00:00 Introducing the Hough Ear Institute

Hazel: Hi everyone, and welcome to the **Tinnitus Talk Podcast.**

Hearing regeneration – It's always a big topic of discussion on the **Tinnitus Talk** forum. Now, a few months ago, we noticed that there was one particularly active thread on this topic, and it was about the **Hough Ear Institute.** It's a non-profit research organization based in **Oklahoma City,** and they are working on two new hearing regeneration treatments. And I had the pleasure of speaking with their **CEO, Dr Richard Kopke,** and their **Chief Philanthropy Officer, Justin DeMoss.**

In the interview we go into depth about the two treatments they are developing. The one that is in the most advanced stage is a pill that was discovered to be able to regenerate damaged nerve endings in the inner ear. Initially, they referred to it as the **"bomb blast pill"** because of its potential to mitigate the effects of an acoustic trauma; and you will notice during the interview that I use this term a couple of times but, in fact, **Hough** now believes the pill will have wider applications for noise-induced hearing loss, and potentially also for tinnitus. So, for now, they refer to it simply as the **"hearing loss drug"** or by its technical name **NHPN-1010**. Alright, I don't want to dwell more on this now, because you'll learn a lot more about it during the interview that's coming up shortly.

Something we're particularly excited about is that the publication of this podcast actually coincides with a big announcement from **Hough** about a new partnership. **Hough** was already partnering with **Auditus**, which is a subsidiary of **Otologic Pharmaceutics.** And **Auditus** has now entered into an agreement with another pharmaceutical company, **Oblato**. As part of this new agreement, **Oblato** is expected to initiate a **Phase II Clinical Trial** to evaluate the potential of **Hough's** drug to prevent and treat hearing loss. In follow-up studies they may test for the efficacy for treating tinnitus and improving ability to understand speech in the presence of background noise. So, this new partnership is very good news for tinnitus patients, because it means that **Hough's** hearing loss drug, which seems to have potential benefits for tinnitus as well, can now proceed to the next phase of clinical trials. So, things are moving ahead.

I should point out that while I was conducting the interview with **Hough** last week, they were not yet allowed to reveal the name of their new pharmaceutical partner, so we're talking

about **"their new partner,"** without naming them, which seems a bit awkward, but we now know they were referring to **Oblato.**

Ok, final note before listening to the interview: we always publish transcripts for all of our podcasts, because we are aware that some of our audience is not able to listen to a long podcast and we want to make sure they can still benefit from it. So, we have an amazing volunteer, Liz, who transcribes the episodes for us which, by the way, takes about 15 hours. However, in this case because we wanted to get this episode out quickly, to coincide with **Hough's** press release on the new partnership, the transcription will follow later, and should be available in about a week.

I want to thank the folks from **Hough** for collaborating with **Tinnitus Talk.** We had a number of preliminary discussions with them and they've been very keen to engage with the tinnitus community. We actually faced a lot of challenges in getting this recording done; there were several test calls and failed recording attempts because we couldn't get sufficient audio quality but **Rick** and **Justin** were very patient and persistent throughout all of this, so I want to thank them for that.

I also want to thank our **Patreon** supporters. We have 49 people by now financially supporting our efforts, and I can't even tell you how much that means to us. We don't get paid for doing this, it's a volunteer effort, so all the money goes directly into producing this podcast. Please consider supporting us through **Patreon** if you value our content.

And now, without further ado, I present to you the **Hough Ear Institute.**

04:41 Vision and origin of the Hough Institute

Hazel: So, I'm here with **Dr Rick Kopke** and **Justin DeMoss** from the **Hough Ear Institute.** Rick, can you tell us what **'Hough'** is all about? You are the **CEO of the Institute,** correct?

Rick: Sure, yes, thank you Hazel, thank you for having us today. I really appreciate it. So, the **Hough Ear Institute** is a non-profit organisation that I lead, and our vision is that all that have ears will hear. Some people have ears that don't hear well and then our mission is to restore hearing worldwide through research, teaching and humanitarian efforts. So, the research we will talk more about. But, teaching, we have ear surgeons from developing countries come and live in our homes and go to the OR with us and learn about ear surgery and then humanitarian efforts. We go to the countries where those fellows came from and I'll work side-by-side with them and just kind of have an on-going relationship and, of course, as we studied noise-induced and blast-induced hearing loss more, you can't study that without starting to think about tinnitus.

Hazel: What made you get involved in this line of work? Was it you actually who started, who created the Institute?

Rick: Well, actually **Jack Hough** started the Institute back in the 80's and he is one of the pioneers with cochlear implants and other devices to help restore hearing. So, he actually started it and then I was in the military for over 22 years and Jack and I met while I was in the

military and we became close friends. He was like a mentor of mine and because of my service in the military I really got sensitized to noise- induced hearing loss and ways to maybe reverse that. So, after I got out of the military, Jack invited me to come here and work on a pharmaceutical, or pharmacological, approach to hearing loss.

Hazel: And did you, because of your time serving in the military, personally suffer from hearing loss or tinnitus?

Rick: Well I have a little bit of hearing loss and tinnitus. We do have to do a weapons qualification, but I used earplugs, but I wasn't deployed in combat. I probably have some hunting and recreational noise damage from when I was a youth.

07:45 Introducing Justin DeMoss

Hazel: I see, and **Justin,** let's introduce you to our audience as well. What's your role at **Hough** and how did you first become involved in this line of work?

Justin: Well, I became involved with **Hough Ear Institute** just over a year and a half ago when I responded to a job posting. They were looking for someone to raise funds from private individuals and foundations and so forth, to complement the Government funds that we receive to advance research and so that is my role. I connect people with the mission and allow them the opportunity to financially support and advance the research.

Hazel: Did you want to work on hearing issues and tinnitus because of any personal connection with these issues?

Justin: Yes, so when I first saw the job posting it made me think of my grandmother. My grandmother and I had a really strong relationship because she raised me when I was a little kid till I was about 10 because my parents were both working two jobs to get us out of poverty. As such, I got really close with Grandma and Grandpa. My Grandfather, shortly after we moved and started kind of living as a traditional family again, my grandfather developed **Lou Gehrig's disease, ALS**, and he was diagnosed and within a year he had passed. So I had taken care of him during that time and my grandmother and I got even closer together and so from that point, you know thirty years plus ago, until about four years ago, my grandmother and I would talk on the phone two, three times a week just to hear each other, support each other and to continue that relationship. About four years ago, her hearing got so bad that she had to get hearing aids and hearing aids and telephones sometimes don't work very well. She has that Capture telephone that reads out what I'm saying. It's nice, but it's still far away from what it used to be, and so it's difficult for her and me. She gets frustrated and so forth and, so, we went from talking literally every single week to talking three or four times a year. So that is my motivation. I see what it does to people's relationships and, I mean, I'd love to help my Grandma if we can, but she's also up there in years so that's the urgency for me to get this research through the trials and so forth, and get it on the market.

10:21 Personal experience of tinnitus

Hazel: Do either of you have tinnitus and, if so, to what degree?

Rick: Yes. I have tinnitus in both ears pretty much 24/7. It's mostly an annoyance. It doesn't keep me awake at night. It doesn't interfere with my lifestyle too much. I notice the things that make it worse and the things that make it better, so I have personal experience of that one.

Justin: For me, my sister - who is five years older than me - when I was seven put a lit firecracker into my right ear and so, from that point I've had this ringing in my right ear and I just thought that was normal, that was just part of life. And then I started working here and then I found out that there's a name called **'tinnitus'** which is usually the term that researchers use, or **'tinn-eye-tus'** which is the term that people who suffer from it usually use and so that's where I've learned about it. It's interesting. As time has progressed, especially when I talk about it, I become more aware of it. I feel like I kind of been able to you know mind over matter it. You know, mine's very, very mild compared to what the people on the Forums and so forth, that we've been talking with experience.

Hazel: Right, so it doesn't, on a daily basis, bother you per se?

Justin: Yes, I just want to be able to deal with it, to be able to just know that it's there and it's going to go away in a few seconds.

Hazel: Yes, as you know we run a support forum where people come for help and advice from others because they're really struggling to cope. For some people you know it's beyond annoying to the point where it's debilitating, and they really can't function in daily life. They can't sleep. They shy away from social interaction. They can't work etc and face concentration issues, but I'm sure you guys are very aware of that and that's one of the reasons you guys are doing this, right?

Rick: Right. I see patients several days a week with hearing loss and tinnitus and a certain percentage of those, for sure Hazel, it's really more than an annoyance. It's really debilitating so it's a fewer number of people, percentagewise, but it's still a huge number of people that are really suffering and having difficulty coping, especially to have an answer for them would be great.

Hazel: Absolutely. When we talk about numbers, I've heard estimates of 1-2% of the total population have tinnitus and describe it as debilitating, so that's a huge number of people. We want to hear, obviously, about the treatments you are developing, and we'll go quite in depth on that but maybe, Rick, you can give just a general outline of what you're working on?

13:42 Treatments in development

Rick: Well we have two therapeutics we're working with in general. One is a pill and the other is an injection therapy, ideally delivered trans-tympanically. The pill is a combination of two drugs: **N-Acetyl Cysteine (NAC)** and a nitrone compound, and initially it was developed as… we call it a **'bomb blast'** pill because in combat in the military, if you get in a combat situation or exposed to an IED, you don't have time to put your hearing protection in, so the idea was

you can take this pill shortly after injury and reduce some of the permanent damage. So that was how it was originally intended and in pre-clinical rodent studies it works very well in that regard. Then, subsequently we found out that it might have some restorative capabilities and may have some efficacy for tinnitus. At least as we've seen in pre-clinical rodent models. It seems to regenerate the afferent nerve endings and synapses at the base of the inner hair cell, quite interestingly.

Hazel: Yes, that is very interesting and is it meant to work right after an acoustic trauma? Is there a certain time window of opportunity there or would it generally regenerate hair cells in any instance?

Rick: Yes, so this doesn't regenerate hair cells, but it regenerates a nerve ending. The injection technology regenerates hair cells. But with regard to the window there for the pill, we know it's effective if given shortly after the injury in animal models for sure. But we've done some delayed studies where it was administered four weeks later and there was regeneration of the nerve endings and reduction of tinnitus percept. So, it may work in chronic situations and we are submitting a grant to that effect right now to look more intently and intensely to see if they can reverse chronic tinnitus. But our pilot data suggests that it may.

16:40 Stage of current research

Hazel: That sounds promising. What stage is this research currently at?

Rick: It's gone through **Phase 1 of the FDA,** so it was found to be quite safe and quite well tolerated with very few side effects at a high dose and the Pharmacokinetics were favourable, so it's ready for a **Phase 2 Study.** Recently the Pill Technology was acquired by a pharmaceutical company and they plan to take it through a **Phase 2 Study** and if that works out, through **Phase 3.**

Hazel: But you guys will remain involved?

Rick: Yes, they'd like us to help them with the effort. They know a lot about pharmaceuticals but not about the ear or tinnitus.

Hazel: Ok, so it's kind of a joint venture situation?

Rick: Yes.

Hazel: Alright, so that's the **'Bomb Blast Pill'** as it's colloquially called, which regenerates nerve endings, I just stood corrected on that count!

18:00 Intra-tympanic injection

Hazel: And then your other treatment is an intra-tympanic injection that is meant to regenerate hair cells, correct? So, can you tell us a bit more about that one?

Rick: Sure, I'd be happy to. So, the injection technology involves **Silencing RNA** that is encapsulated in a **PLGA Nanoparticle**, and we have some data infusing that therapeutic directly into the noise-injured cochlea in a pre-clinical model, with restoration of hearing. But our hope is that it will work by trans-tympanic injection and be able to cross the round window membrane and restore hearing a little bit less invasively. So far, we've shown that trans-tympanic injection does knock down the target in the cochlear quite well. So, with **Silencing RNA** we are trying to knock down **Hess 1** protein levels. **Hess 1** is sort of like a parking brake on regeneration. When you knock **Hess 1** down in supporting cells, it seems to allow them to trans-differentiate into regenerative new cochlear hair cells and restoration of function that goes with that.

Hazel: So, it sounds like you're kind of triggering the natural restorative functions that are already inherent in our inner ear but removing some mechanism that normally inhibits that?

Rick: Correct, yes. **Hess 1** protein is inhibitory so by knocking down the message with **Silencing RNA** it reduces that inhibitory protein level then allows some regeneration to occur.

Hazel: Interesting. And what Phase is that research at?

Rick: This is an earlier stage. We definitely have a **Proof of Concept.** We have been able to reproduce the results in about five different experiments in vivo. Response In vivo is quite robust, quite reproduceable. Clinically relevant amount of hearing loss. We haven't seen any adverse effects so far but, right now, we're working on different delivery routes of formulation and then we'll be ready to do animal toxicology studies in preparation for submission of an **IND and Phase 1 Trial.**

20:54 Benefits to tinnitus or hyperacusis

Hazel: Right. I guess for both of these treatments what our audience really wants to know is, how hopeful are you that they may benefit tinnitus, but also potentially hyperacusis patients?

Rick: I think the pre-clinical data for tinnitus are pretty strong and reproduceable and we have had an outside lab reproduce some of our data. So, I think the pre-clinical data for tinnitus are pretty strong. In addition to decreasing tinnitus percept, we see a number of file markers that are normalised that were previously abnormal from the noise exposure that are associated with tinnitus both in the cochlear and the brain stem and the auditory cortex so we see a correlation between re-grown nerve endings and normalisation of Wave 5 - Wave 1 ratio in the **ABR Tracings** and normalisation of these file markers that are thrown off that are associated with tinnitus. So, really the data are quite robust. All that being said, it's a big jump from small animals to humans. I think that the pre-clinical data are very strong for tinnitus. Hyperacusis, we haven't really looked at that too much. In theory I think it should be helpful, but we really haven't explored that to any degree at this point but would be willing to do so as we have funding and bandwidth.

Hazel: We talk about a reduction in tinnitus. People always ask are you talking about a reduction in loudness or the related distress that comes with tinnitus? But I know these things

are very difficult to measure objectively and, so far, I think it's only been in animals that you've tested it. So, I don't know if you can say anything about that at this time?

Rick: Right, so far the only testing has been in small animals and we use gap inhibition, startle testing method that was popularised by **Jeremy Turner** and others to test that, so in terms of subjective effects like you're talking about we really haven't tested that yet.

Hazel: Yes, that might come with the clinical trials in humans.

23:40 Animal testing

Hazel: Maybe it's also worth asking, because I know there are people out there, even people suffering badly from tinnitus who feel bad when they hear about animal testing, are concerned about it. Maybe it's worthwhile explaining why those tests are necessary?

Rick: Sure, well in research we do as much as we can with cell cultures or test tubes but to study something like tinnitus or hearing loss you need an intact organism and because we're interested in human trials, we need a mammalian system to study and it has to be an intact system. The **FDA** mandates that there are some data that show efficacy, not only a lack of toxicity, but efficacy. So, all of our work is done through very strict **Animal Use Regulations** and we pay a lot of attention to minimising animal stress as much as we can and do everything quite humanely. We work with an **Animal Use Committee** that approves what we do but on that Committee are Scientists and, also, lay people and veterinary staff and so we monitor that very closely and we pay a lot of attention to it. You finally have to study this in some sort of intact system of hearing or tinnitus before you know if it might have any chance to work in humans.

Hazel: Right, so at this point in time, maybe it will be different in the future, but at this point in time we literally can't develop these treatments without animal testing?

Rick: Correct.

25:49 Funding and partnerships

Hazel: Right, we're going to talk more about the treatments, but I also want to touch a bit on the business perspectives. So, the kinds of questions that came up on the **Tinnitus Talk** support forum are about, you know, what other Institutes or researchers, or maybe commercial parties are you guys working with? Can you touch on that?

Rick: Well we have a track record of working through grant funding from the **Department of Defence.** We hold a grant with the **Department of Defence** currently and we have had grants through them in the past, since noise-induced hearing loss and tinnitus are such big disabilities with the military and the **VA** and so they have been good funding partners over the years. Then we also work with some **Oklahoma State Grants, OKAS Grants** they're called, and they have supported a lot of the recent tinnitus work and some of the regenerative work. Then we have both a broad base of generous donors that donate to **The Hough Ear Institute**

and we can use those funds for research, so that's really helpful. Then we licence some of the technology to a company called **Otologics Pharmaceutics** which is a biotech start-up. Their job is to help us commercialise this because **The Hough Institute** really isn't a commercialisation entity. So, **Otologics Pharmaceutics** in turn sub-licence the Pill Technology to a large pharmaceutical company and they are helping to take it through **Phase 2 and Phase 3,** but the injection technology we are still looking for collaborators or investors. We have ongoing discussions with a couple of entities there, and we are in the midst of a **DOD grant** with that particular technology on pre-clinical work.

Hazel: Alright, so you're looking for a commercial partner at the moment for the Injection Technology, ok.

Rick: Yes, we are.

Hazel: Have you been looking to attract capital from investors?

Rick: Yes……

Hazel: Have you been able to do so?

Rick: To a certain degree initially but those discussions are ongoing and there is active interest in that.

28:30 Upcoming partnerships

Hazel: And any upcoming partnerships that you can tell us about?

Justin: Sure, an international Biotech Firm has agreed and licenced the technology from **OPI Biologic Pharmaceuticals Inc**. to take the drug through the remaining clinical trials, well certainly if everything goes well with **clinical 2** they'll move on to **Phase 3 clinical trials.** With that there are many people that have been a part of that. Local companies here and partners and so forth, so we list all those partners out and we also list all the generous donors and that's something that we probably do keep in mind is that a lot of this research was funded by government grants but a good portion of it was also funded by individuals who themselves suffer from tinnitus, hearing loss and want to see a treatment get across and on the market to help them; to help their own families and people after them. As you know, anyone who experiences tinnitus or hearing loss it has a dramatic effect on their social life and the quality of life and their ability to have relationships, their ability to have various opportunities in the world, in the work force and so forth. And what we want to do is that we want to renew those possibilities. We want to reconnect people to the world around them and give them hope and so, a big part of that is having donors and supporters that financially say, you know what? I believe in this. This is something that I want to see happen. And now I want to put a voice to that value by supporting financially the work of research teams all over the world to make it a reality.

30:35 Source of financial donations

Hazel: Right, so individual donations are actually crucial to getting your treatments to market is what you're saying?

Justin: Absolutely. Absolutely. Here would be an example. Right now, we are currently trying to raise $735,000 for a **Proof of Concept Study** for the hearing loss pill for tinnitus that would help us do the research necessary to lend support for **Phase 2 Trials** for that particular indication. So, what that means is that when we go to the clinical trials and **Dr Kopke** will correct me if I say anything wrong, when we get to the clinical trials and so forth and the process of getting it approved by the **FDA,** it's usually approved for certain indications and the pharmaceutical company is going to take whatever approach they feel is best to get the technology to the market. So, if it's a cochlear implant trial or something else, like hearing loss, then that will be what is used for the Trials to get us to that point. Now, afterwards, the doctors can prescribe the pill, or what have you, for something else, but that doesn't necessarily mean that insurance will cover it or that the doctor will prescribe it.

Hazel: You're talking about 'off label' prescriptions, correct?

Justin: Correct. So, if we can demonstrate that indication beforehand that helps it get into the people that have tinnitus more quickly, with insurance. Now, we can't guarantee that any insurance company is going to cover it but if the indication isn't in the research and the clinical trials then that becomes an issue.

Rick: The $700,000 that Justin is referring to is to really nail down the decisive need with additional data that this works for chronic tinnitus, and that we can give it weeks after tinnitus is established and it still reverses tinnitus.

Hazel: Ok, that's great because you're saying that without that **Proof of Concept** you may get the treatment to market but then tinnitus patients may not have access to it, per se. Which would be a real pity. Maybe this is a bit of a side-track question, but do you guys know why pharmaceutical companies in general don't seem that keen to invest in tinnitus treatments?

Rick: I think one challenge is it's such a difficult thing to study because it's so subjective. Treating hearing loss, we have certain audiologic tests, hearing tests that are fairly objective and reproduceable and so it's easier to measure changes in hearing. We have some great questionnaire type instruments for tinnitus for sure, but those are all fairly subjective, so I think that's one of the challenges. Another challenge is that tinnitus is a symptom, not really a diagnosis, so you can have noise-induced tinnitus, toxin-induced tinnitus, age-related tinnitus, tinnitus from acute trauma, tinnitus from blast, tinnitus from chronic noise and so it's very heterogeneous in terms of aetiology and so when you design a study that can be a compounding variable that's hard to deal with but I think that's another challenge. These are challenges. I don't think they're insurmountable. I think sometimes companies may want to shy away from that. I can't really believe that I got into the tinnitus realm because I always thought tinnitus was way more challenging than hearing loss. It's hard to understand the whole system but here we are so we're happy to be here. But tinnitus is challenging for a number of reasons.

Hazel: Yes, that's unfortunately what I've heard from a lot of people, on both the research side and the commercial side. It's exactly those things you've mentioned. It's the lack of any objective way to measure tinnitus and therefore an objective way to measure the effectiveness of the treatment basically and the heterogeneity, there's so many different types of causes. I think the list of potential causes of tinnitus is near to 200 or something like that.

Rick: But on the hopeful side over the last five years there have been more and more clinical trials for tinnitus drugs, so I think pharmaceutical companies are becoming more interested in it and I think they are willing to look at ways to overcome those challenges. There are certainly a lot of people that could be benefitted for sure throughout the world so to come up with something that helps is so very worthwhile so, I think on the hopeful side more and more companies are delving into that realm.

Hazel: That's promising to hear.

36:33 New partnership for the Hough Ear Institute

Hazel: So, if I understand correctly, your new partnership is instrumental or has now helped you get beyond the initial stages of research and will be allowing you to move forward to get the **'bomb blast pill'** through the next clinical trial phases and get it to market right. So, without that partnership you might have been waiting or not have had the funding or the means to do that?

Rick: Yes, that's absolutely correct. That partnership is absolutely essential. As I said we're a non-profit organisation not a commercialisation entity, so our goal is to come up with new discoveries and then partner with someone else to get those discoveries to market. We're so excited and pleased for this opportunity to actually move forward with that sort of a model with a commercialisation partner who wants to take it forward. It is a great partnership.

Hazel: So, the partnership sounds really exciting and especially, the fact I think that it comes from this collaboration between the non-profit space and a commercial party, so I think that really sounds like the way forward to me.

37:59 Other collaborations

Hazel: Can you tell us about other collaborations that you guys have or just, you know, any parties that you are in communication with. I'm particularly interested also if you are connected to any **Patient Organisations** in the hearing or tinnitus space?

Rick: So, I'm also a clinician and ear surgeon and otologist. I have a clinical background there and I work with several other Otologists who also participate in **Hough Ear Institute** and then we have worked a lot with **Yehoash Raphael** at the **University of Michigan** and we have worked a lot with **Jeremy Turner** and his group. **Jim Kaltenbach** has been a big help when we were launching into the tinnitus realm to help us understand the various mechanisms and

whatnot. So those have been a few of our collaborators. **Oklahoma Medical Research Foundation** helped us, actually it was a co-discovery with them on the pill. So, **Bob Floyd** and I worked on this very closely on this together in the initial years. We usually were active in the **Association for Research and Otolaryngology**. We usually presented a paper or two or sometimes a podium presentation at those meetings. I am a member of the **National Hearing Conservation Association** and there are a lot of other organisations we could work with. We just haven't set those up.

Hazel: Haven't got there yet! So, there's no connection for instance with the **American Tinnitus Association** or the **British Tinnitus Association** or any of those types of organisation?

Rick: Well, the connection would be that we would look at their websites and see what information they are generating. We haven't applied for any grants through them as yet because DOD in Oklahoma State Grants have been a bigger source so far, but we're open to lots of different pathways.

Hazel: Yes, who knows in future. Justin, on the **Tinnitus Talk** forum some people have been asking what they can do, or what the tinnitus community can do to help because they are really keen to help you guys move forward basically. What would you say to them?

Justin: I'd say there are four things that the **Tinnitus Talk community,** and people that suffer from tinnitus or hearing loss can do. The first would be to increase our knowledge of the scientific research that's being done, versus the popular fads that don't have Science behind them. One of the things that was very evident in the Forums and with people I talk with on a daily basis, is they are suffering from this and it is very debilitating to them and they want it gone. They want to hear and enjoy the sound of silence and they're willing to try anything to make that happen. Some people will spend $30 or $40 on a supplement. Other people are spending tens of thousands of dollars on some popular fad and they're not getting any results and then they're getting frustrated and, understandably so, but then their frustration creeps over to researchers and research institutes that are trying to push this forward from a scientific perspective and I know one of the things I get asked multiple times is: "Well how can you be sure?" and the bottom line is we can't be sure. We don't know that this is going to get approved and that this is going to work or anything. We just believe that it will and that is why we are working hard to get to that point. So, I think the first step of understanding really what's going on, and what the research is and is there science behind a particular treatment is really a first step.

The second step is to share that knowledge with other people and to have those conversations and to challenge people and to say, hey, several people on the forum say: "Give this guy a chance, he is talking to us, look at their website, they have lots of peer-reviewed journals listed there. Looks like their research team is top-notch." So that was very reaffirming to me. I understand where the hesitation and the suspicion can come from.

The third thing that people can do is to contribute financially to research. It's just like anything else, you know, like children with cancer, or any other cause that is important to you. Whatever it is that you value, then financially support that and that will help advance that research for whatever value it is that you have.

And the fourth would be to invite others to join you. Don't just limit it to just yourself. You know other people that are suffering just like you. Share all of this with them and invite them to join you. I mean $735,000 sounds like an awful lot of money to a lot of people because that's more than many of us make over several years but if you think about it there are 27,000 followers on **Tinnitus Talk** alone and if you take that, and then divide that $735,000 between them you're talking about dollars. So, it is a numbers game. There are some people who will not support financially, cannot support financially, and that's ok but if you can, and this is of value to you, then support the research and I would even go so far as to say, all the research, that you can.

Hazel: I think that's valuable advice Justin and I recognise a lot of what you're saying about there being a certain level of scepticism, maybe sometimes even suspicion, towards researchers. You know, maybe it's understandable to some degree because, as you also pointed out there's also a lot of scam products out there, so you know people get cynical after some time. There have also been in the past decade or so some treatments that have come to market that tinnitus patients thought "Oh, this is really going to be the thing that cures us" and then it turned out to be a disappointment. So I think in that context the attitude is sort of understandable but I think we also have to acknowledge and respect that at this moment in time I don't think there have ever been more people working on tinnitus than today. A lot of researchers, and I have met a lot of them personally, and I know you guys certainly fall into that category, are really doing their best, basically. Genuinely trying to fix that problem and it's difficult and it takes time. Science is a long, hard road with many twists and turns.

Rick: Like watching a glacier melt.

Hazel: So, people get impatient right and it's like: "Why can't you get this to market? Why can't you fast-track it?" It's a difficult discussion, and difficult to explain, I guess.

Justin: And I would say that that is one of the primary drivers for me to do my job well, and to serve Rick and the Institute, because I hear that suffering from people and it moves me to try to do the very best that I can to raise the money necessary to get these treatments advanced further along that scientific pipeline. Because all of those things are completely understandable; why people are sceptical, why people are hurt and, in some cases, even angry. It's all understandable and that's the reason why we're doing the work we do.

Rick: It's kind of hard to explain all of the complexities of research. In research you kind of have to search and then search again. A lot of variables that you have to take into account, but one thing I'm really thankful for is that our research team are top-notch people. They approach this with great passion, and they work really hard: evenings, weekends. They are really motivated to move this quickly and to get it to market too and they put a lot of energy into it and a lot of passion into it and it's really a joy and a privilege to work with a team like that and to have Justin and his team equally passionate. It's a good combination but it's still slower than we'd all like it to be.

Hazel: Yes, for sure. And I think the frustration you point to Justin it's also, part of it is also that people who suffer severely from tinnitus feel that they haven't been taken seriously by

the medical community in general. I guess it's something you guys encounter a lot, that you've encountered a lot of people that they've gone to their doctor and been told that it's nothing, that it's just a sound, learn to live with it. That kind of thing?

Rick: Well, we hope to change that narrative.

Hazel: That's something that in tinnitus healthcare that really has to change. Stop telling people it's nothing and just learn to live with it.

48:48 Future Timelines for Treatment

Hazel: I want to dive a bit deeper into the treatments, but maybe first can we talk about to what extent are you guys able to talk about timelines for the coming years. Do you have any kind of tentative launch dates in mind? You know markets where you will be launching your treatments, etc. Are you able to say anything on that?

Rick: Sure, we can share that information. Of course, it depends on everything going according to plan and funding, but we hope to complete a **Phase 2 Trial** for the pill technology in 2020 and hope to be launching it in the mid-2020's. That's kind of our general roadmap and then, for the injection technology, we're not as far down the road there. We still have to do a **Phase 1 Study** for example, but we're still hoping to launch that by 2027 and we have sort of a **Business and Science roadmap** set up which has us moving through **Phase 2** over the next several years depending on funding and whatnot.

Hazel: Alright, so do you know when you might be able to start **Phase 1** or are there some bottlenecks to resolve first?

Rick: Well, we need to go through toxicology studies after we do formulation. Then we need to make large quantities of the drug under GLP conditions for the Clinical Studies, so there's some work to do that will probably take a couple of years.

Hazel: And in terms of market rollout, I assume you are first focussing on the US and then the rest of the world?

Rick: Probably, although that's probably more of a question for our commercialisation partner, but US markets are often initial focus if the **FDA** pathway is chosen.

51:23 In-depth explanation of hearing loss pill

Hazel: Ok, so let's dive a bit deeper into the treatments and how they work and what the mechanisms behind them are. So, to start with the hearing loss pill, can you just explain the basic mechanisms of how it works?

Rick: Sure, so there are two drugs in the hearing loss pill, in combination. One is **N-Acetyl Cysteine,** or **NAC** and the other is a **Nitrone compound.** The scientific name is too long to repeat but we affectionately call it **HPN07** and they are in combination so, collectively and

synergistically, they deal with free radical toxins. They curtail cell death pathway programmes. They work to reduce reactive oxygen species and reactive nitrogen species. **NAC** serves as a synthetic molecule for **Glutathione** which is one of the cell's most powerful antioxidants. They fight **Glutamatic Cytotoxicity.** They fight the role of ischemia, the damage from ischemia reperfusion and, interestingly, they seem to regenerate these little afferent nerve endings and synapses at the base of the inner hair cell. In addition they seem to prevent the accumulation of pathologic Tao proteins which can be found in the auditory pathway from the cochlea through the central auditory system and those pathologic Tao proteins are neurotoxic and produce neuro-degeneration and **NHPN-1010** is this combination product that can actually robustly prevent the ongoing accumulation of this toxic protein that can be a consequence of noise or blast exposure.

Hazel: Alright, I'm not going to pretend I understood all of that, but I think I get the basic idea. I'm going to also ask a few specific questions that were asked on the **Tinnitus Talk** forum. So, somebody asked if this pill is a combination of a high potency antioxidant and a free radical scavenger, couldn't you get the same effect with just combining **Astaxanthin** and a high dose of Vitamin C?

Rick: I think, in general you can get some effects with other antioxidants. This particular combination that we are using is highly synergistic though, and it's much more than an antioxidant. That's only one of the properties so it's a little different in that regard. There's a lot of literature to support the usefulness of antioxidants in noise induced hearing loss.

Hazel: So, it's not an effect you can replicate by just throwing together some other compounds that are in a similar category?

Rick: Not necessarily.

55:12 Potential side effects

Hazel: And are there any potential side-effects that you know of? Because people always find it hard to imagine how a pill, something you take orally, you know, how it can target such a specific part of the body and it might also affect or potentially damage other systems or organs?

Rick: Yes, that's a great question and it's always a concern and safety studies began in **Phase 1 clinical trials** but they continue on through **Phase 2** and **Phase 3** and post-marketing studies so the combination of **NAC** and **HPNO7** was studied in very high dose in healthy human subjects in the **Phase 1 Study** and there are really almost no side effects in the treatment group that were different in the placebo group so it seems very safe and well-tolerated. One of the compounds, **HPN07,** was used previously as a potential stroke drug and it was given to thousands of patients in much higher doses intravenously and went all the way through **Phase 3 clinical trials** and, again, there were really no safety issues with that. The reason it's not on the market is in **Phase 3 Trials** it didn't seem to be that effective for strokes but lots of patients had exposure to it. Lots of subjects had exposure to it, at very high doses, even higher than you would see with oral dosing and it is very, very safe.

Hazel: Well, alright, that sounds promising, but in terms of the targeting can you explain that a little bit, so when you take a pill like that does it just target the ear or does it affect the whole body, and therefore also the ear?

Rick: Yes, it's distributed throughout the whole body and therefore the ear for a pill, that's for sure.

Hazel: That makes sense, yes.

Rick: But even so, again, we didn't see any side effects or problems from it even though there was that systemic exposure.

57:55 Treatment protocol

Hazel: Right. I think we've addressed this already a little bit, but can you tell us a bit more about what the treatment protocol would look like? So, when would people take it? How often? How long would it take to work, etc?

Rick: Well, you know we just have to speak theoretically again because there haven't been any human clinical trials. Obviously, taking it soon after some injury like unexpected noise exposure or a very loud rock concert or something like that, taking it initially, or even preventatively, would be helpful. It's generally designed to be taken by mouth twice a day and it tends to stay around in the bloodstream for a fair amount of time and I think that, so far, we've tested it out for two weeks of treatment so you might, if you're taking it for tinnitus, you might take it for two weeks and hopefully those regenerated nerve endings and whatnot would remain permanently. So, you might only have to take it for two weeks as opposed to all the time or, perhaps, two weeks every three months or something like that. We've delayed the treatment in a chronic tinnitus model and pre-clinically up to four weeks after onset of tinnitus and we've seen positive results.

Hazel: Alright, and did I recall correctly that you said it might also be effective not only for acute but also chronic tinnitus for someone who's had tinnitus for a decade or so?

Rick: Yes, we're hopeful in that regard so our pilot data looked at that and we waited to treat and tell four weeks after the tinnitus was established and still got reduction in tinnitus.

Hazel: Alright.

Rick: So, we feel hopeful for that indication of chronic tinnitus and that study that we mentioned, the grant we're applying for now is to test this more definitively in the chronic tinnitus model just to make sure.

Hazel: Yes, meaning you will be recruiting people for the trial who have also had tinnitus for a long time for instance?

Rick: Yes, when we get to that point.

Hazel: Yes, once you get there. And will you be looking at different sub-sets of tinnitus, noise induced versus non-noise induced for instance or will you only be looking at noise-induced tinnitus specifically?

Rick: Well we may start with that group of people since it's more of a homogenous group of people but if it shows effectiveness there then we might expand that to other groups as well but we might, just for starters, focus on that situation because that group is more homogenous and then, maybe, for example if it worked in that scenario might try it for age-related tinnitus.

Hazel: That makes sense. Is there anything else you can tell us about the **Phase 1** outcomes in terms of how many people percentage wise benefitted, or in what way they benefitted?

Rick: So, this was a study that was done in healthy subjects that didn't have tinnitus or hearing loss.

Hazel: Ok, so it was just safety testing.

Rick: Right.

Hazel: So, you haven't had a chance to test that yet**.**

Rick: Right.

01:02:10 Hair cell regeneration treatment

Hazel: Let's move on to the **Hair Cell Regeneration Injection Treatment** which, as you pointed out, is in an earlier phase. Again, can you just take us through the basic mechanisms. I think you already explained in general terms that it seemed to regenerate hair cells? How exactly does it do that?

Rick: Well, as you know and as our listeners probably know, with noise-induced hearing loss, blast related hearing loss, age-related hearing loss, the hair cells die off first. Especially in the high frequency region of the cochlea, and supporting cells are left behind. They are more resistant to the damage. In birds, for example, those supporting cells can spontaneously regenerate into new hair cells and the birds can hear again. But in mammals that doesn't happen for some reason and so **HESS 1** is a protein involved in the **'notch system'** and **HESS 1 protein,** when it's expressed in the supporting cells, seems to be inhibitory. It keeps those cells from trans-differentiating into new hair cells so our technology provides a **Silencing RNA molecule** that knocks out the message to that **HESS 1 protein** and reduces the level of **HESS 1** protein in the supporting cells and allows them to trans-differentiate into new hair cells and, based on restoration of hearing in our models, those are functional hair cells.

Hazel: And when you say 'trans-differentiate' you're not talking about 'multiplication' but new cells actually grow or is that how it works?

Rick: There is probably a small amount of cell division that happens but most of it is just transformation of a supporting cell into a new hair cell versus a multiplication effect. So, there's probably some cell division and new cells going on, but that's a smaller component than the actual conversion of a supporting cell into a hair cell.

01:04:50 Treatment protocol

Hazel: So, same question as for the pill earlier can you describe what the treatment protocol might look like? Maybe it's even more difficult to say so for this treatment at this early stage but…?

Rick: We can tell you what our dream is! Well, all our pre-clinical data so far are based on one 24 hour treatment and then a substantial recovery of hair cells and hearing function and then, that hearing function that's restored, remains stable for as long as we've looked at it which is about 10 weeks post-injury. And that's with direct infusion of the material into the cochlear but our ultimate goal is for this to occur with a trans-tympanic injection and diffusion of the medicine into the cochlea or some other created drug delivery approaches that are less invasive. And we've seen knock down of the target, which is necessary with the trans-tympanic injection, so our current grant is looking at the trans-tympanic route in more detail. So right now, we get this substantial recovery of hearing with just one treatment, but we plan to test multiple treatments. There is no reason why multiple treatments might not even get multiple results. And if we use the trans-tympanic routes multiple treatments are quite possible.

Hazel: Is it difficult when you inject a substance into the ear to get the concentration and the localisation just right?

Rick: Well, it involves a surgical opening into the basal turn of the cochlear, so that has to be done very delicately and then we use a mini-osmotic pump which infuses the medicine in solution at a very slow rate, like one microlitre an hour over a 24 hour period. But a similar approach could be used in a human if needed. For example, when you do a cochlear implant you either open up the round window membrane or make a small hole in the cochlear in this case to get an electrode into the cochlear, but in our case to get a drug into the cochlear. But like I said, our hope and our dream is that the trans-tympanic route will work, and we have preliminary data to suggest that it will.

Hazel: Are there other delivery methods that might work? Someone on the Forum mentioned nano-particle delivery. I'm not entirely sure myself what that is?

Rick: So, we encapsulate our **Silencing RNA** into a nanoparticle, because **Silencing RNA** can be digested by enzymes in the cell, so the nanoparticle is protective of the drug, the **Silencing RNA,** until it gets into the cell and then it releases the drug to do its work. Nanoparticles can be a little bit like Trojan Horses, because nanoparticles can actively be taken up by cells and brought into the cells depending on their size so it's not just the process of diffusion. It's a bit like a Trojan Horse situation, but instead of bringing the enemy into the cell we're bringing the good stuff into the cell, so yes, we use nanoparticles for our injection technology for that

reason but I know there are other labs associated with **Harvard** and other places that are looking at micro-fluidic delivery of drugs and those sorts of things. So, while some people are focussing on the drug, other people are focussing on creative and less invasive ways to deliver. So, it's exciting that progress is being made on both fronts.

01:09:28 Benefits for tinnitus

Hazel: So, I guess for this treatment, the same question as for the other treatment, but for this one maybe it's a bit more speculative. To what extent do you think it will help those with acute or chronic tinnitus or hyperacusis?

Rick: Ok, so here comes some speculation. It's thought that perhaps one of the causes of tinnitus is decreased input from the cochlea which leads to increased central gain in a maladaptive way that leads to the tinnitus perception. So, perhaps by restoring hearing, the increased auditory input from the cochlear to the central nervous system will allow readjustment of the gain in the system, so that tinnitus will go away. One of the things that I am kind of interested in is, I'd say about half to two-thirds of patients that I see that have tinnitus, they get hearing aids because they have significant hearing loss. When I see them back three or four months later to see how they are doing, maybe half to two-thirds of them seem to have a reduction in tinnitus or sometimes it actually goes away, or they say: "Well when I have my hearing aids in, I don't get any tinnitus at that point." So, I think, again, thinking about the gain theory of tinnitus that there is more auditory input from the hearing aid and so somehow the central nervous system readjusts. So, my speculation would be that it would help. That's a long way of saying that but it's really speculation and our focus really with that technology is on restoring hearing.

Hazel: Yes, that makes sense. I am particularly interested in this question because there is a very strong faction, let's say, on the **Tinnitus Talk** forum that believes hearing regeneration will be the cure for tinnitus and my sense is always that it might be a cure insofar as tinnitus is caused by hearing loss, so for a certain subset of tinnitus patients, but it won't be **the** cure for everyone. It just seems to make so much sense to me. Would you agree with that?

Rick: Yes, silver bullets are hard to find. Like we said, tinnitus has so many different aetiologies and not all of it is related to cochlear injury though but hopefully for a subset it would be helpful.

Hazel: Absolutely, I would certainly hope so and obviously restoring hearing is, in and of itself a wonderful goal to achieve, but yet there are also, I think, neuroscientists who theorise that even restoring hearing, even if the tinnitus is caused by the hearing loss, it might not cure the tinnitus, because by that time the tinnitus has become centralised in the brain. So even if initially it was triggered by hearing loss, if you restore the hearing the tinnitus might still remain because it's sort of, let's say, ingrained in the brain by that time.

Rick: Sure, that's understandable, and that may be so but, again, like I say, with people who start wearing hearing aids, some of them, a good proportion of them, describe less tinnitus so maybe it's not as ingrained as you think?

Hazel: Exactly, and again, this is just all speculation and you've seen real-life examples of tinnitus reducing or disappearing with hearing aids, so that must mean something.

Alright, well, I hope that you will very soon be able to move to **Phase 1 Trials** for the hearing regeneration injections.

Rick: Well, thank you.

Justin: We appreciate the encouragement. It's what we're working hard for.

Hazel: Well, we're rooting for you. It kind of brings me to the end of a very long list of questions that I had in front of me, but perhaps there's something you guys want to add or conclude with?

Rick: Well, I'd like to say thanks for having the opportunity to visit with you Hazel, and to be part of the **Tinnitus Talk Podcast.** It's really been fun to talk to you and so many good, thoughtful questions and really appreciate your listeners being such advocates for tinnitus and hearing loss and their interest and their great questions. And I guess it just continues to motivate me to keep working. Obstacles come up, but people like your listeners just help motivate me, and our whole team, to keep after it and not let anything be a permanent obstacle. I've really enjoyed this session with you and I really thank you a lot for the opportunity to let people know what we're about.

Hazel: Thank you Rick, it's been a pleasure from my side for sure. Justin, any concluding remarks?

Justin: Yes, I would like to say thank you Hazel and to Markku, and to all of the people who are listening and are engaged on the **Tinnitus Talk** forum. I was really impressed by the civility and just the amazing openness of the people to share their stories and ask questions and I really appreciate their patience with me. I am not a scientist, I am not a doctor and, so, many times I had to come back and ask Rick: "Hey, how do I answer this?" So, I appreciate this and will continue to monitor and try to get on there as often as I can, but as you know, with this new Agreement we're quite busy right now and it's all for the benefit of the listeners here. So, thank you very much for this opportunity to share our Mission and to share the vision that we have, with you.

Hazel: Well, thank you guys, so much, for your time and dedication and well, we hope to hear more updates from you soon.

Rick: Yes, ma'am, thank you.

Justin: Thank you.