are a lot of genomics data basis, but very limited amounts of genomics coupled to other omics coupled to phenotype and natural history and so setting that up is going to be you know just an unbelievable resource that should help solve this disease.

Manish

And I should mention, Stan, that one of the missing pieces sometimes is that fragments of these types of data sets are created, which is in itself part of the equation because as you just articulated, the more comprehensive it is, the better it is. But also, it's a question of getting access to this data set, so putting them on database platforms that are easily accessible and enable analysis at the level that is required are key pieces, and so we are addressing that as well. So, we are going to build a data platform and make that accessible to the worldwide research community as well.

Stan

So, I guess the next question I have is just how did Dr. Neil Shneider come to be involved in Target ALS, and how's all that working out?

Manish

Well, Neil is a, as you know, is a fantastic physician scientist and has unique sort of bandwidth when it comes to understanding basic biology, and obviously the clinical trial spectrum. We were lucky that Neil Shneider got involved with Target ALS early on, and in fact he gets largely the credit for our ability, way back in 2013, to be able to share stem cell lines with the research community. He's the one who allowed us to do that. And he has also been integrally involved in our efforts to collect the power sample effort that I had mentioned earlier. But then again, you also know that he has been a really pioneering figure when it comes to the efforts to treat n of one types of ultra-rare forms of ALS with his trials on first, but then I know he has expanded that in partnership with n-Lorem under the umbrella of Silence ALS program that he has launched. And we are incredibly proud to be associated with that program, and to be partnering with n-Lorem, and with the Columbia University to give seed funding for that, and we are certainly looking forward to expanding that partnership because that very much aligns with our overarching mission to treat all forms of ALS, and as you know, with ultra-rare forms, these are not, since the the number of people worldwide who have these mutations are so small, it is not a commercially viable option for pharma biotech companies. So, we at Target ALS certainly feel that it is our moral imperative that, as a nonprofit working on ALS, we do our level best to further these endeavors that n-Lorem and Columbia University have right now started.

Stan

Well, I think we're entirely in tune with each other about that. These patients who have these nano-rare mutations are desperate, and a commercial solution isn't achievable. And so, we've very much enjoyed the interaction with Silence ALS, Target ALS, all of the other sort of elements there. And as I understand that, you and Dan Doctoroff are in the process of raising a much larger fund that should allow expansion of the effort broadly, but also with regard to the extremely rare forms of ALS that we're interested in helping in n-Lorem.

Manish

Very much so, and really as you mentioned, all the credit goes to Dan, and his vision to found a Target ALS, but also his commitment to scale up the ability of Target ALS to impact the research. And we are committed, as I said, our mission is to find treatments for all forms of ALS and the treatment of ultra-rare forms of ALS is a major component of our sort of what we call the seven-pillar strategy that we have moving forward. So, I expect that starting next year, the community will see a much larger commitment from Target ALS to accelerate the efforts and always as you said, the keyword is to collaborate and accelerate. So those are the operative words when it comes to our efforts to working with you as well.

Stan

Well, we very much look forward to that. And right now, we're working on one patient, and even that is an extraordinary event in the history of drug discovery, that two organizations would come together to focus on helping a single patient. You want to tell us about that?

Manish

Well, I mean what I would say is one could say it's a single patient, but it's not a single person being affected because each person is connected to so many others, and to me that is the sort of gratifying take away that I get from that, it is the amazing feeling of if one could treat even one person, I think that's a crack in the glass ceiling, if you will, for the ALS patient community. And I think it goes far beyond that, the ripple effect, because it's the lessons learned from that one study can have a far wider impact, and that's how we see this effort, is that by treating multiple, let's say ultra-rare forms of ALS, the lessons learned could certainly, and we hope, will point in a direction that will be applicable to the more common forms of ALS, 90% of the cases are sporadic, so in the end there are some common final pathways, and if we can identify those by working on these different familial forms, I think we may find those answers that we are all seeking.

Stan

Couldn't agree with you more. You know, I think what people sometimes don't understand about science is that to understand complex problems, we reduce to the single variable changes and then work from there. And patients with nano-rare mutations present a single variable that has actually caused the disease, and from that then we can extrapolate many important lessons, and we expect to be learning a lot about ALS with our collaboration with Silence ALS.

Manish

Yes, I think it's important to note that although we are talking about what one would call a clinical study, but related to this clinical study under its umbrella are several programs which are what one calls preclinical to understand the fundamental biology underneath these mutations, and that is where the information clean would potentially lead to solutions for other forms of ALS.

Stan

And the beauty of antisense technology is it is specific. So, if we set out to adjust one target, we will adjust one target, and out of that we'll learn what happens with one target being adjusted, and that's a remarkable opportunity to learn in the right test subject human beings while helping them.

Manish

Yes, I mean when people ask, I think this is one of the most hopeful times in the landscape of ALS research and part of it is, at least a major factor is, the availability of this expanded toolbox, and the fact that it's being leveraged not only by the private sector, but by the nonprofit sector now, which is, I feel absolutely remarkable what you are doing with the n-Lorem Foundation, it was a key piece of the puzzle missing, and I think we are just so excited that we have now the opportunity to work with you to make a difference in a bigger way.

Stan

Well, it's mutual. We're very excited to be involved in this. Our goal is to help these patients and learn from them, and I think we share all those motivations. And so it's a match that's ideally made, and we look forward to expanding it.

Manish

Very much so couldn't agree more.

Stan

Any anything I haven't asked you, Manish, that you'd like to tell our folks who are interested in what we're doing.

Manish

You know, I think we, I think we covered like most of it. I think the one thing I would add is that sometimes when people think of, and the topic we're discussing is about clinical trials, and sometimes when we talk about Target ALS, we are known for our ability to connect and break down silos between these research constituencies, academia, and industry, and furthering and accelerating translational research. But I think if people look a little more closely, they will find that what we are doing is we are really funding fundamental biology, but fundamental biology, with an eye on translation. That is a little bit of a nuance, which I think would be important to point out that it is really through quality fundamental biological research, which is the harder thing to do, can one possibly get to potential solutions for this disease, and that's important to note.

Stan

I couldn't agree more. I mean, we are products of the work that preceded us. We stand on the shoulders of the people who did that work, right.

Manish

Me too.

Stan

And so it's been a great pleasure talking with you, Manish, and even a greater pleasure to work with you, and Dan, and Neil in furthering the treatment of patients with ALS. And we look forward to continuing to expand that relationship in the coming year. So, thank you very much.

Manish

Thank you, Stan. It's a pleasure and you know it's quite a privilege every time to get to talk to you. And of course, we, as I said, are looking forward to expanding this partnership to make a difference for the patient community.

Stan

Thank you.

Narrator

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. This video is hosted by Dr. Stan Crooke and produced with the help of the following professionals. Thank you for watching.