

TINNITUS TALK

— PODCAST —

EPISODE 20



## THE MAN WHO DONATED A MILLION DOLLARS TO TINNITUS RESEARCH

### 00:00 Brian Fargo's background and getting tinnitus

**Hazel:** What would you do if you had a million dollars to spare? Maybe spend it on something nice for yourself or your family or maybe donate it to tinnitus research, for instance? Welcome to the **Tinnitus Talk** podcast. I'm Hazel, your host.

A while back we read a good news story about a man who had donated \$1 million to tinnitus research. Now, we all know how underfunded tinnitus research is so that's good news all around. But who is this guy who felt compelled to donate so much money for tinnitus, and why? Well, we have him right here with us – Brian Fargo, welcome Brian.

**Brian:** Thank you for having me.

**Hazel:** We're going to hear all about Brian's personal story with tinnitus, and the motives behind his donation, but before we get there, I would like to introduce our other guest. He is Dr Hamid Djalilian, Professor of Otolaryngology at the University of California. His team is the recipient of this donation. Welcome, Dr Djalilian, or I have been told I can call you Hamid?

**Hamid:** Yes, hi Hazel. Thank you very much.

**Hazel:** Great, so, Brian, let's start with you. Can you tell us a little bit about yourself and what it is you do?

**Brian:** Well, let's see, I'm in the video game development business so I've been on computers since I was 18 years old. Barely got out of my chair. So, when we had to sit home for Covid it was like, no big deal, I've been doing this my whole life but anyway, so, video games have been my whole life and you know I am fortunate that I do what I enjoy, and I have done well with it and then as far as it relates to this subject, I've never had a medical issue my entire life until this one.

And it's very different you know, I've always run my own companies and, you know, as an entrepreneur there was always a way around every obstacle. You could fix everything somehow and this is probably the first time in my life I hit something, and I just can't make it go away, you know. Well, not yet anyway. So, it was quite a change for me to experience something like this.

**Hazel:** So, when did you develop tinnitus, and how?

**Brian:** Well, the 'how' is a good question. I'm not quite sure. It started maybe 15 years ago but it was just a little bit of ringing. I'd hear it go up or down. People couldn't hear it. I could, but it wasn't a big deal and I used to love green tea and I would drink those green teas and it would make it a little bit worse, so I'd cut back. But then it was about four years ago it went to another level, to where it was, like chime bells while I'm trying to sleep, and it translated to where I could physically feel it. You know, either sizzling, coming from my head or it was in my frontal lobe in the beginning and so I didn't know what was going on when I moved into that stage and that sent me on kind of this big, long journey. It's how I met Hamid. I think my story is similar to other people, you know but it is dissimilar in that, I've had the money to go and try everything. You know I float around the world in TMS treatments, and you name it, you know, I've probably tried it. I've had the ability to do so and the money to go to do so and so, you know, it's quite a journey because you quickly discover if you have something like this and I'm sure this applies to other illnesses, you have to become an expert in it yourself, to a degree. Not like the doctor himself, like he could vertically go down much further information-wise, but I need to know a lot about all the different treatments and all the different things and see what applies to me and does anything make me feel better.

And then I think the big component of it is hope. That's like number one to me. It helps you just kind of get through it. I always found it difficult, like I love the Reddit tinnitus research. Love that stuff. The open tinnitus stuff I felt really bad for these people, as you could read the despair, but it was difficult, like I didn't want to read it. I needed to focus on the more optimistic stuff. You know, what could I do. And again, we'll get to that part. A little bit about how I ended up with Dr Djalilian.

## 05:01 Dr Djalilian's professional background and interest in tinnitus

**Hazel:** So, I'll ask you to tell us a bit more in a moment about which treatments you tried and how that ultimately led you also to connect with Hamid. But Hamid, could you first tell us a bit about your professional background?

**Hamid:** Sure, so I'm an Ear, Nose and Throat physician, so an Otolaryngologist. I sub-specialise in the ear. So, the sub-speciality is called 'Neurotology'. I actually have always been fascinated, since

I started my training, with tinnitus and trying to find out how to solve it. So, when I was in my residency I just thought, what is the most difficult problem there is and how can it be solved? So, I tried to do a lot of reading about it, and you would see these papers that apparently were effective treatments and so I would talk to my professors, and I would say 'why didn't this work and why didn't that work, why can't we try such and such', and so that was my initial fascination with it. When I was in my residency training, through my speciality training I actually conducted a randomised clinical trial in antidepressants because I saw somebody had actually reported with four cases that they found where it was effective and then I read that there was another type of antidepressant that had been found to be effective, so I wanted to see if it actually did work so we started out but couldn't finish as I'd finished training. But I sort of had this thing in my mind that I've got to solve this problem and then when I came to UC Irvine, I thought, OK, I have a good team that I can work with here and let's try to come up with an idea that can hopefully solve this issue and so that sort of evolved into the current project that we've been working on.

**Hazel:** So, I am interested to hear a bit more about why you are so interested in tinnitus. Because I've looked up your research profile and I saw a strong focus on head and neck surgery and also tumours in that area like acoustic neuroma. I can see how some of that stuff might be connected to tinnitus, but I'm still interested to hear what was it specifically that triggered your interest?

**Hamid:** My fascination is really with the big problems. What is a difficult problem? How can I potentially solve it? I've always thought about various ways of attacking the problem. So, something like tinnitus for example. Doing something that hopefully can cure it but also, those are more lofty goals. You know doing something where we could restore hearing of course, that could also probably solve tinnitus. That's also a very long-term thing. It could take 20 or 30 years of work to be able to get a potentially cell-based treatment that would restore hair cells for example and then potentially improve tinnitus. But then I also think about how else could we deal with this problem using maybe potentially a device? What is the fundamental question or problem that we need to solve, that would solve this issue? And could that be done with a device, could that be done with molecular pathways addressing those or could it be done with medication potentially?

And so, I always try to think of multiple different ways and tinnitus is really one of those things, at least when I started learning about it, is that it seems like there is really nothing out there that appeared to work for it and there was very poor understanding of it. This was in the mid-1990's. We might have a little bit better understanding of it now but about 25 years ago when I started my training there really there was really not as much known about it as we do know now. And there is a string of uncontrolled studies of various drugs and things and so I thought ok let's try to do this in a more scientific fashion. Try to do it with controls. Do all those things that we should

do when we are conducting clinical trials to see what we can accomplish and attacking it in multiple different ways. So, the project that Brian has been so generous to fund is one of several aspects of tinnitus that we are trying to attack at the same time.

### 09:41 Understanding the mechanism of tinnitus

**Hazel:** Ok, well I will ask you for sure to tell us more about that, but you also alluded to the importance of understanding tinnitus in order to treat it and I agree that I think any successful treatment of tinnitus needs to be based on some kind of underlying model of how tinnitus works. And, of course, we know that the trigger is often in the ear but the phantom sound is created by the brain but there's not really one unifying theory of the exact mechanisms involved and where exactly in the auditory pathway the triggers lie, so do you have a theory on this?

**Hamid:** As you said, basically the initial trigger is at the ear level, and when I say ear, I mean the inner ear and the nerves that are connected to the cells that pick-up sound, our hair cells. And this is our theory that there is a loss of hair cells in the cochlea or there may be loss of the connection between the nerves and those cells, what's termed 'synaptopathy' so the synapse is the connection between the nerve and the hair cell is sometimes lost, especially as a result of loud noise exposure. We think that's where the trigger is and that there is probably a kind of a looped pathway between the ear and the brain meaning that as long as there is input going up to the brain that keeps the brain, if you will, at its normal what we call 'gain' so that the information coming in is then translated into speech and whatnot but if there is loss of cells in the inner ear or loss of connection there is not as much input going into the brain so the brain senses that reduction and then we believe that sort of increases what we call the 'central gain', meaning that the brain is trying to turn up the information.

Now, based on animal studies that have been done one of the things that happens is that when there is a loss of cells in the particular zone of the cochlear when they targeted the specific zones with noise exposure, what they have found is the cells in the auditory cortex that do that function of those frequencies are then kind of redistributed to do the adjacent frequencies. For example, when they cause damage to the 6000 hertz area of the cochlea, the area that coded for 6000 before the damage were then doing the work of the 4000 and the 8000 and a lot less of it was doing the 6000 hertz as aren't that many cells there and information coming in. The change also increases the baseline activity of the brain which then we think that's the combination of the central gain and then what's thought to be maybe a loss of what's called environmental masking. Basically, not as much sound information getting through the ear to the brain.

So, the central gain, redistribution of activity and then loss of peripheral masking are probably the three factors that lead up to tinnitus. The question is why is it that some people have hearing

loss and don't have tinnitus? We don't have a great answer for that just yet. There's still a lot that has to be figured out. There probably is some element, we believe that this is a significant element in tinnitus, of the attention of the brain to that activity. For example, you have a watch on, your brain's not constantly aware of the fact that you have a watch on, because if the brain were to pay attention to all these peripheral pieces of information it wouldn't be able to do all the other things it needs to do like perceive speech and produce speech etc. So, the brain puts that stuff into the background signal and that's probably what happens. Some people are able to push that into the background signal and some people's brains pay more attention to it and we believe that the loudness of the tinnitus, the ups and downs and the loudness probably has more to do with the attention than a continuous fluctuation in the hearing level or cell levels.

**Hazel:** Just to clarify when you say that some people are able to filter out this tinnitus signal whilst other people perceive it consciously, you're not talking about anything that happens at a conscious level, right? These are sort of subconscious processes, or both?

**Hamid:** Correct, I mean most of it is probably subconscious. Probably a portion of it that is conscious in that there are people who, for example, continuously track their tinnitus so, I have patients who come in with big charts and a calendar and day to day and that sort of attention to the tinnitus will definitely make it sound louder to them. So, the more they pay attention to it. One of the classic things when I am seeing patients, I ask them how loud their tinnitus is and they say, well now that we are talking about it, I am paying more attention to it, so it seems louder to me. So, I think most of it is subconscious but there is probably a conscious element to the whole thing.

## 15:02 Which treatments Brian tried

**Hazel:** So, Brian, can you tell us a bit more about what treatments you tried. You said you went through this whole process of trying out different things and how did that ultimately lead you to connect with Hamid?

**Brian:** So, in the beginning, again it was probably a bit like a lot of people, you go to your audiologist. He's usually your first stop and they put you through the different listening tests and, sure enough, you have tinnitus you know. Here is the frequency that your hearing loss is at. There's nothing you can do. Let us sell you some hearing aids and that was pretty much it. You know, the hearing aids, they didn't help me, and I tried all the different kinds, like the Lyric that goes all the way in your ear, and you can't hear it and that was like being at the bottom of a tin barrel, listening to people talk from 20 feet away. I couldn't stand that. But I didn't want the ones like an old man, so I tried all the different ones, and I tried three different audiologists. Everybody would say, go to this one, go to that one.

So, I wasn't getting anywhere you know, other than just to buy hearing aids, so I started doing research on different things. Lidocaine patches, whatever, all the different stuff that you read as you start that journey. But one of the things I noticed is when I would go in for an appointment for an adjustment on the hearing aids or whatever, I would ask them about this study or that study or this thing that was going on, but they really didn't know anything outside of hearing aids. And when I'd bring it up – you know when you're telling somebody something and they have no interest whatsoever? - I could tell the doctor but he's not going to look into it. It was patently obvious, so that struck me that they don't really want to solve this and so I'm really on my own here. I've got to start diving in. One of the first things I did just because it just was randomly, I was driving home one time and I saw this place called The Rejuvenation Brain Spa, and they do TMS Treatments and they did some imaging and they showed how this part of my brain, you know, near the cochlear were red compared to the normal person. Anyway, I went to 30 sessions of TMS.

**Hazel:** TMS is Transcranial Magnetic Stimulation.

**Brian:** Stimulation, yes and you're not being electrocuted but it feels like it sometimes and it's hitting all sorts of parts of the brain, and sometimes you'd go home sometimes and it's oh my gosh but, let me tell you I powered through it all. And remember, this is about the time that I met Hamid. I could tell he wasn't wild about it, but he was like, we'll meet soon, you know. Do what you need to do, you know, contact me. I met him through a mutual friend of mine whose father he helped.

As a side note, I remember going to lunch with someone who was my best friend at the time and saying, oh my gosh this is really starting to affect me. I can feel it, it's loud, it's hard to hear people in restaurants. I don't want to go to restaurants, and he said, do you remember Roger? Yes, he had the same thing. He killed himself. That was the first thing. I thought 'oh gee, thanks for the pep talk on that one, Tom'. But that just kind of threw it out there.

What I wanted to do was just to make sure it was tinnitus, so I did MRI, FMRI, Spect MRI. I did every possible thing, looked at it to make sure nothing else was going that so that was confirmed. But I saw the top neurologists to try different things out. Most of the neurologists say the same thing. "Work out," they said. They didn't give a lot of hope. I had a mild sleep apnoea so, hey, let's see if that affects it. So, I got a CPAP. I think Hamid actually got that one for me.

I tried the TRT, the CBD treatment. That just wasn't helping me. They were surprised because I had a physical sensation with it and that is very unusual so that's when they prescribed me

different things and Hamid also had success, I think mostly with people who were new to having tinnitus as opposed to people who had had it for a long time. So, it was: migraine medicine, a low dosage antidepressant would help people out, Topiramate, Paxil, Nortriptyline, Gabapentin, Elavil, you know, just about everything under the sun, I was willing to give it a try. Then sometimes there were combinations so then you were like "well maybe I'll mix this and that" and some things would make my head sizzle off the chart, and I'd do it for like six or eight weeks pretty much every day in pain and I'd get like I can't do that one anymore and I'd give up.

I was able to fly to Ireland and pick up the Neuromod device. I was really hopeful on that one, you know, very hopeful and it just didn't help. Hamid's great because I'd read something online as a layman and get excited about it, and I'd send it to him, and he'd say there's no control group etc. I shouldn't have been excited, you know, based upon it's that thorough research on some of these things. So that didn't do anything. I got a hyperbaric chamber, meditation, acupuncture, microtoxin tests, sauna with red light tubing, UV tubing, red light up your nose ...

The only thing that is really helping me out at this point is meditation does help because it allows me to take my thoughts off of what's going on. If I really focus on my breathing. You know I tell myself if I was a meditation master, I could probably make it disappear in a second. If I was the guy on the mountain top for 20 years, I could do my thing and it would go away. And I'm way down here and he's way up there, but you can if you just focus on your breathing you can distract from it.

The other thing for me that's helping, and this one doesn't help everyone, I take a very low dosage Klonopin, like a milligram per day. It's quite small, I don't even feel it, but it just calms the nerves a little bit and just makes my days more bearable. Night-time it seems whatever my brain does at night, and if I go to sleep for an hour and then wake up and it is where it is and so I have to play masking so I can go back to sleep but those are the only two things where I've had some relief.

As with everybody you have good days and bad days. You try not to search for patterns because you know some people say you'll never find it but you kind of can't help it. What did I eat? Did I have sugar? Did I do this? If I have red wine, it's going to irritate it. Sure as anything. But sometimes, do you know what, I'm going to have red wine I'm going to pay the price. I don't have it that frequently, but other days, lack of sleep, for sure. There are some obvious things that do it but other days I'll have a lot of sleep and I'll have an unbelievable day and I'll have a one out of ten and other days I will have slept well. I've just got back from Hawaii, and it was great, and I was sleeping as long as you want, laying in the sun, I had several days that were bad and it's not like I was stressed. Anyway, you're always looking for patterns is my point.

**Hazel:** Yes, that sounds familiar Brian. In fact, many of the things you've said sound dreadfully familiar, including physicians who are not interested in understanding tinnitus unfortunately. I must say you've tried almost everything almost that is even remotely available or remotely thought to maybe help with tinnitus so I can imagine that you get really tired of going through that medical stuff.

**Brian:** I was getting ready to fly to South America to try Ayahuasca, or whatever that stuff is. You do get desperate. So, I do want to say that I finally got introduced to Hamid and so why I gravitated towards him is he was well-versed in what everybody else was trying. He had his own, I don't want to say 'silo', but he does have his own focus and is well aware of everything else that was going on and so I was talking about all these different things, he had a knowledge of a lot of them. And that made me feel good.

He was like, we can make this better. We can do this. It wasn't this or that or this or that. He was very positive about it. He was positive backed up by science. Not just a friend who had a positive attitude and so that drew me towards him and then he had some success with a particular device which I'm sure you guys will talk about, that got me excited and kind of felt I think that some people's tinnitus is in a different part of the brain. I mean, I don't know but with mine I just feel that the electrodes are sort of over-firing somehow. When he described what he was doing it felt consistent with what I was experiencing.

Then I guess the last part to your point earlier is there is just no funding. It's really awful. I remember Dr Rauschecker. He did a great TED Talk. It was logical and had some good points that he made but it's on his website. He can't raise \$10,000.

**Hazel:** We tried to help him with that, but it's really difficult.

**Brian:** A lot of people if they have tinnitus. My attitude is like, if you could make it go away tomorrow would you pay a \$1 million and most people would say yes, assuming they had the money, but there isn't enough research going on, so he can't even get \$10,000, but I have been following Dr Shore as much as I can and supposedly that's coming any minute but even they are trying to raise money for marketing and I'm not quite sure where that's at. Anyway, my attitude was that there wasn't enough money being put into this and I'll be one of those guys who puts money towards the research, and hopefully something great comes of it and provides hope for people.



**Hazel:** And so, when you first met Hamid how did he help you specifically because it sounds like you had pretty much already tried everything so was he able to help you with specific treatments or was it more that he was taking the problem seriously and that gives me hope for the future?

**Brian:** Yes, the things that he was trying to help me with in the beginning, one, was he was trying to steer me away from certain things so that was of value, but the other thing was we tried some of the low-dosage antidepressants and things like that. Correct me if I'm wrong doctor but they seem to tend to help people who haven't had tinnitus for a while where I've had it for a decade, only it just got worse about four years ago, so I wasn't getting relief, but I was like, yes, this guy is very serious and very passionate and very knowledgeable and wants to solve this problem. So, I think that stuck with more than like he prescribed something and, oh my gosh I feel better. It wasn't like that.

### 27:53 Dr Djalilian's work with inner ear stimulation

**Hazel:** So, let's get back to the Doctor. Hamid, what is it specifically that Brian's donation is funding?

**Hamid:** Sure, I'll give you a quick background so that it makes sense. So, one of the things that for years I wanted to try. I mean we started this idea in 2006 of actually stimulating the inner ear electrically to be able to basically send a nerve signal to the brain. Because just the quick background is, when you lose hearing, you generally lose the hearing cells, the hair cells. You don't lose the nerve cells. The nerve cells will remain alive for many, many years afterwards. So, the one solution would be to regenerate the hair cells, reconnect them to the nerves and send the signal naturally to the brain. But while hair cell regeneration has been done in animals the reconnection of the nerve to the cell has been a task that no-one has been able to accomplish and people have been working on it for 20 years and I thought we could go the molecular route but that's going to take many, many years and we may not be able to do it.

But I said, what can we do with a device potentially? And we know that a cochlear implant, which is a device that restores hearing for people who have lost significant hearing is basically an electrode that goes inside the inner ear, the cochlea, and from there stimulates those remaining hair cells. And in those people, about 70% of them will have significant improvement or disappearance in their tinnitus when the nerve is being stimulated. But the problem is most people with tinnitus don't have a significant hearing loss so we can't put a cochlear implant in people with tinnitus. So, what is the next best thing would be to try to stimulate the cochlea from the outside somehow to be able to stimulate the nerve. So that was the initial sort of concept.

As we were contemplating doing the electrical stimulation through the ear drum, we had a patient who'd had a cochlear implant who'd gone deaf in one ear had a cochlear implant for the purpose of tinnitus. When they did the implant, they actually couldn't get the tinnitus to get better, so they sent the patient to my colleague Fan Zeng who is in our department. He is a professor, and he is a cochlear implant researcher, and he did a lot of different things to try to make this tinnitus go away and he was finally able to find a certain stimulation that would make the tinnitus disappear. That motivated us and we thought if we can find something very specific that will extinguish the tinnitus electrically could we do that with sound? So, we both kind of went the route of trying to find a sound therapy solution to tinnitus.

So, we each had our own different system that we developed. His became a device and mine became a software and so we basically did that for a while and over time I realised what we are able to accomplish with sound therapy, even though I think the sound therapy that we created. I mean, we tested it, it was more effective than white noise, but we're still not making it disappear in people. And that's what everybody wants. We all look at medicine we say, ok, can we improve it and that's what the studies are saying. Well, we have 20% reduction or 30% reduction in the tinnitus. But if you ask a bunch of patients, what do they want out of your tinnitus therapy, they want this thing to disappear.

And so, once we'd tried our sound therapy for a while Dr Zeng and I got together and said, look, let's try to put an effort into doing this electrical stimulation of the inner ear. If we could accomplish that in a way that doesn't damage the hearing, then we should hopefully be able to get the nerves to stimulate the brain and then the brain to quieten down and the tinnitus to go away. And that's how we arrived at the initial idea and then we did some initial experiments and we got funding from the National Institutes of Health to do experiments where we stimulated various points.

We started actually on the scalp because we wanted to be minimally invasive or non-invasive and we were trying to figure out if there is a pattern of where we can stimulate through the scalp and get it to concentrate into the cochlear on one side hopefully. But what we found, unfortunately, electric stimulation dissipates through the skin. It spreads through the skin. It doesn't penetrate bone very well so you can't get precise stimulation on the inner ear from the scalp.

So, then we tried the ear, the outer ear, the front of the ear, the ear canal and then finally we tried the ear drum itself and still while we were able to get the tinnitus to quiet down in a very small fraction of people, it wasn't enough that we would say this is something that is doing something. Let's try to figure out the next step. We tried to figure out what sort of devices to use and try to get it past the Institutional Review Board which has to approve all research and it then

required approval from the FDA to sort of experimentally do this and we went through all that process.

We were able to make a small incision in the eardrum and pass a small electrode against the so-called round window membrane and the round window membrane is the only area of the inner ear that is not covered by bone. As I said trying to stimulate through bone it doesn't work as well because the electric stimulation spreads and it doesn't penetrate the bone very well. And if you turn it up too much to try and penetrate bone you will get other symptoms as well. You will get the sensory nerves on the surface, feel pain or burning and things like that. So we put it up against the round window and that's when we saw that we were able to get about 60% of the time, we could get the tinnitus to go away and our initial couple of patients were people who had very poor hearing in that ear. And so because we weren't sure if what we were doing was going to potentially damage hearing so we started with patients who had, first, unilateral tinnitus, one-sided tinnitus, and had a significant hearing loss where they had non-usable hearing so their hearing wasn't even good enough to use a hearing aid so in that way we can't potentially damage anything and we haven't caused any significant harm to the patient. So, we did that and we found that actually it doesn't damage hearing at all and that we were able to make the tinnitus go away and one of these patients that had tinnitus for 20 years and after this stimulation for a few minutes the tinnitus went away for several hours.

And that got us very excited that we're maybe onto something, and then we started doing this on more individuals and so then we basically proved the concept that if you stimulate at the round window level you can get stimulation to the nerve and then from there to the brain and then quieten down the tinnitus.

So that then made us think well how can we do this for the long term? Because we can't have people come in and then we stick an electrode through their eardrum. We have to find a way to do this and there are basically two ways to potentially do this. One is the through the traditional approach of a cochlear implant and with a cochlear implant you have to go from behind the ear and make an incision and do a big surgery. You have to drill through the bone of the mastoid. You have to get through this tiny space between a couple of different nerves and then place an electrode by the inner ear. But the problem with that approach is that you are only going to have a limited amount of people who can do this surgery. In the United States there are probably only about 300 people who are ear sub-specialists who very frequently do that type of approach and most general ENT's would not be able to do this. And if we are going to try to help millions of people, we can't have a device that is going to be too complicated to put in so then our next step is can we do something that is essentially doing what we are doing which is to put something in behind the ear drum which allows the eardrum to close. And then we would stimulate it from

the outside so we can essentially get current to the device that is inside and then that would do the stimulation and then you would send the stimulus parameters from the outside device to the inside device.

So that was sort of what we wanted to do but developing a device like that is a very significant undertaking and it was going to at the very least take a few years of development and then testing on animals and what not and then unfortunately as you've alluded to, number one, these things cost a lot of money as we have to have people to do these things and you have to pay those people and, number two, there is very little funding for this type of research so the National Institutes of Health in the United States that funds most medical research, they don't kind of want things that aren't a sure thing. Because they want to be able to show that the taxpayer dollars that went towards research were able to accomplish something. Not that we did this great thing, but it didn't work, so what oftentimes they need is you need to have developed the device, and then have tested it, showed that it works in some people and then they will fund a larger study and until you get the device you can't really do anything and get large funding.

And so that's when Brian sometimes sends me emails about various things that he's read about and asks me what my thoughts are and he sent me something about stimulating the nerves and how that was effective and I think I responded and said, yes, I know that works and we know we've done experiments that if we can just stimulate the nerves of the cochlear we can make the tinnitus go away in at least the majority of the people. I said that's why we really need to take the next step. And he said well, tell me more about it and we talked a little bit more and he said well, how much will this cost and so I talked to my collaborators, Professor Zeng and Professor Green who was an electrical engineer Professor at UC Irvine, and I said what do you think our timeline would be, how much do you think the cost would be and so I got back to Brian.

Brian was very generous to say that he would fund it if we raised the other half of the funding. And so, we got to work to raise the other half and we were very fortunate to have a number of donors including Brian's friends who were very generous to donate money towards that. And we raised a certain amount of money and then we had about \$110,000 I think we raised, and then we had another donor who was very generous, and he asked me what I needed funding for, and I told him. I said we have this challenge from Brian, and we have been able to raise this much, but we have a gap. So, if you could help at least with part of the gap and we were just sitting at lunch and he said, call Brian, I'll cover the rest of it. So, as soon as I got back to my car, I texted Brian and I said, we've got the other half covered. So, if Brian had not put in that initial challenge and the money this would have never been possible.

So now we have been working on developing the chip on the outside device and the inside device which will be doing the communication and the stimulation, and we are now testing the chip to make sure it's doing what it's supposed to be doing and in the next series of experiments will be doing it in cadavers and animals and then eventually humans.

**Hazel:** Wow, that's quite the rollercoaster ride, isn't it? To get some to actually be able to connect to a study like that, yeah. Just to get back to the sort of mechanics of the device, it doesn't stimulate specific frequencies per se, right? It just stimulates sort of across the board?

**Hamid:** No, so you can change it. Part of the problem with electric stimulation is you have a very broad range of things you can do, so there is sort of the frequency and the amplitude and then the shape of the wave that would do the stimulation, so it could be a sinusoidal — a smooth, it could be what we call a square wave — with stimulus on and then off right away, so sinusoidal will go slowly up, slowly down. You can do it with what's called a triangular, which goes up sharply, down sharply. So, you know, there are probably hundreds and hundreds of different ways you can stimulate the inner ear and what we found is that, you know, each person is different and so we can't have a device that can only stimulate a certain frequency. We have to have a broad range of frequencies, broad range of shapes and an amplitude, and so the device is capable of doing this—that's sort of the goal— and what it would initially have to run through is a series of parameters it will run through and then see which one works for the patient, and then it will sort of learn that those are the ones that work for the patient, that patient has significant tinnitus. They will turn on and it will start to run through the most effective ones for them basically.

## 41:20 Challenges ahead

**Hazel:** Brian, how closely are you involved in the research, if at all, at this point?

**Brian:** Well, first, I've always kind of prided myself on my ability to spot people who are talented and smart, and in the video game business, you know... they're starting the business and some other people that ended up being very successful and so I feel that way about the doctor. I just I just feel like, you know, he's smart and he's passionate; he knows what he's doing. As far as being involved, I mean, I don't have anything to add beyond that they just sort of update me on what's going on in the progress and so, really it's just progress, and then, the other thing which you know, I bought, I've seen articles that sort of talk in a similar way about ways of dealing with tinnitus that have to do with electrical stimulating stuff, so I'll send it to the doctor and he's kind enough to kind of go through and go yeah, this part is similar to what we're trying to do and, you know, this particular thing in me and he knows the doctors are trying it and where they're at with

it and that sort of thing, so the doctor's kind enough to help me look at the progress that's being made on all these different fronts and let me know, kind of, what seems to have value and maybe in what part they're not being completely thorough in what they're presenting.

**Hazel:** Yeah, it's something we've seen at **Tinnitus Talk** over the years. I've followed online research and also, we run this online tinnitus community. We see a lot of sort of emerging treatments from time to time that then seem promising and then they'll get hyped. Most recently was Neuromod and Frequency Therapeutics, but I do also think people don't always understand how science works and that it's a long road filled with trial and error, which means that you know even if a particular study gives disappointing results, it doesn't necessarily mean that the treatment is fundamentally flawed, but sometimes you have to go back to the drawing board and adjust the dosage or adjust the frequency or look at a different target group — so it could mean running more trials, spending more money, waiting more years. So, Brian I'm curious how you sort of view the road ahead here.

**Brian:** I try not to get my expectations too high at how quickly anything's going to happen. You know, I'm in the software field and mean I make games and a game takes 4 years plus to make, so and we don't have to go through the FDA and we're not going to harm people and so we don't have near the hoops that we have to jump through. So I don't know. I try not to put a date in my mind. I remember I was on the tinnitus research, and somebody said, when do you think we'll really have a cure? And somebody would say 30 years, you know. And then the people say, I think we will probably have the stuff that will make us feel a lot better, you know, maybe it won't be considered a cure in less than a decade, and most people say, that's probably reasonable, you know. I hope it doesn't take a decade, but I know it takes years.

**Hazel:** And Hamid, how do you see this, because obviously you always hope that your first results will be as positive or even more than you had hoped, but, you know, are there particular things that you're worried about?

**Hamid:** So part of the challenge with obviously any clinical study of any disease really is that everyone's different, and so, you know, a single solution does not help 100% of people probably in anything that we do. We know that we're not going to be able to cure tinnitus for everyone, but we — our hope is that we can at least develop something that's going to help a majority of people in a more simple fashion, and then maybe the other sort of group of individuals it will help by — but maybe a little bit further work using the device or combining the device with the other therapies that we're developing, like medication or potentially molecular therapies, in the future.

## 45:43 What makes this device unique?

**Hazel:** And how do you think your device is different from other types of electrical stimulation devices? I ask this because, you know, if you do a quick Google search for tinnitus electrical stimulation, there's actually quite a few studies coming up. And of course, you know, Neuromod has their device that Brian also tried which also uses a combination of electrical stimulation to the tongue in that case in combination with sound therapy. Obviously, Dr Susan Shore is working on a device, what do you think is unique about the device you're working on?

**Hamid:** Sure. So the electric stimulation that, you know, the Neuromod device, and I know that Dr Lim is sort of the brains behind it, and I have great admiration for his work and Dr Shore's work. Their stimulation is really stimulating somewhere on the surface of the body, so the skin, or the neck, you know, in Dr Shore's device and the tongue in Dr Lim's device, and ours is different in that we're actually stimulating the cochlea itself in a minimally-invasive fashion. So, we're not good putting something inside the cochlea, like a cochlear implant, but we're putting something right on the outside wall and stimulating through there. So that's how ours is different; we're really going to the source. I think their devices are primarily combining stimulation of the trigeminal nerve or other nerves in combination with sound stimulation and, of course, sound and plus other nerve stimulation has been done with the Vagus nerve and other things, so while I think their devices are effective in potentially reducing the tinnitus for some individuals, our goal is really, you know, I want to purchase a cure. I want to be able to make the tinnitus go away completely, and this is the only way we've been able to make it go away completely, at least temporarily. So that's our hope—that we would have a device that people would essentially will turn it on for a few minutes and they will get hopefully a few hours of relief, and then if it comes up and it's loud, they can reactivate the device and sort of turn it on and off as as needed. That's sort of the goal, rather than a daily sort of sound therapy plus electric stimulation, which is what those other devices do now. Is it possible that we might have to add sound therapy to our thing? It's possible. I mean I don't know. It all depends on, of course, how people do once we start placing these in individual patients.

## 48:12 Getting the device to market

**Hazel:** Of course, when anyone's working on a new treatment, people always want to know when is it going to be available—when will it come to the market? I know it's often a very difficult question to answer, but can you enlighten us? Where are you now and what stages do you still have to go, and is there any prognosis for when it might become available?

**Hamid:** We've set ourselves a deadline of trying to put it in experimentally in a small group of individuals in 4 years. So that's our hope. So right now, the main thing was the initial design of

the chips. That sort of thing takes a long time and then the fabrication took a little bit extra time because of all the problems worldwide on chip shortage and stuff like that. And so all of the chip manufacturers were backed up significantly, so it took a little bit longer than we wanted for them to make the chips, but anyways, we now finally have the chip and we just got the other components that we need for the testing, and so that's sort of what we're doing right now, and as you probably know, basically when you make a bunch of them but not all of the chips are going to work, so we have to test all of them to see which ones are actually working and then use those to then do further testing and then create the distance that we would anticipate there being between the device in the ear canal in device behind the eardrum, and then testing it with the membrane in between, you know, like there would be—just do all of the various things that we need to do to make sure this thing is doing what we think it's going to do.

Then trying to make it fit into a model of a cadaver, basically, of the ear, to make sure that this can fit and will stay in place. That requires some other engineering efforts, bio-medical engineering. And then the next step after that would be to actually put it in animals and run it for a while to make sure that we're not causing any damage to their hearing. If someone is, let's say, using this for 6 months in a row, and then sort of the next step would be if everything goes as planned, then we would actually experiment to replace some in humans, but then that also requires a certain type of manufacturing. If you're going to put something in a human, it has to be done in a very particular type of way and that would then require a sort of investigational device approval from the FDA. So, there is a process to be able to do these—to get something into humans that hasn't been done before.

### 50:47 Tinnitus awareness in the medical community

**Hazel:** Well, there's so much more I would like to ask, but I know we have a hard cut off in about 10-15 minutes because, Hamid, you have your clinical practice which is also very important. I'd like to spend maybe the last part discussing awareness about tinnitus. Maybe starting with Brian. You know you've described your frustrations in sort of seeking treatment and not getting people to take the problem seriously. You've also generated a bit of media attention with your large donation. Why do you think it is that the general awareness about the problem of tinnitus is so low, and what do you think should be done about it?

**Brian:** Yeah, especially after—because I read that a lot of people, a lot of our servicemen and women coming back from war, have a real problem with it, so you think there's a lot of sympathy for those people and there's a lot of them and that might have increased it, but I don't know. I mean maybe it's kind of an “out of sight, out of mind” type of thing—like, you know, you can say Oh, my God, my head—and they're just sitting there in complete silence while you're telling them



that church bells are going off, you know. Is there some psychological reason that it doesn't make it more? I don't know. I think that as more—you know, it's typical, right? Like, you know, my donation helps raise it a little bit, and it's been great, and I can say some of the feedback, just from people who are so thankful, you know, that somebody's trying something and willing to put their money where their mouth is, and people who played my games in the past are like, oh, my gosh! You know I have tinnitus, too, and so from that level there's some kind of—it's been raised up a bit. Whenever any celebrity gets it, it's, oh, my gosh, it's terrible and so, you know, that guy from Coldplay had tinnitus. He said he addressed it; I don't know exactly how. So I'm not quite sure, you know, why it doesn't have more.

Maybe as I said just because it's invisible and there's x amount of dollars going around, but I know that it's quite serious for some people; people do, you know—extreme depression, suicide, all sorts of terrible things. So I feel like there's momentum in the space but maybe I'm just paying attention too much now, and it feels like it to me, but the optimistic side of me feels like I'm seeing more articles and more approaches. You always have to check and see, you know, it will be like this, hey, look at this great thing! And then you'll check the date of the article and it's 1995. Well, great, you know, but it sounds like some breakthrough; it's really exciting for today and then you always have to check the date. But, so, you know, I'm not quite sure why there isn't more, but it seems to be increasing.

**Hazel:** Hamid, what's your view in the medical community? From a patient perspective, we always feel like there's not that much attention to it, but how do you see that more from an insider perspective?

**Hamid:** I think, I mean, one of the problems that I think with tinnitus is how it hasn't gotten as much attention and as Brian described, the patients go to a physician or an audiologist, and in a lot of times, it's either, you know, this is a hearing aid, or live with it. Those are sort of the two most common things that happen if somebody goes to see a physician or audiologist. Part of, I think, the problem has been in at least in my subspecialty, is that a lot of physicians don't want to deal with it because, number 1: there isn't a good solution that anyone's come up with, and number 2: people in a surgical specialty like a surgical solution and there isn't a surgical solution for tinnitus, and so that's part of the problem. There's no medical solution; there's no surgical solution, so they're like, I can't do anything for you.

You know our hope is that this device, you know, of course, will do what we think and believe it will. And in the medical side, we're also working on some combination drugs that we have been doing a randomised clinical trial on, and we've been working on internet-based therapies using sound and internet-based cognitive behavioural therapy as another sort of method.

Will awareness increase? I'm really hoping, you know. I think if we have good treatments that are scientifically sound and clinical trials done in the highest level, the clinical trials should be done, which is randomised, double-blind trials, Basically the experimenter and the patient neither of whom will know what they're getting, and it's done in a random fashion. If we get randomised clinical trials showing effectiveness of something, be it a device or a medication, for example, I think that's what's going to help. If people see data and they say, okay it looks like this thing works; I'm going to start doing this.

And, unfortunately, one of the things about medicine is that there's a lot of sort of dogma that's in medicine and so it—from a time that something is discovered until it's practiced by about half the physicians in a specialty, on average takes like 17 years, which is ridiculously long, but the only way one can shorten that is by repeatedly doing studies and good studies that show the effectiveness of something. So you do a small study, then you do a bigger study, then you do a multi-institutional study. You know, these have to continuously tell people and then independent people have to be doing the study, so, you know, if I'm developing the device and I do to study, that's great, but some people will say, well, maybe he's biased; maybe he's doing something that makes the device look better. So then, you know, we need someone outside of me doing the study, so then things like that, that's how people will start treating this condition better, I think, is by people learning about what's out there and stuff. Right now, we don't have a great solution, but we're certainly working on it.

**Hazel:** Great. Well, I want to thank you both so much for your time. I'll ask each of you if there's anything else you want to share. Hamid, do you have any concluding remarks or is there anything that you still wanted to say?

**Hamid:** Sure, I mean, I want to acknowledge my colleagues and my team that's been working on not only the device but also all the other clinical trials that we have going on. You know, while I may sort of come up with the concept and the idea and people like Brian very generously support it, we need the people who are going to be in the trenches doing all the the nitty gritty work and then other sort of—and I don't have enough expertise to develop a device so I need other colleagues who are experts at what they do, and that's why I work with Professors Green, Michael Green, and Fang Ye Zheng. And I just want to acknowledge the work that everyone on the team is doing to get these treatments to fruition.

**Hazel:** Brian, do you have any final remarks to share or do you maybe have advice for people like yourself who are struggling with tinnitus and really would want to just actively do something about it as you have?

**Brian:** Like I said in the beginning, I think the most important thing is that there's a lot of activity in this sector, you know. With Hamid's work and other people's work, there is hope on the horizon and so no matter how down you feel right now, you just got to know that there's a lot of really great, smart people who are now also funded working on these problems and so I think that the hope that something there is critical. And the other thing is that none of this is going to get solved without money. I'm in a fortunate position and not everyone has extra money of any kind so, you know, that aside, but some people do have money, and so if they see researcher or they read research, it's only going to happen if the people get money, so you know I've seen some promising—like we talked about earlier in the program—where they can't even raise \$10,000 to do their tests and if you're suffering from tinnitus, since you do have money I would just implore to pick a cause, you know, whichever one they think might be best. Those would be my two things that I would say on the subject.

**Hazel:** Well, I want to thank you both so much for your time and also for your contributions to tinnitus research.

**Hamid:** Thank you very much, Hazel.

**Brian:** Thank you.