

Linked Clinical Research Centers and their Effect on the Rare Bone Disease Research Community

Dr. Sandesh Nagamani MD, FACMG interviewed by Tracy Hart, OIF CEO

Tracy Hart: Hello and welcome to the Osteogenesis Imperfecta Foundation's monthly podcast. My name is Tracy Hart and I am the CEO of the Osteogenesis Imperfecta Foundation. Each month, the OI Foundation brings you information about the diagnosis and treatment of OI presented by an expert in the field of OI and rare bone disease. The podcasts are a part of the ongoing educational effort of the newly formed Brittle Bone Disorders Consortium, part of the National Institutes of Health's Rare Diseases Clinical Research Network. The professional education activities of the Brittle Bone Disorders Consortium are led by the OIF. Our podcast today will focus on the Linked Clinical Research Centers and their Effect on the Rare Bone Disease Research Community.

We're very excited to have with us today Dr. Sandesh Nagamani. And Dr. Nagamani is with Baylor College of Medicine, and is the Director of Clinical Research, Molecular and Human Genetics and the Director of the Clinic for Metabolic and Genetic Disorders of Bone.

Dr. Nagamani, thank you so much for being with us today and being part of our podcast

Dr. Nagamani: Tracy, thank you very much for having me it's wonderful to be with you

Great, we're going to get right into the first question. The Linked Clinical Research Centers are something that are very near and dear to our heart here at the OI Foundation. Now, could you give us a little history about the Linked Clinical Research Centers and what types of studies have been done?

Of course. The OI LCRC was a collaborative effort between the centers across North America to improve care of individuals with OI and also advance the research pertaining to OI. All the centers included in the LCRC are rather well known for the clinical care of patients with OI and the LCRC was actually born out of foresight from the OI Foundation. The OIF not only has the finger on the pulse regarding the medical needs of the community, but it's also in integral partner in directing the research in the field. The joined initiative between the OIF and the Children's Brittle Bone Foundation the LCRC was set up sometime in the late 2000s. 2009 was the first year of funding where we initially had 3 sites; Baylor College of Medicine in Houston, TX, Kennedy Krieger Institute of Baltimore, MD, along with Nemours/Alfred I. duPont Hospital in Wilmington, DE and the Oregon Health and Science University at Portland, OR. A year later, two additional sites were added; the Shriners Hospital for Children in Chicago, IL and the Shriners Hospital for Children in Montreal, Canada. In addition to these clinical sites, the Linked Clinical Research Centers had two other sites of excellence; one was the Collagen Diagnostic Laboratory at the University of Washington that the genetic sequencing of individuals enrolled, and the University of South Florida which is actually the data managing and coordinating center for the NIH Rare Disease Clinical Research Network. This site served as the data collection and analysis center. So the aims of the LCRC were to perform a Natural History Study. This was basically to understand what organ systems are involved, how OI affects individuals over time, how do various treatments affect the bone, and overall wellbeing of individuals with OI and so on and so forth, many clinically relevant questions that could be answered.

The second aim was to sort of understand the genetic basis of OI and see how it changes in various genes affect bone. The LCRC also aimed to facilitate and integrate research across centers by helping enrollment of patients, which as you may realize, is very important in rare diseases and a critical forthcoming was to train researchers and clinicians in the care of OI and to attract new investigators into the field. The overarching goal was to provide better care and better access for patients and foster better collaboration and better research amongst investigators. One of the pivotal studies for the Linked Clinical Research Centers was the Longitudinal Study of Osteogenesis Imperfecta. This was a Natural History study that enrolled over 540 individuals with OI and clinical data were collected, genetic sequencing was done, this was done in a uniform basis across all sites and there were measures to check the quality of the data. All of this has generated a wealth of information that we are now still analyzing to sort of answer clinically relevant questions as well as foster research for the future. So that, in a nutshell, is the OI LCRC for you.

Thank you and I have a quick follow up question. You said that the Natural History Study was done in a uniform fashion and that was one of the primary objectives of the LCRC, correct, is that everyone would be asking the same questions in the same way, doing the tests in the same way across all of the sites, is that correct?

That is very correct. In rare diseases, because you don't have enough patient population at any site, if each site were to do their own stuff, the collection of the data, the way in which the data were collected, the amount of data collected, all would vary. Putting them together would have been a problem. The LCRC facilitated collection of data in a uniform fashion so that we could agglomerate and have a large sample size to look at multiple things that are important from both the clinical care and the research perspective.

Right, thank you. So, let me ask you another question. In what ways have you seen OI research progress with the centers? Do you feel as though having something like the LCRCs has spring boarded (for lack of a better term) OI clinical research?

I have to put out a disclaimer: I may be biased because I was involved with the LCRC. But, if you would trust me to be objective in spite of the biases that creep in, I personally feel that the LCRCs have had a significant impact on OI research. When we are faced with either research or clinically oriented questions, For example, if one were to ask "what are the pulmonary functions in OI? What actually happens to these?" The first response that comes is "oh, we should mind the data from the LCRC and find out" and this has almost become the norm when we can go back to the data and look at it. This was not possible a few years ago. This LCRC data was very valuable and this process was really important is underlined by the fact that the LCRC was the foundation on which the Brittle Bone Disorders Consortium, a new NIH funded Rare Disease Clinical Research Network, was funded and formed recently. The Brittle Bone Disorders Consortium has not only the sites included in the LCRC, but a few more. The BBD's fostering studies that help get evidence based answers to many clinical questions help identify new biomarkers, and explore novel therapies. This has helped us enroll many new clinical sites and increase the access of not only care, but also research, to patients. So I definitely do think that LCRC was a springboard for OI related clinical research.

Great, thank you. Can you talk a little bit more about study recruitment? I know in the OI community, our community is very interested in participating in studies. Can you talk to us a little bit about what you saw (I hope it's not an unfair question to you Dr. Nagamani) from our community. Were they very involved, were they very passionate about being part of this Natural History Study? In my opinion, we have a very savvy, well-educated community as far as research is concerned, I think you saw that as well.

Absolutely. I think none of the research in any rare diseases, like OI, would be possible without active involvement of the patient community. It blows my mind that many of them have to travel, drive hours even, to get to a clinical site to come in, but they take time out of their personal lives and do it, because it's almost an altruistic sense to them- their participation helps OI research and the OI community at large. And it's not only the involvement that I think is critical, the voice of the OI community and their input in the direction of research are all quite critical, according to me, as to where we proceed as a field and how we make the care better for individuals with OI. I think that both the advocacy groups, such as OIF, and the patient community in large have a very critical role in the research in this field.

Great. And I know it's very exciting that we've had some of the findings published from the LCRC, and you touched on that a little bit, but could you talk a little bit more about that?

Yeah, I'd love to. As you would very well know, rare disease research is hard because no single site would have a huge number of patients and again as we alluded to earlier, the data would not have been collected in a systematic fashion, so that making analysis using robust statistical methods would be a bit harder. But what the LCRC did was to facilitate all of this much better so what we have is multiple data points from their medical history, their family history, their genetic mutations, their fracture history; all of these we put together. There are two major studies that have already been published – one is a cross-sectional study about the clinical characteristics in OI which told us what would be the proportion of individuals with a particular subset of OI, let's say with a particular phenotype. What would be the bone density patterns in a milder form of OI as opposed to a more serious form of OI? Are there any correlations between some of the clinical characteristics in OI and, let's say, fractures or bone mineral density. This was the first publication that was published in clinical genetics and more recently we asked a question that we, as clinicians, often get asked: When there is prenatal diagnosis of OI, what would be the right mode of delivery? Many clinicians did feel that because cesarean section was done under controlled circumstances, this would lead to less trauma to the fetus and thus, probably doing a cesarean section was better in terms of fracture outcomes at birth. We looked at the OI LCRC database and given the number of patients we had, and given how well the data were collected, we were able to show that it doesn't matter whether it was via vaginal delivery or C-section, the type of OI is what determines the at birth fracture risk, and there was not a difference between the birth fracture rates whether the child was delivered via C-section or via vaginal delivery. While there are multiple layers to such simplistic interpretations that I got, if you look at our publication it really gives an evidence based method as to how to approach this and I think that that's one of the achievements of the LCRC. We are now able to answer clinically relevant questions based on evidence, and not just personal experiences.

Very exciting. I want to go back to one thing before we go on to the next question. When the OI Foundation first brought about the idea of the Linked Clinical Research Centers with the OI Medical

Advisory Council and whatnot, it was very important that adults be a part of the effort as well. Can you comment a little bit on that, why it's so important to have both the pediatric population and the adult population- especially in a rare disease like OI?

Yes. I am an internal medicine trained doctor and I typically take care of adults with OI. I think one issue that patients with OI face and we're still struggling with is most pediatric hospitals are well-versed with the management of patients, but once they turn 18 or 21, depending on the hospital policies, they can't be cared for at the pediatric hospitals, which means that they have to transition their care to an adult ward which basically doesn't have much knowledge about a genetic condition. In the LCRC, the representation of a good number of adult patients was pivotal to see the natural history in these adults. As we know, they don't fracture so much, I think, as the pediatric population. What we would want to see going further, is to sort of understand how treatment modalities are different for adults as opposed to children, and what are the newer age-related complications super imposed on OI? For example, once somebody turns 55, how does general age related osteoporosis compound the already existing bone problems? These are questions that are very important so the fact that we had both pediatric and adult patients in the LCRC was quite important.

Yeah, sometimes the word data doesn't sound very exciting, but to us it is. Because we actually have the information now, which is very exciting.

That is true.

So here's a term, Dr. Nagamani, that we hear a lot. Translational research. You are one of those researchers, clinicians, that do both kinds of research, and you see patients as well. Can you talk to us a little bit about how important that is, do you see challenges there, what's exciting about the translational research to you?

That's sort of a term that's thrown out quite often and the people would defer on what constitutes translational research. As I see it, and many probably would agree, is translational research is where your laboratory research is used in order to make a difference in patient related outcomes when the science in the laboratory tries and helps clinical care of patients and vice versa, the observations in patients lead to hypothesis and mechanisms that can be tested in the laboratory. It's sort of a bidirectional process, where both the clinical and research rounds inform each other and interact with one another. While, in the common disorders, this may not be the norm, in rare disorders many clinicians who do provide care are also involved in the research of the diseases to a large extent. As I said, the thing with rare diseases and clinical care of patients and finds are quite closely linked. The research and clinical care are sort of complimentary in making translational research quite attractive in this field. The challenge to this is that there are not too many training sites that can train a translational researcher. You have to be in one of the academic centers, you need to have a good mentor who is not only a strong scientist, but has a chemical perspective and would be able to bridge the gap between the bench and the bedside. You would need laboratory and clinical research opportunities, and most importantly collaboration with other leaders in the field where you interact and work with them to complete what is called circle of translation, when you take something from the bench to the bedside.

The challenges that you asked me about this are conducting rare disease research is a bit difficult given the rarity of conditions, many patients are not local, they have to be flown in and it entails a lot of cost, a lot of effort on the part of families. In many rare diseases the complex natural history is not even known, so if you were to have an intervention you wouldn't know whether it bettered the condition or if it did not do much for altering the course. And even if one were to intervene you don't know what end points to consider when you're designing a clinical trial. The disease is quite variable, as most genetic diseases are and so it makes painting everybody with the same broad brush strokes suboptimal. Funding mechanisms again are a bit more competitive and harder to come by. So there are many levels to rare disease research being complicated, but I think over the last few years with the NIH, the private foundations, as well as patient advocacy groups, there's been a big push towards rare disease research to better the understanding of rare diseases.

Wonderful, thank you. We just have a few minutes left but I wanted to make sure that people understood that the Linked Clinical Research Effort has ended as far as the LCRCs, but it is now part of the Brittle Bone Disorders Consortium, so that we are encouraging people in the OI community to join the contact registry. Our gathering of information from people has only just begun, it hasn't ended, is that correct?

That is very correct and I think that the gathering of the information and participation of the Brittle Bone Disorder Consortium is very critical for us to move forward to get a good amount of data to answer all of the clinically and research relevant questions. I would say that, given that we've already gone through the LCRC, moving forward with the BBD, we are even more careful in what data we are collecting, we've had the experience now of a few years to know what really works and what does not work as well as expected so we have made fine-tuning to the data collection processes and it's very critical that the OI community that participated before continues to participate in the BBD effort.

Wonderful, you can count on all of us here to be partners moving forward. In the last minute or so, is there anything you would like to say to sum up what we've talked about in the last 20/25 minutes?

I really am very excited to move forward with the Brittle Bone Disorders Consortium. If you go onto their website, you will know all of the studies that are being conducted in the Brittle Bone Disorders Consortium. We're also planning one of the first targeted therapies for OI, which is inhibition of TGF-beta using an antibody in collaboration with an industry partner. Again, this sort of exemplifies some of the bench to bedside sort of research which the Rare Disease Clinical Research Network is promulgating right now. I think it's quite exciting to see how we've come up with new biomarkers for diagnoses and new treatments for the disorders. One thing with the rare disease research is that it typically tends to have some impact on a more understanding of the bone biology in general. You may know this, rare bone diseases almost account for 5% of birth defects and studies of many forms of rare bone diseases has been pivotal for coming up with treatments for the garden variety osteoporosis. For example bisphosphonates, denosumab, etc. These are medications that were basically driven by an understanding that was secondary to rare genetic disorders. From the OI perspective, I think we will learn a lot about some of the signaling pathways and matrix signaling could have an impact farther than just the OI community. So I'm really excited about the direction of the research.

Well we can't thank you enough for your support, for all the work you're doing on behalf of people living with OI, we really thank you. We thank you for doing our podcast today. People can find out more information about all the things that Dr. Nagamani was talking about today at our website, www.oif.org, and the podcast will be housed there as well and through our social media. Dr. Nagamani, thank you so much for joining us.

Thank you very much for having me. It was wonderful to speak with you.