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Conversations in Tinnitus:

Hubert Lim on Neuromodulation and Research Behind the Lenire Device

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Welcome to *Conversations in Tinnitus*, a podcast of the American Tinnitus Association. The American Tinnitus Association is a nonprofit organization dedicated to research, advocacy, education, and support for people who live with tinnitus. *Conversations in Tinnitus* podcasts are an extension of ATA's magazine *Tinnitus Today*, the only publication dedicated to educating the public and practitioners about ongoing research, treatments, and management of the condition. [music]

Welcome back to *Conversations in Tinnitus*. I'm John Coverstone, along with Dean Flyger. And joining us today is Dr. Hubert Lim, who is an associate professor of biomedical engineering and otolaryngology in the – at the University of Minnesota, I suppose, and also the chief scientific officer for Neuromod Devices. So welcome. Thank you for joining us today.

Hubert Lim (HL), PhD

Thank you, John and Dean, for having me. Excited to be over here and finally out of my house, out of my home.

JC:

Yes. It is nice to get out of the house. Yeah. You have been involved in some research that Dean and I, I know, have been watching really closely over the last few years because it is in support of a device that's showing some real promise for actual tinnitus treatment. And I, like every other person working with patients who have tinnitus, kind of have to tell them, "No, we can't make your tinnitus go away. All we can really do is manage it and help you to deal with it so that at least it's not a bothersome source of background sound like it has been for me for many years. But there is nothing out – there's no pill you can take. There's no device that, truly, can make your tinnitus go away." And then this research comes out five or so years ago, and Dean and I have talked about this a little bit. We'll bring people up to speed – I'll maybe have you do that – but bimodal stimulation was showing some real promise, and now you are working with Neuromod on a device that employs that strategy to actually help with the tinnitus itself.

HL:

Yeah. Yeah.

JL:

So, remind us what the basis is in research for what they're doing.

HL:

Sure. Sure. And I don't know if you mind, I'll start with some history of kind of how this happened.

Dean Flyger (DF), AuD:

Yeah, absolutely.

HL:

Yeah. So, my research has really been starting in 2000 at University of Michigan doing my PhD. It was in auditory prosthetics, so cochlear implants. And through that research in my PhD, I moved towards developing like an implant electrical stimulation implant to be placed into the auditory midbrain. A lot of that, okay, I was a bit naive. I thought everybody in 10 years from 2000 would have brain implants, and obviously, you see Elon Musk, so it's not so far-fetched. He's building this brain implant company. But the idea was that I wanted to get more channels of information into the brain so you could really try to get more natural hearing. That was the vision. Things worked out quite well. We did animal research at University of Michigan. I worked

with some amazing, brilliant clinicians at Hannover Medical School in Germany, where we were able to start a clinical trial and actually implant several individuals who are deaf who didn't have an auditory nerve, so they couldn't get a cochlear implant, and they also had tumors. So they had to get their tumors removed, and at that time, we were able to implant our device into the inferior colliculus auditory midbrain, the hearing region of the midbrain.

And, of course, the goal was to get into the central region of it. And we ended up, in a kind of unexpected way, getting sites in this more outer region of the inferior colliculus, where the patients said they had paresthesia, this kind of somatic sensory feeling. But what was interesting is two of the patients who had tinnitus, we actually had it that stimulating some of those sites while they had the paresthesia, they actually had their tinnitus suppressed. And so then, kind of for me, that was my entry into tinnitus because it was kind of like, "Whoa. Why the somatic sensory pathways?" And there are many groups working on interactions of somatic sensory and sound. Of course, you know Dr. Susan Shore, which I believe you had on this podcast.

JC: Yep, we talked to her.

HL: And so it was really fascinating for me. So fast forward. I get to University of Minnesota in 2009, and I really wanted to look into this, but I didn't want to do an invasive approach, though I still did look at ways to access those pathways with cortical stimulation, with midbrain stimulation, finding ways to modulate and activate that nonauditory pathway to try to access what happened in those patients. So instead, I looked, also, at can we stimulate, electrically, the body? And the idea was that people were already showing that if you stimulate the body, like the foot or other regions, as Dr. Susan Shore was doing as well, and sound, you could actually start to change the coding patterns, right, of cells in your brain that would be relevant for auditory with tinnitus treatment. And we just decided, "Let's stimulate lots of body regions, lots of sounds, lots of delays, and let's just see what happens." And so I'll get to some mechanisms and how we think it's working, but long story short, we just found that tongue stimulation, electrical ear stimulation seemed to be two regions that could drive a good amount of changes in the brain, and that's just with those two pathways. So that's how I ended up – my lab, if you follow what I do at Minnesota, and there's been people in Minnesota who have been part of our studies, they've been involved with electrical ear and sound stimulation, but it was smaller scale. And then, with Neuromod Devices, I was able to work with them with tongue and sound stimulation on a larger scale. So that's just some history, but then we can get into more about kind of the science mechanisms as we move along here.

JC: Right. And it's interesting. When you mentioned stimulating different parts of the body and even having success stimulating the feet; it kind of makes me think of things like acupuncture or acupressure, where –

DF: Yeah. Eastern medicine, basically.

JC: Yeah.

Yeah, exactly. Exactly. I mean, do you think there's a correlation there?

HL: Yeah. So there's a few ways to look at it. For me, I've been involved with the brain stimulation world not just for tinnitus but – yeah. As you know, in the Twin Cities, we have some of the most brilliant people working in neuromodulation. And when you think about – for example, Parkinson's tremors and those with Parkinson's disease, they don't have refined movements, and then suddenly, they get this deep-brain-stimulation device, where it, with electrical artificial patterns, stimulates the brain. But it's not like they're restoring this refined movement. It's just pulses sent, and then

suddenly, their tremors go away. And there's a new company called Cala Health, where they're electrically stimulating the wrist, and they can also help with these tremors. Right? There's people who have rigidity, and they can't move, and then you play sound, or you tap them, and they can start walking, right, and moving along. So what it tells you is that there's things happening in the body where your brain has just kind of deviated, right, the network. The brain network has deviated. And then, if you just kind of stimulate and perturb that network – that's the belief I have – then you could, potentially, kind of bring the brain away from the tinnitus. Right? So that's one view of it, and we could go even further about kind of how we tried to do that with the Lenire device, the bimodal stimulation.

JC: Yeah. And I mean, we've talked a lot over the last few years on this podcast about just the fact that pathways in the brain have gotten disrupted and didn't recover properly. That's really the predominant line of thinking right now for why tinnitus exists. And then also, how we can maybe address it is re-disrupt those pathways, and then I think, at that point – and correct me if I'm wrong, but I think we're just kind of hoping that they recover properly.

HL: Yeah. Yeah, yeah. Yes. Yes. And I think there's different ways to tackle it, and that's why I think it's encouraging. And I don't know if you all knew this, but – I'm sure you did – there are multiple groups working on this concept of pairing stimulation. My lab was working on it, Dr. Susan Shore at University of Michigan, Neuromod Devices, and even Ross O'Neill, who's the CEO of that company. He was doing this type of stuff for his PhD in the 2000 to 2010 time period. And all of us were finding that we could modulate and alter brain patterns that seemed promising, encouraging for tinnitus treatment. So I think that's the key thing for me. Right? Because when you think about all this bimodal and neuromodulation, you kind of wonder, "How in the heck is this working?" Right? But when you see multiple groups finding similar consistent findings, I think that's where you start to say, "Okay. There's something really there, but now we've just got to optimize it and fine-tune it for each person." Right? Or as many people as we can help.

DF: And clinically, I think it's always more helpful from the rehab standpoint to look at technique but also look at equipment. I think patients can buy in a little better if it's actually tied to a technique or a piece of equipment that is helping them, rather than more of a counseling model. I know we have to use everything, and you always want to use everything in your grasp, but using the neuromodulation really, probably is going to get really good traction with the patients eventually when we get it all sorted out.

HL: That's right. And we hope so. And we think of it as maybe – there's different ways to use it. I mean, use it alone. Potentially, it could be used together with these different approaches. For me, it's just whatever can help the patient, the person, whatever combination they need, and it's not one size fits all. So I think that's the part that we do our best to make something work for as many people as possible, but it may be a combination of things that are effective for some in the future.

JC: Well, and to speak to what Dean just said, I was just looking on Neuromod's website at the devices. They've changed since the last time I saw them, and you probably know when that was. But they're smaller, they look a little more refined, and kind of cool looking actually.

HL: Thank you. Thank you.

JC: No, but they –

HL: Not my doing. We have some great engineers in the company. We're not a huge operation. I think that's the thing people – we ran large-scale studies, and we're making a presence, but I think people always ask, “Why are you taking so long?” And, well, sure, we're a small operation, and we're working lots of hours. We're trying our best. But I give credit to the engineers for really spending a lot of time to make that device look nice.

JC: Yeah. They have. But then, the other side of that too, and this is kind of where I wanted to lead to next, was you guys are doing a ton of research, and – I almost hesitate to say it, but I'm going to say it – I don't think everybody has in this area. But you guys are doing a monumental amount of research with a device not even available in this country, and that speaks volumes to me. But I'm particularly excited about the outcomes, so tell us a little bit about that. Because you're doing multiple clinical trials–

HL: That's right. That's right.

JC: –and you're well into this, and what have you seen so far?

HL: Yeah. So I will give credit, honestly, to a few of the leaders in the field, and you all know them. Dr. Berthold Langguth, you're familiar with, obviously, in Regensburg, and also, he helped initiate Tinnitus Research Initiative, TRI. We also have Dr. Deb Hall, which all of you are familiar with, from the University of Nottingham. And, of course, Dr. Sven Vanneste, who was at Texas but now in Ireland, Trinity College, and also in Belgium. They three have been super helpful in guiding our clinical trial plan. And, of course, from the company, the investors, Fountain Healthcare. They all saw the importance of saying, “Okay. This is a challenging topic and a condition that we want to address, but it's not going to happen with just small pilot studies and kind of dabbling around here. We need to run large-scale studies and try to make sense of what's going on.” And so they really have supported that, and it's not just, “Okay. One study, we're done.” Our first study, we had 326 people enrolled, but then we've got the second study, 191 people enrolled. Right? And we don't want to stop there. We want to keep moving along, and one study builds on the other study.

So to give you context, the first study, it was an exploratory parameter optimization study. The challenge we have here is that we don't know what the best parameters are, and so the idea behind here was that there are so many parameters we need to test, and that's the challenging part. Right? And you could try to test everything, but you need thousands and thousands of participants. So we actually made three different treatment groups that had bundled parameters in them, and the paper talks more about it than the article that you're writing, and we can get to that too. But then the idea was we made them different enough so that we could assess how different features are contributing to the therapeutic outcomes. And then we could then figure out, at that point, for the next study, how we could hone in on more specific features. And that's what we're doing for the second study. We have a protocol paper that's been published, so people - we're trying to be transparent - they can download that now, see what we've done in that study. Same thing with the first study. We've also had a protocol paper that people can see the results of what's going on in the published paper. But that was the idea of that study. And in terms of outcomes, I don't know if you want me to go into detail now or kind of lead into it.

JC: Sure. Yeah.

HL: Yeah. So some key findings that we found, right – we had three different arms. The first one, you could think of it as a synchronized stimulation treatment group. We had sound that was paired with tongue stimulation, where we play, for example, one

kilohertz, and that would be paired with a given location on your tongue. We'd play two kilohertz, another location on your tongue. And then we would randomize that from trial to trial. Right? And that was our synchronized stimulation. And then we had a second group where we added some delays to that stimulation and also jumbled up where the tone was mapped to your tongue. And then a third parameter, much longer delays, slower presentations, but we even shifted the frequency range to lower frequencies. So those were the three parameters. We had two endpoints. One was to show significant improvements in all three arms, within arms, and then we also had a second primary endpoint where we wanted to show differences between the arms. We used two outcome measures: it was Tinnitus Handicap Inventory (THI) and Tinnitus Functional Index (TFI). So we hit our first set of primary endpoints, where we showed significant within-arm benefits. So all three treatment arms showed to be effective. Right? And we had, for those different questionnaires, about 14 points on average, give or take for each of those arms.

JC: Which is pretty significant.

HL: Yeah. And it –

JC: That's a big change.

HL: Yeah. So it was encouraging by that. And if you just look at how many points, at least some change in THI, TFI. I have some numbers here. We had, for TFI, 81.2%. Right? Or had some change in TFI score, and we could get into kind of how much is significant or not. And then THI, we had 86.2%. Right? So regardless of how you want to measure this, I mean, that's quite a high percentage. Now, just for full transparency, if you look at our publication – and this was recommendations by Dr. Rich Tyler, and we appreciate his feedback. He guided us. He said, “You need to plot all the data. Put all the data out there, and let people interpret it.” So that's why we've got 20 plots in our paper. But if you look there, you can see every point of each person and how much they improved. And so we leave it up to the community to look at that plot and make their own assessments, but the data's there. It's all there. And so that was within-arm. Now, the limitation of the study, for us, and we mention that as a limitation in the paper, is that we didn't see between-arm differences across the three arms at the end of treatment. So that was our second set of primary endpoints. However, what was encouraging for us was two factors on that. That when you looked at the long-term data, which – by the way, this was really pushed by our Dr. Berthold and Sven and Deb – was really to track the long-term effects because that's what has been missing in the field. So we went out to 12 months after the treatment ended. I mean, that's not easy to do, but it was done.

DF: Yeah. Wow. Because you've got to keep track of all those people.

JC: Yeah. We've got to keep track of lots of people.

Yeah. It's not easy.

HL: It's a challenging thing to do, and I think people in the field know how challenging that is. But what we saw was that – we were seeing a lot of the individuals, the participants, have sustained improvements out to 12 months after the treatment stopped. Right? And–

DF: That's fantastic.

HL: Yeah. To me, that's the most surprising thing. I didn't expect that. Because I've done bimodal stim in my lab, we've seen Dr. Susan Shore's data in a seminal paper that was also encouraging that had residual effects that were out at least three weeks, but 12 months was – it was astonishing to me. And then we saw that arm one had the most

sustained effect, and then arm three, which is the most orthogonal to it, started to go back to baseline, and then arm two was somewhere in the middle. So this is where we do believe stimulation parameters matter, but it doesn't seem to matter during the treatment on the short term. Where we think it's happening is on the long term, and that's where we believe this bimodal neuromodulation, this long-term changes in the brain, it's consistent with that concept. Right? But now, of course, we've got our second study to really start to dive into what features – so all of the things we added into those stimulation parameters, which ones are really driving the therapeutic outcomes.

JC:

Yeah. And to give some context to that, because I think that's important and especially for people who aren't reading this research on a daily basis like we often are, one of the things I always come back to with any new devices, any new treatment methodology in the world of tinnitus is how does this compare to a more traditional approach or even a placebo-type approach? Because I think all tinnitus professionals, and I've been in rooms with them, and we've talked about this, do believe that's a huge effect on tinnitus. I mean, I literally have had people come into my office for a first appointment and say, "My tinnitus is better just because I scheduled this appointment. It's literally gotten better just because I called you, and I did something about it." And so we know that's a pretty significant effect. And there are studies, if you go back far enough, where they have taken populations of people and paired them by virtually identical measured tinnitus. Now, we do know, now, that measuring tinnitus, it's almost like measuring quantum particles. It's a moving target. And so we know it's not super reliable, but by grouping them in terms of people that had the same tinnitus, they found, pretty consistently, about half of them have bothersome tinnitus and about half of them don't.

And I think all this plays into the fact that, in my mind, and you can tell me if you think something different but about 50% of people probably will have tinnitus where they have a more bothersome reaction to it, and about 50% of people probably will be helped just with the placebo effect, probably for a lot of the same reasons. Because I think a lot of it has to do with psychological state of mind, and we know stress and anxiety affect tinnitus and things like that. And so that's kind of what I look for, and to date, for me, and a lot of people aren't going to like me saying this, but I have not seen a device that I feel exceeds that threshold. And, in fact, there is some data to bear that out. And I can think of one device where they went outside of the company, had somebody do some independent research, and they were not very happy with the results. And so that's what's really excited me here is this bimodal stimulation is showing an effect well beyond that threshold that I hold in my mind for what anything would do if you just stuck it in front of a patient and told them it was going to be effective, whether it was or not. This actually seems to exceed that, so that's what excites me about this.

HL:

Yeah. And thank you, John, for those encouraging comments. And I want to be cautious because, as we were writing this paper, we went back and forth, obviously, with our team: Deb Hall, Berthold Langguth, and Sven. We were thinking about, "How do we compare this to other studies and give a context of it?" And it was challenging because, as you know, there's so much data out there, there's different ways things have been run in the studies, and so I don't want to compare too directly kind of what the other studies have shown or not. But I will give some examples where they have presented some data, and the most closest would be, for example, Dr. Susan Shore's study. She's a great scientist, and she's done great research. That pilot study that she ran, she had her auditory only, and she'd had her bimodal stimulation, and so that gives you a glimpse of what can happen if you're doing bimodal versus sound only.

Right? And you start to see some separation there, right, so there's something going on.

You look at historical controls, right – well, sorry – maybe I'll define that a bit. But when you look at people who have control groups in their clinical studies – and you could tabulate a lot of the data from those, whether it's like waiting to get a treatment, or they had an actual control or a sham condition – and you look at those values, on average – we have looked at those, but you'll get a few points in some studies. There was also the Desyncra study and MicroTransponder studies, and they have some data in there. But you'll get a few points. Sometimes you can get 5 to 10 points. Right? And so if you look at what we're getting, we're getting 14 points on average, right, on these things. So you could look at – there is some separation there. But then, if you look at the literature, of course, there's quite a bit of data out there that have variability, so I want to be cautious with that.

And then, the other piece is that when you look at many different approaches – and you can comment on this, actually. I'd love to get your thoughts on it. But if you look at acoustic maskers, or you look at hearing aid approaches, how many of those studies – they haven't been done systematically but will show a 12-months kind of sustained effect. Right? So this is where, again, all of it, to me, is pointing towards something's going on in the brain. Of course, we need to continue with studies to really nail that down, what's contributing and how much of it is contributed to placebo, how much is it contributed to sound, how much is contributed to the tongue and bimodal component? And those are things that we're continuously striving to achieve with the second study. And now, as we move forward in my lab – and once COVID lets up, I'll be able to do more research in my lab.

JC: Right. Well, and I would go back to some of the research – Dean, do you remember that study Jim Henry and the folks out at the Portland VA NCRAR came out with, oh gosh, five years ago, maybe? Maybe more.

DF: Yeah. Five or six years ago.

JC: And they actually did look at straight masking, which is actually covering up the tinnitus, versus TRT – tinnitus retraining therapy – Jastreboff's approach. And so they looked at – I think they had three different modalities, at least, if not four. And they did look at the long-term effects of that, and they did find that many of those benefits abated over a 12-month period. And I believe there was some benefit out to 18 months, but there definitely was a decline as you got the person out of that therapeutic approach. So there's a little data out there on that.

HL: Yeah. And we were trying to look for that. We had talked to a few people like – obviously, Berthold knows quite a bit, and we talked to Dr. Rich Tyler too, and everyone – there's just a kind of awareness, I guess, with audiologists and clinicians as well that once these kind of sound treatments or other approaches stop, the tinnitus tends to go back. Right? And I think that's where we felt – we tried to look for some more data, but there's just this feeling that the sustained effect is something that's happening in the brain, so that's where we're – we're quite excited about that.

JC: Well, and if that could be an organic sustained effect, so to speak, rather-- for instance, I think that sometimes the reason sound therapy does have a limited effect once you stop it is if we're not addressing the source of the bothersome tinnitus, which, in my mind, is, 9 times out of 10, maybe 10 times out of 10, psychological. And if we're not addressing that, then simply taking away that sound leaves them in a state where that tinnitus is still going to bother them. And if we don't address that psychological component-- and I probably over refer, compared to a lot of colleagues,

to psychology for that reason, and I do a ton of counseling. That was always a bit of a deviation I had, I'll say, with TRT. TRT kind of wants you to explain neuroanatomy to the patient, but I always believed that it fell very short in terms of actual counseling with the patient and addressing the psychological effect, which I always felt was huge in tinnitus.

DF: Well, and, John, don't forget the emotional effect. I mean, it's psychological, but we're talking about that condition that puts some people into perpetual fight and flight and perpetual peril. And you have to break that cycle along with using whatever you can. So that's really the hard part. There are some patients that come in in great distress, along with other things. Example: the VA patients we see. Typically, they come in with tinnitus, maybe some hearing loss but definitely some PTSD, and all of that has to be addressed at some point.

HL: Yeah. A very good point.

JC: Yep. And so to bring that back around to what you're doing, the fact that you have a sustained effect without addressing that psychological component – I mean, you're not talking about people that have also gotten counseling – then, to me, that's profound. And that's why I'm so excited about this is because I've never seen that happen before, literally. Well, nobody has.

HL: Yeah. And we're trying to figure out for those individuals-- obviously, there were a subpopulation of them that did return back towards baseline, so those are the ones we also are interested to find out kind of what extra we can do to drive even stronger and longer-lasting changes.

JC: Well, and from our standpoint, and I think every single one of these podcasts, even, I've done, we talk about not only what you just mentioned, but we want to know, as clinicians on the front end, how do we separate our patients? How do we identify, "You need this. You need this over here. You need this other thing"? That's what we are really lacking. And Grant Searchfield did some work on that a few years ago. He did a literature review, and that was, basically, the conclusion. We just don't have the data right now where we can make clinical decisions, saying, "You need this. You need this. You need this," based on your presentation or type of tinnitus or whatever would identify it. So if you could tease that out, that's additionally exciting to us as clinicians.

HL: Yeah. That's a very good point and, definitely, a challenging one. But at Neuromod Devices, in my lab, many groups, that is definitely on our radar. That is something we're trying to figure out. We approached it more kind of with groups that we could define in the field. We looked at those with hearing loss, a certain amount of hearing loss, types of hearing loss. We looked at different age categories. We looked at type of tinnitus sensations they get, somatic tinnitus, somatic sensory-based tinnitus or not, also hypersensitivity to sounds. So we did do some of that, and that, actually, will be presented in the second paper that we will publish. But we're also taking a different approach because sometimes when you create those buckets, those categories, we're making those somewhat arbitrarily. But now, we also have so much data that we are trying to take a big data approach - well, it's not big data like Google big data, but like little big data - and trying to take it all together and really, without any prior assumptions, try to kind of make some sense out of what combination of things may be predictive of who would benefit this the most and which parameter. So that's something really exciting from a researcher side, and, of course, that's something I want to push forward once our labs can start opening up again.

JC: Absolutely. Absolutely. Well, and what's your feeling on some of the very different types of treatments that we've seen out there? Some people are doing magnetic stimulation versus sound therapy, and some of the research showing potential damage in the synaptic cleft of inside the inner ear between the nerve and the cochlea or damage along the eighth nerve or in the brain stem or, in the case of the transcranial magnetic stimulation, possibly in the prefrontal cortex. All these different sites being identified as contributing. Is that possible that that's an explanation for maybe why some people are benefiting, and some people are not?

HL: I think yes. I mean, to a certain extent, always the source or the underlying mechanism of what's driving their tinnitus. I don't want to say too much on that because I'm not as familiar with some of those conditions and kind of what we-- there's just not enough knowledge in the field to say kind of what's driving that or that.

JC: No, I agree. Yeah.

HL: But I will say, at least for the neuromodulation side and kind of perturbing the brain, like you said, with magnetic stimulation, TDCS – so this is – sorry. For the term, it's transcranial direct current stimulation, and you put some electrodes on the skin surface. And there's others like vagus nerve or on-the-body acupuncture, electroacupuncture, things like this. I'm very open minded to those things because I do believe that tinnitus is representing itself, in some way, a network of cells, right, that are just shifting the brain to a certain state. And the reason why I believe that is because it's not like you've lost your refined ability to hear, and it's not that somehow things have changed so much that you've got to somehow reorganize the circuits to make the tinnitus go away. And we know that because you could do some interesting things where, then, you could shut it off temporarily. So it doesn't mean – because if you think you've got to relearn to shut it off, then there would be some kind of re-circuit mapping. Right? Not for everyone, but for a lot of people, it's about perturbing it to shift away, one way or the other. So I do believe that you can use magnetic stimulation, transcranial direct current stimulation, and these other approaches to kind of shift the brain. But the real question is how do you keep it shifted, right? And that's where –

JC: And those have not done that at all. It's been a matter of hours, in many of those studies, where they've gotten benefit.

HL: Yeah. And the question is, if you do it longer, would it work? A take-home device or you try to combine modalities, right? And the most classic that we all know is Pavlovian conditioning. And we all have heard – and I don't know when – I don't even know anymore as I'm getting older, too. But some time in, probably, elementary or high school, we learned about the dog, and it was–

JC: That's right. Ringing the bell. Yep.

HL: –ringing the bell, and you bring food. And it salivates when you ring the bell. But it's all about this pairing, and the brain likes patterns. Right? So if you can kind of reinforce whatever you're providing to shift it away, then you can have more long-lasting effects. And in the auditory field, we're not new to this, right? I mean, it's not something – in my lab, we've done this research. But we're talking 30, 40 years ago, there were quite impressive experiments, sophisticated experiments where they were pairing, for example, a tone one kilohertz and then stimulating the leg or the body and showing that you could make cells in the auditory brain which maybe weren't as sensitive to that sound to become more sensitive, and they became tuned to that sound. And you could do that with just a few pulses, and the more you did it,

the more you could cause these changes. So all we're doing is leveraging that concept and then taking it one step further to present many different stimuli and make the brain more aware and sensitive to lots of different stimuli. And, in turn, relatively speaking, right, distract it away or shift the brain away from the tinnitus tone. So that's kind of the idea.

- JC:** Right. Yeah. I'm just looking forward to that next round. It's probably still way down the road, but where we take a large population. It's like we give them a certain type of treatment, and then, "Okay. That doesn't work." Then we try this one, and maybe we start teasing out what these different things can do for different people. But I think we're a ways from that because we're still kind of trying to come up with the first one that really works long term. And maybe we have that here, but it would be the first one, so.
- HL:** Yeah. Yeah. I totally agree. I would love to be at that stage.
- DF:** And just to reinforce and to back up a little bit, you were talking that one of the components that you might tease out later is addressing hyperacusis. Wouldn't that be interesting if that is a byproduct of this? That would mean for us – in the clinical field, we deal with hyperacusis often, and if that can be another modality that we could use to lessen that, I mean, that's good for audiologists, that's good for patients. That's an exciting thing to think about.
- HL:** Yeah. It's a good point. Yeah. We don't have enough data at this stage, but definitely, it's something we're always keeping a lookout for.
- JC:** Yeah. Well, and I think every neuroscientist I have ever spoken with that works in this area is absolutely convinced that probably everybody with hearing loss and tinnitus has some degree of hyperacusis. And so I don't know what you're feeling about that is, but that's something that I've just heard time and time again, and we maybe don't measure adequately in the clinic all the time.
- HL:** Yeah. Yeah. And even for me, I – so I know there's been some discussion about even those who have tinnitus who don't have hearing loss at all, but I do believe that there is some modification in their hearing, right, and that is kind of the baseline. Maybe not everyone, but a high percentage of people with tinnitus have some modification of their hearing, and whether that hearing manifests itself as hearing loss or also some readjustment of hypersensitivity, but I think that something like that is there for most of the people with tinnitus.
- JC:** Right. Right. So–
- DF:** Yeah.
- JC:** Go ahead.
- DF:** No. I'm just saying yes. I'm agreeing. [laughter]
- JC:** So talking about this device itself – because I do want to talk a little bit about that. I know our listeners are going to be really curious. Talk about the device, what it kind of looks like, how it works. We don't have one here in front of us, but.
- HL:** Yeah. And so if you go to the University of Minnesota website, or you also can go to Science News, they had some links where – I'm in no way as sophisticated as you are here, John and Dean, with your setup. I just went to my lab and bought a \$20 mic and got my iPhone and a \$20 stand, and put it up there and just did a video where I showed the device and put some clips in, kind of, of the component. So that might be useful, and I could send you the link if you want to share that with your audience. But basically, it has three components. It has headphones that everyone would be familiar

with – these headphones are Bluetooth – and then it connects to a controller. It's just a rectangular, white device that has some buttons on it for turning it on and the volume and adjusting intensity, and then it has a cable that then goes to this paddle. It looks kind of like a lollipop. It goes onto your tongue. And I have to give credit to the engineers at Neuromod Devices. They designed it where you would think it might be kind of bothersome to just leave it in your mouth or a nuisance, but I've done it so many times. You just put it in your mouth, and it's curved in a way that when you shut your mouth, it slightly pushes down on your tongue, and you almost – at least, for me, I always forget that it's in my mouth. And then it sends some electrical pulses to the tongue, which – I used to describe it as Pop Rocks, but Pop Rocks – and maybe when I was younger, I didn't realize it, but it was actually pretty intense. Because recently, we bought Pop Rocks to give it away at our booths, and I put it in my mouth, and actually, it's pretty intense. So it's not like Pop Rocks.

JC: Pop Rocks were. Yeah. [laughter]

HL: It's more like a fizzy – like a soda. Even less than a soda. It's just kind of this tingly feeling on the tongue.

JC: Okay. Like maybe an Alka-Seltzer or something on your tongue, is it?

HL: Yeah, yeah, yeah. It's kind of like tingly on your tongue, and you combine it with the sound then, and that's pretty much the device. You wear it 30-minute sessions. For the clinical trials, we recommended one hour per day, but we specified minimum 36 hours for the 12 weeks. So about three hours per week is what we made as the minimum criteria.

JC: Okay. All right. Did you track how long people used it to see–

HL: That's why–

JC: –whether there was a different effect?

HL: Yeah. So we had sensors, and we could tell how long they were using the device for. So in the paper, we also show, in the 20-plus plots that we have in there, our figures. We also have one showing how much device usage that each participant had, or at least those who came back that we could track.

JC: And did you find much of a difference between those on the lower end and those on the higher end?

HL: So I have to say that I was quite encouraged because the majority of the people used it quite a bit, and so we only had a small number of points that were actually very low usage. And you could see in the plots. So it's hard to do a correlation plot when everything's bundled up around high usage. So I will say, though, it was hard to say any kind of trend because the majority are pretty much using it a large number of hours.

JC: Well, they were motivated–

HL: Yeah. They were motivated. Yeah.

JC: –obviously.

HL: And we had about 84% that used it minimum 36. And then, of course, some we didn't have come back, so we don't know what happened to them. But there was literally just a handful that we had the device that we could track that didn't use it for 36 hours or more, so that's kind of – yeah.

DF: So a fairly uneducated question here, but I want to take us back to baseline. So you have your tongue stimulator. I would like to call that the Kojak effect if we could put a label on it for those people that are older. [laughter] Does the patient have control?

HL: See, I don't know what that is, by the way, so you're going to have to--

JC: So you're going to have to explain that to Hubert. Yeah.

Yeah. To me too.

So--

HL: I'm probably the older but younger generation [here?].

DF: In the '70s, they had a TV show, and it was a detective, and he was Telly Savalas. He was this bald guy, and he was really – he stood out. But his deal was he had lollipops, and so he would pull out his lollipop and solve the crime. [laughter]

HL: Well, thank you, [Dean?].

DF: Anyway. So, lollipops were a Kojak thing. So, coming around patient control, does the patient have control over the intensity of the stimulation or is that tightly controlled?

HL: So, we set it up initially during the fitting process. So, in fact, the headphones are set up per their audiograms, so their hearing thresholds, and then the tongue stimulation is done during the fitting session, where the professional will adjust the stimulation so that it is just superthreshold and comfortable. And then, when it's actually used on a day-to-day basis, it'll always reset to that baseline, and then the individual can adjust, within a limited range, the sound volume as well as the tongue stimulation. Because we realize, I don't know, maybe someone ate something spicy, or maybe someone just woke up, and they're extra sensitive in the morning, whether the sound – so they can adjust it a bit to their comfort.

DF: And is the intensity matched? In other words, is the acoustic intensity matched to the stimulation on the tongue?

HL: Oh, they can independently adjust the two to their comfort level. And we realize they may be – I don't know. Their kids are at home like my kids are these days, and it's quite loud, so they may want to put up the volume a bit more. By the way, I love my kids. I just want to say that in case they listen to this.

That doesn't mean they're not –

That's right.

JC: It does not mean they're not loud, though.

DF: Yeah. Well, thank you for answering that. I was just curious.

JC: Well, that's interesting, though. Have you done anything yet to look at those various parameters, how people are self-adjusting, or force them into a certain level and compare those with people at a different level just to look at the outcomes of that? See, this is my research brain going. It's –

HL: You're just like me. Those are the questions I bring up always to the group and to the investors, and they're like, “Hubert –”

JC: “Stay on track.”

HL: “–stay on track.” Yeah. Yeah. No. Those are very good questions. And we have so much data, it's hard to get through all of it, but that's one thing I'm interested in

further looking into. With over 500 participants and data collected, there's so much things we can analyze. Yeah.

JC: Absolutely. With that in mind, I just want to thank you for joining us. We've been talking with Dr. Hubert Lim, who, again, is an associate professor of biomedical engineering and otolaryngology at the University of Minnesota, as well as the chief scientific officer for Neuromod Devices.

HL: Well, thank you, John and Dean, for this opportunity. Really appreciate it to share our company's product but also some of kind of the history and my experiences and the trajectory in this research field. And as always, we're working hard, the company but also on the research side, and not myself but many people in the field, that we're trying to make a better treatment for all the people suffering from tinnitus. [music]

JC: The American Tinnitus Association is a nonprofit organization dedicated to research, advocacy, education, and support for people who live with tinnitus. Gifts and donations to ATA are used to support research for a cure and other critical missions described on our website at www.ata.org.